Quality of Life in Cutaneous T-Cell Lymphoma Patients Treated with Anti-CCR4 Monoclonal Antibody Mogamulizumab Versus Vorinostat: Results from MAVORIC

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Introduction

- Cutaneous T-cell lymphomas (CTCL) are rare forms of non-Hodgkin's lymphoma (NHL), with an estimated incidence in the United States of 10 cases per million persons.¹
- CTCL affects the skin, presenting as patches, plaques, tumors or erythroderma, and may be associated with severe pruritis, but other compartments such as blood, lymph, and viscera can be involved.²⁻⁴
- The two most common subtypes, accounting for approximately 65% of all CTCL, are mycosis fungoides (MF) and Sézary syndrome (SS).⁵
- Late stage MF/SS are serious, life-threatening diseases associated with adverse quality of life (QoL) and significant morbidity.⁶⁻⁸
- The Phase 3 MAVORIC study was conducted to evaluate the efficacy and safety of mogamulizumab, an anti-CCR4 monoclonal antibody, for the treatment of adult patients with MF/SS after one prior systemic therapy, compared to that of FDA-approved vorinostat (NCT01728805).⁹
 - Mogamulizumab resulted in significantly greater progression-free survival (PFS) compared to vorinostat with a median PFS of 7.7 months versus 3.1 months, respectively (p < 0.0001).
 - The most common treatment-emergent adverse events (TEAEs) that were more frequent in the mogamulizumab arm included infusion-related reactions (33.2% versus 0.5% in the vorinostat arm) and drug rash (24% versus 0.5%). Grade 3–4 adverse events of any cause were reported in 75 (41%) of 184 patients in the mogamulizumab group and 76 (41%) of 186 patients in the vorinostat group.
 - Mogamulizumab received approval from the Food and Drug Administration on August 8, 2018 for the treatment of adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy.

Methods

- Adult patients (stage IB to IVB histologically confirmed MF or SS who had failed ≥1 systemic therapy) were randomized 1:1 to mogamulizumab or vorinostat (**Figure 1**).
- Primary endpoint was investigator-assessed progression-free survival (PFS).
- Key secondary endpoints included global composite response rate (ORR), duration of response, and QoL.
- Patient-reported outcome (PRO) assessments of QoL used Skindex-29, Functional Assessment of Cancer Therapy-General (FACT-G) and European Quality of Life-5 dimensions-3 levels (EQ-5D-3L). EQ-5D-3L will be reported elsewhere.
- QoL instruments were administered at baseline and Day 1 of every other treatment cycle.

Figure 1. MAVORIC Study Design

Patient-Reported Outcomes Measures

Skindex-29

- 29 items assessing three domains: symptoms, functioning, and emotions.
- Items scored on a 5-point Likert-type scale (never, rarely, sometimes, often, all the time).

- Responses were transformed to a linear scale of 100 (never = 0, rarely = 25, sometimes = 50, often = 75, all the time = 100) for scale score calculation. A scale score was the mean of a subject's responses to the items in a given scale, and the composite score was calculated as the average of the three scale scores.

- Higher scores indicated a higher impact of skin disease (worse QoL).

FACT-G

- 27 items in four domains: physical well-being, functional well-being, emotional well-being, and social/family well-being.
- Total score was obtained by summing individual subscale scores. Response scores on negatively-phrased questions were reversed before summing.
- Higher scores indicated better QoL.

Statistical Analyses

Longitudinal Mixed Models of Treatment Effect

- Longitudinal modeling of treatment effect employed a mixed model using treatment group, baseline value, region, age group, gender, race, CC chemokine receptor 4 expression status, disease subtypes, disease stage, and compartment involvement (blood involvement or no blood involvement).

- Least squares (LS) mean, difference in LS mean between treatment arms, and 95% confidence intervals (CIs), and standard error (SE) was calculated for each LS.

Meaningful Change Thresholds (MCT)

- MCT was defined as the smallest difference in score that subjects perceived as meaningful and important. Based on the MCT for each scale of interest, subjects were classified as improving or not and presented by treatment group and status at each cycle.

- Tests of proportions of those who responded for each domain or summary score by cycle were assessed using Chi-square or Fisher's exact test when the expected cell size was less than or equal to 5. Two-sided p-values from these tests are reported.

Time to Clinically Meaningful Worsening

- Time to deterioration was defined as time from day of randomization until the score of the PRO domain of interest had worsened in magnitude of the MCT.

- Subjects whose PRO domain score improved, remained the same, or did not worsen to the magnitude of the MCT were censored at the last dose date of the treatment or the last date of the PRO domain assessment, whichever was first.

- Subjects without a baseline and/or post-baseline PRO domain assessment were censored at the date of randomization.

- Time-to-deterioration endpoints were summarized using the Kaplan-Meier method.

- A Cox proportional hazard model with treatment, disease type, disease stage, and region as covariates was used to assess magnitude of the treatment difference. The hazard ratio along with the 95% CI is presented.

Subjects

- A total of 372 patients were randomized (mogamulizumab n=186; vorinostat n=186) (Intent-to-Treat population)
- The treatment groups were comparable with respect to demographic characteristics, disease characteristics, and prior CTCL therapies (**Table 1**)

Table 1. Baseline Characteristics in MAVORIC

	Mogamulizumab (n = 186)	Vorinostat (n = 186)	Total (N = 372)
Demographic or Clinical Item			
Age group			
< 65 years	99 (53.2%)	89 (47.8%)	188 (50.5%)
≥ 65 years	87 (46.8%)	97 (52.2%)	184 (49.5%)
Gender			
Female	77 (41.4%)	79 (42.5%)	156 (41.9%)
Male	109 (58.6%)	107 (57.5%)	216 (58.1%)
Race			
Black/African American	24 (12.9%)	13 (7.0%)	37 (9.9%)
White	125 (67.2%)	135 (72.6%)	260 (69.9%)
Other	37 (19.9%)	38 (20.4%)	75 (20.2%)
Disease type			
MF	105 (56.5%)	99 (53.2%)	204 (54.8%)
SS	81 (43.5%)	87 (46.8%)	168 (45.2%)
Disease stage			
IB or II	68 (36.6%)	72 (38.7%)	140 (37.6%)
III or IV	118 (63.4%)	114 (61.3%)	232 (62.4%)
Blood involvement			
Yes	123 (66.1%)	122 (66.3%)	245 (66.2%)
No	63 (33.9%)	62 (33.7%)	125 (33.8%)
Missing/no response	0	2	2
Region			
US	98 (52.7%)	103 (55.4%)	201 (54.0%)
Japan	9 (4.8%)	6 (3.2%)	15 (4.0%)
EU/Australia ^a	79 (42.5%)	77 (41.4%)	156 (41.9%)

^a16 patients were enrolled in Australia; 9 mogamulizumab, 7 vorinostat

Skindex-29 and FACT-G Results

- Compliance with PRO measures was >90% throughout study period (**Figure 2**) and was consistent for both arms.

Figure 2. Compliance with Skindex-29 and FACT-G in MAVORIC

- Longitudinal effects by treatment favored mogamulizumab in all Skindex-29 (**Figure 3**) and FACT-G domains (**Figure 4**).

Figure 3. Treatment Effects on Skindex-29

Figure 4. Treatment Effects on FACT-G

- Improvements in Skindex-29 Symptom, Functioning, and Emotional domains were seen at cycle 3 with mogamulizumab and this trend remained until the end of treatment visit.
- Significant improvements in the FACT-G Social domain were observed at cycles 3 and 5.
- Improvements in Physical and Emotional domains were seen as early as cycle 1 with mogamulizumab. All effects remained until the end of treatment visit.

^a p < 0.05

^a Adjusted mixed model contained treatment group, visits, treatment visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Conclusions

- MAVORIC is the largest Phase 3 trial of systemic treatment in CTCL to date (N=372). Patient-reported outcomes, measured by Skindex-29 and FACT-G, demonstrated a significant QoL benefit in MF/SS patients given mogamulizumab compared to vorinostat.**
- A significant benefit for mogamulizumab on symptom, emotional, and functional scales were seen as early as cycle 3 for all domains of Skindex-29 and FACT-G.**
- Mogamulizumab resulted in clinically meaningful improvements in patient-reported symptoms and preservation of physical well-being.**
- At minimum, 61% of patients randomized to mogamulizumab reported clinically meaningful improvements in symptoms beginning at cycle 3 and lasting throughout treatment.**
- Mogamulizumab delayed deterioration from baseline in both symptoms and functional status in this study, where patients were treated until progression or intolerance (a time when decreased QoL is expected). The delay in patient-reported worsening in skin symptoms was most pronounced in SS.**

- More patients reported clinically meaningful improvements in symptoms with mogamulizumab compared to vorinostat at cycles 3, 5, 7, and 11 (**Figure 5**).
- At least 61% of patients randomized to mogamulizumab reported clinically meaningful improvements in symptoms from cycle 3 through cycle 11 (**Figure 5**).
- Significantly more patients reported clinically meaningful declines in physical well-being with vorinostat compared to mogamulizumab at cycles 1, 3, 5, and 7 (**Figure 6**).

Figure 5. Clinically Meaningful Improvements in Patient-Reported Symptoms on Skindex-29

Figure 6. Clinically Meaningful Declines in Patient-Reported Physical Well-Being on FACT-G

- Median time to symptom worsening was 27.4 months (range 27.4–not estimable) for mogamulizumab and 6.6 months (range, 6.1–13.8) for vorinostat.
- Time to worsening was delayed with mogamulizumab overall and on all three Skindex-29 scales, and was most pronounced in SS patients (**Figure 7**).

Figure 7. Time to Clinically Meaningful Worsening on Skindex-29

References

- Kongpakdee K, Xiong M, Watanabe M. Changing incidence trends of cutaneous T-cell lymphoma. *JAMA Dermatol*. 2015;148(11):1295-1299.
- Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and Sézary syndrome: a stage-based approach. *J Natl Cancer Cent*. 2008;6(4):438-442.
- Mayer NJ, Paul G, Mistry L. Pruritus in cutaneous T-cell lymphoma: frequent, often severe and difficult to treat. *Acta Derm Venereol*. 2010;90(1):11-17.
- Kim YH, Liu HL, Mraz-Gerhard S, Varghese A, Hoppel RT. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139(7):857-866.
- Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3788-3795.
- Dennert M, Winkler S, Kim Y, et al. Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL). *J Clin Oncol*. 2009;27(15):2491-2494.
- Dennert MF, Tien A, Miller D. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. *Arch Dermatol*. 2005;141(10):1255-1260.
- Dennert MF, Kim Y, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life. *Cancer*. 2006;107(10):2048-2051.
- Kim Y, Bagat M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018. Online.
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