Preliminary Results of NatHaLi-01: A First-In-Human Phase I/IIa Study of UCART20x22, a Dual Allogeneic CAR-T Cell Product Targeting CD20 and CD22, in Relapsed or Refractory (R/R) Non-Hodgkin Lymphoma (NHL)

P2110

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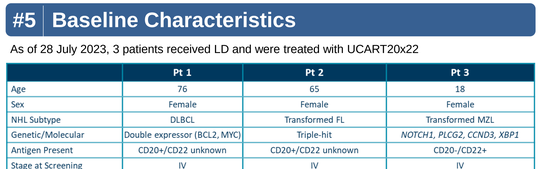
#1 Introduction

- Autologous CD19-directed CAR T-cell therapies have revolutionized the treatment of R/R NHL, but up to approximately 50% of patients treated in the second or third line will ultimately fail these therapies.[1-5]
- Allogeneic chimeric antigen receptor (CAR) T-cell therapies targeting other antigens have the potential to provide benefit to these patients.
- UCART20x22 is the first allogeneic dual CAR T-cell therapy targeting CD20 and CD22 being tested in the clinic for R/R B-cell NHL and is manufactured by Cellectis Biologics.

#2 UCART20x22: Allogeneic "Off-the-Shelf' T-cell Product

UCART20x22 (anti-CD20 and anti-CD22 scFv-41BB-CD3ζ):

- Genetically modified allogeneic T-cell product manufactured from non-HLA–matched healthy donor cells
- CD20 and CD22 surface molecules are validated therapeutic targets in NHL

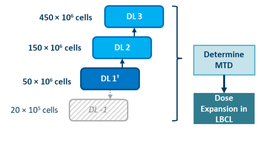


CAR, chimeric antigen receptor; GvHD, graft-vs-host disease; HLA, human leukocyte antigen; KO, knock out; LD, lymphodepletion; NHL, non-Hodgkin lymphoma; pts, patients; scFv, single-chain variable fragment; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

#3 Study Design (NCT05607420)

- **Key inclusion criteria:**
  - Age 18–80 years
  - Mature B-cell NHL except CLL/SLL, Richter's from CLL/SLL, Burkitt's lymphoma, or Waldenstrom's macroglobulinemia
  - Tumor positive for CD20 and/or CD22
  - Received ≥2 prior lines including CD19 CART if eligible
- **Primary objective:**
  - Safety, tolerability, & MTD/RP2D of UCART20x22
- **Additional objectives:**
  - Investigator-assessed response by Lugano
  - UCART20x22 expansion in PB
  - Immune reconstitution

Dose-escalation
BOIN design • 2-4 pts/cohort



FCA LD regimen:
- **Fludarabine** 30 mg/m² × 3d
- **Cyclophosphamide** 0.5 g/m² × 3d
- **Alemtuzumab** 60 mg total over 3 days

†Enrollment is ongoing.
BOIN, Bayesian optimal interval; CART, chimeric antigen receptor T-cell therapy; DL, dose level; d, days; FCA, fludarabine + cyclophosphamide + alemtuzumab; LBCL, large B-cell lymphoma, LD, lymphodepletion; MTD, maximum tolerated dose; PB, peripheral blood; pts, patients; RP2D, recommended phase 2 dose.

#4 Methods

- Primary endpoints are safety, tolerability, and determining the MTD/RP2D of UCART20x22. Additional endpoints include anti-lymphoma activity and expansion of UCART20x22.
- 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 receive a single infusion of UCART20x22.

#5 Baseline Characteristics

As of 28 July 2023, 3 patients received LD and were treated with UCART20x22

	Pt 1	Pt 2	Pt 3
Age	76	65	18
Sex	Female	Female	Female
NHL Subtype	DLBCL	Transformed FL	Transformed MZL
Genetic/Molecular	Double expressor (BCL2, MYC)	Triple-hit	*NOTCH1, PLCG2, CCND3, XBP1*
Antigen Present	CD20+/CD22 unknown	CD20+/CD22 unknown	CD20-/CD22+
Stage at Screening	IV	IV	IV
Number of Prior Therapies	2	4	8
Prior CD19 CART	None	Lisocabtagene maraleucel x2	Axicabtagene ciloleucel
ECOG	0	0	1
Baseline Deauville Score	4	5	5
Disease Status at Screening	Relapsed	Relapsed	Refractory

CART, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LD, lymphodepletion; MZL, marginal zone lymphoma

#6 Safety Summary

- No UCART20x22-related DLTs.
- No ICANS or GVHD was observed.
- One CLLS52-related DLT of bone marrow aplasia after Day 42 thought to be due to cumulative chemotherapy exposure in a patient with baseline grade 1/2 cytopenias and bone marrow hypocellularity at Screening.
- All patients experienced grade 1 or 2 CRS that resolved with treatment
  - Pt 1 had grade 1 CRS for 4 days and was treated with tocilizumab x3 and dexamethasone x1
  - Pt 2 had grade 2 CRS for 2 days and grade 1 CRS for 3 days managed with tocilizumab x3 and dexamethasone x1
  - Pt 3 had grade 1 CRS for 8 days and received tocilizumab x1

UCART20x22-Related Adverse Events (AE) by System Organ Class and Preferred Term

AE, n (%) System Organ Class Preferred Term	Dose Level 1 (n = 3)	
	Any grade	Grade ≥3
Patients with at least 1 UCART20x22-related AE	**3 (100)**	**3 (100)**
Immune system disorders	3 (100)	0
Cytokine release syndrome	3 (100)	0
Hypogammaglobulinemia	1 (33)	0
Nervous system disorders	1 (33)	0
Dizziness	1 (33)	0
Headache	1 (33)	0
General disorders and administration site conditions	1 (33)	0
Fatigue	1 (33)	0
Vascular disorders	1 (33)	0
Hypotension	1 (33)	0
Gastrointestinal disorders	1 (33)	0
Nausea	1 (33)	0
Musculoskeletal and connective tissue disorders	1 (33)	0
Pain in extremity	1 (33)	0
Skin and subcutaneous tissue disorders	1 (33)	0
Pruritus	1 (33)	0
Psychiatric disorders	1 (33)	0
Dysphemia	1 (33)	0
Blood and lymphatic system disorders	3 (100)	3 (100)
Anemia	3 (100)	3 (100)
Neutropenia	2 (67)	2 (67)
Thrombocytopenia	1 (33)	1 (33)
Pancytopenia	1 (33)	1 (33)
Febrile neutropenia	1 (33)	1 (33)
Investigations	1 (33)	0
Alanine aminotransferase increased	1 (33)	0
Aspartate aminotransferase increased	1 (33)	0
Blood alkaline phosphatase increased	1 (33)	0
Blood lactate dehydrogenase increased	1 (33)	0
Metabolism and nutrition disorders	3 (100)	0
Hyponatremia	2 (67)	0
Hypocalcemia	1 (33)	0
Hypophosphatemia	1 (33)	0

Treatment Emergent Serious Adverse Events (SAEs) by System Organ Class & Preferred Term

SAE, n (%) System Organ Class Preferred Term	Dose level 1 (n = 3)		Related to UCART20x22	Related to CLLS52
	Any grade	Grade ≥3	Causality	Causality
Blood and lymphatic system disorders	1 (33)	1 (33)		
Pancytopenia	1 (33)	1 (33)	**Yes**	**Yes***
Infections and infestations	1 (33)	0		
Cytomegalovirus viremia	1 (33)	1 (33)	No	**Yes**
Pseudomonal sepsis	1 (33)	1 (33)	No	No
Nervous system disorders	1 (33)	0		
Neuralgia	1 (33)	0	No	No
Respiratory, thoracic, and mediastinal disorders	1 (33)	1 (33)		
Acute respiratory failure	1 (33)	1 (33)	No	No

*DLT for CLLS52 thought to be due to cumulative chemotherapy exposure in a patient with baseline G1/2 cytopenias and bone marrow hypocellularity at Screening

#7 Response

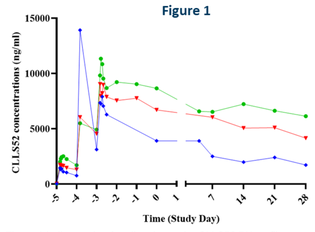
As of July 28, 2023, 3 patients were treated at dose level 1 and were evaluable for response:

- Pt 1 is a 76-year-old female with double-expressor DLBCL relapsed after R-CHOP, radiation therapy, and polatuzumab vedotin with bendamustine/rituximab who achieved a **partial metabolic response** at Day 28.
- Pt 2 is a 65-year-old female with triple-hit transformed follicular lymphoma previously treated with radiation therapy, bendamustine/rituximab, dose-adjusted R-EPOCH, and two lisocabtagene maraleucel treatments who achieved a **complete metabolic response** at Day 28.
- Pt 3 is an 18-year-old female with relapsed/refractory transformed marginal zone lymphoma who previously failed chemoimmunotherapy, venetoclax, ibrutinib, bendamustine/rituximab, axicabtagene ciloleucel, obinutuzumab, glofitamab, tafasitamab/lenalidomide, and an experimental epigenetic modifier who achieved a **complete metabolic response** at Day 28.

#8 Translational Summary

- FCA lymphodepletion led to sustained suppression of endogenous T-cells for the duration of the treatment period, allowing for UCART20x22 expansion.
- Robust peripheral UCART20x22 expansion was observed in all three patients and correlated with CRS and changes in serum ferritin levels.
  - Expanding UCART20x22 cells are predominantly CD8+
- Serum cytokine/inflammatory marker levels increased prior to or during UCART20x22 peak expansion, with comparable results among all patients.
- Patient 3 exhibited low CD20 and high CD22 tumor expression at baseline.
- UCART20x22 cells were observed in day 9 post-treatment biopsy from patient 3.

1 | CLLS52 (Alemtuzumab) Pharmacokinetics and Host Lymphocyte Suppression



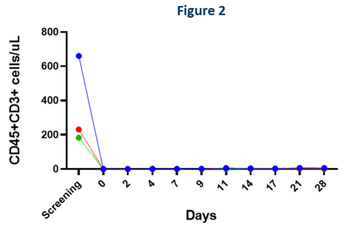
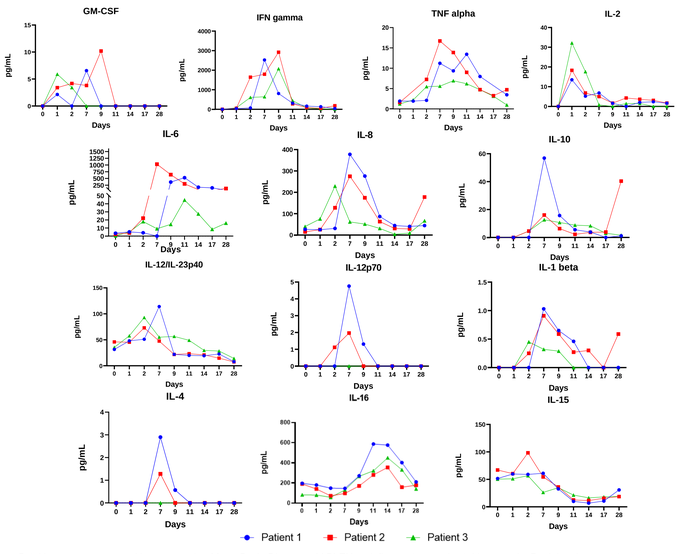


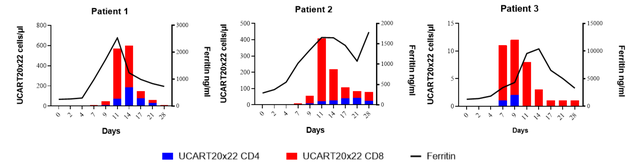
Figure 1 indicates that for all patients, the CLLS52 PK profiles are similar and consistent with literature results.[6] Concentrations increase with each dose administered with Cmax observed following the last dose, then concentrations decrease and were quantifiable at the last collected timepoint. Correlating with the CLLS52 PK profiles, Figure 2 shows adequate lymphodepletion for all patients until at least 28 days post-UCART20x22 administration.

3 | Similar Increase in Serum Cytokines/Inflammatory Markers for all Patients



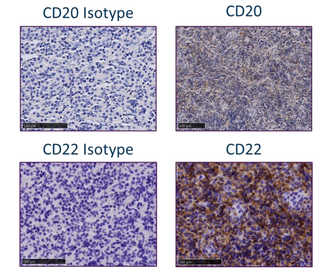
Cytokines were measured in serum using Meso Scale Discovery V-PLEX proinflammatory and cytokine panels. Peak levels were observed at initial expansion of UCART20x22 for GM-CSF, IFNg, TNFa, IL-1b, IL-2, IL-4, IL-8, IL-10, IL-12p40, IL-12p70, IL-15, and at peak expansion for IL-6 and IL-16.

2 | Robust Expansion of UCART20x22 Cells in Peripheral Blood Correlates with an Increase in Ferritin Levels



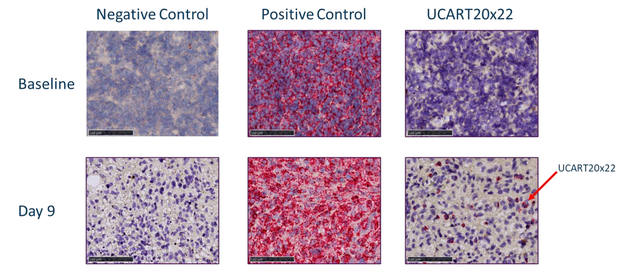
UCART20x22 expansion was observed by flow cytometry in the peripheral blood in all patients, with peaks of ~600 cells/µL in Patient 1 at Day 14, ~400 cells/µL in Patient 2 at Day 11, and ~12 cells/ µL in Patient 3 at Day 9, with predominantly CD8+ cells expanding.

4 | Low CD20 and High CD22 Expression for Patient 3 at Baseline



CD20 and CD22 were measured by IHC (20X resolution) with the corresponding isotype negative control, which showed no staining

5 | UCART20x22 Cells Detected in Day 9 Post-Treatment Biopsy



UCART20x22 cells were measured by RNAscope using a probe set specific for the UCART22 targeted sequence, at 20X magnification. No staining was observed with the negative control DapB (*Bacillus subtilis* strain SMY, a soil bacterium) in situ hybridization (ISH), strong staining with positive control UBC (ubiquitin C) ISH (red), UCART20x22 cells are detected by UCART22 ISH (Red), and hematoxylin counterstain (blue) nuclear staining.

#9 Summary and Conclusions

- UCART20x22 at dose level 1 (50 x 10^6 cells) is preliminarily safe and tolerable, with no grade ≥3 CRS, no ICANS, and no UCART20x22-related DLTs.
- All of the patients responded at the Day 28 disease assessment
  - **2 complete metabolic responses in patients who failed prior CAR19**
  - **1 partial metabolic response**
- UCART20x22 expansion was observed in all patients and associated with changes in inflammatory markers and cytokine levels.
- UCART20x22 was detected in one patient's post-treatment tumor biopsy.
- Overall, these data support the preliminary safety and efficacy of UCART20x22 in this R/R B-cell NHL population.
- The study is currently open and enrolling

#10 References

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