

Phase 1/2 Trial of Bispecific LV20.19 CAR T-cells for Relapsed, Refractory (R/R) Mantle Cell Lymphoma

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Introduction:

Bispecific lentiviral anti-CD20, anti-CD19 (LV20.19) CAR T-cells may improve outcomes in R/R B-cell malignancies by limiting relapse from single antigen downregulation (Shah et al. Nature Med. 2020). In an ongoing phase 1/2 clinical trial we examined the impact of IL7 + IL15 (in lieu of IL-2 in our prior study) and varying lengths of manufacturing on LV20.19 CAR T-cell safety and efficacy in R/R B-cell NHL. Here we report interim Phase 1/2 results from our mantle cell lymphoma (MCL) cohort.

Methods:

This is a Phase 1/2 single center, prospective trial (NCT04186520) evaluating LV20.19 CAR T-cells at a fixed dose of 2.5×10^6 cells/kg for patients (pts) with R/R B-cell NHL. CAR T-cells were locally manufactured in the CliniMACS Prodigy device with IL7+IL15 at varying lengths of time (8 vs 12 days) with goal of a fresh infusion. MCL patients were included in the Phase 1 safety run-in and then enrolled on a dedicated Phase II arm with flexible 8/12 manufacturing length. We used a single-stage Phase II design with 3-month complete response (CR) rate as the primary endpoint. Assuming a CR rate for relapsed MCL with ibrutinib of (~20%) and a target CR rate of 50% with LV20.19 CAR, we designed the study to enroll 14 patients, and consider the result promising, if ≥ 6 patients achieve a CR.

Results:

To date, 9 MCL patients received LV20.19 CAR T-cells at target dose and completed their day 28 assessment. Three patients were enrolled in the Phase 1 run in and 6 patients in the Phase II cohort. The median age was 63 years (50-74) and median lines of therapy was 4 (3-8). All patients had prior exposure to covalent BTK inhibitors (BTKi) and 78% (n=7) had progressed on a covalent BTKi prior to CAR. Four patients had progressed after both covalent and non-covalent BTKi (pirtrobrutinib) as part of a separate clinical trial. Three patients had prior auto-HCT and 2 patients had prior allo-HCT. Two patients on the Phase 1 arm were manufactured using a 12-day process. The remaining patients had product manufactured in 8 days. All patients received a fresh (non-cryopreserved) CAR product with lymphodepletion starting during the manufacturing process.

For all MCL patients, the overall response rate was 100% (CR=56% and PR=44%) at day 28 assessment. 8 patients had an Adaptive Biotechnologies ClonoSeq® assay drawn between day 28-60 post CAR infusion, 6 of which were MRD negative. Of the remaining two MRD positive patients, one became MRD negative at day 90 and the other patient is awaiting repeat MRD assessment at day 90. The median PFS was not reached with median follow-up of 15 months for survivors (see Figure 1). To date no patient has experienced disease relapse. In terms of toxicity, grade 1-2 cytokine release syndrome (CRS) developed in all 9 patients; no patient had grade 3+ CRS. Immune effector cell associated neurotoxicity syndrome (ICANS) occurred in 2/9 patients (22%), one with grade 2 ICANS and the other with grade 3 ICANS. Both had full neurological recovery by day 28 assessment. There was one non-relapse mortality event in the

patient with grade 3 ICANS due to gram negative sepsis at day 46 post-CAR infusion. This patient was post allo-HCT with multiple comorbid conditions placing him at high risk of toxicity including, insulin dependent DM, morbid obesity (BMI ≥ 40), and CKD (baseline Cr 2.5-3 mg/dL) and had developed as secondary HLH treated with anakinra.

Conclusions:

Bispecific LV20.19 CAR T-cells expanded with IL7+IL15 are safe and efficacious for patients with R/R MCL. We report no patients with high grade CRS and a 100% response rate. All assessed patients achieved MRD negativity by day 90 and, to date, there have been no relapses at a median follow-up of 15 months.

Progression Free Survival for MCL (n=9)

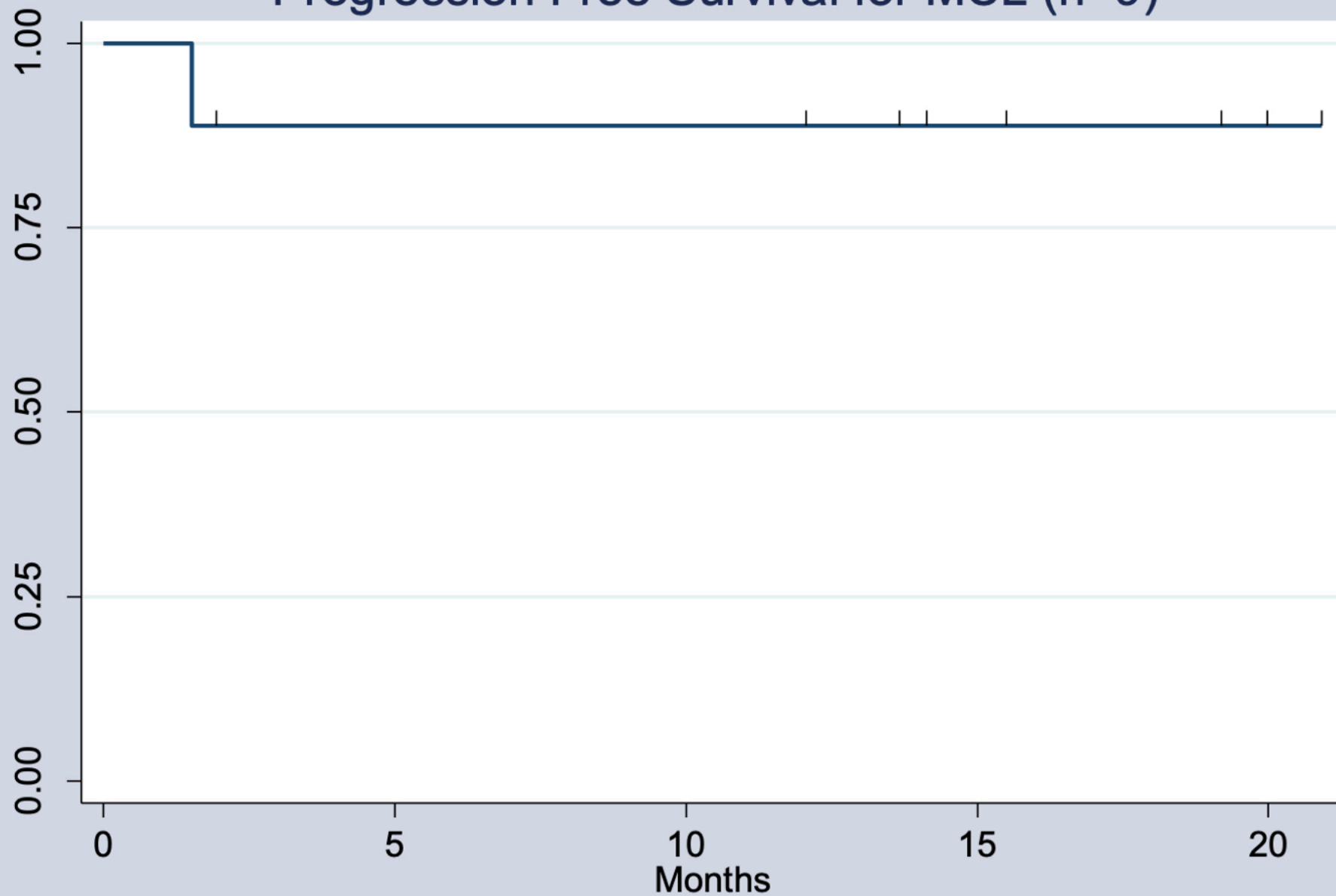


Figure 1. Progression-free survival of the first 9 mantle cell lymphoma patients treated