Tisagenlecleucel (Tisa-cel, Kymriah; Novartis Pharmaceuticals Corporation**)**
FDA Approval Date: 5/1/2018

Maude SL, et al. *N Engl J Med.* 2018 Feb 1;378(5):439-448.

Objectives	Assess the efficacy, safety, and cellular kinetics of tisa-cel in children and young adults with relapsed or refractory B-Cell lymphoblastic leukemia.
Methods	Phase 2, single-cohort, open label, 25-center, global study Inclusion Criteria - at least 3 years of age at screening and no older than 21 years at diagnosis, have at least 5% lymphoblasts in bone marrow at screening. Exclusion Criteria - patients who had previously received anti-CD19 therapy. Tisa-cel was generated ex-vivo with the use of autologous T cells transduced with a lentiviral vector to express a CAR containing CD3-zeta domain to provide T-cell activation signal and a 4-1BB (CD137) domain to provide a costimulatory signal.
Endpoints	Primary Endpoint - overall remission rate higher than 20% (defined as the rate of best overall response of either complete remission or complete remission with incomplete hematologic recovery within 3 months). Secondary Endpoints - rate of complete remission or complete remission with incomplete hematologic recovery with undetectable minimal residual disease (<0.01%), duration of remission, event-free survival (time from infusion to the earliest of the following events: no response, relapse before response was maintained for at least 28 days, or relapse after having complete remission or complete remission with incomplete hematologic recovery), overall survival (OS), cellular kinetics, and safety.
Results	Baseline Characteristics ● n=75 received infusion, n=48 remained in follow-up ● Median follow up of 13.1 months. ● Median age of 11 years, median of 3 previous therapies, and median marrow blast of 74%. ● Of the 75 patients that received infusion, 87% received bridging chemotherapy between enrollment and infusion, and 96% received lymphodepleting chemotherapy. ● Patients received a median weight-adjusted dose of 3.1×10^6 transduced viable T cells/kg; the median total dose was 1.0×10^8. Efficacy ● Overall remission rate: 81% ○ 60% had complete remission ○ 21% had complete remission with incomplete hematologic recovery ● All patients who had a best overall response of complete remission with or without hematologic recovery were negative for minimal residual disease ○ 95% of these patients were negative by day 28 ● Among the 61 patients with complete remission with or without hematologic recovery, the median response duration was not reached. ● Rate of relapse-free survival among patients with a response to treatment ○ 6 months: 80% ○ 12 months: 59% ● Among patients with complete remission, 17 had relapse before receiving additional anticancer therapies ● Rate of event-free survival ○ 6 months: 73% ○ 12 months: 50% ○ Median even-free survival was not reached

	● Rate of OS ○ 6 months: 90% ○ 12 months:76% <u>Safety</u> ● All patients had at least one adverse event during the study, 95% were suspected to be related to tisa-cel. ● The most common non hematologic adverse events of any grade at any time were cytokine release syndrome (77%), pyrexia (40%), decreased appetite (39%), febrile neutropenia (36%), and headache (36%). ● 88% of patients had grade 3 or 4 adverse events, 73% had grade 3 or 4 tisa-cel-related adverse events. ● **Cytokine Release Syndrome (CRS)** ○ Incidence: 77% ○ Median time to onset: 3 days ○ Median duration: 8 days ○ 47% of patients were admitted to the ICU, with a median stay of 7 days. ○ 25% were treated with high-dose vasopressors, 44% received oxygen supplementation, 13% received mechanical ventilation, 9% underwent dialysis, and 37% received tocilizumab for management of the CRS. ● **Neurologic Toxicities** ○ Incidence: 40%, 13% had grade 3, no grade 4 or cerebral edema reported. ○ Among grade 3 episodes that were resolved, 50% resolved within 10 days, and 75% resolved within 18 days. ● Cytopenia's ○ 41% of patients had grade 3 or 4 decreased platelet counts that had not resolved by day 28. ○ 53% of patients had grade 3 or 4 decreased neutrophil count that had not been resolved by day 28. ■ 45% of these patients had grade 3 or 4 infections. ● B-cell aplasia ○ All patients with a response to treatment had B-cell aplasia, most patients received immunoglobulin replacement. ○ Median time to B-cell recovery was not reached. ○ Probability of maintenance of B-cell aplasia at 6 months after infusion: 83% ● 19 deaths occurred after tisa-cel infusion. <u>Cellular Kinetics</u> ● n=60 ● Median time to maximum expansion (T_{max}): 10 days, 6 patients with no response T_{max}: 20 days. ● Median duration of persistence in blood: 168 days ● Geometric mean of the area under the concentration-time curve in peripheral blood from time 0 to day 28 ○ 315,000 copies/microgram of DNA x days in patients with a response ○ 301,000 copies/microgram of DNA x days in patients without a response
Conclusion	Tisa-cel produced high remission rates and durable remissions without additional therapy in high-risk pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.

Schuster SJ, et al. JULIET. *N Engl J Med.* 2019 Jan 3;380(1):45-56

Objectives	Evaluate the efficacy and safety of tisa-cel in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
Methods	International, phase 2, single-group, 27-site, open-label, pivotal study Inclusion Criteria - ≥18 years; previously received at least two lines of therapy including rituximab and an anthracycline; DLBCL that had transformed from follicular lymphoma as well as patients who had high-grade B-cell lymphoma with *MYC* rearrangement plus rearrangement of *BCL2, BCL6*, or both. Exclusion Criteria - previously received CD19-directed therapy; primary mediastinal DLBCL; previously received an allogeneic transplant; active central nervous system involvement of their DLBCL. Before therapy, patients received one cycle of lymphodepleting chemotherapy (fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 daily for 3 days, or bendamustine 90 mg/m^2 for 2 days). Single infusion of tisagenlecleucel median dose: 3.0×10^8 CAR^+ viable T cells.
Endpoints	Primary Endpoint - Best overall response rate (ORR; i.e. the combined percentage of patients who had a complete or partial response) Secondary Endpoints - Response duration (DOR), overall survival (OS), safety, and cellular kinetics
Results	Baseline Characteristics ● n=111 ● Median age ~56 ● Median time from enrollment to infusion: 54 days ● Median time from infusion to data cutoff: 14 months ● 92% of patients received bridging therapy. Efficacy ● Among the 93 patients in efficacy analysis who had 3 months or more of follow-up, best overall response rate: 52%. ○ Complete response: 40% ○ Partial response: 12% ● Median response duration: not reached ○ 79% (complete response) and 65% (all response) are projected to remain relapse-free at 12 months after having a response. ● Durable responses were seen up to 18.4 months after infusion. ● Median progression-free survival has not been reached for patient who had complete response. ○ Estimated PFS at 12 months was 83% among patients who had a complete or partial response at 3 months. ● Median overall survival: 12 months ○ Estimated probability of survival at month 12: 49% (all patients), 90% (CR) ○ Intention-to-treat analysis: median overall survival 8.3 months, estimated probability of survival at month 12: 40% Safety ● The most common adverse events of any grade were cytokine release syndrome (58%), anemia (48%), pyrexia (35%), decreased neutrophil count (34%), decreased platelet count (33%), decreased white-cell count (33%), and diarrhea (32%). ● **Cytokine Release Syndrome (CRS)** ○ Any grade incidence: 58%, grade 3 or 4: 22% ○ Median time to onset: 3 days ○ Median time to onset of grade 3 or 4 CRS: 4 days

	○ Median duration: 7 days ○ Tocilizumab use: 14%, tocilizumab and corticosteroids: 10% ● **Neurologic Toxicities** ○ Any grade incidence: 21%, grade 3 or 4: 12% ○ Median time to onset: 6 days ○ Median duration: 14 days ● 3 patients died within 30 days after infusion, from lymphoma progression. No deaths after infusion were attributed to tisa-cel. <u>Cellular Kinetics</u> ● Median time to maximum transgene level and mean area under the concentration-time curve from day 0 to 28 were observed in patients who had a response and those who did not. ○ No apparent effect of exposure on clinical outcome was observed. ● Persistent CAR transgene levels were observed for up to 2 years after infusion in patients with durable responses. ● No relationship between dose and maximal in vivo expansion was apparent.
Conclusion	Tisa-cel showed high and durable response rates, though follow-up was short and there is a potential for long-term toxic effects that requires further analysis.