MAVORIC

Mogamulizumab anti-CCR4 Antibody Versus ComparatOR In CTCL

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

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POTELIGEO is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

Important Safety Information

Warnings and Precautions

Dermatologic toxicity: Monitor patients for rash throughout the course of treatment. For patients who experienced dermatologic toxicity in Trial 1, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. Interrupt POTELIGEO for moderate or severe rash (Grades 2 or 3). Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

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Objective

Evaluate the efficacy and safety of POTELIGEO (mogamulizumab-kpkc) Injection compared with vorinostat in patients with previously treated cutaneous T-cell lymphoma (CTCL) subtypes mycosis fungoides (MF) or Sézary syndrome (SS)[1]

Trial Design

- Open-label, international, randomized controlled phase 3 trial done at 61 medical centers in the US, Denmark, France, Italy, Germany, the Netherlands, Spain, Switzerland, the UK, Japan, and Australia[1,2]
- Adult patients (N=372) were randomized to receive either POTELIGEO (1 mg/kg once weekly for the first 5 infusions, then once every 2 weeks therafter) or voninostat (400 mg PO) and treated until disease progression or intolerable toxicity[1,2]
- Included patients with stages IB-IVB histologically confirmed relapsed or refractory MF and SS, with ECOG score of 1 or less who had failed at least 1 prior systemic therapy[1,2]
- CCR4 expression was not a requirement for participation[1,2]
- Crossover from vorinostat was permitted upon disease progression or intolerable toxicity (grade ≥3)[1,2]

Primary endpoint

- Progression-free survival (PFS)[a] assessed by investigator based on global composite score of response in each disease compartment (skin, blood, lymph nodes, viscera)[1,2]

Secondary endpoints included

- Overall response rate (ORR)[b] based on global composite score of response in each disease compartment (skin, blood, lymph nodes, viscera)[1,2]
- Duration of confirmed response (DOR)[1,2]
- Response by disease compartment and by CTCL subtypes MF and SS (predefined subgroups)[2]

[a] Defined as the time from randomization to treatment until documented progressive disease or death due to any cause.
[b] ORR defined as complete response (CR) + partial response (PR).

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

Infusion reactions: Most infusion reactions occur during or shortly after the first infusion. Infusion reactions can also occur with subsequent infusions. Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly. Permanently discontinue POTELIGEO for any life-threatening (Grade 4) infusion reaction.

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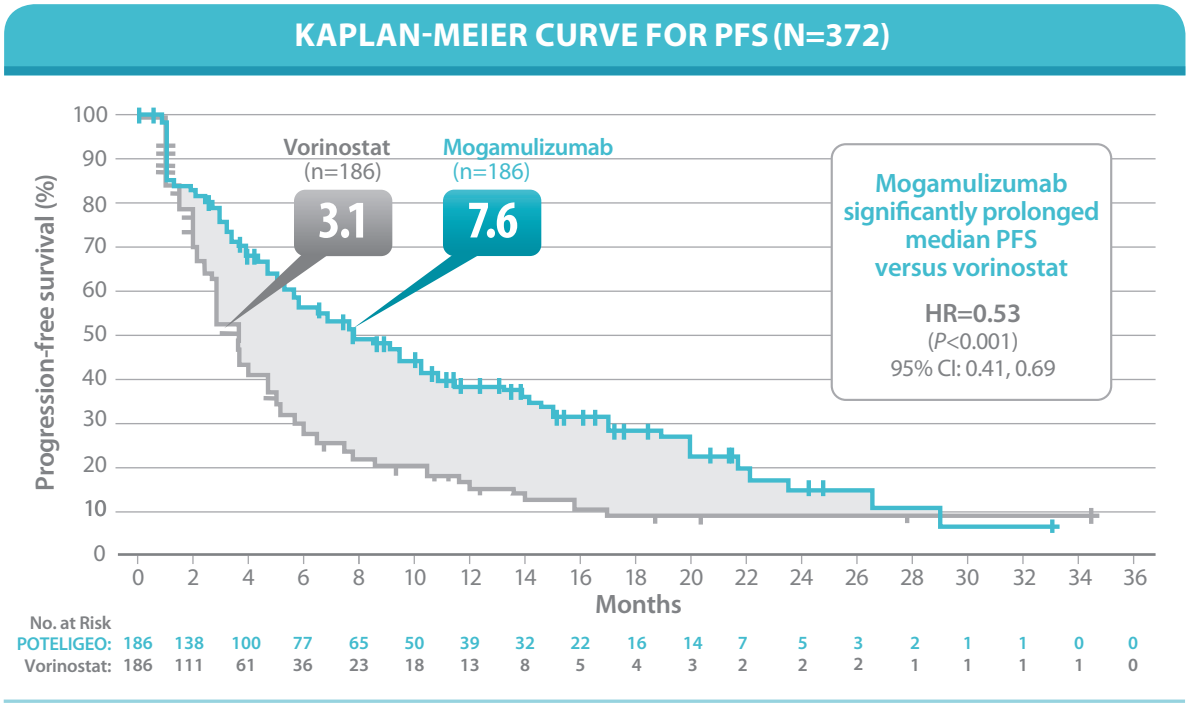
Efficacy

- Mogamulizumab therapy resulted in superior investigator-assessed PFS compared with vorinostat (median 7.6 months [95% CI: 5.6, 10.2] vs 3.1 [95% CI: 2.8, 4.0]; hazard ratio 0.53, 95% CI: 0.41, 0.69]; *P*<0.001; Figure 1)[1]
- The proportion of patients achieving an overall response was significantly higher for patients in the mogamulizumab group versus vorinostat (ORR 28% [95% CI: 22, 35] vs 5% [95% CI: 2, 9]; *P*<0.001; Figure 2)[1,2]
- Mogamulizumab demonstrated higher response rates in skin, blood, and lymph nodes across predefined subgroup of disease type (MF/SS) and disease stages (IB-IV), with a longer duration of response (Figure 3)[1,2]

Figure 1. Primary endpoint: Investigator-assessed PFS[1]



CI=confidence interval; HR=hazard ratio

- PFS was also evaluated by blinded independent review (Figure 2)

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

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Autoimmune complications: Interrupt or permanently discontinue POTELIGEO as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of POTELIGEO in patients with a history of autoimmune disease.

POTELIGEO® (mogamulizumab-kpkc) Injection

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Data on this page are sourced from the POTELIGEO USPI and may differ slightly from data reported in the published article.

Figure 2. Significantly higher response rates (*P*<0.001) and longer response duration in patients in the mogamulizumab group

Secondary endpoints	Mogamulizumab	Vorinostat
ORR by global assessment[1,2,a] (n/N)	28% (52/186)	5% (9/186)
DOR, median, months (95% CI)[1]	13.9 (9.3-18.9)	9.0 (4.6-NE)
PFS by independent review, median (months) *P*<0.0007 (HR 0.65; 95% CI: 0.49, 0.84)[2]	6.7 (95% CI: 5.6, 9.4)	3.8 (95% CI: 3.0, 4.7)

[a] ORR and response rate are the percentage of patients with confirmed complete or partial response.

CI=confidence interval; DOR=duration of response; HR=hazard ratio; NE=not estimable; ORR=overall objective response rate; PFS=progression-free survival

- Patients were discontinued from the trial upon progression in any 1 disease compartment, regardless of response in other compartments[1,2]
- Patients continuing treatment beyond data cutoff: 27 mogamulizumab patients, 31 patients who crossed over to mogamulizumab, and 10 vorinostat patients[2]
- Median relative dose intensity for mogamulizumab was 97.5% and 95.1% for vorinostat[2]

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

Complications of allogeneic HSCT after POTELIGEO: Increased risks of transplant complications have been reported in patients who received allogeneic HSCT after POTELIGEO. Follow patients closely for early evidence of transplant-related complications.

Adverse Reactions

The most common adverse reactions (reported in ≥10% of patients) with POTELIGEO in the clinical trial were rash, including drug eruption (35%), infusion reaction (33%), fatigue (31%), diarrhea (28%), drug eruption (24%), upper respiratory tract infection (22%), musculoskeletal pain (22%), skin infection (19%), pyrexia (17%), edema (16%), nausea (16%), headache (14%), thrombocytopenia (14%), constipation (13%), anemia (12%), mucositis (12%), cough (11%), and hypertension (10%).

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Figure 3. ORR and DOR by CTCL subtype, and response by disease compartment (skin, blood, lymph nodes) with mogamulizumab

Subgroup analysis	Mogamulizumab	Vorinostat
Response rate by compartment[1,2,a,b] (n/N) (ad hoc analysis of secondary endpoint)		
Skin	42% (78/186)	16% (29/186)
Blood	67% (83/124)	18% (23/125)
Lymph nodes	15% (21/136)	4% (5/133)
Viscera	0% (0/6)	0% (0/4)
ORR by CTCL subtype[2,a] (n/N) (predefined subgroup analysis)		
MF	21% (22/105)	7% (7/99)
SS	37% (30/81)	2% (2/87)
DOR by CTCL subtype, median months (range)[2] (predefined subgroup analysis)		
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)

[a] ORR or compartmental response rate is the percentage of patients with confirmed CR or PR.
[b] Denominator includes patients with compartmental disease at baseline.

Treatment exposure and discontinuation rates

- Median treatment exposure was 170 days for mogamulizumab and 84 days for vorinostat[2]
- Discontinuation rates were 18% in the mogamulizumab group and 23% (43/186) in the vorinostat group[1,2]
- The most frequent adverse reactions leading to discontinuation were drug rash (7.1%) in the mogamulizumab group and fatigue (4.0%) in the vorinostat group[2]
- 73% (136/186) of patients randomized to vorinostat crossed over to mogamulizumab due to disease progression (80%) or intolerable toxicity (20%)[2]

"…in patients with previously treated mycosis fungoides or Sézary syndrome, treatment with mogamulizumab, a first-in-class anti-CC chemokine receptor 4 monoclonal antibody, resulted in superior progression-free survival, a higher proportion of patients achieving an overall response…than vorinostat, a US Food and Drug Administration-approved histone deacetylase inhibitor."

—MAVORIC Investigators[2]

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Safety

Adverse reactions in ≥10% of patients with ≥2% higher incidence within the mogamulizumab treatment arm[1]

Adverse reactions[a,b]	Mogamulizumab IV (n=184)		Vorinostat PO (n=186)	
Body system	**All grades (%)**	**≥grade 3 (%)**	**All grades (%)**	**≥grade 3 (%)**
Skin and subcutaneous tissue disorders				
Rash, including drug eruption	35	5	11	2
Drug eruption[c]	24	5	<1	0
Procedural complications				
Infusion related reaction[c]	33	2	0	0
Infections				
Upper respiratory tract infection	22	0	16	1
Skin infection	19	3	13	4
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	22	<1	17	3
General disorders				
Pyrexia	17	<1	7	0
Gastrointestinal				
Mucositis	12	1	6	0

[a] Adverse reactions include groupings of individual preferred terms.

[b] Includes adverse reactions reported up to 90 days after randomized treatment.

[c] Per study protocol, no prophylactic premedication with corticosteroids was permitted; however, patients taking low-/intermediate-potency topical steroids or low-dose (≤20 mg) systemic steroids for at least 4 weeks could continue.

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Laboratory test[a]	Mogamulizumab IV (n=184)		Vorinostat PO (n=186)	
	All grades (%)	≥grade 3 (%)	All grades (%)	≥grade 3 (%)
Chemistry				
Albumin decreased	34	2	27	3
Calcium decreased	30	3	20	2
Uric acid increased	29	29	11	11
Phosphate decreased	27	5	26	5
Magnesium decreased	17	<1	8	<1
Glucose decreased	14	0	8	<1
Calcium increased	12	<1	8	<1
Hematology				
CD4 lymphocytes decreased[b]	63	43	17	8
Lymphocytes decreased	31	16	12	4
White blood cells decreased	33	2	18	2

[a] Includes lab abnormalities reported up to 90 days after treatment that were new or worsening in grade or with worsening from baseline unknown.

[b] Out of 99 evaluated recipients of POTELIGEO and 36 evaluable recipients of vorinostat.

- No specific laboratory test is required to prescribe POTELIGEO

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Indication

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You are encouraged to report suspected adverse reactions to Kyowa Kirin, Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information.

References: 1. POTELIGEO [package insert]. Kyowa Kirin Inc., Bedminster, NJ USA. **2.** Kim YH, Bagot 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. [published online August 9, 2018] *Lancet Oncol*. DOI:10.1016/S1470-2045(18)30379-6.

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