CHARACTERIZATION OF PERIPHERAL BIOMARKERS OF GS-1423, A FIRST IN CLASS BIFUNCTIONAL ANTI-CD73-TGFβ RECEPTOR II- TRAP MOLECULE, IN A PHASE 1 DOSE ESCALATION STUDY IN PATIENTS WITH ADVANCED SOLID TUMORS

¹Marianna Zavodovskaya*, ²Anthony Tolcher, ³Michael Gordon, ⁴James Strauss, ⁵Kathleen Mahoney, ¹Ping Cheng Yi, ¹Rick Sorensen, ⁶Xiaoyun Yang, ¹Kai-Wen Lin, ¹Biao Li, ¹Anna Seto, ¹Matthew Peach, ¹Audrey Goddard, ¹Tianling Chen, ¹Juliane Jürgensmeier. ¹Gilead Sciences, Woodside, CA, USA; ²NEXT Oncology, San Antonio, TX, USA; ³HonorHealth Research Institute, Scottsdale, AZ, USA; ⁴Mary Crowley Research Center, Dallas, TX, USA; ⁵Beth Israel Deaconess Medical Center, Boston, MA, USA; ⁶Roche, South San Francisco, CA, USA

Background GS-1423 is a first-in-class bifunctional molecule comprised of an anti-CD73 antibody fused to the extracellular domain of TGFβ receptor II (TGFβRII). GS-1423 is designed to inhibit CD73-mediated adenosine production and neutralize active TGFβ within the tumor microenvironment. Dual antagonism of these 2 broadly immunosuppressive barriers is anticipated to facilitate productive anti-tumor immunity.

Methods This open label Phase 1a study (NCT03954704) evaluated the safety, tolerability, and pharmacokinetics of GS-1423. Exploratory biomarkers included the evaluation of the inhibition of GS-1423 targets, i.e. CD73 and TGFβ, in the periphery. Biomarker assessments were performed in serial blood samples from patients receiving GS-1423 every two weeks (Q2W). Biomarker assays, unless otherwise stated, were custom built and qualified to measure the following: 1) TGF-beta 1/2/3 (Luminex, Bio-Rad) in platelet poor plasma, 2) CD73 target occupancy (TO) on B and CD8 T cells in whole blood, 3) free soluble CD73 (sCD73) not bound to GS-1423, and 4) sCD73 activity in platelet poor plasma. Biomarker values were plotted longitudinally by patient and by dose.

Results A dose dependent decrease in TGF-beta 1/2/3 in plasma of patients was observed on treatment. There was no detectable TGFβ at the 20 mg/kg dose level and above at 2 hours post first dose and for the duration of the Q2W dosing interval. A dose dependent increase in CD73 TO on B and CD8 T cells was also observed with treatment, and complete TO was achieved at 20 mg/kg and above at 2 hours post first dose for the duration of the Q2W dosing interval. Free sCD73 decreased at 2 hours post first dose, while remaining above the lower limit of quantitation, and then increased above baseline after 24 hours post-dose at the 3 mg/kg dose level and above. The sCD73 activity in blood correlated with changes in free sCD73 levels.

Conclusions Blood biomarker analyses of GS-1423 in patients with advanced solid tumors demonstrated undetectable soluble TGFβ1/2/3 and complete TO of CD73 on B and T cells at the 20 mg/kg dose level and above. The mechanism underlying the increase in sCD73 following GS-1423 treatment remains to be elucidated.

Ethics Approval The study obtained ethics approval from the IRB/IEC and all participants gave informed consent before taking part in the study.

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