Abstract

B cell malignancies treated with CD19-directed immunotherapies can relapse, in some cases due to clonal selection for reduced CD19 antigen expression or enhancement of immunoresponsive phenotypes. Here we demonstrate that a Guidance and Navigation Control (GNC) tetra-specific antibody, GNC-038, binds to CD19, CD3, PD-L1, and 4-1BB and mediates cytolysis of human leukemia and lymphoma cells by T cells.

Redirected T cell cytolytic (RTCC) occurs in the presence of GNC-038 (Emfizamab), resulting in the killing of CD19+ leukemia and lymphoma cell lines. The cytolytic functions induced by GNC-038 are similar to Blinatumomab in vitro, as indicated by T cell degranulation and production of IFN-gamma. Human T cells in PBMC exposed to GNC-038 in vitro proliferate in a dose-dependent fashion. Proliferation is further enhanced upon rechallenge with leukemia target cells. Proliferation of T cells from individuals with higher PD-1+ and Effector polarized compartments is enhanced by GNC-038 compared to Blinatumomab. To evaluate the contribution of each binding domain of GNC-038 in mediating RTCC function, versions of GNC-038 were prepared, replacing each antigen binding domain with anti-FITC binding domains. Under assay conditions using PBMC for RTTC toward the CD19+ target cell line Nalm-6, the results demonstrate the contribution of each domain to the overall, anti-leukemic cytolytic activity.

To evaluate the potential for GNC-038 to mediate cytokine release syndrome, the molecule is evaluated in soluble, and plate bound formats in the presence of PBMC and CD19+ leukemia target cells. In comparison to Blinatumomab, the production of cytokines is comparable, with some notable differences. PBMC exposed to GNC-038 for 48 hours produced more IFN-y, IL-2 and TNF-α, while showing no significant difference in production of IL-6. Based on these results, the primary indicator of CRS, IL-6, did not suggest increased risk compared to Blinatumomab, while the type of T cell activity induced by GNC-038 in PBMC with leukemia cells is distinct.

Collectively, the GNC-038 represents a class of multi-specific and multi-modal immune cell engagers with potential to mediate CD19+ cancer killing, while also increasing the T cell compartment’s therapeutic potential to respond to T cell redirection upon subsequent cycles of therapy. The clinical phase I study of GNC-038 is under way and the available data exhibit strong signals of efficacy with acceptable tolerability.

GNC-038 specifically binds target antigens and exhibits anti-tumor activity in vivo

GNC-038: Tetra-specific T cell engager

GNC-Enhanced Effector T cell

GNC Synthetic Synapse

Tumor Antigen Specificity

Increasing Cytotoxicity

Decreasing T cell Suppression

Target

GNC-038 induces unique cytokine release profile and higher threshold of IL-6 production relative to Blinatumomab Biosimilar

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1st tetra-specific antibody therapy in human trials

GNC-038 exhibits cytolytic function against multiple malignant B cell lines

4-1bb null

GNC-038

Agonistic 4-1bb domain modulates effector phenotype in vitro

Elevated Ki-67 and 4-1bb expression is observed in presence of 4-1bb domain.

Summary

- GNC-038 effectively drives T cell mediated killing of malignant B cells in vitro and in vivo models.
- GNC-038 induces greater PBMC proliferation in the presence of target cells in donors with higher proportions of PD-1+ T cells, suggesting beneficial proliferation of effector cells may be achieved in donors with more exhausted/effector polarized T cell phenotype (ref 1,2).
- GNC-038 4-1bb domain polarizes T cells towards activated, proliferative 4-1bb+ T cells.
- GNC-038 induces cytokine profile linked to anti-cancer effector function with GNC treatment.
- Inflammatory cytokine profile does not suggest increased CRS risk.
- Concentration at which measurable cytokine is produced is greater than observed EC50 concentration.

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References

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