# FDA Approval Summary: Tisagenlecleucel for Treatment of Patients with Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

**Running Title**: FDA Approval Summary: Tisagenlecleucel for R/R BCP ALL

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**Abstract**

Tisagenlecleucel (Kymriah, Novartis Pharmaceuticals, East Hanover, NJ) is a CD19-directed genetically-modified autologous T-cell immunotherapy. On August 30, 2017, the U.S. Food and Drug Administration approved tisagenlecleucel for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Approval was based on the complete remission (CR) rate, durability of CR and minimal residual disease (MRD) < 0.01% in a cohort of 63 children and young adults with relapsed or refractory ALL treated on a single-arm trial (CCTL019B2202). Treatment consisted of fludarabine and cyclophosphamide followed 2 to14 days later by a single dose of tisagenlecleucel. The CR rate was 63% (95% CI 50% - 75%) and all CRs had MRD < 0.01%. With a median follow-up of 4.8 months, the median duration of response was not reached. Cytokine release syndrome (79%) and neurological events (65%) were serious toxicities reported in the trial. With implementation of a Risk Evaluation and Mitigation Strategy, the benefit-risk profile was considered acceptable for this patient population with such resistant ALL. A study of safety with 15 years of follow-up is required as a condition of the approval.

## Introduction

Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R BCP ALL) responds poorly to standard treatments. Observed rates of complete remission (CR) following single agent clofarabine or blinatumomab, both approved for treatment of R/R BCP ALL in children, were 11.5% and 17.1%, respectively [1,2]. The potential for cure of R/R BCP ALL is greatest using intensive induction followed by allogeneic stem cell transplantation (HSCT). Survival after HSCT for relapsed ALL is improved if the patient is transplanted in a minimal residual disease (MRD)-negative remission [3].

Tisagenlecleucel is a CD19-directed, genetically-modified, autologous T-cell immunotherapy. The autologous T cells are transduced using a lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR). The CAR is a single protein comprised of the single-chain fragment (scFv) from a murine monoclonal antibody specific for CD19, the human CD8 hinge and transmembrane regions, and the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, and target cell elimination.

Tisagenlecleucel was the first gene-modified cell therapy approved by the U.S. Food and Drug Administration (FDA). Herein, we provide a summary of the FDA review and clinical rationale for approval of tisagenlecleucel for treatment of children and young adults with R/R BCP ALL.

## Drug Product

Tisagenlecleucel drug product is prepared from an apheresis collection of the patient's peripheral blood mononuclear cells. The mononuclear cells are enriched for T cells, transduced with

the lentiviral vector containing the anti-CD19 CAR transgene, activated with anti-CD3/CD28 antibody-coated beads, expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. In addition to T cells, other cell populations, including monocytes, NK cells and B cells, may be present. The formulation also contains dextran 40, human serum albumin (HSA), and dimethyl sulfoxide (DMSO). The number of cells in a patient-specific single dose of tisagenlecleucel is variable and may be up to 2.5 x $10^8$ CAR-positive viable T cells. The actual number of CAR-positive T cells in the tisagenlecleucel drug product is reported on the Certificate of Analysis shipped with the patient-specific infusion bag.

**Nonclinical Pharmacology and Toxicology**

Nonclinical safety studies were conducted with lentivirus-transduced T cells prepared from healthy donors and patients in a manner similar to the manufacturing process of tisagenlecleucel. *In vitro* expansion studies showed no evidence of transformation and/or clonal cell expansion. *In vivo* evaluation did not show signs of abnormal cell growth for up to 7 months following administration of the transduced T cells in immunocompromised mice. A genomic insertion site analysis performed with tisagenlecleucel prepared from 14 individuals showed no evidence for preferential vector insertion sites near genes of concern, nor preferential clonality of the sequences harboring the insertion sites of concern.

**Clinical Pharmacology**

Following infusion, tisagenlecleucel exhibited an initial rapid expansion phase achieving maximal concentration (Cmax) around day 10 followed by a slower bi-exponential decline. The Cmax and $AUC_{0\text{-}28d}$ of tisagenlecleucel were higher in responding patients than in nonresponders (Supplementary Table 1). Cmax and $AUC_{0\text{-}28d}$ decreased with increasing patient age, were higher

with greater baseline tumor burden, and were not impacted significantly by race or gender. Greater T-cell expansion trended with higher cytokine release syndrome (CRS) grades. Tocilizumab treatment did not interfere with tisagenlecleucel expansion or persistence. Tisagenlecleucel was detected in both marrow and blood, and it was still measurable in blood beyond 2 years.

**Clinical Trial Design**

CCTL019B2202 (NCT02435849) was a multicenter, open-label, single-arm trial of lymphodepleting chemotherapy and tisagenlecleucel for treatment of R/R BCP ALL.[4] Eligible patients were at least 3 years old at screening and up to 21 years old at diagnosis with CD19-positive ALL that was refractory to induction, refractory to re-induction, in second or later untreated relapse, relapsed after HSCT, or not being considered for HSCT. Patients with Ph-positive ALL had to have received at least two tyrosine kinase inhibitors. Patients treated with prior CD19-targeted therapies were excluded.

Figure 1 shows the overview of study procedures. The protocol procedures included apheresis, bridging chemotherapy, lymphodepleting chemotherapy followed 2 to14 days later by a single weight-based dose of tisagenlecleucel (0.2 to 5 x $10^6$ viable transduced T cells/kg body weight for patients $\leq$ 50 kg or a flat dose of 0.1 to 2.5 x $10^8$ viable transduced T cells for those > 50 kg).

The primary objective was to evaluate efficacy in all patients as measured by overall remission rate (ORR) (complete remission [CR] + CR with incomplete hematologic recovery [CRi]) within 3 months after tisagenlecleucel infusion as adjudicated by an Independent Review Committee. Confirmation of response was required. The initial response evaluation included assessments of

peripheral blood, bone marrow, central nervous system (CNS) symptoms, physical exam, cerebral spinal fluid assessment, and testing for MRD in marrow by 8-color flow cytometry in a central laboratory. A reported value of MRD < 0.01% was considered MRD-negative. Additional marrow testing was recommended for later efficacy assessments, but continued response could be established solely on the basis of physical exam, assessment for CNS symptoms, and examination of peripheral blood.

The planned sample size of 76 patients would provide 95% power to exclude an ORR rate of 20% or less with an expected ORR rate of 45% and one-sided cumulative alpha of 0.025. One interim analysis was planned to be performed when the first 50 patients completed 3 months of follow-up. A minimum of 6 months of follow-up data was provided in the application to assess the durability of remissions. The final analysis of the primary endpoint was performed when all patients completed 3 months of follow-up. Because comparability was not yet established at the time of analysis for the products from the European manufacturing site, assessment of the primary endpoint was limited to patients treated with product from the U.S. manufacturing site. This analysis was prespecified as a key secondary objective with the intent to exclude an ORR of 20% or less in up to 66 patients infused with product from the U.S. manufacturing facility.

**Results**

Overall, the trial enrolled 88 patients. The disposition of all enrolled patients is described in Supplementary Table 2. Of the enrolled patients, 78 were to receive products from the U.S. manufacturing site. Of these 78 patients, 7 were not treated due to manufacturing failures, and 8 were withdrawn from the study prior to infusion due to intercurrent adverse events or death due to progressive ALL, leaving 63 patients infused with tisagenlecleucel and evaluable for efficacy. The demographics and disease characteristics of the 63 efficacy-evaluable patients are shown in Table 1.

Of the 63 efficacy-evaluable patients, 53 (84%) received bridging chemotherapy during the tisagenlecleucel manufacturing period and 61 (97%) received lymphodepleting chemotherapy prior to tisagenlecleucel infusion. The median time from enrollment to infusion was 41 days (range, 29 to 104 days). The tisagenlecleucel dose administered was within the target range for 56 (89%) patients, below the target range for 5 (8%) patients, and above the target range for 2 (3%) patients. Six patients went on to hematopoietic stem cell transplantation (HSCT) after treatment with tisagenlecleucel.

Efficacy: Among the 63 efficacy-evaluable patients, ORR was achieved by 52 (83%; 95% CI 71% - 91%), and all responses were MRD-negative. Median time to onset of response was 29 days. Forty (63%; 95% CI 50% - 75%) of the 63 efficacy-evaluable patients achieved a CR with a median duration of CR that was not estimable within the follow-up period (median 4.8 months, range 1.2 to 14.1 months). When all 78 enrolled patients were included in the denominator, the CR rate was 51% (95% CI 40% - 63%). The durations of remission for the 40 patients with CR are shown in the Supplementary Figure.

Safety: The safety population consisted of all 68 patients who received an infusion of tisagenlecleucel on CCTL019B2202 (see Supplementary Table 2). Two patients died within 30 days of infusion of tisagenlecleucel: one with cytokine release syndrome (CRS) and progressive leukemia and the second with resolving CRS, abdominal compartment syndrome, coagulopathy, renal failure, and intracranial hemorrhage. The most common grade ≥3 adverse reactions were cytokine release syndrome (49%), febrile neutropenia (37%), hypotension (22%), viral infectious disorders (18%), hypoxia (18%), infections-pathogen unspecified (16%), pyrexia (15%), decreased appetite (15%), acute kidney injury (13%), bacterial infectious disorders (13%), encephalopathy (10%), and pulmonary edema (10%). Four (6%) patients had grade ≥3 congestive heart failure. The most common adverse reactions of any grade are shown in Table 2.

The most common (>20%) laboratory abnormalities worsening from grade 0-2 to grade 3-4 included increased aspartate aminotransferase (AST) (28%), hypokalemia (27%), increased alanine transaminase (ALT) (21%), and increased bilirubin (21%). All patients experienced neutropenia, anemia, and thrombocytopenia following administration of lymphodepleting chemotherapy, but of the responding patients, 17% had grade 3-4 neutropenia and 12% had grade 3-4 thrombocytopenia lasting for more than 56 days. Hypogammaglobulinemia was reported for 43% of patients.

CRS occurred in 54 (79%) patients, including grade ≥3 (by Penn Grading Criteria [5]) CRS in 33 (49%) patients. Two patients with CRS had fatal outcomes. The median time to onset of CRS was 3 days (range, 1 to 22 days), and the median time to resolution of CRS was 8 days (range, 1

to 36 days). Of the 54 patients with CRS, all received standard supportive care, 27 (50%) were treated with tocilizumab, and high-dose corticosteroids were added for 14 (26%) patients. The advanced supportive care measures included fluids and/or vasopressors for 36 (53%) patients, intensive care unit admission for 32 (47%) patients, mechanical ventilation for 11 (16%) patients, and dialysis for 8 (12%) patients.

Neurological toxicities were reported for 44 (65%) patients, including 12 (18%) patients with grade $\geq$ 3 neurological toxicities. No fatal neurological toxicities were reported. Most of the neurological events occurred within 8 weeks of infusion of tisagenlecleucel, and 75% of events resolved within 12 days. The most common neurological toxicities were headache (37%), encephalopathy (34%), delirium (21%), anxiety (13%), and tremor (9%). Other manifestations of neurological toxicities included disturbances in consciousness, disorientation, confusion, agitation, seizures, mutism, and aphasia. No treatment for neurological toxicity was prespecified; most patients received supportive care alone.

**Regulatory Insights**

As CRi is not an established surrogate of clinical benefit, the efficacy of tisagenlecleucel for treatment of R/R BCP ALL was established on the basis of the CR rate, duration of CR, and the proportion of patients with CR who were MRD-negative in CCTL019B2202. For the 63 patients in the efficacy analysis population, the CR rate was 63% (95% CI 50 - 75), and all patients in CR had MRD levels <0.01%. With a median follow-up of 4.8 months, the median duration of CR was not reached. The review team weighed accelerated approval and regular approval for this product. The CR rate in a single-arm trial is frequently used as a surrogate reasonably likely to predict clinical benefit for accelerated approval of new drugs for acute leukemia However, a

durable MRD-negative CR rate of remarkably high magnitude might be considered an actual clinical benefit for patients who have failed multiple therapies and have no reasonable alternative treatments; this would apply to the CR rate and study population in CCTL019B2202, supporting regular approval of tisagenlecleucel.

The approval consideration was complicated by the trial design, which a) did not require restaging prior to start of study treatment with lymphodepleting chemotherapy and tisagenlecleucel, and b) included use of two active chemotherapeutics (fludarabine and cyclophosphamide) in the trial regimen in addition to tisagenlecleucel. Under such circumstances, a randomized add-on trial is generally expected in order to assess the effect of the new agent in isolation. However, the magnitude of the CR rate in CCTL019B2202 was far greater than would be anticipated with any chemotherapy for treatment of R/R BCP ALL, raising questions about whether there would be sufficient equipoise to pursue such a randomized trial.

Based on the biology of the disease and the mechanism of action of tisagenlecleucel, one might expect that the efficacy of this product could be extrapolated to a wider range of patients with R/R BCP ALL. However, the safety of tisagenlecleucel for treatment of ALL in patients over the age of 25 years has not been established. Therefore, the review team concluded that based on the population accrued to CCTL019B2202, it was appropriate to limit the indication to pediatric and young adult patients up to age 25 years.

Cytokine release syndrome and persistent hypogammaglobulinemia are serious risks of tisagenlecleucel related to its mechanism of action. The mechanism of the neurologic toxicities is

not well-characterized, but this spectrum of neurological toxicities has been observed with other drugs that activate T cells [2,6]. During the trial, the risk of fatal toxicity was moderated in part by special training of the healthcare providers and patients, preparations at the study sites (including having tocilizumab available), and careful monitoring of the patients so that supportive care measures could be instituted as quickly as possible. To minimize fatal risks in practice, a required Risk Evaluation and Mitigation Strategy (REMS) will implement similar elements. Although the REMS limits distribution to specialized centers, this restriction was considered essential to ensure safe use of tisagenlecleucel.

The genetic modification and cellular nature of tisagenlecleucel generate additional safety concerns not usually posed by conventional biologics. In the production of tisagenlecleucel, there is a potential for integration of the lentiviral vector into critical sites in the genome that regulate cell cycling or genome stability, which may result in preferential clonal outgrowth or neoplastic transformation of transduced host cells. The duration of this risk is unknown, but it is assumed to be for an extended period, since tisagenlecleucel may persist *in vivo* for years. Cases of late onset secondary malignancies associated with insertional mutagenesis have been reported for genetically-modified stem cell products [7,8]. Although no cases of secondary leukemia were identified within the short duration of follow-up on CCTL019B2202, characterization of this risk in the patients treated with tisagenlecleucel is a postmarketing requirement (PMR) issued with the approval. This PMR requires 15 years of follow-up for patients treated with commercial tisagenlecleucel.

This approval does not establish how tisagenlecleucel should be placed in the R/R BCP ALL treatment paradigm. The CR rate achieved with tisagenlecleucel is clearly higher than expected

with conventional combination chemotherapy or single-agent use of the recently-approved targeted therapies for this patient population (Table 3). On the basis of registry or single-arm trials, only allogeneic HSCT (13) or combinations of chemotherapy with a targeted agent (14) provide for CR rates comparable to those demonstrated with tisagenlecleucel in CCTL019B2202, but the duration of response after these types of therapies is known to be quite limited (13-15). The optimal sequencing of therapies for R/R BCP ALL based on safety and efficacy considerations therefore remains to be determined.

**Conclusion**

Patients with R/R BCP ALL that is refractory to induction therapy or after multiple relapses have few meaningful treatment options. In CCTL019B2202, treatment of R/R BCP ALL in children and young adults with lymphodepleting chemotherapy and a single infusion of tisagenlecleucel was associated with considerable serious and life-threatening toxicity, but the CR rate was substantial (63%), all CRs were MRD-negative, and the median duration of response was not reached with a median follow-up of 4.8 months. With a stringent risk mitigation plan in place, the potential benefit from treatment with tisagenlecleucel appears to outweigh the risks for these patients.

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**Table 1. Patient Characteristics in the CCTL019B2202 Efficacy-Evaluable Population**

| | |
|---|---|
| ***Demographics*** | |
| Number of patients | 63 |
| Median age (range) | 12 yrs (3-23 yrs) |
| ≥17 years old | 16 (25%) |
| Sex | |
| Male | 35 (56%) |
| Female | 28 (44%) |
| Performance status[a] | |
| ≥90 | 41 (65%) |
| <90 | 22 (35%) |
| ***Disease Characteristics*** | |
| Disease status at screening | |
| Primary refractory | 6 (9%) |
| Refractory relapse | 8 (13%) |
| Untreated relapse | 49 (78%) |
| Relapse number | |
| 0 | 6 (9%) |
| 1 | 12 (19%) |
| 2 | 18 (29%) |
| ≥3 | 27 (43%) |
| Prior allogeneic transplantation | 35 (56%) |
| High-risk mutation[b] | 20 (32%) |

[a]Karnofsky (age ≥16 years) or Lansky (age < 16 years)

[b]Includes 16 patients with complex karyotype, 1 with Ph-positive karyotype, 1 with hypodiploidy, and 1 each with complex karyotype and MLL rearrangement or hypodiploidy.

**Table 2: Common Adverse Reactions Reported in the CCTL019B2202 Safety Population**

| | Percentage with Adverse Reaction (N=68) | |
|---|---|---|
| **Adverse Reaction** | **All Grades** | **Grades 3 or Higher** |
| Cytokine release syndrome | 79 | 49 |
| [c]Hypogammaglobulinemia | 43 | 7 |
| Infections-pathogen unspecified | 41 | 16 |
| Pyrexia | 40 | 15 |
| Decreased appetite | 37 | 15 |
| [d]Headache | 37 | 3 |
| [e]Encephalopathy | 34 | 10 |
| Hypotension | 31 | 22 |
| Viral infectious disorders | 26 | 18 |
| [a]Tachycardia | 26 | 4 |
| Nausea | 26 | 3 |
| Diarrhea | 26 | 1 |
| Vomiting | 26 | 1 |
| Hypoxia | 24 | 18 |
| [g]Acute kidney injury | 22 | 13 |
| Fatigue | 22 | 0 |
| [f]Delirium | 21 | 4 |
| Bacterial infectious disorders | 19 | 13 |
| Hypertension | 19 | 6 |
| Cough | 19 | 0 |
| Constipation | 18 | 0 |
| Pulmonary edema | 16 | 10 |
| [b]Abdominal pain | 16 | 3 |
| Pain in extremity | 16 | 1 |
| Myalgia | 15 | 0 |
| Fungal infectious disorders | 13 | 7 |
| Anxiety | 13 | 3 |
| International normalized ratio increased | 13 | 0 |
| Tachypnea | 12 | 6 |
| Arthralgia | 12 | 1 |
| Fluid overload | 10 | 7 |
| Pleural effusion | 10 | 4 |
| Back pain | 10 | 3 |
| Face edema | 10 | 1 |
| Edema peripheral | 10 | 1 |
| Chills | 10 | 0 |
| Nasal congestion | 10 | 0 |

[a]Tachycardia includes tachycardia and sinus tachycardia.
[b]Abdominal pain includes abdominal pain, abdominal pain upper, gastrointestinal pain, abdominal pain lower.
[c]Hypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, hypogammaglobulinemia.
[d]Headache includes headache and migraine.
[e]Encephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, posterior reversible encephalopathy syndrome, somnolence, and automatism.
[f]Delirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.
[g]Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis.

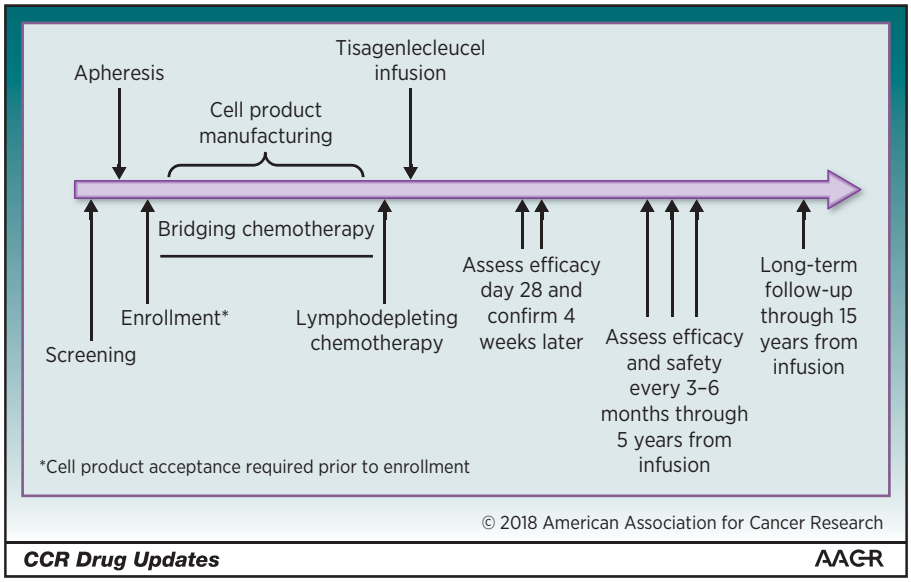
**Table 3. Treatments for Relapsed or Refractory ALL**

| | Population | Number of Patients | % CR (95% CI) |
|---|---|---|---|
| ***Single Agents*** | | | |
| Clofarabine (1) | Children | 61 | 12% (5% - 22%) |
| Vincristine liposome (9) | Adults | 65 | 5% (1% - 13%) |
| Blinatumomab (2) | Children | 70 | 17% (9% - 28%) |
| | Adults | 185 | 32% (26% - 40%) |
| | Adults | 271 | 34% (28% - 40%) |
| Inotuzumab ozogamicin (10) | Adults | 109 | 36% (27% - 46%) |
| ***Combinations*** | | | |
| Tisagenlecleucel (this report) | Children and young adults | 63 [78]* | 63% (50% - 75%) [51% (40% - 63%)]* |
| Combination chemotherapy (11) | Children | | |
| | Salvage 2 | 108 | 44% (35% - 54%) |
| | Salvage ≥3 | 121 | 19% (12% - 27%) |
| Combination chemotherapy (12) | Adults | | |
| | Salvage 2 | 275 | 21% (16% - 26%) |
| | Salvage 3 | 125 | 11% (6% - 18%) |
| Allogeneic HSCT (13) | Adults | 84 | 79% (68% - 87%) |

*Based on 78 enrolled patients.

**Figure 1. CCTL019B2202 Study Schema.** Eligible patients underwent apheresis and were considered enrolled if the cell collection was acceptable for manufacturing. Bridging chemotherapy was administered during the manufacturing period at the discretion of the investigator. Protocol 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 2 to14 days later by a single weight-based dose of tisagenlecleucel (0.2 to 5 x $10^6$ viable transduced T cells/kg body weight for patients $\leq$ 50 kg or a flat dose of 0.1 to 2.5 x $10^8$ viable transduced T cells for those > 50 kg).

**Figure 1:**



AACR American Association for Cancer Research

Clinical Cancer Research

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