Title: A First in human clinical trial to assess the anti-IL18 BP antibody, COM503 (GS-0321) in Participants with Advanced Solid Malignancies

Authors: Manish R Sharma[1], David Sommerhalder[2], Drew Rasco[3], Daniel Vaena[4], Bruno Bockorny[5], Assaf Menachem[6], Pierre Ferre[7], Eran Ophir[6], Ilana Lorber[6], Michelle Mahler[6]

1. START Midwest, Grand Rapids, MI; 2 Next Oncology, San Antonio, TX; 3 START, San Antonio, TX; 4. West Cancer Center Memphis, TN; Beth Israel Medical Center, Boston; 6. Compugen Ltd., Holon, Israel; 7. Compugen Ltd., Toulouse, France.

Background:

Conventional cytokines have limited anti-cancer efficacy mostly due to narrow therapeutic window and systemic adverse effects [1]. IL-18 is an inflammasome induced proinflammatory cytokine that activates T and NK cells and stimulates IFNγ production [2,3]. The activity of IL-18 is naturally blocked by a high affinity endogenous binding protein (IL-18BP) [2], which is induced in response to IFNγ upregulation as a negative feedback mechanism [4]. An anti-mouse IL-18BP Ab induces potent anti-tumor responses either alone or in combination with anti-PD-L1 Ab coupled with pronounced TME-constrained immune modulation [5]. This is in contrast to systemically administered therapeutic cytokines, which generate a non-localized inflammatory response [6]. COM503 (also known as GS-0321), a high-affinity anti-IL -18BP Ab, as monotherapy as well as in combination with anti-PD-1 antibodies has been shown to induce human T and NK cell responses in vitro [5] and is currently undergoing clinical evaluation.

Methods: NCT06759649 is an ongoing Phase 1 dose escalation and dose expansion trial to assess the safety and tolerability of COM503 as monotherapy and in combination therapy with zimberelimab (anti-PD-1) in participants with advanced solid malignancies. Enrollment of approximately 200 participants is planned across part 1, the dose escalation and backfill cohorts and part 2, the expansion cohorts. The primary objectives are to assess the safety and tolerability of COM503 as monotherapy and in combination with zimberelimab and identify the maximum tolerated dose / maximum administered dose and/or recommended Phase 2 dose. Inclusion criteria: Participants ≥ 18 yr with histologically/cytologically confirmed advanced recurrent or metastatic solid tumor malignancy. In part 1 participants must have had disease progression on or following all available standard of care (SOC) therapies known to confer clinical benefit. In part 2 participants may be enrolled following disease that has progressed after at least 1 available standard therapy; or for whom standard therapy has proven to be ineffective or intolerable or is considered inappropriate; or for whom a clinical trial of an investigation agent is a recognized SOC. Participants must have solid tumor measurable per Response Evaluation Criteria in Solid Tumors version 1.1. Exclusion Criteria include therapy with immunosuppressive doses of systemic medications, known active central nervous system metastases and/or leptomeningeal disease, and active and clinically relevant bacterial, fungal, or viral infection that is not controlled or requires systemic antibiotics, antifungals, or antivirals, respectively.

References:

1. Schwartz RN, Stover L, Dutcher JP. Managing toxicities of high-dose interleukin-2. Oncol Williston Park N. 2002 Nov;16(11 Suppl 13):11–20.

2. Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. Front Immunol. 2013 Oct 8;4:289.

3. Swain SL. Interleukin 18: Tipping the Balance towards a T Helper Cell 1 Response. J Exp Med. 2001 Aug 6;194(3):F11–4.

4. Paulukat J, Bosmann M, Nold M, Garkisch S, Kämpfer H, Frank S, Raedle J, Zeuzem S, Pfeilschifter J, Mühl H. Expression and release of IL-18 binding protein in response to IFN-gamma. J Immunol Baltim Md 1950. 2001 Dec 15;167(12):7038–43.

5. Menachem A, Alteber Z, Cojocaru G, Fridman Kfir T, Blat D, Leiderman O, Galperin M, Sever L, Cohen N, Cohen K, Granit RZ, Vols S, Frenkel M, Soffer L, Meyer K, Menachem K, Galon Tilleman H, Morein D, Borukhov I, Toporik A, Perpinial Shahor M, Tatirovsky E, Mizrachi A, Levy-Barda A, Sadot E, Strenov Y, Eitan R, Jakobson-Setton A, Yanichkin N, Ferre P, Ophir E. Unleashing Natural IL18 Activity Using an Anti-IL18BP Blocker Induces Potent Immune Stimulation and Antitumor Effects. Cancer Immunol Res. 2024 Jun 4;12(6):687–703.

6. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. Nat Rev Clin Oncol. 2022 Apr;19(4):237–53.