

May 2, 2018

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Kymriah® (tisagenlecleucel) in Relapsed/Refractory Large B-cell Lymphoma

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NCCN Guidelines Panel: B-cell Lymphomas

To Whom It May Concern:

As the NCCN B-cell Lymphomas Panel reviews the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for B-cell Lymphomas v.3.2018 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with Kymriah® (tisagenlecleucel) for your consideration:

- Data to support the use of tisagenlecleucel for the treatment of relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL), DLBCL arising from follicular lymphoma and high-grade B-cell lymphoma

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Tisagenlecleucel for the treatment of relapsed/refractory large B-cell lymphomas

This request is for the Panel to consider the inclusion of tisagenlecleucel as a treatment option for relapsed/refractory DLBCL, DLBCL arising from follicular lymphoma and high-grade B-cell lymphoma in the Guidelines and the associated NCCN Drugs and Biologics Compendium™.

The efficacy and safety of tisagenlecleucel was evaluated in the open-label, multicenter, single-arm JULIET trial. Eligible patients included those ≥ 18 years of age with relapsed or refractory DLBCL who received ≥ 2 lines of therapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT), or were ineligible for autologous HSCT.¹ Of the 160 patients enrolled, 106 patients received tisagenlecleucel, including 92 patients who received product manufactured in the US, in either an inpatient or outpatient setting at the investigator's discretion. Twenty-seven percent were infused in the outpatient hospital setting. Bridging chemotherapy between leukapheresis and lymphodepleting (LD) chemotherapy was permitted to control disease burden.¹ Treatment consisted of LD chemotherapy consisting of either fludarabine (25 mg/m² IV daily for 3 days) and cyclophosphamide (250 mg/m² IV daily for 3 days starting with the first dose of fludarabine) or bendamustine (90 mg/m² IV daily for 2 days), followed by a single dose of tisagenlecleucel.¹⁻³

Of the 92 patients receiving tisagenlecleucel, a retrospectively identified subgroup of 68 patients was evaluable for the major efficacy outcome measures. Among the efficacy-evaluable population, the median age was 56 years (range: 22-74 years); 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma. Seventeen percent of these lymphomas were high grade, and 44% of patients had

undergone prior autologous HSCT. The median number of prior therapies was 3 (range: 1-6), 56% had refractory disease and 44% relapsed after their last therapy. Ninety-nine patients (93%) received lymphodepleting chemotherapy prior to tisagenlecleucel, that included fludarabine (n = 77) or bendamustine (n = 22). The median dose was 3.5×10^8 CAR-positive viable T cells (range: 1.0 - 5.2×10^8 cells).¹

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee. The objective response rate (ORR) was 50% (34/68) with a CR rate of 32% (22/68) and partial response (PR) rate of 18% (12/68). The median time to first response (CR or PR) was 0.9 months (range: 0.7-3.3 months). The median DOR was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of PR. Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after tisagenlecleucel infusion.¹

The most common adverse reactions (incidence >20%) were cytokine release syndrome (CRS), infections-pathogen unspecified, diarrhea, nausea, pyrexia, fatigue, hypotension, edema and headache. CRS occurred in 74% (78/106), including 23% who experienced \geq Grade 3 CRS (Penn grading system). The median time to onset was 3 days (range 1-51 days), and in only two patients was onset after day 10. The median time to resolution of CRS was 8 days (range 1-36 days). Of the 3 DLBCL patients who died within 30 days of infusion, all had CRS in the setting of stable to progressive underlying disease, one of whom developed bowel necrosis. Among patients with CRS, key manifestations include fever (92%), hypotension (47%), hypoxia (35%) and tachycardia (14%). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.¹

Neurological toxicities occurred in 58% (62/106), including \geq Grade 3 in 18% of patients. Among patients who had a neurological toxicity, 88% occurred within 8 weeks following infusion. Median time to the first event was 6 days from infusion (range: 1-359), and the median duration was 14 days. Resolution occurred within 3 weeks in 61% of patients. Encephalopathy lasting up to 50 days was noted.¹ There were no cases of cerebral edema or death due to neurological events.²

Because of the risk of CRS and neurological toxicities, KYMRIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIA REMS.¹

Specific changes recommended for the Guidelines & Compendium

- Please consider including tisagenlecleucel as a treatment option in sections BCEL-7, FOLL-7, HGBL-1 and update relevant discussion sections.

FDA status

Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL NOS, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of use: Tisagenlecleucel is not indicated for treatment of patients with primary central nervous system lymphoma.

Rationale for recommended change

- A 2017 retrospective study of patients with DLBCL (including transformed follicular lymphoma, primary mediastinal B-cell lymphoma [N=636]) who were refractory to chemotherapy or had relapsed within 12 months of autologous HSCT demonstrated an ORR of 26% (CR of 7%) to the next line of therapy, and a median overall survival of 6.3 months.⁴
- Based on the FDA-approved labeled indication and data from the pivotal JULIET trial,

tisagenlecleucel has demonstrated safety and efficacy in large B-cell lymphomas after two or more lines of systemic therapy including DLBCL NOS, DLBCL arising from follicular lymphoma and high-grade B-cell lymphoma¹⁻³

Literature support

1. Kymriah [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.
2. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of JULIET: a global, pivotal, phase 2 trial of tisagenlecleucel (CTL019) in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Oral presented at: American Society of Hematology; December 9–12, 2017; Atlanta, GA. Oral S577.
3. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017; 377(26):2545-2554.
4. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN B-cell Lymphomas Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at Neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
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Novartis Pharmaceuticals Corporation

Enclosures: Copy of Prescribing Information and referenced primary literature; Author disclosures within included references.