Efficacy and Safety of Mogamulizumab by Patient Blood Classification

Julia Scarisbrick[1], Pier Luigi Zinzani[2], Richard Cowan[3], Jan P. Nicolay[4], Dolores Caballero[5], Lubomir Sokol[6], Lauren Pinter-Brown[7], Jan-Paul Rosen[8]

[1]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [2]Institute of Hematology "Lorenzo e Ariosto Seràgnoli", University of Bologna/ Sant'Orsola-Malpighi Polyclinic, Bologna, Italy; [3]Cancer Research UK, The Christie NHS Foundation Trust, Manchester, UK; [4]University Medical Centre Mannheim, Mannheim, Germany; [5]University Hospital of Salamanca, Salamanca, Spain; [6]Division of Medical Oncology, Moffitt Cancer Center, Tampa, FL, USA; [7]University of California-Irvine Chao Family Comprehensive Cancer Center, Orange, CA, USA ; [8]Kyowa Kirin International, Marlow, UK

P138

Introduction

- Cutaneous T-cell lymphomas (CTCLs) are rare, serious, and potentially life-threatening forms of non-Hodgkin lymphoma that primarily present in the skin
- The most studied forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS), which account for approximately 60% and <5% of all CTCL cases, respectively[1,2]
- Initial methods of disease staging in MF and SS were based on the tumour-node-metastasis (TNM) classification and involved disease-specific findings
- Disease staging in MF and SS was revised in 2007 and blood classification (blood tumour burden B0, B1, or B2) was added based on the recognition of blood involvement as a prognostic factor[3]
  - Increasing blood tumour burden portends worse overall and disease-specific survival and an increased risk of disease progression[4]
  - The median survival time for patients with blood tumour burden B1 and B2 is 3.2 years and 3.1 years, respectively[4]
- Mogamulizumab was compared with vorinostat in the international, open-label, randomized, controlled phase 3 MAVORIC trial in patients with relapsed or refractory MF or SS (disease stages IB–IVB) who had failed at least 1 prior systemic therapy[5]
  - Mogamulizumab significantly improved progression-free survival (PFS) and overall response rates (ORRs) versus vorinostat
  - 68% of patients treated with mogamulizumab achieved a response in the blood at a median of 1.1 months
  - The duration of response in the blood with mogamulizumab was 25.5 months

Objective

- The objective of this post hoc analysis was to examine the efficacy and safety of mogamulizumab compared with vorinostat in patients in the MAVORIC trial, stratified by patient blood classification

Methods

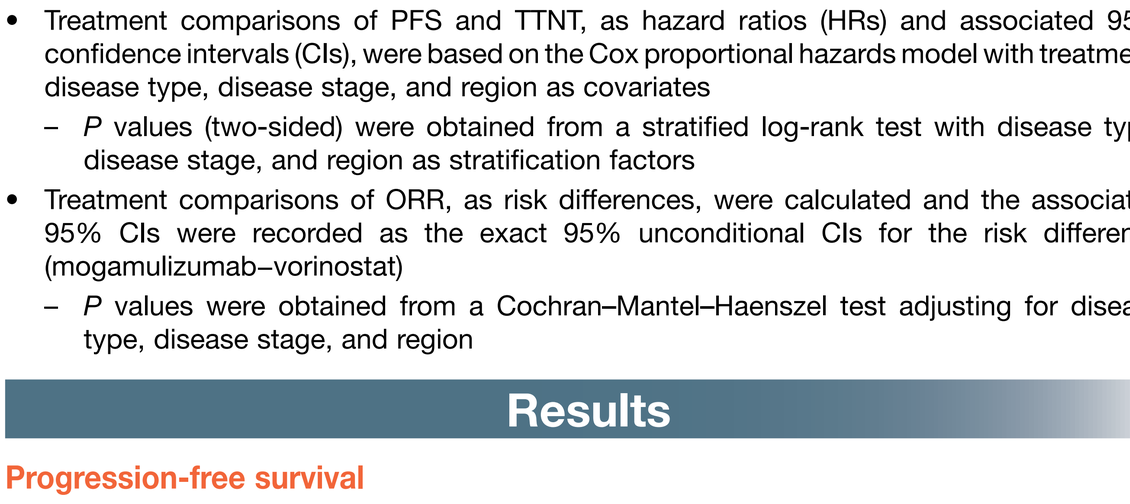
- Patients were randomized 1:1 to receive either intravenous mogamulizumab 1.0 mg/kg once weekly for the first 28-day cycle, then on Days 1 and 15 of subsequent cycles, or oral vorinostat 400 mg once daily
- Investigator-assessed PFS, ORR, and time to next treatment (TTNT) were assessed for each treatment group
- ORR was based on a global composite response score in each of the 4 assessable disease compartments (skin, blood, lymph nodes, and viscera) and confirmed at 2 consecutive visits
- TTNT was defined as the time from randomisation to the date of the first new systemic therapy
- Patients in each treatment group were stratified by blood classification, blood tumour burden B0, B1, or B2
  - B0: <15% CD4+CD26– cells or CD4+CD7– cells by flow cytometry. B1: ≥15% CD4+CD26– cells or CD4+CD7– cells by flow cytometry. B2: ≥1,000 mg/L Sézary cells with positive clone, CD4/CD8 ratio ≥10, 40% CD4+CD7– cells, or ≥30% CD4+ CD26– cells.
- Treatment comparisons of PFS and TTNT, as hazard ratios (HRs) and associated 95% confidence intervals (CIs), were based on the Cox proportional hazards model with treatment, disease type, disease stage, and region as covariates
  - *P* values (two-sided) were obtained from a stratified log-rank test with disease type, disease stage, and region as stratification factors
- Treatment comparisons of ORR, as risk differences, were calculated and the associated 95% CIs were recorded as the exact 95% unconditional CIs for the risk difference (mogamulizumab–vorinostat)
  - *P* values were obtained from a Cochran–Mantel–Haenszel test adjusting for disease type, disease stage, and region

Results

Progression-free survival

- In the MAVORIC trial, investigator-assessed PFS was significantly longer with mogamulizumab versus vorinostat in the overall population (7.7 months versus 3.1 months; *P*<0.0001) (**Figure 1**)[5]
- When stratified by patient blood classification, investigator-assessed PFS was longer with mogamulizumab versus vorinostat in patients in both the blood tumour burden B1 and B2 groups, with the HRs significantly favouring mogamulizumab (0.32 [95% CI 0.16–0.64] and 0.36 [95% CI 0.24–0.53], respectively) (**Figure 1**)

Figure 1. Investigator-Assessed PFS in the Overall Population and by Patient Blood Classification



Overall response rate

- In the MAVORIC trial, ORRs were significantly higher with mogamulizumab versus vorinostat in the overall population (28.0% versus 4.8%; *P*<0.0001) (**Table 1**)[5]
- When stratified by patient blood classification, ORRs were higher with mogamulizumab versus vorinostat in all blood tumour burden groups, and the risk difference, defined as the excess 'risk' of a patient achieving an overall response with mogamulizumab versus vorinostat, was significantly higher with mogamulizumab in patients in the blood tumour burden B2 group (37.4% versus 3.2% for mogamulizumab versus vorinostat; risk difference *P*<0.0001; **Table 1**)
- For patients in the blood tumour burden B1 group, the same trend in ORR was shown (25.8% versus 6.5% for mogamulizumab versus vorinostat; risk difference *P*=0.2758)
- The risk difference increased with increasing blood tumour burden, from 9.2 in the B0 group to 19.4 in the B1 group and to 34.1 in the B2 group

Time to next treatment

- TTNT in the MAVORIC trial was significantly longer with mogamulizumab versus vorinostat in the overall population (11.0 versus 3.5 months; *P*<0.0001) (**Table 2**)
- When stratified by patient blood classification, there was no statistically significant difference in TTNT between mogamulizumab and vorinostat in patients in the blood tumour burden B0 group (6.77 versus 4.13 months; HR 0.68 [95% CI 0.45–1.02]; *P*=0.0992); however, TTNT was significantly longer with mogamulizumab versus vorinostat in patients in both the blood tumour burden B1 (12.63 versus 3.07 months; HR 0.32 [95% CI 0.16–0.67]; *P*=0.0018) and B2 groups (13.07 versus 3.53 months; HR 0.30 [95% CI 0.21–0.43]; *P*<0.0001) (**Table 2**)
- The Kaplan–Meier curves of TTNT with mogamulizumab and vorinostat by patient blood classification are shown in **Figure 2**

Safety

- Regardless of blood tumour burden, treatment-related treatment-emergent adverse events (TEAEs) were similar in all patients and less frequent in those treated with mogamulizumab versus vorinostat (**Table 3**)

Table 1. Investigator-Assessed ORR in the Overall Population and by Patient Blood Classification

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

**P* values were obtained from a Cochran–Mantel–Haenszel test adjusting for disease type, disease stage, and region. **95% CI for response rate is the exact 95% CI. ***Risk difference (i.e. 'attributable risk') is the excess 'risk' of a patient achieving an overall response with mogamulizumab versus vorinostat. The 95% CI for risk difference is the exact 95% unconditional CI for the risk difference (mogamulizumab–vorinostat).

Table 2. TTNT* in the Overall Population and by Patient Blood Classification

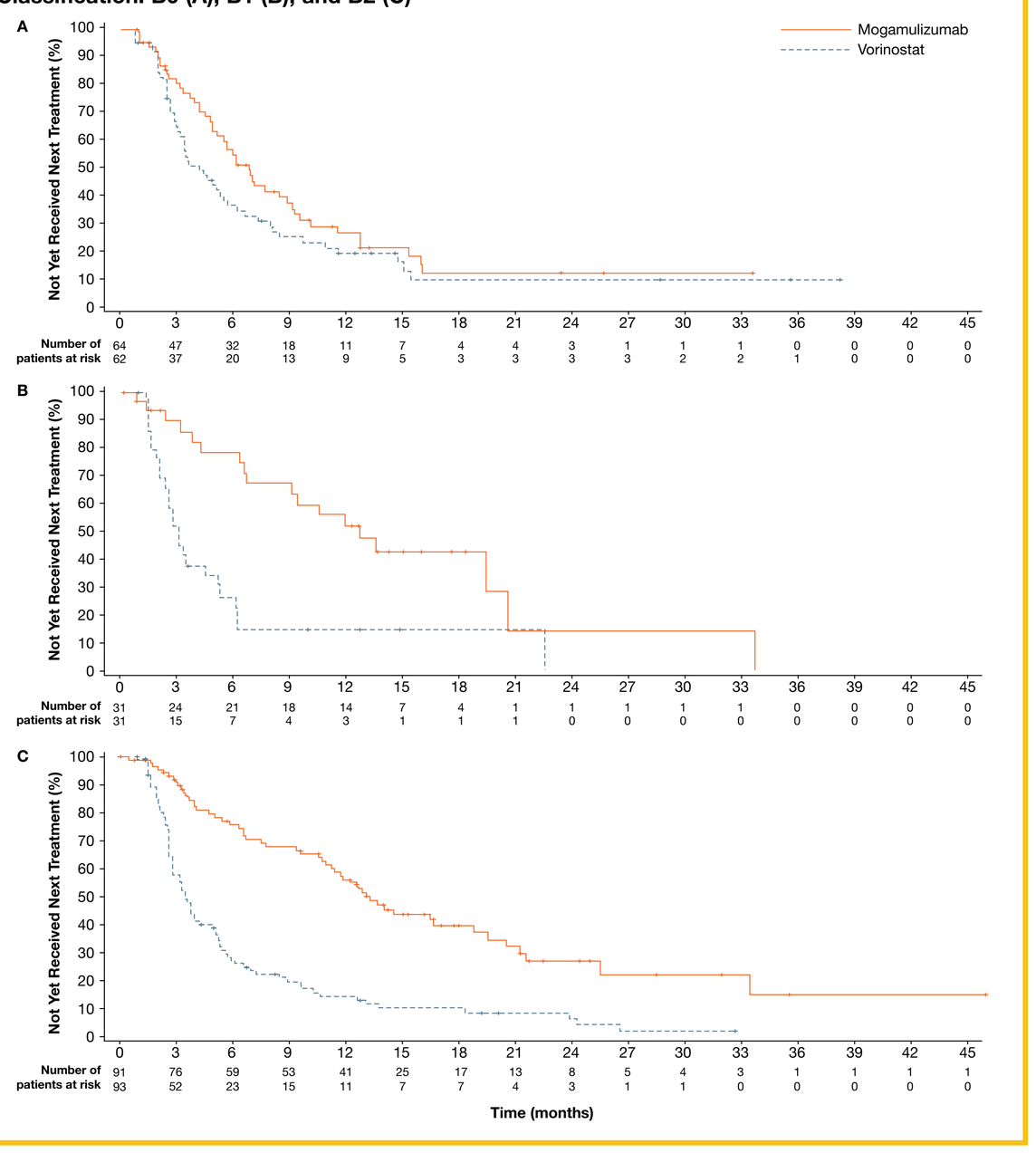
	Vorinostat (n=186)	Mogamulizumab (n=186)	*P* value**
TTNT in the overall population, median (95% CI)*, months**	**3.5 (3.1–4.3)**	**11.0 (8.8–12.6)**	**<0.0001**
TTNT by patient blood classification, median (95% CI), months			
B0	n=49 4.13 (3.00–5.60)	n=46 6.77 (4.87–8.80)	0.0992
HR (95% CI)****	0.68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

*TTNT was defined as the time from randomisation to the date of the 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. **P values (two-sided) were obtained from a stratified log-rank test with disease type, disease stage, and region as stratification factors. ***95% CIs were obtained from the SAS LIFETEST Procedure using log-log transformation. ****HR and 95% CIs were based on the Cox proportional hazards model with treatment, disease type, disease stage, and region as covariates.

Table 3. Treatment-Related TEAEs by Patient Blood Classification

Treatment-related TEAEs, n (%)	Vorinostat (n=186)			Mogamulizumab (n=186)		
	Patient blood classification (n)			Patient blood classification (n)		
	B0 (62)	B1 (31)	B2 (93)	B0 (64)	B1 (31)	B2 (91)
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)
Grade 5	0	3 (9.7)	0	0	0	1 (1.1)

Figure 2. Kaplan–Meier Curves of TTNT with Mogamulizumab and Vorinostat by Patient Blood Classification: B0 (A), B1 (B), and B2 (C)



Conclusions

- **When stratified by blood classification, patients treated with mogamulizumab had equivalent or better outcomes when compared with patients treated with vorinostat**
- **Mogamulizumab was effective in patients with blood involvement (blood tumour burden B1 and B2), often showing a greater clinical benefit in patients in the B1 and B2 groups than those in the B0 group, which demonstrated a moderate clinical effectiveness**
- **Drug safety was similar in all patients irrespective of blood tumour burden**

References

1. Willemze R, et al. *Blood.* 2019;133:1703-14.
2. Willemze R, et al. *Blood.* 2005;105:3768-85.
3. Olsen E, et al. *Blood.* 2007;110:1713-22.
4. Agar NS, et al. *J Clin Oncol.* 2010;28:4730-9.
5. Kim YH, et al. *Lancet Oncol.* 2018;19:1192-204.

Acknowledgements

The study was sponsored by Kyowa Kirin. Medical writing assistance and graphical support were provided by Excerpta Medica (Amsterdam, Netherlands) and were funded by Kyowa Kirin Pharmaceutical Development, Inc. (Princeton, NJ, USA).

Disclosures

JS: Kyowa Kirin: Consultancy, Membership on an entity's Board of Directors or advisory committees; Takeda: Consultancy, Membership on an entity's Board of Directors or advisory committees; Recordat: Consultancy; 4SC: Consultancy, Membership on an entity's Board of Directors or advisory committees; Innate Pharma: Consultancy, Membership on an entity's Board of Directors or advisory committees; Helsinn: Consultancy, Membership on an entity's Board of Directors or advisory committees. **PLZ**: MSD: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; EUSA Pharma: Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Sanofi: Consultancy; Celltrion: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Gilead: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Janssen-Cilag: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; BMS: Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Servier: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Sandoz: Membership on an entity's Board of Directors or advisory committees; Immune Design: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Celgene: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Portola: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Roche: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Kyowa Kirin: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; TG Therapeutics: Honoraria, Speakers Bureau; Verastem: Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **RC**: Kyowa Kirin: Consultancy **JLP**: Teva Pharmaceutical Industries: Honoraria, Other: Conference participation fees; Novartis AG: Consultancy, Honoraria; Biogen GmbH: Consultancy, Honoraria; Almirall Hermal AG: Consultancy, Honoraria; Actelion Pharmaceuticals: Consultancy, Honoraria; Innate Pharma: Consultancy; Kyowa Hakko Kirin: Consultancy, Honoraria; Takeda Pharmaceuticals: Consultancy. **LS**: EUSA Pharma: Consultancy. **LPB**: Millennium Pharmaceuticals: Consultancy, Honoraria. **JPR**: Kyowa Kirin, Inc.: Employment. **DC**: Nothing to disclose

Presented at the 16th European Association of Dermato Oncology (EADO) Virtual Congress, 12–14 October 2020; Vilnius, Lithuania.

This study was sponsored by Kyowa Kirin.