Lisocabtagene maraleucel (liso-cel, Breyanzi; Juno Therapeutics, inc., a Bristol-Myers Squibb Company**)**
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Objectives	Assess the safety and activity of liso-cel in a broad population of patients with relapsed or refractory large B-cell lymphomas, including lymphomas with diverse histological features and patients with aggressive disease and high-risk features.
Methods	Multi-centre, multicohort, seamless design study at 14 cancer centers in the USA. Inclusion Criteria - aged ≥18 years, relapsed or refractory B-cell non-Hodgkin lymphoma (DLBCL or MCL), PET-positive disease, ECOG of 0 or 1, adequate organ function, received ≥2 lines of systemic treatment (including previous chemoimmunotherapy containing anti-CD20 and anthracycline) with subsequent relapse, adequate vascular access, adequate contraception methods for males and females. Exclusion Criteria - central nervous system (CNS)-only involvement by malignancy, history of another primary malignancy that had not been in remission for at least 2 years, active Hep B, Hep C, or HIV, uncontrolled infections, acute or chronic GVHD, variety of cardiovascular conditions (i.e. NYHA Class III or IV HF, myocardial infarction, etc.), clinically relevant CNS pathology (i.e. epilepsy, aphasia, stroke, etc.), pregnant, prior CAR- T cell therapy. Lymphodepleting chemotherapy consisting of fludarabine (30mg/m^2) and cyclophosphamide (300 mg/m^2) was administered IV for 3 days. After 2-7 days, liso-cel was administered as two sequential infusions of CD8 and CD4 CAR^+ T cells. ● Dose level 1 - 50 x 10^6 CAR^+ T cells ● Dose level 2 - 100 x 10^6 CAR^+ T cells ● Dose level 3 - 150 x 10^6 CAR^+ T cells
Endpoints	Primary Endpoints - Treatment-related adverse events (AEs), dose-limiting toxicities, and objective response rate (ORR) Secondary Endpoints - Complete response rate (CR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and cellular kinetic variables
Results	Baseline Characteristics ● n= 269 ● Median age ~ 63 years ● Median follow-up of 18.8 months. ● Median of 3 previous lines of systemic therapy. ● 67% of patients had chemotherapy-refractory disease and 44% had never achieved a complete response with previous therapy. ● Bridging therapy was administered in 59% of patients. ● Large B-cell lymphoma not otherwise specified in 59%, diffuse large B-cell lymphoma transformed from indolent lymphomas in 29%, and high-grade B-cell lymphoma with gene rearrangements of MYC and either BCl2 or BCL6 or both, in 13% of patients. ○ 3% of patients had secondary CNS involvement. Primary Endpoints ● Treatment-related adverse events (AEs), any grade (n=267, 99%), grade ≥3 (n=213, 79%) ○ Neutropenia: n=169 (63%) ○ Anemia: n=129 (48%) ○ Fatigue: n=119 (44%) ○ **Cytokine release syndrome**: n=113 (42%) ■ Median onset of 5 days

	■ Most common symptoms - fever and hypotension ■ Tocilizumab use 10%, corticosteroid use 2%, both 8%) ○ **Neurological events**: n=80 (30%) ■ Median time to onset of 9 days ○ Nausea: n=90 (33%) ● Dose-limiting toxicities ○ n= 9 (6%) ○ One patient death due to alveolar damage at dose level 1 ● ORR ○ n=186, (73%, 95% CI 66.8-78.0; p<0.0001) <u>Secondary Endpoints</u> ● CR ○ n=136, (53%, 95% CI 46.8-59.4; p<0.0001) ● DOR (95% CI, n=256) ○ Median: NR (8.6-NR) ○ 6 months: 60.4% (52.6-67.3) ○ 12 months: 54.7% (46.7-62.0) ● PFS (95% CI, n=256) ○ Median: 6.8 months (3.3-14.1) ○ 6 months: 51.4% (44.6-57.7) ○ 12 months: 44.1% (37.3-50.7) ● OS (95% CI, n=256) ○ Median: 21.1 months (13.3-NR) ○ 6 months: 74.7% (68.9-79.6) ○ 12 months: 57.9% (51.3-63.8) ● Cellular kinetic variables ○ Median time to CAR T cell peak expansion across all dose levels was 12 days ○ Median maximum expansion was 23,928.2 copies/ug ○ Median area under the curve from 0-28 days post infusion was 213,730.1 copies/ug
Conclusion	Treatment with liso-cel can lead to rapid and durable remission, with low incidence of all-grade and severe cytokine release syndrome and neurological events among patients with high-risk aggressive relapsed or refractory large B-cell lymphomas. Clinically meaningful activity was noted in those with uncommon histological subtypes and patients with poor prognosis.