Axicabtagene Ciloleucel (Axi-cel, Yescarta; Kite Pharma, Inc**)**
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Neelapu SS, et al. ZUMA-1. *N Engl J Med.* 2017 Dec; 377 (26): 2531-2544

Objectives	Assess the efficacy, safety, and cellular kinetics of axi-cel in patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease despite undergoing recommended prior therapy.
Methods	Multicenter (22 sites), phase 2, single-arm trial Inclusion Criteria - ≥ 18 years; histologically confirmed large B-cell lymphoma (including DLBCL and primary mediastinal B-cell lymphoma or transformed follicular lymphoma); chemotherapy-refractory disease. Exclusion Criteria - CNS involvement; clinically significant infection; prior CD19 targeted therapy or CAR T therapy; contraindications to use. After receiving lymphodepleting chemotherapy (low-dose cyclophosphamide and fludarabine), patients received a target dose of 2 x 10^6 anti- CD19 CAR T cells/kg of axi-cel.
Endpoints	Primary Endpoint - rate of objective response (ORR, combined rates of complete and partial response) Secondary Endpoints - duration of response (DOR), progression-free survival (PFS), overall survival (OS), incidence of adverse events, and blood levels of CAR T cells and serum cytokines.
Results	Baseline Characteristics ● n= 101 received axi-cel ○ 77 with DLBCL ad 24 with primary mediastinal B-cell lymphoma or transformed follicular lymphoma. ● Median follow up ~8.7 months, updated analysis median followup 15.4 months ● Median age ~58 years ● Most patients (85%) had stage III or Iv disease. ● 77% of patients had disease that was resistant to second-line or later therapies. ● 21% had disease relapse after transplantation. ● 69% had received at least 3 previous therapies. ● 26% had a history of primary refractory disease. Efficacy ● ORR among protocol-specified 91 patients: 82% ○ Complete response rate: 52% ● ORR among those who received axi-cel: 82% ○ Complete response rate: 54% ● Median DOR ○ 6 months: 8.1 months ○ 12 months: 11.1 months ● PFS at 12 months: 5.8 months, rate of 49% at 15 months ● Median OS: not yet reached ● OS rates ○ 6 months: 78% ○ 12 months: 59% ○ 18 months: 52% Safety ● All patients with axi-cel infusion had adverse events, with 95% grade 3 or higher. ● Most common adverse events of any grade - pyrexia (85%), neutropenia (84%), and anemia (66%).

	● Most common adverse events of grade 3 or higher - neutropenia (78%), anemia (43%), and thrombocytopenia (38%). ● **Cytokine Release Syndrome (CRS)** ○ Overall incidence: 93%, grade 3 or higher: 13% ○ Median time to onset: 2 days ○ Median duration: 8 days ○ Tocilizumab use: 43%, glucocorticoid use: 27% (CRS, neuro, or both) ○ Vasopressor use: 17% ● **Neurologic Toxicities** ○ Overall incidence: 64%, grade 3 or higher: 28% ○ Median time to onset: 5 days ○ Median duration: 17 days ○ Tocilizumab use: 43%, glucocorticoid use: 27% (CRS, neuro, or both) <u>Cellular Kinetics</u> ● CAR T levels peaked in the peripheral blood within 14 days after infusion and were detectable in most patients after 180 days. ● Expansion was significantly associated with response ○ Area under the curve within the first 28 days after treatment was 5.4 times as high in those that had a response. ● Peak expansion and area under the curve were significantly associated with neurologic events of grade 3 or higher, but not with CRS.
Conclusion	Patients with relapsed or refractory large B-cell lymphoma after two prior systemic therapies who received CAR T-cell therapy with axi-cel had high levels of durable response, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.

Jacobsen C, et al. ZUMA-5. *Blood*. 2020; 136 (Supp 1): 40-41

Objectives	Assess the efficacy, safety, and cellular kinetics of axi-cel in adults with relapsed or refractory advanced-stage indolent Non-Hodgkin Lymphoma (follicular lymphoma (FL) and marginal zone lymphoma(MZL)).
Methods	Phase 2, multicenter, single-arm trial. <u>Inclusion Criteria</u> - <u>≥</u> 18 years; patients with follicular lymphoma (grades 1-3a) or marginal zone lymphoma (nodal or extra nodal); relapsed or refractory disease; <u>≥</u> 2 previous lines of therapy (including anti-CD20 mAb plus an alkylating agent); ECOG 0-1. <u>Exclusion Criteria</u> - not disclosed in primary analysis. Following lymphodepleting chemotherapy (cyclophosphamide and fludarabine), patients received a single infusion of axi-cel at 2 x 10^6 CAR T cells/kg.
Endpoints	<u>Primary Endpoint</u> - objective response rate (ORR) <u>Secondary Endpoints</u> - complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS), incidence of adverse events, and levels of CAR T cells in blood and cytokines in serum.
Results	<u>Baseline Characteristics</u> ● n=146 ● Median age ~61 ● 57% of patients were male. ● 38% of patients had ECOG 1, 86% had stage III/IV disease, 47% had <u>≥</u> 3 FLIPI, and 49% had high tumor bulk. ● Patients had a median of 3 prior lines of therapy.

	● Median follow up of 17.5 months. Efficacy ● ORR: 92% ○ FL: 94% ○ MZL: 85% ● CR: 76% ○ FL: 80% ○ MZL 60% ● Median DOR was not reached. Estimated 12-month rate 72% ● Median PFS was not reached. Estimated 12-month rate 74% ● Median OS was not reached. Estimated 12-month rate 93% Safety ● AEs of any grade occurred in 99% of all treated patients; grade ≥ 3: 86% ● Most commonly neutropenia (33%), decreased neutrophil count (27%), and anemia (23%) ● **Cytokine Release Syndrome** (CRS) grade ≥ 3: 7% (6% FL, 9% MZL) ● **Neurologic toxicities** grade ≥3: 19% (15% FL, 41% MZL) Cellular Kinetics ● Median peak CAR T cell level was 38 cells/uL (36 cells/uL FL, 53 cells/uL MZL). ○ Numerically greater in those with ongoing response at 12 months than in those we relapsed. ○ CAR T cell peak was associated with grade ≥ 3 CRS and neurotoxicity's. ● AUC day 0-28 was 448 cells/uL x days (422 in FL, 552 in MZL). ● Median time to peak was 9 days (8 days FL, 15 days MZL).
Conclusion	Axi-cel had considerable and durable clinical benefit (ORR and CR rates) in patients with indolent non-Hodgkin's Lymphoma, with a manageable safety profile.