

# Mogamulizumab-kpkc: A Novel Therapy for the Treatment of Cutaneous T-Cell Lymphoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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## Abstract

Mogamulizumab-kpkc provides a novel mechanism of action for the treatment of mycosis fungoides and Sézary syndrome. The efficacy and safety of mogamulizumab-kpkc for the treatment of relapsed or refractory mycosis fungoides and Sézary syndrome were demonstrated in a multicenter, open-label, randomized phase III trial comparing mogamulizumab-kpkc with vorinostat. Patients treated with mogamulizumab-kpkc showed a statistically significant increased progression-free survival (PFS; 7.7 months) compared with vorinostat (3.1 months). Overall response rates were higher with mogamulizumab-kpkc compared with vorinostat (28% vs. 5%;  $p < .0001$ ). The most common adverse events (> 20%) associated with mogamulizumab-kpkc include rash, infusion-related reaction, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection. The use of mogamulizumab-kpkc up to 50 days prior to allogeneic hematopoietic stem cell transplantation has been associated with an increased risk of severe acute graft-vs.-host disease, steroid-refractory graft-vs.-host disease, and mortality. Additional labeled warnings include dermatologic toxicity, infection, and autoimmune complications. The overall benefit to risk assessment of mogamulizumab-kpkc is acceptable, but its use is constrained by the high cost of treatment and the short-term benefit.

Cutaneous T-cell lymphoma (CTCL) is a rare non-Hodgkin lymphoma (NHL) that primarily arises in the skin but may involve the viscera, lymphatic system, and blood (National Comprehensive Cancer Network [NCCN], 2019). The overall prevalence is approximately 7.5 cases for every 1 million people in the

United States (Korgavkar, Xiong, & Weinstock, 2013). Mycosis fungoides (MF) is the most common subtype of CTCL, with 1,620 incidences reported in 2016, and is often characterized by patches, plaques, and erythroderma. Sézary syndrome (SS) is a much more rare and aggressive leukemic variant of CTCL, with an incidence of 70 in the same year (Teras et al.,

2016). These two diseases account for nearly two thirds of CTCL cases (Scarlsbrick et al., 2015). Patients with advanced-stage disease have a median survival of only 5 years (Scarlsbrick et al., 2015).

Early-stage MF is largely managed with skin-directed therapies, while later stage MF and SS require management with systemic therapies such as chemotherapy, retinoids, interferons, and histone deacetylase inhibitors (NCCN, 2019; Trautinger et al., 2017). These treatment options aim to maintain disease control and improve quality of life; allogeneic hematopoietic stem cell transplantation remains the only curative option for these patients.

The management of late-stage MF and SS is not standardized and largely dependent on patient-specific factors. Due to the rarity of this disease, most therapies utilized today have received approval following results of small, single-arm studies. The largest phase III clinical trial to date evaluated the use of brentuximab vedotin in 131 patients (Prince et al., 2017). The overall response rate (ORR) at 4 months reported for brentuximab vedotin was 56%, with only 16% of patients achieving complete response (CR). This was statistically significant when compared to the 12.5% ORR at 4 months seen with standard therapies such as methotrexate or bexarotene (Prince et al., 2017). The median PFS for brentuximab vedotin was 17.2 months compared to 3.5 months for patients receiving skin-directed therapies. Although PFS is an ideal outcome, the grading of PFS has not been reliable, making it difficult to compare results between trials (Olsen et al., 2011). This is consistent with the fact that most CTCL patients often show progression of disease on treatment. Therefore, more effective therapies are needed to improve the management of this disease (Kim et al., 2018). Mogamulizumab-kpkc (Poteligeo) is a novel therapy option for late-stage MF and SS that showcases an innovative mechanism of action.

### MECHANISM OF ACTION

Mogamulizumab-kpkc is a first-in-class defucosylated, humanized monoclonal antibody recently U.S. Food & Drug Administration (FDA) approved in August of 2018 for the treatment of relapsed or refractory MF and SS in adults. Mogamulizumab-kpkc selectively targets CC chemokine receptor 4 (CCR4), a receptor consistently expressed on

the surface of T cells in T-cell malignancies (Kim et al., 2018). CCR4 is normally expressed on T helper cells (Th2) and regulatory T cells (Treg) to mediate cell trafficking of lymphocytes to various organs, including the skin. Extranodal T-cell migration to the skin is seen in MF and SS due to the combined effect of CCR4 overexpression on malignant T cells and overproduction of CCR4 ligands by various skin cells (Ferenczi, Fuhlbrigge, Kupper, Pinkus, & Pinkus, 2002; Ishii et al., 2010).

Upon binding to CCR4, the T cell is marked for destruction via antibody-dependent cellular cytotoxicity (ADCC). This process is activated when the Fc portion of mogamulizumab-kpkc interacts with the Fcγ receptor IIIa (FcγRIIIa) on the natural killer (NK) effector cells (FDA, 2018). The removal of fucose moieties through glycoengineering enhances the binding affinity and effectively lowers the effector-target cell ratio required for adequate ADCC (Ni et al., 2015; Ogura et al., 2014). In addition to the destruction of malignant cells, Th2 and Treg cells are also depleted. Treg cell depletion may be an inadvertent but beneficial consequence of mogamulizumab-kpkc therapy. The upregulation of Treg cells in the tumor microenvironment has been implicated as a mechanism that allows cancerous cells to evade the immune system (Whiteside, 2015). Thus, depletion of Treg cells by mogamulizumab-kpkc may indirectly limit the propagation of malignant cells by taking away the tumor's ability to sustain growth and survival within the tumor microenvironment (Ni et al., 2015; Ogura et al., 2014).

### CLINICAL TRIALS AND EFFICACY

Mogamulizumab-kpkc has been approved in Japan to treat patients with CTCL since 2014 but has only recently gained FDA approval for use in the United States following results of a multinational study published in 2018. The safety and efficacy of mogamulizumab-kpkc for the treatment of relapsed or refractory MF/SS were first demonstrated in phase II of a two-part phase I and II study. Phase II included 41 patients with either MF (n = 22) or SS (n = 19). Of the 38 evaluable patients, the overall response rate (ORR) observed was 36.8%, with a higher response rate in patients with SS (47.1%) compared with MF (28.6%). The median duration of response and median PFS were 10.4 months and 11.4 months, respectively (Duvic et al., 2015).

In the subsequent phase III clinical trial, mogamulizumab-kpkc was compared to vorinostat in patients with relapsed or refractory MF (56%) or SS (44%) who had received at least one prior systemic therapy. The trial enrolled a total of 372 patients from 61 sites in 11 different countries, including the United States. Patients were included if they failed at least one prior systemic therapy and had an Eastern Cooperative Oncology Group (ECOG) performance status of one or less. Patients were randomized 1:1 to receive either mogamulizumab-kpkc or vorinostat in 28-day cycles. Mogamulizumab-kpkc was given as 1 mg/kg over 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and then on days 1 and 15 of all subsequent 28-day cycles until disease progression. Vorinostat was dosed as 400 mg to be given by mouth daily with food. Vorinostat was chosen since it is FDA approved for the treatment of CTCL and is not a first-line treatment. Previous studies of vorinostat showed an ORR close to 30% (Duvic et al., 2007; Olsen et al., 2007). Patients who experienced either disease progression or intolerable side effects after the completion of two 28-day cycles were allowed to cross over into the mogamulizumab-kpkc group. The mean exposure in the vorinostat group was similar to the FDA approval–reported exposure (144 and 110 days, respectively); this is unlikely to have contributed to the low response seen with vorinostat. A total of 133 patients originally assigned to vorinostat crossed over into the mogamulizumab-kpkc group: 80% due to disease progression and 27% due to intolerable toxicities experienced with vorinostat. Only 41 (31%) of these patients achieved some response (Kim et al., 2018).

Patients enrolled had received a median of three previous systemic therapies, and 52% of patients had stage IV disease, 10% stage III disease, and 38% stages IB to II disease. The average age of participants was 64 years old, with the majority of patients being white (70%) and male (58%). Patients received mogamulizumab-kpkc for a median of 5.6 months; 48% had exposure for at least 6 months and 23% had exposure for at least 12 months. Treatment with mogamulizumab-kpkc showed a statistically significant increased time of PFS (7.7 months) compared with vorinostat (3.1 months). Higher ORR was observed with

mogamulizumab-kpkc compared with vorinostat (28% vs. 5%;  $p < .0001$ ; Kim et al., 2018). The MAVORIC trial reports promising results, but the open-label design, weak comparator, and heavily pretreated patients suggest that further study is required before a robust conclusion can be drawn.

## ADVERSE EFFECTS

The most common adverse events (> 20%) associated with mogamulizumab-kpkc include dermatologic toxicities, infusion-related reaction, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection (Kyowa Kirin, Inc, 2018). Serious adverse events ( $\geq$  grade 3) were reported in 36% of patients in the phase III trial, with 18% of these serious adverse events due to infection. The most common types of infection included sepsis, pneumonia, and skin infections. Fatal adverse events associated with mogamulizumab-kpkc were experienced by 2.2% of patients, with the majority attributable to infection.

Discontinuation was necessary in 18% of patients and was most commonly related to rashes. In the MAVORIC trial, skin rashes were biopsied prior to treatment with topical steroids due to difficulty differentiating between the rash and disease progression (Kim et al., 2018). There are no black box warnings for mogamulizumab-kpkc. Additional warnings and precautions include dermatologic toxicities, infusion-related reactions, and autoimmune complications. Immune-mediated complications include pneumonitis, hepatitis, myositis, myocarditis, and polymyositis. Approximately 1.9% of patients in the MAVORIC trial required systemic immunosuppressants for their immune-mediated complications. Hypothyroidism has been reported in 1.3% of patients and can be managed with levothyroxine (Kim et al., 2018; Kyowa Kirin, Inc, 2018). The most commonly reported adverse reactions are highlighted in Table 1. Of note, myelosuppression was seen in the phase I and II trial, but this was not reported in the phase III clinical trial. This may be due to the requirement of adequate cell counts at baseline for enrollment (Duvic et al., 2015; Kim et al., 2018).

## DOSING AND ADMINISTRATION

The recommended dose of mogamulizumab-kpkc is 1 mg/kg administered as an IV infusion over

**Table 1. Most Common Adverse Drug Reactions**

| Adverse drug reaction             | Grade 1 or 2, % | Grade $\geq$ 3, % |
|-----------------------------------|-----------------|-------------------|
| Rash, including drug eruption     | 35              | 5                 |
| Drug eruption                     | 24              | 5                 |
| Infusion-related reaction         | 33              | 2                 |
| Upper respiratory tract infection | 22              | 0                 |
| Skin infection                    | 19              | 3                 |
| Musculoskeletal pain              | 22              | < 1               |
| Pyrexia                           | 17              | < 1               |
| Mucositis                         | 12              | 1                 |

Note. Information from Kyowa Kirin, Inc (2018).

at least 60 minutes. For the first 28-day cycle, mogamulizumab-kpkc is administered on days 1, 8, 15, and 22, and for each subsequent 28-day cycle, mogamulizumab-kpkc is infused on days 1 and 15 only. This results in the patient receiving the first five doses over five consecutive weeks. Doses should be given within 2 days of the scheduled dose. Any missed doses should be administered as soon as possible, and the original schedule resumed thereafter.

Diphenhydramine and acetaminophen should be given prior to the first treatment to prevent infusion-related reactions and may be necessary for subsequent infusions. Infusion reactions are usually limited to the first two infusions and occur within the first 30 to 60 minutes. Mild to moderate infusion reactions may be acutely managed by temporarily interrupting the infusion for 15 to 30 minutes until symptom resolution and by reducing the infusion rate by at least 50%. For patients experiencing mild to moderate infusion reactions, premedication is warranted in all subsequent infusions. For more severe reactions, dexamethasone should be administered at 20 mg IV or equivalent, oxygen by nasal cannula, and bronchodilator for bronchospasm (Kim et al., 2018).

There are no dose modifications needed for specific populations of age, sex, race, renal impairment, mild to moderate hepatic impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. The administration of mogamulizumab-kpkc requires a dedicated lumen and a low protein binding, 0.22 micron in-line fil-

ter for infusion. Mogamulizumab-kpkc is available as 20 mg per 5 mL vials and should be diluted in 0.9% sodium chloride injection, USP. The diluted solution is compatible with both polyvinyl chloride and polyolefin infusion bags. The diluent volume should be adjusted to ensure a final concentration between 0.1 mg/mL and 3.0 mg/mL. If the diluted solution cannot be used immediately, it may be stored under refrigeration at 2°C to 8°C for up to 4 hours (Kyowa Kirin, Inc, 2018).

## PRACTICE IMPLICATIONS

Mogamulizumab-kpkc provides a novel mechanism of action for the treatment of MF and SS. Given the chronic course of disease, an additional agent to deploy with encouraging PFS, improved quality-of-life outcomes, and a reasonable safety profile is a potential breakthrough in the treatment of these diseases (Kim et al., 2018). Mogamulizumab-kpkc is a reasonable second-line agent to consider in the treatment of CTCL, but advanced practitioners should be aware of some obstacles associated with the management of patients receiving mogamulizumab-kpkc.

During the phase III trial, systemic steroid use was not permitted to be initiated during the study, although topical steroids to treat drug rash was allowed. Systemic steroid use prior to treatment is not explicitly contraindicated, nor is the initiation of steroids for the treatment of drug rash (Kim et al., 2018; Kyowa Kirin, Inc, 2018). It is a theoretical concern that corticosteroids can limit the effectiveness of ADCC in the body (Nair & Schwartz, 1984). This does seem to be an implicit suggestion to avoid steroid use if possible while further study of drug rash associated with mogamulizumab-kpkc continues to be analyzed and clarified (Kim et al., 2018). If the rash does not respond to steroids, a skin biopsy is indicated to rule out progressive disease (Kyowa Kirin, Inc, 2018).

There have been multiple cases of hepatitis B reactivation following the administration of mogamulizumab-kpkc (Ifuku et al., 2015; Nakano et al. 2014; Totani et al., 2015). While a direct association between hepatitis B reactivation and mogamulizumab-kpkc administration has not been fully clarified, providers should screen for hepatitis B prior to the initiation of treatment (Kyowa Kirin, Inc, 2018).

The information regarding prophylaxis for infection in CTCL is limited and largely drawn from other T-cell lymphomas. Hepatitis B should be resolved prior to starting treatment. There are general recommendations to screen for cytomegalovirus, herpes simplex virus, and pneumocystis prior to treatment and provide prophylaxis for these opportunistic pathogens during treatment with mogamulizumab-kpkc (Drgona et al., 2018).

There is an elevated risk of complication among patients who go on to receive allogeneic hematopoietic stem cell transplantation following mogamulizumab-kpkc. This risk arises from the depletion of Treg cells (Ni et al., 2015). These include severe and steroid-refractory graft-vs.-host disease and transplant-related death. In a case series of eight patients with CTCL receiving transplantation, one patient developed severe GVHD (Dai et al., 2018). Transplantation should be delayed for at least 50 days from the last dose of mogamulizumab-kpkc, and Treg cells should be evaluated before transplant (Kyowa Kirin, Inc, 2018). Providers should be vigilant in monitoring and preparing for this complication because allogeneic hematopoietic stem cell transplantation remains the only curative option for CTCL.

The cost of mogamulizumab-kpkc can be a barrier for patients to receive this novel therapy. The average wholesale price for a 20 mg vial is \$4,548 (UpToDate, 2019). The cost of the first cycle of treatment, four doses, for an 80-kg patient would be approximately \$73,000. Using this price data, subsequent cycles would cost approximately \$36,000, and an entire year would cost \$473,000. This price does not account for nondrug costs such as regular lab monitoring, recurrent biopsies, and the management of toxicities (Kyowa Kirin, Inc, 2018). Given that mogamulizumab-kpkc is used until disease progression or unacceptable toxicity, the cost may be incurred indefinitely (Kim et al., 2018).

## SUMMARY

Mycosis fungoides and SS are rare diseases with no standardized therapy and few treatment options available for advanced-stage patients. Despite early management of MF and SS, most patients have progressive disease while on treatment. Mogamulizumab-kpkc has recently been approved for the

treatment of MF or SS after at least one prior systemic therapy. Mogamulizumab-kpkc provides an additional mechanism of action for the treatment of MF and SS that can treat the disease systemically. The utilization of mogamulizumab-kpkc is limited by the high cost of treatment and the short-term benefit. ●

## Disclosure

The authors have no conflicts of interest to disclose.

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