NON-CLINICAL EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF A NOVEL BI-FUNCTIONAL ANTI-CD73-TGF β RII-TRAP MOLECULE IN COMBINATION WITH IMMUNE CHECKPOINT THERAPY

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<http://dx.doi.org/10.1136/jitc-2021-SITC2021.577>

Background A novel murine bi-functional molecule, G04-trap, comprised of an anti-CD73 antibody fused to the extracellular domain of TGF β receptor II, is designed to potently antagonize two prominent immunosuppressive and pro-tumorigenic pathways present across a variety of cancer types. Inhibition of both CD73-adenosine and TGF β pathways is expected to create favorable conditions within the tumor microenvironment and restore antitumor immune responses.

Methods G04-trap was evaluated in Detroit562, MC38, and Hepa1-6 efficacy tumor models. Tumor growth inhibition (TGI) was determined when ≥ 9 animals were alive in each group. Tumor-bearing mice received isotype control (200 microgram), G04-trap (246 microgram), anti-PD-(L)1 (200 microgram) or G04-trap + anti-PD-(L)1 twice per week for 3 weeks. Pharmacokinetic (PK) and pharmacodynamic (PD) assessment was performed on MC38 tumor-bearing mice dosed with 3 mg/kg, 10 mg/kg, or 30 mg/kg G04-trap. Plasma and tumor PK, CD73 target occupancy on T cells, plasma TGF β , plasma free-sCD73, and tumor CD73 activity were measured after a single dose administration of G04-trap.

Results Administration of G04-trap to mice harboring TGF β -dependent human pharyngeal Detroit562 xenograft tumors led to a dose-dependent anti-tumor response (83% TGI, at 246 microgram vs. isotype control on day 21). In addition, treatment with G04-trap in combination with immune checkpoint inhibition showed anti-tumor activity in MC38 and Hepa1-6 syngeneic mouse models. In MC38 on day 18, there was a statistically significant TGI with G04-trap + anti-PD-L1 (99% TGI vs. isotype control or 98% TGI vs. anti-PD-L1 alone). A more modest effect was observed in Hepa1-6, with 47% TGI in mice receiving G04-trap + anti-PD-1 vs. isotype control on day 27. To further interpret the efficacy observed in the MC38 tumor model, we performed in-depth PK/PD analysis. Intravenous administration of G04-trap at 3-30 mg/kg resulted in 10% tumor-to-plasma exposure ratio. Full TGF β target coverage and full CD73 target occupancy on blood T cells was sustained for >3 days, supporting a BIW dosing schedule in non-clinical studies. Treatment also resulted in a dose-dependent inhibition of CD73 activity in tumors. In contrast to cellular CD73, a dose-dependent increase in free sCD73 concentration above baseline was measured in the plasma, consistent with previous reports evaluating anti-CD73 antibodies [1].

Conclusions Dual inhibition of CD73 and TGF β in combination with immune checkpoint blockade resulted in enhanced anti-tumor activity in xenograft and syngeneic tumor models. These results suggest that further exploration of this approach is warranted.

REFERENCES

1. Zhao Y, Gu H, Postelnek J, DeMichele M, Yuan L, Zhang YJ, et al. Fit-for-purpose protein biomarker assay validation strategies using hybrid immunocapture-liquid chromatography-tandem-mass spectrometry platform: Quantitative analysis of total soluble cluster of differentiation 73. *Anal Chim Acta*. 2020;1126:144–53.