August 31, 2017

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Kymriah™ (tisagenlecleucel, CTL019) in Relapsed/Refractory B-cell Acute Lymphoblastic Leukemia

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NCCN Guidelines Panel:	Acute Lymphoblastic Leukemia

To Whom It May Concern:

As the Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Acute Lymphoblastic Leukemia v.1.2017 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with tisagenlecleucel for your consideration:

- Data to support the use of tisagenlecleucel for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse

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Tisagenlecleucel for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse

This request is for the Panel to consider the inclusion of tisagenlecleucel as a treatment option in the Acute Lymphoblastic Leukemia Guidelines® and the associated NCCN Drugs and Biologics Compendium™.

The efficacy of tisagenlecleucel in pediatric and young adults with r/r B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial. In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects did not receive the product due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females with a median age of 12 years (range, 3-23 years). Seventy-three percent of patients were white, 10% were Asian, and 17% were of other races. Six (10%) had primary refractory disease, 30 (48%) had 1 prior stem cell transplantation, and 5 patients (8%) had 2 stem cell transplantations. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of tisagenlecleucel. Of the 22 patients who had a WBC count <1000/µL, 20 received lymphodepleting chemotherapy prior to tisagenlecleucel while 2 received tisagenlecleucel infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy. [1]

The efficacy was established on the basis of complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) <0.01% by flow cytometry (MRD-negative). Among the 63 infused patients, 52 (83%) achieved CR/ or CR with incomplete hematological response (CRi), all of whom were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2

to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52). [1]

The safety data described reflect exposure to tisagenlecleucel in the clinical trial in which 68 patients with pediatric and young adult r/r B-cell ALL received CAR-positive viable T cells. Based on a recommended dose that was weight-based, all patients received a single intravenous dose of tisagenlecleucel. The most common adverse reactions were cytokine release syndrome (CRS) (79%), hypogammaglobulinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%), tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (22%), acute kidney injury (22%), and delirium (21%).[1]

Eleven deaths were reported for patients who received tisagenlecleucel, of which 2 deaths occurred within 30 days of infusion. Seven were disease-related, 3 were attributed to infections, and 1 to intracerebral hemorrhage. Of the 2 deaths before Day 30, 1 patient died with CRS and progressive leukemia and the second patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred.[1]

Specific changes recommended for the Guidelines & Compendium

- Please consider including tisagenlecleucel as a treatment option of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse in section ALL-9 and updating relevant discussion sections.

FDA status

Kymriah is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Rationale for recommended change

Based on the FDA-approved labeled indication and data from the pivotal ELIANA trial and ENSIGN trial, tisagenlecleucel has demonstrated efficacy and safety in pediatric and young adult patients with relapsed/refractory B-cell ALL.

Literature support

1. Kymriah [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; 2017

2. Buechner J, Grupp SA, Maude SL, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia: an update to the interim analysis. Oral presented at: European Hematology Association; June 22, 2017; Madrid, Spain. Presentation S476.

3. Maude SL, Pulsipher MA, Boyer MW, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: Results of an interim analysis. Poster presented at: American Society of Hematology; December 3, 2016; San Diego, California/USA. Poster 2801.

4. Maude SL, Grupp SA, Pulsipher MA, et al. Analysis of safety data from 2 multicenter trials of CTL019 in pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Poster presented at: European Hematology Association; June 20, 2017; Madrid, Spain. Poster P517.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Acute Lymphoblastic Leukemia 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 reference