

Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study

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Summary

This multicentre, randomized, phase II study was conducted to examine whether the addition of mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, to mLSG15, a dose-intensified chemotherapy, further increases efficacy without compromising safety of patients with newly diagnosed aggressive adult T-cell leukaemia-lymphoma (ATL). Patients were assigned 1:1 to receive mLSG15 plus mogamulizumab or mLSG15 alone. The primary endpoint was the complete response rate (%CR); secondary endpoints included the overall response rate (ORR) and safety. The %CR and ORR in the mLSG15-plus-mogamulizumab arm ($n = 29$) were 52% [95% confidence interval (CI), 33–71%] and 86%, respectively; the corresponding values in the mLSG15 arm ($n = 24$) were 33% (95% CI, 16–55%) and 75%, respectively. Grade ≥ 3 treatment-emergent adverse events, including anaemia, thrombocytopenia, lymphopenia, leucopenia and decreased appetite, were observed more frequently ($\geq 10\%$ difference) in the mLSG15-plus-mogamulizumab arm. Several adverse events, including skin disorders, cytomegalovirus infection, pyrexia, hyperglycaemia and interstitial lung disease, were observed only in the mLSG15-plus-mogamulizumab arm. Although the combination strategy showed a potentially less favourable safety profile, a higher %CR was achieved, providing the basis for further investigation of this novel treatment for newly diagnosed aggressive ATL. This study was registered at ClinicalTrials.gov, identifier: NCT01173887.

Keywords: adult T-cell leukaemia-lymphoma, CCR4, mogamulizumab, randomized phase II study, antibody therapy.

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Adult T-cell leukaemia-lymphoma (ATL) is an aggressive, peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type I (Uchiyama *et al*, 1977; Matsuoka & Jeang, 2007), and is classified into four clinical subtypes: smouldering, chronic, lymphoma and acute (Shimoyama, 1991). Intensive chemotherapy has been recommended for patients with newly diagnosed acute lymphoma or with unfavourable chronic subtypes of ATL (i.e. aggressive ATL) (Tsukasaki *et al*, 2009). A phase III trial was performed in previously untreated patients with aggressive ATL to compare the effects of a dose-intensified multidrug regimen, namely the modified LSG15 (mLSG15) regimen (VCAP-AMP-VECP: vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vindesine, etoposide, carboplatin and prednisolone) (Yamada *et al*, 2001) with the effects of CHOP-14 (cyclophosphamide, doxorubicin, vincristine and prednisolone). The complete response rate (% CR) was higher in the mLSG15 arm (40%) than in the CHOP-14 arm (25%; $P = 0.020$). The overall survival (OS) rates at 3 years were 24% and 13% in the mLSG15 and CHOP-14 arms, respectively, with a significant difference ($P = 0.028$) observed between the two arms after adjustment for imbalances in baseline prognostic factors (Tsukasaki *et al*, 2007). However, the median survival time of 12.7 months in the mLSG15 arm (CHOP-14 arm, 10.9 months) was lower than that observed for other haematological malignancies. Moreover, allogeneic haematopoietic cell transplantation (allo-HCT) has been explored as a promising treatment for ATL, and it has been reported that allo-HCT can potentially provide cures for 30–40% of transplant recipients. However, only few ATL patients benefit from transplantation, such as those who are younger, achieve sufficient disease control and have an appropriate stem cell source (Hishizawa *et al*, 2010; Ishida *et al*, 2012a).

Because CC chemokine receptor 4 (CCR4) is expressed on the surface of the tumour cells of most patients with ATL (Yoshie *et al*, 2002; Ishida *et al*, 2003), it has been postulated

to represent a novel molecular target for immunotherapy for ATL. Therefore, a humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region, mogamulizumab (KW-0761) was developed, and has been shown to markedly enhance antibody-dependent cellular cytotoxicity (Shinkawa *et al*, 2003; Ishii *et al*, 2010). A phase I clinical study of mogamulizumab was performed in patients with relapsed CCR4-positive peripheral T-cell lymphoma (PTCL), including ATL (Yamamoto *et al*, 2010). This study showed good tolerability, predictable pharmacokinetics and preliminary evidence of the antitumour activity of mogamulizumab, and the recommended dose was determined to be 1.0 mg/kg (Yamamoto *et al*, 2010). In the subsequent phase II study, mogamulizumab monotherapy showed an overall response rate (ORR) of 50% in patients with relapsed ATL, with an acceptable toxicity profile (Ishida *et al*, 2012b). Accordingly, mogamulizumab was approved in Japan in 2012 for patients with CCR4-positive relapsed/refractory ATL.

Herein, we report the results of a multicentre, randomized phase II study, the aim of which was to evaluate whether or not the addition of mogamulizumab to mLSG15 increases efficacy without compromising safety for patients with newly diagnosed aggressive ATL.

Patients and methods

Patients

Eligible patients included those newly diagnosed with CCR4-positive aggressive ATL who were aged ≥ 20 years. CCR4 expression was determined by using immunohistochemistry or flow cytometry with a mouse anti-CCR4 monoclonal antibody (KM2160) (Ishida *et al*, 2003; Yamamoto *et al*, 2010) and confirmed by a central review committee. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2. Furthermore, the eligibility criteria included the following laboratory parameters: abso-

lute neutrophil count $\geq 1.5 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$, haemoglobin level ≥ 80 g/l, aspartate aminotransferase level $\leq 2.5 \times$ the upper limit of the normal range (ULN), alanine aminotransferase level $\leq 2.5 \times$ ULN, total bilirubin level ≤ 2.0 mg/dl, serum creatinine level ≤ 1.3 mg/dl, and arterial partial oxygen pressure ≥ 65 mmHg or arterial blood oxygen saturation $\geq 93\%$. Patients were excluded if they had a severe infection, a history of organ transplantation, active concurrent cancer, central nervous system involvement, a bulky mass requiring emergent radiotherapy, or seropositivity for hepatitis B virus surface antigen, hepatitis C virus antibody or human immunodeficiency virus antibody.

Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups based on dynamic allocation and minimization (Pocock & Simon, 1975) by a central randomization centre (Bell Medical Solutions, Inc., Tokyo, Japan). For randomization, the first stratification factor was clinical subtype, and the second was age (<56 or ≥ 56 years). The study had an open-label design.

Procedures

This was a multicentre, randomized, phase II study to compare the efficacy and safety of mLSG15 plus mogamulizumab with that of mLSG15 alone. Subjects assigned to the mLSG15-plus-mogamulizumab arm received eight intravenous 1.0 mg/kg mogamulizumab infusions during four mLSG15 cycles. Typically, mogamulizumab was

administered the day before VCAP and VECP administration except for the first VCAP administration (Fig 1). When VCAP or VECP administration was delayed for any reason, mogamulizumab administration was delayed accordingly.

The primary endpoint was %CR, and the secondary endpoints included ORR, %CR and response rate according to disease site; progression-free survival (PFS); OS and safety. We estimated that 22 patients per arm would be required to achieve an 80% probability of detecting a higher %CR in the mLSG15-plus-mogamulizumab arm than in the mLSG15 arm, based on the selection design (Simon *et al*, 1985). We assumed that an increased %CR of 15% achieved upon adding mogamulizumab would imply clinical significance. This 15% increase in the %CR corresponded to the difference observed between mLSG15 and CHOP-14, with a previous phase III study showing that the former treatment prolonged OS (Tsukasaki *et al*, 2007). Thus, if the true difference is 15%, there is an 80% chance of selecting the right treatment when one chooses the treatment with the higher CR rate. Objective responses were assessed after the second and fourth chemotherapy cycles in each arm by an independent efficacy assessment committee according to the modified response criteria for ATL (Tsukasaki *et al*, 2009). Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for AEs version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf), and were summarized according to the Medical Dictionary for Regulatory Activities System Organ Class and preferred terms. The presence of human anti-mogamulizumab antibodies in plasma was also determined. Blood samples were collected from

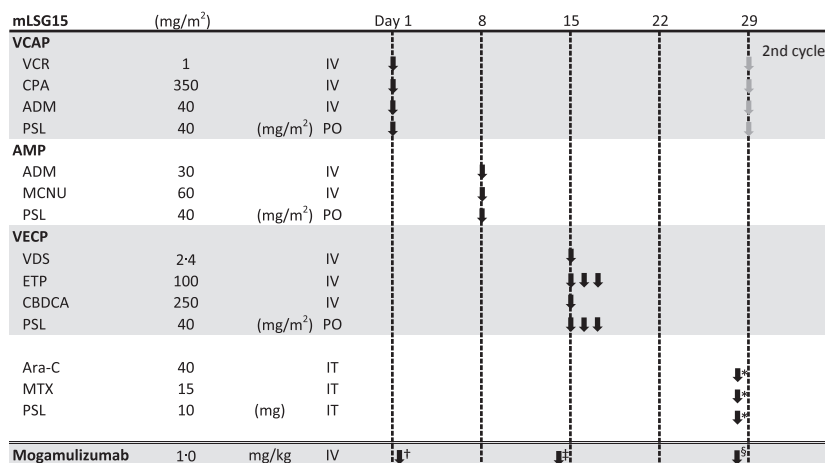


Fig 1. Treatment protocol. The mLSG15 protocol consists of three chemotherapeutic regimens, namely VCAP, AMP and VECP. Subjects assigned to the mLSG15-plus-mogamulizumab arm received up to eight infusions of mogamulizumab during four cycles of mLSG15. Cytarabine, methotrexate and prednisolone were intrathecally injected before initiation of VCAP administration in cycles 2 and 4. VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisolone; AMP: doxorubicin, ranimustine, and prednisolone; VECP: vindesine, etoposide, carboplatin, and prednisolone; IV, intravenous; PO, per os (oral administration); IT, intrathecal; VCR, vincristine; CPA, cyclophosphamide; ADM, doxorubicin; PSL, prednisolone; MCNU, ranimustine; VDS, vindesine; ETP, etoposide; CBDCA, carboplatin; Ara-C, cytarabine; MTX, methotrexate. *Before cycles 2 and 4 (Days -2 to -1). †After VCAP in Cycle 1 (Days 2 to 5). ‡Preceding VECP in Cycles 1-4 (Days 12 to 14). §Preceding VCAP in Cycles 2-4 (Days -3 to -1).

patients who had received at least one dose of mogamulizumab at time points determined by the protocol for the pharmacokinetic analysis. The maximum drug concentration (C_{max}) and trough drug concentration (C_{trough}) for each mogamulizumab administration were calculated. We also investigated the distributions of blood T-cell subsets (CD4/CD25/CCR4-positive cells and CD4/CD25/FOXP3-positive cells) during and after treatment in each arm.

Statistical analysis

Survival estimates were calculated by using the Kaplan–Meier method. PFS was defined as the time from the day of starting the protocol treatment to progression, relapse, or death from any cause. OS was measured from the day of starting the protocol treatment to death from any cause. The numbers of T-cell subsets in the two arms were compared by employing the Wilcoxon signed-rank test for each sampling point at a significance level of 0.05.

Study oversight

The study was sponsored by Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan. The academic investigators and the sponsor were jointly responsible for the study design. The protocol was approved by the institutional review boards at each participating site and all patients provided written informed consent before enrolment, in accordance with the Declaration of Helsinki.

Results

Patients

Between August 2010 and September 2011, 54 patients with newly diagnosed aggressive ATL were enrolled at 18 institutions. Of these 54 patients, 29 in the mLSG15-plus-mogamulizumab arm and 24 in the mLSG15 arm received treatment according to our study protocol. One patient assigned to the mLSG15 arm was withdrawn from the study, owing to the patient's treatment having to be deferred due to abnormal laboratory values that met the protocol criteria, and the patient was unable to wait for the protocol treatment due to deterioration of his/her general condition. The demographics and characteristics of the remaining 53 patients are summarized in Table I. Fifteen patients in the mLSG15-plus-mogamulizumab arm did not complete the planned treatment; of these, seven dropped out because of AEs, including infectious diseases; four dropped out because of progressive disease (PD); and the remaining four dropped out for different reasons, including withdrawal of consent and start of an alternative treatment. Thirteen patients in the mLSG15 arm did not complete the planned treatment; among these, four had AEs, four had PD, and the remaining five dropped out for other reasons (Fig 2).

Table I. Demographics and clinical characteristics.

	mLSG15 + mogamulizumab (n = 29)	mLSG15 (n = 24)*
ATL subtype		
Acute	20 (69%)	17 (71%)
Lymphoma	6 (21%)	7 (29%)
Chronic†	3 (10%)	0 (0%)
Age, years		
Median	61	64
Range	49–81	37–74
<56	11 (38%)	6 (25%)
≥56	18 (62%)	18 (75%)
Sex		
Male	12 (41%)	16 (67%)
Female	17 (59%)	8 (33%)
ECOG PS		
0	16 (55%)	13 (54%)
1	10 (35%)	9 (38%)
2	3 (10%)	2 (8%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

*25 patients were randomized; 24 were treated.

†Chronic type with poor prognostic factors.

Efficacy

Of the 29 and 24 patients evaluable for efficacy in the mLSG15-plus-mogamulizumab and the mLSG15 arms, 25 patients [ORR, 86%; 95% confidence interval (CI), 68–96%] and 18 patients (ORR, 75%; 95% CI, 53–90%), respectively, had objective responses. The %CR, including unconfirmed CR, was higher in the mLSG15-plus-mogamulizumab arm (52%; 95% CI, 33–71%) than in the mLSG15 arm (33%; 95% CI, 16–55%), with a between-group difference of 18.4% (95% CI, –8.9 to 43.8%; Table II). The %CR according to the disease site in the mLSG15-plus-mogamulizumab and mLSG15 arms were 100% (14/14) and 43% (3/7) for blood, 92% (24/26) and 73% (16/22) for nodal and extranodal lesions and 50% (4/8) and 60% (3/5) for skin lesions, respectively. The response rate according to the disease site in the mLSG15-plus-mogamulizumab and mLSG15 arms were 100% (14/14) and 100% (7/7) for blood, 92% (24/26) and 77% (17/22) for nodal and extranodal lesions and 75% (6/8) and 80% (4/5) for skin lesions, respectively. The median PFS in the mLSG15-plus-mogamulizumab and mLSG15 arms were 8.5 months and 6.3 months, respectively (Fig 3A). The median OS was not reached in either arm (Fig 3B).

AEs

The treatment-emergent AEs (TEAEs) of ≥grade 3 that occurred in at least two patients are listed in Table III. The most common TEAEs of any grade in the mLSG15-plus-mogamulizumab arm were neutropenia (100%), thrombocytopenia (100%), leucopenia (100%), lymphopenia (97%),

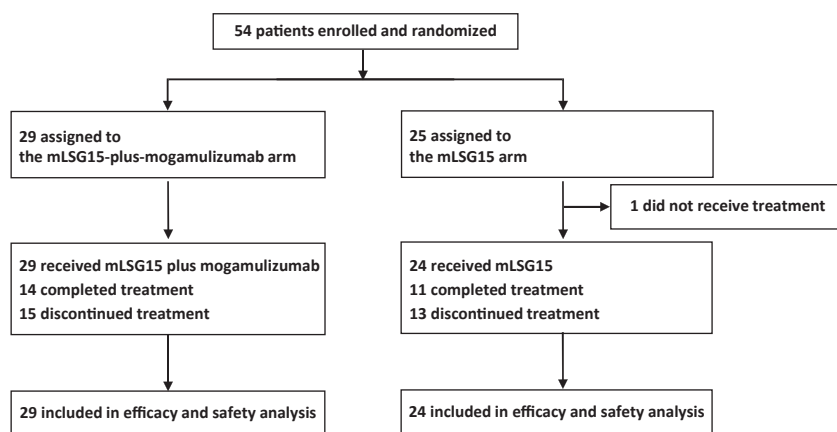


Fig 2. CONSORT diagram. Patients with newly diagnosed CC chemokine receptor 4 - positive aggressive adult T-cell leukaemia-lymphoma were assigned in a 1:1 ratio to receive treatment with mLSG15 plus mogamulizumab or mLSG15 alone. One patient assigned to the mLSG15 arm was withdrawn from the study, owing to the patient's treatment having to be deferred due to abnormal laboratory values that met the protocol criteria, and the patient was unable to wait for the protocol treatment due to deterioration of their general condition.

Table II. Response to treatment.

	mLSG15 + mogamulizumab (<i>n</i> = 29)	mLSG15 (<i>n</i> = 24)
CR	9	5
CRu	6	3
PR	10	10
CR + CRu	15	8
% CR (95% CI)	52% (33–71)	33% (16–55)
Between-group difference (95% CI)	18.4% (−8.9 to 43.8)	
CR + CRu + PR	25	18
ORR (95% CI)	86% (68–96)	75% (53–90)

CR, complete response; CRu, uncertified complete response; PR, partial response; %CR, complete response rate; CI, confidence interval; ORR, overall response rate.

anaemia (97%) and febrile neutropenia (90%). The corresponding percentages in the mLSG15 arm were 96%, 96%, 92%, 96%, 92% and 88%, respectively. The following TEAEs of grade ≥ 3 were more frequently observed ($\geq 10\%$ difference) in the mLSG15-plus-mogamulizumab arm than in the mLSG15 arm: anaemia (97% vs. 79%), thrombocytopenia (90% vs. 71%), lymphopenia (97% vs. 75%), leucopenia (100% vs. 88%) and decreased appetite (28% vs. 13%). Papular rash (21%), hyperglycaemia (14%), pyrexia (14%), interstitial lung disease (10%), erythematous rash (7%), cytomegalovirus infection (7%) cytomegaloviral pneumonia (7%) and oxygen saturation decreased (7%) occurred only in the mLSG15-plus-mogamulizumab arm.

Twenty serious AEs (SAEs) were reported in 12 patients in the mLSG15-plus-mogamulizumab arm. These included pneumonia in two patients, cytomegalovirus infection in two, interstitial lung disease in two, and the following events occurred in one patient each: febrile neutropenia, septic shock, cytomegaloviral pneumonia, pneumonitis, generalized erythema, viral encephalitis, oral disorder, bacteraemia, infection, exfoliative rash, ileus, cholecystitis, haemorrhagic cystitis

and disease progression. The patient with septic shock did not recover and ultimately died. Another patient with haemorrhagic cystitis, which was suspected to be due to a viral infection, showed disease progression and died during the follow-up period due to the haemorrhagic cystitis as an SAE. The remaining 17 SAEs in the mLSG15-plus-mogamulizumab arm all improved or resolved.

Eleven SAEs were reported in nine patients in the mLSG15 arm. These included two patients with bacteraemia, and the following events in one patient each: infection, enterocolitis, pneumonia, soft tissue inflammation, myelodysplastic syndrome, ischaemic colitis, herpes zoster, neurogenic bladder and febrile neutropenia. The outcomes of all SAEs in the mLSG15 arm, with the exception of myelodysplastic syndrome, improved or resolved. There were no deaths during the treatment or follow-up period in the mLSG15 arm.

Pharmacokinetics and immunogenicity

Of the 29 patients enrolled in the mLSG15-plus-mogamulizumab arm, 16 (55%) completed the eight doses of mogamulizumab. The C_{max} (at the end of the eighth infusion) and C_{trough} (14 days after the eighth infusion) of mogamulizumab were 22.8 ± 4.6 and 94 ± 3.8 $\mu\text{g/ml}$ (mean \pm SD), respectively. None of the patients developed detectable levels of anti-mogamulizumab antibodies.

T-cell subset analysis

The numbers of circulating CD4/CD25/CCR4-positive cells in the blood immediately before VCAP therapy for cycle three in the mLSG15-plus-mogamulizumab arm (mean, $0.0246 \times 10^9/l$; median, $0.015 \times 10^9/l$; range, 0.004 – $0.094 \times 10^9/l$) were significantly lower than those in the mLSG15 arm (mean, $0.4693 \times 10^9/l$; median, $0.234 \times 10^9/l$; range, 0.077 – $3.991 \times 10^9/l$) ($P < 0.001$). The corresponding numbers of these cells 28 days after VCAP therapy (Cycle 4) in the mLSG15-plus-mogamulizumab arm ($0.0173 \times 10^9/l$; $0.0095 \times 10^9/l$; 0.001 – $0.133 \times 10^9/l$) were significantly lower

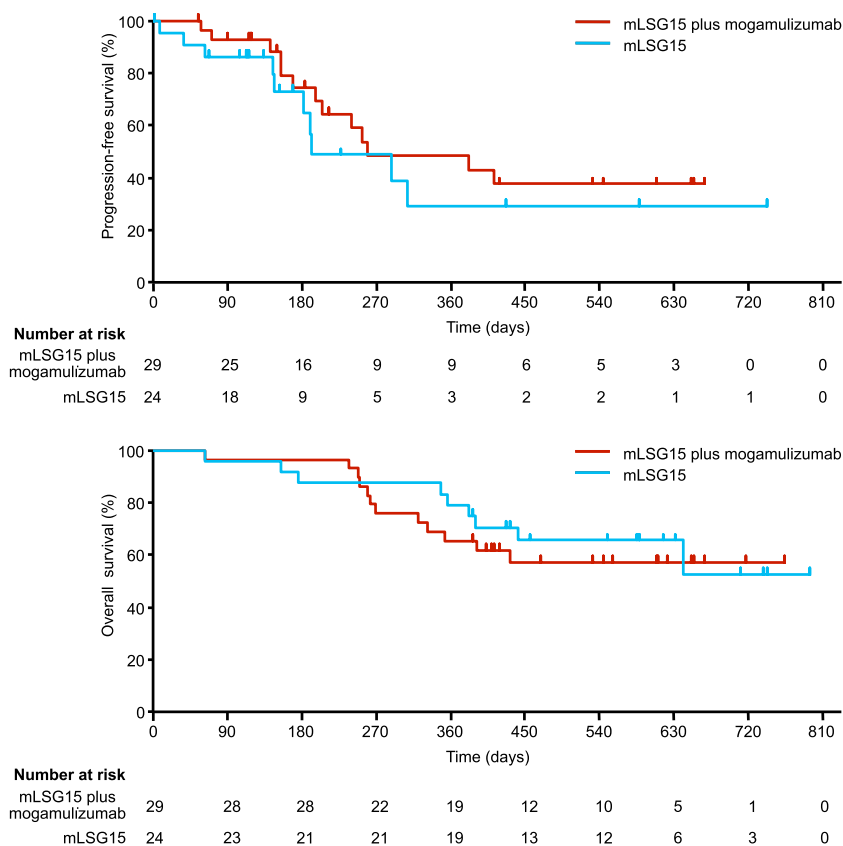


Fig 3. Progression-free survival and overall survival. (A) Kaplan–Meier curve of estimated progression-free survival (median, 8.5 months and 6.3 months in the mLSG15-plus-mogamulizumab and mLSG15 arms, respectively). (B) Kaplan–Meier curve of estimated overall survival (median, not achieved in either arm). The median follow-up periods in the mLSG15-plus-mogamulizumab and mLSG15 arms were 413 days (range, 63–764 days) and 502 days (range, 62–794 days), respectively.

than those in the mLSG15 arm ($0.1478 \times 10^9/l$; $0.133 \times 10^9/l$; $0.059\text{--}0.368 \times 10^9/l$) ($P < 0.001$) (Fig 4A). Similarly, the numbers of CD4/CD25/FOXP3-positive cells in the blood immediately before VCAP therapy (Cycle 3) in the mLSG15-plus-mogamulizumab arm ($0.0085 \times 10^9/l$; $0.004 \times 10^9/l$; $0\text{--}0.048 \times 10^9/l$) were significantly lower than those in the mLSG15 arm ($0.2432 \times 10^9/l$; $0.074 \times 10^9/l$; $0.018\text{--}2.77 \times 10^9/l$) ($P < 0.001$), and the numbers of these cells 28 days after VECP therapy (Cycle 4) in the mLSG15-plus-mogamulizumab arm ($0.0054 \times 10^9/l$; $0.003 \times 10^9/l$; $0\text{--}0.037 \times 10^9/l$) were significantly lower than those in the mLSG15 arm ($0.0684 \times 10^9/l$; $0.0435 \times 10^9/l$; $0.016\text{--}0.25 \times 10^9/l$) ($P < 0.001$, Fig 4B).

Discussion

This study showed that the %CR in patients who received mLSG15 plus mogamulizumab was higher than that obtained in those treated with mLSG15 alone (52% vs. 33%; difference, 18.4%). The increase in the %CR with the addition of mogamulizumab observed in this study surpassed the predicted, targeted, clinically significant 15% increase in patients with ATL. Importantly, the %CR in patients with lesions in the blood compartment was higher in the combination arm, leading to the increase in overall %CR. This finding was consistent with that observed in previous studies, in which ATL lesions in the blood were found to be more sensitive to

mogamulizumab monotherapy than ATL lesions at other disease sites (Yamamoto *et al*, 2010; Ishida *et al*, 2012b).

Infections were more frequent in the combination arm. In particular, cytomegalovirus infection was observed in 14% of patients in the combination arm, whereas it was not observed in the chemotherapy alone arm. Furthermore, cytomegalovirus-related SAEs occurred in three patients in the combination arm. Cytomegalovirus reactivation is observed in approximately 60% of patients with ATL during systemic chemotherapy (Ogata *et al*, 2011). Our study suggests that the addition of mogamulizumab to systemic chemotherapy might further increase the incidence of cytomegalovirus infection; therefore, careful monitoring for cytomegalovirus infection and appropriate use of antiviral therapy are recommended when systemic chemotherapy in combination with mogamulizumab is administered to patients with ATL.

In our previous study of mogamulizumab monotherapy for patients with relapsed ATL, skin rashes, including Stevens–Johnson syndrome, were the most frequently observed AEs (63%) (Ishida *et al*, 2012b, 2013). In the present study, as expected, AEs involving skin and subcutaneous tissue disorders were more frequent in the combination arm than in the chemotherapy alone arm. Even though no severe skin-related AEs, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, occurred in the present study, special attention should be paid to these skin-related AEs

Table III. Treatment-emergent adverse events in the mLSG15-plus-mogamulizumab ($n = 29$) and mLSG15 ($n = 24$) arms.

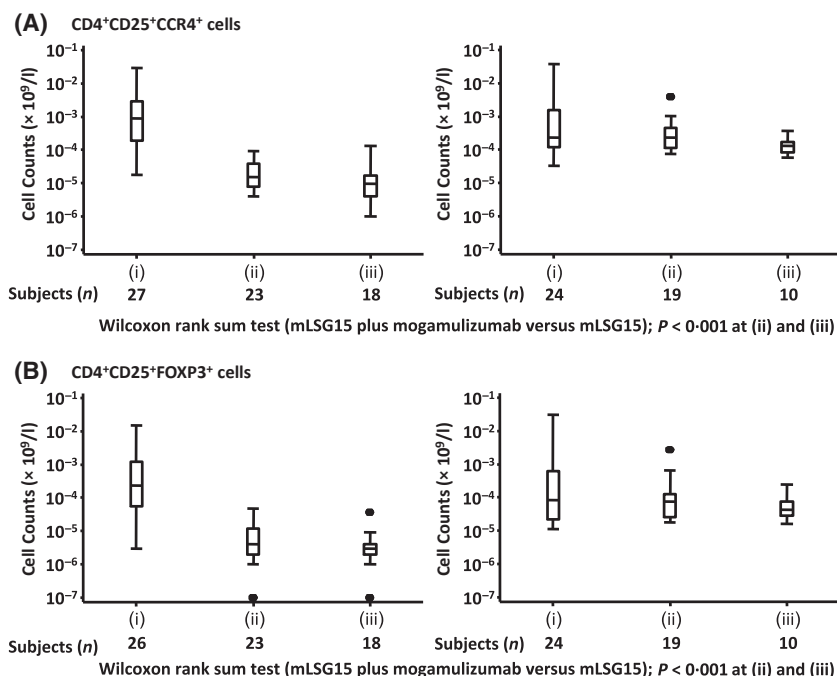
	All grades		≥Grade3	
	mLSG15 + mogamulizumab $n = 29$	mLSG15 $n = 24$	mLSG15 + mogamulizumab $n = 29$	mLSG15 $n = 24$
Blood and lymphatic system disorders	29 (100%)	22 (92%)	29 (100%)	22 (92%)
Anaemia	28 (97%)	22 (92%)	28 (97%)	19 (79%)
Febrile neutropenia	26 (90%)	21 (88%)	26 (90%)	21 (88%)
Gastrointestinal disorders	29 (100%)	23 (96%)	7 (24%)	7 (29%)
Stomatitis	16 (55%)	13 (54%)	4 (14%)	4 (17%)
General disorders and administration site conditions	29 (100%)	21 (88%)	6 (21%)	0 (0%)
Pyrexia	24 (83%)	15 (63%)	4 (14%)	0 (0%)
Infections and infestations	19 (66%)	16 (67%)	10 (34%)	7 (29%)
Bacteraemia	4 (14%)	3 (13%)	3 (10%)	3 (13%)
Pneumonia	4 (14%)	2 (8%)	3 (10%)	1 (4%)
Cytomegalovirus infection	4 (14%)	0 (0%)	2 (7%)	0 (0%)
Cytomegaloviral pneumonia	2 (7%)	0 (0%)	2 (7%)	0 (0%)
Investigations	29 (100%)	24 (100%)	29 (100%)	24 (100%)
Neutropenia	29 (100%)	23 (96%)	29 (100%)	22 (92%)
Thrombocytopenia	29 (100%)	23 (96%)	26 (90%)	17 (71%)
Lymphopenia	28 (97%)	23 (96%)	28 (97%)	18 (75%)
Leucopenia	29 (100%)	22 (92%)	29 (100%)	21 (88%)
Albuminaemia	12 (41%)	11 (46%)	2 (7%)	1 (4%)
Alanine transaminase increased	12 (41%)	10 (42%)	2 (7%)	2 (8%)
Aspartate transaminase increased	9 (31%)	8 (33%)	2 (7%)	1 (4%)
Potassium decreased	9 (31%)	6 (25%)	3 (10%)	1 (4%)
Sodium decreased	8 (28%)	7 (29%)	4 (14%)	2 (8%)
Phosphorus decreased	8 (28%)	3 (13%)	3 (10%)	1 (4%)
Blood pressure increased	7 (24%)	2 (8%)	5 (17%)	2 (8%)
Oxygen saturation decreased	4 (14%)	1 (4%)	2 (7%)	0 (0%)
Metabolism and nutrition disorders	27 (93%)	19 (79%)	14 (48%)	6 (25%)
Decreased appetite	23 (79%)	15 (63%)	8 (28%)	3 (13%)
Hyperglycaemia	13 (45%)	7 (29%)	4 (14%)	0 (0%)
Hyponatraemia	4 (14%)	3 (13%)	2 (7%)	2 (8%)
Hypophosphataemia	4 (14%)	3 (13%)	4 (14%)	2 (8%)
Hypokalaemia	5 (17%)	1 (4%)	2 (7%)	1 (4%)
Respiratory, thoracic and mediastinal disorders	21 (72%)	9 (38%)	4 (14%)	1 (4%)
Interstitial lung disease	3 (10%)	0 (0%)	3 (10%)	0 (0%)
Skin and subcutaneous tissue disorders	29 (100%)	20 (83%)	15 (52%)	1 (4%)
Papular rash	12 (41%)	0 (0%)	6 (21%)	0 (0%)
Erythematous rash	8 (28%)	0 (0%)	2 (7%)	0 (0%)

when mogamulizumab is administered to patients with ATL.

Adult T-cell leukaemia-lymphoma cells constitutively express CD25 (Waldmann *et al*, 1984), and the present study had an eligibility criterion of CCR4 positivity. Hence, most of the CD4/CD25/CCR4-positive cells were considered ATL cells. Compared to the chemotherapy alone arm, the combination arm showed a significant

reduction in the number of CD4/CD25/CCR4-positive cells. This finding is consistent with the proposed antitumour mechanism of mogamulizumab, in that mogamulizumab kills CCR4-expressing ATL cells by increasing antibody-dependent cellular cytotoxicity (Shinkawa *et al*, 2003; Ishii *et al*, 2010; Yamamoto *et al*, 2010). In humans, CCR4 is expressed on CD45RO-positive, CD45RA-negative, FOXP3-positive activated regulatory T (Treg) cells (Miyara *et al*,

Fig 4. T-cell subset analysis. Blood samples were taken (i) immediately before the initiation of treatment, (ii) immediately before VCAP therapy for cycle three, and (iii) 28 days after VECP therapy for cycle four. The numbers of CD4/CD25/CC chemokine receptor 4 (CCR4)-positive cells (A) and CD4/CD25/FOXP3-positive cells (B) are shown as box and whisker plots indicating the minimum, lower, median, upper quartile, and maximum values. The number of samples used for analysis at each point is indicated below the graph. The differences of each point [(ii) & (iii)] between the mLSG15-plus-mogamulizumab and mLSG15 arms are indicated as p-values (Wilcoxon signed-rank test) below the graphs. CCR4 was detected by using a monoclonal antibody (clone 1G1), with its binding to CCR4 being unaffected by the presence of mogamulizumab. VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisolone; VECP: vindesine, etoposide, carboplatin, and prednisolone.



2009; Ishida & Ueda, 2011; Sugiyama *et al*, 2013). In addition, ATL cells from a subset of patients express FOXP3 and function as Treg cells (Yano *et al*, 2007). Thus, the CD4/CD25/FOXP3-positive cells included not only endogenous activated Treg cells, but also ATL cells, in some patients. Our study indicated that compared to the chemotherapy alone arm, the combination arm showed a significant reduction in the number of CD4/CD25/FOXP3-positive cells, which is consistent with the findings from our previous study of mogamulizumab monotherapy. In general, decreasing the number of Treg cells is considered a promising strategy for boosting antitumour immunity in patients with cancer, because the numbers of these cells increase in the tumour microenvironment, and they may play an important role in the ability of the tumour to escape host immunity in several different types of cancer (Ishida & Ueda, 2011; Jacobs *et al*, 2012). On the other hand, because alterations in Treg cell frequencies and/or function may contribute to various autoimmune diseases (Michels-van Amelsfort *et al*, 2011), immune-related AEs, such as skin disorders, which were also observed in our study, should be carefully monitored.

The present study was conducted according to the premise that mLSG15 is the most recommended chemotherapeutic regimen for patients with newly diagnosed aggressive ATL. We found higher rates of treatment-related toxicities with mLSG15 compared to what has been reported for CHOP-14 (Tsukasaki *et al*, 2007). In the context of this scenario, this study suggests that a younger patient population, particularly those aged <56 years, will benefit from VCAP-AMP-VECP, while an older population consisting of those aged 56–69 years will not; there are no data regarding mLSG15 ther-

apy for patients with ATL aged >69 years (Tsukasaki *et al*, 2007). In the present study, the median ages in the mLSG15-plus-mogamulizumab and mLSG15 arms were 61 years and 64 years, respectively; patients potentially benefiting from mLSG15 (<56 years) accounted for only 38% of the patients in the mLSG15-plus-mogamulizumab arm and 25% of those in the mLSG15 arm. Adult T-cell leukaemia-lymphoma generally occurs in older individuals, with a median age at diagnosis of approximately 66 years (Iwanaga *et al*, 2012); therefore, further investigations are needed to determine whether mLSG15 is indeed the most suitable systemic chemotherapeutic regimen when combined with mogamulizumab.

CCR4 is expressed on the surface of tumour cells of patients from a subgroup of PTCL other than ATL, which also has an unfavourable prognosis (Ishida *et al*, 2004; Nakagawa *et al*, 2009). We have already completed a multicentre phase II study of mogamulizumab monotherapy for patients with relapsed CCR4-positive PTCL in Japan (Clinicaltrials.gov: NCT01192984) (Ogura *et al*, 2014). Furthermore, other clinical trials of mogamulizumab for PTCL (Clinicaltrials.gov: NCT01611142) or cutaneous T-cell lymphoma (Clinicaltrials.gov: NCT01728805) are currently underway worldwide. Further studies are expected to allow the determination of the efficacy of combining mogamulizumab with chemotherapy or other novel molecular target therapies for PTCL subtypes other than ATL.

Although this study offers a novel treatment option for newly diagnosed aggressive ATL, some limitations should be discussed. First, this study was designed to set the %CR as a primary endpoint; as a result, this study does not have enough power or a long enough follow-up period to detect

PFS and OS differences between the two arms. Thus, although a tendency towards prolongation of PFS in the combination arm was observed in the present study, this was not confirmed. Second, the treatment after the study protocol, including allo-HCT and mogamulizumab, varied among the patients. Because the use of mogamulizumab for relapsed/refractory ATL was approved in Japan during the study period, the patients, including those in the chemotherapy alone arm, may have a chance to receive this drug. Both of these factors may affect the OS (Chihara *et al*, 2013).

In conclusion, although mLSG15 plus mogamulizumab was found to be associated with a potentially less favourable safety profile, particularly for infectious and skin-related events, the majority of the AEs were manageable. The %CR was higher with combination therapy. Accordingly, this combination treatment appears to be a better option for managing patients with newly diagnosed aggressive ATL. Further clinical studies are necessary to evaluate the survival parameters in patients treated with chemotherapy plus mogamulizumab and to determine a more suitable combination regimen.

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Author contributions

T.I., K.U., K.Y., N.U., A.U., K.T., S.A. and R.U. contributed to the conception and design of the study; T.I., T.J., S.T., H.S., K.U., K.Y., N.U., Y.S., K.N., A.U., K.T., H.F., K. Ishitsuka, S.Y., N.T., Y.M., K. Imada and T.M. contributed to the acquisition of data; T.I., K.T., S.A., M.T. and R.U. analysed and interpreted the data; all authors drafted and reviewed the manuscript and approved the final version for submission.

Conflicts of interest

T.I. has received honoraria and travel grants from Kyowa Hakko Kirin, and research funding from Kyowa Hakko Kirin, Chugai, Bayer and Celgene, and has served on the speakers bureau for Kyowa Hakko Kirin. T.J. has received honoraria and travel grants from Kyowa Hakko Kirin. S.T. has received travel grants and research funding from Kyowa Hakko Kirin. H.S. has served on the speakers bureau for Kyowa Hakko Kirin. K.Y. has a consultancy/advisory role with Kyowa Hakko Kirin and Novartis, has received

honoraria from Kyowa Hakko Kirin, Novartis, Takeda and Janssen, and has received research funding from Kyowa Hakko Kirin, Novartis, Pfizer and ARIAD. Y.S. has received honoraria and research funding from Kyowa Hakko Kirin. K.N. has received honoraria from Kyowa Hakko Kirin. A.U. has received honoraria and research funding from Kyowa Hakko Kirin. K.T. has received honoraria from Kyowa Hakko Kirin and research funding from Kyowa Hakko Kirin, Celgene, Eisai, Solasia Pharma and Mundipharma. S.Y. has received honoraria and research funding from Kyowa Hakko Kirin. Y.M. has received honoraria, travel grants and research funding from Kyowa Hakko Kirin. K. Imada has received research funding from Kyowa Hakko Kirin. S.A. is employed by Kyowa Hakko Kirin, and is a stock owner. M.T. has a consultancy/advisory role with Kyowa Hakko Kirin, and has received honoraria from Kyowa Hakko Kirin. R.U. has a consultancy/advisory role with Mundipharma, and has received honoraria, travel grants and research funding from Kyowa Hakko Kirin and Chugai, and has served on the speakers bureau for Kyowa Hakko Kirin. The remaining authors declare no competing financial interests.

Appendix I

List of the review committees and medical experts who participated in this trial:

- 1 Junji Suzumiya, Shimane University Hospital
- 2 Takashi Terauchi, Research Centre for Cancer Prevention and Screening National Cancer Centre
- 3 Ukihide Tateishi, Yokohama City University Graduate School of Medicine
- 4 Junichi Tsukada, University of Occupational and Environmental Health
- 5 Koichi Nakata, University of Occupational and Environmental Health
- 6 Shigeo Nakamura, Nagoya University Graduate School of Medicine
- 7 Hiroshi Inagaki, Nagoya City University Graduate School of Medical Sciences
- 8 Koichi Ohshima, Kurume University School of Medicine
- 9 Michinori Ogura, Nagoya Daini Red Cross Hospital
- 10 Tetsuo Nagatani, Hachioji Medical Centre of Tokyo Medical University
- 11 Akimichi Morita, Nagoya City University Graduate School of Medical Sciences
- 12 Kazunari Yamaguchi, Institute of Molecular Embryology and Genetics, Kumamoto University
- 13 Yasuaki Yamada, Nagasaki University Graduate School of Biomedical Sciences
- 14 Shuichi Hanada, National Hospital Organization Kago-shima Medical Centre.

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