

(LB5006) First-in-human trial of LB2501, an in vivo CD19/CD20 dual targeting CAR-T therapy, in relapsed/refractory B-Cell NHL

Topic: 26. Gene therapy, cellular immunotherapy and vaccination - Clinical

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Background

Ex vivo CAR-T therapies have advanced treatment for relapsed/refractory non-Hodgkin lymphoma (R/R NHL) but are limited by complex manufacturing and lymphodepletion. In vivo CAR-T offers an off-the-shelf alternative that generates CAR-T cells directly in patients without requiring lymphodepletion. While feasibility has been shown in multiple myeloma, clinical data for B-cell malignancies remain unreported. LB2501, a third-generation, replication-incompetent lentiviral vector (LVV) pseudotyped with a modified fusion glycoprotein and a CD3 binder for T-cell-specific transduction, encodes a CD19/CD20 dual targeting CAR to generate CAR-T in vivo.

Aims

To evaluate the safety, pharmacokinetics, and preliminary efficacy of LB2501 in R/R B-NHL.

Methods

This ongoing phase 1 trial (NCT07002112) enrolled patients with measurable R/R NHL who had primary refractory disease or progression after ≥ 2 prior lines of therapy. A 3+3 dose-escalation design with backfilling was used across dose levels (DLs). LB2501 was administered as a single intravenous infusion without lymphodepletion.

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Results

As of April 1, 2026, 12 patients had been dosed with LB2501 at DL1 (n=6) or DL2 (n=6). The median age was 58.5 years, median prior therapy lines was 3, and 58.3% were refractory to last line. Patients included 7 (58.3%) LBCL, 3 (25%) FL and 2 (16.7%) MCL. No DLT, SAE or fatal cases were reported. Infusion-related reactions occurred in 9 patients (75.0%); all were grade 1 or 2, resolved within a median of 2.0 days, and required no tocilizumab or glucocorticoids. Cytokine release syndrome (CRS) occurred in 66.7% patients (grade 1 in 58.3%, grade 2 in 8.3%); No neurotoxicity (ICANS) was observed. Grade $\geq$ 3 LVV-related and CAR-T-related adverse events were limited to decreased lymphocyte count (33.3% each) and decreased neutrophil count (25.0% and 50.0%, respectively). The objective response rate (ORR) was 50% (6/12), with a complete response rate (CR) of 41.7% (5/12). At DL2, the ORR was 100% (6/6) and the CR was 83.3% (5/6). All responses were ongoing at cut-off date (Figure 1). The median follow-up for DL2 was 2.2 months (range, 2.0 to 3.8). PK analysis via qPCR confirmed dose-dependent in vivo CAR-T cell expansion in 83% (5/6) of patients at DL1 and 100% (6/6) at DL2. At DL2, the median C_{max} was 109,117.5 copies/ μ g DNA (vs. 1,068.0 at DL1), with a median T_{max} of 15.0 days. At the time of data cutoff, patients exhibited persistent PK, with CAR-T cells detectable in peripheral blood for up to 116 days. Insertion site analyses indicate in vivo transduction is highly T cell specific, polyclonal, and diverse with mostly single copy insertion per T cell.

Summary/Conclusion

This study represents the initial clinical cohort of in vivo CAR-T therapy in relapsed/refractory non-Hodgkin lymphoma. LB2501, a first-in-class CD19/CD20 dual-targeting in vivo vector, introduces a novel paradigm by eliminating the need for ex vivo manufacturing and lymphodepletion. LB2501 has demonstrated a favorable safety profile and encouraging efficacy with a 100% ORR and 83.3% CR at DL2. While a longer-follow up is warranted, these data highlight the potential of LB2501 as a scalable, readily accessible “off-the-shelf” immunotherapy for B-cell malignancies.

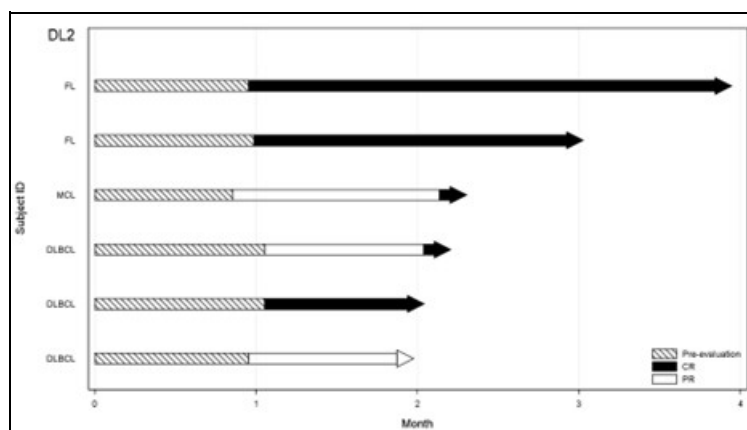


Figure 1: Patient Responses to DL2

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