ORIGINAL ARTICLE

Efficacy and safety of mogamulizumab by patient baseline blood tumour burden: a post hoc analysis of the MAVORIC trial

R.A. Cowan,[1,*] J.J. Scarisbrick,[2] P.L. Zinzani,[3,4] J.P. Nicolay,[5] L. Sokol,[6] L. Pinter-Brown,[7] P. Quaglino,[8] L. Iversen,[9] R. Dummer,[10] A. Musiek,[11] F. Foss,[12] T. Ito,[13] J-P. Rosen,[14] M.C. Medley[14]

[1]Christie Hospital Foundation NHS Trust, University of Manchester, Manchester, UK
[2]University Hospital Birmingham, Birmingham, UK
[3]IRCCS Azienda Ospedaliero, Universitaria di Bologna, Bologna, Italia
[4]Istituto di Ematologia 'Seràgnoli', Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università degli Studi, Bologna, Italia
[5]University Medical Centre Mannheim, Mannheim, Germany
[6]Moffitt Cancer Center, Tampa, FL, USA
[7]Chao Family Comprehensive Cancer Center, University of California-Irvine, Orange, CA, USA
[8]University of Turin, Turin, Italy
[9]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
[10]Universitäts Spital Zürich, Zürich, Switzerland
[11]Division of Dermatology, Washington University in Saint Louis, St. Louis, Missouri, USA
[12]Hematology and Stem Cell Transplantation, Yale School of Medicine, New Haven, Connecticut, USA
[13]Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA
[14]Kyowa Kirin International, Buckinghamshire, UK
*Correspondence: R.A. Cowan. E-mail: richard.cowan5@nhs.net

Abstract

Background Mogamulizumab was compared with vorinostat in the phase 3 MAVORIC trial (NCT01728805) in 372 patients with relapsed/refractory mycosis fungoides (MF) or Sézary syndrome (SS) who had failed ≥1 prior systemic therapy. Mogamulizumab significantly prolonged progression-free survival (PFS), with a superior objective response rate (ORR) vs. vorinostat.

Objectives This post hoc analysis was performed to evaluate the effect of baseline blood tumour burden on patient response to mogamulizumab.

Methods PFS, ORR, time to next treatment (TTNT), skin response (modified Severity-Weighted Assessment Tool [mSWAT]) and safety were assessed in patients stratified by blood classification (B0 [n = 126], B1 [n = 62], or B2 [n = 184], indicating increasing blood involvement).

Results Investigator-assessed PFS was longer for mogamulizumab versus vorinostat across all blood classes, significantly so for B1 and B2 patients. ORR was higher with mogamulizumab than with vorinostat in all blood classification groups and more markedly so with escalating B class (B0: 15.6% vs. 6.5%, P = 0.0549; B1: 25.8% vs. 6.5%, P = 0.2758; B2: 37.4% vs. 3.2%, P < 0.0001). TTNT was significantly longer for patients treated with mogamulizumab versus vorinostat with B1 (12.63 vs. 3.07 months; HR 0.32 [95% CI 0.16–0.67]; P = 0.0018) and B2 (13.07 vs. 3.53 months; HR 0.30 [95% CI 0.21–0.43]; P < 0.0001) blood involvement. In the mogamulizumab arm, 81 patients (43.5%) had ≥50% change in the mSWAT vs. 41 patients (22.0%) with vorinostat; mSWAT improvements with mogamulizumab occurred most often in B1 and B2 patients. Rapid, sustained reductions were seen in $CD4^+CD26^-$ cell counts and CD4:CD8 ratios in mogamulizumab patients for all B classes. Treatment-emergent adverse events were less frequent overall with mogamulizumab and similar in frequency regardless of B class.

Conclusions This post hoc analysis indicates greater clinical benefit with mogamulizumab vs. vorinostat in patients with MF and SS classified as having B1 and B2 blood involvement.

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Conflict of Interest

RC is a consultant for Kyowa Kirin and served on an advisory board for Helsinn. JJS is a consultant for Kyowa Kirin, Takeda, Recordat, 4SC, Innate Pharma and Helsinn. She received a 1-year educational grant from Kyowa Kirin for work

on quality of life in CTCL. She also has membership on an entity's Board of Directors or advisory committees for Kyowa Kirin, Takeda, 4SC, Innate Pharma, Miragen and Helsinn. PLZ has received honoraria from MSD, Celltrion, Gilead, Janssen-Cilag, BMS and TG Therapeutics. He is also a consultant for MSD, EUSA Pharma, Sanofi and Verastem. He also has membership on an entity's Board of Directors or advisory committees for MSD, Eusa Pharma, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, Immune Design, Celgene, Portola, Roche, Kyowa Kirin, TG Therapeutics, and Verastem. He has also been on a Speakers Bureau for MSD, EUSA Pharma, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Immune Design, Celgene, Portola, Roche, Kyowa Kirin and Verastem. JPN has received honoraria from Pharmaceutical Industries, TEVA, Novartis AG, Biogen GmbH, Almirall Hermal AG, Actelion Pharmaceuticals, UCB Pharma, LaRoche Posay, Takeda Pharmaceuticals and Kyowa Kirin. He is also a consultant for Novartis AG, Biogen GmbH, Almirall Hermal AG, Actelion Pharmaceuticals, Innate Pharma, Kyowa Kirin and Takeda Pharmaceuticals. He has also received grants and personal fees from Pharmaceutical Industries outside of the submitted work. LS is a consultant for Dren Bio and served on an advisory board for Kyowa Kirin, Kymera Therapeutics and EUSA Pharma. LP-B has been an advisory board for Epizyme, Morphosys, Helsinn, Verastem and Actelion. She is also a consultant for Acrotech. PQ has received honoraria from Actelion, Innate Pharma, Takeda, Kyowa Kirin, Helsinn and Therakos. He also been on an advisory board for Actelion, Innate Pharma, Takeda, Kyowa Kirin, Helsinn and Therakos. LI has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen-Cilag, Kyowa Kirin, LEO Pharma, MSD, Novartis, Pfizer, Sun Pharma and UCB. RD is a consultant for Merck Sharp & Dohme, Novartis, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym and Second Genome. AM is an investigator for Menlo, Soligenix, Pfizer, Elorac and miRagen. She has also received honoraria from Kyowa Kirin. She also has a membership on an entity's Board of Directors or advisory committees for Helsinn. FF has received honoraria from Seagen, Mallinckrodt and Kyowa Kirin. She is also a consultant for Miragen. She had also served on a Data Safety Monitoring Board for Celgene. She was also the President of the US Cutaneous Lymphoma Consortium. TI is an employee of Kyowa Kirin, Inc. J-PR is an employee of Kyowa Kirin, Inc. MCM is an employee of Kyowa Kirin, Inc.

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Introduction

Cutaneous T-cell lymphomas (CTCLs) are rare, can cause considerable distress and are potentially life-threatening forms of non-Hodgkin lymphoma that present primarily in the skin. Several subtypes exist, with mycosis fungoides (MF) being the most common, accounting for approximately 60% of all CTCL cases.[1–3] MF is generally an indolent neoplasm characterized by variable type and extent of skin infiltration that may include patches, plaques, tumours and erythroderma.[3] This may be associated with extracutaneous disease. Sézary syndrome (SS) is more aggressive and accounts for <5% of all CTCL cases. With a median survival of only around 3 years,[4] SS is characterized by erythroderma, significant blood involvement and small volume lymphadenopathy.[3]

Diagnosis and staging of MF and SS are based upon multicompartmental assessment of the skin (tumour [T]), lymph nodes (N), visceral organs (metastasis [M]) and peripheral blood (B), referred to collectively as TNMB staging.[5] Blood classifications (B0–2) were formally added to the staging in 2007 based upon the recognition of blood involvement as a prognostic factor and then updated in 2011 to include flow cytometry definitions, with further clarifications made in 2018[5,6] (Table 1). Increasing blood tumour burden has previously been linked with worsening of overall survival (OS), disease-specific survival and an increased risk of disease progression.[4,7] Median survival for patients with B1 levels of blood involvement has been reported at 3.2 years, similar to that for patients with B2 (3.1 years), and also similar to that of patients with SS (3.13 years).[4] Further, the risk of disease progression associated with B1 level blood involvement was found to be around 4.5 times that for B0 patients.[4] The literature however is not clear, and the full significance of B1 level blood involvement remains the subject of further research.

Patients with advanced MF and SS suffer profound negative effects in many aspects of their quality of life secondary to frank skin manifestations, intractable pruritus and sleep disturbance, resulting in erosion of their functional, emotional and social well-being.[8,9] Disease progression while on therapy is common,[10] and patients can cycle through a number of available treatment lines relatively quickly. There is, therefore, an unmet need for treatments with multicompartmental efficacy that provide durable response and are also well tolerated.

Mogamulizumab (KW-0761; Kyowa Kirin, Tokyo, Japan) is a first-in-class defucosylated, humanized, IgG-kappa monoclonal antibody that selectively binds to C-C chemokine receptor 4

Table 1 Blood classification by flow cytometry

Blood classification stage	Description
B0	<250/μL, or <15% $CD4^+CD26^-$ or $CD4^+CD7^-$ cells by flow cytometry
B1	≥250/μL and <1000/μL, or ≥15% $CD4^+CD26^-$ or $CD4^+CD7^-$ cells by flow cytometry
B2	≥1000/μL Sézary cells with positive clones matching that of the skin, or CD4:CD8 ratio ≥10, or $CD4^+CD7^-$ cells ≥40%, or $CD4^+CD26^-$ cells ≥30%

Olsen E, 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(18):2598-2607. https://doi.org/10.1200/JCO.2010.32.0630. Scarisbrick JJ, Hodak E, Bagot M, et al. Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC Cutaneous Lymphoma Task Force. *Eur J Cancer*. 2018;93:47-56.

(CCR4).[11] CCR4 is involved in cell trafficking of lymphocytes to skin[11] and is consistently expressed on the surface of tumour cells in mature T-cell malignancies, including MF and SS[12–15]; CCR4 expression in MF and SS may also indicate a poor prognosis.[15]

In the international, open-label, randomized, controlled, phase 3 MAVORIC trial for patients with relapsed or refractory MF or SS stages IB–IVB who had failed at least one prior systemic therapy, mogamulizumab was compared with vorinostat, an oral histone deacetylase inhibitor.[16] Mogamulizumab significantly prolonged progression-free survival (PFS) and showed superior objective response rates (ORR) compared to vorinostat in these patients.[16] Responses in skin (assessed by the modified Severity-Weighted Assessment Tool [mSWAT]) in patients treated with mogamulizumab and vorinostat were observed in 42% and 16% of patients, respectively, while responses in the blood compartment were observed in 68% and 19% of patients, respectively. When time to compartmental response was assessed, patients treated with mogamulizumab had an early response in blood of 1.1 months compared with 3.0 and 3.3 months in skin and lymph nodes, respectively. The compartmental duration of response with mogamulizumab was 15.5 months in lymph nodes, 20.6 months in skin and 25.5 months in blood.

This post hoc analysis sets out to correlate overall response, PFS and TTNT with the extent of blood involvement at baseline. Skin response and adverse events were also assessed to determine correlation with degree of blood involvement at baseline.

Methods

Study design and patients

The MAVORIC trial (NCT01728805) was conducted in the USA, Europe, Japan and Australia in patients with stage IB–IVB relapsed or refractory MF or SS.[16] The trial was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation's consolidated Good Clinical Practice guideline and any applicable national and local laws and regulations. The protocol was approved by institutional review boards or independent ethics committees at each site. All patients provided written informed consent. Dosing, randomization and outcomes were described previously.[16] Patients were randomized 1:1 to mogamulizumab or vorinostat and stratified by CTCL subtype (MF vs SS) and disease stage (IB–II vs. III–IV). Intravenous mogamulizumab 1.0 mg/kg was given weekly for the first 28-day cycle and then on days 1 and 15 of subsequent cycles. Oral vorinostat 400 mg was given once daily.

Patients continued treatment until disease progression or unacceptable toxicity or intolerance to therapy.[16] Vorinostat-treated patients who experienced disease progression or intolerable toxicity following at least two cycles, despite dose reduction and appropriate management, could cross over to the mogamulizumab treatment arm.

The primary endpoint was investigator-assessed PFS, defined as the time from randomization until disease progression or death from any cause. The proportion of patients achieving an ORR was a secondary endpoint and included only those patients with confirmed global response at two or more successive evaluations at least 8 weeks apart.

Assessments and outcomes

In this post hoc analysis, investigator-assessed PFS, ORR, TTNT, skin response (mSWAT) and frequency of treatment-emergent adverse events (TEAEs) were assessed in patients in each treatment arm stratified by baseline blood classification B0, B1 or B2. In MAVORIC, blood classification was defined according to thresholds set out in international consensus guidelines[5,6] (Table 1).

Global composite response scores, used to assess PFS and ORR for skin and blood were assessed every 4 weeks; response in blood was assessed by flow cytometry using central assessment for standardization, and skin response by mSWAT, as previously described.[6] Lymph node and visceral disease were identified by size criteria and evaluated by computed tomography scans at 4 weeks, then every 8 weeks for the first year and every 16 weeks thereafter.

To evaluate compartmental skin response according to baseline B classification, median percentage change in mSWAT per treatment cycle and best overall response by percentage change in mSWAT were examined. The analyses were limited to the first 12 treatment cycles to ensure patient numbers were sufficient to obtain meaningful results.

In order to better understand the disposition of patients in MAVORIC with respect to their baseline blood tumour burden, and in line with the most recent EORTC recommendations (Scarisbrick 2018), absolute counts by flow cytometry of $CD4^+CD7^-$ and $CD4^+CD26^-$ cells, and CD4:CD8 ratios were assessed for each B class across both treatment arms. A further

analysis of median dynamic (by treatment cycle) blood tumour burden, as represented by the above cell populations, was performed; median values were plotted so as to be less liable to distortion by the wide range of values within each B class category observed in the MAVORIC dataset.

Finally, adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. TEAEs were considered to be adverse events not present prior to treatment start or an adverse event that worsens in intensity or frequency after exposure to treatment and that occurs within the first 90 days after treatment initiation.

Statistical analysis

Kaplan–Meier estimates of median PFS were generated based on the intent-to-treat (ITT) population, which was defined as all patients randomized to each treatment. Associated 95% confidence intervals (CIs) were obtained with the 'proc lifetest' procedure in SAS software using log-log transformation. Treatment comparisons of PFS, as hazard ratios (HRs) and associated 95% CIs, were generated and are based on Cox proportional hazards model with treatment, disease type, disease stage and region as covariates.

Treatment comparisons of ORR (complete response [CR] + partial response [PR]), as risk differences (RD), were calculated, and associated 95% CIs are the exact 95% unconditional CI for the risk difference (mogamulizumab – vorinostat).

TTNT was defined as the duration from randomization to the date of the first new systemic therapy.[17] The length of TTNT was assessed in the overall ITT population and by blood classification group (B0, B1 and B2), and 95% CIs were obtained with SAS 'proc lifetest' using log-log transformation. Treatment comparisons of TTNT, as HRs and 95% CIs, were based on the Cox proportional hazards model with treatment, disease type, disease stage and region as covariates.

Table 2 Baseline characteristics for intent-to-treat set by blood classification

	B0		B1		B2	
	Vorinostat (*n* = 62)	Mogamulizumab (*n* = 64)	Vorinostat (*n* = 31)	Mogamulizumab (*n* = 31)	Vorinostat (*n* = 93)	Mogamulizumab (*n* = 91)
Age (yrs)						
Mean (SD)	58.2 (13.6)	58.5 (12.9)	63.4 (11.7)	57.8 (15.0)	66.6 (11.1)	67.5 (11.4)
Median (min, max)	58.5 (25, 88)	56.5 (26, 84)	65.0 (28, 84)	61.0 (25, 88)	68.0 (40, 89)	69.0 (34, 101)
Age Group						
<65 years, *n* (%)	41 (66.1)	43 (67.2)	14 (45.2)	24 (77.4)	34 (36.6)	32 (35.2)
≥65 years, *n* (%)	21 (33.9)	21 (32.8)	17 (54.8)	7 (22.6)	59 (63.4)	59 (64.8)
Gender						
Female, *n* (%)	19 (30.6)	28 (43.8)	14 (45.2)	9 (29.0)	46 (49.5)	40 (44.0)
Male, *n* (%)	43 (69.4)	36 (56.3)	17 (54.8)	22 (71.0)	47 (50.5)	51 (56.0)
Disease Type						
Mycosis fungoides, *n* (%)	61 (98.4)	63 (98.4)	27 (87.1)	29 (93.5)	11 (11.8)	13 (14.3)
Sézary syndrome, *n* (%)	1 (1.6)	1 (1.6)	4 (12.9)	2 (6.5)	82 (88.2)	78 (85.7)
Clinical Stage						
IB-IIA, *n* (%)	30 (48.4)	26 (40.6)	19 (61.3)	10 (32.3)	0 (0)	0 (0)
IIB-IV, *n* (%)	32 (51.6)	38 (59.4)	12 (38.7)	21 (67.7)	93 (100.0)	91 (100.0)
T-Score						
1, *n* (%)	1 (1.6)	1 (1.6)	1 (3.2)	0 (0)	2 (2.2)	0 (0)
2, *n* (%)	30 (48.4)	26 (40.6)	19 (61.3)	10 (32.3)	20 (21.5)	19 (20.9)
3, *n* (%)	20 (32.3)	27 (42.2)	6 (19.4)	8 (25.8)	3 (3.2)	3 (3.3)
4, *n* (%)	11 (17.7)	10 (15.6)	5 (16.1)	13 (41.9)	68 (73.1)	69 (75.8)
ABS $CD4^+CD7^-$ (/μL), *n*	59	63	30	31	89	90
Mean	182	142	314	262	3791	4955
Median	110	100	200	170	1070	1270
ABS $CD4^+CD26^-$ (/μL), *n*	59	63	30	31	89	90
Mean	203	164	330	333	4986	5113
Median	140	130	260	250	2350	2150
CD4:CD8 ratio, *n*	59	63	31	31	89	90
Mean	3.333	2.960	3.472	3.333	48.140	109.572
Median	2.990	2.300	2.930	2.740	19.430	22.430

ABS, absolute blood count; T-score, degree of skin involvement according to TNMB staging; SD, standard deviation

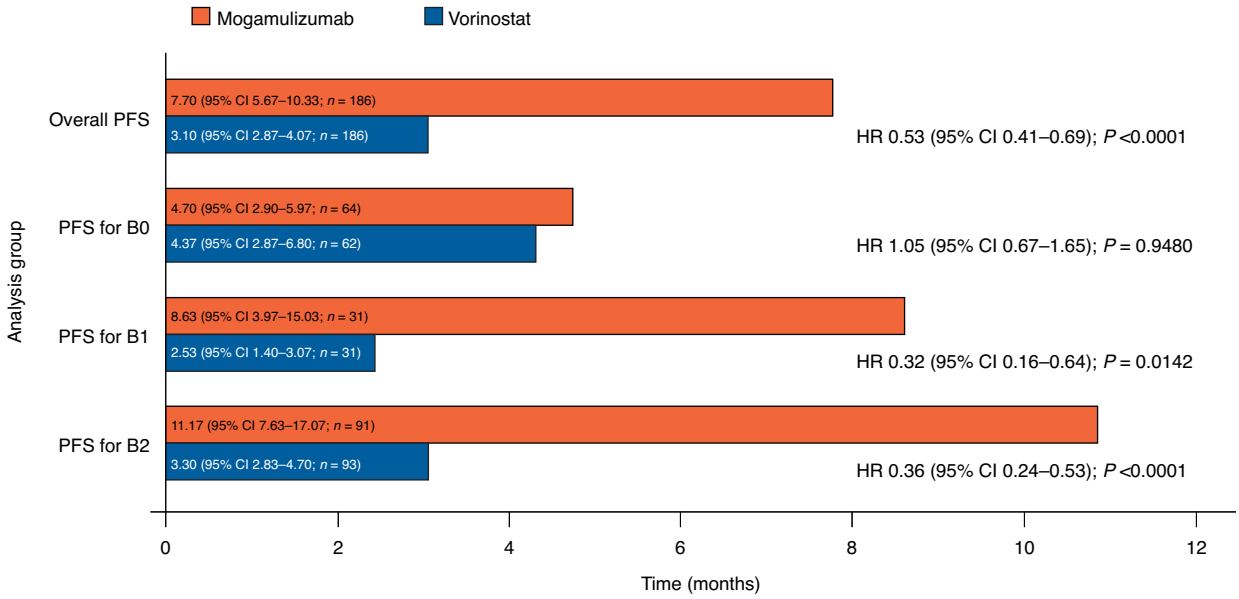


Figure 1 Investigator-assessed progression-free survival (PFS) in the overall population (Kim 2018) and by blood tumour classification. B0: <15% $CD4^+CD26^-$ or $CD4^+CD7^-$ cells by flow cytometry. B1: ≥15% $CD4^+CD26^-$ or $CD4^+CD7^-$ cells by flow cytometry. B2: ≥1000 mg/L Sézary cells with positive clone, CD4/CD8 ratio ≥ 10, $CD4^+CD7^-$ cells ≥40%, or $CD4^+CD26^-$ cells ≥30%. CI, confidence interval; HR, hazard ratio.

Results

Patients

The ITT population contained a total of 186 patients in the mogamulizumab arm (105 patients with MF and 81 with SS) and 186 in the vorinostat arm (99 with MF and 87 with SS). In total, 136/186 patients crossed over from vorinostat to mogamulizumab, 109 due to disease progression and 27 due to toxicity.

In the mogamulizumab group, 64, 31 and 91 patients were classified as B0, B1 and B2, respectively (Table 2). In the vorinostat group, 62, 31 and 93 patients were classified as B0, B1 and B2, respectively.

When baseline blood tumour burden of the MAVORIC population was analysed by absolute cell counts, median $CD4^+CD7^-$ and $CD4^+CD26^-$ counts were found to be low, 200 (range: 40–1460) and 260 (range: 70–1220) for mogamulizumab, and 170 (range: 20–1690) and 250 (range:40–2030) for vorinostat, respectively, for the B1 population (Table 2). Patients were allocated a B class using the highest of the two absolute counts of either aberrant cell population (or CD4:CD8 ratio for B2); hence, the lower bound for an individual marker could sit outside of the allowed range (250–1000 for B1), as long as the other marker was within said range for an individual patient.

Efficacy by blood classification

After a median follow-up of 17.0 months, the primary analysis of investigator-assessed PFS was significantly greater for mogamulizumab than vorinostat in the overall population of MAVORIC (7.70 vs. 3.10 months, respectively; $P < 0.0001$)[16] (Fig. 1). When stratified by blood classification, investigator-assessed PFS appeared longer for mogamulizumab, as compared to vorinostat, across all B classes; the difference was significant in patients with B1 (8.63 vs. 2.53 months; HR 0.32 [95%CI: 0.16–0.64]; $P < 0.0142$) and B2 (11.17 vs. 3.30 months; HR 0.36 [95% CI: 0.24–0.53]; $P < 0.0001$) blood involvement. PFS was not significantly different between treatment arms (4.70 vs. 4.37 months; HR 1.05 [95% CI: 0.67–1.65]; $P = 0.9480$) in patients with B0 disease (Fig. 1).

The ORR in the overall study population of MAVORIC was significantly greater for mogamulizumab than vorinostat (28.0% vs. 4.8%, respectively; $P < 0.0001$) (Kim 2018; Table 3). When stratified by patient baseline blood classification, the ORR appeared higher with mogamulizumab than vorinostat in all blood classification groups and was significantly so in patients with B2 disease (37.4% vs. 3.2%; RD 34.1 [95% CI: 22.9–45.2]; $P < 0.0001$; Table 3). For patients classified as B1, a trend was shown (25.8% vs. 6.5% for mogamulizumab and vorinostat, respectively; RD 19.4 [95% CI: 0.6–38.6]; $P = 0.2758$). The ORR in patients with B0 blood involvement was not significantly

Table 3 Investigator-assessed ORR overall[16] and by blood classification

	Vorinostat	Mogamulizumab	*P* value*
n	186	186	
Overall ORR % (95% CI)†	4.8 (2.2–9.0)	28.0 (21.6–35.0)	<0.0001
Investigator-assessed ORR by blood classification, % (95% CI)			
n	62	64	
B0	6.5 (1.8–15.7)	15.6 (7.8–26.9)	0.0549
Risk Difference (95% CI)‡	9.2 (−2.4–21.2)		
n	31	31	
B1	6.5 (0.8–21.4)	25.8 (11.9–44.6)	0.2758
Risk Difference (95% CI)‡	19.4 (0.6–38.6)		
n	93	91	
B2	3.2 (0.7–9.1)	37.4 (27.4–48.1)	<0.0001
Risk Difference (95% CI)‡	34.1 (22.9–45.2)		

CI, confidence interval; ORR, overall response rate.
**P* value is obtained from Cochran-Mantel-Haenszel test adjusting for disease type, disease stage and region.
†95% confidence interval for response rate is the exact 95% confidence interval.
‡Risk difference (ie, 'attributable risk') is the excess 'risk' of a patient achieving an overall response with mogamulizumab versus vorinostat. The 95% confidence interval for risk difference is the exact 95% unconditional confidence interval for the risk difference (mogamulizumab–vorinostat).

different between treatment arms (15.6% vs. 6.5%; RD 9.2 [95% CI: −2.4–21.2]; $P = 0.0549$).

Time to next treatment

Overall median TTNT in MAVORIC was significantly superior for mogamulizumab vs. vorinostat (11.0 vs 3.5 months; $P < 0.0001$)[17] (Table 4). In patients with B0 classification, TTNT was not significantly different between the treatment arms (6.77 vs. 4.13 months; HR 0.68 [95% CI 0.45–1.02]; $P = 0.0992$), but it was significantly longer for mogamulizumab in patients with B1 (12.63 vs. 3.07 months; HR 0.32 [95% CI 0.16–0.67]; $P = 0.0018$) and B2 (13.07 vs. 3.53 months; HR 0.30 [95% CI 0.21–0.43]; $P < 0.0001$) blood involvement, exceeding one year in both groups (Table 4; Fig. 2).

Skin response

Over 12 cycles of treatment, mogamulizumab-treated patients with blood involvement (B1 or B2) experienced greater mSWAT skin score improvement than patients with no blood involvement (B0) (Fig. 3a). The change in mSWAT score over time in patients treated with vorinostat seemed to have little-to-no correlation with blood classification (Fig. 3b).

Complete or partial responses in skin seen with mogamulizumab treatment occurred more often in patients with B1 (14/31 [45.2%])

Table 4 Time to next treatment (TTNT)† in the overall population (Kim 2019) and by blood classification

	Vorinostat	Mogamulizumab	*P* value
n	186	186	
TTNT in overall population, median (95% CI), months	3.5 (3.1–4.3)	11.0 (8.8–12.6)	<0.0001
TTNT by blood classification, median (95% CI), months			
n	49	46	
B0	4.13 (3.00–5.60)	6.77 (4.87–8.80)	0.0992
Hazard Ratio (95% CI)	0.68 (0.45–1.02)		
n	25	18	
B1	3.07 (2.13–5.13)	12.63 (6.63–20.57)	0.0018
Hazard Ratio (95% CI)	0.32 (0.16–0.67)		
n	82	52	
B2	3.53 (2.83–4.27)	13.07 (11.00–18.80)	<0.0001
Hazard Ratio (95% CI)	0.30 (0.21–0.43)		

95% confidence intervals are obtained from SAS 'proc lifetest' using log-log transformation.
Hazard ratio and 95% confidence intervals are based on Cox proportional hazards model with treatment, disease type, disease stage and region as covariates. *P* value (two-sided) is obtained from a stratified log rank test with disease type, disease stage and region as stratification factors.
CI, confidence interval.
†TTNT was defined as duration from randomization to the date of first new systemic therapy. Mogamulizumab, which was used as the crossover drug, is regarded as systemic therapy. Patients who did not receive any subsequent therapy were censored at last survival follow-up. The number of patients censored in each blood class was B0: 18 and 13; B1: 13 and 6; B2: 39 and 11; for mogamulizumab and vorinostat, respectively.

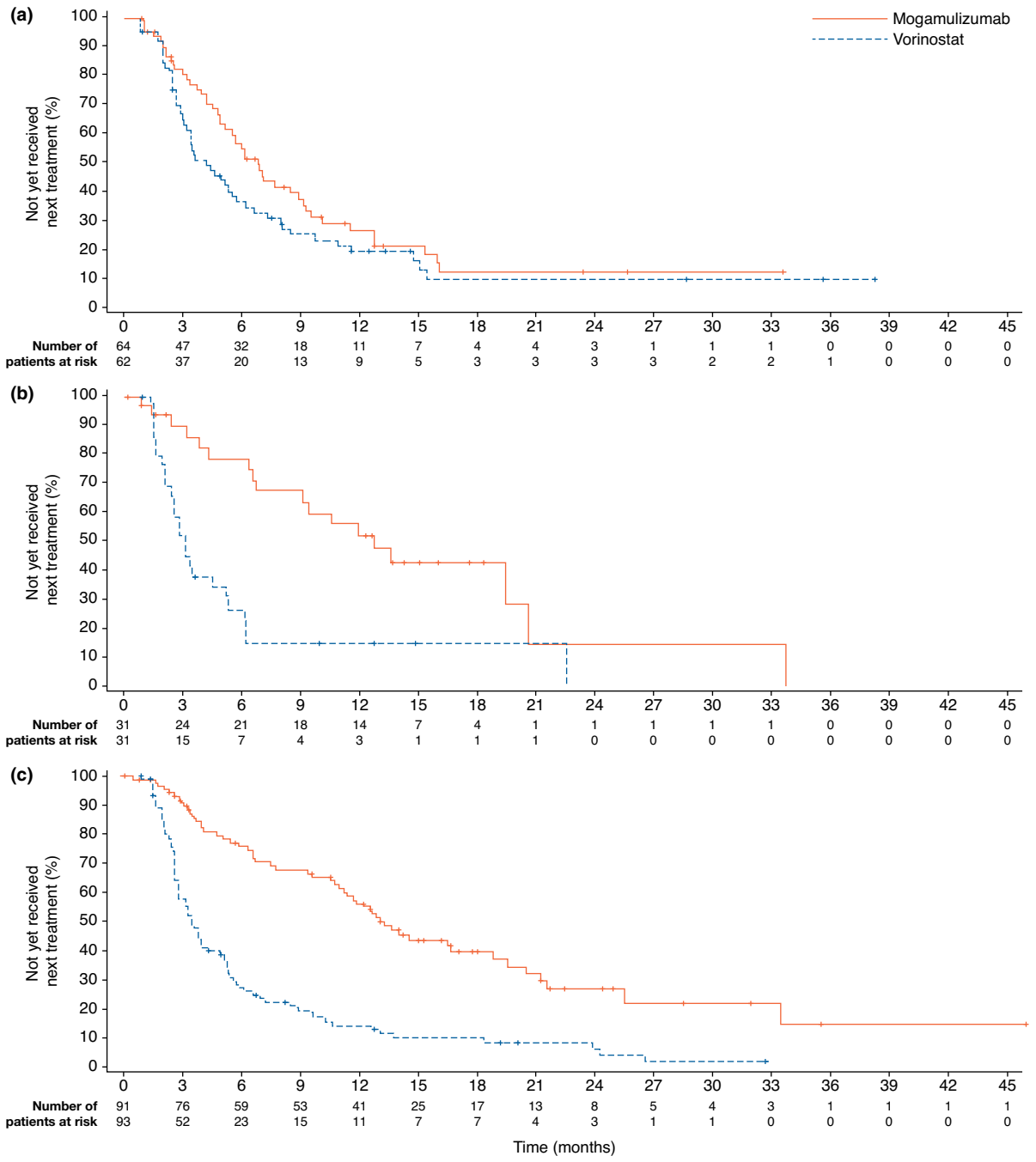


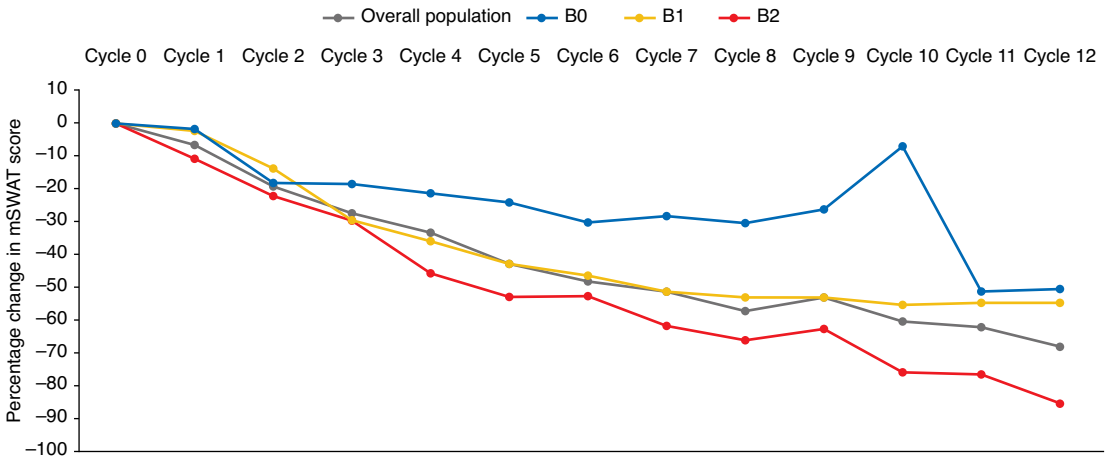
Figure 2 Kaplan–Meier curve of time to next treatment by treatment and blood tumour classification. (a) Blood classification B0. (b) Blood classification B1. (c) Blood classification B2.

and B2 (51/91 [56.0%]) level blood involvement, compared to B0 (16/64 [25.0%]). Additionally, 16/91 (17.6%) patients with B2 blood classification treated with mogamulizumab had a 100% improvement (Fig. 3c) compared to 3/93 (3.2%) patients with B2 blood classification treated with vorinostat (Fig. 3d).

Dynamic analysis of blood tumour burden

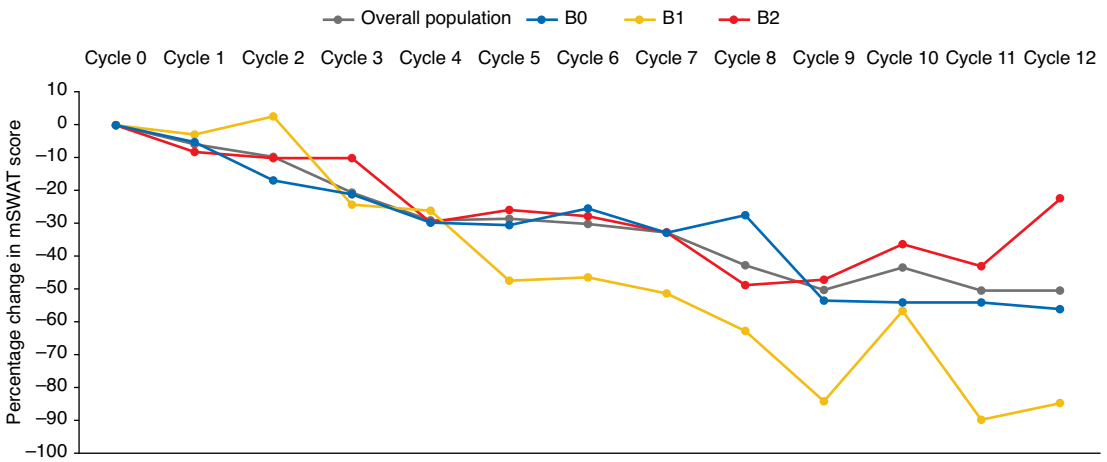
Analysis of median absolute $CD4^{+}CD26^{-}$ cell counts showed a rapid reduction of cell counts by Cycle 1 across all blood classes in mogamulizumab patients, but not vorinostat patients (Fig. 4a). This reduction was sustained throughout

(a)



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12
Overall population	186	174	155	129	112	103	96	88	81	75	62	55	45
B0	64	61	51	39	32	27	21	19	14	12	9	7	7
B1	31	30	25	21	19	17	19	18	16	15	13	11	9
B2	91	83	79	69	61	59	56	51	51	48	40	37	29
MF, *n* (%)	105 (56.5)												20 (44.4)
SS, *n* (%)	81 (43.5)												25 (55.6)
T4, *n* (%)	92 (49.5)												31 (68.9)

(b)



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12
Overall population	186	174	136	96	66	58	48	39	34	27	25	22	19
B0	62	54	44	35	26	23	20	15	14	10	9	9	8
B1	31	29	19	13	8	6	6	4	4	3	4	2	3
B2	93	91	73	48	32	29	22	20	16	14	12	11	8
MF, *n* (%)	99 (53.2)												14 (73.3)
SS, *n* (%)	87 (46.8)												5 (26.3)
T4, *n* (%)	84 (45.2)												5 (26.3)

Figure 3 Skin response based on the modified Severity-weighted Assessment Tool (mSWAT) by treatment and blood classification. (a) Percentage change in mSWAT over time for patients treated with mogamulizumab. (b) Percentage change in mSWAT over time for patients treated with vorinostat. (c) Best overall response in mSWAT score by individual patients treated with mogamulizumab. (d) Best overall response in mSWAT score by individual patients treated with vorinostat. MF: mycosis fungoides; SS: Sézary syndrome.

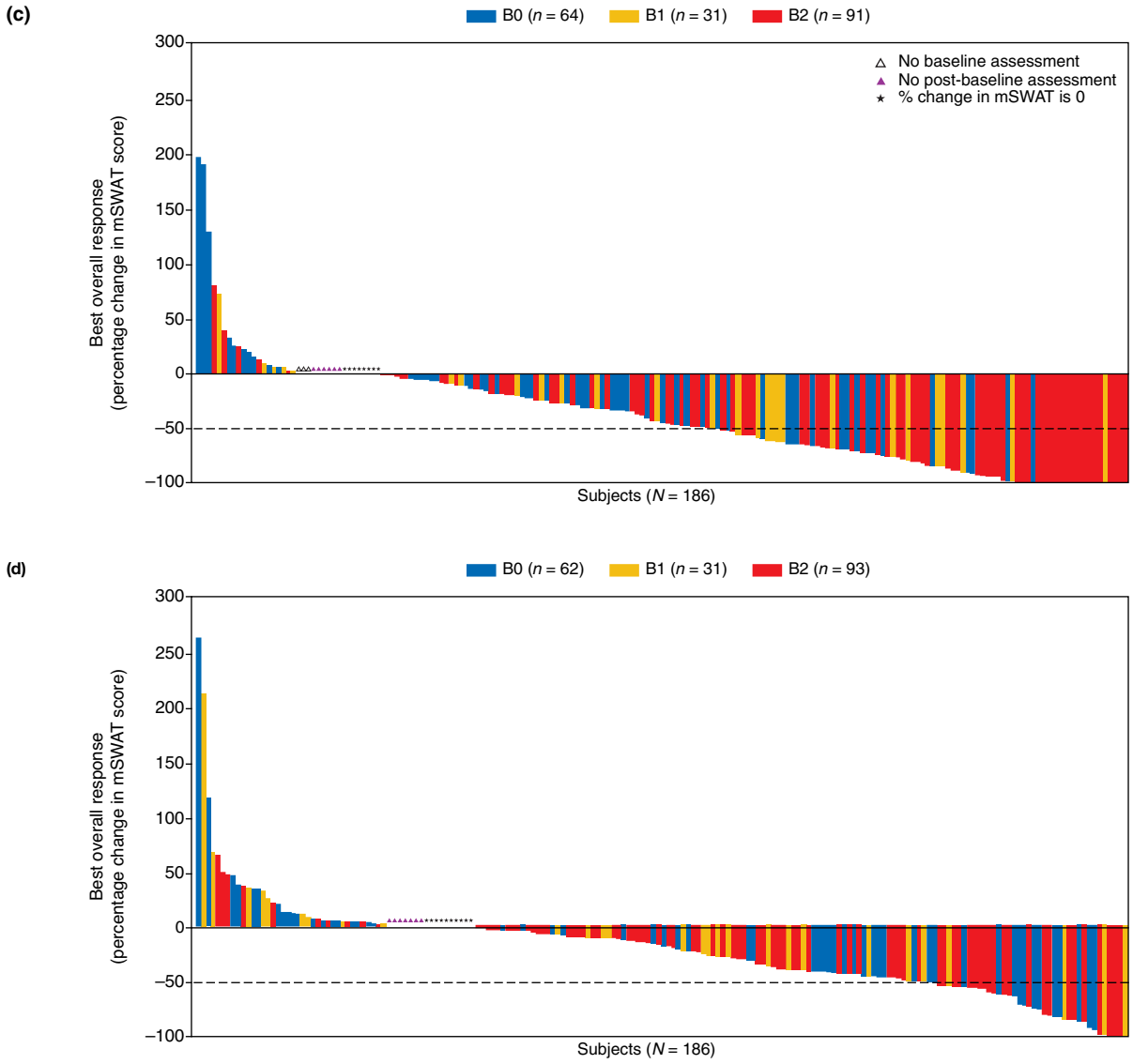


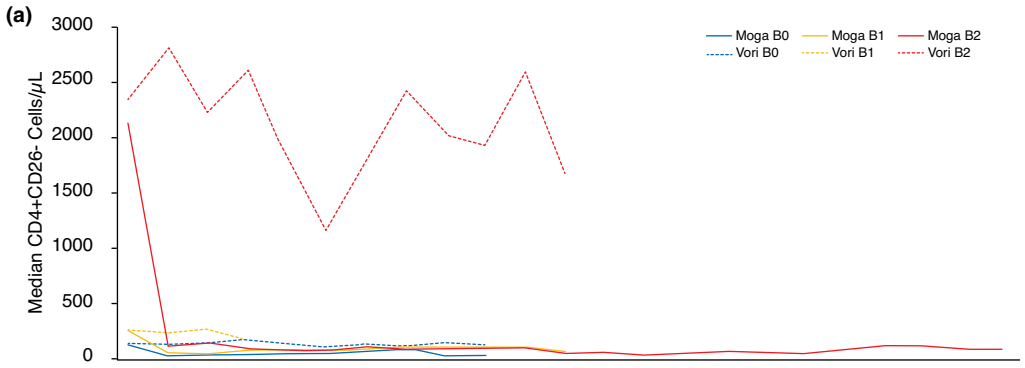
Figure 3 Continued

mogamulizumab treatment cycles and never reached pretreatment values; this sustained reduction was most marked in B2 patients (Fig. 4b,c). Interestingly, the B2 population saw not only the largest reduction of absolute $CD4^{+}CD26^{-}$ cell counts, but also the largest proportional reduction, measured by median percentage change from baseline (Fig. 5).

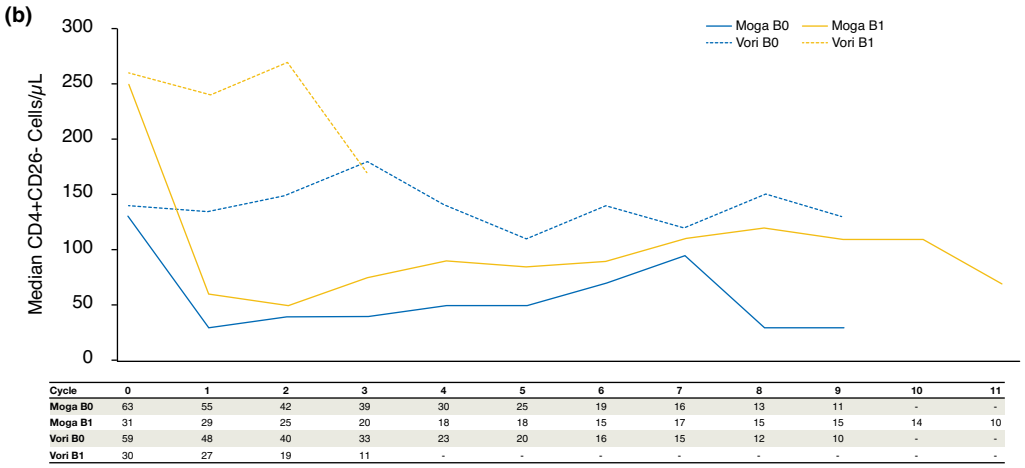
CD4:CD8 ratios were also rapidly reduced by Cycle 1 of treatment with mogamulizumab across all blood classes (Fig. 6a); this reduction was maintained or further improved in B1 (Fig. 6b) and B2 (Fig. 6c) patients across subsequent evaluable cycles. In vorinostat patients with B0 and B1 blood involvement (Fig. 6b), CD4:CD8 ratios gradually increased across evaluable cycles, and there was an unpredictable response in B2 patients (Fig. 6c). Proportional reductions in CD4:CD8 ratio increased with escalating B class in mogamulizumab-treated patients, where no trend existed for vorinostat (Fig. 7).

Treatment-emergent adverse events

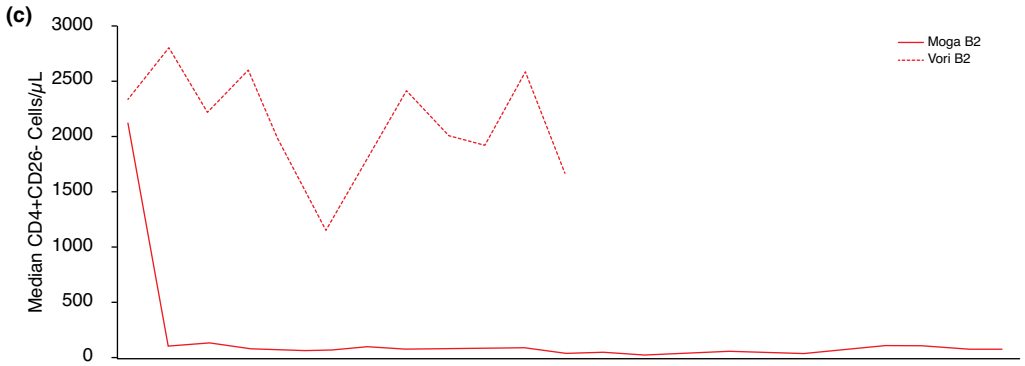
Any grade treatment-related TEAEs occurred at similar rates regardless of blood involvement and were numerically lower for mogamulizumab than for vorinostat at each blood classification level (Table 5). Grade ≥3, treatment-related TEAEs were



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Moga B0	63	55	42	39	30	25	19	16	13	11	-	-	-	-	-	-	-	-	-	-	-	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10	-	-	-	-	-	-	-	-	-	-	-
Moga B2	90	80	70	62	59	57	55	49	51	46	36	32	27	27	25	22	20	16	14	11	12	12	10
Vori B0	59	48	40	33	23	20	16	15	12	10	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B2	89	79	63	38	31	21	21	19	16	13	12	11	-	-	-	-	-	-	-	-	-	-	-

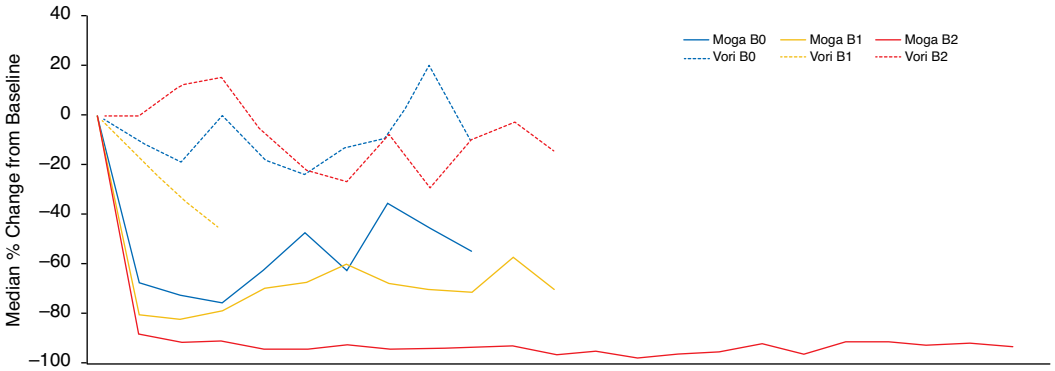


Cycle	0	1	2	3	4	5	6	7	8	9	10	11
Moga B0	63	55	42	39	30	25	19	16	13	11	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10
Vori B0	59	48	40	33	23	20	16	15	12	10	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	11
Moga B2	90	80	70	62	59	57	55	49	51	46	36	32	27	27	25	22	20	16	14	11	12	12	10
Vori B2	9	79	63	38	31	21	21	19	16	13	12	11	-	-	-	-	-	-	-	-	-	-	-

Figure 4 Median absolute $CD4^{+}CD26^{-}$ cell count by Cycle by baseline blood classification. (a) B0–B2 (b) B0 and B1 (c) B2.



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Moga B0	63	54	42	38	30	24	19	16	13	11	-	-	-	-	-	-	-	-	-	-	-	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10	-	-	-	-	-	-	-	-	-	-	-
Moga B2	90	79	69	61	58	56	54	49	50	45	35	31	26	26	25	22	20	16	14	11	12	12	10
Vori B0	59	45	40	33	23	20	16	15	12	10	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B2	89	75	60	36	29	21	20	18	15	13	12	11	-	-	-	-	-	-	-	-	-	-	-

Figure 5 Median by Cycle percentage change from baseline in absolute $CD4^{+}CD26^{-}$ cell count.

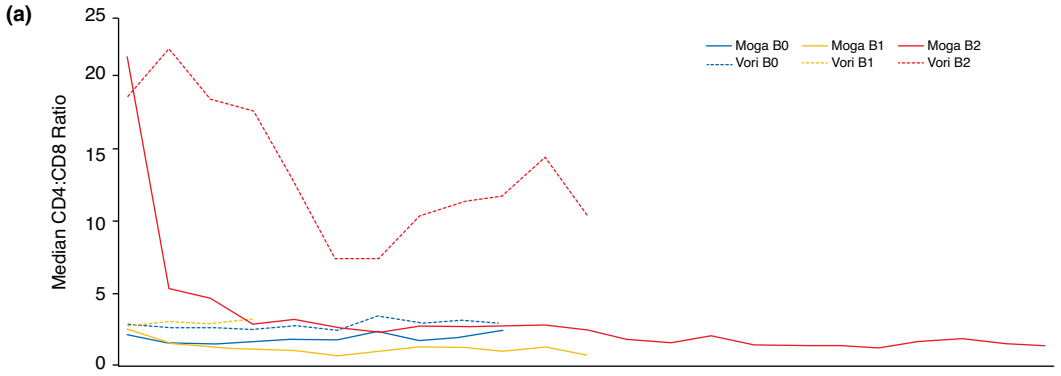
numerically lower for mogamulizumab than for vorinostat in each blood classification category and did not seem to be related to increasing levels of blood involvement (Table 5). In patients with B0 blood classification, there were no Grade 5 treatment-related TEAEs in either treatment group. Three of 31 patients (9.7%) with B1 classification in the vorinostat group, and 1 of 91 patients (1.1%) with B2 blood classification in the mogamulizumab group, experienced Grade 5 events. Of note, only two of 184 patients (1.1%) treated with mogamulizumab in MAVORIC experienced tumour lysis syndrome (TLS), one Grade 1 and one Grade 3; both patients were classified as B2 at baseline. A small number of patients (n = 8) in both the mogamulizumab and vorinostat treatment arms received TLS prophylaxis as this was not prohibited per the protocol for the MAVORIC study. However, TLS prophylaxis is not mandated in the approved prescribing information for mogamulizumab as the incidence of TLS was very low even for patients with Sézary syndrome with significant blood involvement at baseline.

Discussion

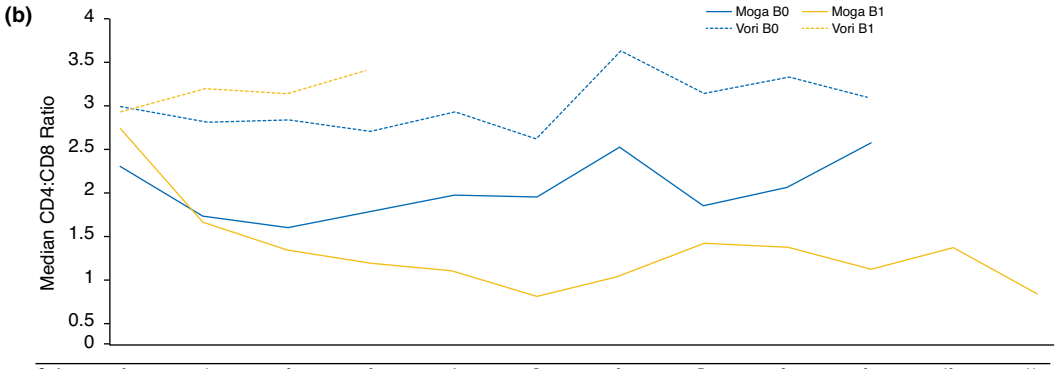
This post hoc analysis of the MAVORIC trial showed that patients with blood involvement, defined as B1 and B2, treated with mogamulizumab had improved outcomes compared to patients treated with vorinostat. In the previously published results of the trial (Kim 2018), mogamulizumab showed significantly greater benefit in investigator-assessed PFS, based upon global composite scores of response in each disease compartment (i.e. skin, blood and lymph nodes), compared with vorinostat. In this post hoc analysis assessing outcomes according to blood classification, PFS was significantly longer in both B1 and B2 patients treated with mogamulizumab compared to similar patients treated with vorinostat. The ORR was 28.0% for patients treated with mogamulizumab compared to 4.8% for patients treated with vorinostat.[16] In this post hoc analysis, ORR with mogamulizumab treatment increased with increasing baseline blood tumour burden and was again consistently superior to that for vorinostat across all B classes.

In clinical trials of MF and SS, TTNT is becoming an increasingly meaningful endpoint as it takes into account patients for whom the disease progresses, but to a minimal degree and with an indolent course, and as such does not require immediate intervention.[18] The historical median TTNT for patients with MF and SS treated with systemic therapies is 5.4 months.[19] In the MAVORIC trial, TTNT for patients treated with mogamulizumab was 11.0 months.[17] When stratified by blood classification, TTNT was significantly longer for patients with B1 and B2 blood classification treated with mogamulizumab compared to vorinostat, reflecting the overall improvement in response rate and PFS in these groups and exceeded the whole cohort median TTNT.

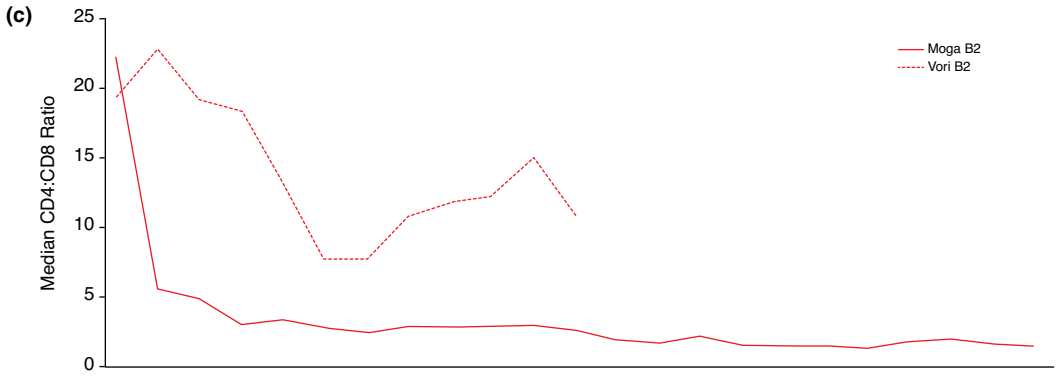
Increasing blood tumour burden in patients with MF or SS is recognized as a negative prognostic factor for survival and risk of progression.[5,6] A key finding of the present post hoc analysis is the improved efficacy outcomes in patients with B1 and B2 blood classification after treatment with mogamulizumab. From the demographic data (Table 2), it can be seen that patients classified as B1 in the MAVORIC trial had relatively low mean and median absolute $CD4^{+}CD7^{-}$ and $CD4^{+}CD26^{-}$ counts within the full range allowed for in recent guidelines and recommendations (250 to <1000 cells/μL).[5,6] It should be noted that in MAVORIC when $CD4^{+}CD7^{-}$ and $CD4^{+}CD26^{-}$ counts were both performed, the larger value was used to assign blood class. However, patients classified as B1 who were treated with mogamulizumab often experienced results similar to those classified as B2, suggesting



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Moga B0	63	55	42	39	30	25	19	16	13	11	-	-	-	-	-	-	-	-	-	-	-	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10	-	-	-	-	-	-	-	-	-	-	-
Moga B2	90	80	70	62	59	57	55	49	51	46	36	32	27	27	25	22	20	16	14	11	12	12	10
Vori B0	59	48	40	33	23	20	16	15	12	10	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B2	89	79	63	38	31	21	21	19	16	13	12	11	-	-	-	-	-	-	-	-	-	-	-

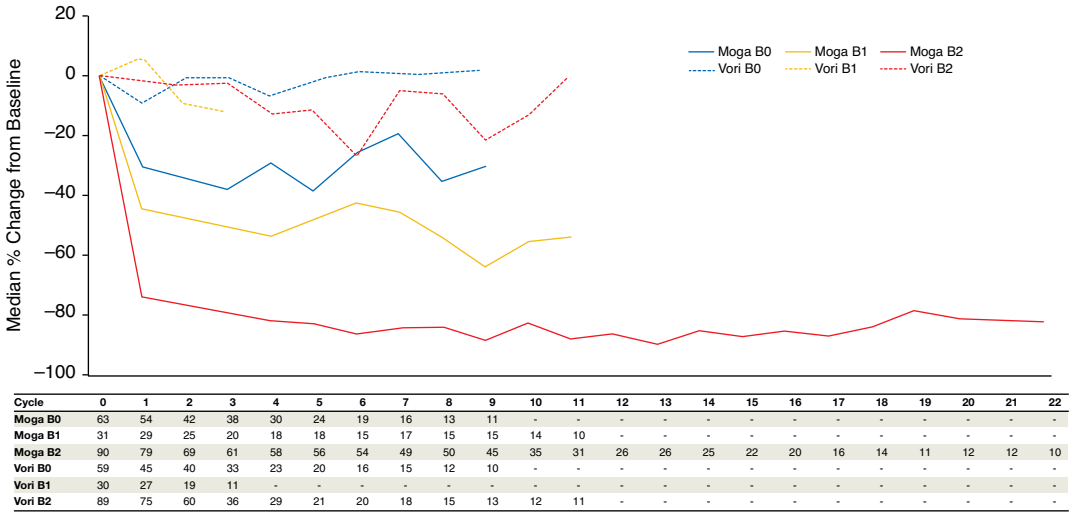


Cycle	0	1	2	3	4	5	6	7	8	9	10	11
Moga B0	63	55	42	39	30	25	19	16	13	11	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10
Vori B0	59	48	40	33	23	20	16	15	12	10	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Moga B0	63	55	42	39	30	25	19	16	13	11	-	-	-	-	-	-	-	-	-	-	-	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10	-	-	-	-	-	-	-	-	-	-	-
Moga B2	90	80	70	62	59	57	55	49	51	46	36	32	27	27	25	22	20	16	14	11	12	12	10
Vori B0	59	48	40	33	23	20	16	15	12	10	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B2	89	79	63	38	31	21	21	19	16	13	12	11	-	-	-	-	-	-	-	-	-	-	-

Figure 6 Median CD4:CD8 ratio by Cycle by baseline blood classification. (a) B0–B2 (b) B0 and B1 (c) B2.



Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Moga B0	63	54	42	38	30	24	19	16	13	11	-	-	-	-	-	-	-	-	-	-	-	-	-
Moga B1	31	29	25	20	18	18	15	17	15	15	14	10	-	-	-	-	-	-	-	-	-	-	-
Moga B2	90	79	69	61	58	56	54	49	50	45	35	31	26	26	25	22	20	16	14	11	12	12	10
Vori B0	59	45	40	33	23	20	16	15	12	10	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B1	30	27	19	11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vori B2	89	75	60	36	29	21	20	18	15	13	12	11	-	-	-	-	-	-	-	-	-	-	-

Figure 7 Median percentage change from baseline in absolute CD4:CD8 ratio.

Table 5 Treatment-related treatment-emergent adverse events by treatment and blood classification

Blood classification (*n*)	Vorinostat (*N* = 186)			Mogamulizumab (*N* = 186)		
	B0 (62)	B1 (31)	B2 (93)	B0 (64)	B1 (31)	B2 (91)
Treatment-related TEAEs, *n* (%)†						
Any grade	58 (93.5)	30 (96.8)	90 (96.8)	51 (79.7)	25 (80.6)	80 (87.9)
Grade ≥3	18 (29.0)	14 (45.2)	33 (35.5)	11 (17.2)	8 (25.8)	28 (30.8)

†The frequency of TEAEs was calculated based on the safety population, which included all patients who received at least one dose of study drug. TEAE: treatment-emergent adverse event.

that this treatment may be effective in patients with both 'high' and 'low' levels of blood tumour burden. In contrast, patients treated with vorinostat showed little difference in outcomes when stratified by blood classification compared with the overall group assigned to vorinostat.

A possible explanation for this is that blood may be the malignant cell reservoir in patients with blood involvement. The mogamulizumab mechanism of action blocks the transition from blood to skin via inhibition of the interaction between CCR4 and CCL17 by targeting CCR4-expressing cells, while the vorinostat mechanism of action is independent of this transition.[20] Nevertheless, this is not yet sufficiently proven and is thus speculative.

Palliation of skin-related symptoms and improvement in skin manifestations of the disease have a significant overall impact on quality of life for patients with MF/SS. The MAVORIC trial[16] demonstrated overall skin response by cycles for patients treated with mogamulizumab occurred at all degrees of blood involvement, thereby suggesting that the activity of mogamulizumab to reduce circulating malignant cells resulted in overall symptomatic benefit. Even patients with advanced disease (B2) had improvement in skin manifestations which was correlated with overall improvement in disease-related outcomes. In a disease such as this which in the vast majority of cases are incurable, symptomatic improvement is an extremely important goal of our therapies.

Mogamulizumab is the first agent where a preferential benefit is seen in patients with more aggressive disease, characterized by higher circulating blood tumour burden. This reflects a significant step forward for this group of patients, for whom our therapeutic options are very limited and who have a notoriously short overall survival.

Further, management guidelines often list treatments in no particular order of preference. By identifying factors such as B1/2 blood involvement, where patients may benefit more, allows drugs to be selected for those likely to benefit most, leading to cost-effective medical practice.

In a disease such as this which in the vast majority of cases is incurable, symptomatic improvement is an extremely important goal of our therapies. It is therefore also important to focus on treatment toxicity. This study has demonstrated an improved toxicity profile for mogamulizumab compared with vorinostat,

and, in addition, the toxicity profile of mogamulizumab was similar irrespective of the degree of blood involvement.

These data indicate that in patients with MF and SS, mogamulizumab, having already displayed multicompartmental efficacy in the phase 3 MAVORIC study, may offer a well-tolerated and effective systemic treatment option, particularly for patients with blood involvement (B1 or B2), who are thought to have a relatively worse prognosis.

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Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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