Abstracts

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

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Background A novel murine bi-functional molecule, G04-trap, comprised of an anti-CD73 antibody fused to the extracellular domain of TGFβ 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 TGFβ 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 TGFβ, 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 TGFβ-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 TGFβ 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 TGFβ 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