Phase 1 trial of first-in-class anti-CD96 monoclonal antibody inhibitor, GSK6097608, monotherapy and in combination with anti–PD-1 monoclonal antibody, dostarlimab, in advanced solid tumors

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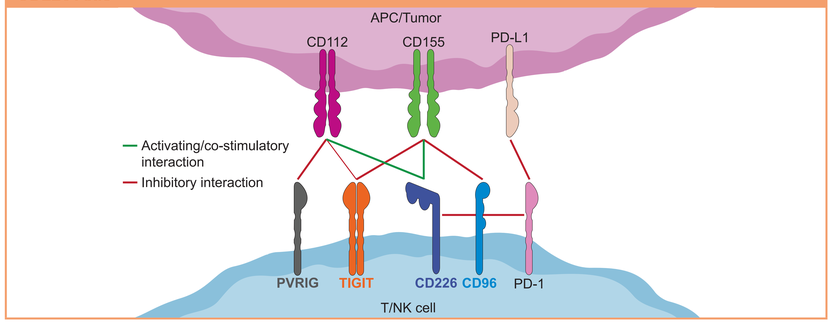
BACKGROUND

CD226 axis

- The CD226 axis plays an important role in NK- and T-cell biology and cancer immune surveillance[1-4]
  - CD226 is an immune costimulatory molecule expressed on T and NK cells
  - CD226 binds to ligands CD155 and CD112 on tumors and antigen-presenting cells and stimulates an immune response
  - The immune checkpoints CD96, TIGIT, and PVRIG compete with CD226 binding to CD155 and CD112 to suppress immune activation
- Growing preclinical (CD96) and clinical (PVRIG and TIGIT) evidence underscore the important roles of CD96, PVRIG, and TIGIT in promoting immune suppression and tumor evasion[3,5-9]

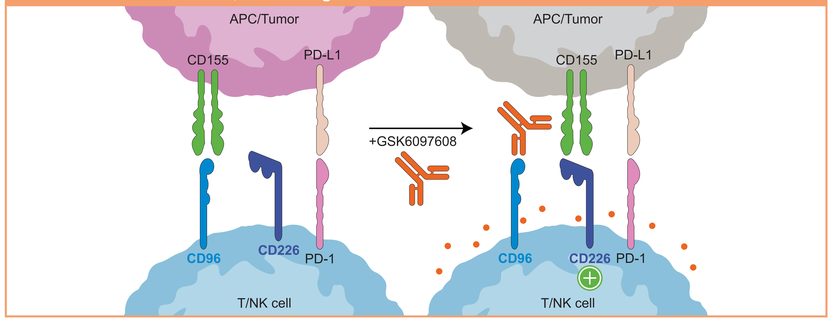
CD226 Axis



CD96

- CD96 is an immune checkpoint that modulates T- and NK-cell activity to promote tumor immune evasion[10,11]
- Similar to the CTLA-4/CD28 pathway, CD96 sequesters a shared ligand (CD155) away from the costimulatory receptor (CD226), effectively attenuating T- and NK-cell antitumor immune responses[11]
  - CD96 also harbors inhibitory signaling domains, suggesting intrinsic immunomodulatory activity
- The immunosuppressive effects of CD96 and expression of CD96 and CD155 across tumor types suggest a broad role in promoting tumor progression and metastasis[5,10-16]
- Preclinical evidence supports targeting CD96, especially in combination with other CD226 axis agents and/or anti–PD-1 antibodies[5-6,17]
- GSK6097608 is a monoclonal antibody that blocks CD96, enhancing CD155-CD226 NK- and T-cell activation[18]
- Blocking CD96 with GSK6097608 potentiates IFN-γ release and anticancer activity by T and NK cells without evidence of target cell depletion[18]

GSK6097608 Blocks CD96, Enhancing CD226 NK- and T-Cell Activation



OBJECTIVE

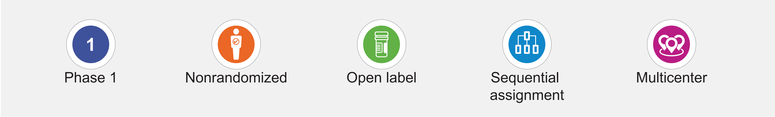
- To explore treatment with GSK6097608, an anti-CD96 monoclonal antibody, alone and in combination with the anti–PD-1 monoclonal antibody, dostarlimab, in a phase 1, dose-escalation trial in solid tumors[19]

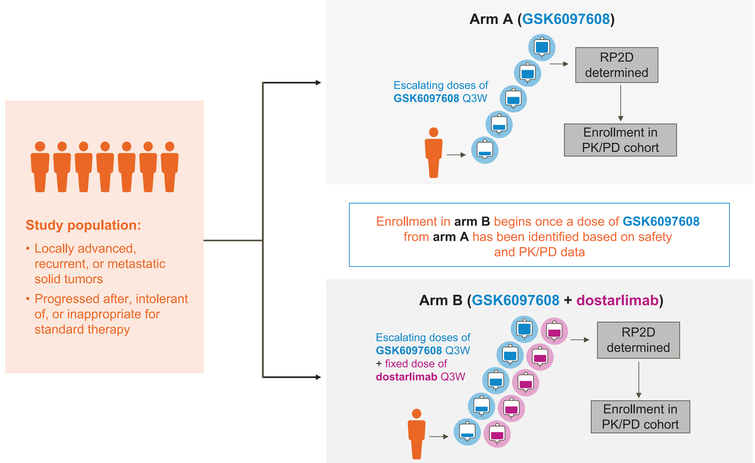
METHODS

Study design

- In this open label, nonrandomized, sequential assignment trial (NCT04446351), patients will receive IV infusion of GSK6097608 every 3 weeks as monotherapy or in combination with IV dostarlimab
  - Patients will be given IV GSK6097608 alone or in combination with IV dostarlimab until disease progression, unacceptable toxicity, death, or withdrawal of consent
  - Based on the safety, pharmacokinetics, and pharmacodynamics of monotherapy, the combination arm will be opened

Study Design





Study population

- Adults (≥18 years old) 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 if the last dose of anti–PD-1 therapy is given ≥4 weeks prior to first dose of study treatment
- Patients with prior bone marrow or solid organ transplant, uncontrolled central nervous system metastases, or active autoimmune disease are ineligible

Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Adults ≥18 years old	• Prior anticancer treatment, including investigational agents, immune checkpoint inhibitiors, (such as PD-(L)1 and CTLA-4 inhibitors), chemotherapy, targeted therapy, and biological therapy, within 4 weeks or 5 half-lives of the drug, whichever is shorter
• Measurable disease per RECIST 1.1	• Prior bone marrow or solid organ transplant
• Histological or cytological documentation of locally advanced, recurrent, or metastatic solid malignancy[a]	• Uncontrolled CNS metastases
• Disease that has progressed after, is intolerant of, or is considered inappropriate for standard therapy	• Active autoimmune disease
• ECOG PS 0 to 1	• Concurrent medical condition requiring use of systemic immunosuppressive treatment
• Adequate organ function	
• Adequate cardiac ejection fraction as measured by echocardiogram	
• Life expectancy of ≥12 weeks	

[a]The PK/PD cohorts are restricted to non-small cell lung cancer, head and neck squamous cell carcinoma, or an alternative immunogenic tumor type with medical monitor approval.

Outcome measures

- The primary endpoint is safety (DLTs and AEs)
- Secondary endpoints include additional safety parameters, ORR, and PK
- The trial is actively recruiting patients

Study Endpoints

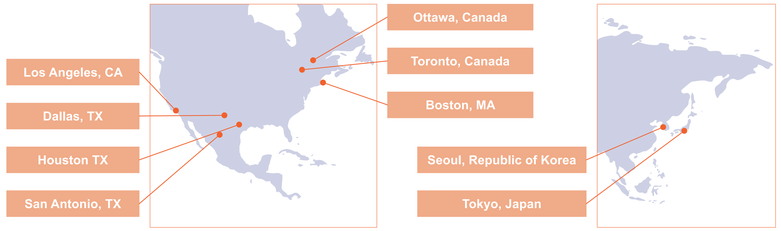
Primary	• Dose limiting toxicities • Adverse events	• Serious adverse events
Secondary	• ORR per RECIST 1.1 • ADAs against GSK6097608 and dostarlimab • PK parameters of GSK6097608 and dostarlimab	• Clinically important changes in laboratory parameters, electrocardiograms, and vital signs • Dose reductions or delay • Withdrawal due to AEs

Current Status

The study is currently open and recruiting.

OPEN

Current Trial Sites



US GSK Clinical Trials Call Center 877-379-3718
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Abbreviations

ADA, antidrug antibody; AE, adverse event; APC, antigen presenting cell; CD, cluster of differentiation; CNS, central nervous system; CTLA-4, cytotoxic lymphocyte T-lymphocyte-associated protein 4; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IFN-γ, interferon gamma; IV, intravenous; mAb, monoclonal antibody; NK, natural killer; ORR, overall response rate; PD, pharmacodynamics; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PK, pharmacokinetic; PVRIG, poliovirus receptor related immunoglobulin domain containing; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

Disclosures

OH: consulting/advisory boards with Aduro, Akeso, Amgen, Beigene, Bioatla, Bristol Myers Squibb, Roche Genentech, GSK, Immunocore, Idera, Incyte, Janssen, Merck, Nextcure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Tempus, and Zelluna; speaker bureau with Bristol Myers Squibb, Novartis, Pfizer, and Sanofi/Regeneron; and contracted research (for institution) with Arcus, Aduro, Akeso, Amgen, Bioatla, Bristol Myers Squibb, CytomX, Exelixis, Roche Genentech, GSK, Immunocore, Idera, Incyte, Ivunce, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Torque, and Zelluna. DB and RE are employees of GSK. LLS: consulting/advisory arrangements with Merck, Pfizer, Celgene, AstraZeneca, Morphosys, Roche, Oncorus, Symphogen, Seattle Genetics, GSK, Voronoi, Arvinas, Tessa, Navire, Relay, Rubius, Janpix, and Daiichi Sanyko; stock ownership of Agios (spouse); leadership position in Treadwell Therapeutics (spouse); and clinical trials support from Novartis, Bristol Myers Squibb, Pfizer, Boehringer-Ingelheim, GSK, Roche/Genentech, Karyopharm, AstraZeneca, Merck, Celgene, Astellas, Bayer, AbbVie, Amgen, Symphogen, Intensity Therapeutics, Mirati Therapeutics, Shattucks, and Avid.

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