Managing Myeloma

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

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Welcome to *Managing Myeloma*. Today I will be reviewing the results of the study titled "Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen, in Patients with Relapsed and Relapsed/Refractory Multiple Myeloma." B-cell maturation antigen is a transmembrane glycoprotein. It is expressed at significantly higher levels on all patient myeloma cells and normal plasma cells but not on other normal tissues, making it a very unique target for myeloma therapeutics. JNJ-4528 is a CAR-T therapy containing two BCMA targeting single domain antibodies confer avidity, is identical to the L-CAR B38M concept from China used in LEGEND2 study among 74 patients showing extremely promising efficacy in relapsed/refractory multiple myeloma. The study took a little heat as the patients were not as heavily pre-treated as we see in the US trials. In the current study CARTITUDE-1, JNJ-4528 evaluated the safety, recommended phase 2 dose and the preliminary efficacy of this CAR-T construct in the United States. For the 29 patients that received JNJ-4528 in the phase 1B portion, the median age was 60 years, median time from diagnosis to CAR-T therapy is six years. Patients had received a median of five prior lines of therapy, 86 patients were triple-refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody; 72% were penta-exposed and 31% were penta-refractory. The median administered dose was 0.73×10^6 CAR-T viable cells per kilogram. The most frequently reported adverse events were CRS and neutropenia seen in 93% of the patients, anemia and thrombocytopenia seen in 86% of the patients. Hematological adverse events of greater than grade 3 included neutropenia of 93%, thrombocytopenia in 69%, and anemia in 55% of the patients. Majority of the patients who had CRS had grade 1 to 2 CRS with only one grade 3 event and one grade 5 event. This was at day 99 from the sequelae of a grade 4 CRS. The CRS events had a generally predictable time to onset occurring at a median time of seven days post infusion. The median duration of CRS was around four days. Ninety-one percent of the patients received tocilizumab, and corticosteroids were administered in 27% of patients with CRS. Three patients had CAR-T related neurotoxicity of grade 1 and one patient had grade 3 events. All these events occurred in the context of a CRS and resolved within one to two days. Twenty-nine patients were evaluable for response which is a post-baseline evaluation at day 28 with a median follow-up of six months. Overall responses were seen in 100% of the patients, including greater than CR rates in

69% in VGPR rates seen in 86% of the patients. Median time to first response was one month. Of the 17 patients that had post-infusion day-28 evaluable bone marrow samples, 14 patients were MRD negative at the 10^{-5} sensitivity level, three 10^{-4} sensitivity level. Twenty-seven of the 29 patients are progression-free at a median of six-month follow-up. JNJ-4528 CAR-T cellular and transgene levels showed expansion and persistence in both the blood and the bone marrow, and median time to peak of expansion was around 13 days after the infusion. Preferential CD8 positive central mammary phenotype was observed at the peak of expansion.

In conclusion, first two dose of 0.75 x 10^6 CAR-T cells per kg was confirmed. JNJ-4528 has a manageable safety profile with CRS reported in 93% of the patients with majority of these were grade 1 to 2 with one grade 3 and one grade 5 event reported. The incidence of neurotoxicity was extremely low and only one grade 3 event was reported, and this correlated with CRS events all the time. Early and deep responses were observed in these heavily pre-treated patients; 100% of the patients received an overall response rate, greater than CR rates were seen in two-thirds of the patients and the majority of the patients, 86% of the patients, achieved greater than VGPR at six-month post-follow-up. Median time to first response was very short at one month. Fourteen of the 17 patients had MRD negative at 10^{-5}, 27 of the 29 patients are progression-free at a median six-month follow-up. The phase 2 portion of the study is fully enrolled. JNJ-4528 has received FDA breakthrough designation for relapsed/refractory multiple myeloma. Thank you for reviewing this activity.

Reference:

Madduri D, Usmani S, Jagannath S, et al. 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). *Blood.* 2019;134 (Supplement_1): 577. https://ashpublications.org/blood/article/134/Supplement_1/577/426449/Results-from-CARTITUDE-1-A-Phase-1b-2-Study-of-JNJ?searchresult=1