Trial In Progress: Open-Label Dose-Finding and Dose-Expansion Study to Evaluate the Safety, Expansion, Persistence, and Clinical Activity of UCART20x22 in Subjects with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma (B-NHL) NatHali-01

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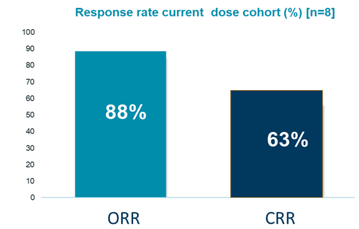
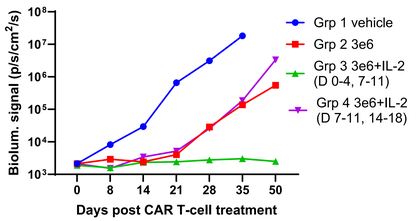
BACKGROUND AND RATIONALE:

- UCART20x22 is a **first-in-class** allogeneic, non-alloreactive, engineered human CAR T-cell product endowed with dual CAR expression, targeting both CD20 and CD22 antigens and represents a potential new therapeutic option for patients with R/R B-NHL. TALEN ® gene editing technology is used to inactivate the TRAC and CD52 genes to minimize graft-versus-host disease (GvHD) and allow for the use of alemtuzumab (CLLS52, an anti-CD52 monoclonal antibody) in the lymphodepletion (LD) regimen.
- Clinical and preclinical studies suggest that exogenous low dose Interleukin-2 (IL-2) administration can enhance the expansion and persistence of CAR-T cells significantly to boost CAR-T efficacy without exacerbating toxicity.*

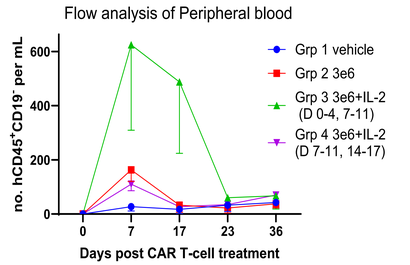


- Clinical data from the NatHaLi-01 study has demonstrated encouraging response rates with UCART20x22 in subjects with NHL
- *In vivo data* of UCART20x22 in combination with IL-2 demonstrated that IL-2 dosing may increase persistent circulating levels of UCART20x22 in a mouse model harboring disseminated tumors and enhance anti-tumor efficacy, without inducing treatment-associated toxicity.

Increased anti-tumor activity with IL-2

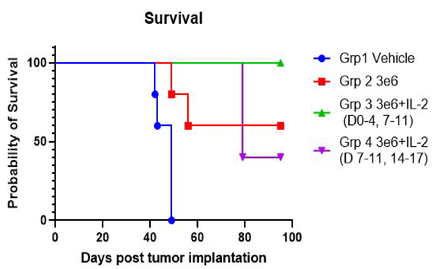


Increased expansion and persistence with IL-2



*Day 0 theoretical levels pre-UCART injection

Increased survival with IL-2

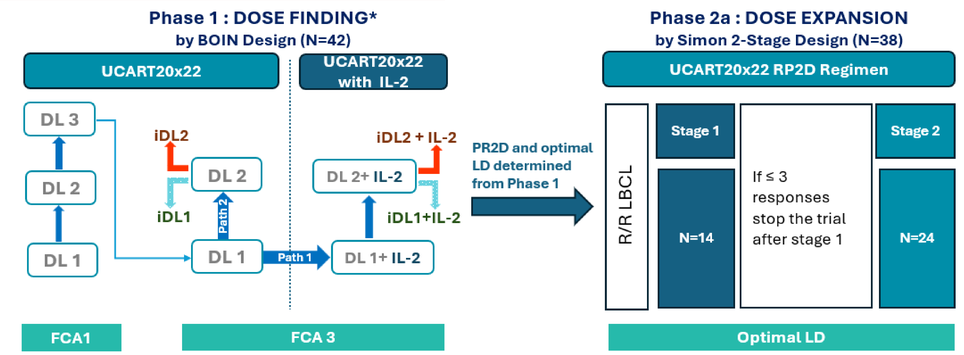


UCART20x22 monotherapy is being evaluated in an ongoing first-in-human, open-label Phase 1/2a dose-finding and dose-expansion study (Nathali-01, NCT05607420) in patients with R/R B-NHL. The protocol is now amended to add a treatment cohort of UCART20x22 in combination with low-dose IL-2 in dose- finding and dose expansion

*Gattinoni, L., et al. (2005). Acquisition of full effector function in vitro paradoxically impairs the in vivo antitumor efficacy of adoptively transferred CD8+ T cells. journal of Clinical Investigation, 115(6). https://doi.org/10.1172/JCI24480

*https://imugene.com/wp-content/uploads/2025/02/ASTCT-Maakaron-Poster-Feb-2025.pdf

TRIAL DESIGN

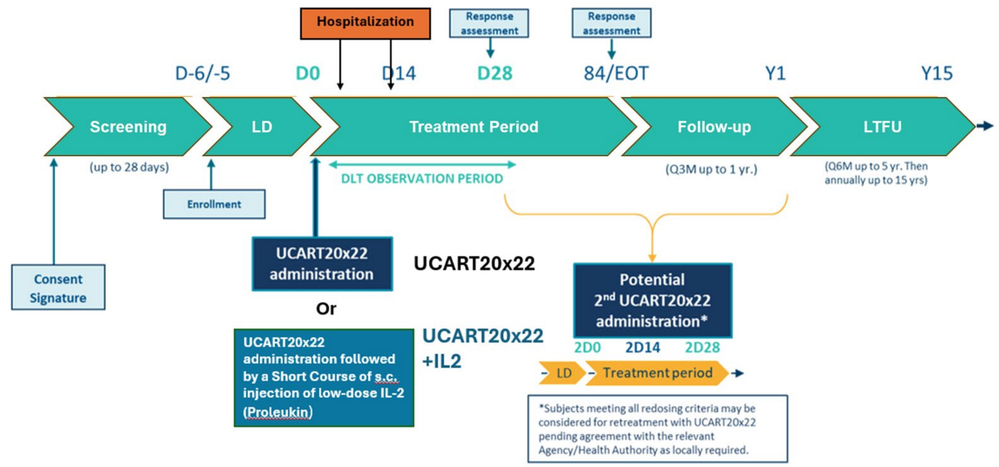


DL 1: 50 x 10^6 cells/subject
DL 2: 150 x 10^6 cells/subject

FCA: Fludarabine, Cyclophosphamide and Alemtuzumab (CLLS52)- Lymphodepletion Regimen
FCA1: FCA with a flat dose of CLLS52. Dose finding in 3 DLs with FCA1 has been completed.
FCA3: FCA with the weight-based dosing of CLLS52. Enrollment was initiated in May 2025.

*Note: Up to 10 subjects may be enrolled to backfill cohort(s)

Subject Flow Diagram



Abbreviations: D=day; (i)DL = UCART20x22 (intermediate) Dose level; EOT=end of treatment; FCA = Flu/Cy/alemtuzumab; LBCL = Large B Cell Lymphoma; LD = Lymphodepletion; LTFU=long term follow up; Q3M=Every 3 months; RP2D = Recommended Phase 2 Dose; IL-2 =Interleukin-2 S.C.=subcutaneous; Y=year, yr=year

OBJECTIVE AND ENDPOINTS

Primary objective is to assess the safety and tolerability of UCART20x22, and to determine the MTD and/or RP2Dof UCART20x22 in subjects with R/R B-NHL. Incidence of DLT or TEAE as primary endpoint.

Secondary objectives are

- To assess anti-tumor activity by objective response rate, duration of response, progression-free survival, and overall survival.
- To evaluate CLLS52 PK by PK parameters

Key Assessments: AEs are assessed according to CTCAE v5. Tumor response is determined according to Lugano 2014 criteria. Safety findings are reviewed by the PSRC, which will determine the RP2D and/or MTD.

ELIGIBILITY

Key Inclusion Criteria:

- Age 18- 80 years old,
- Have ECOG ≤1,
- Adequate organ functions,
- CD20+ and/or CD22+ B-NHL with relapsed or refractory disease after ≥2 lines of systemic therapy

Key Exclusion Criteria:

- Active CNS lymphoma,
- > 4 lines of therapy on R/R B-NHL prior to enrollment
- GvHD or MAS
- Hypersensitivity to alemtuzumab or IL-2 if applicable,
- History of ADA against alemtuzumab or IL-2 if applicable.

TRIAL ACCRUAL AND PROGRESS

- Up to 80 eligible patients (42 in dose finding and 38 in dose expansion) will be enrolled.
- Dose finding up to 3 cohorts of UCART20x22 monotherapy under FCA1 has been completed.
- Enrollment to dose finding of UCART20x22 monotherapy at dose cohort 1 with FCA3 began in May 2025.
- 14 patients were enrolled and treated as of 30-Oct-2025. 10 sites from US, France and Spain are participating in the trial.

ACKNOWLEDGEMENTS

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