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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

High Efficacy and Excellent Safety Profile of Actalycabtagene Autoleucel, a Humanized CD19 CAR-T Product in r/r B-Cell Malignancies: A Phase II Pivotal Trial

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Background: Commercially approved CD19 CAR-T cell therapies are effective in r/r B cell malignancies, but are associated with significant albeit manageable toxicities. These toxicities contribute to significant morbidity. We have developed a novel, humanized CD19 CAR-T cell therapy, Actalycabtagene autoleucel (Actaly-cel) and previously reported the safety in Phase I study (Dwivedi et al. Mol Cancer Ther.2021, Karulkar et al. ASH 2022). Here, we present the pooled results from Phase I and a planned interim analysis of the Phase II study evaluating Actaly-cel.

Materials and methods: The Phase I study (n=10) was a single-center trial to test the safety of Actaly-cel at a dose of 1x10 ^{7} to 5x10 ^{9} CAR-T cells in patients with r/r DLBCL, tFL and PMBCL (CTRI/2021/04/032727). The Phase II study (n=50) was a single-arm, multi-center study conducted across 3 centers in India (CTRI/2022/12/048211). Patients with r/r B-cell malignancies (including aggressive and indolent B-cell lymphomas and acute lymphoblastic leukemia) aged ≥ 15 years, with normal organ function, ECOG PS 0-2 and measurable disease were eligible. Actaly-cel was manufactured using an integrated semi-automated system. Bridging therapy was allowed at the clinician's discretion. Patients received infusion of Actaly-cel two days after conditioning with fludarabine plus cyclophosphamide. The target dose was ≥5x10 ^{6}/kg CAR T-cells (efficacy-evaluable cohort), however doses of ≥0.5x 10 ^{6}/kg CAR-T cells were allowed. Patients who received Actaly-cel at any dose were considered in the safety analysis. The primary endpoint was objective response rate, with duration of response, adverse events,

PFS and OS as the secondary endpoints. A Simon II-stage design was used to test the hypothesis that the ORR would increase from 25% (historical data) to 40% (α- 0.1 and β- 0.2), >15 responses were required out of 50 patients to reject the null hypothesis. The CRS and neurotoxicities (ICANS) were graded and treated as per ASTCT guidelines, other toxicities were graded as per CTCAE v5. Exploratory studies were performed to study the correlation between patient and product related characteristics with response.

Results: A total of 59 patients with r/r DLBCL (41), ALL (16) and indolent lymphomas (2) were enrolled (Phase I; 06/2021 till 06/2022 and Phase II; 12/2022 till 07/2023), 56 underwent leukapheresis (ITT set) and 47 received Actaly-cel (safety set). 43 patients received the target dose (Figure 1A). The median age was 43 years (16-71) with 46 (65%) male patients. Patients had a median of 2 prior lines of therapy (1-6), 65% had refractory disease,25% of lymphoma patients had bulky disease, and the median bone marrow blast was 69% (6-98%) in the B-ALL cohort. The median vein-to-vein time was 17(7-132) days.

Total 78%(33/43) patients reached the day 28 timepoint at the time of analysis (Figure 1B). The ORR was 70% (23/33), including 58% (19/33) with a CR. In the lymphoma cohort, the ORR was 71%(17/24) and CR was observed in 54%(13/24), while in the leukemia cohort, the CR rate was 66% (6/9, n=5 MRD negative). The median follow-up of evaluable patients was 57 days (21-453). All nine patients and 3 out of 4 patients maintained the response after 3 months and 12 months follow-up, respectively. None of the patients developed ICANS of any grade. CRS developed in 22/33(66%) cases (grade 1/2 in 61%, grade 3/4 in 6%). Of note, no grade >3 CRS was noticed in the lymphoma cohort. Grade 3/4 cytopenias developed in all cases. The median duration of neutropenia was 7 (4-32) days. On Day 28, grade 3/4 neutropenia was observed in 11/33(33%) cases, grade 3/4 thrombocytopenia was observed in 7/33 (21%). Only 1(3%) patient required ICU admission, 2(6%) required vasopressor support, tocilizumab was administered to 18 (55%) patients, median 1 dose (1-4) and steroids were used in 5 (15%) cases. Patients were hospitalized for a median of 8 days (7-19).

There were no treatment-related deaths.

On exploratory analysis, higher CAR-T dose, fewer prior lines of therapy and higher peak CAR-T copies/µg DNA correlated with response.

Conclusions: Actaly-cel demonstrated efficacy in r/r B-cell malignancies with a very favorable safety profile. The absence of ICANS, shorter duration of cytopenias and a lower incidence of grade 3/4 CRS makes it one of the safest CD19 CAR-T cell therapy products. Actaly-cel can improve the ease of delivery of CAR T-cell therapy in a wide-range of settings.

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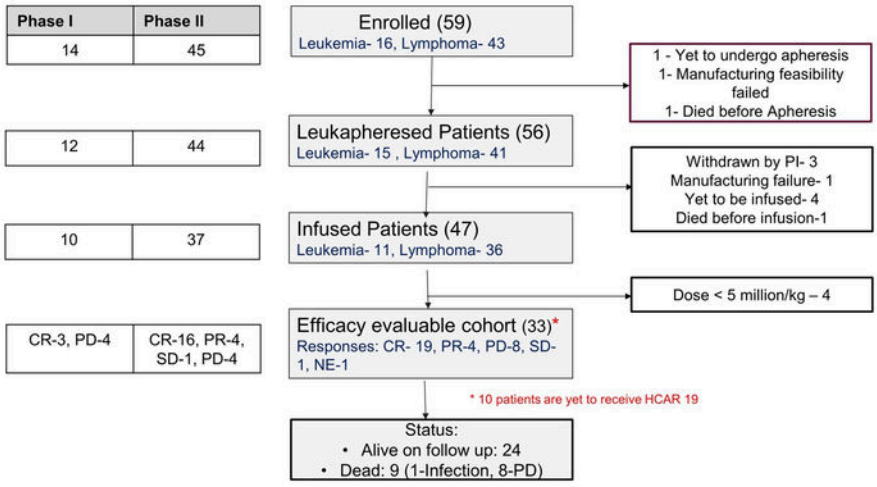
(A)



(B)

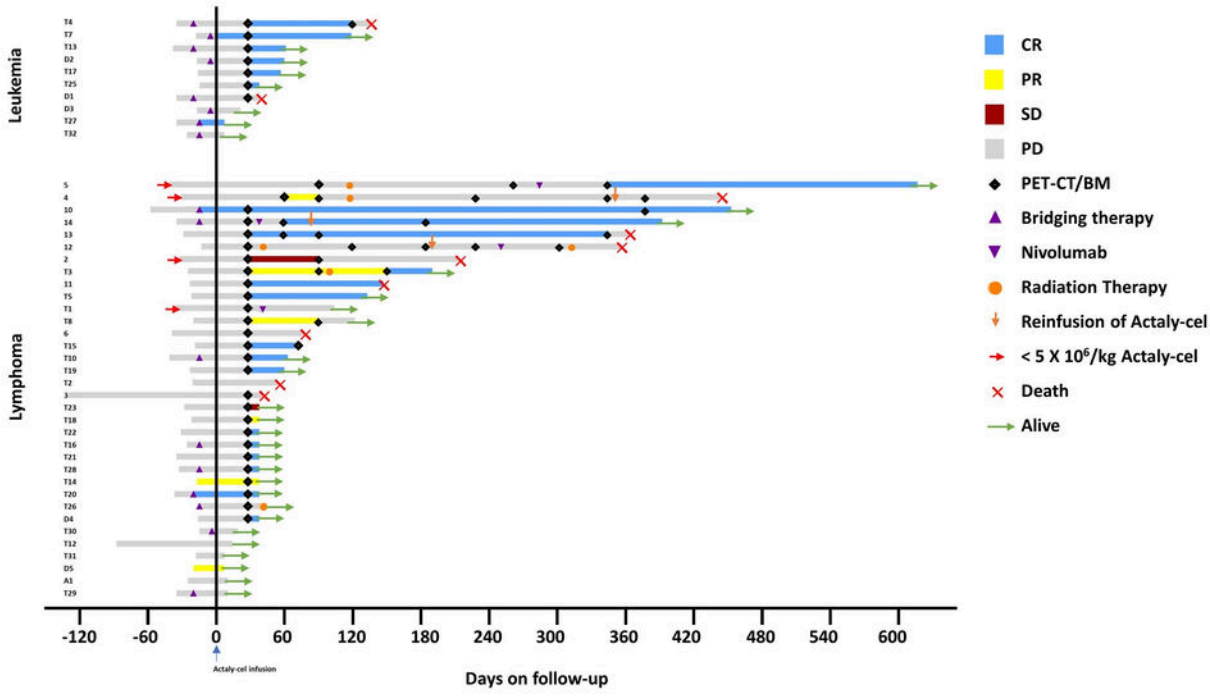


Figure 1: (A) CONSORT Diagram (B) Swimmers plot to depict the responses of the patients receiving Actalycabtagene autoleucel.

Figure 1

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