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Dear NCCN T-cell Lymphoma Guidelines Panel:

On behalf of Kyowa Kirin, Inc., I respectfully request that the NCCN T-cell Lymphoma Guidelines Panel review the enclosed data regarding the use of POTELIGEO® (mogamulizumab) for treatment of mycosis fungoides (MF) or Sézary syndrome (SS) subtypes of cutaneous T-cell lymphoma (CTCL).

Specific Request: Please consider including the results from the phase 3, randomized MAJORIC (Mogamulizumab anti-CCR4 Antibody Versus ComparatOR In CTCL) trial as evidence supporting the use of mogamulizumab in patients with previously treated MF or SS subtypes of CTCL.

FDA Status: Mogamulizumab is a C-C chemokine receptor type 4 (CCR4)-directed monoclonal antibody currently under review by the FDA for the treatment of adult patients with relapsed or refractory MF or SS after at least one prior systemic therapy.¹ Mogamulizumab was granted Breakthrough Therapy Designation status by the US Food and Drug Administration (FDA) in August 2017 and has received a PDUFA date of September 4, 2018. At this time mogamulizumab is an investigational biologic and has not yet been established as safe and effective by the FDA.

Rationale: CTCLs, including the forms of MF and SS, are rare non-Hodgkin lymphomas associated with compromised quality of life, due to intractable itching and recurrent infections, and mortality in advanced-stage disease.²⁻⁴ Advanced disease requires systemic treatment, however the average time on treatment is 4.5 months and patients tend to cycle through available options.⁵ Therefore, there is an unmet need for efficacious, durable, and tolerable treatments for this disease. Most prospective clinical trials of systemic agents in CTCL have been of small sample size and either single-arm or randomized to compare different doses of the same agent, with or without a placebo/observational arm. No previous randomized CTCL trials of systemic agents have assessed progression-free survival (PFS) as a primary endpoint. Response rates in previous trials have been calculated via a range of methods, some of which have assessed improvement in only one pre-defined disease compartment.

Data Summary:

Based on results from a phase 1/2 study in CTCL and a phase 2 study in peripheral T-cell lymphoma (PTCL)/CTCL,^{6,7} the open-label, multi-national, randomized, phase 3 MAJORIC study [NCT01728805] was conducted to evaluate the efficacy of mogamulizumab — a first-in-class humanized anti-CCR4 monoclonal

antibody — compared to vorinostat in patients with previously treated CTCL. This study is the largest randomized trial in CTCL to test a novel systemic agent, mogamulizumab, against an FDA-approved comparator for the treatment of CTCL and the first to use PFS as a primary endpoint.

Adults with histologically-confirmed MF or SS who failed ≥ 1 systemic therapy were randomized 1:1 to mogamulizumab at a dose of 1 mg/kg once weekly for the first 28-day cycle (on days 1, 8, 15, and 22), and on days 1 and 15 of subsequent 28-day cycles or vorinostat at a dose of 400 mg orally once daily beginning on day 1 for 28-day cycles. The primary efficacy endpoint was investigator-assessed PFS using a global composite response criteria based on response in each compartment (skin, blood, lymph nodes, and viscera).⁸ Of note, progression in any one of the disease compartments was considered in overall PFS assessment. Secondary endpoints included, but were not limited to, global composite overall response rate (ORR), patient-reported outcomes (PROs), and safety. Patients initially randomized to vorinostat who demonstrated confirmed disease progression verified via a complete protocol evaluation, or who experienced intolerable toxicity, despite dose reduction and appropriate management of side effects, could cross over to treatment with mogamulizumab.

In total, 372 patients were randomized (mogamulizumab, n=186; vorinostat, n=186), with a median age of 64 years. In the primary efficacy analysis, mogamulizumab significantly delayed time to disease progression or death from any reason compared to vorinostat (hazard ratio = 0.53; 95% CI, 0.41, 0.69; $p < 0.001$) (2-sided, stratified log rank test). Median PFS for the mogamulizumab group was 7.6 months (95% CI, 5.6, 10.2) and 3.1 months (95% CI, 2.8, 4.0) for the vorinostat group.

The ORR, comprising all 4 compartments, was significantly higher with mogamulizumab than vorinostat (28% vs 5%, respectively; $P < 0.001$). ORR, DOR, and response by disease compartment were higher for mogamulizumab-treated patients than for vorinostat-treated patients across subgroups. PROs, measured by Skindex-29 and FACT-G, showed significantly greater symptom reduction and improved functional status for mogamulizumab vs vorinostat in earlier and later cycles, including Cycles 3 and 5 ($P < 0.05$). Primary data from the Skindex-29 and Fact-G quality of life outcomes from the MAVORIC study were presented at the 2018 ASCO Annual Congress on June 4, 2019 and is included in this submission.⁹

The median duration of exposure was 5.6 months with mogamulizumab and 2.8 months with vorinostat. Mogamulizumab was discontinued for adverse events in 18% of randomized patients, most often due to rash or drug eruption (7.1%). The most common adverse events (reported in $\geq 20\%$ of patients randomized to mogamulizumab) were rash, including drug eruption (35%; 24% for drug eruption alone); infusion-related reactions (33%); fatigue (31%); diarrhea (28%); upper respiratory tract infection (22%); and musculoskeletal pain (22%). Serious adverse events (SAEs) occurred in 36% of patients receiving mogamulizumab. SAEs reported in $> 2\%$ of patients randomized to mogamulizumab were pneumonia (5%), sepsis (4%), pyrexia (4%), and skin infection (3%).

With limited systemic treatment options currently available, the phase 3 (MAVORIC) results support mogamulizumab as an added therapeutic option for patients with the MF or SS subtypes of CTCL with the potential to improve patient outcomes. Primary results of the MAVORIC study were shared as an oral presentation at the annual meeting of the American Society of Hematology (ASH), on Monday, December 11, 2017, in Atlanta, GA (abstract #817).¹⁰ Further, a manuscript containing these primary results has been accepted for publication in the *Lancet Oncology* journal.

Please find enclosed a confidential, near final USPI that has been developed in conjunction with the FDA,

the MAVORIC ASH presentation, and publications of clinical trial data of mogamulizumab use in CTCL. This submission will be amended when we receive the final USPI and published manuscript.

Please do not hesitate to contact me should you have further questions.

Thank you for your time and consideration.

Sincerely,

Deborah Braccia, PhD, MPA
VP, Medical Affairs
Kyowa Kirin, Inc.

References:

1. POTELIGEO® prescribing information.
 2. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005;105:3768-85.
 3. Demierre MF, Tien A, Miller D. Health-related quality-of-life assessment in patients with cutaneous T-cell lymphoma. *Arch Dermatol* 2005;141:325-30.
 4. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer* 2006;107:2504-11.
 5. Hughes CF, Khot A, McCormack C, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. *Blood*. 2015;125:71-81.
 6. Duvic M, Pinter-Brown LC, Foss FM, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. *Blood* 2015;125:1883-9.
 7. Ogura M, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol*. 2014 Apr 10;32(11):1157-63.
 8. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary 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;29:2598-607.
 9. Porcu P, Hudgens S, Quaglino P, et al. Quality of life in cutaneous T-cell lymphoma subjects treated with anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat: results from the Phase 3 MAVORIC trial. *Journal of Clinical Oncology* 36, no. 15_suppl (May 20 2018) 7577-7577.
 10. Kim YH, Bagot M, Pinter-Brown LC, et al. MDAnti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): Results from the Phase III MAVORIC Study. *Blood* 130.Suppl 1 (2017): 817.
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Materials provided in full in the supplement:

1. POTELIGEO® prescribing information (confidential near final USPI that has been developed in conjunction with the FDA).
2. Duvic M, Pinter-Brown LC, Foss FM, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. *Blood* 2015;125:1883-9.
3. Ogura M, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol*. 2014 Apr 10;32(11):1157-63.
4. Kim YH, Bagot M, Pinter-Brown LC, et al. MDAnti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): Results from the Phase III MAVORIC Study. *Blood* 130.Suppl 1 (2017): 817.
5. Porcu P, Hudgens S, Quaglino P, et al. Quality of life in cutaneous T-cell lymphoma subjects treated with anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat: results from the Phase 3 MAVORIC trial. *Journal of Clinical Oncology* 36, no. 15_suppl (May 20 2018) 7577-7577.