POTELIGEO®
(mogamulizumab-kpkc)

Targeted for Control

Practical Use Guide

VERSION 2.0

Indication

POTELIGEO (mogamulizumab-kpkc) injection for intravenous infusion 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).

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.

See accompanying full Prescribing Information.

KYOWA KIRIN

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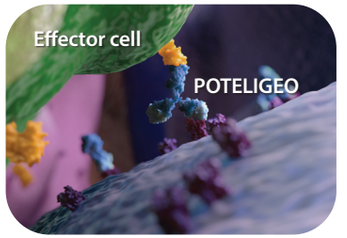
POTELIGEO
A humanized mAb—uniquely targets CCR4+ T-cells for destruction via ADCC

A *nonchemotherapeutic* biologic therapy; recruits the body's own immune cells to kill CCR4+ malignant T-cells[1-3]



Patients may continue POTELIGEO therapy until disease progression or unacceptable toxicity[1]

- No cumulative safety issues associated with long-term exposure[4,5]

CCR4
An important target in MF and SS

CCR4 and its ligands are overexpressed on the surface of malignant T-cells at all stages of MF and SS[6-8]

- CCR4 ligands (TARC and MDC) are involved in T-cell migration; they help recruit CCR4+ T-cells to skin lesions[6,7]

ADCC=antibody-dependent cellular toxicity; CCR4=C-C chemokine receptor type 4; MDC=macrophage-derived chemokine; TARC=thymus and activation-regulated chemokine

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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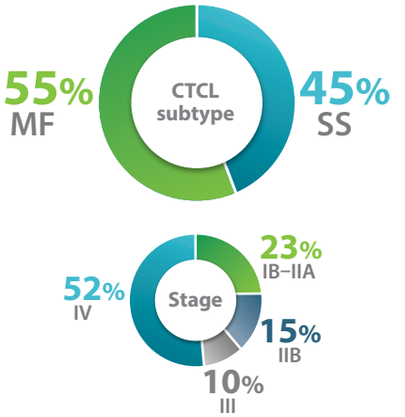
POTELIGEO was studied in a broad range of patients

Baseline clinical disease status (N=372)[1,9]



SELECT DEMOGRAPHICS	
Median age (years)	64
Age range (years)	25 to 101
Sex	58% male
Race	
White	70%
African American	13%
Asian	7%
Other/not reported	10%
Prior systemic therapies	3 (median)

KEY EXCLUSION CRITERIA
Large cell transformation at study entry
Active autoimmune diseases
CNS metastasis
Active infection requiring therapy
Medical conditions requiring systemic corticosteroids or other immunosuppressive medication

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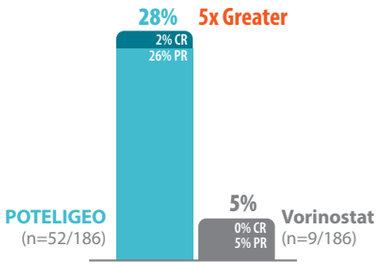
POTELIGEO more than doubled median PFS vs vorinostat

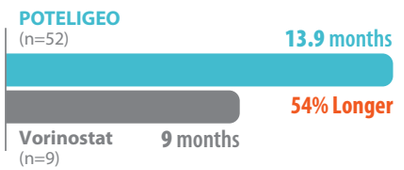
7.6 months vs 3.1 months; *P*<0.001

Greater overall response rate (CR + PR) and longer duration of response

Overall response rate
(*P*<0.001)[a,b]
(Secondary endpoint)



Duration of response
(median)[1]
(Secondary endpoint)



Median time to overall response[c]
(Post hoc analysis)

3.3 months | **5.1 months**

[a] Response was defined by current international response criteria for MF and SS.[10]

[b] **Overall response was defined as ≥50% improvement in skin + ≥50% improvement in at least 1 other involved compartment + no progression of disease in any compartment.[10]**

[c] **Findings from post hoc analyses cannot be used to demonstrate differences between treatments and may not be applicable to all patients initiating POTELIGEO.**

In the first year of treatment, overall response was assessed at the end of Cycle 1 and every 8 weeks thereafter (Cycles 3, 5, 7, etc). After the first year, overall response was assessed every 16 weeks (Cycles 17, 21, 25, etc). Responses from baseline had to be demonstrated at 2 consecutive assessments for patient to be considered a responder.[9]

Median dose intensity was >95% for both treatment arms.[9]

ITT=intent to treat

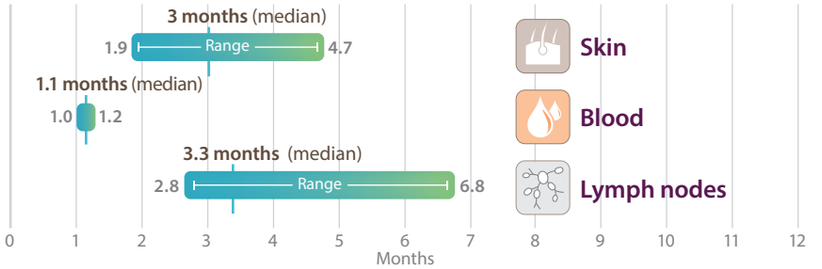
Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

Infections: Monitor patients for signs and symptoms of infection and treat promptly.

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
See accompanying full Prescribing Information.

Time to response[9,a-e]
(Post hoc analysis)



When to expect adverse reactions that may require dosing adjustments[1]

Adverse Reactions can occur at any time during treatment with POTELIGEO. If an adverse reaction occurs always assess the benefit-risk.

Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly. Infusion reactions can also occur with subsequent infusions.

The onset of drug eruption is variable, and the affected areas and appearance vary. Monitor patients for rash throughout the treatment course. Management of dermatologic toxicity includes topical corticosteroids and interruption or permanent cessation of POTELIGEO. Consider skin biopsy to help distinguish drug eruption from disease progression.

[a] Responses in skin and blood must have persisted for ≥4 weeks to be confirmed and were evaluated every 4 weeks during treatment.[9]

[b] Responses in lymph nodes were evaluated at 4 weeks, then every 8 weeks for the first year and every 16 weeks thereafter.[10]

[c] Response defined as ≥50% clearance of skin disease without new tumors, evaluated using the modified Severity Weighted Assessment Tool (mSWAT).[10]

[d] Response defined as >50% decrease in blood tumor burden, assessed by central flow cytometry.[10]

[e] Response defined as cumulative reduction ≥50% of measurable disease of each abnormal lymph node and no new abnormal lymph nodes, evaluated by computed tomography (CT) scans.[10]

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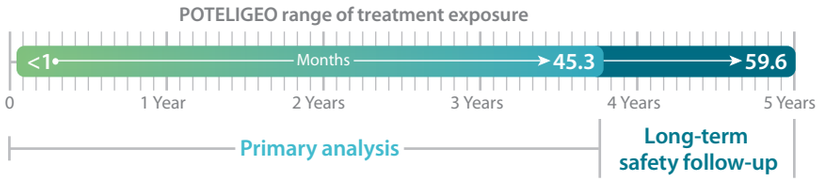
Consistent safety profile with long-term use

No cumulative safety issues associated with long-term exposure[4,5]

- No increase in rates of drug eruption or infusion reaction from primary analysis[4,5]
- No new safety or autoimmune concerns emerged with higher exposure[4,5]

No new safety issues with exposure up to 5 years[4,5]



48% treated for at least 6 months[1]

23% treated for at least 12 months[1]

- Patients may continue POTELIGEO therapy until disease progression or unacceptable toxicity[1]
- Median treatment exposure was 2x longer (POTELIGEO, 5.6 months; vorinostat, 2.8 months)[1]

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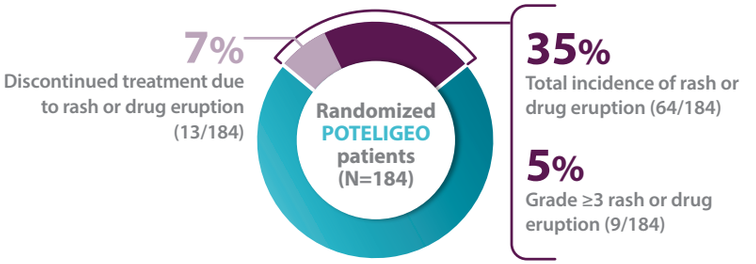
Discontinuation rate due to rash or drug eruption[1,a]



Once drug eruption was resolved, some patients in MAVORIC chose to continue POTELIGEO therapy treatment for as long as they derived clinical benefit.

Discontinuation due to adverse reactions

- POTELIGIO: 18%[1]
- Vorinostat: 23%

[a] Rash/drug eruption was most common reason for discontinuation.

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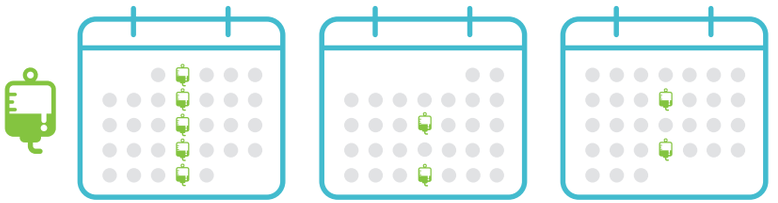
Dosing[1]

RECOMMENDED DOSE: 1 mg/kg

Administer intravenous infusion over at least 1 hour through a 0.22 micron (or equivalent) in-line filter

DOSING SCHEDULE



Administer once weekly for the first 5 infusions, then once every 2 weeks thereafter

RECOMMENDED PREMEDICATIONS FOR PROPHYLAXIS

First infusion	Administer premedication with diphenhydramine and acetaminophen prior to the first POTELIGEO infusion
If infusion reaction occurs	Prior to subsequent infusions, administer diphenhydramine and acetaminophen

33% of patients (61/184) experienced an infusion reaction[1]

- 2% (4/184) were >grade 3
- ~90% occurred during or shortly after first infusion

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

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.

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
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No dosing changes required in special populations[1]

No clinically significant changes in pharmacokinetics based on:

- ☑ Age (range 22-101 years)
- ☑ Renal impairment (mild, moderate, or severe)
- ☑ Hepatic impairment (mild or moderate)
- ☑ Disease subtype (MF or SS)
- ☑ CCR4 expression level
- ☑ Eastern Cooperative Oncology Group (ECOG) status
- ☑ Sex
- ☑ Ethnicity

No differences in efficacy between older and younger patients:

- ☑ <65 years of age
- ☑ ≥65 years of age
  In the phase 3 trial, 51% of patients were ≥65 years of age (range: 25 to 101)

Drug interactions

- No drug interaction studies have been conducted with POTELIGEO

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Dose modifications for adverse reactions[1]

Monitor for infusion reactions

Common signs of infusion reactions

chills | nausea | fever | tachycardia | rigors | headache | vomiting

FOR INFUSION REACTIONS

3% incidence in phase 3 trial

Grade	CTCAE v4.03 description[a]	Management and dosing recommendations
4 (life-threatening)	Life-threatening consequences; urgent intervention indicated	Permanently discontinue POTELIGEO
3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Temporarily interrupt the infusion of POTELIGEO and treat symptoms • Slow infusion rate by at least 50% when restarting the infusion after symptoms resolve • If reaction recurs and is not manageable, discontinue infusion • Prior to subsequent infusions, administer diphenhydramine and acetaminophen
2 (moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	
1 (mild)	Mild transient reaction	

[a] CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Monitor patients for rash throughout the treatment course

Rash (drug eruption) may be visually indistinguishable from disease progression. Consider skin biopsy to help make a differential diagnosis.

FOR DERMATOLOGIC TOXICITY

4% incidence in phase 3 trial

Grade	CTCAE v4.03 description[a]	Management and dosing recommendations
4 (life-threatening)	Life-threatening consequences; urgent intervention indicated	Permanently discontinue POTELIGEO for a life-threatening rash • Permanently discontinue POTELIGEO for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) • If SJS or TEN is suspected, stop POTELIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has been resolved to grade 1 or less
3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Temporarily interrupt treatment and administer at least 2 weeks of topical corticosteroids • If, after administration of topical corticosteroids, the rash improves to grade 1 or less, POTELIGEO may be resumed
2 (moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	
1 (mild)	Mild transient reaction	Consider using topical corticosteroids

[a] CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

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Dose scheduling adjustments[1]

Administration timing

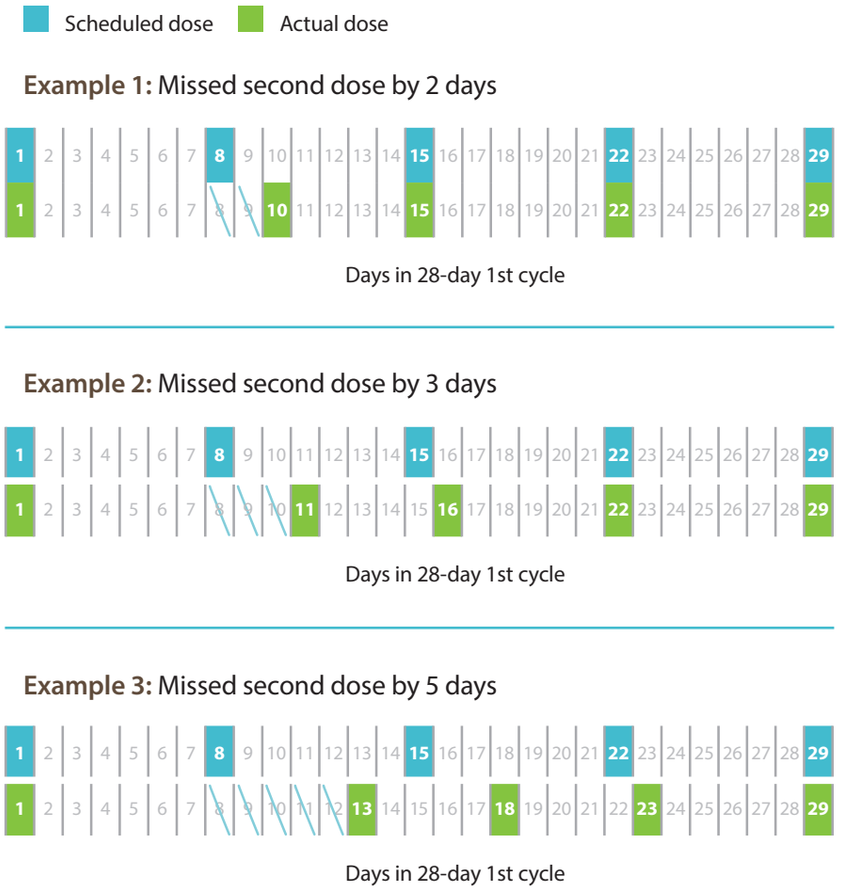
If a dose is missed, administer the next dose as soon as possible, with these schedule adjustments:

- If dose is administered within 2 days of schedule, continue original schedule (Example 1)
- Do not administer doses closer than 5 days apart
- If dose is administered within 3 to 4 days of schedule, reschedule subsequent doses (Example 2)
- If dose is administered 5 or more days beyond schedule, reschedule subsequent doses (Example 3)

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.



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Adverse reactions

In ≥10% of patients with a ≥2% higher incidence within the POTELIGEO treatment arm[1,a,b]

ADVERSE REACTIONS	POTELIGEO (n=184)	
Body system	**All grades (%)**	**≥grade 3 (%)**
Skin and subcutaneous tissue disorders		
Rash, including drug eruption[c]	35	5
Drug eruption[c]	24	5
Procedural complications		
Infusion-related reaction[c]	33	2
Infections		
Upper respiratory tract infection	22	0
Skin infection	19	3
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	22	<1
General disorders		
Pyrexia	17	<1
Gastrointestinal		
Mucositis	12	1

20% crossed over to POTELIGEO due to adverse reactions.[10]

No specific laboratory test is required to prescribe POTELIGEO.

[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.

See adverse reactions section 6 in the full Prescribing Information for more common adverse events.

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Laboratory abnormalities

In ≥10% of patients with a ≥2% higher incidence within the POTELIGEO treatment arm[1,a]

LABORATORY TEST	POTELIGEO (n=184)	
	All grades (%)	**≥grade 3 (%)**
Chemistry		
Albumin decreased	34	2
Calcium decreased	30	3
Uric acid increased	29	29
Phosphate decreased	27	5
Magnesium decreased	17	<1
Glucose decreased	14	0
Calcium increased	12	<1
Hematology		
CD4 lymphocytes decreased[b]	63	43
Lymphocytes decreased	31	16
White blood cells decreased	33	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 evaluable recipients of POTELIGEO.

- No specific laboratory test is required to prescribe POTELIGEO

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Monitoring for adverse reactions[1]

Infections

- Monitor patients for signs and symptoms of infection and treat promptly
- Infections such as pneumonia, skin infection, and sepsis (including fatal or life-threatening outcomes) have occurred in patients treated with POTELIGEO
- In the phase 3 clinical trial, 18% (34/184) of patients randomized to POTELIGEO had ≥grade 3 infections or infection-related serious adverse reactions

Autoimmune complications

- Consider the benefit/risk of POTELIGEO in patients with a history of autoimmune disease
- Interrupt or permanently discontinue POTELIGEO as appropriate for suspected immune-mediated adverse reactions
- Immune-mediated complications, including fatal and life-threatening outcomes, have been reported
- ≥Grade 3 immune-mediated or possibly immune-mediated reactions have included:
    - Myositis
    - Myocarditis
    - Polymyositis
    - Hepatitis
    - Pneumonitis
    - A variant of Guillain-Barré syndrome

Complications of allogeneic hematopoietic stem cell transplantation (HSCT) after POTELIGEO

- Follow patients closely for early evidence of transplant-related complications
- Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after POTELIGEO, including:
    - Severe (grades 3 or 4) acute graft-versus-host disease (GVHD)
    - Steroid-refractory GVHD
    - Transplant-related death
- If POTELIGEO is given within a shorter time frame (~50 days) before HSCT, higher risk of transplant complications has been reported

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How to calculate a dose

DOSING CALCULATION EXAMPLE FOR PATIENT WEIGHING 67 kg (147 lbs)	
Formula	**Sample calculation**
1. Calculate dose • Patient weight (kg) x 1 mg per kg = total dose	67 kg x 1 mg per kg = 67 mg
2. Calculate number of vials • Each 5 mL POTELIGEO vial contains 20 mg of mogamulizumab-kpkc antibody for IV injection (4 mg/mL) • To determine the number of vials that will be needed for a patient's dose, divide the total milligram dose by 20 or **see vial calculation table on opposite page**	67 mg ÷ 20 mg/vial = 3.35 (4 vials needed) Note: Dose is based on total milliliters (mL), not the number of vials. Please see step 3 to calculate dose volume.
3. Calculate total volume of POTELIGEO IV solution required to provide the prescribed dose • Volume of 4 mg/mL POTELIGEO = prescribed dose ÷ 4 mg/mL	67 mg ÷ 4 mg/mL = 16.75 mL (3 full vials + 1.75 mL from 4th vial needed)
4. Calculate final concentration of diluted solution • Note: The final concentration of the diluted solution should be between 0.1 mg/mL and 3.0 mg/mL • Typically, a 100 mL infusion bag will be appropriate for most patients and doses, but total infusion volumes ranging from 50 mL to 250 mL may be used • To verify concentration, use this formula: final concentration = total dose (mg) ÷ total volume (mL)	If using a 100 mL infusion bag: 67 mg ÷ (100 mL + 16.75 mL) = 0.57 mg/mL √ In range If using a 250 mL infusion bag: 67 mg ÷ (250 mL + 16.75 mL) = 0.25 mg/mL √ In range

VIAL CALCULATION BY PATIENT WEIGHT	
Patient weight	**Number of vials**
≤40 kg (≤88 lbs)	2 (40 mg)
>40 kg to 60 kg (88 lbs to 132 lbs)	3 (60 mg)
>60 kg to 80 kg (132 lbs to 176 lbs)	4 (80 mg)
>80 kg to 100 kg (176 lbs to 220 lbs)	5 (100 mg)

For more information on how to prepare and administer POTELIGEO, visit the Resources section of www.poteligeohcp.com and view a video presentation by a Nurse Practitioner and an Infusion Nurse.

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Preparation[1]

How to mix POTELIGEO

1. Visually inspect drug product solution for particulate matter and discoloration prior to administration. POTELIGEO is a clear to slightly opalescent colorless solution. Do not use the vial if cloudiness, discoloration, or particulates are observed.

2. Calculate the dose (mg/kg) and number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight. Each vial contains 20 mg of POTELIGEO, which is enough for 20 kg of body weight. Please see page 20 for dosing calculation example.

3. Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an IV bag[a] containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL and 3.0 mg/mL.

4. Mix diluted solution by gentle inversion. Do not shake. After preparation, infuse the POTELIGEO solution immediately or store under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation. Do not freeze. Do not shake.

5. Discard any unused portion left in the vial.

[a] The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

How supplied

POTELIGEO is supplied in a carton containing one 20 mg/5 mL (4 mg/mL), single-dose glass vial (NDC 42747-761-01).

Storage and handling

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original package to protect from light until time of use. Do not freeze. Do not shake.

For more information on how to prepare and administer POTELIGEO, visit the Resources section of www.poteligeohcp.com and view a video presentation by a Nurse Practitioner and an Infusion Nurse.

Important Safety Information *(continued)*

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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Access and reimbursement assistance

KYOWA KIRIN cares
ACCESS • ASSISTANCE • UNDERSTANDING

Available support

The Kyowa Kirin Cares program supports patients throughout their POTELIGEO treatment, providing:

- Reimbursement support services
- Copay program (for eligible patients, subject to complete terms and conditions)
- Access to an oncology nurse specialist

To learn more about Kyowa Kirin Cares or to enroll a patient, call **1-833-KKCARES (1-833-552-2737)** or visit **www.KyowaKirinCares.com.**

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
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Ordering

Order now through McKesson

NDCs for POTELIGEO
42747-761-01

To convert the 10-digit NDC registered with the Food and Drug Administration (FDA) for POTELIGEO to an 11-digit NDC, a payer may require you to add a leading **zero (0) or an asterisk (*)** to the first position in the middle set of numbers.

42747-0761-01 or 42747-*761-01

To help facilitate reimbursement, it is recommended that initial claims are submitted with:

A copy of the purchase invoice | **Patient medical records**

To place your order, log on to **www.mckesson.com/customer-login/** or call **1-800-482-6700.**

For informational purposes only; not a statement, representation, promise or guarantee that this code will be appropriate, or that reimbursement will be made for any particular claim. Each hospital/physician must use independent clinical judgement to select the code(s) that most accurately reflect a patient's condition and the procedure(s) performed.

Effective October 1, 2019
Permanent J Code 9204

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Frequently asked questions

Q How does POTELIGEO work?

A POTELIGEO is a *nonchemotherapeutic* biologic therapy; it is a targeted monoclonal antibody that recruits the body's own immune cells to kill CCR4+ malignant T-cells. CCR4 is an important target in MF and SS; CCR4 and its ligands are overexpressed on the surface of malignant T-cells at all disease stages and they are involved in T-cell migration to skin lesions.[1-3,6-8]

Q Does a patient need to be tested for CCR4 prior to administering POTELIGEO?

A No, it is not required. In the phase 3 clinical trial, 75% (n=140) of patients were tested for CCR4 status and all had CCR4 detected on ≥1% of lymphocytes on skin biopsy. CCR4 was detected on ≥10% of malignant lymphocytes in 96% (n=134) of patients tested.[1]

Q How soon can a response to POTELIGEO treatment be expected?

A In the MAVORIC trial, median time to overall response was 3.3 months (compared with 5.1 months with vorinostat). Median times to response with POTELIGEO in individual disease compartments were[1]:

- Skin, 3 months (range: 1.9–4.7)
- Blood, 1.1 months (range: 1–1.2)
- Lymph nodes, 3.3 months (range: 2.8–6.8)

Important Safety Information *(continued)*

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).

Q What should be done if a patient misses a dose?

A The first 5 doses of POTELIGEO should be administered weekly. This means on Days 1, 8, 15, and 22 of the first 28-day cycle, and on Day 1 of the second 28-day cycle. If the dose is administered within 2 days of these scheduled doses, continue the original schedule. If the scheduled dose is missed by more than 2 days, administer the missed dose as soon as possible and resume dosing schedule, but do not administer doses closer than 5 days apart. After the 5th infusion, administer POTELIGEO once every 2 weeks (on Days 1 and 15 of every 28-day cycle, beginning with Cycle 2). See pages 14-15 for examples of modifications to dosing schedule.

Q What should be done if a patient wishes to travel while being administered POTELIGEO?

A Make sure they take along the phone numbers of all their healthcare providers and a complete list of all medications they are taking, including the dosages, schedules, and generic names.

Write a letter on official stationery explaining the patient's condition, treatment regimen, and medications, and advise the patient to keep it with them at all times.

Advise the patient to compile a list of resources available at their destination, such as an oncology hospital, an oncologist, and emergency facility.

Have the patient contact their insurance company to see what medical coverage it provides when away from home and if there are preferred or in-network facilities under their plan at their destination.

While traveling, the patient should seek immediate emergency medical care if they experience skin problems, infusion reactions, serious infections, autoimmune complications, or complications of stem cell transplant. The patient should have the on-call physician contact their oncologist to discuss the patient's medical situation and how best to respond. (Source: NCCN: Patient and Caregiver Resources: Traveling with Cancer)[11]

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
See accompanying full Prescribing Information.

POTELIGEO®
(mogamulizumab-kpkc)
Targeted for Control

Frequently asked questions *(cont'd)*

Q How often did patients discontinue treatment with POTELIGEO as a result of adverse reactions in clinical trials?

A POTELIGEO was discontinued for adverse reactions in 18% (33/184) of patients. The most common cause (7%) was rash or drug eruption.[1]

Q How long will a patient be on POTELIGEO?

A Patients can continue on treatment until disease progression or unacceptable toxicity occurs. During a clinical trial, the range of POTELIGEO treatment exposure was up to 59.6 months. No new safety or autoimmune concerns emerged with higher exposure.[4,5]

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.

Q How is a POTELIGEO dose calculated?

A Calculate a dose by taking the patient's weight in kilograms (kgs) and multiplying 1 mg per kg. For example, for a patient weighing 147 pounds, calculate the total dose using the following formula:

147 lbs = 67 kg x 1 mg per kg = 67 mg

POTELIGEO comes in 20 mg per vial. Each single-use vial contains 20 mg of POTELIGEO in 5 mL of solution. See pages 20-21 for more information on dosing calculations.

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
See accompanying full Prescribing Information.

POTELIGEO®
(mogamulizumab-kpkc)
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Treatment checklists

Prior to treatment

- ☐ This document has been reviewed in its entirety
- ☐ The Prescribing Information has been reviewed
  - Dose modifications for infusion reactions, dermatologic toxicity, and autoimmune complications (*see sections 2.2 and 5.4 of Prescribing Information*)
  - Warnings and precautions (*see section 5 of Prescribing Information*)
- ☐ The "A Guide to Scheduling and Monitoring Your Treatment" tool has been reviewed with the patient and the infusion schedule confirmed
- ☐ For a female patient with reproductive potential, her pregnancy status has been verified (*see section 8.1 of Prescribing Information*)
  - If the patient has reproductive potential, she has been advised to use effective contraception during treatment with POTELIGEO and for at least 3 months following the last POTELIGEO dose (*see section 8.3 of Prescribing Information*)
- ☐ The patient knows about support services available through the Kyowa Kirin Cares program

Important Safety Information *(continued)*

Warnings and Precautions *(continued)*

Infections: Monitor patients for signs and symptoms of infection and treat promptly.

Administering an infusion

- ☐ The patient's laboratory results have been reviewed per the institution's routine monitoring protocol
- ☐ Monitoring for infusion reactions is being done
- ☐ The patient's weight has been confirmed to calculate dosage (*see section 2.1 of Prescribing Information*)
- ☐ If this is the patient's first infusion, premedication with diphenhydramine and acetaminophen has been administered
  - A drug reaction response protocol is in place (highly recommended; *see monitoring and management of adverse reactions on pages 16-19*)
- ☐ After mixing POTELIGEO, it appears clear or opalescent and contains no particulates
- ☐ POTELIGEO is being administered through a 0.22 micron (or equivalent) in-line filter
- ☐ POTELIGEO is being infused over AT LEAST 1 hour. Slow that rate down if patient has had a reaction in the past

Throughout treatment

- ☐ The patient is being monitored for rash (drug eruption) (*see section 5.1 of Prescribing Information*)
- ☐ The patient is being monitored for signs and symptoms of infections, autoimmune complications, and complications of allogeneic HSCT (*see pages 18-19*)

Please see additional Important Safety Information throughout and full Important Safety Information on pages 32-33.
See accompanying full Prescribing Information.

POTELIGEO® (mogamulizumab-kpkc)
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Indication

POTELIGEO (mogamulizumab-kpkc) injection for intravenous infusion 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).

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.

Infections: Monitor patients for signs and symptoms of infection and treat promptly.

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.

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%).

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.

References: 1. POTELIGEO [package insert]. Kyowa Kirin Inc., Bedminster, NJ USA. **2.** Ishida T, Iida S, Akatsuka Y, et al. The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-cell leukemia/lymphoma. *Clin Cancer Res*. 2004;10:7529-7539. **3.** Duvic M, Evans M, Wang C. Mogamulizumab for the treatment of cutaneous T-cell lymphoma: recent advances and clinical potential. *Ther Adv Hematol*. 2016;7: 171-174. **4.** Kim Y, Bagot MD, Zinzani PL, et al. Safety of mogamulizumab in mycosis fungoides and Sézary syndrome: final results from the phase 3 MAVORIC study. *Blood*. 2019;134(suppl):5300 [abstract]. **5.** Bagot M, Dalle S, Lubomir S, et al. Long-term clinical benefit to anti-CCR4 mogamulizumab: results from the phase 3 MAVORIC study in previously treated cutaneous T-cell lymphoma (CTCL). Presented at the American Society of Hematology (ASH) 60th Annual Meeting: December 1-4; San Diego, CA, USA. **6.** Ferenczi K, Fuhlbrigge RC, Pinkus J, et al. Increased CCR4 expression in cutaneous T cell lymphoma. *J Invest Dermatol*. 2002;119: 1405-1410. **7.** Kakinuma T, Sugaya M, Nakamura K, et al. Thymus and activation-regulated chemokine (TARC/CCL17) in mycosis fungoides: serum TARC levels reflect the disease activity of mycosis fungoides. *J Am Acad Dermatol*. 2003;48:23-30. **8.** Kallinich T, Muche JM, Qin S, et al. Chemokine receptor expression on neoplastic and reactive T cells in the skin at different stages of mycosis fungoides. *J Invest Dermatol*. 2003;121:1045-1052. **9.** 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. *Lancet Oncol*. 2018;19:1192-1204. **10.** Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29:2598-2607. **11.** National Comprehensive Cancer Network. Traveling with cancer. https://www.nccn.org/patients/resources/life_with_cancer/traveling.aspx. Accessed February 1, 2020.

POTELIGEO®
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Please see accompanying full Important Safety Information.

Available support

The Kyowa Kirin Cares program supports patients throughout their POTELIGEO treatment, providing:

- Reimbursement support services
- Copay program (for eligible patients, subject to complete terms and conditions)
- Access to an oncology nurse specialist

For more information:
1-833-KKCARES (1-833-552-2737)
or **www.KyowaKirinCares.com.**

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www.poteligeohcp.com

PM-US-POT-0142 July 2020

KYOWA KIRIN

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use POTELIGEO safely and effectively. See full prescribing information for POTELIGEO.

POTELIGEO® (mogamulizumab-kpkc) injection, for intravenous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

POTELIGEO is a CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy [1].

----------DOSAGE AND ADMINISTRATION----------

1 mg/kg as an intravenous infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle [2].

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 20 mg/5 mL (4 mg/mL) solution in a single-dose vial [3].

----------CONTRAINDICATIONS----------

None [4].

----------WARNINGS AND PRECAUTIONS----------

- Dermatologic Toxicity: Temporarily interrupt POTELIGEO for moderate or severe skin rashes. Permanently discontinue POTELIGEO for life-threatening rash [5.1].
- Infusion Reactions: Temporarily interrupt POTELIGEO for any infusion reaction. Permanently discontinue POTELIGEO for any life-threatening infusion reaction [5.2].
- Infections: Monitor and treat promptly [5.3].
- Autoimmune Complications: Interrupt or permanently discontinue POTELIGEO as appropriate [5.4].
- Complications of Allogeneic HSCT after POTELIGEO: Monitor for severe acute graft-versus-host disease (GVHD) and steroid-refractory GVHD. Transplant-related mortality has occurred. [5.5].

----------ADVERSE REACTIONS----------

The most common adverse reactions (reported in ≥20% of patients) were rash, infusion related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection [6.1].

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA- approved patient labeling.

Revised: 08/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of POTELIGEO 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.

Administer POTELIGEO within 2 days of the scheduled dose. If a dose is missed, administer the next dose as soon as possible and resume dosing schedule.

Do not administer POTELIGEO subcutaneously or by rapid intravenous administration.

Recommended Premedications
Administer premedication with diphenhydramine and acetaminophen for the first POTELIGEO infusion.

2.2 Dose Modifications for Toxicity

Dermatologic Toxicity

- Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [*see Warnings and Precautions (5.1)*]. If SJS or TEN is suspected, stop POTELIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has resolved to Grade 1 or less.
- If moderate or severe (Grades 2 or 3) rash occurs, interrupt POTELIGEO and administer at least 2 weeks of topical corticosteroids. If rash improves to Grade 1 or less, POTELIGEO may be resumed [*see Warnings and Precautions (5.1)*].
- If mild (Grade 1) rash occurs, consider topical corticosteroids.

Infusion Reactions

- Permanently discontinue POTELIGEO for a life-threatening (Grade 4) infusion reaction [*see Warnings and Precautions (5.2)*].
- Temporarily interrupt the infusion of POTELIGEO for mild to severe (Grades 1 to 3) infusion reactions and treat symptoms. Reduce the infusion rate by at least 50% when restarting the

infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion. [*see Warnings and Precautions (5.2)*].
- If an infusion reaction occurs, administer premedication (such as diphenhydramine and acetaminophen) for subsequent POTELIGEO infusions.

2.3 Preparation and Administration

Preparation

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. POTELIGEO is a clear to slightly opalescent colorless solution. Discard the vial if cloudiness, discoloration, or particulates are observed.
- Calculate the dose (mg/kg) and number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight.
- Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

Administration

- Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron (or equivalent) in-line filter.
- Do not mix POTELIGEO with other drugs.
- Do not co-administer other drugs through the same intravenous line.

Storage of Diluted Solution

After preparation, infuse the POTELIGEO solution immediately, or store under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation. Do not freeze. Do not shake.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 mg/5 mL (4 mg/mL) as a clear to slightly opalescent colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Dermatologic Toxicity

Fatal and life-threatening skin adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in recipients of POTELIGEO. Rash (drug eruption) is one of the most common adverse reactions associated with POTELIGEO. In Trial 1, 25% (80/319) of patients treated with POTELIGEO had an adverse reaction of drug eruption, with 18% of these cases being severe (Grade 3) and 82% of these cases being Grade 1 or 2. Of 528 patients treated with POTELIGEO in clinical trials, Grade 3 skin adverse reactions were reported in 3.6%, Grade 4 skin adverse reactions in <1%, and SJS in <1%.

The onset of drug eruption is variable, and the affected areas and appearance vary. In Trial 1, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. The more common presentations reported included 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 throughout the treatment course. Management of dermatologic toxicity includes topical corticosteroids and interruption or permanent cessation of POTELIGEO [*see Dosage and Administration (2.2)*]. Consider skin biopsy to help distinguish drug eruption from disease progression.

Discontinue POTELIGEO permanently for SJS or TEN or for any life-threatening (Grade 4) reaction. For possible SJS or TEN, interrupt POTELIGEO and do not restart unless SJS or TEN is ruled out and the cutaneous reaction has resolved to Grade 1 or less.

5.2 Infusion Reactions

Fatal and life-threatening infusion reactions have been reported in patients treated with POTELIGEO. In Trial 1, infusion reactions occurred in 35% (112/319) of patients treated with POTELIGEO, with 8% of these reactions being severe (Grade 3). Most reactions (approximately 90%) occur during or shortly after the first infusion. Infusion reactions can also occur with subsequent infusions. The most commonly reported signs include chills, nausea, fever, tachycardia, rigors, headache, and vomiting.

Consider premedication (such as diphenhydramine and acetaminophen) for the first infusion of POTELIGEO in all patients. Whether premedication reduces the risk or severity of these reactions is not established. In Trial 1, infusion reactions occurred in 42% of patients without premedication and 32% of patients with premedication. Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly [*see Dosage and Administration (2.2)*].

5.3 Infections

Fatal and life-threatening infections have occurred in patients treated with POTELIGEO, including sepsis, pneumonia, and skin infection. In Trial 1, 18% (34/184) of patients randomized to POTELIGEO had Grade 3 or higher infection or an infection-related serious adverse reaction. Monitor patients for signs and symptoms of infection and treat promptly.

5.4 Autoimmune Complications

Fatal and life-threatening immune-mediated complications have been reported in recipients of POTELIGEO. Grade 3 or higher immune-mediated or possibly immune-mediated reactions have included myositis, myocarditis, polymyositis, hepatitis, pneumonitis, and a variant of Guillain-Barré syndrome. Use of systemic immunosuppressants for immune-mediated reactions was reported in 1.9% (6/319) of recipients of POTELIGEO in Trial 1, including for a case of Grade 2 polymyalgia rheumatica. New-onset hypothyroidism (Grade 1 or 2) was reported in 1.3% of patients and managed with observation or levothyroxine. 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.

5.5 Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after POTELIGEO

Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after POTELIGEO including severe (Grade 3 or 4) acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and transplant-related death. Among recipients of pre-transplantation POTELIGEO, a higher risk of transplant complications has been reported if POTELIGEO is given within a shorter time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Dermatologic Toxicity [*see Warnings and Precautions (5.1)*].
- Infusion Reactions [*see Warnings and Precautions (5.2)*].
- Infections [*see Warnings and Precautions (5.3)*].
- Autoimmune Complications [*see Warnings and Precautions (5.4)*].
- Complications of Allogeneic HSCT after POTELIGEO [*see Warnings and Precautions (5.5)*].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Trial 1
The data described below reflect exposure to POTELIGEO in a randomized, open-label, actively controlled clinical trial for adult patients with MF or SS who received at least one prior systemic therapy [*see Clinical Studies (14)*]. Of 370 patients treated, 184 (57% with MF, 43% with SS) received POTELIGEO as randomized treatment and 186 (53% with MF, 47% with SS) received vorinostat. In the vorinostat arm, 135 patients (73%) subsequently crossed over to POTELIGEO for a total of 319 patients treated with POTELIGEO.

POTELIGEO was administered at 1 mg/kg intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles. Premedication (diphenhydramine, acetaminophen) was optional and administered to 65% of randomized patients for the first infusion. The comparator group received vorinostat 400 mg orally once daily, given continuously in 28-day cycles. Treatment continued until unacceptable toxicity or progressive disease.

The median age was 64 years (range, 25 to 101 years), 58% of patients were male, 70% were white, and 99% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median of 3 prior systemic therapies. The trial required an absolute neutrophil count (ANC) ≥1500/μL (≥1000/μL if bone marrow was involved), platelet count ≥100,000/μL (≥75,000/μL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL, and hepatic transaminases ≤2.5 times upper limit of normal (ULN) (≤5 times ULN if lymphomatous liver infiltration). Patients with active autoimmune disease, active infection, autologous HSCT within 90 days, or prior allogeneic HSCT were excluded.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months, with 48% (89/184) of patients with at least 6 months of exposure and 23% (43/184) with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months, with 22% (41/186) of patients with at least 6 months of exposure.

Fatal adverse reactions within 90 days of the last dose occurred in 2.2% (7/319) of patients who received POTELIGEO as randomized or crossover treatment.

Serious adverse reactions were reported in 36% (66/184) of patients randomized to POTELIGEO and most often involved infection (16% of patients; 30/184). Serious adverse reactions reported in >2% of patients randomized to POTELIGEO were pneumonia (5%), sepsis (4%), pyrexia (4%), and skin infection (3%); other serious adverse reactions, each reported in 2% of patients, included hepatitis, pneumonitis, rash, infusion related reaction, lower respiratory tract infection, and renal insufficiency. POTELIGEO was discontinued for adverse reactions in 18% of randomized patients, most often due to rash or drug eruption (7.1%).

Common Adverse Reactions
The most common adverse reactions (reported in ≥20% of patients randomized to POTELIGEO) were rash (including drug eruption), infusion related reactions, fatigue, diarrhea, upper respiratory tract infection and musculoskeletal pain. Other common adverse reactions (reported in ≥10% of patients randomized to POTELIGEO) included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough and hypertension. Table 1 summarizes common adverse reactions having a ≥2% higher incidence with POTELIGEO than with vorinostat in Trial 1.

Table 1: Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Adverse Reactions by Body System [a, b]	POTELIGEO (N=184)		Vorinostat (N=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Skin and Subcutaneous Tissue Disorders				
Rash, Including Drug Eruption	35	5	11	2
Drug Eruption	24	5	<1	0
Procedural Complications				
Infusion Related Reaction	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.

Rash/Drug Eruption includes: dermatitis (allergic, atopic, bullous, contact, exfoliative, infected), drug eruption, palmoplantar keratoderma, rash (generalized, macular, maculopapular, papular, pruritic, pustular), skin reaction, toxic skin eruption

Upper Respiratory Tract Infection includes: laryngitis viral, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

Skin Infection includes: cellulitis, dermatitis infected, erysipelas, impetigo, infected skin ulcer, periorbital cellulitis, skin bacterial infection, skin infection, staphylococcal skin infection

Musculoskeletal Pain includes: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity

Mucositis includes: aphthous stomatitis, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, stomatitis

Other Common Adverse Reactions in ≥10% of POTELIGEO Arm [a, b]

- **General disorders:** fatigue (31%), edema (16%)
- **Gastrointestinal disorders:** diarrhea (28%), nausea (16%), constipation (13%)
- **Blood and lymphatic system disorders**: thrombocytopenia (14%), anemia (12%)
- **Nervous system disorders:** headache (14%)
- **Vascular disorders:** hypertension (10%)
- **Respiratory disorders:** cough (11%)

Adverse Reactions in ≥5% but <10% of POTELIGEO Arm [a, b]

- **Infections:** candidiasis (9%), urinary tract infection (9%), folliculitis (8%), pneumonia (6%), otitis (5%), herpesvirus infection (5%)
- **Investigations:** renal insufficiency (9%), hyperglycemia (9%), hyperuricemia (8%), weight increase (8%), weight decrease (6%), hypomagnesemia (6%)
- **Psychiatric disorders:** insomnia (9%), depression (7%)
- **Skin and subcutaneous disorders:** xerosis (8%), alopecia (7%)
- **Nervous system disorders:** dizziness (8%), peripheral neuropathy (7%)
- **Metabolism and nutrition disorders:** decreased appetite (8%)
- **Respiratory disorders:** dyspnea (7%)
- **General disorders:** chills (7%)
- **Gastrointestinal disorders:** vomiting (7%), abdominal pain (5%)
- **Injury, poisoning and procedural complications:** fall (6%)
- **Musculoskeletal disorders:** muscle spasms (5%)
- **Cardiovascular disorders:** arrhythmia (5%)
- **Eye disorders:** conjunctivitis (5%)

Selected Other Adverse Reactions [a, b]

- Tumor lysis syndrome (<1%)
- Myocardial ischemia or infarction (<1%)
- Cardiac failure (<1%)

[a] Includes grouped terms
[b] From 184 patients randomized to POTELIGEO

Table 2 summarizes common treatment-emergent laboratory abnormalities having a ≥2% higher incidence with POTELIGEO than with vorinostat.

Table 2: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Laboratory Test [a]	POTELIGEO (N=184)		Vorinostat (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 laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.

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

Other common treatment-emergent laboratory abnormalities in the POTELIGEO arm included hyperglycemia (52%; 4% Grade 3-4), anemia (35%; 2% Grade 3-4), thrombocytopenia (29%, none Grade 3-4), aspartate transaminase (AST) increased (25%; 2% Grade 3-4), alanine transaminase (ALT) increased (18%; 1% Grade 3-4), alkaline phosphatase increased (17%; 0% Grade 3-4), and neutropenia (10%; 2% Grade 3-4). Grade 4 treatment-emergent laboratory abnormalities observed in ≥1% of the POTELIGEO arm included lymphopenia (5%), leukopenia (1%), and hypophosphatemia (1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to POTELIGEO with the incidences of antibodies in other studies or to other products may be misleading.

Among 258 patients treated with POTELIGEO in Trial 1, 10 (3.9%) tested positive for treatment-emergent (treatment-induced or treatment-boosted) anti-mogamulizumab-kpkc antibodies by an electrochemiluminescent assay. There were no positive neutralizing antibody responses.

6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of POTELIGEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infections: Hepatitis B virus reactivation
- Cardiac disorders: Stress cardiomyopathy

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on POTELIGEO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of mogamulizumab-kpkc to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for adverse developmental outcomes at maternal systemic exposures 27 times the exposure in patients at the recommended dose, based on AUC (*see Data*).

In general, IgG molecules are known to cross the placental barrier and in the monkey reproduction study mogamulizumab-kpkc was detected in fetal plasma. Therefore, POTELIGEO has the potential to be transmitted from the mother to the developing fetus. POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

The effects of mogamulizumab-kpkc on embryo-fetal development were evaluated in 12 pregnant cynomolgus monkeys that received mogamulizumab-kpkc once weekly by intravenous administration from the start of organogenesis through delivery at an exposure level 27 times higher than the clinical dose. Mogamulizumab-kpkc administration did not show a potential for embryo-fetal lethality, teratogenicity, or fetal growth retardation and did not result in spontaneous abortion or increased fetal death. In surviving fetuses (10 of 12 compared with 11 of 12 in the control group) of cynomolgus monkeys treated with mogamulizumab-kpkc, a decrease in CCR4-expressing lymphocytes due to the pharmacological activity of mogamulizumab-kpkc was noted; there were no apparent mogamulizumab-kpkc -related external, visceral, or skeletal abnormalities.

8.2 Lactation

Risk Summary

There is no information regarding the presence of POTELIGEO in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTELIGEO and any potential adverse effects on the breastfed child from POTELIGEO or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

Pregnancy Testing

For females of reproductive potential, verify pregnancy status prior to initiating POTELIGEO.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with POTELIGEO and for at least 3 months following the last dose of POTELIGEO.

8.4 Pediatric use

The safety and effectiveness of POTELIGEO in pediatric patients have not been established.

8.5 Geriatric use

Of 319 patients with MF or SS who received POTELIGEO in Trial 1, 162 (51%) were ≥65 years. No overall differences in effectiveness were observed between these patients and younger patients. In patients aged ≥65, Grade 3 or higher adverse reactions were reported in 45% and serious adverse reactions in 36%, whereas in patients aged <65, Grade 3 or higher adverse reactions were reported in 36% and serious adverse reactions in 29%.

11 DESCRIPTION

Mogamulizumab-kpkc is a recombinant humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4)-expressing cells. Mogamulizumab-kpkc is an IgG1 kappa immunoglobulin that has a calculated molecular mass of approximately 149 kDa. Mogamulizumab-kpkc is produced by recombinant DNA technology in Chinese hamster ovary cells.

POTELIGEO (mogamulizumab-kpkc) injection is a sterile, ready-to-use, preservative-free, clear to slightly opalescent colorless solution in a single-dose vial for dilution prior to intravenous infusion. Each vial contains 20 mg of mogamulizumab-kpkc in 5 mL of solution. Each mL of solution contains 4 mg of mogamulizumab-kpkc and is formulated in: citric acid monohydrate (0.44 mg), glycine (22.5 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP. May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Mogamulizumab-kpkc exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3 Pharmacokinetics

Mogamulizumab-kpkc pharmacokinetics (PK) was evaluated in patients with T-cell malignancies. Parameters are presented as the geometric mean [% coefficient of variation (%CV)] unless otherwise specified. Mogamulizumab-kpkc concentrations increased proportionally with dose over the dose range of 0.01 to 1.0 mg/kg (0.01 to 1 times the approved recommended dosage).

Following repeated dosing of the approved recommended dosage, steady state concentrations were reached after 8 doses (12 weeks), and the systemic accumulation was 1.6-fold. At steady state, the peak concentration ($C_{max,ss}$) is 32 (68%) µg/mL, the trough concentration ($C_{min,ss}$) is 11 (239%) µg/mL, and AUC_{ss} is 5577 (125%) µg•hr/mL.

Distribution
The central volume of distribution is 3.6 L (20%).

Elimination
The terminal half-life is 17 days (66%), and the clearance is 12 mL/h (84%).

Specific Populations:
No clinically significant changes in the PK of mogamulizumab-kpkc were observed based on age (range: 22 to 101 years), sex, ethnicity, renal impairment (creatinine clearance <90 mL/min, estimated by Cockcroft-Gault), 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) hepatic impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on mogamulizumab-kpkc PK is unknown.

Drug Interaction Studies
No drug interaction studies have been conducted with POTELIGEO.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with POTELIGEO.

No specific studies have been conducted to evaluate potential effects of POTELIGEO on fertility. No mogamulizumab-kpkc -related toxic effects in the male and female reproductive organs were observed in sexually mature monkeys in repeat-dose toxicology studies up to 26 weeks in duration.

14 CLINICAL STUDIES

Trial 1
A randomized, open-label, multicenter trial (Study 0761-010; NCT01728805) evaluated the efficacy of POTELIGEO in adult patients with MF or SS after at least one prior systemic

therapy. The trial randomized 372 patients 1:1 to either POTELIGEO (186 patients; 56% with MF, 44% with SS) or vorinostat (186 patients; 53% with MF, 47% with SS). The trial included patients regardless of tumor CCR4 expression status and excluded patients with histologic transformation, prior allogeneic HSCT, autologous HSCT within 90 days, active autoimmune disease, or active infection. The trial required patients to have ANC ≥1500/μL (≥1000/μL if bone marrow was involved), platelet count ≥100,000/μL (≥75,000/μL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL and hepatic transaminases ≤2.5 times ULN (≤5 times ULN if lymphomatous liver infiltration).

The dose of POTELIGEO was 1 mg/kg administered intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Vorinostat-treated patients with disease progression or unacceptable toxicities were permitted to cross over to POTELIGEO.

The median age was 64 years (range: 25 to 101), 58% of patients were male, and 70% were white. At study baseline, 38% had stage IB-II disease, 10% stage III, and 52% stage IV. The median number of prior systemic therapies was 3. In the POTELIGEO arm, baseline CCR4 expression status by immunohistochemistry was available in 140 patients (75%), of whom all had CCR4 detected on ≥1% of lymphocytes on skin biopsy, and 134/140 (96%) had CCR4 detected on ≥10% of the lymphocytes. CCR4 expression status was similar in the vorinostat arm.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months (range: <1 to 45.3 months), with 48% of patients with at least 6 months of exposure and 23% with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months (range: <1 to 34.8 months), with 22% of patients with at least 6 months of exposure.

Efficacy was based on investigator-assessed progression-free survival (PFS), which was defined as the time from the date of randomization until documented progression of disease or death. Other efficacy measures included overall response rate (ORR) based on global composite response criteria that combine measures from each disease compartment (skin, blood, lymph nodes and viscera). Responses required confirmation at two successive disease assessments, which included the modified Severity Weighted Assessment Tool, skin photographs, central flow cytometry, and computed tomography.

The trial demonstrated that POTELIGEO significantly prolonged PFS compared to vorinostat (Table 3). The Kaplan-Meier curve for PFS by Investigator is shown in Figure 1. The estimated median follow-up for investigator-assessed PFS was 13 months in the POTELIGEO arm and 10.4 months in the vorinostat arm. By independent review committee assessment, the estimated median PFS was 6.7 months (95% CI, 5.6 to 9.4) in the POTELIGEO arm and 3.8 months (95% CI, 3.0 to 4.7) in the vorinostat arm (hazard ratio 0.64; 95% CI: 0.49, 0.84).

Figure 1 Kaplan-Meier Curve for Progression-Free Survival per Investigator

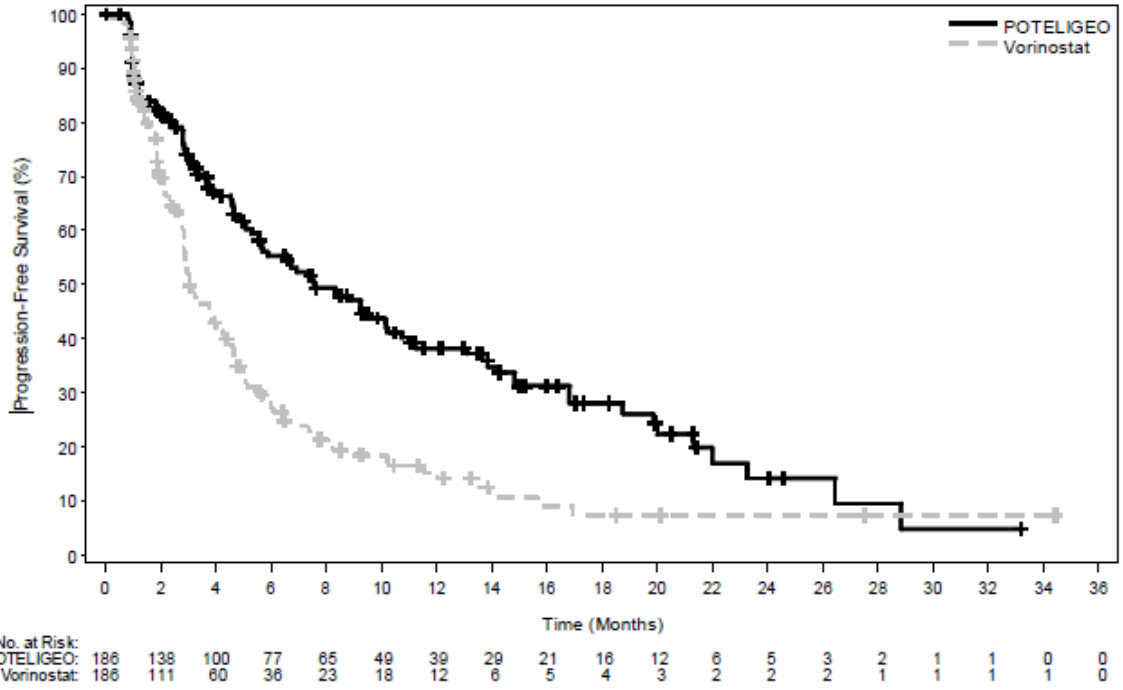

Table 3 also summarizes investigator-assessed confirmed response rates, overall and by disease compartment. The trial demonstrated improvement in ORR with POTELIGEO.

Table 3 Efficacy of Randomized Treatment (Trial 1)

Outcome per Investigator	**POTELIGEO N=186**	**Vorinostat N=186**
PFS		
Number of events, n	110	131
Progressive disease	104	128
Death	6	3
Median PFS (95% CI) (months) [a]	7.6 (5.6, 10.2)	3.1 (2.8, 4.0)
Hazard ratio (95% CI) Log rank p-value	0.53 (0.41, 0.69) <.001	
Overall response rate (confirmed CR + PR), n (%) [b, c]	52 (28)	9 (5)
95% CI	(22, 35)	(2, 9)
P-value [d]	<.001	
Duration of overall response (months)		
Median (95% CI) [a]	13.9 (9.3, 18.9)	9.0 (4.6, NE)
Confirmed best overall response [b]		
CR, n (%)	4 (2)	0 (0)
95% CI	(1, 5)	(0, 2)
PR, n (%)	47 (25)	9 (5)
95% CI	(20, 33)	(2, 9)

Response by compartment (confirmed CR + PR) [c]		
Blood	n=124	n=125
Response rate, n (%)	83 (67)	23 (18)
95% CI	(58, 75)	(12, 26)
Skin	n=186	n=186
Response rate, n (%)	78 (42)	29 (16)
95% CI	(35, 49)	(11, 22)
Lymph nodes	n=136	n=133
Response rate, n (%)	21 (15)	5 (4)
95% CI	(10, 23)	(1, 9)
Viscera	n=6	n=4
Response rate, n (%)	0 (0)	0 (0)
95% CI	(0, 46)	(0, 60)

[a] Kaplan-Meier estimate.

[b] Based on Global Composite Response score.

[c] Responses in blood and skin must have persisted for at least 4 weeks to be considered confirmed and were evaluated every 4 weeks for the first year. Responses in lymph nodes, visceral disease and overall were evaluated every 8 weeks for the first year.

[d] From Cochran-Mantel-Haenszel test adjusted for disease type, stage, and region.

CI=confidence interval; CR=complete response; NE=not estimable; PR=partial response

16 HOW SUPPLIED/STORAGE AND HANDLING

POTELIGEO (mogamulizumab-kpkc) injection is a sterile, preservative-free, clear to slightly opalescent colorless solution supplied in a carton containing one 20 mg/5 mL (4 mg/mL), single-dose glass vial (NDC 42747-761-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original package to protect from light until time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the risk of the following adverse reactions that may require additional treatment and/or withholding or discontinuation of POTELIGEO including:

- Dermatological Toxicity: Advise patients to contact their healthcare provider immediately for new or worsening skin rash [*see Warnings and Precautions (5.1)*]. Advise patients that the rash can happen at any time while receiving POTELIGEO.
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions [*see Warnings and Precautions (5.2)*].
- Infections: Advise patients to contact their health care provider for fever or other evidence of infection [*see Warnings and Precautions (5.3)*].

- Autoimmune Complications: Advise patients to notify their healthcare provider of any history of autoimmune disease [*see Warnings and Precautions (5.4)*].
- Complications of Allogeneic HSCT after POTELIGEO: Advise patients of potential risk of post-transplant complications [*see Warnings and Precautions (5.5)*].
- Females of Reproductive Potential: Advise use of effective contraception during treatment with POTELIGEO and for at least 3 months following the last dose of POTELIGEO [*see Use in Specific Populations (8.3)*].

POTELIGEO® (mogamulizumab-kpkc)
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