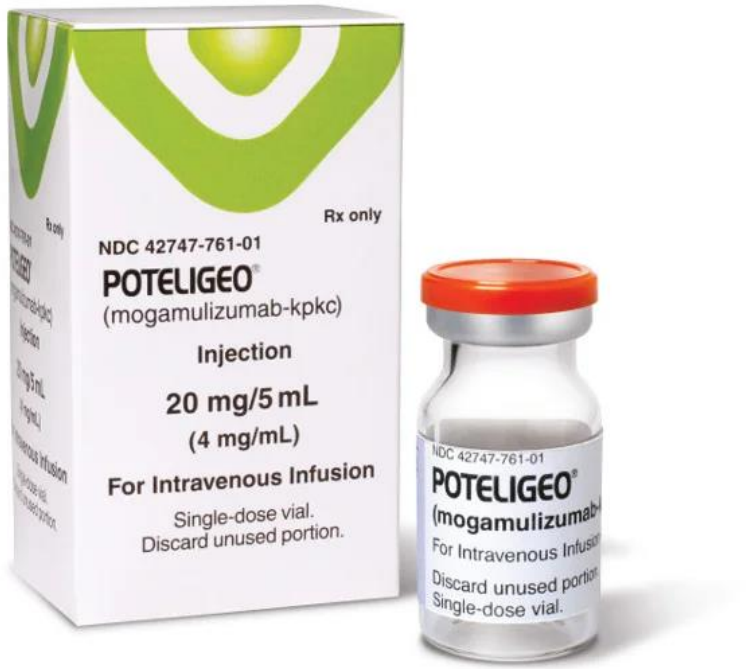
INPHARMD™ **MONOGRAPHS**

Poteligeo®

(mogamulizumab-kpkc)

The latest evidence on drug efficacy & recommendations.



InpharmD™

UPDATED JULY 2023

OVERVIEW

REGIMEN

Generic Name	mogamulizumab-kpkc
Trade Name	Poteligeo®
Manufacturer	Kyowa Kirin
FDA Approval	August 8, 2018
Dosage	1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity
Therapeutic Class	Antineoplastic agents (monoclonal antibody)

Indications

Treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

PHARMACOLOGY

Mogamulizumab-kpkc is a defucosylated, humanized IgG1 kappa monoclonal antibody that binds to CCR4, a G protein-coupled receptor for CC chemokines involved in the transferring lymphocytes to various organs and expressed on the surface of some T-cell malignancies, regulatory T-cells (Treg), and a subset of Th2 T-cells. In vitro studies showed mogamulizumab-kpkc binding targets a cell for antibody-dependent cellular cytotoxicity (ADCC) resulting in depletion of the target cells.

PHARMACODYNAMICS

The exposure-response and time course response are currently unknown.

PHARMACOKINETICS

Absorption: Not defined

Distribution: Vd=3.6 L (20%)

Metabolism: Metabolism studies were not conducted

Elimination: Excretion studies were not conducted

Half Life: 17 days (66%); clearance: 12 mL/h (84%)

CLINICAL DATA OVERVIEW

n = 372 • Kim YH, et al, 2018 • Open-label, international, phase 3, randomised controlled trial

POPULATION

Objective:

Evaluate efficacy and safety of mogamulizumab to vorinostat in patients with previously treated cutaneous T-cell lymphoma

N=372
Mogamulizumab (n=186)
Vorinostat (n=186)

METHODS

Inclusion: Stage Ib-IVB, histologically confirmed relapsed or refractory mycosis fungoides or Sézary syndrome, at least 18 years (>20 years in Japan), failed at least one previous systemic therapy, ECOG score of 1 or less, adequate, hematological, hepatic, and renal function, previously treated with anti-CD4 antibody or alemtuzumab with CD4 cell counts at 200/mm^3

Exclusion: Large cell transformation at study entry, previous mogamulizumab treatment, previous vorinostat treatment (brief exposure without evidence of progression or toxicity on treatment was allowed with sponsor approval), CNS metastasis, active autoimmune disease, clinically significant uncontrolled intercurrent illness, and previous allogeneic transplant

Intervention: Participants received either mogamulizumab 1.0mg/kg (over at least 1 hour on days 1, 8 15, 22 of the first cycle and on days 1 and 15 of subsequent cycles) or vorinostat 400mg once daily with food. Each treatment cycle was 28 days and given until disease progression or other toxicities.

METHODS

Primary Outcome: Progression-free survival was higher in the mogamulizumab group (median 7.7 months [95% CI 5.7–10.3] compared with vorinostat therapy (3.1 months [2.9–4.1]), HR 0.53, 95% CI (0.41-0.69); p<0·0001)

Secondary Outcome:

- A higher percentage of patients achieved an overall response in the mogamulizumab group (28%) compared to vorinostat (5%)
- Duration of response was higher in mogamulizumab patients than the vorinostat group.
- Improvement on the Skindex-29, FACT-G, 3-level

EQ-5D, and Itchy QoL was statistically higher in the mogamulizumab group at the 6-month assessment than in the vorinostat group

Adverse Events: The most common treatment-emergent adverse events were infusion-related reactions, drug rash, diarrhea, and fatigue in the mogamulizumab group. Diarrhea, nausea, thrombocytopenia, and fatigue were the most common adverse events in the vorinostat group.

Deaths occurred in 12/372 patients; 5 in the mogamulizumab group (2 were due to sepsis and polymyositis) and nine in the vorinostat group (2 cases of pulmonary embolism and one of bronchopneumonia)

CONCLUSIONS

Authors' conclusions: Mogamulizumab significantly prolonged progression-free survival compared with vorinostat, and could provide a new, effective treatment for patients with mycosis fungoides and, importantly, for Sézary syndrome, a subtype that represents a major therapeutic challenge in cutaneous T-cell lymphoma.

Critique: Vorinostat is not the first line treatment for treatment of mycosis fungoides or Sézary syndrome; therefore, this may not an appropriate comparator chosen for the study. Additionally, the study was not powered to detect overall survival differences between the groups. Note the study is open-label and may have biases related to non-blinding of the treatments along with the subjectivity of the patient-reported outcomes

n = 372 • Porcu P, et al. (2020) • Open-label, international, phase 3, randomised controlled trial (MAVORIC)

POPULATION

Objective:
Using data from the MAVORIC trial, this study longitudinally assessed the results of the Skindex-29 and FACT-G for symptomatic burden of this disease

N=372
Mogamulizumab (n=186)
Vorinostat (n=186)

METHODS

Inclusion: Same as study conducted by Kim YH, et al. (2018)

Exclusion: Same as study conducted by Kim YH, et al. (2018)

RESULTS

The effects of treatment on HRQoL favored mogamulizumab over vorinostat in all Skindex-29 and FACT-G domains

Median time to symptom worsening on Skindex-29 was 27.4 months for mogamulizumab group compared to 6.6 months for vorinostat group. The time to worsening favored mogamulizumab ($P<0.005$) on all Skindex-29 domains in patients with Sézary Syndrome and time to worsening was similar between MF treatment arms.

CONCLUSIONS

Authors' conclusions: Mycosis fungoides and Sézary Syndrome patients' symptoms, function, and overall QoL favored mogamulizumab over vorinostat across time points. Patients with highest symptom burden and functional impairment derived the most quality of life benefit from mogamulizumab.

Critique: There was missing quality of life data at later cycles due to treatment discontinuation. The FACT-G test was based on patient observations and the Skindex-291 test may be susceptible to recall error after 4 weeks.

ADVERSE EFFECTS

Cardiovascular	Hypertension (≥10%)
Dermatologic	Rash (≥20%), infusion related reactions (≥20%), skin infection (≥10%)
Gastrointestinal	Diarrhea (≥20%), nausea (≥10%), constipation (≥10%), mucositis (≥10%)
Hematologic	Thrombocytopenia (≥10%), anemia (≥10%)
Miscellaneous	Fatigue (≥20%), pyrexia (≥10%), headache (≥10%)
Neuromuscular and Skeletal	Musculoskeletal Pain (≥10%)
Respiratory	Upper Respiratory Tract Infection (≥20%), cough (≥10%)

CONTRA-INDICATIONS

Known hypersensitivity to Vascepa or any of its components

STORAGE

Store intact vials at 2°C to 8°C (36°F to 46°F). Store in original package to protect from light until time of use. Do not freeze. Do not shake. If not used immediately, solution diluted for infusion may be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation; do not freeze or shake diluted solution.

DRUG INTERACTIONS

No drug interaction studies have been conducted with POTELIGEO.

SAFETY CONSIDERATIONS

BOXED WARNINGS

None

WARNINGS & PRECAUTIONS

Dermatologic Toxicity

- Fatal and life-threatening skin reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis have occurred in those who received mogamulizumab-kpkc. Rash (drug eruption) occurred in 25% (30/319) patients treated with mogamulizumab-kpkc and 18% was Grade 3 while 82% of the cases were Grade 1 or 2. In 528 patients in the clinical trial, Grade 3 and 4 skin adverse reactions were reported in 3.6% and <1%, respectively, and <1% was Stevens-Johnson Syndrome.
- The onset of drug eruption was reported in a median time of 15 weeks with 25% of cases occurring after 31 weeks in the clinical trial setting. The common signs and symptoms reported were papular or maculopapular rash, lichenoid, spongiotic or granulomatous dermatitis, and morbilliform rash. Other presentations included scaly plaques, pustular eruption, folliculitis, non-specific dermatitis, and psoriasiform dermatitis.
- Monitor patients for rash through treatment course and manage the toxicities with topical corticosteroids. Consider interruption or discontinuance of the product when necessary. Skin biopsy may also help differentiate drug eruption from disease progression.
- Permanently discontinue mogamulizumab-kpkc for Steven-Johnson Syndrome, toxic epidermal necrolysis, or life-threating Grade 4 reaction. If Steven-Johnson Syndrome or toxic epidermal necrolysis is suspected, interrupt therapy and do not restart until Steven-Johnson Syndrome or toxic epidermal necrolysis is ruled out and the reaction has resolved to Grade 1 or less.

Infusion Reactions

- Fatal and life-threatening infusion reactions have been reported in 35% (112/319) of patients treated with mogamulizumab-kpkc with 8% (being Grade 3) in the clinical trial setting. The reactions (~90%) occurred during or shortly after the first infusion with signs including chills, nausea, fever, tachycardia, rigors, headache, and vomiting.

- Premedication with diphenhydramine and acetaminophen should be considered for the first infusion in all patients. Infusion reactions occurred in 42% of patients without premedication and 32% of those with premedication; therefore, the reduction of the infusion reactions with premedication has not been established.
- Monitor patients for signs and symptoms of infusion reactions and stop the infusion for reactions at any grade and treat appropriately.

Infections

- Fatal and life-threatening infections such as sepsis, pneumonia, and skin infection have occurred. In the clinical trial, 18% (34/184) of patients had a Grade 3 or higher infection or infection-related serious adverse reaction. Monitor patients for signs and symptoms of infection and treat appropriately.

Autoimmune Complications

- Fatal and life threatening immune-mediated complications of Grade 3 or higher such as myositis, myocarditis, polymyositis, hepatitis, pneumonitis, glomerulonephritis, and variant of Guillain-Barre Syndrome have been reported. In the clinical trial setting, systemic immunosuppressants were used in 1.9% (6/319) of participants including a case of Grade 2 polymyalgia rheumatica. New-onset hypothyroidism (Grade 1 or 2) was managed with observation or treatment with levothyroxine in 1.3% of patients. Stop or permanently discontinue mogamulizumab-kpkc for suspected immune-mediated adverse reactions and consider the benefit and risks in patients with a history of autoimmune disease.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after mogamulizumab-kpkc

An increased risk of transplant complications such as acute-graft versus-host-disease, steroid refractory GVHD, and transplant-related death has been reported in those who received allogeneic HSCT after mogamulizumab-kpkc treatment. Those who received mogamulizumab-kpkc prior to the transplant had a higher risk of transplant complications if mogamulizumab-kpkc is given within a shorter time frame (~50 days) before HSCT. Monitor patients for early evidence of transplant-related complications.

IMMUNOGENICITY

There were 44/313 (14.1%) patients treated with mogamulizumab-kpkc who tested positive for anti-mogamulizumab-kpkc antibodies; however, no clinically significant effect of anti-drug antibodies was found related to the pharmacokinetics, safety, or effectiveness of the drug. There were no positive neutralizing antibody responses.

Comparison of incidence of antibodies to mogamulizumab-kpkc with the incidences of antibodies in other studies or to other products may be misleading.t

SAFETY ALERTS

None

USE IN SPECIFIC POPULATIONS

Renal impairment	CrCl <90 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; however, no clinically significant pharmacokinetic changes were observed based on renal impairment.
Hepatic impairment	Mild (total bilirubin ≤ ULN and AST < ULN, or total bilirubin <1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, no clinically significant pharmacokinetic changes were observed based on mild or moderate hepatic impairment. Severe impairment (total bilirubin >3 times ULN and any AST): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Geriatrics	No overall differences in effectiveness were observed between patients >65 years of age and the younger patients. A higher rate of adverse events of Grade 3 or higher were reported in patients >65 years of age compared to those who were less than <65 years of age.
Pediatrics	The safety and effectiveness have not been established in this population.
Reproductive potential	Use of mogamulizumab-kpkc is not recommended during pregnancy or females of childbearing potential not using contraception. Verify pregnancy status prior to initiating the medication. Females of reproductive potential should use effective contraception during treatment and for 3 months following the last dose.
Pregnancy	No data are currently available to inform the use of mogamulizumab-kpkc in pregnant females. In animal studies, no adverse developmental outcomes were seen after exposure to 27 times the recommended human dose; however, mogamulizumab-kpkc was detected in fetal plasma and is not recommended during pregnancy or females of childbearing potential not using contraception.
Lactation	No information is available on the presence of mogamulizumab-kpkc in human milk, the effect on the breastfed child or the effects on milk production. The benefits of using the product for the mother and the potential adverse effects of breastfeeding should be considered.
Pharmacogenomics	N/A

DOSAGE & ADMINISTRATION

Do not give mogamulizumab-kpkc subcutaneously or as a rapid intravenous administration.

Administer diphenhydramine and acetaminophen for the first infusion as premedication.

The recommended dose is 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Mogamulizumab-kpkc should be given within 2 days of the scheduled dose. If a dose is missed, give the next dose as soon as possible and resume the dosing schedule.

No clinically significant changes in the PK of mogamulizumab-kpkc were observed based on renal and hepatic impairment.

Administration: Withdraw the required volume of mogamulizumab into a syringe and transfer to an IV bag containing NS. The final concentration of the diluted solution should be between 0.1 to 3 mg/mL. Gently invert to mix; do not shake. Discard any unused medication left in the vial. Solution diluted for infusion is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

REFERENCES

1. Poteligeo® (mogamulizumab-kpk.) Prescribing Information. Kyowa Kirin, Inc.; 2022.
2. National Comprehensive Cancer Network (*NCCN*). *NCCN* Clinical Practice *Guidelines* in Primary Cutaneous Lymphomas. Mycosis Fungoides/Sézary Syndrome Version 1.2023. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1491. Accessed May 2, 2023.
3. Neelapu SS, Adkins S, Ansell SM, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lymphoma. *Journal for ImmunoTherapy of Cancer.* 2020;8:e001235. doi:10.1136/jitc-2020-001235
4. Grimm SE, Witlox W, Wolff R, et al. Mogamulizumab for previously treated mycosis fungoides and Sézary Syndrome: An evidence review group perspective of a NICE single technology appraisal [published correction appears in Pharmacoeconomics. 2022 Apr 1. *Pharmacoeconomics*. 2022;40(5):509-518. doi:10.1007/s40273-021-01098-3
5. Food and Drug Administration. FDA approves mogamulizumab-kpkc for mycosis fungoides or Sézary syndrome. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-mogamulizumab-kpkc-mycosis-fungoides-or-Sézary-syndrome. Accessed April 27, 2023.
6. Kyowa Kirin. Poteligeo: Resources and Support-Kyowa Kirin Cares—the patient support program for POTELIGEO**.** Available at: https://poteligeo.com/resources-support/patient-support. Accessed April 27, 2023.
7. Center for Drug Evaluation and Research. Poteligeo: Multi-Discipline Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761051Orig1s000MultidisciplineR.pdf. Accessed May 2, 2023.
8. 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 correction appears in Lancet Oncol. 2018 Nov;19(11):e581]. *Lancet Oncol*. 2018;19(9):1192-1204. doi:10.1016/S1470-2045(18)30379-6
9. Porcu P, Hudgens S, Horwitz S, et al. Quality of life effect of the anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in patients with cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):97-105. doi:10.1016/j.clml.2020.09.003
10. Lexicomp Online, Mogamulizumab Drug Monograph Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; July 30, 2021. https://online.lexi.com. Accessed May 2, 2023.
11. IBM Micromedex® Redbook® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com. Accessed April 27, 2023.