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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Updated Results of the Phase I BALLI-01 Trial of UCART22 Process 2 (P2), an Anti-CD22 Allogeneic CAR-T Cell Product Manufactured By Cellectis Biologics, in Patients with Relapsed or Refractory (R/R) CD22+ B-Cell Acute Lymphoblastic Leukemia (B-ALL)

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Introduction: UCART22 is a genetically modified allogeneic T-cell product manufactured from healthy donor cells. Donor-derived T-cells are transduced using a lentiviral vector to express the anti-CD22 chimeric antigen receptor (CAR) and are further modified using Cellectis' TALEN ® technology to disrupt the T-cell receptor alpha constant (*TRAC*) and *CD52* genes to minimize risk of graft-vs-host disease (GvHD) and allow use of an anti-CD52 antibody for lymphodepletion (LD). Preliminary results from patients treated with UCART22 manufactured by a CMO (Process 1 (P1)) showed that UCART22 was well-tolerated and meaningful responses were achieved at the highest dose level (DL 3; 5 x 10^6 cells/kg). The fludarabine, cyclophosphamide, and alemtuzumab (FCA) LD regimen was also shown to extend host lymphocyte suppression and improve UCART22 expansion versus fludarabine and cyclophosphamide (FC) alone (Boissel N, et al. EHA 2023). We now report updated results from the BALLI-01 study that includes the first patients treated with UCART22 Process 2 (P2) manufactured by Cellectis Biologics.
Methods: The primary endpoints are safety, tolerability, and determining the MTD/RP2D of UCART22. Additional endpoints are anti-leukemic activity and expansion of UCART22. Eligibility criteria include age 15–70y, B-ALL blast CD22 expression ≥ 70%, and ≥ 2 prior treatment regimens. After FCA (F 30 mg/m^2 × 3d, C 0.5g/m^2 × 3d, A 20 mg/d × 3d) LD regimen, pts received a single infusion of UCART22-P2. *In vitro* comparability assays suggested that UCART22 P2 was more potent than UCART22 P1, so dose escalation with UCART22 P2 started at DL2 (1 x 10^6 cells/kg) compared to the highest studied dose DL3 (5 x 10^6 cells/kg) with UCART22 P1.
Results: As of 01 July 2023, 3 pts were enrolled into the first UCART22 P2 cohort at DL2. Pt 1 is a 17yo female with B-ALL with a hypodiploid karyotype and a germline *TP53* mutation whose disease had previously failed to respond to multiagent chemotherapy, blinatumomab (blina), inotuzumab (ino), venetoclax (ven), allogeneic hematopoietic stem cell transplantation (HSCT), and autologous CD19 CAR T-cell therapy (CAR19) x2. Pt 2 is a 68yo female with Ph-negative B-ALL who relapsed with CD19-low disease after multiagent chemotherapy, ino, and blina. Pt 3 is a 27yo male with B-ALL with an *ABL2* fusion who had failed multiagent chemotherapy, ino, blina, TKIs, and an experimental autologous CAR19.
UCART22 P2 administered after the FCA LD regimen was well tolerated. No DLTs or ICANS were observed. Cytokine release syndrome (CRS) occurred in 2/3 (67%) pts, with one G1 that resolved without treatment and one G2 that resolved after tocilizumab x1. There was one G5 sepsis SAE at D40 considered related to UCART22 P2 and FCA LD in Pt 1.

Responses were assessed beginning on D28. Up to FC/FCA-DL3 with 18 pts treated with UCART22 P1, 1 CR, 4 CRi, and 2 morphologic leukemia-free states (MLFS) were observed, with 3 responses occurring out of 6 (50%) patients treated with FCA-DL3 (previously reported, EHA 2023). For UCART22 P2, FCA-DL2, 2/3 pts (67%) responded: Pt 2 achieved an MRD neg CR lasting over 84 days after UCART22 infusion; Pt 1 achieved an MRD negative MLFS up to D40. Pt 3 was refractory to treatment, however this pt received bridging therapy with dasatinib for his *ABL2* fusion, and on Day -1, only 47% of the leukemic cells expressed CD22 (down from 88% at screening).

UCART22 P2 expansion was observed by flow cytometry in peripheral blood with peak of 79 cells/μl in Pt 1 and 225 cells/μl in Pt 2, both at D11, with predominantly CD8 cells expanding. Inflammatory markers such as ferritin, IFN-γ, TNF-α and IL-6 levels increased more than 3-fold, correlating with UCART22 P2 expansion and CRS.

Summary : *In vitro* comparability studies indicated that UCART22 P2 was more potent than UCART22 P1, and this was suggested clinically, as there was a 67% response rate at DL2 with UCART22 P2 compared to 50% at DL3 with UCART22 P1. Use of UCART22 P2 did not lead to any grade $\geq$3 CRS, and no DLTs or ICANS was observed. UCART22 P2 expansion was seen in the two responders, which closely correlated with CRS and changes in inflammatory markers. These data support the safety and preliminary efficacy of UCART22 P2 in this poor-risk R/R B-ALL population. The study continues to enroll pts treated with UCART22 P2 at dose level 2i (2.5 x 10^6 cells/kg), and updated data will be presented.

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