CAR T-Cell Therapy Shows Durable Responses in Indolent NHL

Advanced-stage indolent non-Hodgkin lymphoma (NHL) histologies, including follicular lymphoma (FL) and marginal zone lymphoma (MZL), are characterized by multiple relapses for many patients. Early relapse, defined as progression of disease within 24 months (POD24), predicts worse outcomes. Among patients with FL treated with frontline anti-CD20-targeted immunochemotherapy regimens, POD24 is associated with a 5-year overall survival (OS) rate of 50% [1]. By comparison, the 5-year OS is 90% for patients with later disease progression following frontline therapy.

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of relapsed/refractory large B-cell lymphoma after ≥2 prior lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from FL. In the phase II ZUMA-1 trial, axi-cel was associated with an overall response rate (ORR) of 83%, including a complete response (CR) rate of 58%, in patients with relapsed/refractory DLBCL [2].

To date, most of the clinical experience with CAR T-cell therapy in NHL has involved aggressive histologies, including DLBCL. The ZUMA-5 trial is the first trial to examine the safety and efficacy of CAR T-cell therapy in patients with relapsed/refractory indolent NHL [3].

ZUMA-5: Study Design

The phase II ZUMA-5 trial is an ongoing multicenter, single-arm study evaluating axi-cel in patients with relapsed/indolent FL (grades 1–3a) or MZL (nodal or extranodal) after ≥2 prior lines of therapy. Prior treatment must have included an anti-CD20 monoclonal antibody combined with an alkylating agent.

All patients underwent leukapheresis and received 3 days of conditioning chemotherapy with fludarabine and cyclophosphamide, beginning 5 days prior to the CAR T-cell infusion. Patients then received a single axi-cel infusion at 2×10^6 CAR T cells/kg.

The primary endpoint was ORR by independent review. Key secondary endpoints included CR by independent review, duration of response (DOR), progression-free survival (PFS), OS, safety, and blood levels of cytokines and CAR T cells.

As of December 16, 2019, 140 patients with FL (n = 124) or MZL (n = 16) had received treatment with axi-cel. The median follow-up for the efficacy analysis was 15.3 months and the median follow-up for the safety analysis was 12.8 months (range, 1.9–28.8 months).

The median patient age was 63 years (range, 34–79 years), and half of patients (49%) were male. Baseline disease characteristics illustrated extensive disease in this heavily pretreated population. Approximately half of patients had stage IV disease (52%), a Follicular Lymphoma International Prognostic Index (FLIPI) score of ≥3 (51%), and high tumor bulk (49%). Patients had a median of 3 prior lines of therapy (range, 2–9 prior lines), including 23% who had undergone prior stem cell transplantation. The majority of patients (73%) had refractory disease, and 54% experienced POD24.

ZUMA-5: Key Findings

The ORR was 93% and the CR was 80% among 96 patients evaluable for treatment efficacy. Patients with FL experienced a slightly higher rate of response relative to those with MZL (95% versus 81%, respectively) (Table 1). Response rates were consistently high across patient subgroups defined by age,

Table 1. ZUMA-5: Efficacy endpoints in relapsed/refractory FL and MZL

Endpoint	FL (n = 80)	MZL (n = 16)
Overall response	95%	81%
Complete response	81%	75%
Partial response	14%	6%
Median DOR	20.8 months	10.6 months
Median PFS	23.5 months	11.8 months
12-month OS	93.4%	100%

Abbreviations: DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival.

Table 2. ZUMA-5: Cytokine release syndrome and neurotoxicity in relapsed/refractory FL and MZL

TEAE of special interest	FL (n = 124)	MZL (n = 16)
Cytokine release syndrome		
Any grade	77%	100%
Grade ≥3	7%	13%
Median time to onset	4 days	4 days
Median duration	6 days	6 days
Patients with resolved events	99%	100%
Neurotoxicity		
Any grade	55%	81%
Grade ≥3	15%	38%
Median time to onset	7 days	7 days
Median duration	14 days	13 days
Patients with resolved events	96%	92%

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event.

http://dx.doi.org/10.1634/theoncologist.2020-0559

number of prior lines of therapy, time to relapse to prior anti-CD30-targeted therapy, FLIPI score, presence of bulky disease, and relapsed versus refractory status.

Responses were durable, with a median DOR of 20.8 months for all patients. In the FL group, 68% of patients had an ongoing response at the time of data cut-off. The median PFS was 23.5 months for all patients, and 23.5 months and 11.8 months, respectively, for patients with FL and MZL. The median OS had yet to be reached, with 12-month OS rates of 93.4% and 100% in the FL and MZL groups, respectively.

The most common treatment-emergent adverse events (TEAE) of any grade were pyrexia (84%), hypotension (49%), fatigue (44%), headache (44%), nausea (39%), neutropenia (36%), anemia (35%), and sinus tachycardia (34%). In total, 85% of patients experienced grade ≥3 TEAEs, most commonly neutropenia (34%) and anemia (22%). Two grade 5 adverse events occurred: multisystem organ failure in the context of cytokine release syndrome (CRS) related to axi-cel and aortic dissection unrelated to axi-cel.

CRS and neurotoxicity are TEAEs of special interest during CAR T-cell therapy. Grade ≥3 CRS and neurotoxicity occurred in 8% and 17% of patients, respectively, with slightly lower rates observed in the FL group than in the MZL group (Table 2). The majority of cases of CRS and neurotoxicity resolved as of the data cutoff date.

In summary, data from the ongoing ZUMA-5 trial support CAR T-cell therapy as a potential treatment approach for patients with relapsed/refractory indolent FL and MZL.

References

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