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AN UPDATED PHASE 1 STUDY OF A NOVEL FULLY HUMAN BCMA-TARGETING CAR-T CELLS (CT103A) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Background: About 33 to 88% of patients with relapsed/refractory multiple myeloma (RRMM) had objective anti-myeloma responses after treatment with anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cells. However, it remains a great challenge to achieve durable responses, and relapse or disease progression is observed in approximately 28 to 88% of patients. Previous studies suggest that CARs with humanized or fully human single-chain variable fragments (scFvs) may bypass the potential host anti-CAR immunogenicity and retain anti-tumor activity.

Aims: We developed a novel BCMA-targeting CAR construct (CT103A) with a fully human scFv, and conducted an open-label, single-arm phase I clinical trial to evaluate the safety and efficacy, including overall response rate (ORR), minimal residual disease (MRD), and also pharmacokinetics, and pharmacodynamics. The initial results in RRMM have been previously reported. Here, we report updated data of its safety and efficacy in the phase I trial.

Methods: Written informed consent was obtained from each participant, in compliance with the Declaration of Helsinki. Enrolled patients had at least three lines of prior therapies that must include a proteasome inhibitor and an immunomodulatory agent. Clinical response and disease progression were evaluated according to the IMWG consensus criteria at serial time points after CT103A infusion. The definition of extramedullary myeloma (EMM) is the presence of soft tissue masses in extraosseous locations resulting from hematogenous spread, which are not contiguous to the involved bone. MRD was assessed by multiparametric flow cytometry, and CAR transgene copies in the patient peripheral blood mononuclear cell were monitored by digital droplet polymerase chain reaction.

Results: A total of 35 patients were enrolled, among which 29 had high-risk cytogenetics. All patients received 1.0, 3.0, or 6.0 × 10⁶/kg CAR-T cells after leukapheresis in the dose-escalation phase and 1.0 dose in the dose-expansion cohort. In escalation, 1.0 dose was determined as RP2D. The cut-off date was December 31, 2020. The median follow-up after CT103A infusion was 520 days (121 to 832 days). Hematologic toxicities were the most common adverse events. 74.3% of the patients experienced grade 1 or 2 cytokine release syndromes (CRS). All CRS could be efficiently controlled. Neurotoxicity (grade 2 ICANS) was observed only in one patient with the symptom

of drowsiness, who was later spontaneously relieved without any treatment. For efficacy, 3m ORR rate was 94.2%, \geq VGPR was 74.3%, CR/sCR was 45.7%. 5/8 patients with EMM achieved \geq VGPR, among whom one with both EMM and plasma cell leukemia achieved VGPR. Moreover, 6/9 patients who have received prior CAR-T treatment achieved \geq VGPR. Besides, all 34 patients who performed MRD detection were MRD-negative at one month, and 31 patients kept negative until the last follow-up. The median time to reach the peak of CT103A expansion in 35 patients was 12 (7, 17) days. CAR-T cells were persistent in 100% of the patients, among whom maximum duration had exceeded two years. What's more, only 1 of 35 patients were detected positive for anti-drug antibody, which was reported to be a high-risk factor for disease relapse/progression after CAR-T therapy.

Summary/Conclusion: CT103A is safe, highly productive, and long persistent in RRMM patients and can be developed as a promising therapy for RRMM. Patients who relapsed from prior non-human BCMA CAR T-cell therapy could still benefit from CT103A. This approach is being explored in the phase II study.

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