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LETTER

Long-term disease control and safety with the anti-CCR4 antibody mogamulizumab: Post-hoc analyses from the MAVORIC trial of patients with previously treated cutaneous T-cell lymphoma

Dear Editor,

Mogamulizumab is an anti-CCR4 antibody that was investigated in the phase 3 MAVORIC study (NCT01728805) of adult patients with previously treated mycosis fungoides (MF) or Sézary syndrome (SS).[1] In the primary analysis (December 31, 2016 cutoff), progression-free survival (PFS) and confirmed global overall response rate were significantly better with mogamulizumab compared with vorinostat. The most common treatment-emergent adverse events (TEAEs) among mogamulizumab-treated patients were infusion-related reactions (33%) and drug eruptions (24%).

This post-hoc analysis assessed the long-term safety of mogamulizumab using non-overlapping exposure quartiles based on a final safety cutoff of January 3, 2019. Rates of TEAEs in the overall safety population were compared with those of patients in the highest exposure quartile. Efficacy data from the primary analysis for patients within each quartile were described - no additional efficacy follow-up was conducted.

In total, 184 patients (105 MF, 79 SS) were randomized to mogamulizumab and received at least one dose of study drug (safety population), with a median mogamulizumab exposure of 170 days (range: 1–1813). Based on quartile assessment, patients with >351 days of exposure were defined as the long-term exposure (LTE) population. Across the quartiles, significant trends were observed in Eastern Cooperative Oncology Group performance status (ECOG PS), disease type, clinical stage IIB or III-IV, and blood involvement (Table 1).

In total, 97.3% of patients experienced a TEAE, 85.9% experienced a drug-related TEAE, and 39.7% experienced a serious TEAE. Lymphopenia, a pharmacologic effect of the drug, was not considered an AE. Similar percentages of patients in the overall safety and LTE populations reported TEAEs, although slightly higher percentages of patients in the LTE group reported SAEs and drug-related TEAEs. Patients from the first two exposure quartiles reported the majority of Grade ≥3 events, with a median time to onset for a Grade ≥3 event of 109 days (interquartile range [IQR]: 34–280 days).

In the overall safety population, 9 patients experienced Grade 3 drug eruptions that were attributed to mogamulizumab (20.5%), with the remainder experiencing Grade 1–2 eruptions (79.5%). Drug eruption had a variable time to onset (median, 107 days; IQR: 43–256 days). All 16 cases of thrombocytopenia attributed to mogamulizumab were Grade 1–2. Median time to onset of thrombocytopenia was 43 days (IQR: 8–196 days). Eleven (6.0%) patients developed an autoimmune event vs 2 (4.4%) patients in the LTE group.

Rates of discontinuation due to AEs increased in the longest exposure group (15.6%) compared with the shortest exposure group (9.6%); however, no clear trend was observed across the four groups. Discontinuation rates related to progressive disease were lower in the longest exposure group (22.2%) compared with the shortest exposure group (46.2%); however, again no clear trends were seen.

Across all quartiles, the disease control rate (DCR) was 78.8% (145/184), 76.2% (80/105) for MF patients, and 82.3% (65/79) for SS patients. Assessed by exposure quartile, DCR was: 46.2% (<72 days), 85.0% (72–170 days), 93.6% (171–351 days), and 95.6% (>351 days). Among MF + SS patients with a best response of SD, 10.0% (8/80) stayed on therapy >351 days.

Limitations of the current analysis include the post-hoc nature of the study, the comparatively small n values for the quartile assessments, and the potential for bias in interpretation of quartile-based efficacy. However, no new safety signals in patients treated with mogamulizumab for >351 days were identified. The quartile analysis also did not find an increased incidence of autoimmune events over time. As expected, the patients with the longest exposure to mogamulizumab had higher rates of TEAEs than the overall safety population but also showed acceptable disease control, suggesting that TEAEs were generally manageable and patients were able to stay on treatment.

TABLE 1 Summary of baseline characteristics by exposure quartile, and safety results overall and in the long-term exposure population

Baseline characteristics and DCR by exposure quartile					
	Exposure to mogamulizumab				
	<72 days	72–120 days	171–351 days	>351 days	Linear trend test *p* value[a]
n (%)	52 (28)	40 (22)	48 (26)	44 (24)	
ECOG PS, n (%)					
0	20 (38.5)	28 (70.0)	29 (61.7)	28 (62.2)	0.04[b]
1	31 (59.6)	12 (30.0)	19 (38.3)	15 (35.6)	
2	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.2)	
Disease type, n (%)					
MF	35 (67.3)	24 (60.0)	26 (53.2)	20 (46.7)	0.03
SS	17 (32.7)	16 (40.0)	22 (46.8)	24 (53.3)	
Current clinical stage, n (%)					
IB/IIA	8 (15.4)	9 (22.5)	15 (29.8)	4 (11.1)	0.80
IIB	16 (30.8)	6 (15.0)	7 (14.9)	3 (6.7)	0.002
III/IV	28 (53.8)	25 (62.5)	26 (55.3)	37 (82.2)	0.007
Blood involvement[c], n (%)					
No	21 (40.4)	20 (50.0)	17 (34.0)	5 (13.3)	<0.001
Yes	31 (59.6)	20 (50.0)	31 (66.0)	39 (86.7)	
DCR in MF, n/N (%)	18/35 (51.4)	20/24 (83.3)	22/25 (88.0)	20/21 (95.3)	
SD	16/35 (45.7)	18/24 (75.0)	15/25 (60.0)	6/21 (28.6)	–
PR	2/35 (5.7)	2/24 (8.3)	7/25 (28.0)	14/21 (66.7)	
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
DCR in SS, n/N (%)	6/17 (35.3)	14/16 (87.6)	22/22 (100)	23/24 (95.8)	
SD	4/17 (23.5)	7/16 (43.8)	12/22 (54.5)	2/24 (8.3)	
PR	2/17 (11.8)	6/16 (37.5)	9/22 (40.9)	18/24 (75.0)	–
CR	0	1/16 (6.3)	1/22 (4.5)	3/24 (12.5)	

Safety results overall and in the long-term exposure population		
	Overall safety population (*N* = 184) *n* (%)	**Long-term (>351 days) exposure population (*n* = 45) *n* (%)**
All TEAEs	179 (97.3)	45 (100.0)
SAEs	73 (39.7)	23 (51.1)
All drug-related TEAEs	158 (85.9)	44 (97.8)
Drug-related TEAEs occurring in ≥20% of patients in either group[d]		
Drug eruption	44 (23.9)	16 (35.6)
Infusion-related reaction	61 (33.2)	15 (33.3)
Fatigue	34 (18.5)	10 (22.2)
Thrombocytopenia	16 (8.7)	9 (20.0)
AEs of special interest		
Autoimmune[a]	11 (6.0)	2 (4.4)
Hypothyroidism	5 (2.7)	1 (2.2)
Autoimmune hepatitis	2 (1.1)	0 (0)
Myositis	2 (1.1)	0 (0)
Myocarditis	1 (0.5)	0 (0)
Pneumonitis	1 (0.5)	1 (2.2)
Polymyositis	1 (0.5)	0 (0)

Abbreviations: *CCR4*, C-C chemokine receptor 4; DCR, disease control rate (stable disease + partial response + complete response); *ECOG PS*, Eastern Cooperative Oncology Group performance status; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event.
[a]For baseline characteristics with ≤2 categories, *p*-values are reported for only one category since the second category will be the same. For current clinical stage, since there are >2 categories, *p*-values are reported based on rates by category.
[b]For ECOG PS, PS level 2, with only two patients, was not used; thus, only one *p*-value is reported.
[c]Defined as ≥B1 per Olsen et al.[2]
[d]Patients could have had more than one event.

AUTHOR CONTRIBUTIONS

Marine Bagot and Youn H. Kim were involved in designing the initial post-hoc analysis. Takahiro Ito performed the statistical analyses. Martine Bagot, Stéphane Dalle, Lubomir Sokol, Athansios Tsianakas, Amy Musiek, Pablo L. Ortiz-Romero, Brian Poligone, Madeleine Duvic, Craig Elmets, Mollie Leoni, Karen Dwyer, Takahiro Ito, Fiona Herr, Youn H. Kim contributed to data collection and acquisition, interpretation of the present findings and provided approval of the final version of the article for publication.

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CONFLICT OF INTEREST

MB reports personal fees from and serving on an advisory board for Kyowa Kirin during the conduct of the study and reports personal fees from and serving on an advisory board for Takeda, Innate, and Helsinn/Recordati outside the submitted work. SD has nothing to disclose.

LS reports personal fees from and serving on an advisory board for Kyowa Kirin during the conduct of the study. AT has nothing to disclose. AM reports serving on an advisory board for Kyowa Kirin during the conduct of the study and serving on an advisory board for Kyowa Kirin and Helsinn and serving as an investigator for Pfizer, Menlo, Elorac, Soligenix, miRagen, and Connect outside the submitted work. P.L.O-R. reports personal fees from and serving on an advisory board for Takeda, Kyowa Kirin, Recordati, Innate, Helsinn, 4SC, and miRagen outside the submitted work. In addition, he has a patent for PLCG1 issued. BP reports grants, personal fees, and speaker honoraria from and serving on an advisory board and as an investigator for Kyowa Kirin during the conduct of the study. Outside the submitted work, he reports grants from and serving as an investigator for Replimune, miRagen, Soligenix, and Astex Pharmaceuticals, and he reports grants, personal fees, and speaker bureau honoraria from and serving as an investigator and consultant for Helsinn. MD was an investigator for Kyowa Kirin during part of the study. She reports non-financial support from Acrotech Biopharma and USCLC, personal fees from and serving as a consultant for Almirall and Guidepoint Global, personal fees from and serving on an advisory board for Bausch, and personal fees from T-Cell Lymphoma Forum outside the submitted work. CE served as an investigator for Kyowa Kirin during the conduct of the study. ML, KD, TI, and FH report employment by Kyowa Kirin during the conduct of the study. YHK reports grants and personal fees from and serving on an advisory board for Kyowa Kirin during the conduct of the study.

DATA AVAILABILITY STATEMENT

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

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