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

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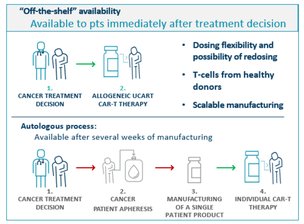
Introduction

- There is a high unmet medical need in relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL)
  - Standard therapy for adults with B-ALL involves multi-agent chemotherapy ± allogeneic stem cell transplant[1]
  - 30-60% of patients with newly diagnosed B-ALL who attain complete remission (CR) will relapse[2]
  - Prognosis is poor for R/R B-ALL (~10% overall survival at 5 years)[2]
- Allogeneic chimeric antigen receptor (CAR) T-cell therapies have the potential to provide benefit in aggressive hematologic malignancies (**Figure 1**)

UCART22 (anti-CD22 scFv-41BB-CD3ζ):

- Genetically modified allogeneic T-cell product manufactured from non-HLA–matched healthy donor cells
- CD22 surface molecule is a validated therapeutic target in B-ALL
- *TRAC* disrupted using TALEN® to eliminate TCRαβ from the cell surface and reduce risk of GvHD
- *CD52* disrupted using TALEN® to eliminate sensitivity to LD with alemtuzumab



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.

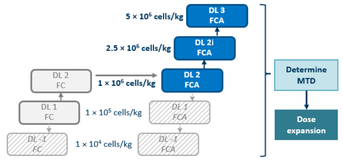
Figure 1. UCART22: Allogeneic "Off-the-Shelf" T-cell Product

- Preliminary results from the BALLI-01 study (NCT04150497) showed that UCART22 was well tolerated, and clinical responses were achieved. The fludarabine, cyclophosphamide, and alemtuzumab (FCA) lymphodepletion (LD) regimen was well tolerated and associated with extended host lymphocyte suppression and UCART22 expansion[3]

Study Design

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

- **Key inclusion criteria:**
  - Age 15–70 years, adequate organ function, ECOG PS ≤1
  - B-ALL blast CD22 expression ≥70%
  - Received ≥1 standard chemotherapy regimen and 1 salvage regimen
- **Primary objective:**
  - Safety, tolerability, & MTD of UCART22
- **Additional objectives:**
  - Investigator-assessed response
  - UCART22 expansion, trafficking, persistence in PB and BM
  - Immune reconstitution



LD regimens:
- **FC: fludarabine** 30 mg/m² × 4d + **cyclophosphamide** 1 g/m² × 3d
- **FCA: fludarabine** 30 mg/m² × 3d + **cyclophosphamide** 0.5 g/m² × 3d + **alemtuzumab** 20 mg/d × 3d

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. BALLI-01 Study Design

Objectives

- To evaluate safety, tolerability, and maximum tolerated dose/recommended phase 2 dose (MTD/RP2D) of UCART22. Dose-limiting toxicities (DLT) are assessed over a 28-day observation period after UCART22 infusion
- To evaluate the anti-leukemic activity and expansion of UCART22; monitoring inflammatory markers

Patients

- As of 31 December 2021, 19 patients were treated in 6 cohorts: FC-DL1 (n=3); FC-DL2 (n=2); FCA-DL2 (n=3); FCA-DL2i (n=4); and FCA-DL3 (n=6). Note that 1 patient received LD but no UCART22.

Characteristic	Total (N = 19)
Age, median (range), years	28 (17-61)
Female, n (%)	8 (42)
ECOG PS 1, n (%)	13 (68)
WHO 2016 Classification, n (%)	
B-ALL with recurrent genetic abnormalities	8 (42)
B-ALL with *CRLF2* rearrangement (*BCR-ABL1* like)	4 (21)
B-ALL with t(1;19)(q23;p13.3); *TCF3-PBX1*	1 (5)
B-ALL with t(9;22)(q34.1;q11.2); *BCR-ABL1*	1 (5)
B-ALL with hypodiploidy	1 (5)
B-ALL with hyperdiploidy	1 (5)
B-ALL not otherwise specified	10 (53)
Missing	1(5)
Number of prior treatments, median (range)	4 (2-8)
Prior HSCT, n (%)	8 (42)
Prior blinatumomab, n (%)	12 (63)
Prior inotuzumab, n (%)	10 (53)
Prior CD19 CAR T-cell therapy, n (%)	8 (42)

Table 1. Baseline characteristics

B-ALL, B-cell acute lymphoblastic leukemia; BCR, breakpoint cluster region; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; LD, lymphodepletion; WHO, World Health Organization.

Safety

- The FCA LD regimen was well tolerated; most treatment-emergent adverse events (TEAEs) were manageable with standard guidelines
- No dose-limiting toxicities (DLT)
- No immune effector cell-associated neurotoxicity syndrome (ICANS)
- One Grade 2 GvHD limited to the skin was reported in the setting of reactivation of prior allogeneic transplant donor stem cells
- Grade 1 CRS in 8/18 (44%) of patients
- Grade 2 CRS in 3/18 (17%) of patients
- 7/18 (39%) of patients had Grade ≥3 infections not related to UCART22

SAE, n (%) System Organ Class Preferred Term	Combined FC cohorts (n = 5)		Combined FCA cohorts (n = 13)		All patients (N=18)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with at least 1 UCART22 related AE	**3 (60)**	**0**	**9 (69)**	**2 (15)**	**12 (67)**	**2 (11)**
Immune system disorders	3 (60)	0	8 (62)	0	11 (61)	0
Cytokine release syndrome[4]	3 (60)	0	8 (62)	0	11 (61)	0
Graft versus host disease in skin	0	0	1 (8)	0	1 (6)	0
Hypogammaglobulinemia	0	0	1 (8)	0	1 (6)	0
Nervous system disorders	1 (20)	0	1 (8)	1 (8)	2 (11)	1 (6)
Headache	1 (20)	0	1 (8)	1 (8)	2 (11)	1 (6)
Skin and subcutaneous tissue disorders	0	0	2 (15)	1 (8)	2 (11)	1 (6)
Rash maculo-papular	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Pruritus	0	0	1 (8)	0	1 (6)	0
Rash	0	0	1 (8)	0	1 (6)	0
General disorders and administration site conditions	0	0	2 (15)	0	2 (11)	0
Asthenia	0	0	1 (8)	0	1 (6)	0
Oedema peripheral	0	0	1 (8)	0	1 (6)	0
Cardiac disorders	0	0	1 (8)	0	1 (6)	0
Sinus tachycardia	0	0	1 (8)	0	1 (6)	0
Gastrointestinal disorders	0	0	1 (8)	0	1 (6)	0
Nausea	0	0	1 (8)	0	1 (6)	0
Injury, poisoning and procedural complications	0	0	1 (8)	0	1 (6)	0
Infusion related reaction	0	0	1 (8)	0	1 (6)	0
Musculoskeletal and connective tissue disorders	0	0	1 (8)	0	1 (6)	0
Arthralgia	0	0	1 (8)	0	1 (6)	0
Myalgia	0	0	1 (8)	0	1 (6)	0

Table 2. UCART22-Related Adverse Events (AE) by System Organ Class and Preferred Term

SAE, n (%) System Organ Class Preferred Term	Combined FC cohorts (n = 5)		Combined FCA cohorts (n = 13)		All patients (N=18)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with at least 1 SAE	**3 (60)**	**3 (60)**	**10 (77)**	**10 (77)**	**13 (72)**	**13 (72)**
Infections and infestations	2 (40)	2 (40)	6 (46)	5 (39)	8 (44)	7 (39)
Pneumonia	0	0	2 (15)	2 (15)	2 (11)	2 (11)
Sepsis	1 (20)	1 (20)	1 (8)	1 (8)	2 (11)	2 (11)
Bacteraemia	0	0	2 (15)	1 (8)	2 (11)	1 (6)
Bacterial sepsis	1 (20)	1 (20)	0	0	1 (6)	1 (6)
Herpes simplex reactivation	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Respiratory tract infection fungal	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Blood and lymphatic system disorders	1 (20)	1 (20)	4 (31)	4 (31)	5 (28)	5 (28)
Febrile neutropenia	1 (20)	1 (20)	4 (31)	4 (31)	5 (28)	5 (28)
Respiratory, thoracic and mediastinal disorders	1 (20)	1 (20)	2 (15)	2 (15)	3 (17)	3 (17)
Acute respiratory failure	1 (20)	1 (20)	0	0	1 (6)	1 (6)
Epistaxis	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Pleural effusion	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Gastrointestinal disorders	0	0	2 (15)	2 (15)	2 (11)	2 (11)
Abdominal pain	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Colitis ischaemic	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Nervous system disorders	1 (20)	1 (20)	1 (8)	1 (8)	2 (11)	2 (11)
Haemorrhage intracranial	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Subarachnoid haemorrhage	1 (20)	1 (20)	0	0	1 (6)	1 (6)
Hepatobiliary disorders	1 (20)	0	1 (8)	1 (8)	2 (11)	1 (6)
Hyperbilirubinemia	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Hepatic haematoma	1 (20)	0	0	0	1 (6)	0
Injury, poisoning and procedural complications	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Infusion related reaction	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Vascular disorders	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Air embolism	0	0	1 (8)	1 (8)	1 (6)	1 (6)
Cardiac disorders	0	0	1 (8)	0	1 (6)	0
Sinus tachycardia	0	0	1 (8)	0	1 (6)	0
Immune system disorders	0	0	1 (8)	0	1 (6)	0
Graft versus host disease in skin	0	0	1 (8)*	0	1 (6)	0

Table 3. Serious Adverse Events (SAE) by System Organ Class and Preferred Term

*Grade 2 GvHD limited to the skin was reported in the setting of reactivation of prior allogeneic transplant donor stem cells (UCART22 dose level 2i – 2.5 x 10^6 cells/kg)[5]

Efficacy

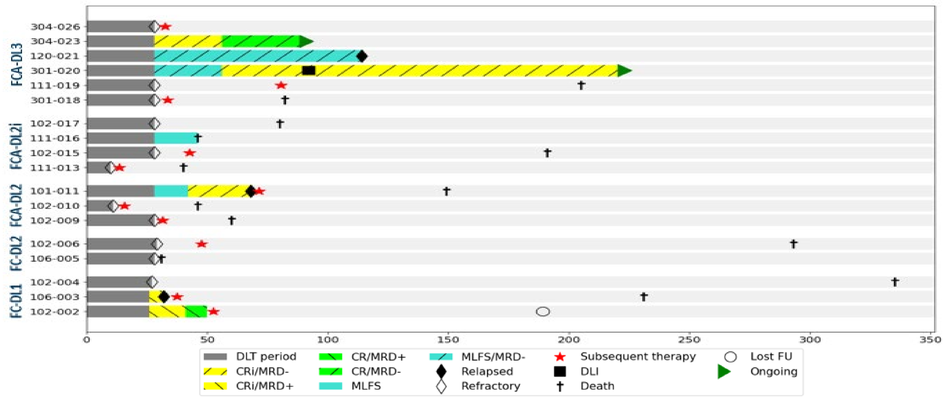


Figure 3. Anti-Leukemic Activity

In FCA cohorts, UCART22 expansion correlates with clinical response

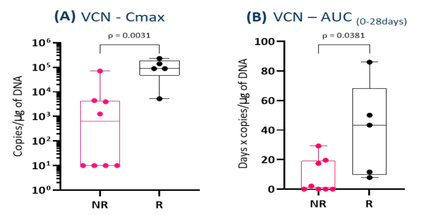
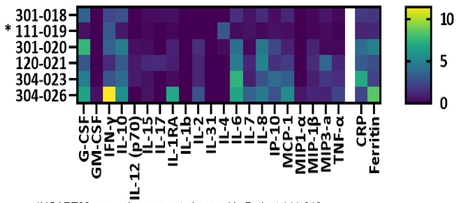


Figure 4. UCART22 vector copy number (VCN) quantified by qPCR from whole blood. Thirteen patients from the FCA cohorts were grouped in responders [R] or not responders [NR]. (A) UCART22 maximum concentration (Cmax) of VCN detected (B) UCART22 VCN area under the curve (AUC) over time (from day 0 through day 28, calculated by linear trapezoidal method by GraphPad. Non-parametric t-test was used to calculate the p values using GraphPad

Increases in inflammatory markers are observed in serum of patients from DL3



*UCART22 expansion was not observed in Patient 111-019

Figure 5. Twenty-one cytokines were measured in serum from subject samples using a multiplex Luminex assay. Each row represents an individual subject, and columns 1-21 show the fold-change of the peak serum concentration from baseline (day 0 before UCART cells infusion). The last two columns are representing C-Reactive Protein (CRP) and ferritin measured by the sites and shows the fold-change of the peak serum concentration from baseline (day 0 before UCART cells infusion)

Summary and Conclusions

- UCART22 continues to be safe and tolerable, with no UCART22-related Grade ≥3 AE or CRS and no DLTs or ICANS
- Overall, 5/18 (28%) of patients achieved CR/CRi
- In the FCA-DL3 cohort, there is a 50% response rate (3/6 patients)
  - Patient 304-023 failed 4 prior lines of therapy (including multiagent chemotherapy, blinatumomab, inotuzumab, autologous CD19 CAR T-cell, and allo HSCT) – achieved an MRD negative CR lasting over 90 days after UCART22 infusion
  - Patient 301-020 failed 4 prior lines of therapy (including multiagent chemotherapy, venetoclax, autologous CD19 CAR T-cell, and allo HSCT) - achieved an MRD negative CRi consolidated with donor lymphocyte infusion after D90 and remains MRD negative CRi past 7 months
  - Patient 120-021 failed 3 prior lines of therapy (including multiagent chemotherapy, venetoclax, autologous CD19 CAR T-cell, and allo HSCT) – achieved an MRD negative MLFS up to D114
- UCART22 expansion was associated with clinical response
- Overall, these data support the safety and preliminary efficacy of UCART22 in this heavily pretreated R/R B-ALL population
- The study is currently open and now enrolling patients using a wholly manufactured product at Cellectis

References

1. Terwilliger T, et al. Blood Cancer J. 2017;7(6):e577.
2. Gökbuget N, et al. Haematologica. 2016;101(12):1524-33.
3. Jain N, et al. Blood. Blood 2021;138(Suppl 1):1746)
4. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.
5. Harris AC, et al. *Biol Blood Marrow Transplant*. 2016;22:4-10

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