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

Anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, randomized, phase 3 trial

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ABSTRACT **[word limit 300; current 300]**

Background: Cutaneous T-cell lymphomas (CTCLs) are rare non-Hodgkin lymphomas with significant morbidity/mortality in advanced stages. We compared the efficacy of mogamulizumab, a novel monoclonal antibody directed against C-C chemokine receptor 4 (CCR4), versus vorinostat in patients with previously-treated CTCL.

Methods: In this open-label, international, phase 3 study (ClinicalTrials.gov: NCT01728805), adults with mycosis fungoides (MF) or Sézary syndrome (SS) who failed ≥1 systemic therapy were randomized 1:1 using an Interactive Voice/Web Response System to mogamulizumab (1·0 mg/kg weekly for the first 28-day cycle, Days 1 and 15 of subsequent cycles) or vorinostat (400 mg daily). Stratification was by disease type and stage. Primary endpoint was progression-free survival (PFS) by Investigator assessment in the intention-to-treat (ITT) population. Safety analyses were done in patients who received ≥1 dose of study drug. The study is ongoing; enrollment is complete.

Findings: Between December 12, 2012, and January 29, 2016, 372 patients were randomized (186 per arm), comprising the ITT population. Mogamulizumab resulted in superior PFS compared to vorinostat, median 7·7 vs 3·1 months (hazard ratio, 0·53; 95% CI, 0·41, 0·69; P<0·0001). Grade 3-4 adverse events were reported in 75 (41%) of 184 patients in the mogamulizumab group and 76 (41%) of 186 patients in the vorinostat group. Most common serious adverse events were pyrexia in eight (4·3%) and cellulitis in five (2·7%) of mogamulizumab patients; cellulitis in six (3·2%), pulmonary embolism in six (3·2%), and sepsis in five (2·7%) of vorinostat patients. Two of three on-treatment deaths with mogamulizumab (sepsis/polymyositis) and three of nine with vorinostat (pulmonary embolism [2]/bronchopneumonia) were considered treatment-related.

Interpretation: Mogamulizumab provided significantly better overall disease control, by objective and patient-reported endpoints, than vorinostat. Mogamulizumab is a new, effective treatment for patients with MF and, importantly, for SS, which has so far presented the greatest therapeutic challenge in CTCL.

Funding: Kyowa Kirin.

RESEARCH IN CONTEXT

Evidence before this study

Mycosis fungoides (MF) and Sézary syndrome (SS) jointly represent the most common subtype of cutaneous T-cell lymphomas (CTCLs), a heterogeneous group of rare extranodal T-cell lymphomas with a chronic clinical course. Persistent severe cutaneous symptoms and recurrent infections negatively impact quality of life in the vast majority of patients with MF or SS. Advanced-stage MF and SS are aggressive neoplasms with compromised survival (median of 5 years). Few systemic agents have demonstrated a convincing clinical benefit, using comprehensive, global response criteria in prospective, randomized studies.

Mogamulizumab is an investigational, first-in-class defucosylated humanized IgG1 kappa monoclonal antibody that selectively binds to C-C chemokine receptor 4 (CCR4), which is consistently expressed on malignant cells in mature T-cell lymphomas, including CTCL. Mogamulizumab is approved in Japan for CCR4-positive adult T-cell leukemia-lymphoma (ATL) and relapsed or refractory peripheral T-cell lymphoma (PTCL) and CTCL.

We searched PubMed, Embase, and Cochrane for phase 2 or phase 3 clinical trials in CTCL patients over the past 20 years (January 1, 1998, to January 17, 2018) with the following search string: ("cutaneous T-cell lymphoma" OR "CTCL" OR "mycosis fungoides" OR "Sézary syndrome"). In the previous two decades, most prospective phase 2 or 3 clinical trials of systemic agents were either non-randomized (67 studies total) or randomized to compare one or more doses of an agent, with or without a placebo/observational arm (five studies total). Two non-randomized mogamulizumab trials were identified in the search, one phase 1/2 trial and one phase 2 trial. Prior to this study, there have not been any randomized phase 3 trials with mogamulizumab in CTCL. One trial published in 2017 (N=131)

was a phase 3, randomized study comparing systemic agents (brentuximab vedotin versus physician's choice of methotrexate or bexarotene) in previously treated patients with CD30-positive MF or primary cutaneous anaplastic large-cell lymphoma (pcALCL), the ALCANZA study – with exclusion of patients with SS – and utilizing objective global response lasting at least 4 months as the primary endpoint. In general, throughout the literature analysis, overall response rates (ORRs) were determined via a range of methods, with older trials using less comprehensive assessments.

*Added value of this stud**y***

Prior studies of systemic agents in CTCL that include SS as a major subtype have mostly used ORR as the primary efficacy endpoint and have been single-arm trials. As measures of efficacy, both ORR and progression-free survival (PFS) are clinically relevant endpoints in CTCL. However, in contrast to ORR, PFS also captures the duration of disease control (absence of disease progression) with treatment, and therefore may more broadly reflect overall meaningful clinical benefit in patients with CTCL who often have a chronic course. The phase 3 MAVORIC study (N=372) is the largest randomized study of systemic therapy in CTCL and, to our knowledge, the first to compare systemic therapies using PFS as primary endpoint. Consensus global composite response criteria, based on response in each disease compartment (skin, blood, lymph nodes, and viscera), were used to determine disease progression and ORR. Vorinostat was chosen as comparator as it was an FDA-approved agent for CTCL with demonstrated activity across disease compartments, and was not readily used in first-line treatment of MF/SS, unlike other standards of care such as bexarotene. This facilitated the efficient accrual of a large study of relapsed/refractory patients with an uncommon disease. Mogamulizumab was superior to vorinostat not only for PFS (7·7 vs 3·1 months, respectively; P<0·0001), the study's primary efficacy endpoint, but also for ORR (28·0% vs 4·8%; P<0·0001). These efficacy benefits were confirmed by independent review. Analysis of PFS for predefined subgroups shows that mogamulizumab was superior

to vorinostat with longer time to disease progression across disease types (MF and SS) and disease stages (IB-IV). In particular, mogamulizumab showed highly superior responses in the blood and skin compartments. Patient-reported outcomes (PROs) showed significantly greater improvements in symptoms and functional status with mogamulizumab than vorinostat. The safety profile of mogamulizumab was consistent with previous reports, and common adverse events were manageable.

Implications of all the available evidence

The MAVORIC study shows that, in patients with previously treated MF or SS, mogamulizumab, an investigational, first-in-class anti-CCR4 monoclonal antibody, resulted in superior PFS, ORR, and PROs compared to vorinostat, a Food and Drug Administration (FDA)-approved drug for this patient population. Mogamulizumab is a valuable new therapeutic option for patients with CTCL.

BACKGROUND

Cutaneous T-cell lymphomas (CTCLs) are a rare and heterogeneous group of extranodal lymphomas of T-cells characterized by skin involvement, with an overall incidence in the United States (US) of 7·5 cases per million.[1] The most common type of CTCL is mycosis fungoides (MF), an overall indolent T-cell neoplasm characterized by variable type and extent of skin disease (patches, plaques, tumor-type, and erythroderma), with a subset of patients either presenting with or developing extracutaneous disease. Sézary syndrome (SS) is a much rarer but more aggressive type of CTCL, characterized by erythroderma, lymphadenopathy, and blood involvement with neoplastic T-cells. Together, MF and SS represent approximately two thirds of all CTCL.[2] With substantial clinical and biological overlap, both MF and SS can cause lifelong morbidity, decreased quality of life (QoL) due to chronic skin impairment with intractable itching, recurrent infections and/or disfiguring skin lesions with frequent weeping and ulcerations, sleep disturbance, and psychosocial problems.[3] The burden of disease in the skin and the presence of extracutaneous disease are primary determinants of survival.[4–7] Patients with advanced-stage MF and SS (stages IIB-IVB) have a median overall survival (OS) of approximately 5 years.[6]

Patients with early-stage MF (IA-IIA) are treated primarily with skin-directed therapies, while those with treatment-resistant early-stage MF or advanced-stage MF and SS generally require systemic agents, including retinoids, methotrexate, interferons, histone deacetylase (HDAC) inhibitors (eg, vorinostat and romidepsin), brentuximab vedotin, or cytotoxic chemotherapeutic agents.[8,9] Many of these agents were approved based on small, single-arm or non-randomized trials with inconsistent response assessment criteria. The largest phase 3 trial comparing systemic therapies reported to date included 131 patients.[10] With the exception of allogeneic hematopoietic stem cell transplantation (HSCT), there are no curative options for CTCL. Patients with CTCL frequently progress through or become resistant to existing

treatments, resulting in a need for new therapies that target all disease compartments (skin, blood, lymph nodes, and viscera) and provide a durable response.

Mogamulizumab (KW-0761; Kyowa Kirin) is a first-in-class defucosylated humanized IgG1 kappa monoclonal antibody that selectively binds to C-C chemokine receptor 4 (CCR4) and has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity because of reduced fucose content.[11] CCR4, which is involved in cell trafficking of lymphocytes to skin, is consistently expressed on the surface of tumor cells in T-cell malignancies, such as CTCL (including MF/SS), adult T-cell leukemia-lymphoma (ATL), and peripheral T-cell lymphoma (PTCL).[12–15]

Mogamulizumab has been approved in Japan for relapsed or refractory CCR4-positive ATL, PTCL, and CTCL.[16] In a US-based phase 1/2 study in CTCL, mogamulizumab demonstrated an acceptable safety profile and promising efficacy, with a 37% overall response rate (ORR) and a 95% response rate in blood.[17] These encouraging results led to the development of the phase 3 MAVORIC study, which compares mogamulizumab to vorinostat, a Food and Drug Administration (FDA)-approved agent with established clinical activity,[18,19] in previously treated patients with MF or SS. As measures of efficacy, both ORR and progression-free survival (PFS) are clinically relevant endpoints in CTCL. However, in contrast to ORR, PFS is informative about the duration of disease control (absence of disease progression) with treatment, and therefore may more broadly reflect overall meaningful clinical benefit in patients with CTCL who often have a chronic course. To our knowledge, MAVORIC is the largest randomized study to compare systemic therapies and the first pivotal trial to use PFS as a primary endpoint in CTCL.

METHODS

Study design and patients

MAVORIC is an open-label, international, randomized phase 3 study of mogamulizumab vs vorinostat. Patients with stage IB to IVB (appendix p 9-11),[20] histologically confirmed MF or SS, who had failed at least one prior systemic therapy, were enrolled at sites in the US, Europe, Japan, and Australia.

Eligible patients were ≥18 years of age (in Japan, ≥20 years of age); had an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤1; and had adequate hematological, hepatic, and renal function. Patients previously treated with anti-CD4 antibody or alemtuzumab were eligible provided their CD4+ cell counts were ≥200/mm^3. Exclusion criteria included evidence of large cell transformation at study entry and prior vorinostat (patients exposed for a short time without evidence of progression or toxicity while on treatment were allowed with Sponsor approval). CCR4 expression was not a requirement for participation (full eligibility criteria are provided in the appendix p 61-64). Compartmental disease was evaluated by the modified Severity Weighted Assessment Tool (mSWAT) in the skin, computed tomography scans, and flow cytometry data (appendix p 12-17).[20]

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

Randomization and masking

Patients were randomized 1:1 to mogamulizumab or vorinostat and stratified by CTCL subtype (MF or SS) and disease stage (IB/II or III/IV). Screening numbers were assigned using an interactive voice/web

response system (IVRS). When the patient was determined to be eligible for randomization, the Investigator/designee contacted IVRS to obtain the randomization assignment for the patient.

To assess for any potential bias during the randomized treatment period in this open-label study, a blinded independent review was conducted to assess response and date of progression. This consisted of independent radiologic evaluation (two-reader paradigm) and comprehensive review of all mSWAT and flow cytometry data by an independent hematologist with experience in treating patients with CTCL. A separate Independent Data Monitoring Committee monitored patient safety.

Procedures

Patients were to receive either mogamulizumab 1·0 mg/kg or vorinostat at the standard dose of 400 mg. Treatment was administered on an outpatient basis. Each treatment cycle was 28 days. Patients received mogamulizumab intravenously over at least 1 hour on Days 1, 8, 15, and 22 of the first cycle and on Days 1 and 15 of subsequent cycles.[17] 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 dose modifications, targeting the maximal tolerated effective dose.

Patients could continue treatment until progressive disease, drug intolerance, unacceptable toxicity, or until any of the other criteria for treatment discontinuation were met. If the patient experienced a global complete response (ie, complete response [CR] in the skin and CR or no involvement in the other three disease compartments),[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 demonstrated confirmed disease progression or experienced intolerable toxicity (grade ≥3 adverse events [AEs],

excluding inadequately treated nausea, vomiting, and diarrhea; 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 approval from the Sponsor in order to ensure that patients on vorinostat were not discontinued prematurely and the protocol criteria for crossover were met. Patients were assessed for potential AEs from the time of informed consent until 90 days after the last dose or initiation of alternative therapy.

Clinical response to treatment for skin and blood was assessed every 4 weeks. Skin disease was evaluated by investigators specifically trained in using the mSWAT.[2,21] The response in blood was assessed by flow cytometry (for a representative example, see appendix p 20) conducted at a central laboratory (Q2 Solutions, a Quintiles Quest Joint Venture, Morrisville, NC). Lymph nodes and visceral disease were determined based upon size criteria and evaluated by computed tomography (CT) scans at 4 weeks, then every 8 weeks in Year 1 and every 16 weeks thereafter. ORR included only those patients with confirmed global response at two (or more) successive evaluations at least 8 weeks apart.

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

Outcomes

The primary endpoint was PFS based on assessment by the Investigator and defined as the time from randomization until documented disease progression or death due to any cause (for additional details on primary and secondary endpoints and other study methodology, see the full protocol, starting on appendix p 23). The MAVORIC study was designed in accordance with the published international consensus guidelines at the time, which recommended the use of PFS as a meaningful primary endpoint for all patients with MF/SS.[20] Secondary endpoints included ORR and patient-reported outcome (PRO) assessments of QoL using the Skindex-29 and Functional Assessment of Cancer Therapy-General (FACT-G). A global composite response score, based on response in each compartment (skin, blood, lymph nodes, and viscera), was used to determine disease progression for the primary endpoint of PFS and for the secondary endpoint of ORR (details regarding disease assessments are provided in the appendix p 12-17).[20] Other secondary endpoints included duration of response (DOR), time to response, best overall global response, ORR in the crossover portion of the trial, and safety. Exploratory endpoints included clinical response based on CCR4 expression status. The level of CCR4 expression was determined by a pre-treatment skin biopsy using a fully automated and standardized immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ, USA). Furthermore, OS was also considered exploratory due to the one-way crossover design.

Statistical analysis

Unless specified, all efficacy and safety analyses were performed based on the first assigned (randomized) treatment. The original protocol was time-driven and powered at 80% to detect a 50% increase in PFS, using a reference median PFS for vorinostat of 169 days,[22] with a calculated sample size of 217. The protocol was amended early on to an event-driven study and concurrent increase in power to 90%., resulting in 255 PFS events needed and an enrollment of 288 patients. The sample size was then further increased by approximately 10% to account for patients lost to follow-up prior to

documented progression, resulting in a projected enrollment of 317 patients The primary comparison of PFS between mogamulizumab and vorinostat was performed on the intention-to-treat set – defined as all patients randomized to a therapy and assigned a study number – based upon the results of the onsite Investigator's assessment using a stratified log-rank test at the one-sided 2·5% significance level. Safety was assessed in all patients who received at least one dose of study drug. No interim analyses were planned. A Cox proportional hazard model with treatment, disease type, disease stage, and region as covariates was used to assess the magnitude of the treatment difference in PFS. The hazard ratio (HR) and the 95% confidence interval (CI) obtained from the Cox proportional hazard model were calculated. The median PFS and the two-sided 95% CI for each treatment were estimated using Kaplan-Meier survival analysis methods.

Death due to any cause was considered an event for the PFS analysis. Randomized patients who withdrew from the study for any reason before documented progression per protocol criteria, including those who initiated a new anticancer therapy, were censored at the time of last efficacy evaluation (of any compartment). Analyses were done with SAS version 9.3.

This study was registered with ClinicalTrials.gov, number NCT01728805 (EUDRACT: 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 for MAVORIC, consisting of principal investigators who are considered world experts in CTCL, was involved in study design and conduct. The Investigators and sponsor gathered and analyzed the data. All authors attest to the accuracy of the data and analyses reported. The authors participated in

writing the manuscript with assistance of a medical writer who was funded by Kyowa Kirin. All authors had full access to the data. YHK had the final responsibility to submit for publication.

RESULTS

Between December 12, 2012, and January 29, 2016 we enrolled and randomly assigned 372 patients to treatment across 61 centers in 11 countries, 186 to mogamulizumab and 186 to vorinostat comprising the intention-to-treat population (Figure 1). The total number randomized (n=372) exceeded the planned enrollment (n=317) due to large numbers of subjects enrolled after sites were notified of the last day to screen, and an allowance by the Sponsor for newly initiated sites to screen subjects through December 30, 2015. Two patients randomized to mogamulizumab withdrew consent prior to receiving study treatment; thus 370 patients were included in the Safety population.

Treatment groups were comparable with respect to demographic and physical characteristics, disease characteristics, and prior CTCL therapies (Table 1). At the time of data cut-off, 27 patients randomized to mogamulizumab and ten patients randomized to vorinostat were still continuing treatment; additionally, 31 patients originally randomized to vorinostat but who crossed over to mogamulizumab were continuing treatment with mogamulizumab.

The median follow-up time was 17·0 months (interquartile range [IQR] 11·6-26·9) overall in the randomized part of the study. Median relative dose intensities were 97·5% (IQR 90·9-100) formogamulizumab and 95·1% (IQR 80·3-100) for vorinostat.

In the primary analysis (utilizing data from investigator assessment), the median PFS was 7·7 months (95% CI, 5·7, 10·3) for mogamulizumab versus 3·1 months (95% CI, 2·9, 4·1) for vorinostat (HR, 0·53; 95% CI, 0·41, 0·69; P<0·0001 for the risk difference) (stratified log-rank test) (Figure 2). With independent review, the median PFS was 6·7 months (95% CI, 5·6, 9·4) for mogamulizumab and 3·8 months (95% CI, 3·0, 4·7) for vorinostat (HR, 0·64; 95% CI, 0·49, 0·84; P<0·0007). Analysis of PFS for predefined subgroups showed that mogamulizumab prolonged time to disease progression across analyzed subgroups, including disease type and stage (Figure 3). In a post hoc analysis, the median PFS for stage IIB patients with tumor-type advanced skin disease was 4·2 months (95% CI, 2·2, 9·4) for mogamulizumab and 3·9 months (95% CI, 1·8, 5·7) for vorinostat.

The ORR, based on Investigator assessment, was significantly higher for mogamulizumab (28·0%; 95% CI, 21·6, 35·0) compared to vorinostat (4·8%; 95% CI, 2·2, 9·0) (risk difference, 23·1; 95% CI, 12·8, 33·1; P<0·0001) (Table 2), and this benefit was confirmed by independent review (43/186, 23·1% [95% CI, 17·3, 29·8] vs 7/186, 3·8% [95% CI, 1·5, 7·6], respectively; P<0·0001). ORR, DOR, and response by disease compartment were higher for mogamulizumab-treated patients than for vorinostat-treated patients across subgroups. Specifically, mogamulizumab therapy resulted in higher ORR in patients with both MF and SS. Although not a predefined analysis, ORR was higher with mogamulizumab than vorinostat across all disease stages. When analyzed by disease compartment, mogamulizumab resulted in a better confirmed response rate than vorinostat, notably in the skin and blood. Four patients in the mogamulizumab arm, versus none in the vorinostat arm, achieved a global CR during randomized treatment.

Best overall global and skin responses, defined as the best response recorded across all time points (including unconfirmed responses), favored mogamulizumab (Figure 4). Mogamulizumab patients had a

best overall response in 65 (34·9%) of 186 patients, and 81 patients (43·5%) experienced at least 50% improvement in skin. Best overall and skin responses for vorinostat patients were 6·5% (12/186) and 22·0% (41/186), respectively.

Median times to overall response were 3·3 months (IQR 2·0-6·4) for mogamulizumab (52 responders) and 5·1 months (IQR 2·9-8·5) for vorinostat (nine responders). When time to response was assessed by compartment, patients randomized to mogamulizumab had a median time to response in blood of 1·1 months (IQR 1·0-1·2) and in skin of 3·0 months (IQR 1·9-4·7). Vorinostat patients had a median time to response in blood of 1·9 months (IQR 1·0-2·1) and in skin of 2·7 months (IQR 1·1-5·6). Likewise, when DOR was assessed by compartment, mogamulizumab responders (n=52) had a median DOR in blood of 25·5 months (IQR 15·9-not estimable) and in skin of 20·6 months (IQR 11·2-not estimable). In vorinostat responders (n=9), median DOR in blood was not estimable, whereas median DOR in skin was 10·7 months (IQR 4·8-not estimable).

Of the 186 patients randomized to vorinostat, 136 crossed over to treatment with mogamulizumab, 80% (109/136) after disease progression and 20% (27/136) after intolerable toxicity. Three patients approved for crossover did not receive mogamulizumab due to AEs unrelated to vorinostat.

In crossover patients, median PFS calculated from the first dose of mogamulizumab was 8·9 months (95% CI: 5·4, 14·8). Across all patients who were either randomized to mogamulizumab or received mogamulizumab with crossover (n=319), the median PFS was 8·4 months (95% CI: 6·1, 10·3). In crossover patients who received mogamulizumab, the ORR was 30·8% (41/133).

For PRO endpoints, mogamulizumab compared favorably to vorinostat across the domains of multiple PRO instruments, including Skindex-29 Symptoms and Functional scales, and FACT-G Physical Well-Being, Functional, and Emotional scales. Statistically significant differences were reported in favor of mogamulizumab on the Skindex-29 symptoms domain at Cycle 3 (-13·7 versus -6·4 for the mogamulizumab and vorinostat groups, respectively; P=0·0092), Cycle 5 (-12·0 versus -5·0, respectively; P = 0·0307), and Cycle 7 (-14·2 versus -5·7, respectively; P=0·0208). Significant differences in favor of mogamulizumab were also observed on the Skindex-29 Functional scale at Cycle 3 (-4·9 versus 2·7 for the mogamulizumab and vorinostat groups, respectively; P=0·0032) and Cycle 5 (-6·4 versus 3·3, respectively; P=0·0011). Importantly, patients treated with mogamulizumab had prolonged median time to symptom worsening (27·4 months, range 27·4 – not estimable) compared to vorinostat (6·6 months, range 6·1 – 13·8). A full report of PRO results from MAVORIC is being prepared for presentation elsewhere.

A total of 280 (96·6%) of the 290 patients with evaluable skin samples had a positive CCR4 expression status, predefined as ≥10% of infiltrating lymphoid cells. All of the samples demonstrated at least 1% positive infiltrating lymphoid cells, with a median percent CCR4 expression level – on a continuous scale – for the 290 evaluable patients of 80% (range, 1%, 100%). There were no apparent differences in ORR based on skin CCR4 expression; the median levels of CCR4 expression in mogamulizumab responders were 80% (range 15%-100%) vs non-responders 80% (range 1%-100%) (appendix p 21).

There was no evidence of a survival advantage or disadvantage for mogamulizumab compared to vorinostat. In the randomized mogamulizumab group, the median OS was not reached compared to 43·9 months in the vorinostat group (HR, 0·93; 95% CI, 0·61, 1·43). Exploratory analyses of OS adjusting for crossover are outlined in the appendix (p 19).

Median treatment exposures were 170 days (IQR 71-348) with mogamulizumab and 84 days (IQR 48-169) with vorinostat (mean treatment exposures, 245 [SD 234] and 144 [SD 172] days, respectively). The most common TEAEs with mogamulizumab were infusion-related reactions in 61 (33·2%), drug rash in 44 (23·9%), diarrhea in 43 (23·4%), and fatigue in 43 (23·4%) of 184 patients (Table 3). The most common TEAEs with vorinostat were diarrhea in 115 (61·8%), nausea in 79 (42·5%), fatigue in 70 (37·6%), and thrombocytopenia in 57 (30·6%) of 186 patients. Among patients randomized to vorinostat who crossed over to receive mogamulizumab (n=136), the incidence of TEAEs was similar to that observed for patients randomized to mogamulizumab.

Serious AEs (SAEs) were experienced by 69 (37·5%) of 184 patients in the mogamulizumab group and 46 (24·7%) of 186 patients in the vorinostat group. In the mogamulizumab group, the most frequently reported SAEs were pyrexia in eight (4·3%) and cellulitis in five (2·7%) of 184 patients. In the vorinostat group, the most frequently reported SAEs were cellulitis in six (3·2%), pulmonary embolism in six (3·2%), and sepsis in five (2·7%) of 186 patients. SAEs considered treatment-related were reported for 36 (19·6%) of 184 patients in the mogamulizumab group and 30 (16·1%) of 186 patients in the vorinostat group.

During the randomized period, grade 5 TEAEs occurred in 12 patients. Three patients who received mogamulizumab had a grade 5 event, with two patients having an event considered related to treatment (sepsis, polymyositis), and one patient having unrelated disease progression. Nine patients who received vorinostat had a grade 5 event, with three considered related to treatment (2 patients with pulmonary embolism and one with bronchopneumonia) and six considered unrelated (1 each,

disease progression, intestinal obstruction/sepsis/septic shock, endocarditis, pneumonia, depressed level of consciousness, and skin disorder).

In total, 19% (35/184) of patients in the mogamulizumab group and 23% (43/186) of patients in the vorinostat group discontinued treatment due to AEs. The most frequent AEs leading to discontinuation of treatment were drug rash in 13 patients (7·1%) in the mogamulizumab group and fatigue in 8 patients (4·3%) in the vorinostat group.

DISCUSSION

In this international, randomized phase 3 study in previously treated CTCL, the new anti-CCR4 antibody mogamulizumab demonstrated significantly superior PFS, median 7·7 months (95% CI 5·7, 10·3), over vorinostat, 3·1 months (95% CI 2·9, 4·1). In addition to meeting the primary endpoint of MAVORIC, mogamulizumab was also superior to vorinostat in ORR, and resulted in improved DOR and higher response by disease compartment. Despite heterogeneity of treatment practices in MF/SS, patients in MAVORIC were balanced in the number and types of prior therapies and, in general, a benefit for mogamulizumab was seen across stages. Importantly, mogamulizumab demonstrated improved PFS and ORR in the subset of patients with SS which have very poor OS.[4] The AE profile of mogamulizumab revealed no new safety concerns in the MAVORIC CTCL population, with drug rash being the most frequent AE leading to discontinuation, similar to that seen in the phase 1/2 trial.[17] Improvements in PROs, as measured by Skindex-29 Symptoms and Functional scales, of mogamulizumab versus vorinostat support improvements in function and disease-related symptoms in those treated with mogamulizumab.

Clinical response to mogamulizumab was not associated with skin CCR4 expression levels, evaluated as an exploratory endpoint. Lack of correlation between levels of drug targets and objective clinical response has been observed with other well-known targeted therapies, such as brentuximab vedotin.[23–25] Future translational studies of mechanism and/or biomarkers linked with global and/or compartmental response to mogamulizumab are planned.

Prior trials of new systemic therapies in CTCL have been relatively small (<150 patients), mostly single-arm or with no active comparator, and with ORR as the primary endpoint.[10,18,19,24–30] Efficacy analyses that are focused on ORR do not capture key elements of clinical benefit such as duration of response and PFS, and thus cannot fully assess the overall clinical impact of new therapies in this study population with chronic disease course, although recent efforts have been made to address this shortcoming.[10] The MAVORIC study utilized PFS as the primary endpoint in accordance with international guidelines that recommend PFS as a meaningful primary endpoint in the context of ORR and duration of response.[20]

Given that the current study to our knowledge is the first randomized trial in CTCL to compare systemic agents with PFS as a primary endpoint, and employed rigorous consensus global response criteria with more frequent compartmental assessment, it is difficult to make direct comparisons to previous trials. Furthermore, the study sub-populations often differ in these CTCL trials. For example, the randomized phase 3 ALCANZA study of brentuximab vedotin in CD30-positive CTCL included patients with primary cutaneous anaplastic large-cell lymphoma (pcALCL).[10] In addition, ALCANZA excluded patients with SS, whereas the MAVORIC study had 45% of patients with SS, the very rare type of CTCL with unfavorable prognosis. Despite the high proportion of previously-treated SS, the overall median PFS for mogamulizumab was significantly improved over vorinostat (P<0·0001). The ORR for mogamulizumab

was 28·0%; whereas rates reported in smaller, mostly non-randomized studies of systemic agents in CTCL with varying subpopulations have ranged from 17% (24/139) to 70% (21/30).[24–27,29,30]

The MAVORIC study chose vorinostat as the comparator due to its being an FDA-approved standard-of-care option for CTCL, with demonstrated activity across disease compartments.[22] However, ORR of vorinostat (4·8%; 95% CI, 2·2, 9·0) is notably lower than that reported in previous single-arm studies of 29·7% (95% CI, 19·7, 41·5)[18] to 30·8% (95% CI, 9·1, 61·4).[19] Our data show that patients in the vorinostat arm had appropriate drug exposure (>95% dose intensity) as well as mean duration of treatment exposure (144 days), compared to that reported in the FDA's drug approval package for vorinostat (110 days),[22] suggesting that inadequate exposure to vorinostat was not the reason for the low response rates observed in the MAVORIC study. The pivotal vorinostat trial by Olsen and colleagues enrolled a similar proportion of advanced stage (IIB and higher) and SS, and patients had received a similar number of prior treatments to those in MAVORIC[18]; therefore, differences in the study population are unlikely to account for the response findings. Differences in response findings might be partially explained by the randomized design against a comparator, the large study size, and differences in disease assessments. It is important to note the use of global composite response criteria in this study, whereas in the pivotal vorinostat study by Olsen and colleagues, the reported ORR of 29·7% was based only on skin response (mSWAT score), a result more comparable to the skin compartment response rate of 15.6% observed with vorinostat in this study.[18] Furthermore, the ORR of 28·0% in patients treated with mogamulizumab in the current study was also lower than in the previous phase 1/2 study (36·8%),[17] highlighting the effect of a large, randomized design on the ability to rigorously define efficacy and safety of both experimental and comparator agents in this rare disease population.

As in other indolent lymphomas, intervention trials aimed at showing the impact of new therapies on OS are particularly challenging in CTCL and further complicated by the infrequency of these malignancies. Thus, the MAVORIC study was not powered to detect survival differences between the two arms within the defined follow-up period. Moreover, the analysis of OS is confounded by the one-way crossover design, which was offered to allow patients in the comparator arm to receive a potentially promising new therapy. Given these limitations, differences in OS could not be adequately evaluated in the MAVORIC study and at the time of analysis, OS outcome was similar between the two arms (HR=0·93). The challenge of OS as an endpoint is demonstrated further by the median OS for mogamulizumab, which had not yet been reached after 4 years of study enrollment.

The safety of mogamulizumab in this trial aligns with what was seen in earlier studies. The most common AEs were infusion-related reactions and drug eruption. Infusion-related reactions with mogamulizumab were mostly limited to early infusions (infusions 1-2), mainly grade 1, and managed with standard protocols familiar to practitioners. Drug eruption also appeared to be mild in most cases. Although 7·1% of patients treated with mogamulizumab discontinued due to drug rash, the protocol did not allow treatment with systemic steroids which may be utilized in clinical practice. Further analyses of mogamulizumab-associated drug rash, including detailed histopathology, mechanism, and impact on outcomes and safety are ongoing.

Limitations of this large, randomized trial of systemic therapy in CTCL include the relatively small size of some patient subsets, such as stage-specific and visceral involvement, and the exclusion of patients with transformed MF, which limited the ability to draw definitive conclusions on the efficacy and safety of mogamulizumab in these patient subsets. Further, study stratification for all clinical stages was not feasible in such a rare disease. So we chose to include stage IIB within the low-stage disease category.

Although the stage groupings may not reflect the true heterogeneity of the disease, the allocation among stages was balanced but with slightly more stage IIB patients in the mogamulizumab arm.

Despite these limitations, and the fact that the treatment landscape inevitably changed during enrollment of the MAVORIC study, this large prospective dataset provides an opportunity to rigorously describe outcomes of a therapeutic intervention with both a new agent and the FDA-approved standard therapy available at the time of the study inception. It is anticipated that in the future, additional treatment options will become available in CTCL, and studies that compare mogamulizumab with newer therapies, either as monotherapy or in combination, will be warranted.

In summary, the randomized phase 3 study MAVORIC demonstrated that mogamulizumab, a novel CCR4-directed monoclonal antibody, was significantly superior to vorinostat in PFS, ORR, and PRO assessments of QoL in previously treated patients with the MF/SS types of CTCL. The safety profile was manageable and consistent with previous reports. This study supports mogamulizumab as a valuable new therapeutic option in patients with MF/SS types of CTCL.

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: Eisai, Innate Pharma, Seattle Genetics, Medivir, KKD, Millennium/Takeda, Actelion: on board of directors or advisory committee(s); Eisai, Millennium/Takeda, Soligenix, Seattle Genetics, Portola, Neumedicine, miRagen, Merck, KKD, Innate Pharma, Horizon Pharma, Forty Seven, Inc., Tetralogic, Galderma: research funding. **MB:** Innate Pharma: equity ownership; Innate Pharma, Actelion, Takeda, Kyowa: on board of directors or advisory committee(s). **SMH:** Kyowa-Hakko-Kirin, Mundipharma, Forty Seven, Infinity/Verastem, HUYA, Millennium/Takeda, BMS, Seattle Genetics, Celgene: consultancy; Kyowa-Hakko-Kirin, ADC Therapeutics, Forty Seven, Infinity/Verastem, Millennium/Takeda, Seattle Genetics, Celgene, Aileron Therapeutics: research funding. **SW:** Celgene: honoraria; Galderma: research funding. **MV:** Innate: IPH4102-101 pharma safety board. **PLZ:** Roche, Celgene, Merck, Takeda, J&J, Servier, Verastem, BMS, Karyopharma, Bayer, Gilead: honoraria, on board of directors or advisory committee(s). **LS:** Spectrum Pharmaceuticals: consultancy, research funding. **EJK:** Actelion, Galderma, Medscape/WebMD, Seattle Genetics: consultancy; Cutaneous Lymphoma Foundation, US Cutaneous Lymphoma Consortium: on board of directors or advisory committee(s); Galderma, KKD, MedImmune, Soligenix: clinical trials investigator. **PLO-R:** ACTELION, 4SC, Innate Pharma, Takeda: consultancy; MEDA: research funding. **HE:** AbbVie, Genentech, Roche, Gilead, Pharmacyclics: consultancy; AbbVie, Genentech, Gilead: honoraria, speakers bureau; AbbVie, Genentech, Roche, Novartis, Celgene, Gilead, Pharmacyclics: research funding. **JS:** 4SC, Takeda, Mallinckrodt, Innate Pharma, Actelion: consultancy. **CE:** Ferndale Labs: consultancy; NCI, Veterans Administration, California Wine Grape Assn, Soligenix, Idera, Elorac, Ferndale Labs, Astellas Pharma: research funding. **SD:** KKD: research funding. **DF:** Celgene, Seattle Genetics: on board of directors or advisory committee(s). **AH:** Amgen, Pharmacyclics, Takeda,

Genenech Inc., Roche/Genentech Inc., Seattle Genetics, BMS, Kyowa Hakko Kirin, AbbVie, Immune Design, miRagen: research funding. **BPoligone:** Actelion Pharmaceutical, Celgene: consultancy; Actelion Pharmaceutical, Kyowa Hakko Kirin, Soligenix: research funding; Actelion Pharmaceutical: speakers bureau. **AK:** Celgene, Janssen: consultancy; Amgen: travel grant. **AJM:** BMS: consultancy; Takeda, Seattle Genetics: honoraria; Incyte, BMS, ADC Therapeutics, Seattle Genetics: research funding. **AM:** Actelion: speakers bureau; Actelion, Seattle Genetics: advisory board. **AS:** Kyowa Kirin: consultancy; Spectrum: grants. **BPro:** Seattle Genetics, Takeda: honoraria; Kyowa Kirin: advisory board. **LJG:** Kyowa Kirin: advisory board. **KD, JM, ML, JH, DOG:** KKD: employment. **SH:** Clinical Outcomes Solutions: consultancy, research funding. **KT:** Celgene, Daiichi Sankyo Co., Ltd: consultancy; Chugai, Kyowa Hakko Kirin, Eisai, Zenyaku Kogyo, Takeda, Celgene, Janssen, HUYA Bioscience, Daiichi Sankyo Co., Ltd, Mundipharma, Ono Pharmaceutical: honoraria; AbbVie, Chugai, Kyowa Hakko Kirin, Eisai, GSK, Takeda, Celgene, Servier, Janssen, Mundipharma, Ono Pharmaceutical: research funding. **MD:** MDACC: safety oversight committee, research funding. All other authors **(LP-B, AHR, PP, YT, SM, AT, JG, MTF)** declare no relevant competing interests.

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Table 1. Baseline characteristics

	Mogamulizumab N=186	**Vorinostat N=186**
Median age, yrs	64 (54-73)	65 (56-72)
Age Group		
<65 yrs	99 (53)	89 (48)
≥65 yrs	87 (47)	97 (52)
Sex		
Male	109 (59)	107 (58)
Female	77 (41)	79 (43)
Race		
White	125 (67)	135 (73)
Other	37 (20)	26 (14)
Not reported[a]	24 (13)	25 (13)
ECOG Performance Status[b]		
0	106 (57)	104 (56)
1	78 (42)	82 (44)
2	2 (1)	0
Median time from initial diagnosis, months[c]	41·0 (17·4-78·8)	35·4 (16·2-68·2)
Disease Type		
MF	105 (57)	99 (53)
SS	81 (44)	87 (47)
Current clinical stage		
IB–IIA	36 (19)	49 (26)
IIB	32 (17)	23 (12)
IIIA–IIIB	22 (12)	16 (9)
IVA1	73 (39)	82 (44)
IVA2	19 (10)	12 (7)
IVB[d]	4 (2)	4 (2)
Median number of prior systemic regimens received	3·0 (2-5)	3·0 (2-5)
Prior CTCL therapies		
Bexarotene	107 (58)	110 (59)
Interferon	81 (44)	94 (51)
Conventional chemotherapy[e]	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 (%).

[a]Not applicable = not reported for those countries that do not allow race/ethnicity to be collected.

[b]For ECOG performance status, baseline is defined as the last measurement obtained prior to the first dose of study drug; 2 patients in the mogamulizumab arm had an ECOG performance status <2 at screening but = 2 at baseline.

[c]Time from initial diagnosis (months) is calculated as (date of first dose of study medication – date on initial diagnosis + 1)/30. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1 for the calculation.
[d]Two patients (one on each treatment arm) were noted to be Stage IVB at baseline but did not have measurable visceral disease at baseline.
[e]Systemic therapies may have been used as monotherapy or in combination with other agents.
CTCL=cutaneous T-cell lymphoma; ECOG=Eastern Cooperative Oncology Group; MF=mycosis fungoides; SS= Sézary syndrome; IFN=interferon.

Table 2. Measures of response for mogamulizumab vs vorinostat by Investigator's assessment

	Mogamulizumab	**Vorinostat**
ORR[a,b]	52/186 (28·0)	9/186 (4·8)
MF	22/105 (21·0)	7/99 (7·1)
SS	30/81 (37·0)	2/87 (2·3)
Stage IB/IIA	7/36 (19·4)	5/49 (10·2)
Stage IIB	5/32 (15·6)	1/23 (4·3)
Stage III	5/22 (22·7)	0/16 (0)
Stage IV	35/96 (36·5)	3/98 (3·1)
DOR, median, months	14·1 (8·4-19·2)	9·1 (5·6-NE)
MF	13·1 (4·7-18·0)	9·1 (5·6-NE)
SS	17·3 (9·4-19·9)	6·9 (6·9-6·9)
Compartment response[a,c]		
Skin	78/186 (41·9)	29/186 (15·6)
Blood	83/122 (68·0)	23/123 (18·7)
Lymph nodes	21/124 (16·9)	5/122 (4·1)
Viscera	0/3 (0)	0/3 (0)

Data are median (IQR) or n (%).

ORR is based on Global Composite Response score.

[a]ORR or compartmental response rate is the percentage of patients with confirmed CR or confirmed PR.

[b]P<0·0001.

[c]Denominator includes patients with compartmental disease at baseline.

CI=confidence interval; CR=complete response; DOR=duration of response; MF=mycosis fungoides; NE=not estimable; ORR=overall response rate; PR= partial response; SS=Sézary syndrome.

Table 3. Treatment-emergent adverse events

	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								
Anaemia	17 (9.2)	2 (1.1)	0	0	17 (9.1)	1 (0.5)	1 (0.5)	0
Eosinophilia	4 (2.2)	0	0	0	0	1 (0.5)	0	0
Febrile Neutropenia	0	0	0	0	0	1 (0.5)	0	0
Leukocytosis	0	0	0	0	1 (0.5)	2 (1.1)	0	0
Leukopenia	1 (0.5)	0	0	0	3 (1.6)	1 (0.5)	0	0
Neutropenia	4 (2.2)	1 (0.5)	0	0	7 (3.8)	2 (1.1)	1 (0.5)	0
Thrombocytopenia	21 (11.4)	0	0	0	44 (23.7)	11 (5.9)	2 (1.1)	0
Cardiac Disorders								
Acute Myocardial Infarction	0	1 (0.5)	0	0	0	0	0	0
Angina Unstable	0	0	0	0	0	1 (0.5)	0	0
Atrial Tachycardia	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Cardiac Failure	0	1 (0.5)	0	0	0	0	0	0
Coronary Artery Disease	0	1 (0.5)	0	0	0	0	0	0
Left Ventricular Hypertrophy	0	0	0	0	0	0	0	1 (0.5)
Myocarditis	0	1 (0.5)	0	0	0	0	0	0
Ventricular Tachycardia	0	1 (0.5)	0	0	0	0	0	0
Eye Disorders								
Lagophthalmos	0	1 (0.5)	0	0	0	0	0	0
Lens Dislocation	0	1 (0.5)	0	0	0	0	0	0
Retinal Vein Occlusion	0	1 (0.5)	0	0	0	0	0	0
Gastrointestinal Disorders								
Abdominal Pain	7 (3.8)	0	0	0	21 (11.3)	0	0	0
Abdominal Pain Upper	1 (0.5)	0	0	0	10 (5.4)	1 (0.5)	0	0
Anal Fistula	0	0	0	0	0	1 (0.5)	0	0
Constipation	20 (10.9)	1 (0.5)	0	0	32 (17.2)	2 (1.1)	0	0
Diarrhoea	42 (22.8)	1 (0.5)	0	0	106 (57.0)	9 (4.8)	0	0
Gastric Haemorrhage	0	1 (0.5)	0	0	0	0	0	0
Ileitis	0	0	0	0	0	1 (0.5)	0	0

Intestinal Obstruction	0	0	0	0	0	0	0	1 (0.5)
Mouth Ulceration	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Nausea	27 (14.7)	1 (0.5)	0	0	76 (40.9)	3 (1.6)	0	0
Vomiting	11 (6.0)	0	0	0	23 (12.4)	1 (0.5)	0	0
General Disorders and Administration Site Conditions								
Asthenia	10 (5.4)	0	0	0	23 (12.4)	4 (2.2)	0	0
Disease Progression	2 (1.1)	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.5)
Fatigue	40 (21.7)	3 (1.6)	0	0	59 (31.7)	11 (5.9)	0	0
General Physical Health Deterioration	0	1 (0.5)	0	0	0	1 (0.5)	0	0
Generalised Oedema	1 (0.5)	1 (0.5)	0	0	1 (0.5)	0	0	0
Oedema	0	1 (0.5)	0	0	1 (0.5)	0	0	0
Oedema Peripheral	27 (14.7)	0	0	0	26 (14.0)	1 (0.5)	0	0
Pain	5 (2.7)	1 (0.5)	0	0	1 (0.5)	0	0	0
Pyrexia	30 (16.3)	1 (0.5)	0	0	11 (5.9)	0	0	0
Hepatobillary Disorders								
Cholangitis	0	0	0	0	0	0	1 (0.5)	0
Cholecystitis	0	0	0	0	1 (0.5)	1 (0.5)	0	0
Hepatitis Acute	0	1 (0.5)	0	0	0	0	0	0
Hepatocellular Injury	0	0	1 (0.5)	0	1 (0.5)	0	0	0
Immune System Disorders								
Contrast Media Allergy	3 (1.6)	1 (0.5)	0	0	1 (0.5)	0	0	0
Drug Hypersensitivity	2 (1.1)	1 (0.5)	0	0	1 (0.5)	0	0	0
Hypersensitivity	0	1 (0.5)	0	0	0	0	0	0
Infections and Infestations								
Abscess Limb	0	1 (0.5)	0	0	0	0	0	0
Atypical Pneumonia	0	1 (0.5)	0	0	0	0	0	0
Bacteraemia	0	2 (1.1)	0	0	0	0	0	0
Bronchitis	4 (2.2)	0	1 (0.5)	0	4 (2.2)	0	0	0
Bronchopneumonia	0	0	0	0	0	0	0	1 (0.5)
Cellulitis	2 (1.1)	3 (1.6)	1 (0.5)	0	6 (3.2)	4 (2.2)	0	0
Cytomegalovirus Infection	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Endocarditis	0	0	0	0	0	0	0	1 (0.5)
Folliculitis	13 (7.1)	0	0	0	3 (1.6)	1 (0.5)	0	0

Gastroenteritis	3 (1.6)	0	0	0	3 (1.6)	1 (0.5)	0	0
Herpes Simplex	2 (1.1)	2 (1.1)	0	0	0	0	0	0
Infection	0	1 (0.5)	0	0	0	0	0	0
Influenza	5 (2.7)	1 (0.5)	0	0	3 (1.6)	1 (0.5)	0	0
Lower Respiratory Tract Infection	1 (0.5)	1 (0.5)	0	0	2 (1.1)	1 (0.5)	0	0
Meningitis	0	1 (0.5)	0	0	0	0	0	0
Oral Herpes	2 (1.1)	1 (0.5)	0	0	2 (1.1)	0	0	0
Osteomyelitis	0	2 (1.1)	0	0	0	0	0	0
Periorbital Cellulitis	0	1 (0.5)	0	0	0	0	0	0
Pneumocystis Jiroveci Pneumonia	0	1 (0.5)	0	0	0	0	0	0
Pneumonia	2 (1.1)	3 (1.6)	1 (0.5)	0	0	1 (0.5)	0	1 (0.5)
Pneumonia Influenzal	0	1 (0.5)	0	0	0	0	0	0
Pneumonia Legionella	0	1 (0.5)	0	0	0	0	0	0
Pneumonia Pneumococcal	0	0	0	1 (0.5)	0	0	0	0
Respiratory Tract Infection	0	1 (0.5)	0	0	0	0	0	0
Sepsis	1 (0.5)	2 (1.1)	0	1 (0.5)	1 (0.5)	0	4 (2.2)	1 (0.5)
Sepsis Syndrome	0	0	0	0	0	0	1 (0.5)	0
Septic Embolus	0	1 (0.5)	0	0	0	0	0	0
Septic Shock	0	0	0	0	0	0	0	1 (0.5)
Skin Infection	17 (9.2)	0	0	0	10 (5.4)	3 (1.6)	0	0
Staphylococcal Abscess	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Staphylococcal Bacteraemia	0	1 (0.5)	0	0	0	1 (0.5)	0	0
Staphylococcal Infection	2 (1.1)	1 (0.5)	0	0	2 (1.1)	0	0	0
Staphylococcal Sepsis	0	1 (0.5)	0	0	0	0	1 (0.5)	0
Superinfection	0	1 (0.5)	0	0	1 (0.5)	0	0	0
Tooth Abscess	1 (0.5)	0	0	0	0	1 (0.5)	0	0
Tooth Infection	0	1 (0.5)	0	0	0	0	0	0
Upper Respiratory Tract Infection	19 (10.3)	0	0	0	7 (3.8)	2 (1.1)	0	0
Wound Infection	2 (1.1)	1 (0.5)	0	0	0	0	0	0
Injury, Poisoning And Procedural Complications								
Ankle Fracture	0	1 (0.5)	0	0	0	0	0	0
Fall	10 (5.4)	1 (0.5)	0	0	3 (1.6)	0	0	0
Infusion Related Reaction	58 (31.5)	3 (1.6)	0	0	1 (0.5)[b]	0	0	0
Laceration	2 (1.1)	1 (0.5)	0	0	4 (2.2)	0	0	0

Pelvic Fracture	0	0	0	0	0	1 (0.5)	0	0
Subdural Haematoma	0	0	0	0	0	1 (0.5)	0	0
Vascular Access Complication	0	1 (0.5)	0	0	0	0	0	0
Investigations								
Alanine Aminotransferase Increased	10 (5.4)	0	0	0	8 (4.3)	1 (0.5)	0	0
Aspartate Aminotransferase Increased	6 (3.3)	2 (1.1)	0	0	11 (5.9)	1 (0.5)	0	0
Blood Bilirubin Increased	0	1 (0.5)	0	0	8 (4.3)	1 (0.5)	0	0
Blood Creatine Phosphokinase Increased	2 (1.1)	1 (0.5)	0	0	2 (1.1)	0	0	0
Blood Creatinine Increased	6 (3.3)	0	0	0	52 (28.0)	0	0	0
Blood Glucose Increased	1 (0.5)	1 (0.5)	0	0	6 (3.2)	0	0	0
Blood Lactate Dehydrogenase Increased	3 (1.6)	0	0	0	2 (1.1)	1 (0.5)	0	0
Blood Pressure Increased	0	0	0	0	0	2 (1.1)	0	0
Electrocardiogram Qt Prolonged	1 (0.5)	0	0	0	0	1 (0.5)	0	0
Hepatic Enzyme Increased	0	0	0	0	2 (1.1)	1 (0.5)	0	0
International Normalised Ratio Increased	0	1 (0.5)	0	0	1 (0.5)	0	0	0
Neutrophil Count Decreased	3 (1.6)	0	0	0	1 (0.5)	1 (0.5)	0	0
Platelet Count Decreased	4 (2.2)	0	0	0	19 (10.2)	0	0	0
Protein Total Decreased	0	0	0	0	1 (0.5)	1 (0.5)	0	0
Weight Decreased	10 (5.4)	1 (0.5)	0	0	31 (16.7)	2 (1.1)	0	0
Weight Increased	13 (7.1)	1 (0.5)	0	0	2 (1.1)	0	0	0
White Blood Cell Count Increased	1 (0.5)	1 (0.5)	0	0	1 (0.5)	0	0	0
Metabolism And Nutrition Disorders								
Decreased Appetite	12 (6.5)	2 (1.1)	0	0	44 (23.7)	2 (1.1)	0	0

Dehydration	2 (1.1)	1 (0.5)	0	0	7 (3.8)	2 (1.1)	0	0
Diabetes Mellitus	1 (0.5)	1 (0.5)	0	0	2 (1.1)	0	0	0
Gout	5 (2.7)	1 (0.5)	0	0	1 (0.5)	0	0	0
Hypercalcaemia	2 (1.1)	1 (0.5)	1 (0.5)	0	1 (0.5)	0	0	0
Hyperglycaemia	13 (7.1)	2 (1.1)	0	0	12 (6.5)	1 (0.5)	1 (0.5)	0
Hyperkalaemia	5 (2.7)	0	1 (0.5)	0	7 (3.8)	1 (0.5)	0	0
Hyperuricaemia	8 (4.3)	0	0	0	3 (1.6)	1 (0.5)	0	0
Hypoalbuminaemia	3 (1.6)	0	1 (0.5)	0	3 (1.6)	1 (0.5)	0	0
Hypokalaemia	10 (5.4)	0	0	0	10 (5.4)	1 (0.5)	1 (0.5)	0
Hypophosphataemia	5 (2.7)	3 (1.6)	0	0	3 (1.6)	3 (1.6)	0	0
Metabolic Acidosis	0	0	0	0	0	1 (0.5)	0	0
Tumour Lysis Syndrome	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Type 2 Diabetes Mellitus	0	0	0	0	0	1 (0.5)	0	0
Musculoskeletal And Connective Tissue Disorders								
Arthralgia	12 (6.5)	1 (0.5)	0	0	11 (5.9)	0	0	0
Back Pain	17 (9.2)	1 (0.5)	0	0	8 (4.3)	1 (0.5)	0	0
Muscle Spasms	9 (4.9)	0	0	0	27 (14.5)	2 (1.1)	0	0
Muscular Weakness	7 (3.8)	1 (0.5)	0	0	9 (4.8)	0	0	0
Myalgia	11 (6.0)	0	0	0	6 (3.2)	2 (1.1)	0	0
Myositis	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Pain In Extremity	12 (6.5)	0	0	0	8 (4.3)	1 (0.5)	0	0
Polymyositis	0	0	0	1 (0.5)	0	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)								
Adenocarcinoma	0	1 (0.5)	0	0	0	0	0	0
Colon Cancer	0	0	0	0	0	1 (0.5)	0	0
Malignant Melanoma	0	0	1 (0.5)	0	0	0	0	0
Malignant Pleural Effusion	0	0	1 (0.5)	0	0	0	0	0
Mycosis Fungoides	0	0	0	0	0	0	0	1 (0.5)
Ovarian Cancer	0	0	1 (0.5)	0	0	0	0	0
Squamous Cell Carcinoma	6 (3.3)	1 (0.5)	0	0	2 (1.1)	1 (0.5)	0	0
Nervous System Disorders								
Depressed Level Of Consciousness	0	0	0	0	1 (0.5)	0	0	1 (0.5)
Dizziness	12 (6.5)	0	0	0	19 (10.2)	0	0	0
Dysgeusia	6 (3.3)	0	0	0	53 (28.5)	1 (0.5)	0	0
Headache	23 (12.5)	0	0	0	28 (15.1)	1 (0.5)	0	0

Miller Fisher Syndrome	0	1 (0.5)	0	0	0	0	0	0
Monoparesis	0	0	0	0	0	1 (0.5)	0	0
Neuropathy Peripheral	7 (3.8)	0	0	0	4 (2.2)	1 (0.5)	0	0
Polyneuropathy	0	0	0	0	0	1 (0.5)	0	0
Presyncope	2 (1.1)	1 (0.5)	0	0	0	0	0	0
Syncope	0	0	0	0	1 (0.5)	1 (0.5)	0	0
Psychiatric Disorders								
Confusional State	0	0	0	0	1 (0.5)	1 (0.5)	0	0
Depression	9 (4.9)	1 (0.5)	1 (0.5)	0	6 (3.2)	0	0	0
Emotional Distress	0	0	0	0	0	1 (0.5)	0	0
Renal and Urinary Disorders								
Haematuria	4 (2.2)	1 (0.5)	0	0	2 (1.1)	0	0	0
Proteinuria	4 (2.2)	1 (0.5)	0	0	1 (0.5)	0	0	0
Renal Failure	0	1 (0.5)	0	0	9 (4.8)	0	0	0
Renal Failure Acute	6 (3.3)	1 (0.5)	0	0	7 (3.8)	0	0	0
Renal Impairment	1 (0.5)	0	0	0	4 (2.2)	1 (0.5)	0	0
Urinary Retention	1 (0.5)	1 (0.5)	0	0	2 (1.1)	0	1 (0.5)	0
Reproductive System And Breast Disorders								
Prostatitis	0	0	0	0	0	1 (0.5)	0	0
Uterine Prolapse	0	0	0	0	0	1 (0.5)	0	0
Respiratory, Thoracic And Mediastinal Disorders								
Acute Respiratory Distress Syndrome	0	1 (0.5)	0	0	0	0	0	0
Bronchitis Chronic	0	1 (0.5)	0	0	0	0	0	0
Chronic Obstructive Pulmonary Disease	1 (0.5)	2 (1.1)	0	0	0	0	0	0
Haemoptysis	0	1 (0.5)	0	0	2 (1.1)	0	0	0
Oropharyngeal Pain	9 (4.9)	1 (0.5)	0	0	5 (2.7)	0	0	0
Pulmonary Embolism	0	0	0	0	0	4 (2.2)	1 (0.5)	2 (1.1)
Respiratory Failure	0	0	2 (1.1)	0	0	0	0	0
Skin And Subcutaneous Tissue Disorders								
Alopecia	13 (7.1)	0	0	0	36 (19.4)	0	0	0
Dermatitis Exfoliative	3 (1.6)	0	0	0	2 (1.1)	0	1 (0.5)	0
Drug Eruption	36 (19.6)	8 (4.3)	0	0	1 (0.5)	0	0	0
Pain Of Skin	5 (2.7)	1 (0.5)	0	0	5 (2.7)	3 (1.6)	0	0
Photosensitivity Reaction	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Pruritus Generalised	0	0	0	0	0	1 (0.5)	0	0
Rash	6 (3.3)	0	0	0	8 (4.3)	1 (0.5)	0	0
Rash Generalised	2 (1.1)	0	0	0	0	1 (0.5)	0	0

Skin Disorder	0	0	0	0	1 (0.5)	0	0	1 (0.5)
Skin Fissures	6 (3.3)	0	0	0	2 (1.1)	1 (0.5)	0	0
Skin Ulcer	4 (2.2)	1 (0.5)	0	0	2 (1.1)	0	0	0
Surgical and Medical Procedures								
Hysterectomy	0	0	0	0	0	1 (0.5)	0	0
Vascular Disorders								
Air Embolism	0	0	0	0	0	0	1 (0.5)	0
Embolism	0	2 (1.1)	0	0	0	0	0	0
Essential Hypertension	0	1 (0.5)	0	0	0	0	0	0
Hypertension	9 (4.9)	8 (4.3)	0	0	13 (7.0)	12 (6.5)	0	0
Jugular Vein Thrombosis	0	0	0	0	0	1 (0.5)	0	0
Peripheral Arterial Occlusive Disease	0	1 (0.5)	0	0	0	0	0	0

Data are n (%). Events that occurred as grade 1-2 in at least 10% of patients in either treatment group, and any grade 3, 4, or 5 event.

[a]Skin rashes that were assessed by Investigator or sponsor as possibly, probably, or definitely related to study drug.

[b]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).

Figure Legends

Figure 1. Patient disposition

[a]Of the 109 patients who crossed over to mogamulizumab due to disease progression, 6 patients had worsening disease and/or symptoms that did not meet the criteria for progression per CTCL response criteria (clinical progression).

[b]Patients crossed over due to the following toxicities: fatigue (5); pulmonary embolism (4); thrombocytopenia (3); diarrhea (3); asthenia (2); deep vein thrombosis (1); peripheral neuropathy (1); myalgia (1); blood creatinine increased (1); sepsis syndrome (1); renal failure chronic (1); dysgeusia (1); emotional distress (1); dermatitis (1); skin rash (1).

Note: Efficacy evaluable set was defined as all patients who received the first cycle of treatment (at least one dose) and who had a baseline tumor assessment and at least one post-baseline assessment for response (mogamulizumab n=180; vorinostat n=181).

Figure 2. Progression-free survival by Investigator's assessment

Figure 3. Hazard ratios for progression-free survival based on Investigator's assessment by predefined subgroups

Figure 4. Best global and skin* responses

*Best skin response represented by maximum % change in skin mSWAT score.

Note: Two patients in the mogamulizumab arm and 2 patients in the vorinostat arm experienced a >100% change in mSWAT.

mSWAT=modified Severity Weighted Assessment Tool.

Figure 1. Patient disposition

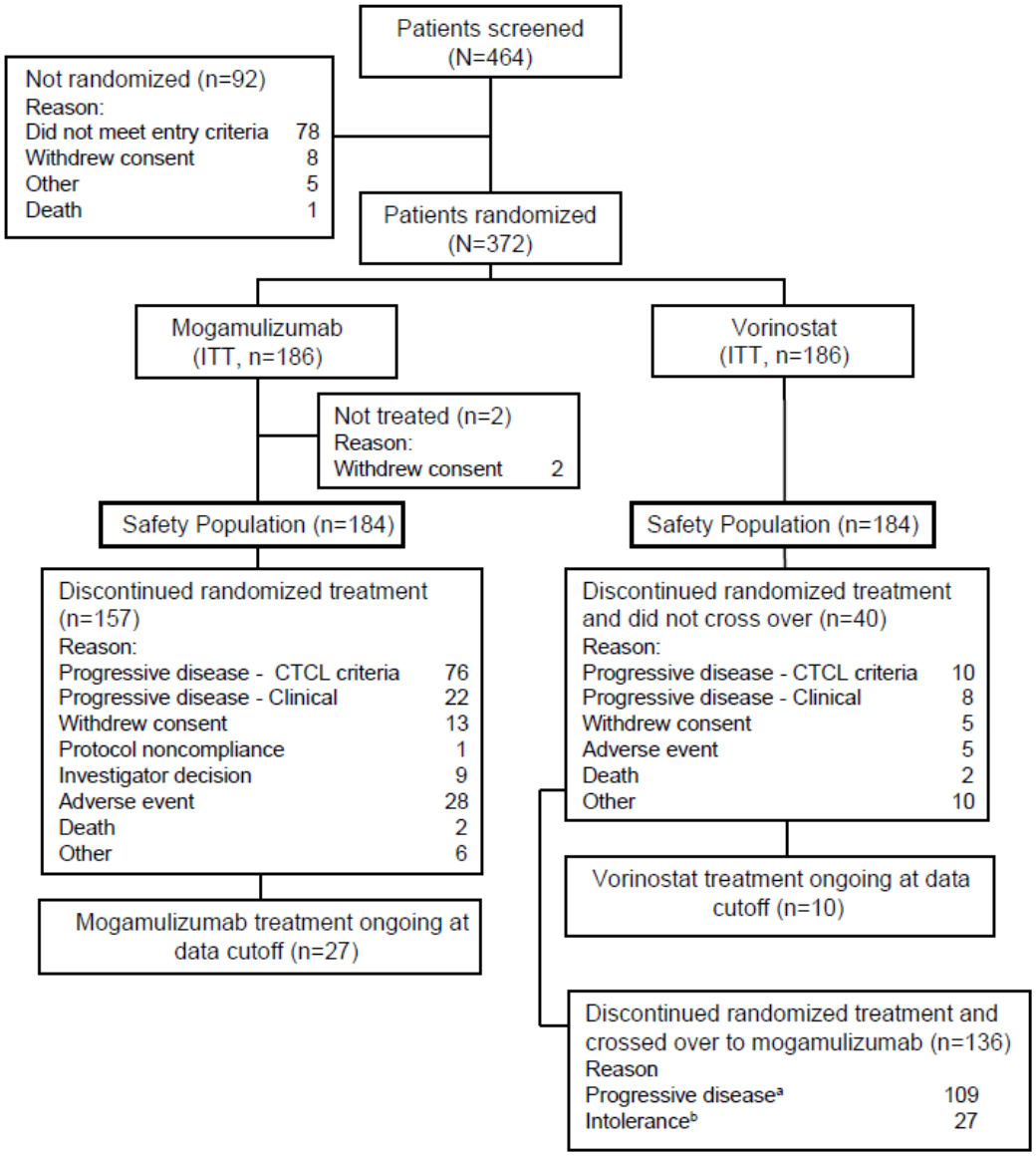

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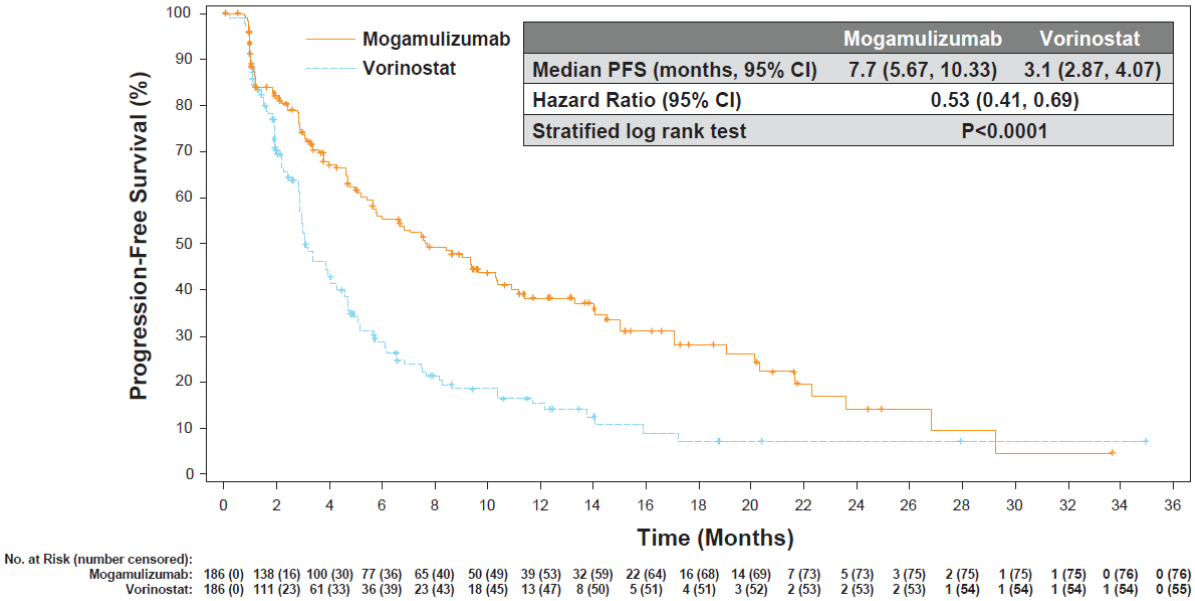
Figure 2. Progression-free survival by Investigator's assessment



	Mogamulizumab	Vorinostat
Median PFS (months, 95% CI)	7.7 (5.67, 10.33)	3.1 (2.87, 4.07)
Hazard Ratio (95% CI)	0.53 (0.41, 0.69)	
Stratified log rank test	P<0.0001	

No. at Risk (number censored):

Mogamulizumab:	186 (0)	138 (16)	100 (30)	77 (36)	65 (40)	50 (49)	39 (53)	32 (59)	22 (64)	16 (68)	14 (69)	7 (73)	5 (73)	3 (75)	2 (75)	1 (75)	1 (75)	0 (76)	0 (76)
Vorinostat:	186 (0)	111 (23)	61 (33)	36 (39)	23 (43)	18 (45)	13 (47)	8 (50)	5 (51)	4 (51)	3 (52)	2 (53)	2 (53)	2 (53)	1 (54)	1 (54)	1 (54)	1 (54)	0 (55)

Figure 3. Hazard ratios for progression-free survival based on Investigator's assessment by predefined subgroups

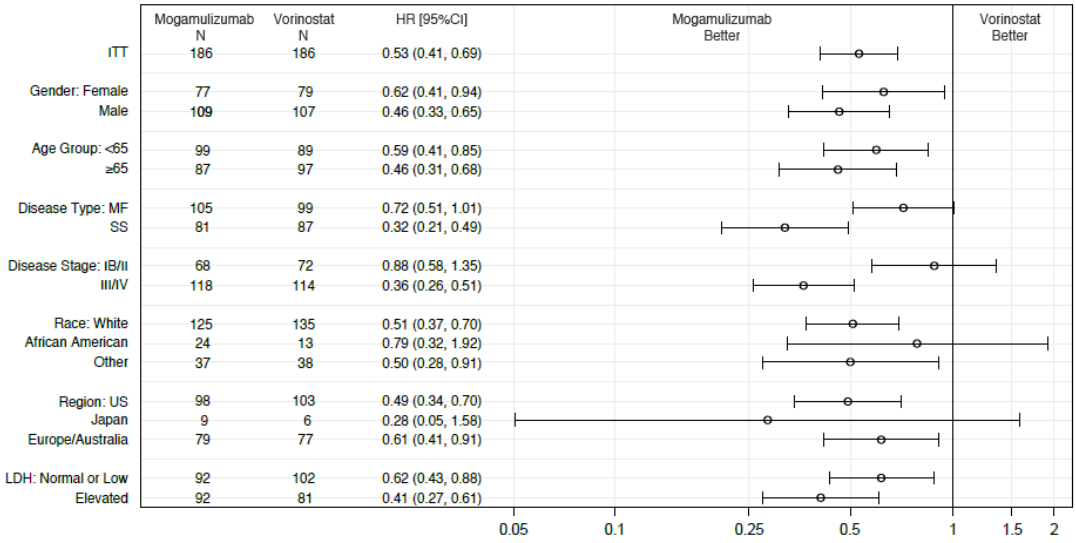
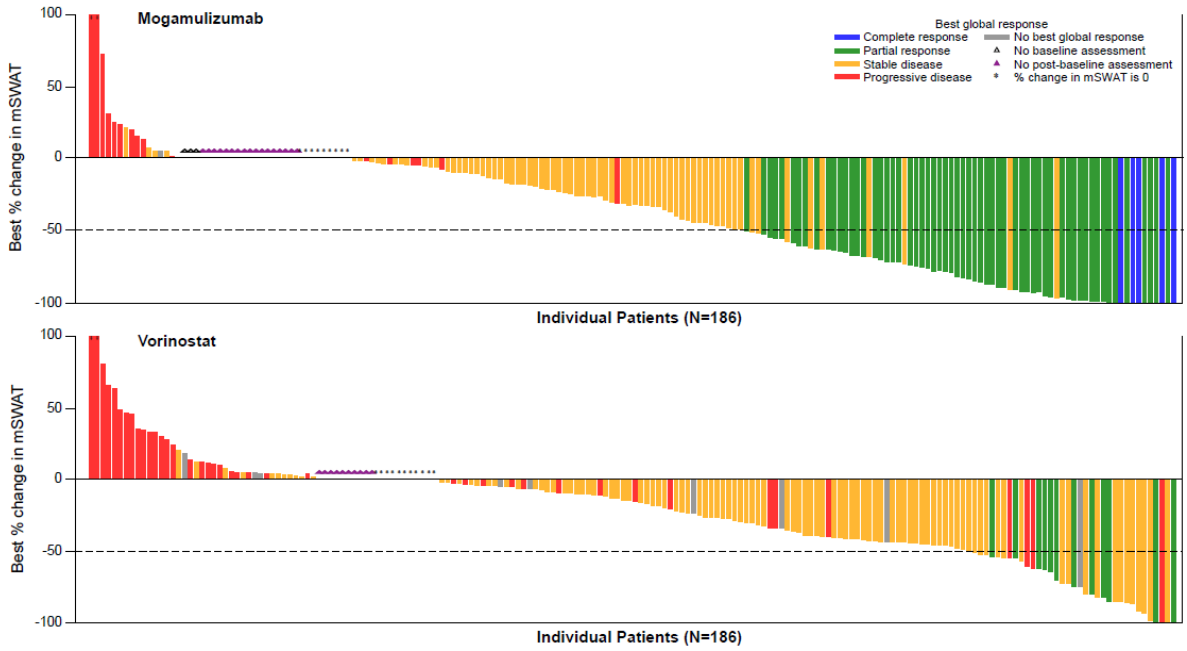


Figure 4. Best global and skin* responses



*Best skin response represented by maximum % change in skin mSWAT score.
Note: Two patients in the mogamulizumab arm and 2 patients in the vorinostat arm experienced a >100% change in mSWAT.

mSWAT=modified Severity Weighted Assessment Tool.