Preliminary Results from the Flu/Cy/Alemtuzumab arm of the Phase I BALLI-01 Trial of UCART22, an Anti-CD22 Allogeneic CAR T-Cell Product, in Adult Patients with Relapsed or Refractory CD22+ B-Cell Acute Lymphoblastic Leukemia

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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 cancers (**Figure 1**)
- Lymphodepletion (LD) before CAR T-cell therapy prolongs the persistence of CAR T-cells and increases effectiveness of treatment. Although fludarabine/cyclophosphamide (FC) provides effective LD in multiple tumor types, there is opportunity for optimization
- UCART19 with an LD regimen that also included alemtuzumab (FCA) demonstrated efficacy in R/R B-ALL patients[3]

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

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

"Off-the-shelf" availability
Available to patients immediately after treatment decision

- Dosing flexibility and possibility of redosing
- T-cells from healthy donors
- Scalable manufacturing

Autologous process:
Available after several weeks of manufacturing

*Incidence and severity of adverse events and serious adverse events were assessed throughout the study. †Enrollment is ongoing.
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.

- Preliminary results from the phase 1, open-label, dose-escalation BALLI-01 study in patients with R/R B-ALL showed that UCART22 is tolerable and has demonstrated anti-leukemic activity after LD with FC[4]
- Host T-cell recovery was observed in all patients receiving LD with FC between days 7–28, potentially interfering with UCART22 expansion and persistence
- Alemtuzumab was added to the LD regimen to improve host lymphocyte suppression

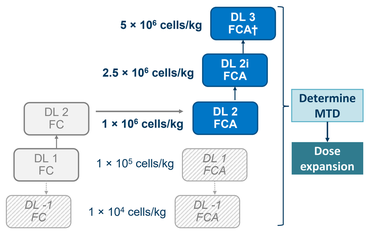
Study Design

- BALLI-01 is an ongoing phase 1, open-label, dose-escalation trial (ClinicalTrials.gov NCT04150497) to evaluate the safety and efficacy of UCART22 (**Figure 2**)

Figure 2. BALLI-01 Study Design (NCT04150497)

- **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

Dose-escalation
Up to 30 patients • mTPI design • 2-4 patients/cohort



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

*Incidence and severity of adverse events and serious adverse events were assessed throughout the study. †Enrollment is ongoing.
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.

Aims

- To evaluate the safety and anti-leukemic activity of UCART22 after an FCA LD regimen
- To assess whether the addition of alemtuzumab to the FC LD regimen can deepen and sustain host lymphocyte depletion and promote CAR T-cell expansion and persistence

Study Objectives

- The primary objective is the safety, tolerability, and maximum tolerated dose (MTD) of UCART22
  - Dose-limiting toxicities (DLT) are assessed over a 28-day observation period after UCART22 infusion
- Additional objectives include:
  - Anti-leukemic activity by investigator assessment
  - Expansion, trafficking, and persistence of UCART22 in peripheral blood (PB) and bone marrow (BM) by phenotypic analysis using flow cytometry and vector copy number (VCN) using quantitative PCR
  - Immune reconstitution
  - Monitoring inflammatory markers

Patients

- As of 1 October 2021, 12 patients received LD; 11 patients were treated with UCART22, 6 of whom received LD with FCA
  - FC-DL1; n = 3
  - FC-DL2; n = 2
  - FCA-DL2; n = 3
  - FCA-DL2i; n = 3

Table 1. Baseline Characteristics

Characteristic	Total N = 12*
Age, median (range), years	30.5 (20-61)
Female, n (%)	7 (58)
ECOG PS 1, n (%)	8 (67)
WHO 2016 Classification, n (%)	
B-ALL with recurrent genetic abnormalities	7 (58)
B-ALL with CRLF2 rearrangement	4 (33)
B-ALL with t(1;19)(q23;p13.3); *TCF3-PBX1*	1 (8)
B-ALL with t(9:22)(q34.1;q11.2); *BCR-ABL1*	1 (8)
B-ALL with hypodiploidy	1 (8)
B-ALL not otherwise specified	5 (42)
Number of prior treatments, median (range)	3 (2-6)
Prior HSCT, n (%)	3 (25)
Prior blinatumomab, n/N (%)	8/11 (73)
Prior inotuzumab, n/N (%)	5/11 (45)
Prior CD19 CAR T-cell therapy, n/N (%)	3/11 (27)

*11 of the 12 patients who received LD with FC or FCA were treated with UCART22.
B-ALL, B-cell acute lymphoblastic leukemia; BCR, breakpoint cluster region; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; HSCT, hematopoietic stem cell transplantation; LD, lymphodepletion; TCF3, transcription factor 3; t, translocation; PBX1, pre-B-cell leukemia homeobox 1; WHO, World Health Organization.

Safety

- The FCA LD regimen was well tolerated, and most treatment-emergent adverse events (TEAEs) of interest (**Table 2**) were manageable with standard guidelines
  - No DLTs were observed
  - No immune effector cell-associated neurotoxicity syndrome (ICANS)[5]
  - 3 patients experienced cytokine release syndrome (CRS) (grade [G]1, n = 2; G2, n = 1) for 2, 4, and 6 days[5]
  - 1 patient experienced GII graft-vs-host disease (GvHD) of the skin[6]
  - 2 patients experienced 3 G ≥3 infections that were not related to study drug
    - Pneumonia, septic shock, staphylococcal bacteremia
  - Serious TEAEs (all cause) are shown in **Table 3**

Table 2. UCART22-Related TEAEs*

TEAE, n (%)	Combined FC cohorts n = 5		FCA-DL2 n = 3		FCA-DL2i n = 3		Combined FCA cohorts n = 6		All patients N =11	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	**Any grade**	**Grade ≥3**
CRS[5]	3 (60)	0	1 (33)	0	2 (67)	0	3 (50)	0	**6 (55)**	**0**
Headache	2 (40)	0	0	0	0	0	0	0	**2 (18)**	**0**
Arthralgia	0	0	0	0	1 (33)	0	1 (17)	0	**1 (9)**	**0**
GvHD in skin[6]	0	0	0	0	1 (33)	0	1 (17)	0	**1 (9)**	**0**
Hypotension	1 (20)	0	0	0	0	0	0	0	**1 (9)**	**0**
Myalgia	0	0	0	0	1 (33)	0	1 (17)	0	**1 (9)**	**0**
Pruritus	0	0	1 (33)	0	0	0	1 (17)	0	**1 (9)**	**0**
Pyrexia	1 (20)	0	0	0	0	0	0	0	**1 (9)**	**0**
Rash	0	0	1 (33)	0	0	0	1 (17)	0	**1 (9)**	**0**

CRS, cytokine release syndrome; DL, dose level; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; GvHD, graft-vs-host disease; TEAE, treatment-emergent adverse event.

Table 3. Serious TEAEs (All Cause)

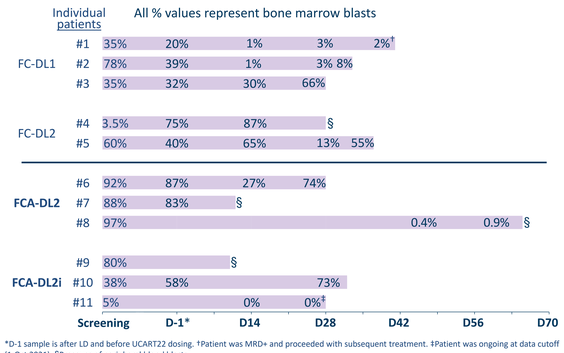
TEAE, n (%)	Combined FC cohorts n = 5		FCA-DL2 n = 3		FCA-DL2i n = 3		Combined FCA cohorts n = 6		All patients N =11	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	**Any grade**	**Grade ≥3**
Febrile neutropenia	1 (20)	1 (20)	1 (33)	1 (33)	1 (33)	1 (33)	2 (33)	2 (33)	**3 (27)**	**3 (27)**
Acute respiratory failure	1 (20)	1 (20)	0	0	1 (33)	1 (33)	1 (17)	1 (17)	**2 (18)**	**2 (18)**
Bacterial sepsis	1 (20)	1 (20)	0	0	0	0	0	0	**1 (9)**	**1 (9)**
Colitis ischemic	0	0	0	0	1 (33)	1 (33)	1 (17)	1 (17)	**1 (9)**	**1 (9)**
Epistaxis	0	0	0	0	1 (33)	1 (33)	1 (17)	1 (17)	**1 (9)**	**1 (9)**
Hyperbilirubinemia	0	0	1 (33)	1 (33)	0	0	1 (17)	1 (17)	**1 (9)**	**1 (9)**
Pneumonia	0	0	0	0	1 (33)	1 (33)	1 (17)	1 (17)	**1 (9)**	**1 (9)**
Sepsis	1 (20)	1 (20)	0	0	0	0	0	0	**1 (9)**	**1 (9)**
Subarachnoid hemorrhage	1 (20)	1 (20)	0	0	0	0	0	0	**1 (9)**	**1 (9)**
Embolic hemorrhagic and non-hemorrhagic infarct*	0	0	0	0	1 (33)	1 (33)	1 (17)	1 (17)	**1 (9)**	**1 (9)**
GvHD in skin	0	0	0	0	1 (33)	0	1 (17)	0	**1 (9)**	**0**
Hepatic hematoma	1 (20)	1 (20)	0	0	0	0	0	0	**1 (9)**	**0**
Pyrexia	0	0	1 (33)	0	0	0	1 (17)	0	**1 (9)**	**0**
Sinus tachycardia	0	0	0	0	1 (33)	0	1 (17)	0	**1 (9)**	**0**

*Verbatim term (not coded).
DL, dose level; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; GvHD, graft-vs-host disease; TEAE, treatment-emergent adverse event.

Anti-leukemic Activity

- Anti-leukemic activity was seen in 2 patients in the FCA cohort (**Figure 3**)

Figure 3. Investigator-assessed Anti-leukemic Activity

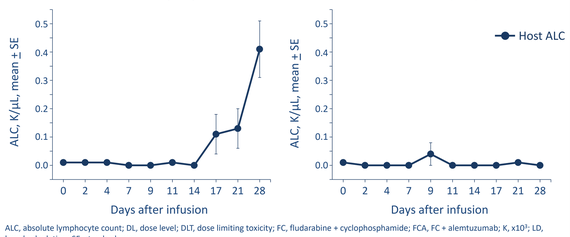


*D-1 sample is after LD and before UCART22 dosing. †Patient was MRD+ and proceeded with subsequent treatment. ‡Patient was ongoing at data cutoff (1-Oct 2021). §Presence of peripheral blood blasts.
D, day; DL, dose level; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; LD, lymphodepletion; SCR, screening; MRD, measurable residual disease.

Host Lymphocyte Suppression and UCART22 Expansion

- Host lymphocytes on average remained suppressed throughout the 28-day DLT observation period for all 6 patients in the FCA-DL2 and DL2i cohorts (**Figure 4**)
- UCART22 proliferation was observed in 3 patients in the FCA cohorts (**Figure 5**) and correlated with changes in inflammatory cytokines (**Figure 6**)

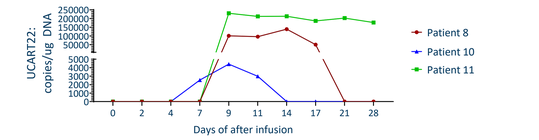
Figure 4. Host Lymphocyte Suppression After UCART22 Infusion



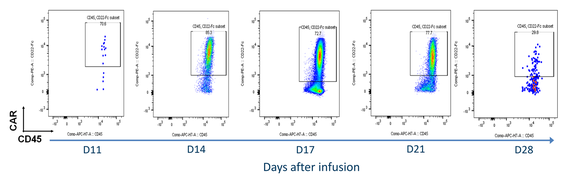
ALC, absolute lymphocyte count; DL, dose level; DLT, dose limiting toxicity; FC, fludarabine + cyclophosphamide; FCA, FC + alemtuzumab; K, x10³; LD, lymphodepletion; SE, standard error.

Figure 5: Detection of UCART22 Expansion in Patients Receiving FCA LD Regimen

Vector Copy Number Analysis



Flow Cytometry Analysis (Patient 11) Peaking at Day 17 and Decreasing by Day 28



D, day; DL, dose level; FCA, fludarabine + cyclophosphamide + alemtuzumab; LD, lymphodepletion.

Figure 6. Changes in Inflammatory Markers in Patients With Detectable UCART22 Cell Expansion

DL, dose level; FCA, fludarabine + cyclophosphamide + alemtuzumab.

Conclusions

- The FCA LD regimen was well tolerated and associated with improved host lymphocyte suppression and UCART22 expansion
- UCART22 expansion correlated with antileukemic activity with changes in relevant inflammatory markers
- 1 serious AESI was reported (grade II GvHD of the skin)
- Overall, these data support the safety and antileukemic activity of UCART22 after FCA LD in patients with R/R B-ALL
- The study is currently open and enrolling patients at FCA-DL3 (5 × 10^6 UCART22 cells/kg)

References

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