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ALEMTUZUMAB EXPOSURE AND SUSTAINED IL-2 DRIVE UCART20X22 EXPANSION AND CLINICAL RESPONSE IN ADULTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN LYMPHOMA: NATHALI-01 STUDY

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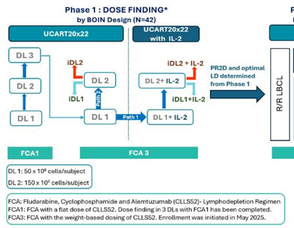
INTRODUCTION

UCART20x22 is a dual-targeted, allogeneic CAR T-cell therapy directed against the B-cell antigens CD20 and CD22. Donor-derived T cells are genetically engineered using TALEN® technology to disrupt TRAC and CD52, eliminating T-cell receptor expression to reduce the risk of graft-versus-host disease and enabling Alemtuzumab-based lymphodepletion. In preclinical studies, UCART20x22 demonstrated robust and sustained antitumor activity *in vitro* and *in vivo*[1]. NatHaLi-01 (NCT05607420) is an open-label, Phase 1/2a, dose-finding and expansion study evaluating UCART20x22 in patients with ≥2 prior lines of therapy with primary objectives of assessing safety, tolerability, and selection of the recommended Phase 2 dose, and secondary objectives including preliminary antitumor activity and cellular pharmacokinetics. The study also investigates Alemtuzumab-based lymphodepletion in combination with fludarabine and cyclophosphamide. Initial clinical findings from the first-in-human NatHaLi-01 study, presented at ASH 2023, showed that UCART20x22 was tolerable and clinically active in heavily pretreated patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL)[2]. Based on prior disclosures and emerging clinical and pharmacodynamic data, the protocol was amended to include a cohort evaluating weight-based Alemtuzumab dosing and low-dose subcutaneous interleukin-2 (IL-2) in combination with UCART20x22, with the aim of enhancing CAR T-cell expansion and persistence[3].

Trial Design

Figure 1: Study Design



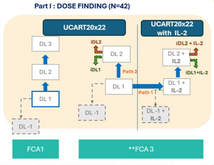
AIM

This preliminary analysis explores the relationships between Alemtuzumab exposure, UCART20x22 cellular kinetics, cytokine responses, and clinical outcomes in patients with R/R B-NHL treated with UCART20x22.

METHOD

Alemtuzumab dose normalized by body weight and exposure, UCART20x22 cellular kinetics (expansion and persistence), cytokine dynamics, endogenous T-cell recovery, and tumor best objective response assessed according to Lugano 2014 criteria were analyzed to evaluate their associations with clinical outcomes in Part I (dose-finding) of the trial.

Figure 2: Dose-Finding Study Schema



FCA = Fludarabine, Cyclophosphamide, Alemtuzumab (CLLS52)
FCA1: FCA with flat dose of CLLS52, FCA 3 = FCA with the weight-based dosing of CLLS52. UCART20x22 Dose Levels (DL): DL1: 50x10⁶ cells DL2: 150 x10⁶ cells DL3: 450 x10⁶ cells; iDL1: intermedial DL between DL1 and DL2. iDL2: intermedial DL between DL2 and DL3; IL-2: Interleukin 2. C_{max}: peak concentration; AUC_{last}: area under the curve to the last quantifiable concentration; C_{last}: last measurable concentration; T_{max}: time to peak concentration; T_{last}: time to last detection

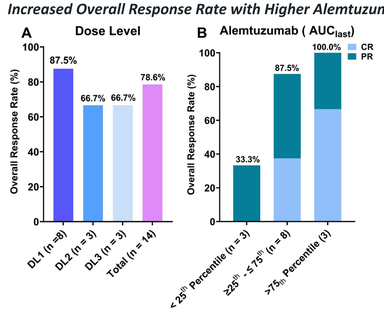
RESULTS

Table 1: Patient Demographics /Baseline Characteristics

LD Regimen	FCA1	FCA3	
UCART20x22 Dose/ Demographic & Baseline Characteristics	All DLs (1/2/3) n=12 (%)	DL1 n=2 (%)	Total n=14 (%)
Age, median (min, max)	64(18, 78)	53 (47, 59)	62 (18, 78)
Sex, Male	8 (66.7)	1 (50)	9 (64.3)
NHL Subtypes	12 (100)	2 (100)	14 (100)
DLBCL, NOS	10 (83.3)	2 (100)	12 (85.7)
tMZL	1(8.3)	0	1 (7.1)
HGBCL	1(8.3)	0	1 (7.1)
Stage IV Disease at Study Entry	12(100)	2(100)	14(100)
Elevated LDH prior to LD	10(83.3)	1 (50)	11(78.6)
No. of Prior Lines, median (min, max)	4 (2, 8)	3 (2, 3)	3 (2, 8)
Prior CD19 CAR-T	11(91.7)	2 (100)	13 (92.8)
Prior Bi-Specific T Cell Engager Therapy	5 (41.6)	1 (50)	6 (42.9)
Primary Refractory Disease	2(16.7)	1 (50)	3(21.4)
Refractory to Last Line of Therapy	5 (41.6)	0	5(35.7)

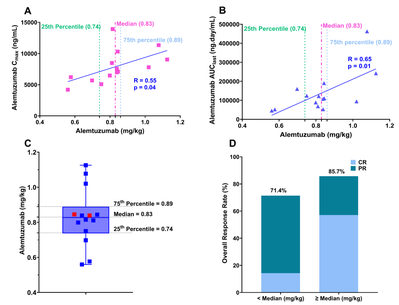
FCA1: FCA w flat dose of CLLS52, FCA 3 = FCA w the weight-based dosing of CLLS52
UCART20x22 Dose Levels (DL): DL1: 50x10⁶ cells DL2: 150 x10⁶ cells DL3: 450 x10⁶ cells

Figure 3: Increased Overall Response Rate with Higher Alemtuzumab Exposure



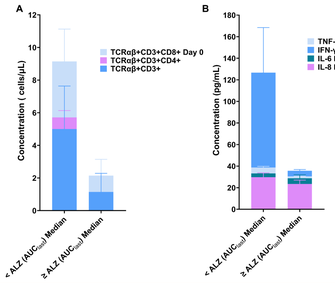
- At the data cutoff on February 3, 2026, overall response rates (ORR) were 87.5% in DL1 (n=8), 66.7% in DL2 (n=3), and 66.7% in DL3 (n=3), corresponding to an overall ORR of 78.6%
- When stratified by Alemtuzumab exposure (AUC_{last}), clinical responses increased in an exposure-dependent manner, with higher response rates observed at higher exposure levels.

Figure 4: Impact of Alemtuzumab Dosing Strategy on Exposure and Clinical Response



- A strong association was observed between body weight–normalized Alemtuzumab dose (mg/kg) and key pharmacokinetic parameters, including AUC_{last} and C_{max} (Figure 4A–B).
- Flat dosing (blue square) led to greater inter-patient variability compared with weight-based dosing (red square) (Figure 4C).
- Patients receiving ≥ 0.83 mg/kg (median) demonstrated significantly higher complete response rates (Figure 4C–D), supporting weight-based dosing strategies to optimize clinical outcomes.

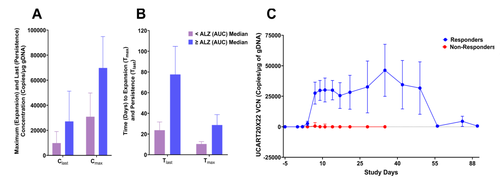
Figure 5: Higher Alemtuzumab Exposure Creates a Favorable Inflammatory Homeostatic Milieu Prior to UCART20x22 Infusion



Prior to UCART20x22 infusion, Analysis of inflammatory cytokines and residual host T-cell levels in relation to Alemtuzumab exposure (AUC_{last}) Showed:

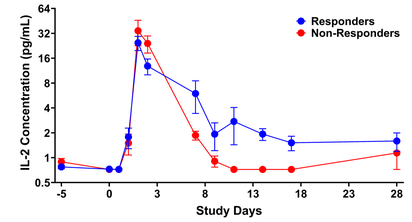
- Patients with Alemtuzumab exposure at or below the median exhibited a higher inflammatory milieu and increased residual host T cells compared with those with exposure above the median (Figure 5A and 5B)
- Higher levels of host T cells and pro-inflammatory markers during this pre-infusion period were inversely associated with Alemtuzumab exposure and clinical outcomes (data not shown)

Figure 6: Higher Alemtuzumab Exposure Facilitates Better UCART20x22 Expansion/Proliferation with Improved Clinical Response



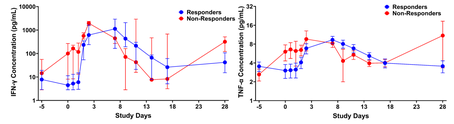
- Patients with higher alemtuzumab exposure (AUC_{last} ≥ median) showed higher UCART20x22 cytokinetic parameters associated with expansion and persistence, including maximal concentration (C_{max}), time to maximal concentration (T_{max}), last measurable concentration (C_{last}), and time to last quantifiable concentration (T_{last}) (Figure 6A–B).
- Responders demonstrated greater UCART20x22 expansion and longer persistence compared with non-responders (Figure 6C)
- These differences in expansion and persistence between responders and non-responders were consistently observed across both ddPCR-based vector copy number (VCN) and flow cytometry (data not shown) methods for the quantification of UCART20x22 in peripheral blood.

Figure 7: Sustained Low-Level IL-2 Production Observed in Subjects Who Achieved Clinical Response



- Early IL-2 production was similar across groups, but only responders maintained sustained low-level IL-2 secretion.
- Sustained IL-2 signaling may support UCART20x22 proliferation, persistence, and improved clinical response.

Figure 8: Delayed and Sustained TNF-α and IFN-γ Production Characterizes UCART20x22 Responders



- Responders showed delayed but sustained IFN-γ and TNF-α production after infusion, whereas non-responders had an early transient cytokine increase before infusion.
- In combination with IL-2 kinetics, these findings suggest that sustained IL-2 signaling supports UCART20x22 persistence.
- Prolonged IFN-γ and TNF-α production appears to reflect durable CAR T-cell effector function, which is associated with improved clinical response.

CONCLUSIONS

- UCART20x22 demonstrated encouraging preliminary clinical activity in heavily pretreated R/R B-NHL, with an ORR of 78.6% in all dosed patients in NatHaLi-01.
- Lymphodepletion intensity, driven by Alemtuzumab exposure (PK), influenced clinical outcomes, supporting Alemtuzumab as a key determinant of treatment efficacy.
- Higher weight-normalized Alemtuzumab exposure was associated with:
  - ❑ Sustained endogenous IL-2 production in responders
  - ❑ Delayed and prolonged IFN-γ and TNF-α responses
  - ❑ Improved CAR T-cell expansion and persistence, translating into higher ORR
- These findings underscore the importance of optimizing lymphodepletion strategies to maximize the clinical benefit of allogeneic CAR T-cell therapy.
- Weight-based alemtuzumab dosing may optimize the balance between adequate exposure and toxicity mitigation.
- Ongoing cohorts are evaluating the weight-based Alemtuzumab LD with low-dose subcutaneous IL-2 in combination with UCART20x22 to further enhance efficacy and durability of the response (NCT05607420); enrollment is ongoing in the United States, France, and Spain, and will soon open in Italy.

REFERENCES

1. Aranda-Orgilles B, et al. Cancer Immunology Research. 2023. 2. Abramson JS, et al. Blood. 2023;142(Suppl 1):2110. 3. Abramson JS, et al. Blood (2025) 146 (Supplement 1): 3731.

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