488 PHASE 1 TRIAL OF FIRST-IN-CLASS ANTI-CD96 MONOCLONAL ANTIBODY INHIBITOR, GSK6097608, MONOTHERAPY AND COMBINATION WITH ANTI–PD-1 MONOCLONAL ANTIBODY, DOSTARLIMAB, IN ADVANCED SOLID TUMORS

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Background The CD226 axis plays an important role in natural killer (NK)- and T-cell biology and cancer immune surveillance.[1–4] CD226 is an immune costimulatory molecule expressed on T and NK cells, which binds to its ligands, CD155 and CD112, on tumors and antigen-presenting cells to stimulate an immune response. The immune checkpoints TIGIT, CD96, and PVRIG compete with CD226 binding to CD155 and CD112 to suppress immune activation. Combinations of agents that target these checkpoints and PD(L)1 could augment CD226-mediated antitumor activity. Inhibition or deletion of CD96 resulted in antitumor activity in syngeneic mouse tumor models alone and in combination with PD-1 inhibition.[5 6] GSK6097608 is a monoclonal antibody that blocks CD96, enhancing CD155-CD226 NK/T-cell activation.[7] Based on these results, GSK6097608 is being explored alone and in combination with the anti–PD-1 monoclonal antibody, dostarlimab, in a phase 1, dose-escalation trial.[8]

Methods Adults (≥18 years of age) with histological or cytological documentation of locally advanced, recurrent, or metastatic solid malignancy that has progressed after standard therapy for the specific tumor type are eligible. Prior anti–PD-1 therapy is allowed. Other key inclusion criteria include Eastern Cooperative Oncology Group performance status 0–1, adequate organ function, and life expectancy of ≥12 weeks. Patients with prior bone marrow or solid organ transplant, uncontrolled central nervous system metastases, or active autoimmune disease are ineligible. In this open label, nonrandomized, sequential assignment trial (N≈100; NCT04446351), patients will receive intravenous infusion GSK6097608 every 3 weeks as monotherapy alone or in combination with intravenous dostarlimab (every 3 weeks for 4 doses and every 6 weeks thereafter). Based on the safety, pharmacokinetics, and pharmacodynamics of monotherapy, the combination arm will be opened. The primary endpoints are dose-limiting toxicities and adverse events. Secondary endpoints include abnormal laboratory values, cardiac parameters, and vital signs; dose reduction, dose delay, or withdrawal due to adverse events; overall response rate per Response Evaluation Criteria in Solid Tumors version 1.1; and antidrug antibodies against and pharmacokinetic parameters of GSK6097608 and dostarlimab. The trial is actively recruiting patients.

Acknowledgements The authors thank the participating patients, families, investigators, site staff, and colleagues at GlaxoSmithKline (GSK) and 23andMe. Funding for the study was provided by GSK (study 212214). Writing and editorial support, funded by GSK (Waltham, MA, USA) and coordinated by Hasan H. Jamal, of GSK, was provided by MediTech Media.

Trial Registration www.ClinicalTrials.gov, NCT04446351

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Ethics Approval The study was reviewed and approved by the institutional review board and independent ethics committee before the study sites were initiated.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.488