CD19/CD22 Dual-Targeted CAR-T Therapy Active in Relapsed/Refractory DLBCL

Advances in CD19-targeted chimeric antigen receptor (CAR) T-cell therapies have led to a new standard of care for heavily pretreated relapsed/relapsed diffuse large B-cell lymphoma (DLBCL). Despite the clinical benefits of CAR T-therapy, however, the limited duration of response remains an unmet clinical need. In trials of axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), approximately 29% to 37% of patients with relapsed/refractory DLBCL achieved a durable complete response (CR) [1, 2].

Several potential mechanisms of resistance to CD19-directed CAR T-cell therapy have been proposed, including CD19 antigen loss and programmed death-ligand 1 (PD-L1) upregulation, leading to CAR T-cell exhaustion [3, 4]. Strategies to overcome these resistance mechanisms include the simultaneous targeting of both CD19 and CD22 to reduce the probability of antigen loss, as well as the use of a checkpoint inhibitor to prevent PD-L1-mediated CAR T-cell exhaustion.

AUTO3 is an investigational CAR T-cell product that delivers two CARs targeting CD19 and CD22, respectively, in a single retroviral vector. The bicistronic CAR is therefore the first to independently target both CD19 and CD22. The phase I/II Alexander study is an ongoing, single-arm, open-label, multicenter trial designed to evaluate the safety and efficacy of AUTO3 in combination with pembrolizumab in patients with relapsed/refractory DLBCL [5].

Alexander Trial: Study Design

The Alexander trial enrolled 23 patients with relapsed, refractory, or transformed DLBCL who experienced relapse after ≥2 prior lines of therapy or autologous stem cell transplant (ASCT). The median patient age was 57 years (range, 28–83 years). The median number of prior therapies was 3 (range, 2–10), and 4 patients had a prior ASCT.

All patients underwent lymphodepletion with fludarabine and cyclophosphamide. Patients then received escalating doses of AUTO3 alone (50, 150, or 450 $\times 10^6$ cells); AUTO3 plus 3 doses of pembrolizumab 200 mg every 3 weeks starting on day 14; or AUTO3 plus a single dose of pembrolizumab 200 mg on day 1.

The primary endpoints were frequency of dose-limiting toxicities (DLTs) and incidence of grade 3–5 adverse events (AEs) occurring within 75 days of AUTO3 infusion. Secondary endpoints included overall response rate (ORR) and complete response rate (CRR).

Aravind Ramakrishnan, M.D., of the Sarah Cannon Research Institute, presented findings from the phase I dose-escalation cohort.

Alexander Trial: Key Findings

Results from the Alexander study support the safe use of AUTO3 in patients with relapsed/refractory DLBCL (Table 1). No DLTs were observed at any AUTO3 dose. The majority of grade >3 AEs were hematologic AEs, including neutropenia (87%), thrombocytopenia (57%), and anemia (48%). There were no grade 5 AEs and no AUTO3-related deaths.

Cytokine release syndrome (CRS) and neurotoxicity are AEs of special interest following CAR T-cell therapy. In prior trials of CD19-targeted CAR T-cell therapy, 13%–22% of patients experienced severe CRS and 12%–28% experienced severe neurotoxicity [2, 4].

In the Alexander study, no cases of severe CRS were observed (Table 1). In total, 9 patients (39%) experienced CRS, including grade 1 CRS in 26% and grade 2 CRS in 13% of patients. The median time to CRS was 7 days (range, 1–36 days), and the median duration was 5 days (range, 1–19 days). Treatment included tocilizumab in 4 patients.

One patient (4.3%) developed grade 3 neurotoxicity on day 53 following AUTO3 infusion (50 $\times 10^6$ cells) without pembrolizumab. The patient was treated with steroids, and

Table 1. Alexander: Treatment-emergent adverse events with AUTO3

Adverse event	All grades	Grades 3–4
Neutropenia	87%	87%
Thrombocytopenia	65%	57%
Anemia	57%	48%
Cytokine release syndrome	39%	0%
Fever	39%	0%
Constipation	30%	0%
Fatigue	26%	0%

Table 2. Alexander: Preliminary efficacy of AUTO3 in relapsed/refractory DLBCL

Response	All patients (*N* = 23)	AUTO3 dose ≥150 $\times 10^6$ (*n* = 16)	AUTO3 dose ≥150 $\times 10^6$ + pembrolizumab on day 1 (*n* = 8)
ORR	65%	69%	75%
CRR	48%	56%	63%

Abbreviations: CRR, complete response rate; ORR, overall response rate.

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symptoms improved in 3 days. No cases of neurotoxicity of any grade were observed in patients treated with AUTO3 plus pembrolizumab.

Preliminary efficacy endpoints include an ORR of 65% and a CRR of 48% for all patients (Table 2). The most promising responses were observed in patients treated with AUTO3 at a dose of ≥150 $\times$ 10^6 cells plus pembrolizumab on day 1. In this group, the ORR was 75% and CRR was 63%.

Responses appear to be durable. After a median follow-up of 3 months (range, 1–12 months), all complete responses are ongoing among patients treated with ≥150 $\times$ 10^6 cells.

In summary, preliminary findings from Alexander highlight the potential safety and efficacy benefits of dual-targeted anti-CD19/CD22 CAR T-cell therapy in patients with relapsed/refractory DLBCL. The outpatient expansion cohort of the Alexander study will enroll soon.

References

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