



March 29, 2018

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Updated 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 an addendum to the submission to the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Acute Lymphoblastic Leukemia (ALL) Guidelines® and the associated NCCN Drugs and Biologics Compendium™ dated August 31, 2017, we are enclosing more recent, peer-reviewed, published data in support of the use of Kymriah™ (tisagenlecleucel) for the treatment of patients under 26 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

We respectfully request the Panel to consider changing the category recommendation for the use of tisagenlecleucel from Category 2A to Category 1 as a treatment option for patients up to 25 years (<26 years) of age with B-cell precursor ALL that is refractory or in second or later relapse.¹

The publication reported updated data on an additional 12 patients (N=75) who received tisagenlecleucel infusion and had at least 3 months of follow-up (median follow-up of 13.1 months [range: 2.1-23.5]). In the updated analysis of the Phase II, single-cohort, 25-center, global ELIANA study of tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL, the overall response rate (ORR) was 81% (95% CI: 71-89%) with 45 patients (60%) achieving a complete remission (CR) and 16 (21%) achieving CR with incomplete hematologic recovery (CRi). All infused patients with best overall response of CR/CRi were minimal residual disease (MRD) negative; 95% (58/61) achieved MRD negative status by day 28. Among patients who achieved CR/CRi, median duration of response was not reached. Six-month relapse-free survival was 80%. Probability of event-free survival (EFS) was estimated to be 73% at 6 months (95% CI: 60-82%) and 50% at 12 months (95% CI: 35-64%), with median EFS not yet reached. Probability of overall survival (OS) in the 75 infused patients was estimated to be 90% (95% CI: 81-95%) at 6 months and 76% (95% CI: 63-86%) at 12 months.¹

The most common any-Grade nonhematologic adverse events (AEs) any time after infusion in the 75 patients were cytokine release syndrome (CRS; 77%), pyrexia (40%), decreased appetite (39%), febrile neutropenia (36%) and headache (36%).¹

Sixty-six patients (88%) experienced a Grade 3 or 4 AE and 55 (73%) experienced a Grade 3 or 4

AE suspected to be tisagenlecleucel-related. Cytokine release syndrome occurred in 58 patients (77%). Median time to CRS onset was 3 days (range: 1-22); median CRS duration was 8 days (range: 1-36). Thirty-five patients (47%) were admitted to the intensive care unit for management of CRS, with a median stay of 7 days (range: 1-34). Neurologic events occurred in 30 patients (40%) within 8 weeks of infusion. Ten patients (13%) had Grade 3 neurologic events; no Grade 4 events or cerebral edema were reported. The majority of neurologic events occurred during CRS or shortly following CRS resolution. Severe neurologic events occurred more frequently in patients with higher-grade CRS (per University of Pennsylvania and Children's Hospital of Philadelphia Scale). Neurologic events were managed with best supportive care after exclusion of other causes for symptoms.¹

There were 19 deaths following tisagenlecleucel infusion. Within 30 days of infusion, one patient died from cerebral hemorrhage in the setting of coagulopathy abdominal compartment syndrome, renal failure and resolving CRS 15 days after infusion, and one died from progressive ALL and CRS. Seventeen patients died more than 30 days after infusion: ALL relapse or progression (n=12), human herpes virus-6 positive encephalitis in association with prolonged neutropenia and lymphopenia (n=1), systemic mycosis in association with prolonged neutropenia (n=1), cause of death unknown (n=1) and in two patients following new therapies for ALL (pneumonia, hepatobiliary disease; n=1 each).¹

Specific changes recommended for the Guidelines & Compendium

Please consider changing tisagenlecleucel from a Category 2A recommendation to a Category 1.

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.²

Rationale for recommended change

- The FDA granted Kymriah a full approval on August 30, 2017 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.²
- The peer-reviewed, updated analysis of the Phase II ELIANA trial published in the *New England Journal of Medicine* demonstrated high response rate and safety for a patient population with otherwise limited options.¹
- Although there are no head-to-head trials and no cross-trial comparisons can be made, historical response and survival rates were lower with then-available therapies as presented by Novartis during the FDA Oncologic Drugs Advisory Committee on July 12, 2017. As presented, ORR for clofarabine monotherapy and combination regimens (across 3 trials) ranged from 20-76%, with median OS ranging from 2.5 to 9 months, a 12-month OS ranging from 20% to 33% and early mortality (within 30 days) reported at 20% to 25%. As presented for blinatumomab, ORR was 39%, median OS was 7.5 months, 12-month OS was 40% and early mortality (within 30 days) was 7%.³

Literature support

1. Maude SL, Laetsch TW, Buechner S, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. December 3, 2018. Feb 1. [Epub ahead of print]
2. Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
3. Novartis Presentations for the July 12, 2017 Meeting of the Oncologic Drugs Advisory Committee. Slide CU-15. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567383.pdf>. Accessed Feb 2, 2018.

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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,

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Enclosures: Copy of Prescribing Information and referenced primary literature; author disclosures within included reference