TPS2668

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

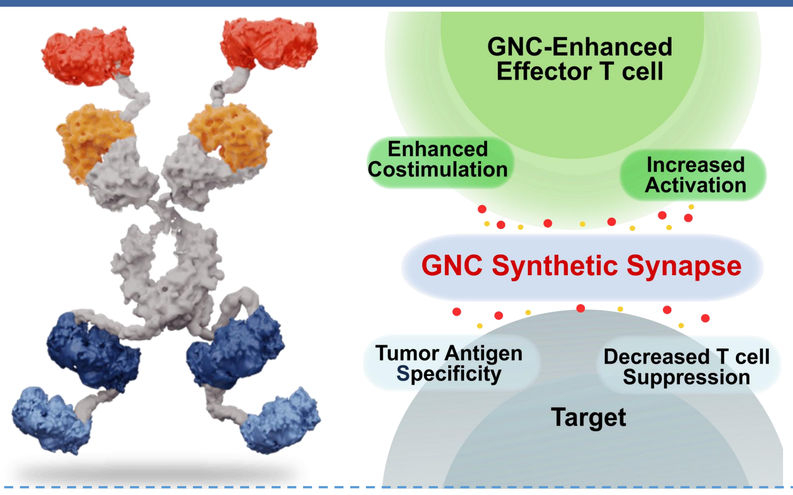
Jianxiang Wang [1], Junyuan Qi [2], Wenyu Li [3], Zhimin Zhai [4], Ping Li [5], Wen Zou [6], Muran Ding [7], Xue Yang [6], Rong Wang [6], Wanjing Guo [6], Sa Xiao [6], Jahan S. Khalili [8], Hai Zhu [8], Martin Sebastian Olivo [8], Yi Zhu [6, 7, 8]

[1] Institute of Hematology, Chinese Academy of Medical Sciences, Tianjin, China; [2] Blood Institute of the Chinese Academy of Medical Sciences, Tianjin, China; [3] Department of Lymphoma, Guangdong Provincial People's Hospital(Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong 510080, China; [4] Anhui Medical University Second Affiliated Hospital, Anhui, China; [5] School of Medicine, Tongji Hospital of Tongji University, Shanghai, China; [6] Baili-Bio (Chengdu) Pharmaceutical Co., Ltd. Chengdu, China; [7] Sichuan Baili-pharmaceutical Co., Ltd., Chengdu Sichuan, China; [8] SystImmune, Inc. Redmond, WA.

Background

Bispecific T cell engagers can mediate single antigen-specific cell cytolysis, 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 (αCD19, αCD3, αPD-L1, and α4-1BB). 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 additivity target PD-L1 on CD19 low cancer cells, which represent a clonal resistant phenotype after single antigen CD19-targeted therapies.

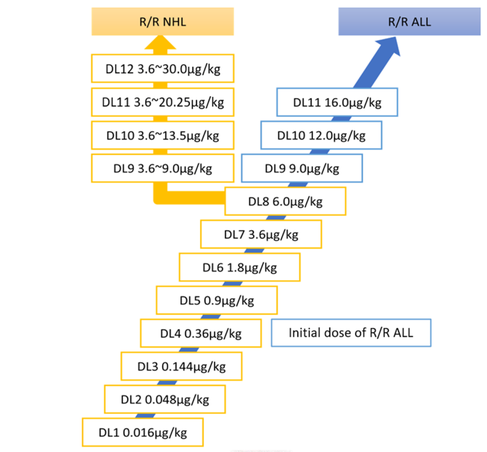
Study design

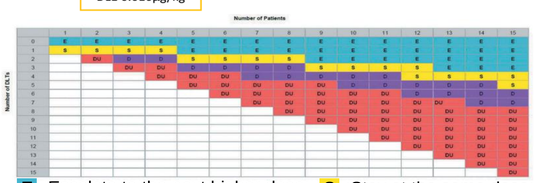
Dose-escalation phase (Ia)

In the escalation phase, R/R-NHL patients will receive GNC-038 (0.016-6 μg/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 μg/kg/d GNC-038 was administered on week 1 followed by higher doses on subsequent 7 weeks (9, 13.5, 20.25 or 30 μg/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 μg/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.





E :Escalate to the next higher dose; S :Stay at the same dose;
D :De-escalate to the previous lower dose;
DU :De-escalate to the previous lower dose and the current will never be used again in the trial

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

1. Age: ≥18 years old.
2. Expected survival time ≥ 3 months.
3. 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.
4. 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).
5. Physical status score ECOG ≤2.

Key exclusion criteria

1. Patients who received major surgery within 28 days prior to administration of the drug or planned to undergo major surgery during the study period.
2. Defined as ≥ Grade 3 pulmonary diseases according to NCI-CTCAE v5.0; Patients with present or history of interstitial lung disease (ILD).
3. Systemic serious infections occurred within 1 week before screening.
4. Active tuberculosis.
5. People with active autoimmune disease, or a history of autoimmune disease.
6. 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.
7. HBsAg positive; HBcAb positive and HBV-DNA detection ≥ lower limit of detection value; HCV antibody positive and HCV-RNA≥ lower limit of detection value; HIV antibody positive.
8. A history of severe cardiovascular and cerebrovascular diseases.
9. Patients with central nervous system invasion.
10. 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) 2. Maximum tolerated dose (MTD) or maximum administrated dose (MAD)
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).	3. Treatment-Emergent Adverse Event (TEAE) 4. The recommended dose for future clinical study
Secondary	Secondary
To obtain pharmacokinetics, immunogenicity and early clinical efficacy of GNC-038 in patients with R/R-NHL and R/R-ALL.	1. Pharmacokinetics: Cmax, Css, Tmax, T1/2, AUC0-inf, AUC0-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)
Exploratory	Exploratory
To assess relationships among effect, biomarkers, ADA and pharmacodynamics.	1. The expression level of biomarkers 2. Lymphocyte subpopulation, release of cytokines, receptor occupancy 3. Pharmacological tests of immune cells from peripheral blood

Acknowledgments

We thank all the patients and their families for their participation.
We also thank all the investigators, study nurses, and other study staffs for their contributions.

References

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

Poster presented at the American Society of Clinical Oncology 2023 Annual Meeting. June 3, 2023, Chicago. Developmental Therapeutics—Immunotherapy.