Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

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JNJ-68284528 (JNJ-4528) is a chimeric antigen receptor T cell (CAR-T) therapy containing two BCMA-targeting single-domain antibodies designed to confer avidity. A first-in-human phase 1 study (LEGEND-2) conducted in China of LCAR-B38M, an identical CAR to JNJ-4528, showed high overall response and manageable safety in 74 patients (pts) with R/R MM. Phase 1b results from the ongoing CARTITUDE-1 study conducted in the US with JNJ-4528 are presented here (NCT03548207).

Eligible pts (≥18 years) were diagnosed with MM per International Myeloma Working Group (IMWG) criteria, had measurable disease as assessed by M-protein or serum free light chain levels, received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and received an anti-CD38 antibody. Bridging therapy was allowed after apheresis. Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 over 3 days were used as the conditioning regimen. A single infusion of JNJ-4528 at the targeted 0.75x10^6 CAR+ cells/kg (target range 0.5-1.0x10^6) dose was administered 5-7 days after the start of the conditioning regimen. Primary objectives for phase 1b were to characterize the safety of JNJ-4528 and confirm the recommended phase 2 dose (RP2D).

Adverse events (AEs) were graded using CTCAE, v5.0, cytokine release syndrome (CRS) using Lee *et al.* (*Blood* 2014;124:188), and neurotoxicity using both CTCAE, v5.0 and the ASTCT grading system (Lee *et al. Biol Blood Marrow Transplant* 2019 25(4):625). Response was assessed per IMWG criteria, and minimal residual disease (MRD) was assessed by next generation flow cytometry and/or next generation sequencing.

As of 24 Jun 2019, 25 pts had been infused with JNJ-4528 in the phase 1b portion of the study. Median age was 61 years (range 50-75), pts had received a median of 5 (range 3-16) prior lines of treatment, 88% were triple-refractory to a PI, IMiD, and anti-CD38 antibody, 72% were penta-exposed, and 36% were penta-refractory. The median administered dose was $0.73x10^6$ CAR+ cells/kg (range $0.5-0.9x10^6$).

Most frequently reported AEs were CRS (88%), neutropenia (80%), anemia (76%), and thrombocytopenia (72%). Hematologic AEs of grade ≥3 included neutropenia (76%), thrombocytopenia (60%), and anemia (48%). The majority of pts (80%) had grade 1-2 CRS, with 1 grade 3 event and 1 grade 5 event at day 99 from sequalae of grade 4 CRS (dose-limiting toxicity).

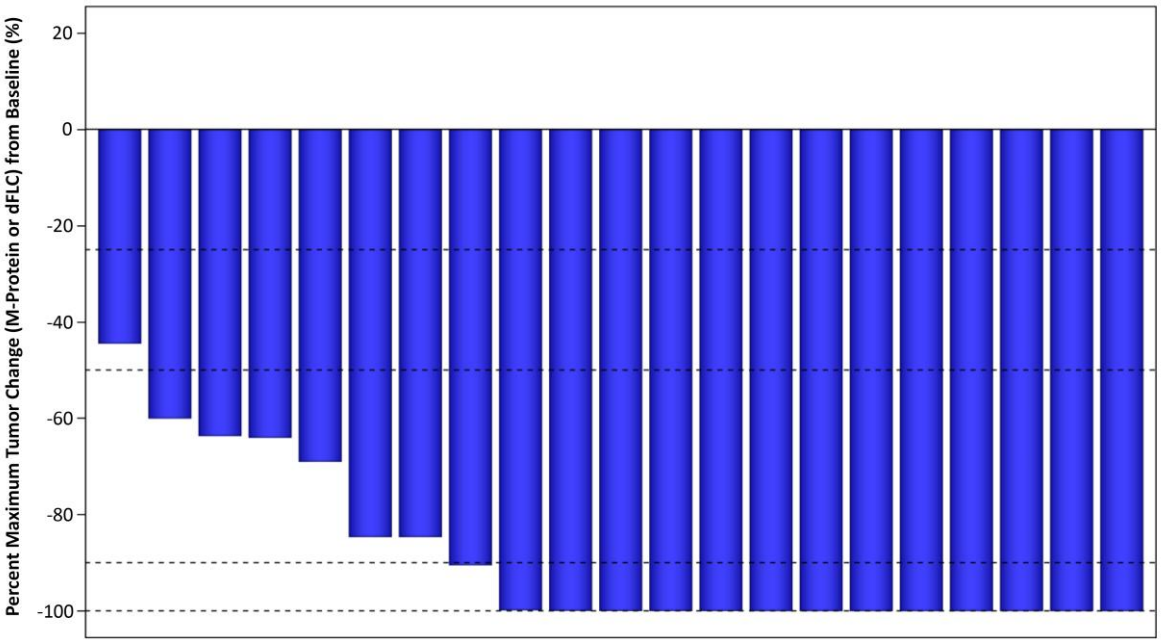
CRS events had a generally predictable time to onset, occurring at a median of 7 days (range 2-12) post-infusion with a median duration of 4 days (range 1-60). Tocilizumab and corticosteroids were administered in 91% and 27% of pts with CRS (n=22), respectively. Three pts had CAR-T-related neurotoxicity of grade 1 (n=2) and grade 3 (n=1); all events occurred in the context of CRS and resolved within 1-2 days.

At data cut-off, 21 pts were evaluable for response (postbaseline evaluation at day 28) with a median follow-up of 3 months (range 1-10). Reduction in tumor burden was observed for all pts (Figure). An overall response rate of 91% was observed, with 4 stringent complete responses (sCRs), 2 CRs, 7 very good partial responses, and 6 partial responses. Of the 15 pts with post-infusion day 28 evaluable bone marrow (BM) samples, 10 were MRD-negative at the 10^{-5} sensitivity level, 2 at the 10^{-4} sensitivity level, and 3 had unidentified clones. No pts had progressed at the time of data cutoff. Responses were independent of baseline BCMA expression.

JNJ-4528 CAR+ cellular and transgene levels showed expansion and persistence in both blood and BM, with peak expansion 9-14 days after dosing in a majority of pts. All pts showed similar kinetics of decline in soluble BCMA (sBCMA) levels, and continued depletion in sBCMA suggests CAR-T-mediated pharmacodynamic activity. Serum cytokine levels (i.e., IL-6, IFNγ, IL-10) increased post-infusion and peaked around day 10, coinciding with peak expansion of CAR+ T cells. Increases in some proinflammatory cytokines (i.e., IL-6) correlated with onset of CRS symptoms.

Collectively these results demonstrate that JNJ-4528 at a target dose of $0.75x10^6$ CAR+ cells/kg delivers early and deep responses, including MRD negativity in all evaluable pts tested, with a manageable safety profile in pts with refractory MM. The safety and efficacy results from the ongoing CARTITUDE-1 study are consistent with the LEGEND-2 study and confirm the $0.75x10^6$ CAR+ cells/kg dose as the RP2D for further clinical development.

Figure. Maximum Reduction in Tumor Burden from Baseline in Response-Evaluable Patients (n=21)



Tumor burden represents the type of measurable disease: serum M-protein, urine M-protein, or dFLC for patients with light chain only disease.