Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial

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Summary

Background Cutaneous T-cell lymphomas are rare non-Hodgkin lymphomas with substantial morbidity and mortality in advanced disease stages. We compared the efficacy of mogamulizumab, a novel monoclonal antibody directed against C-C chemokine receptor 4, with vorinostat in patients with previously treated cutaneous T-cell lymphoma.

Methods In this open-label, international, phase 3, randomised controlled trial, we recruited patients with relapsed or refractory mycosis fungoides or Sézary syndrome at 61 medical centres in the USA, Denmark, France, Italy, Germany, the Netherlands, Spain, Switzerland, the UK, Japan, and Australia. Eligible patients were aged at least 18 years (in Japan, ≥20 years), had failed (for progression or toxicity as assessed by the principal investigator) at least one previous systemic therapy, and had an Eastern Cooperative Oncology Group performance score of 1 or less and adequate haematological, hepatic, and renal function. Patients were randomly assigned (1:1) using an interactive voice web response system to mogamulizumab (1·0 mg/kg intravenously on a weekly basis for the first 28-day cycle, then on days 1 and 15 of subsequent cycles) or vorinostat (400 mg daily). Stratification was by cutaneous T-cell lymphoma subtype (mycosis fungoides *vs* Sézary syndrome) and disease stage (IB–II *vs* III–IV). Since this study was open label, patients and investigators were not masked to treatment assignment. The primary endpoint was progression-free survival by investigator assessment in the intention-to-treat population. Patients who received one or more doses of study drug were included in the safety analyses. This study is ongoing, and enrolment is complete. This trial was registered with ClinicalTrials.gov, number NCT01728805.

Findings Between Dec 12, 2012, and Jan 29, 2016, 372 eligible patients were randomly assigned to receive mogamulizumab (n=186) or vorinostat (n=186), comprising the intention-to-treat population. Two patients randomly assigned to mogamulizumab withdrew consent before receiving study treatment; thus, 370 patients were included in the safety population. Mogamulizumab therapy resulted in superior investigator-assessed progression-free survival compared with vorinostat therapy (median 7·7 months [95% CI 5·7–10·3] in the mogamulizumab group *vs* 3·1 months [2·9–4·1] in the vorinostat group; hazard ratio 0·53, 95% CI 0·41–0·69; stratified log-rank p<0·0001). Grade 3–4 adverse events of any cause were reported in 75 (41%) of 184 patients in the mogamulizumab group and 76 (41%) of 186 patients in the vorinostat group. The most common serious adverse events of any cause were pyrexia in eight (4%) patients and cellulitis in five (3%) patients in the mogamulizumab group; and cellulitis in six (3%) patients, pulmonary embolism in six (3%) patients, and sepsis in five (3%) patients in the vorinostat group. Two (67%) of three on-treatment deaths with mogamulizumab (due to sepsis and polymyositis) and three (33%) of nine on-treatment deaths with vorinostat (two due to pulmonary embolism and one due to bronchopneumonia) were considered treatment-related.

Interpretation Mogamulizumab significantly prolonged progression-free survival compared with vorinostat, and could provide a new, effective treatment for patients with mycosis fungoides and, importantly, for Sézary syndrome, a subtype that represents a major therapeutic challenge in cutaneous T-cell lymphoma.

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Introduction

Cutaneous T-cell lymphomas are a rare and heterogeneous group of extranodal T-cell lymphomas characterised by skin involvement, with an overall US incidence of 7·5 cases per 1 million people.[1] The most common type of cutaneous T-cell lymphoma is mycosis fungoides, an indolent neoplasm characterised by variable type and extent of skin disease (patches, plaques, tumour-type, and

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed, Embase, and Cochrane Library for phase 2 and phase 3 clinical trials in patients with cutaneous T-cell lymphoma done in the past 20 years (between Jan 1, 1998, and Jan 17, 2018) with the following search string: ("cutaneous T-cell lymphoma" OR "CTCL" OR "mycosis fungoides" OR "Sézary syndrome"), with no language restrictions. In the previous two decades, most prospective phase 2 or 3 clinical trials of systemic agents were either non-randomised (67 studies in total) or randomised to compare one or more doses of an agent, with or without a placebo or observational arm (five studies in total). Two non-randomised mogamulizumab trials were identified in our search—one phase 1/2 trial and one phase 2 trial. One phase 3 randomised trial published in 2017 (n=131; ALCANZA) compared systemic drugs (brentuximab vedotin *vs* physician's choice of methotrexate or bexarotene) in previously treated patients with CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma—with exclusion of patients with Sézary syndrome—and used objective global response lasting at least 4 months as the primary endpoint. In published studies, the proportion of patients who achieved an objective response was determined by a range of methods, with trials before 2011 generally using less comprehensive assessments.

Added value of this study

Previous studies of systemic agents in cutaneous T-cell lymphoma that included Sézary syndrome as a major subtype were single-arm trials that mostly used the proportion of patients achieving an overall response as the primary endpoint. Although both overall response and progression-free survival are clinically relevant endpoints in cutaneous T-cell lymphoma, progression-free survival also captures the duration of disease control (absence of disease progression) with treatment, and therefore might more broadly reflect the overall clinical benefit in patients with cutaneous T-cell lymphoma, who often have a chronic disease course. To our knowledge, the phase 3 MAVORIC trial is the largest randomised study of systemic therapy in cutaneous T-cell lymphoma and the first to compare systemic therapies using progression-free survival as a primary endpoint. Our results show that mogamulizumab was superior to vorinostat for investigator-assessed median progression-free survival, the study's primary efficacy endpoint, and also for the proportion of patients who achieved an overall response and for quality-of-life outcomes, with a manageable safety profile consistent with previous studies.

Implications of all the available evidence

Our MAVORIC study found that, in patients with previously treated mycosis fungoides or Sézary syndrome, treatment with mogamulizumab, a first-in-class anti-CC chemokine receptor 4 monoclonal antibody, resulted in superior progression-free survival, a higher proportion of patients achieving an overall response, and better patient-reported outcomes than vorinostat, a US Food and Drug Administration-approved histone deacetylase inhibitor. Therefore, mogamulizumab could be a valuable new therapeutic option for patients with cutaneous T-cell lymphoma.

erythroderma), with a subset of patients either presenting with or developing extracutaneous disease. Sézary syndrome is a much rarer but more aggressive type of cutaneous T-cell lymphoma, characterised by erythroderma, lymphadenopathy, and blood involvement with neoplastic T cells. Together, mycosis fungoides and Sézary syndrome account for about two-thirds of all cutaneous T-cell lymphomas.[2] With substantial clinical and biological overlap, both disease types can cause lifelong morbidity, decreased quality of life due to chronic skin impairment with intractable itching, recurrent infections, disfiguring skin lesions, sleep disturbance, and psychosocial problems.[3] The burden of disease in skin and the presence of extracutaneous disease are primary determinants of survival.[4–7] Patients with advanced-stage mycosis fungoides and Sézary syndrome (stages IIB–IVB disease) have a median overall survival of approximately 5 years.[6]

Patients with early-stage mycosis fungoides (IA–IIA) are treated primarily with skin-directed therapies, whereas those with treatment-resistant early-stage mycosis fungoides, advanced-stage mycosis fungoides, or Sézary syndrome require systemic drugs, including retinoids, methotrexate, interferons, histone deacetylase inhibitors (eg, vorinostat and romidepsin), brentuximab vedotin, or cytotoxic chemotherapeutic drugs.[8,9] Many of these drugs were approved on the basis of small, single-arm or non-randomised trials with varied response criteria. The largest phase 3 trial comparing systemic therapies reported so far included 131 patients.[10] Except for allogeneic haemopoietic stem cell transplantation, there are no curative options for cutaneous T-cell lymphoma. Patients with cutaneous T-cell lymphoma often experience disease progression on therapy or become resistant to existing treatments, resulting in a need for newer therapies that target all disease compartments (skin, blood, lymph nodes, and viscera) and provide a durable response.

Mogamulizumab (KW-0761; Kyowa Kirin, Tokyo, Japan), a first-in-class defucosylated humanised IgG1 κ monoclonal antibody, selectively binds to C-C chemokine receptor 4 (CCR4) with enhanced antibody-dependent cellular cytotoxicity activity.[11] CCR4, which is involved in cell trafficking of lymphocytes to skin, is consistently expressed on the surface of tumour cells in T-cell malignancies, such as cutaneous T-cell lymphoma (including mycosis fungoides and Sézary syndrome), adult T-cell leukaemia-lymphoma, and peripheral T-cell lymphoma.[12–15]

Mogamulizumab has been approved in Japan for relapsed or refractory CCR4-positive adult T-cell

leukaemia-lymphoma (2012), peripheral T-cell lymphoma (2014), and cutaneous T-cell lymphoma (2014).[16] In a US-based phase 1/2 study in patients with cutaneous T-cell lymphoma, mogamulizumab showed an acceptable safety profile and promising efficacy, with 37% of patients achieving an overall response, and 95% achieving a response in the blood compartment.[17] These encouraging results led to the development of our phase 3 MAVORIC study, which compared mogamulizumab to vorinostat, a US Food and Drug Administration (FDA)-approved drug with established clinical activity,[18,19] in previously treated patients with mycosis fungoides or Sézary syndrome. Both the proportion of patients achieving an overall response and progression-free survival are clinically relevant efficacy endpoints in cutaneous T-cell lymphoma. However, in contrast to the proportion of patients achieving an overall response, progression-free survival also provides information about the duration of disease control (ie, absence of disease progression) with treatment, and therefore might more broadly reflect overall meaningful clinical benefit in patients with cutaneous T-cell lymphoma, who often have a chronic disease course. Therefore, we undertook a phase 3 randomised trial comparing systemic therapies in previously treated patients with cutaneous T-cell lymphoma in which we used progression-free survival as the primary endpoint.

Methods

Study design and participants

MAVORIC is an open-label, international, randomised controlled phase 3 trial done at 61 medical centres in the USA, Denmark, France, Italy, Germany, the Netherlands, Spain, Switzerland, the UK, Japan, and Australia.

Eligible patients had stage IB–IVB (appendix pp 10–12),[20] histologically confirmed relapsed or refractory mycosis fungoides or Sézary syndrome, were aged at least 18 years (in Japan, ≥20 years), had failed (for progression or toxicity as assessed by the principal investigator) at least one previous systemic therapy, and had an Eastern Cooperative Oncology Group performance score of 1 or less and adequate haematological, hepatic, and renal function. Patients on stable (at least 4 weeks) low-potency or intermediate-potency topical steroids or low-dose (≤20 mg) systemic steroids could continue steroid use, but initiation of steroids on study (except topical steroids to treat drug rash) was not permitted. Patients previously treated with anti-CD4 antibody or alemtuzumab were eligible for inclusion provided their CD4+ cell counts were at least 200 per mm³. Key exclusion criteria were large cell transformation at study entry, previous mogamulizumab treatment, previous vorinostat treatment (brief exposure without evidence of progression or toxicity on treatment was allowed with sponsor approval), CNS metastasis, active autoimmune disease, clinically significant uncontrolled intercurrent illness, and previous allogeneic transplant. Previous cutaneous T-cell lymphoma skin-directed therapy within 2 weeks or systemic therapy within 4 weeks of randomisation was not allowed. CCR4 expression was not a requirement for participation (for full eligibility criteria see appendix pp 70–73).

The trial was done in accordance with the Declaration of Helsinki, the International Conference on Harmonisation consolidated Good Clinical Practice guideline, and any applicable national and local laws and regulations. The protocol and all subsequent amendments were reviewed and approved by institutional review boards or independent ethics committees at each site. An independent data monitoring committee oversaw patient safety. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive mogamulizumab or vorinostat and stratified by cutaneous T-cell lymphoma subtype (mycosis fungoides *vs* Sézary syndrome) and disease stage (IB–II *vs* III–IV). We assigned screening numbers using an interactive voice web response system. When the patient was determined eligible for randomisation, the investigator or designee contacted the interactive voice web response system to obtain the randomisation assignment for the patient.

In this open-label study, patients and investigators were not masked to treatment assignment; thus, a blinded independent review was done to assess response and date of progression and account for potential bias during the randomised treatment period. This blinded review consisted of independent radiological evaluation (two-reader framework) and comprehensive review of all modified Severity Weighted Assessment Tool (mSWAT)[21] and flow cytometry data by an independent haematologist with experience in treating patients with cutaneous T-cell lymphoma.

Procedures

Patients received either mogamulizumab 1·0 mg/kg or vorinostat 400 mg. Treatment was administered on an outpatient basis. Each treatment cycle was 28 days. Patients received mogamulizumab intravenously over at least 1 h on days 1, 8, 15, and 22 of the first cycle, and on days 1 and 15 of subsequent cycles. No dose reductions were permitted for mogamulizumab. Vorinostat was administered orally, once daily with food, beginning on day 1. Investigators followed US prescribing information for vorinostat (appendix pp 80–81).[22]

Patients could continue treatment until disease progression, drug intolerance, unacceptable toxicity, or any other criteria for treatment discontinuation were met. If the patient had a global complete response (ie, complete response in the skin, and complete response or no involvement in the other three disease compartments [blood, lymph nodes, and viscera]),[20] the patient could continue treatment for up to 12 months or until progression, whichever came first. Patients on vorinostat for at least two cycles who showed confirmed

disease progression or had intolerable toxicity (grade ≥3 adverse events, excluding inadequately treated nausea, vomiting, diarrhoea, and alopecia), despite dose reduction and appropriate management of side-effects, could cross over to treatment with mogamulizumab. Crossover was allowed only after discussion with the medical monitor and receipt of sponsor approval to ensure that patients on vorinostat were not discontinued prematurely and protocol criteria for crossover were met. Patients were assessed at least once every 2 weeks for potential adverse events from the time of informed consent until 90 days after the last dose or initiation of alternative therapy.

Compartmental disease was evaluated by the mSWAT, CT scans, and flow cytometry (appendix pp 13–18).[20] Clinical response to treatment in skin and blood was assessed every 4 weeks. Investigators specifically trained in mSWAT evaluated skin disease.[2,21] We assessed response in the blood compartment by flow cytometry done at a central laboratory (Q2 Solutions; Morrisville, NC, USA). Lymph nodes and visceral disease were identified by size criteria and evaluated by CT scans at

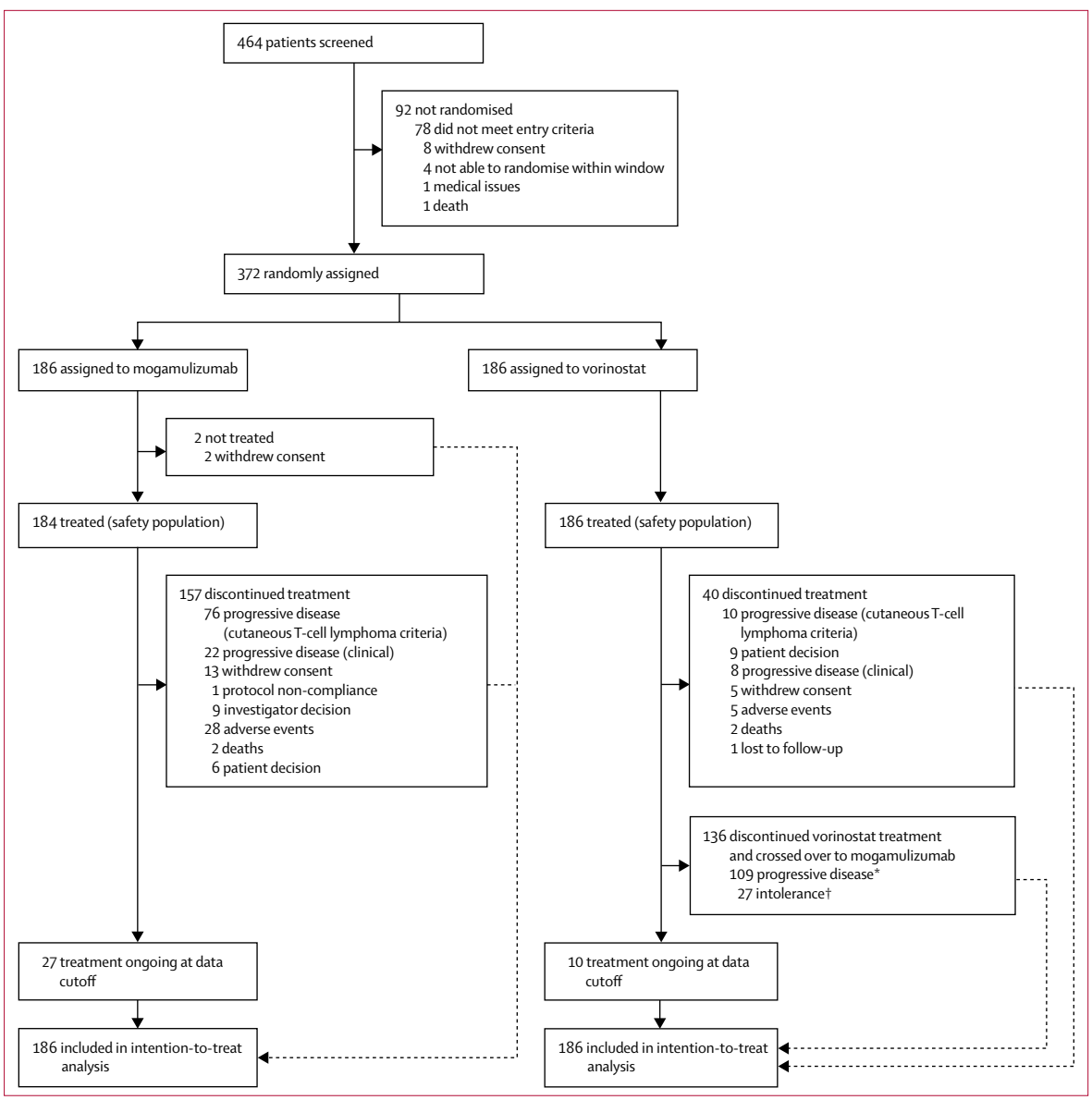

Figure 1: **Trial profile**

*Of the 109 patients who crossed over to mogamulizumab because of disease progression, six had worsening disease or symptoms that did not meet the criteria for progression according to cutaneous T-cell lymphoma response criteria (clinical progression). †Patients crossed over due to the following toxicities: fatigue (five patients); pulmonary embolism (four patients); thrombocytopenia (three patients); diarrhoea (three patients); asthenia (two patients); deep vein thrombosis (one patient); peripheral neuropathy (one patient); myalgia (one patient); blood creatinine increased (one patient); sepsis syndrome (one patient); chronic renal failure (one patient); dysgeusia (one patient); emotional distress (one patient); dermatitis (one patient); and skin rash (one patient).

4 weeks, then every 8 weeks for the first year, and every 16 weeks thereafter.

A pretreatment skin biopsy was done to assess CCR4 expression status, which was measured using a fully automated and standardised immunohistochemistry assay (Ventana Medical Systems; Tucson, AZ, USA).

Treatment-emergent adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. In patients receiving mogamulizumab who developed skin rash of grade 2 or worse, or if the drug rash could not be differentiated from a new area of lymphoma, a skin biopsy was done before the start of topical steroid treatment. In all patients who crossed over from vorinostat to mogamulizumab, the causality of any reported adverse event was assessed for both drugs.

Outcomes

We designed MAVORIC in accordance with the published international consensus guidelines at the time, which recommended progression-free survival as a meaningful primary endpoint for all patients with mycosis fungoides or Sézary syndrome.[20] Thus, the primary endpoint was progression-free survival based on investigator assessment and defined as the time from randomisation until documented disease progression or death due to any cause (for additional details on endpoints and other study methods, see appendix pp 69–106). We used a global composite response score, based on responses (complete and partial) in each compartment (skin, blood, lymph nodes, and viscera), to determine disease progression for the primary endpoint of progression-free survival and for the secondary endpoint of the proportion of patients achieving an overall response (for details regarding disease assessments, see appendix pp 13–18).[20] The proportion of patients who achieved an overall response included only those patients with confirmed global response at two (or more) successive evaluations at least 8 weeks apart. Other secondary endpoints were duration of response (time from first achievement of an overall response to progression or death); the proportion of patients with an overall response in the crossover portion of the trial; assessment of quality of life using the Skindex-29, Functional Assessment of Cancer Therapy-General (FACT-G), 3-level EQ-5D, pruritus evaluation (Likert scale), ItchyQoL outcome measures; immunogenicity, and safety. Exploratory endpoints were overall survival and exposure–response relationship of mogamulizuamab (to be reported separately). Ad-hoc analyses included compartmental response and clinical response depending on CCR4 expression status. Post-hoc analyses included time to response (time from randomisation to first achievement of an overall response) and best overall global response.

	Mogamulizumab (n=186)	Vorinostat (n=186)
Age, years	64 (54–73)	65 (56–72)
Age group, years		
<65	99 (53%)	89 (48%)
≥65	87 (47%)	97 (52%)
Sex		
Male	109 (59%)	107 (58%)
Female	77 (41%)	79 (42%)
Race		
White	125 (67%)	135 (73%)
Other	37 (20%)	26 (14%)
Not reported*	24 (13%)	25 (13%)
ECOG performance status†		
0	106 (57%)	104 (56%)
1	78 (42%)	82 (44%)
2	2 (1%)	0
Time from initial diagnosis, months‡	41·0 (17·4–78·8)	35·4 (16·2–68·2)
Disease type		
Mycosis fungoides	105 (56%)	99 (53%)
Sézary syndrome	81 (44%)	87 (47%)
Current clinical stage		
IB–IIA	36 (19%)	49 (26%)
IIB	32 (17%)	23 (12%)
IIIA–IIIB	22 (12%)	16 (9%)
IVA_1	73 (39%)	82 (44%)
IVA_2	19 (10%)	12 (6%)
IVB§	4 (2%)	4 (2%)
Number of previous systemic regimens received	3 (2–5)	3 (2–5)
Previous cutaneous T-cell lymphoma therapies		
Bexarotene	107 (58%)	110 (59%)
Interferon	81 (44%)	94 (51%)
Conventional chemotherapy¶	108 (58%)	94 (51%)
Romidepsin	45 (24%)	32 (17%)
Alemtuzumab	19 (10%)	16 (9%)
Pralatrexate	14 (8%)	13 (7%)
Brentuximab vedotin	16 (9%)	4 (2%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *Not reported for those countries that do not allow race or ethnicity data to be collected. †For ECOG performance status, baseline is defined as the last measurement obtained before the first dose of study drug; two patients in the mogamulizumab group had an ECOG performance status <2 at screening but equal to 2 at baseline. ‡Time from initial diagnosis (months) was calculated as (date of first dose of study medication − date on initial diagnosis + 1) divided by 30. If the month and year of diagnosis were provided but the day was missing, the missing day was imputed as 15. If only the year was provided, then the missing month and day were imputed as July 1 for the calculation. §Two patients (one in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline. ¶Systemic therapies might have been used as monotherapy or in combination with other agents.

Table 1: **Baseline characteristics**

Statistical analysis

Unless otherwise specified, all efficacy and safety analyses were done on the basis of the first assigned (randomised) treatment. The original protocol was time-driven and powered at 80% to detect a 50% increase in progression-free survival, using a reference median progression-free

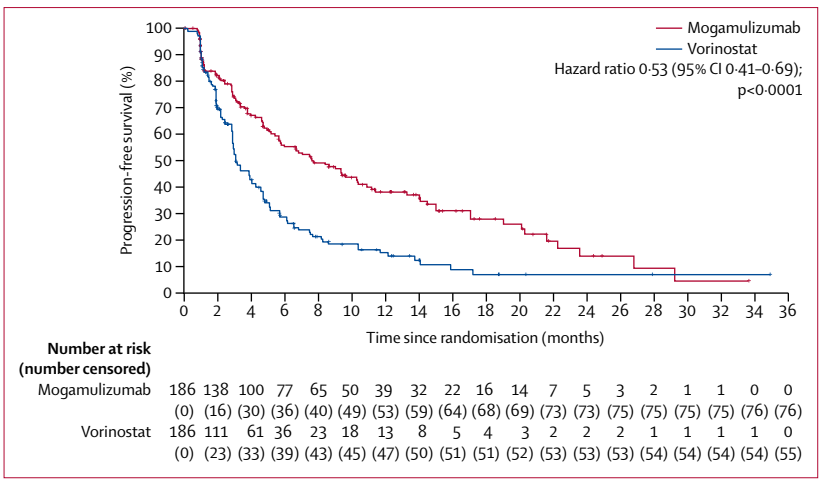

Figure 2: **Progression-free survival by investigator assessment**

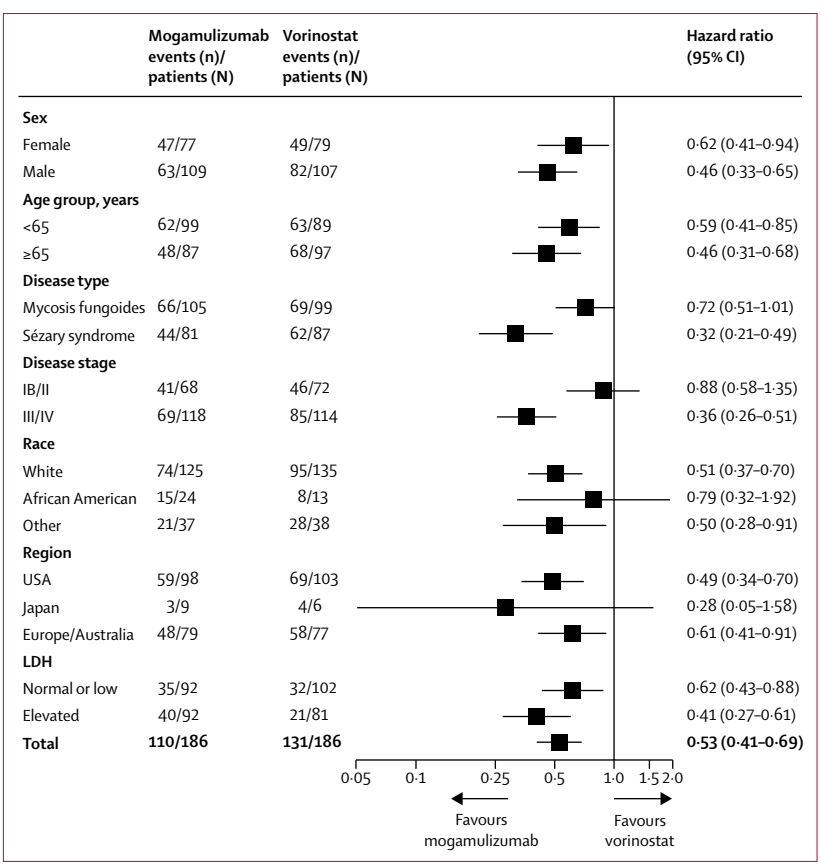

Figure 3: **Hazard ratios for progression-free survival based on investigator assessment in predefined subgroups**
LDH=lactate dehydrogenase.

survival for vorinostat of 169 days,[22] with a calculated sample size of 217 participants. We amended the protocol in February, 2013, to an event-driven study and concurrent increase in power to 90%, resulting in 255 progression-free survival events needed and a required enrolment of 288 patients. Sample size was then further increased by around 10% to account for patients lost to follow-up before documented progression, resulting in a projected enrolment of 317 patients. The primary outcome analysis of progression-free survival between mogamulizumab and vorinostat was done on the intention-to-treat population—defined as all patients randomly assigned to a therapy and assigned a study number—and was based on the results of the onsite investigator's assessment (and confirmed by independent review) using a stratified log-rank test at a one-sided 2·5% significance level. The efficacy evaluable population was patients who had received at least one dose of treatment, had a baseline tumour assessment, and had at least one post-baseline assessment. Safety was assessed in all patients who received at least one dose of study drug. No interim analyses were planned. We used a Cox proportional hazards model with treatment, disease type, disease stage, and region as covariates to assess the magnitude of the treatment difference in progression-free survival; hazard ratios (HRs) and 95% CIs were calculated. We estimated median progression-free survival and duration of response with two-sided 95% CIs for each treatment using Kaplan-Meier survival analysis. Disease type, stage, blood involvement, region, age group, sex, race category, and lactate dehydrogenase were prespecified subgroup analyses for progression-free survival. Randomly assigned patients who withdrew from the study for any reason before documented progression according to the protocol criteria, including those who initiated a new anticancer therapy, were censored at the time of their last efficacy evaluation (of any compartment). We did four preplanned sensitivity analyses for progression-free survival: two modifying censoring rules to incorporate a time component into the definition of progression-free survival event criteria (with death during a specific duration regarded as an event, as follows: within 56 days after last tumour assessment or within 90 days after the last dose of randomised drug, whichever was later, or within 56 days after last tumour assessment); one including progressions that did not meet consensus criteria as progression-free survival events; and one modifying censoring rules when investigator and independent assessments were discordant. For assessments where progression was reported by the investigator but was not confirmed by the independent reviewer, the progression date was set to the last tumour assessment plus 1 day in the mogamulizumab treatment arm and was censored in the vorinostat treatment arm. For response, exact 95% CIs were calculated for the intention-to-treat population, along with the difference in responses between groups. We analysed quality-of-life assessments with mixed-effect model repeated measures using timepoints throughout the assessment period and with mixed model ANCOVA for each timepoint. All statistical analyses were done with SAS version 9.3.

This study is registered with ClinicalTrials.gov, number NCT01728805, and with EUDRACT, number 2012-004766-17.

Role of the funding source

The trial was designed by Kyowa Kirin, in close collaboration with the investigators. A scientific advisory committee, consisting of principal investigators who are considered world experts in cutaneous T-cell lymphoma, was involved in study design and conduct. The investigators and funder collected, analysed, and interpreted the data. All authors attest to the accuracy of the data and analyses reported. The authors participated in writing the report, with assistance of a medical writer and medical editor funded by Kyowa Kirin. All authors had full access to the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 12, 2012, and Jan 29, 2016, we enrolled 372 patients and randomly assigned them to receive mogamulizumab (n=186) or vorinostat (n=186); these patients comprised the intention-to-treat population (figure 1). The total number of patients enrolled and randomly assigned to a treatment group exceeded the planned enrolment (n=317) because large numbers of participants were enrolled after sites were notified of the last day to screen, and an allowance by the sponsor for newly initiated sites to screen subjects until Dec 30, 2015. Two patients randomly assigned to mogamulizumab withdrew consent before receiving study treatment; thus, 370 patients were included in the safety population.

Treatment groups were similar with respect to demographic and physical characteristics, disease characteristics, and previous cutaneous T-cell lymphoma therapies (table 1). At the time of data cutoff, 27 patients assigned to mogamulizumab and ten patients assigned to vorinostat remained on treatment. Additionally, 31 patients originally assigned to vorinostat who crossed over to mogamulizumab remained on treatment. The median duration of follow-up was 17·0 months (IQR 11·6–26·9) overall in the randomised part of the study. The median relative dose intensity for mogamulizumab was 97·5% (90·9–100·0). For vorinostat, although 98 (53%) of 186 patients either missed a dose or had a dose reduction, the median relative dose intensity was 95·1% (IQR 80·3–100·0). Median treatment exposure was 170 days (71–348) for mogamulizumab and 84 days (48–169) for vorinostat (mean treatment exposures: 245 days [SD 234] for mogalizumab and 144 days [172] for vorinostat).

At data cutoff (Dec 31, 2016), 110 (59%) of 186 patients assigned to mogamulizumab had disease progression or died (104 [95%] disease progressions and six [5%] deaths) and 131 (70%) of 186 patients assigned to vorinostat had disease progression or died (128 [98%] disease progressions and three [2%] deaths). In the primary analysis, investigator-assessed median progression-free survival was 7·7 months (95% CI 5·7–10·3) for patients assigned to mogamulizumab versus 3·1 months (2·9–4·1) for patients assigned to vorinostat (HR 0·53, 95% CI 0·41–0·69; stratified log-rank p<0·0001; figure 2). According to independent review, median progression-free survival was 6·7 months (95% CI 5·6–9·4) in the mogamulizumab group and 3·8 months (3·0–4·7) in the vorinostat group (HR 0·64, 95% CI 0·49–0·84; p<0·0007). Analysis of progression-free survival in predefined subgroups is shown in figure 3. In a post-hoc exploratory analysis, median progression-free survival for patients with tumour-type stage IIB disease was 4·2 months (95% CI 2·2–9·4) in patients assigned to mogamulizumab and 3·9 months (1·8–5·7) in patients assigned to vorinostat (HR 0·94, 95% CI 0·46–1·92; p=0·75). Improved progression-free survival times with mogamulizumab versus vorinostat were consistent across all four sensitivity analyses for progression-free survival (data not shown).

The investigator-assessed proportion of patients achieving an overall response was significantly higher for patients assigned to mogamulizumab (52 [28%] of 186 patients, 95% CI 21·6–35·0) than for patients assigned to vorinostat (nine [5%] of 186, 2·2–9·0; risk ratio [RR] 23·1, 95% CI 12·8–33·1; p<0·0001; table 2), and this benefit was confirmed by independent review (43 [23%] of 186 patients assigned to mogamulizumab [95% CI 17·3–29·8] *vs* seven [4%] of 186 assigned to vorinostat [1·5–7·6]; RR 19·4, 95% CI 9·0–29·4; p<0·0001). The proportions of patients with an overall response, duration of response, and response by disease

	Mogamulizumab (n=186)	Vorinostat (n=186)
Proportion of patients with an overall response by global assessment*†	52/186 (28%)	9/186 (5%)
Overall responses in patient subgroups		
Mycosis fungoides	22/105 (21%)	7/99 (7%)
Sézary syndrome	30/81 (37%)	2/87 (2%)
Stage IB or IIA	7/36 (19%)	5/49 (10%)
Stage IIB	5/32 (16%)	1/23 (4%)
Stage III	5/22 (23%)	0/16 (0)
Stage IV	35/96 (36%)	3/98 (3%)
Duration of response, months	14·1 (8·4–19·2)	9·1 (5·6–NE)
Mycosis fungoides	13·1 (4·7–18·0)	9·1 (5·6–NE)
Sézary syndrome	17·3 (9·4–19·9)	6·9 (6·9–6·9)
Compartment response*‡		
Skin	78/186 (42%)	29/186 (16%)
Blood	83/122 (68%)	23/123 (19%)
Lymph nodes	21/124 (17%)	5/122 (4%)
Viscera	0/3 (0%)	0/3 (0%)

Data are n/N (%) or median (IQR). The proportion of patients achieving an overall response is based on the Global Composite Response score. NE=not estimable. *Proportion of patients with an overall response or compartmental response is the percentage of patients with confirmed complete response or confirmed partial response. †p<0·0001. ‡Denominator includes patients with measurable compartmental disease at baseline.

Table 2: **Measures of response by investigator assessment**

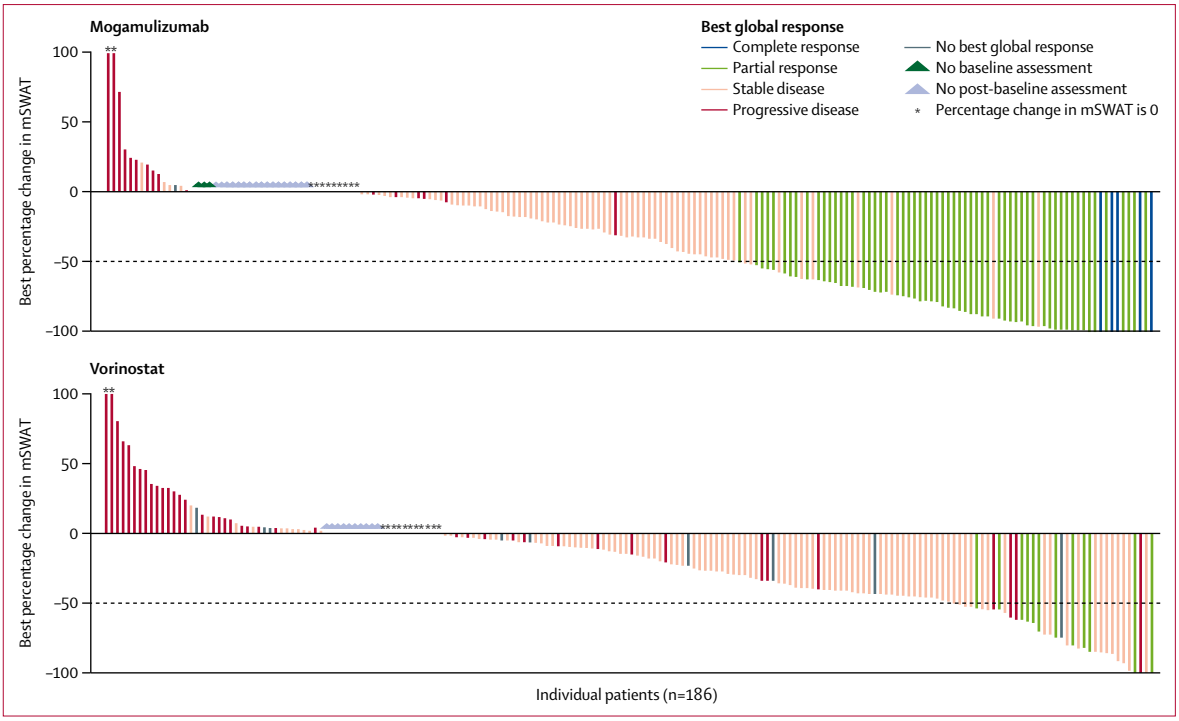

Figure 4: **Best global and skin responses**
Best skin response represented by maximum percentage change in skin mSWAT score. *Two patients in the mogamulizumab group and two in the vorinostat group had a more than 100% increase in mSWAT from baseline. mSWAT=modified Severity Weighted Assessment Tool.

compartment were higher for patients assigned to mogamulizumab than for patients assigned to vorinostat across the predefined subgroup of disease type and post-hoc subgroup involving individual stages (table 2). Five patients in the mogamulizumab group achieved a global complete response, compared with no patients in the vorinostat group (figure 4).

A best overall global response was achieved by 65 (35%) of 186 patients assigned to mogamulizumab, and 81 (44%) patients had at least a 50% improvement in skin response (figure 4). Best overall global responses for patients assigned to vorinostat were reported in 12 (6%) of 186 patients, and 41 (22%) patients had at least a 50% improvement in skin response.

In post-hoc analyses, overall median times to response were 3·3 months (IQR 2·0–6·4) in the mogamulizumab group (52 responders) and 5·1 months (2·9–8·5) in the vorinostat group (nine responders). When we assessed time to response by compartment, patients randomly assigned to mogamulizumab had a median time to response of 1·1 months (1·0–1·2) in blood, 3·0 months (1·9–4·7) in skin, and 3·3 months (2·8–6·8) in lymph nodes. Patients assigned to vorinostat had a median time to response of 1·9 months (1·0–2·1) in blood, 2·7 months (1·1–5·6) in skin, and 2·9 months (1·1–8·5) in lymph nodes. When we assessed duration of response by compartment, the 52 patients on mogamulizumab who responded had a median duration of response in blood of 25·5 months (15·9–not estimable), in skin of 20·6 months (11·2–not estimable), and in lymph nodes of 15·5 months (15·5–15·5). In the nine patients who responded to vorinostat, median duration of response in blood and lymph nodes was not estimable, whereas median duration of response in skin was 10·7 months (4·8–not estimable).

Of the 186 patients randomly assigned to vorinostat, 136 crossed over to mogamulizumab therapy—109 (80%) patients after disease progression and 27 (20%) patients after intolerable toxicity. Three patients approved for crossover did not receive mogamulizumab because of adverse events unrelated to vorinostat. In patients who crossed over from vorinostat to mogamulizumab and subsequently received mogamulizumab, 41 (31%) of 133 patients achieved an overall response. In these patients, post-hoc analysis found that the median progression-free survival from the first dose of mogamulizumab was 8·9 months (95% CI 5·4–14·8). In the 319 patients who were either randomly assigned to mogamulizumab or received mogamulizumab with crossover, post-hoc analysis found that the median progression-free survival time was 8·4 months (6·1–10·3).

The preplanned analyses of Skindex-29, FACT-G, 3-level EQ-5D, and ItchyQoL found mogamulizumab-treated patients had a greater improvement in patient-reported outcomes at the 6-month assessment than did vorinostat-treated patients; these findings were statistically significant (appendix p 20). A comprehensive report of patient-reported outcomes is planned for future publication.

In an exploratory analysis, a total of 280 (97%) of 290 patients with evaluable skin samples had positive CCR4 expression status, predefined as at least 10% infiltrating lymphoid cells. All the samples showed at least 1% positive infiltrating lymphoid cells, with a median percentage CCR4 expression—on a continuous scale—of 80% (range 1–100) for the 290 evaluable patients. There were no apparent differences in the proportions of patients achieving an overall response on the basis of skin CCR4 expression (appendix p 30).

Our exploratory analysis of overall survival showed no evidence of a survival advantage or disadvantage for

	Mogamulizumab (n=184)				Vorinostat (n=186)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Thrombocytopenia*	25 (14%)	0	0	0	63 (34%)	11 (6%)	2 (1%)	0
Gastrointestinal disorders								
Abdominal pain	7 (4%)	0	0	0	21 (11%)	0	0	0
Constipation	20 (11%)	1 (1%)	0	0	32 (17%)	2 (1%)	0	0
Diarrhoea	42 (23%)	1 (1%)	0	0	106 (57%)	9 (5%)	0	0
Nausea	27 (15%)	1 (1%)	0	0	76 (41%)	3 (2%)	0	0
Vomiting	11 (6%)	0	0	0	23 (12%)	1 (1%)	0	0
General disorders and administration-site conditions								
Asthenia	10 (5%)	0	0	0	23 (12%)	4 (2%)	0	0
Fatigue	40 (22%)	3 (2%)	0	0	59 (32%)	11 (6%)	0	0
Peripheral oedema	27 (15%)	0	0	0	26 (14%)	1 (1%)	0	0
Pyrexia	30 (16%)	1 (1%)	0	0	11 (6%)	0	0	0
Infections and infestations								
Cellulitis	2 (1%)	3 (2%)	1 (1%)	0	6 (3%)	4 (2%)	0	0
Pneumonia†	2 (1%)	6 (3%)	1 (1%)	1 (1%)	0	1 (1%)	0	2 (1%)
Sepsis	1 (1%)	2 (1%)	0	1 (1%)	1 (1%)	0	4 (2%)	1 (1%)
Upper respiratory tract infection	19 (10%)	0	0	0	7 (4%)	2 (1%)	0	0
Injury, poisoning, and procedural complications								
Infusion-related reaction	58 (32%)	3 (2%)	0	0	1 (1%)‡	0	0	0
Investigations								
Aspartate aminotransferase increased	6 (3%)	2 (1%)	0	0	11 (6%)	1 (1%)	0	0
Blood creatinine increased	6 (3%)	0	0	0	52 (28%)	0	0	0
Weight decreased	10 (5%)	1 (1%)	0	0	31 (17%)	2 (1%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	12 (7%)	2 (1%)	0	0	44 (24%)	2 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Muscle spasms	9 (5%)	0	0	0	27 (15%)	2 (1%)	0	0
Nervous system disorders								
Dizziness	12 (7%)	0	0	0	19 (10%)	0	0	0
Dysgeusia	6 (3%)	0	0	0	53 (28%)	1 (1%)	0	0
Headache	23 (13%)	0	0	0	28 (15%)	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Pulmonary embolism	0	0	0	0	0	4 (2%)	1 (1%)	2 (1%)
Skin and subcutaneous tissue disorders								
Alopecia	13 (7%)	0	0	0	36 (19%)	0	0	0
Drug eruption§	36 (20%)	8 (4%)	0	0	1 (1%)	0	0	0
Vascular disorders								
Hypertension	9 (5%)	8 (4%)	0	0	13 (7%)	12 (6%)	0	0

Data are n (%). Events that occurred in either treatment group as grade 1–2 in at least 10% of patients or grade 3–5 in ≥2% of patients. For a full table of adverse events see the appendix (pp 21–26). *Adverse events reported as thrombocytopenia and decreased platelet count are combined into this row. †Adverse events reported as pneumonia, influensal pneumonia, legionella pneumonia, pneumococcal pneumonia, atypical pneumonia, and bronchopneumonia are combined into this row. ‡One patient had an infusion reaction on day 1 of crossover to mogamulizumab treatment (17 days after the last dose of vorinostat) that was indicated as possibly related to vorinostat (and mogamulizumab). §Skin rashes that were assessed by the investigator or sponsor as possibly, probably, or definitely related to study drug.

Table 3: **Treatment-emergent adverse events in the safety population**

mogamulizumab compared with vorinostat. In the mogamulizumab group, median overall survival was not reached compared with 43·9 months (95% CI 43·6–not reached) in the vorinostat group (HR 0·93, 95% CI 0·61–1·43; p=0·9439; appendix p 20).

The most common treatment-emergent adverse events of any cause or grade in the 184 patients in the safety population in the mogamulizumab group were infusion-related reactions, drug rash, diarrhoea, and fatigue (table 3). The most common treatment-emergent adverse events in the 186 patients originally assigned to vorinostat were diarrhoea, nausea, fatigue, and thrombocytopenia. In the 136 patients randomly assigned to vorinostat who crossed over to receive mogamulizumab, the incidence of treatment-emergent adverse events was similar to that observed for patients originally randomly assigned to mogamulizumab (infusion-related reactions in 50 [37%], drug rash in 34 [25%], diarrhoea in 19 [14%], and fatigue in 12 [9%] of 136 crossover patients; appendix pp 21–26).

Grade 3–4 adverse events of any cause were reported in 75 (41%) of 184 patients in the mogamulizumab group and 76 (41%) of 186 patients in the vorinostat group. Serious adverse events of any cause were reported in 69 (38%) of 184 patients in the mogamulizumab group and 46 (25%) of 186 patients in the vorinostat group (appendix pp 27–29). In the mogamulizumab group, the most frequently reported serious adverse events of any cause were pyrexia in eight (4%) and cellulitis in five (3%) of 184 patients. In the vorinostat group, the most frequently reported serious adverse events were cellulitis in six (3%), pulmonary embolism in six (3%), and sepsis in five (3%) of 186 patients. Serious adverse events considered treatment-related were reported for 36 (20%) of 184 patients in the mogamulizumab group and 30 (16%) of 186 patients in the vorinostat group. The most common treatment-related serious adverse events were pneumonia in four (2%) patients and pyrexia in four (2%) patients for mogamulizumab, and pulmonary embolism in five (3%) patients and thrombocytopenia in three (2%) patients for vorinostat.

During the randomised period, deaths attributable to adverse events occurred in 12 (3%) of 372 patients. Three (2%) of 184 patients who received mogamulizumab died from an adverse event, two (1%) of which were related to treatment (sepsis and polymyositis), and one (1%) patient having unrelated disease progression. Nine (5%) of 186 patients who received vorinostat died due to an adverse event, of which three (2%) deaths were related to treatment (two cases of pulmonary embolism and one of bronchopneumonia) and six (3%) were considered unrelated to treatment (one each of disease progression; intestinal obstruction, sepsis, or septic shock; endocarditis; pneumonia; depressed level of consciousness; and skin disorder).

In total, 35 (19%) of 184 patients who received mogamulizumab and 43 (23%) of 186 patients who received vorinostat discontinued treatment due to adverse events. The most frequent adverse events leading to discontinuation were drug rash in 13 (7%) patients in the mogamulizumab group and fatigue in eight (4%) patients in the vorinostat group.

Discussion

In the international, randomised, controlled phase 3 MAVORIC trial in previously treated patients with relapsed or refractory mycosis fungoides or Sézary syndrome, the anti-CCR4 antibody mogamulizumab showed statistically significantly superior progression-free survival compared with vorinostat. In addition to meeting the primary endpoint of the trial, mogamulizumab was also superior to vorinostat in terms of the proportion of patients who achieved an overall response, and resulted in improved duration of response and better response by disease compartment. Despite heterogeneity of treatment practices in mycosis fungoides and Sézary syndrome, patients in MAVORIC were balanced in the number and types of previous therapies and, in general, a benefit for mogamulizumab in terms of the proportion of patients achieving an overall response was seen across disease stages. Mogamulizumab showed improved progression-free survival and proportion of patients with an overall response in the subset of patients with Sézary syndrome, who have very poor overall survival.[4] The adverse event profile of mogamulizumab revealed no new safety concerns in the MAVORIC cutaneous T-cell lymphoma population, with drug rash being the most frequent adverse event leading to discontinuation, similar to that seen in the phase 1/2 trial.[17] Patient-reported outcomes support improvements in disease-related symptoms and functioning in those treated with mogamulizumab.

Clinical response to mogamulizumab was not associated with skin CCR4 expression, which we evaluated as an exploratory endpoint. Absence of correlation between concentrations of drug targets and objective clinical response has been observed with other targeted therapies, such as brentuximab vedotin.[23–25] Future translational studies of mechanisms or biomarkers linked with global and compartmental responses to mogamulizumab are planned.

Previous trials of new systemic therapies in cutaneous T-cell lymphoma have been quite small (<150 patients), mostly single-arm or with no active comparator, and with the proportion of patients achieving an overall response as the primary endpoint.[10,18,19,24–30] Efficacy analyses that are focused on such a primary endpoint do not capture key elements of clinical benefit such as duration of response or progression-free survival, and thus cannot fully assess the overall clinical impact of new therapies in this study population with a chronic disease course, although efforts have been made to address this shortcoming.[10] MAVORIC used progression-free survival as the primary endpoint in accordance with international guidelines that recommend this measure as a meaningful primary

endpoint in the context of the proportion of patients with an overall response and duration of response.[20]

Given some of the unique features of our trial—including the large randomised design to compare systemic therapies, the use of progression-free survival as the primary endpoint, and the use of rigorous consensus global response criteria with more frequent compartmental assessment—direct comparisons to previous trials are difficult. Furthermore, study subpopulations often differ between cutaneous T-cell lymphoma trials. For example, the randomised phase 3 ALCANZA study[10] of brentuximab vedotin in CD30-positive cutaneous T-cell lymphoma included patients with primary cutaneous anaplastic large-cell lymphoma. Additionally, ALCANZA excluded patients with Sézary syndrome, whereas 45% of patients in our study had Sézary syndrome. Despite our high proportion of previously treated patients with Sézary syndrome, the overall median progression-free survival of the whole study population was significantly improved with mogamulizumab compared with vorinostat. The proportion of patients who achieved an overall response with mogamulizumab was 28%, whereas proportions reported in smaller, mostly non-randomised studies of systemic drugs in cutaneous T-cell lymphoma with varying subpopulations have ranged from 24 (17%) of 139 patients to 21 (70%) of 30 patients.[24–27,29,30]

We chose vorinostat as our comparator drug because it is an FDA-approved standard of care option for cutaneous T-cell lymphoma treatment, with proven activity across disease compartments[22] and was not used for first-line systemic treatment of mycosis fungoides or Sézary syndrome, unlike other standards of care such as bexarotene. This choice facilitated accrual in a large study of relapsed or refractory patients with an uncommon disease. However, the proportion of patients who achieved an overall response with vorinostat (5%, 95% CI 2·2–9·0) in our study was notably lower than that reported in previous single-arm studies (29·7%, 19·7–41·5,[18] to 30·8%, 9·1–61·4[19]). Our data showed that patients in the vorinostat group had appropriate drug exposure (>95% dose intensity) and a sufficient mean duration of treatment exposure (144 days), compared with that reported in the FDA drug approval package for vorinostat (110 days),[22] suggesting that inadequate exposure to vorinostat was not the reason for the low response in this group in MAVORIC. The pivotal phase 2 vorinostat trial by Olsen and colleagues[18] enrolled a similar proportion of people with advanced-stage disease (IIB and higher) and Sézary syndrome, and patients had received a similar number of previous treatments to those in MAVORIC; therefore, differences in the study populations are unlikely to account for the response findings. Differences in response might be partly explained by the randomised design against a comparator, the large study size, and different disease assessments. We used global composite response criteria in our study, whereas in the study by Olsen and colleagues,[18] the reported proportion of patients achieving an overall response (29·7%) was based only on skin response (mSWAT score)—a result more comparable to the skin compartment response of 16% observed with vorinostat in our study.[18] Furthermore, the 28% of patients treated with mogamulizumab who achieved an overall response in our study was also lower than in a previous phase 1/2 study (36·8%),[17] highlighting the ability of a large, randomised design to rigorously define efficacy and safety in this rare disease.

As is the case for other indolent lymphomas, intervention trials aimed at showing the effect of new therapies on overall survival are particularly challenging in cutaneous T-cell lymphoma and are further complicated by the rarity of these malignancies. Thus, MAVORIC was not powered to detect overall survival differences between the two groups within the defined follow-up period. Moreover, the analysis of overall survival is confounded by the one-way crossover design, which was offered to allow patients in the comparator group to receive a potentially promising new therapy. Given these limitations, differences in overall survival could not be adequately evaluated in the MAVORIC study, and at the time of analysis, overall survival outcomes were similar between the two groups. The challenge of overall survival as an endpoint is further shown by the median overall survival for mogamulizumab, which had not yet been reached after 4 years of study enrolment.

The safety of mogamulizumab in MAVORIC aligns with that reported in previous studies. The most common adverse events were infusion-related reactions and drug eruption. Infusion-related reactions with mogamulizumab were mostly limited to early infusions (occurring during the first one or two infusions), mainly grade 1, and managed with standard protocols familiar to practitioners. Drug eruption was also mild in most cases. Although 7% of patients treated with mogamulizumab discontinued treatment because of drug rash, our protocol did not allow treatment with systemic steroids, which can be used in clinical practice to manage this adverse event. Further analyses of mogamulizumab-associated drug rash, including detailed histopathology, mechanism, and effect on outcomes and safety, are ongoing.

Limitations of our trial, including the relatively small size of some patient subsets, clinical heterogeneity according to stage and compartments affected (patch or plaque, tumour, Sézary syndrome, and nodal or visceral disease), and the exclusion of transformed patients with mycosis fungoides, compromised our ability to draw definitive conclusions on the efficacy and safety of mogamulizumab in selected patient subsets. Study stratification for all clinical stages was not feasible in such a rare disease. Therefore, we included stage IIB within the low-stage disease category. Although stage groupings might not reflect the spectrum of clinical heterogeneity in cutaneous T-cell lymphoma, the allocation of patients to treatment across stages was generally balanced but with

slightly more patients with stage IIB disease in the mogamulizumab group than in the vorinostat group.

Despite these limitations, and the fact that the treatment landscape inevitably changed during enrolment of MAVORIC, this large prospective dataset provides an opportunity to rigorously describe outcomes of a therapeutic intervention with both a new drug and an FDA-approved therapy available at the time of study inception. We anticipate that in the future, additional treatment options will become available for cutaneous T-cell lymphoma, and studies that compare mogamulizumab with newer therapies, either as monotherapy or in combination, will be warranted.

In summary, our randomised, controlled phase 3 trial showed that mogamulizumab, a novel CCR4-directed monoclonal antibody, was significantly superior to vorinostat, an FDA-approved drug, for progression-free survival, the proportion of patients achieving an overall response, and quality of life in previously treated patients with mycosis fungoides or Sézary syndrome types of cutaneous T-cell lymphoma. The safety profile was manageable and consistent with previous reports. Our study supports mogamulizumab as a valuable new therapeutic option in patients with mycosis fungoides and Sézary syndrome types of cutaneous T-cell lymphoma.

Contributors

All authors had full access to the data, participated fully in drafting and revising the manuscript, approved the final manuscript, and agreed to submit it to *The Lancet Oncology*. All authors contributed to the acquisition and interpretation of the data. YHK, MD, LP-B, and AHR contributed to the conception and design of this study.

Declaration of interests

YHK reports personal fees and grants from Kyowa Kirin during the conduct of the study; and grants from Merck, Soligenix, Forty Seven, Neumedicines, Portola Pharma, and Horizon; personal fees from Actelion, Takeda, and Medivir; and grants and personal fees from Eisai, Millennium/Takeda, Seattle Genetics, miRagen, and Innate outside the submitted work. MB reports personal fees from Kyowa Kirin during the conduct of the study; and personal fees from Innate Pharma and Takeda outside the submitted work. PP reports honoraria from Innate Pharma and Spectrum; research funding from miRagen and Kura Pharmaceuticals; and honoraria and research funding from Viracta outside the submitted work. SMH reports grants from Spectrum Pharmaceuticals, ADC Therapeutics, and Aileron Therapeutics; grants and personal fees from Celgene, Millennium Pharmaceuticals/Takeda Oncology, Kyowa Kirin, Seattle Genetics, Infinity Pharmaceuticals, and Forty Seven; and personal fees from Mundipharma outside the submitted work. SW reports biopsy reporting for Kyowa Kirin during the conduct of the study. LS reports personal fees from Celgene, Spectrum Pharmaceuticals, and Seattle Genetics outside the submitted work. EJK reports clinical trial grant funding from Kyowa Kirin during the conduct of the study. PLO-R reports personal fees from Kyowa Kirin, Takeda, and Actelion; and providing drug for the Meda PimToMF clinical trial outside the submitted work. HE reports research support from Kyowa Kirin during the conduct of the study; and consulting fees from and serving on a speaker bureau for Genentech/Roche, AbbVie, and Janssen outside the submitted work. AH reports grants from Bristol-Myers Squibb, Kyowa Kirin, Seattle Genetics, Roche-Genentech, miRagen, Immune Design, Takeda, Amgen, Pharmacyclics, and AbbVie during the conduct of the study. BPo reports being a Site Investigator for Kyowa Kirin during the conduct of the study; and personal fees from Actelion, Mallinckrodt, and Seattle Genetics outside the submitted work. AK reports grants and personal fees from Celgene; and personal fees from Janssen and Amgen outside the submitted work. AJM reports consulting for Bristol-Myers Squibb, Cell Medica, Erytech, Kyowa Kirin, and Seattle Genetics outside the submitted work. AM reports being an investigator for Kyowa Kirin during the conduct of the study. AS reports consulting for Kyowa Kirin during the conduct of the study; and grants from Spectrum outside the submitted work. BPr reports personal fees from Kyowa Kirin outside the submitted work. LJG reports serving on an Advisory Board for Kyowa Kirin during the conduct of the study. KD, JM, ML, JSH, and DOG report employment with Kyowa Kirin during the conduct of the study. KT reports grants and personal fees from Kyowa Kirin during the conduct of the study; and grants and personal fees from Eisai, Takeda, Mundipharma International, Janssen, Celgene, Chugai Pharma, and Ono Pharmaceutical; grants from GlaxoSmithKline, SERVIER, and AbbVie; and personal fees from HUYA Bioscience International and Zenyaku Kogyo outside the submitted work. MD reports serving on a safety committee for and grant funding for study conduct from Kyowa Kirin during the conduct of the study. All other authors declare no competing interests.

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References

1 Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. *JAMA Dermatol* 2013; **149:** 1295–99.

2 Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110:** 1713–22.

3 Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation survey. *Cancer* 2006; **107:** 2504–11.

4 Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010; **28:** 4730–39.

5 Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol* 2003; **139:** 857–66.

6 Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium study of outcome in advanced stages of mycosis fungoides and Sézary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. *J Clin Oncol* 2015; **33:** 3766–73.

7 Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. *Clin Cancer Res* 2012; **18:** 5051–60.

8 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®): T-cell lymphomas. Version 3. Fort Washington, PA: National Comprehensive Cancer Network, 2018.

9 Trautinger F, Eder J, Assaf C, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome—update 2017. *Eur J Cancer* 2017; **77:** 57–74.

10 Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017; **390:** 555–66.

11 Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res* 2010; **16:** 1520–31.

12 Ferenczi K, Fuhlbrigge RC, Pinkus J, Pinkus GS, Kupper TS. Increased CCR4 expression in cutaneous T cell lymphoma. *J Invest Dermatol* 2002; **119:** 1405–10.

13 Yoshie O, Fujisawa R, Nakayama T, et al. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood* 2002; **99:** 1505–11.

14 Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. *Clin Cancer Res* 2003; **9** (10 Pt 1)**:** 3625–34.

15 Ishida T, Inagaki H, Utsunomiya A, et al. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. *Clin Cancer Res* 2004; **10:** 5494–500.

16 Ishida T, Jo T, Takemoto S, et al. 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:** 672–82.

17 Duvic M, Pinter-Brown LC, Foss FM, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. *Blood* 2015; **125:** 1883–89.

18 Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2007; **25:** 3109–15.

19 Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* 2007; **109:** 31–39.

20 Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011; **29:** 2598–607.

21 Stevens SR, Ke MS, Parry EJ, Mark J, Cooper KD. Quantifying skin disease burden in mycosis fungoides-type cutaneous T-cell lymphomas: the severity-weighted assessment tool (SWAT). *Arch Dermatol* 2002; **138:** 42–48.

22 Center for Drug Evaluation and Research. Zolinza (vorinostat) capsules. Medical review part I. Application number: 21-991. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021991s000_Zolinza_MedR_P1.pdf. (accessed Feb 26, 2018).

23 Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood* 2014; **123:** 3095–100.

24 Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J Clin Oncol* 2015; **33:** 3750–58.

25 Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30$^+$ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J Clin Oncol* 2015; **33:** 3759–65.

26 Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001; **19:** 2456–71.

27 Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28:** 4485–91.

28 Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. *Blood* 2012; **119:** 4115–22.

29 Olsen E, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19:** 376–88.

30 Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28:** 1870–77.