

GNC-038, a tetra-specific antibody, in patients with R/R Non-Hodgkin Lymphoma or Acute Lymphoblastic Leukemia: Phase 1 study design and rationale

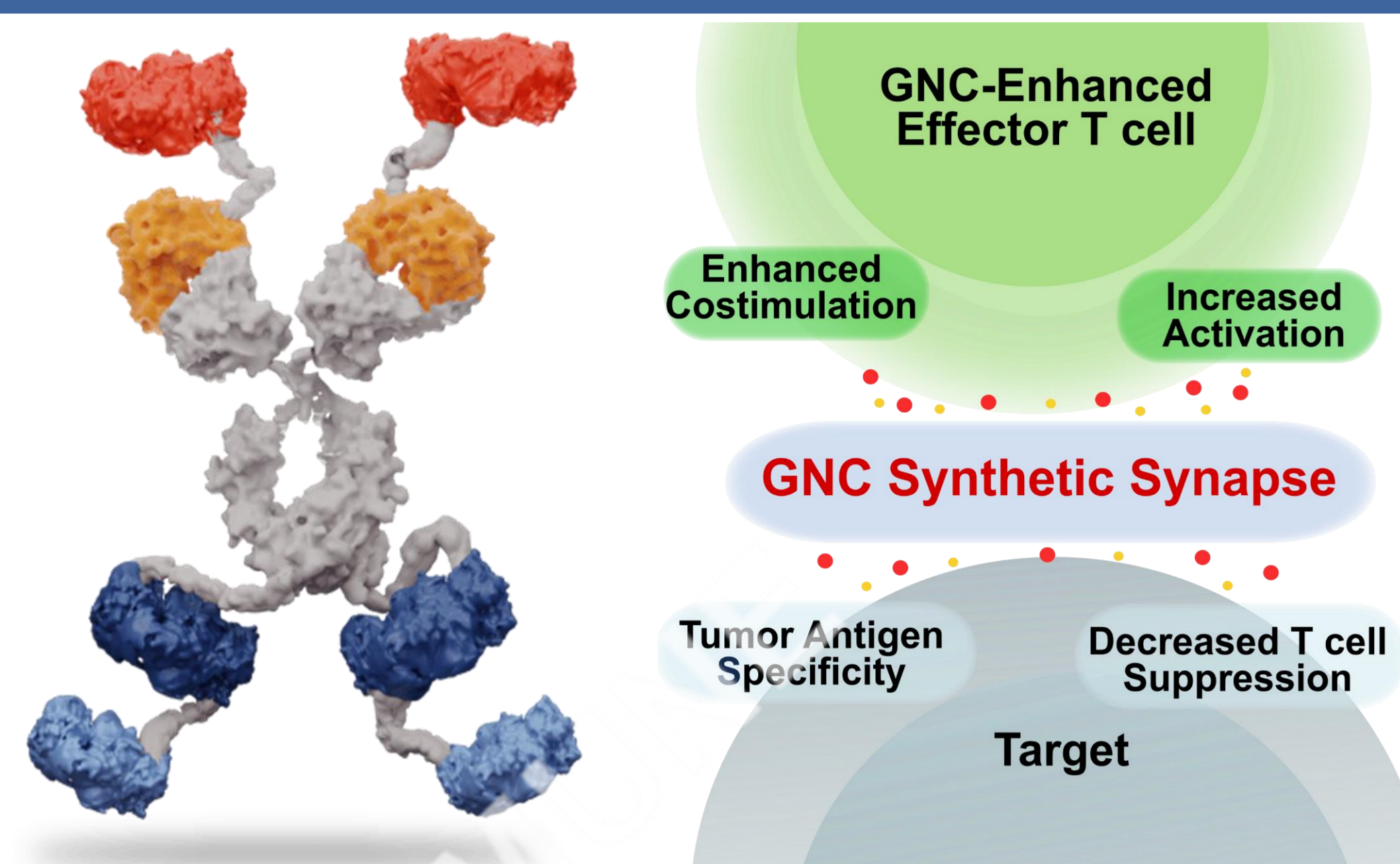
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Background

Bispecific T cell engagers can mediate single antigen-specific cell cytotoxicity, but cannot preempt clonal relapse, or modify the immunosuppressive cancer cell surfaceome. The octavalent, tetra-specific antibody, GNC-038, functions as a CD19-specific T cell engager by mediating direct antitumor activity, but further, GNC-038 overcomes inhibition of T cells by PD-L1, based on its 4 binding sites (α CD19, α CD3, α PD-L1, and α 4-1BB). The antitumor activity of GNC-038 is mediated by activating CD3 and 4-1BB signaling on T cells and additively targeting CD19 and PD-L1 expressed on malignant cells. Preclinical studies showed GNC-038 has robust anti-malignant cell activity. Considering its favorable tolerance and pharmacokinetics in cynomolgus monkeys, we developed a phase I study to investigate GNC-038 for the treatment of relapsed/refractory non-Hodgkin lymphoma (NHL) and relapsed/refractory acute lymphoblastic leukemia (ALL).

Mechanisms of action



Summaries

- GNC-038 markedly drives the proliferation and differentiation of CD4⁺/CD8⁺ T cells *in vitro*.
- GNC-038 induces a significant increase in the counts of IFN- γ , granzyme-B and several other cytokines *in vitro*.
- GNC-038 effectively drives T cell mediated killing of malignant B cells *in vitro*, at levels similar to Blinatumomab.
- GNC-038 induces greater PBMC proliferation and higher cytokine release in donors with high frequencies of PD-1 positive T cells compared to Blinatumomab, suggesting beneficial proliferation of effector cells may be achieved in patients with more exhausted/effector polarized T cell phenotypes (ref 1,2).
- GNC-038 can additively target PD-L1 on CD19 low cancer cells, which represent a clonal resistant phenotype after single antigen CD19-targeted therapies.

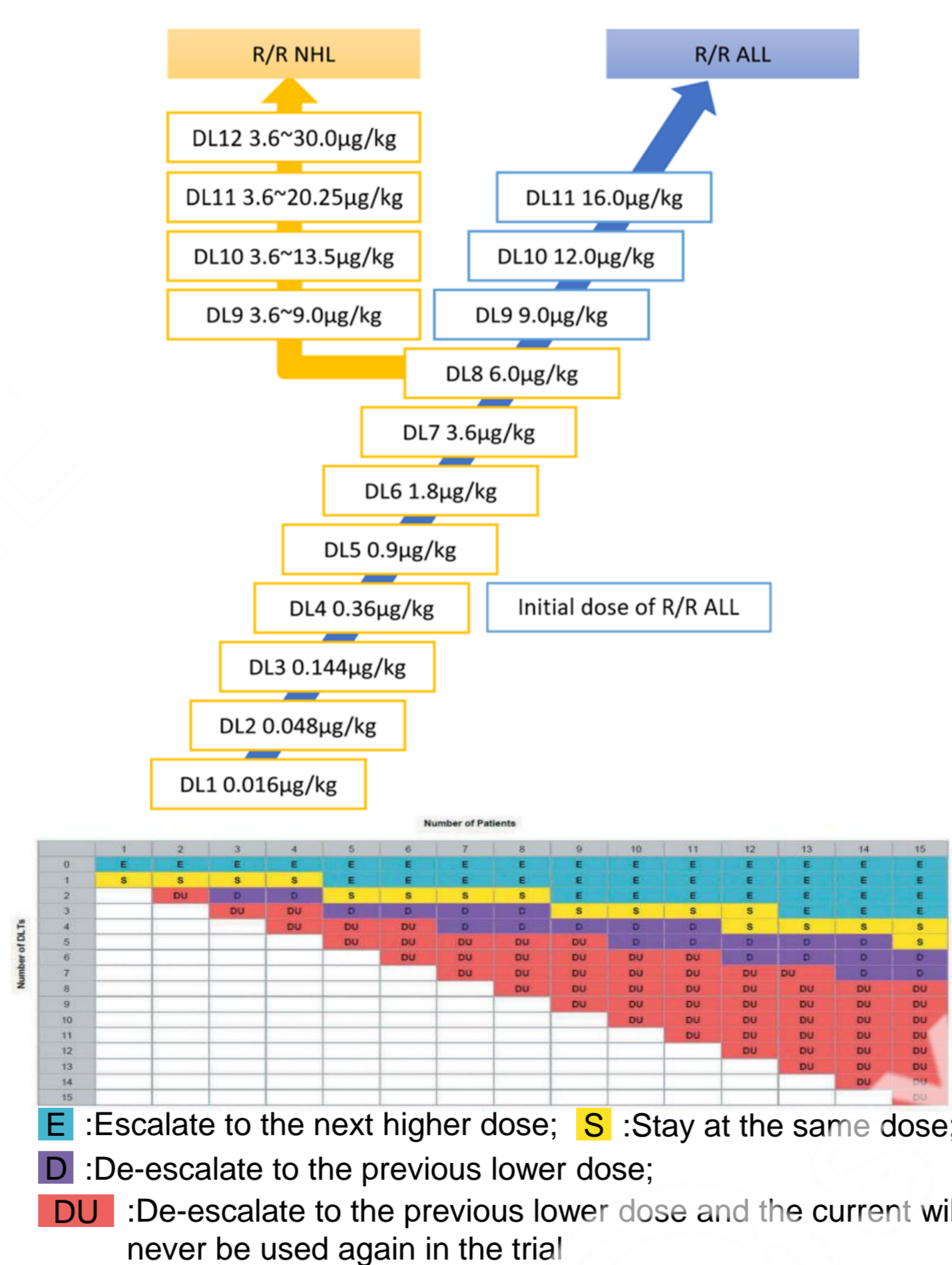
Study design

Dose-escalation phase (Ia)

In the escalation phase, R/R-NHL patients will receive GNC-038 (0.016-6 μ g/kg/d) as continuous intravenous (civ) infusion in 8-week treatment. The further escalation will be conducted with step-up dosing: civ infusion of 3.6 μ g/kg/d GNC-038 was administered on week 1 followed by higher doses on subsequent 7 weeks (9, 13.5, 20.25 or 30 μ g/kg/d). R/R-ALL patients will receive GNC-038 by civ infusion within 8 weeks and the escalation in range of 0.36-16 μ g/kg/d.

Dose-expansion phase (Ib)

In the dose-expansion phase, several dosages will be chosen for further investigation in specific tumors based on the previous phase.



Summary

- GNC-038 is the first tetra-specific antibody which was approved for clinical trials and trial in progress support potential safety and strong signals of efficacy. Clinical trial information: NCT04606433
- We have begun the QW regimens dose escalations in other studies: NCT05623982, NCT05627856, NCT05485753, NCT05192486

Key eligibility criteria

Key inclusion criteria

- Age: \geq 18 years old.
- Expected survival time \geq 3 months.
- Patients with histologically or cytologically confirmed relapsed refractory non-Hodgkin lymphoma (R/R NHL), who had relapsed after or failed to respond to at least two prior treatment regimens.
- Patients with histologically or cytologically confirmed relapsed refractory acute lymphoblastic leukemia (R/R ALL), with any of the following:
 - no response after more than 6 weeks or 2 cycles of induction chemotherapy or
 - a second or more recurrence of bone marrow or
 - relapsed or refractory after at least 1 cycle of salvage therapy or
 - relapsed or refractory of autologous hematopoietic stem cell transplantation (auto-HSCT).
- Physical status score ECOG \leq 2.

Key exclusion criteria

- Patients who received major surgery within 28 days prior to administration of the drug or planned to undergo major surgery during the study period.
- Defined as \geq Grade 3 pulmonary diseases according to NCI-CTCAE v5.0; Patients with present or history of interstitial lung disease (ILD).
- Systemic serious infections occurred within 1 week before screening.
- Active tuberculosis.
- People with active autoimmune disease, or a history of autoimmune disease.
- R/R NHL or R/R ALL that were combined with other malignant tumors within 5 years prior to the first administration of the drug.
- HBsAg positive; HBcAb positive and HBV-DNA detection \geq lower limit of detection value; HCV antibody positive and HCV-RNA \geq lower limit of detection value; HIV antibody positive.
- A history of severe cardiovascular and cerebrovascular diseases.
- Patients with central nervous system invasion.
- Previous recipients of organ transplantation or allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Objectives and outcome measures

Objectives	Endpoints
Primary	Primary
To evaluate the tolerance and safety of GNC-038 in patients with R/R-NHL and R/R-ALL; To determine the MTD (or MAD), DLT of GNC-038 and doses in phase Ib trial (Phase Ia).	1. Dose limiting toxicity (DLT)
To further evaluate the tolerance and safety of GNC-038 in patients with R/R-NHL and R/R-ALL and determine the RP2D of GNC-038 (Phase Ib).	2. Maximum tolerated dose (MTD) or maximum administrated dose (MAD)
Secondary	Secondary
To obtain pharmacokinetics, immunogenicity and early clinical efficacy of GNC-038 in patients with R/R-NHL and R/R-ALL.	3. Treatment-Emergent Adverse Event (TEAE)
Exploratory	Exploratory
To assess relationships among effect, biomarkers, ADA and pharmacodynamics.	4. The recommended dose for future clinical study
	1. Pharmacokinetics: C _{max} , C _{ss} , T _{max} , T _{1/2} , AUC _{0-inf} , AUC _{0-t} , CL
	2. Immunogenicity: incidence and titer of ADA, incidence and titer of Nab
	3. Clinical efficacy: ORR, DCR, PFS, DOR, and OS
	4. Adverse Events of Special Interest (AESI)
	1. The expression level of biomarkers
	2. Lymphocyte subpopulation, release of cytokines, receptor occupancy
	3. Pharmacological tests of immune cells from peripheral blood

Acknowledgments

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References

- Riches et al. T cells from CLL patients exhibit features of T-cell exhaustion but retain capacity for cytokine production. *Blood* 2013
- Roufaiel et al. Impaired T-cell function in B cell lymphoma: A direct consequence of events at the immunological synapse? *Frontiers in Immunology* 2015