Brexucabtagene autolecuel (Brexu-cel, Tecartus; Kite Pharma, a Gilead Sciences Company)
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Wang M, et al. ZUMA-2. *N Engl. J Med.* 2020; 382(14):1331-1342

Objectives	Evaluate the efficacy and safety of KTE-X19 (Tecartus) in patients with relapsed or refractory mantle-cell lymphoma.
Methods	Single-group, multicenter, open-label phase 2 ZUMA-2 trial Inclusion Criteria - ≥18 years of age; histologically confirmed mantle-cell lymphoma with either cyclin D1 overexpression or presence of translocation t(11;14) and had disease that was either relapsed or refractory to up to give previous regimens for mantle-cell lymphoma; Previous therapy must have included anthracycline- or bendamustine-containing chemotherapy, and BTK inhibitor therapy with ibrutinib or acalabrutinib; absolute lymphocyte count of at least 100 cells per cubic centimeter. Exclusion Criteria - known history of HIV, HepB, or HepC infection; history of seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement; prior allogeneic transplantation; presence of fungal, bacterial, viral, or other infection that is not controlled or requires IV antimicrobials. All patients underwent leukapheresis to obtain cells for KTE-X19 manufacturing. Conditioning chemotherapy (fludarabine 30mg/m^2 and cyclophosphamide 500 mg/m^2) was administered on days -5, -4, and -3 before a single IV infusion of KTE-X19 2x10^6 CAR T cells/kg on day 0.
Endpoints	Primary Endpoint - percentage of patients with an objective response (ORR, complete or partial response) as assessed by the independent radiology review committee according to the Lugano classification. Secondary Endpoints - duration of response (DOR), progression-free survival (PFS), overall survival (OS), the percentage of patients with investigator-assessed objective response according to criteria of Cheson et al., the incidence of adverse events, the level of CAR T cells in blood and cytokines in serum, and changes in scores from baseline to month 6 in the five-level version of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. Exploratory Analysis - Minimal residual disease (MRD)
Results	Baseline Characteristics ● n=74, successfully manufactured for 71 patients and administered to 68 patients. ● Median age ~65 years ● Median time from leukapheresis to delivery of KTE-X19 at the trial site was 16 days. ● 55% of patients has ≥3 previous lines of therapy. ○ 100% of patients had previous BTK inhibitor therapy. ○ 29% of patients had previous autologous stem-cell transplantation. ● 62% of patients had disease that did not respond to BTK inhibitor therapy and 26% had a relapse after having an initial response while receiving BTK inhibitor therapy. ○ 88% of the treated patients had disease that was considered refractory to BTK inhibitor therapy. ● 37% of patients received bridging therapy with ibrutinib, acalabrutinib, dexamethasone, or methylprednisolone. Efficacy ● 60 treated patients who had at least 7 months of follow-up (per-protocol analysis) ○ ORR - 93% [95% CI, 84-98] ○ CR - 67% [95% CI, 53-78] ○ PR - 27% [CI not reported]

	● All 74 enrolled patients (intention-to-treat analysis) ○ ORR - 85% ○ CR - 59% ● 57% of all the patients in the primary efficacy analysis and 78% of those with complete response were continuing to have a response after a median follow-up of 12.3 months. ● DOR - NR [95% CI, 8.6-NR] ○ Patients alive around 24-30 months ● PFS - 61% at 12 months ● OS - 83% at 12 months ● MRD analyzed in 29/74 (39%) ○ 83% had no detectable residual disease at week 4. <u>Safety</u> ● All 68 patients had at least 1 AE of any grade; AEs of grade 4 or higher occurring in 99% ● Most common adverse events of grade 3 or higher ○ Cytopenia's - 94% ■ Neutropenia - 85% ■ Thrombocytopenia - 51% ■ Anemia - 50% ○ Infections - 32% ● **Cytokine Release Syndrome** - 91% ○ Grade 1 or 2 (76%), grade 3 or higher (15%) ○ Tocilizumab (59%), glucocorticoids (22%), and vasopressors (16%) ○ Median time to onset - 2 days ○ Median duration - 11 days ○ No patients died from CRS. ● **Neurologic Toxicities** - 63% ○ Grade 1 or 2 (32%), grade 3 or higher (31%) ○ Tocilizumab (26%), glucocorticoids (38%) ○ Median time to onset - 7 days ○ Median duration - 12 days ○ No patients died from neurologic events. ● Serious adverse events - 68% ○ Infection of grade 3 or higher - 32% ■ Most common - pneumonia (9%) ○ Grade 2 cytomegalovirus infection (3%) ○ Grade 3 hypogammaglobulinemia and grade 3 tumor lysis syndrome (1%) <u>Biomarker Analysis</u> ● Median time to peak anti-CD19 CAR T-cell levels - 15 days; cells were still detectable at 24 months in 6/10 (60%) of patients. ● Expansion was associated with response; peak level and AUC were more than 80 times as high among patients without MRD; expansion was greater in those with grade 3 or higher cytokine release syndrome or neurologic events; highest peak and AUC values in those receiving tocilizumab with or without glucocorticoids. ● Median time to peak levels of cytokines - 8 days; most values resolved by 28 days.
Conclusion	KTE-X19 (Tecartus) as a single infusion induces durable remission in patients with relapsed or refractory mantle-cell lymphoma after the failure of BTK inhibitor therapy. Serious and life-threatening toxic events occurred that are largely consistent with those reported in previous studies of anti-CD19 CAR T-cell therapies in patients with aggressive B-cell lymphoma.

Shah BD, et al. ZUMA-3. *Lancet.* 2021 Aug; 398(10299):491-502.

Objectives	Evaluate the efficacy and safety of KTE-X19 in adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).
Methods	Phase 2, multicenter (25 sites), single-arm, open label trial Inclusion Criteria - ≥ 18 years; bone marrow blasts >5%; ECOG 0-1. Exclusion Criteria - CNS abnormalities, active infection, prior use of CD19-directed therapy. After lymphodepleting chemotherapy (cyclophosphamide and fludarabine), patients received a single infusion of KTE-X19 at a target dose of 1 or 2 x 10^6 anti-CD19 CAR^+ T cells//kg.
Endpoints	Primary Endpoint - overall complete remission rate (CR + CR with incomplete hematologic recovery) Secondary Endpoints - duration of remission (DOR), relapse-free survival (RFS), overall survival (OS), measurable residual disease negativity (MRD^-) rate, and safety.
Results	Baseline Characteristics ● n=55 ● Median age ~40 ● 47% of patients had received 3 or more previous therapies. ● 33% had primary refractory disease, 44% had relapsed or refractory disease, 78% had relapsed or refractory disease to 2 or more lines of systemic therapy. ● 93% of patients received bridging chemotherapy. Efficacy ● Overall complete remission: 71% ○ Complete remission: 56% ● Median duration of remission: 12.8 months ● Median RFS: 11.6 months in all, 14.3 months in responders, 58% at 6 months ● Median overall survival: 18.2 months, rate at 12 months: 71% ● MRD: 76%, among responders: 97% had MRD^- Safety ● The most common adverse events of ≥ grade 3 were anemia (49%) and pyrexia (36%). ● **Cytokine Release Syndrome (CRS)** ○ Overall incidence: 89%, grade 3 or 4: 24% ○ Median time to onset: 5 days ○ Median duration: 7.5 days ○ Tocilizumab use: 80%, steroid use: 75%, and vasopressors: 40% ● **Neurologic toxicities** ○ Overall incidence: 60%, grade 3 or higher: 25% ○ Median time to onset: 9 days ○ Median duration: 7 days ● Grade 3 or higher cytopenia: 76% ● Grade 3 or higher infections: 25% ● 36% of treated patients died, primarily from progressive disease. Cellular Kinetics ● Median time to peak CAR T-cell levels in blood: 15 days ● CAR T cells were no longer detectable by PCR in 79% of 28 patients at 6 months. ● Inverse relationship between CAR T-cell expansion and bone marrow blasts. ○ Median peak CAR T-cell level in blood was 40.47 cells/uL ● Most cytokines peaked at 8 days after infusion.
Conclusion	A single infusion of KTE-X19 could induce durable remission with manageable safety in heavily pretreated adults with relapsed or refractory B-precursor acute lymphoblastic leukemia.