A phase I/II study of GSK3145095 alone and in combination with anticancer agents including pembrolizumab in adults with selected solid tumors

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Background

- Pancreatic ductal adenocarcinoma (PDAC) has remained unresponsive to the current generation of immunotherapies. One hallmark of PDAC that contributes to this unresponsiveness is the vast infiltrate of tumor associated macrophages (TAMs)⁴⁻⁵.
- TAMs often correlate with a worse patient prognosis, and are increasingly recognized as key drivers of an immunosuppressive tumor microenvironment (TME) contributing to therapeutic resistance.⁶ For these reasons, immunomodulation of TAMs within the TME is an attractive target for next-generation therapeutics in PDAC.
- Increased receptor-interacting protein kinase 1 (RIP1) expression has been reported in human pancreatic,⁷ hepatocellular,⁸ melanoma,⁹ gallbladder,⁸ and colorectal biopsies,¹⁰ as well as gliomas from resected brain tumors.¹¹ In each of these studies, RIP1 expression correlated with a worse patient prognosis.
- In an unbiased screen, RIP1 was identified as a top gene contributing to resistance to immunotherapy¹².
- In the necrosome, RIP1 kinase activity can drive necroptosis, but also has cell-death independent signaling functions.¹³,¹⁴
- In murine models, RIP1 kinase activity has been shown to reprogram TAMs toward an immunogenic phenotype¹³ and has been reported to drive pancreatic oncogenesis by promoting an immunosuppressive TME.¹³ (Figure 1)

GSK3145095 is a highly selective oral inhibitor of RIP1 kinase.

Here we describe preclinical results supporting the therapeutic potential of targeting RIP1 with a small molecule inhibitor in PDAC (Figure 2), along with the phase I/II study design for GSK3145095 (NCT03681951).

Figure 1. The Necrosome Promotes Pancreatic Oncogenesis¹³

Figure 2. RIP1i Decreases PDAC Oncogenesis¹³

(A) RIP1i extends survival in KPC orthotopic model.
(B) RIP1i sensitizes tumors to anti-PD1 treatment.

Study 205013 Objectives

- The objective of this phase I/II study is to investigate the safety, clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD) of GSK3145095 administered alone and in combination with anticancer agents including pembrolizumab in adult participants with selected advanced solid tumors.

Study 205013 Design

- This is a 4-part, open-label, multicenter study (NCT03681951).

Part 1 GSK3145095 Monotherapy:

- Part 1 (open/recruiting) is being conducted in approximately 30 adults with advanced or metastatic PDAC with escalating doses of GSK3145095.

Part 2 will combine escalating doses of GSK3145095 with 200 mg pembrolizumab and may be conducted in a broader population of selected solid tumors.

Part 3 represents a cohort expansion of Part 2.

Part 4 may investigate the combination of additional anticancer agent(s) with one or more doses of GSK3145095 identified as safe in Part 1.

6 sites (US only) are currently open and actively recruiting for Part 1.

References


Disclosures

D Cohen (Deidre.Cohen@nyulangone.org) declares the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: DC has served as a consultant or advisor for AstraZeneca/MedImmune, Bristol-Myers Squibb (BMS), Celgene, GlaxoSmithKline (GSK), Merck Sharp & Dohme, Taiho Pharmaceutical, and Vicus Therapeutics, and her institution has received funding from BMS, Eisai, and Merck; SP has served as a consultant or an advisor for Celgene, Halozyme, and TYME, and received honoraria from 4D Pharma, and his institution has received funding from BMS, Eisai, and Merck; OH has served as a consultant or advisor for AstraZeneca/MedImmune, Bristol-Myers Squibb, and Viatris, and her institution has received funding from BMS, Eisai, and Merck; SA has served as a consultant or advisor for MedImmune, and her institution has received funding from Janssen, Merck, and Novartis; JS has also received travel, accommodations, and expenses from Cambridge Healthtech Institute and GSK.

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