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)

P4847

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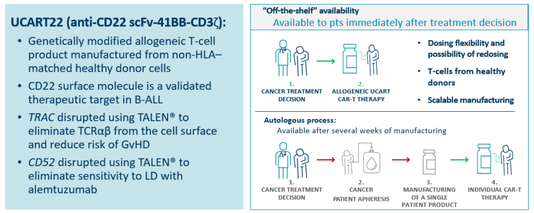
Introduction

- Allogeneic chimeric antigen receptor (CAR) T-cell therapies have the potential to provide benefit in aggressive hematologic malignancies
- Preliminary results from the BALLI-01 study (NCT04150497) showed that UCART22 manufactured by a Contract Manufacturing Organization (Process 1 [P1]) was well tolerated, and meaningful clinical responses were achieved at the highest dose level DL3 (5 x 106 cells/kg), with 3/6 (50%) patients responding1
- The fludarabine, cyclophosphamide, and alemtuzumab (FCA) lymphodepletion (LD) regimen was well tolerated and associated with host lymphocyte suppression of at least 28 days and UCART22 expansion
- Aim: updated results from the BALLI-01 study of the first 3 patients treated with UCART22 Process 2 (P2) manufactured by Cellectis Biologics

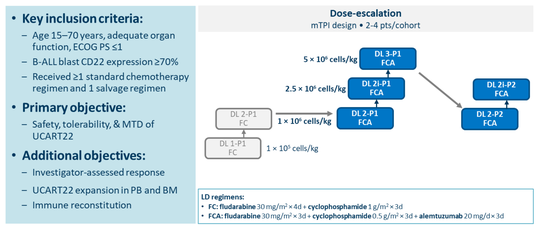


B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; GvHD, graft-vs-host disease; HLA, human leukocyte antigen; LD, lymphodepletion; pts, patients; scFv, single-chain variable fragment; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

Figure 1. UCART22: Allogeneic "Off-the-Shelf" T-cell Product

Study Design

- BALLI-01 is an ongoing phase 1, open-label, dose-escalation trial to evaluate the safety and efficacy of UCART22 (Figure 2)



P1 cells manufactured by external CDMO. P2 cells manufactured by Cellectis Biologics.
B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; DL, dose level; d, days; ECOG PS, Eastern Cooperative Oncology Group performance status; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; LD, lymphodepletion; MTD, maximum tolerated dose; mTPI, modified Toxicity Probability Interval; PB, peripheral blood; pts, patients.

Figure 2. BALL-01 Study Design

Objectives

- Primary endpoints are safety, tolerability, and determining the MTD/RP2D of UCART22. Additional endpoints are anti-leukemic activity and expansion of UCART22
- After FCA (fludarabine 30 mg/m2 × 3 days, cyclophosphamide 0.5 g/m2 × 3 days, CLLS52 [alemtuzumab] 60 mg total dose over 3 days) lymphodepletion, patients 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 106 cells/kg) compared to the highest studied dose DL3 (5 x 106 cells/kg) with UCART22-P1

Patients Baseline Characteristics

Three patients were enrolled into the first UCART22-P2 cohort at DL2

- Patient 1:
  - 17-year-old female with Ph-negative B-ALL with a hypodiploid karyotype and a germline TP53 mutation
  - Prior therapies included multiagent chemotherapy, blinatumomab, inotuzumab, venetoclax, allogeneic stem cell transplantation, and autologous CD19 CAR T-cell therapy (tisagenlecleucel) x 2 infusions
- Patient 2:
  - 68-year-old female with Ph-negative B-ALL
  - Relapsed with CD19-low disease after multiagent chemotherapy, blinatumomab, and inotuzumab
- Patient 3:
  - 27-year-old male with B-ALL with an ABL2 fusion
  - Prior therapies included multiagent chemotherapy, blinatumomab, inotuzumab, tyrosine kinase inhibitors, and an experimental autologous CAR19

Safety

- No dose-limiting toxicities (DLT)
- No immune effector cell-associated neurotoxicity syndrome (ICANS)
- No GvHD
- CRS in 2/3 (67%) patients with one G1 that resolved without treatment and one G2 that resolved after tocilizumab x1
- Patient 1 had a G5 sepsis SAE at D40 considered related to UCART22 and FCA LD

SAE, n (%) System Organ Class Preferred Term	FCA-DL2-P2 cohort (N=3)	
	Any grade	Grade ≥3
Patients with at least 1 UCART22 related AE	**2 (67)**	**1 (33)**
Immune system disorders	2 (67)	0
Cytokine release syndrome[2]	2 (67)	0
General disorders and administration site conditions	2 (67)	0
Asthenia	1 (33)	0
Chills	1 (33)	0
Pyrexia	1 (33)	0
Infections and infestations	1 (33)	1 (33)
Sepsis	1 (33)	1 (33)
Skin and subcutaneous tissue disorders	1 (33)	0
Rash	1 (33)	0
Vascular disorders	1 (33)	0
Hypotension	1 (33)	0

Table 1. UCART22-Related Adverse Events (AE) by System Organ Class and Preferred Term

SAE, n (%) System Organ Class Preferred Term	FCA-DL2-P2 cohort (N=3)	
	Any grade	Grade ≥3
Patients with at least 1 SAE	**1 (33)**	**1 (33)**
Infections and infestations	1 (33)	1 (33)
Sepsis	1 (33)	1 (33)

Table 2. Serious Adverse Events (SAE) by System Organ Class and Preferred Term

Translational results

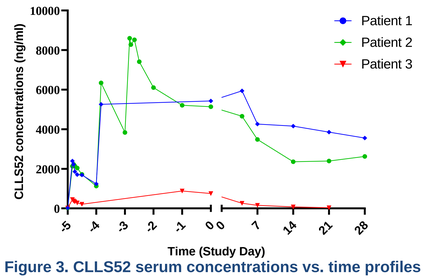


Figure 3. CLLS52 serum concentrations vs. time profiles

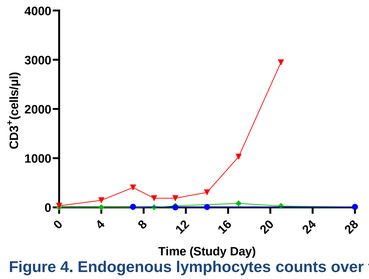


Figure 4. Endogenous lymphocytes counts over time

- Figure 3 indicates that for patients 1 and 2, CLLS52 PK profiles are similar and consistent with literature results[3]; concentrations increase with each dose administered , with Cmax observed following the last dose; then concentrations decrease and were quantifiable up to day 28. Patient 3 showed much lower concentrations as compared to the other 2 patients.
- Correlating with the CLLS52 PK profiles, Figure 4 shows adequate lymphodepletion for patients 1 and 2 until at least 28 days post-UCART22 administration, while for patient 3, CD3+ endogenous cell recovery is observed during the first 28 days.

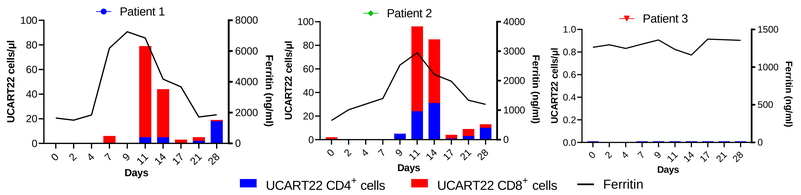


Figure 5. UCART22 cells expansion and ferritin levels over time

UCART22 expansion was observed by flow cytometry in the peripheral blood with peaks of ~80 cells/µL in patient 1 and ~100 cells/µL in patient 2, both at D11, with predominantly CD8 cells expanding. Expansion correlates with changes in ferritin levels. For patient 3, no UCART22 expansion was observed, and ferritin levels were mostly unchanged during the 28 days following UCART22 administration.

Patient 1: CRS G1 D4-5; G2 D5-6. Patient 2: CRS G1 D4-5, D7-8, and D10-11. Patient 3: no CRS

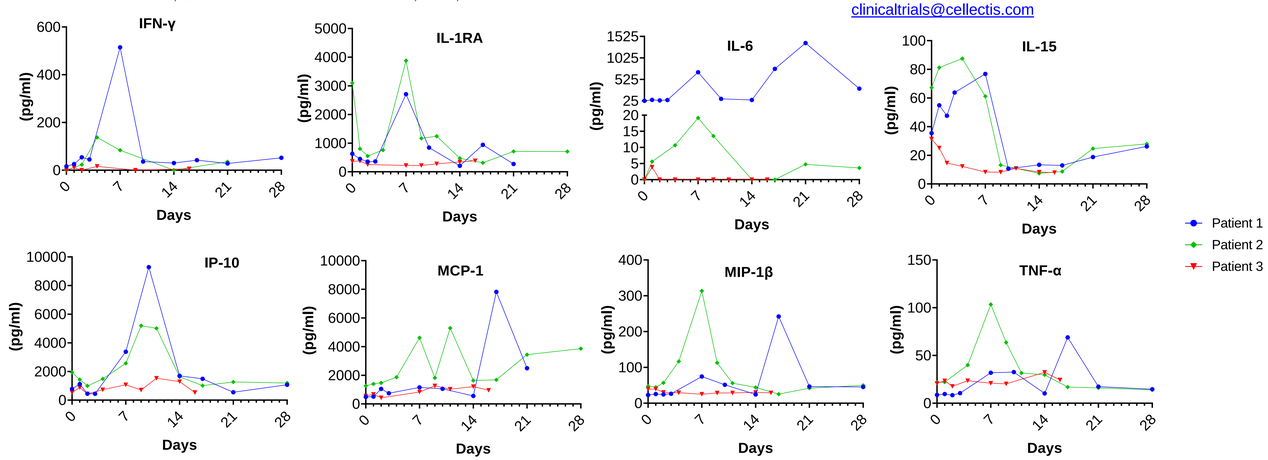


Figure 6. Cytokine/Inflammatory marker profiles

Cytokines were measured in serum from subject samples using a multiplex Luminex assay. Serum inflammatory markers increased in responding patients and correlated with UCART22 cells expansion and CRS

Efficacy

- Responses were assessed beginning on Day 28
- 2/3 patients (67%) treated at DL2 with UCART22-P2 responded
  - Patient 1 had 40% BM blasts at screening and achieved an MRD negative (by flow cytometry and clonoSEQ at 10^{-4}) MLFS up to D40
  - Patient 2 had 80% BM blasts at screening and achieved an MRD negative (by clonoSEQ at 10^{-4}) CR lasting over 84 days after UCART22 infusion
  - Patient 3 had 84% BM blasts at screening and was refractory to treatment

  Note that the CLLS52 PK profile concentration vs time for this patient is much lower than the other 2 patients and translates into a less than optimal lymphodepletion (see Figure 3), and no UCART22 expansion was observed

Summary and Conclusions

- UCART22 continues to be safe and tolerable, with no Grade ≥3 CRS and no DLTs or ICANS
- UCART22 expansion was seen in the 2 responders, which closely correlated with CRS and changes in inflammatory markers
- Overall, 2/3 (67%) of patients responded at DL2 (1.0 x 10^6 cells/kg) with UCART22-P2 compared to 3/6 (50%) at DL3 (5.0 x 10^6 cells/kg) with UCART22-P1. In addition, responding patients had failed prior CD19-directed therapies
- The study is currently open and enrolling patients at DL2i (2.5 x 10^6 cells/kg) with UCART22-P2

References

1.Boissel N, et al. HemaSphere 2023;7(S3):2732-2733
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3.Li Z , et al. Clin Exp Immunol. 2018;194(3):295-314

Acknowledgments

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- For more information, please contact clinicaltrials@cellectis.com

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