2021 ESMO congress

965MO

GTB-3550 tri-specific killer engager safely activates and delivers IL-15 to NK cells, but not T-cells, in immune suppressed patients with advanced myeloid malignancies, a novel paradigm exportable to solid tumors expressing Her2 or B7H3

J.S. Miller[1], E.D. Warlick[1], R. Wangen[2], N. Zorko[3], P. Hinderlie[1], D. Lewis[1], D.A. Vallera[4], M. Felices[1]

[1] Medicine, Masonic Cancer Center - University of Minnesota, Minneapolis, MN, USA, [2] Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA, [3] Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA[4] Radiation Oncology, Masonic Cancer Center - University of Minnesota, Minneapolis, MN, USA

Background

Refractory cancers exhibit profound tumor-induced immune suppression. IL-15, the homeostatic factor stimulating NK cells and T-cells, has shown little antitumor activity as a monotherapy and exhibits dose limiting toxicities. We hypothesized that simultaneous targeted delivery of IL-15 and cancer antigen directed NK cell killing would restore a patient's endogenous NK cells from tumor induced immune suppression. We developed a novel Tri-Specific Killer Engager protein therapeutic, GTB-3550 TriKE™, comprised of two engagers targeting CD16 on NK cells, CD33 on myeloid malignancies, and an IL-15 linker.

Methods

Relapsed/refractory CD33+ malignancies were treated with three consecutive weeks of GTB-3550 (5-150 mcg/kg/day) by continuous infusion (CI x 4 days) in a phase I study (NCT03214666). Immune monitoring was assessed. Preclinically, a second generation TriKE using a single domain camelid (cam) anti-CD16, IL-15 and targeting Her2 or B7H3 was tested.

Results

GTB-3550 administered at >10 times the molar equivalent MTD of rhIL-15 was found to be safe. All lymphocytes decreased from blood during CI egressing into tissues with a dose-dependent proliferative rebound after 3 days of rest. After week 2 and 3 of CI, almost all NK cells were proliferating (Ki-67+) with little proliferation of CD4 or CD8 T-cells. GTB-3550 rescued patient's NK cells from immune suppression resulting in cells that were highly functional, predominantly CD16+, and retained enhanced killing for weeks after CI was discontinued. Preclinically, second generation TriKEs against Her2 and B7H3 showed the same targeted delivery of IL-15 to NK cells, in vitro activity to relevant antigen expressing targets, rescue of tumor-induced immune suppression from blood of advanced cancer patients and in vivo activity in xenogeneic models of human tumor.

Conclusions

GTB-3550 TriKE given as a monotherapy safely induced a sustained functional expansion of endogenous NK cells with anti-tumor activity in advanced AML and MDS patients treated with at least 25 mcg/kg/day. Second generation solid tumor TriKE therapeutics against HER2 and B7H3 will be tested clinically next year.

Clinical trial identification

NCT03214666.

Legal entity responsible for the study

The authors.

Funding

NIH, GT Biopharma.

Disclosure

J.S. Miller: Financial Interests, Personal and Institutional, Advisory Board, Consulting and reserach support: GT Biopharma. D.A. Vallera: Financial Interests, Personal and Institutional, Funding: GT Biopharma. M. Felices: Financial Interests, Personal and Institutional, Research Grant: GT Biopharma. All other authors have declared no conflicts of interest.