

PERIO-03: Pressure Enabled Intrapancreatic Delivery of SD-101 With Checkpoint Blockade for Locally Advanced Pancreatic Adenocarcinoma – Initial Safety and Feasibility Experience

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Word Count: 395/400

Background: Immune checkpoint inhibitors (ICI) have not demonstrated clinical benefit in the majority of pancreatic ductal adenocarcinomas (PDAC). Drug delivery challenges due to a high-pressure desmoplastic stroma and myeloid driven immunosuppression are therapeutic barriers. Delivery of SD-101, a class C TLR9 agonist via a Pressure Enabled Drug Delivery (PEDD) system, has been associated with encouraging outcomes in patients with hepatic tumors using hepatic artery infusion. Given the anatomic challenges of intra-arterial delivery for PDAC, we developed a novel pancreatic retrograde venous infusion (PRVI) approach to enable PEDD of SD-101 for locally advanced PDAC (LA-PDAC).

Methods: Patients with LA-PDAC are eligible for enrollment. Oligometastatic disease is permitted. A phase 1 dose-escalation with single agent SD-101 is underway, to be followed by phase 1b of SD-101 PRVI combined with ICI. SD-101 is delivered over 2 cycles (1 dose/cycle), during outpatient PRVI procedures using transhepatic access with the TriSalus Infusion System PEDD device. The PEDD infusion system is inserted into the portal venous system, and then tracked into the target pancreatic vein. Serial blood and tumor biopsies are collected. The primary endpoints are safety and optimal SD-101 dose determination.

Results: We enrolled 3 patients at the lowest (0.5 mg) SD-101 dose. All 3 patients are male (ages 57, 63, and 66). The average tumor size was 2.6 cm (range 1.9-3.6). Two patients remain on study, with one discontinuing due to extra-pancreatic progression. All PRVI procedures were successfully completed, with no safety events related to the infusions. All 3 patients experienced at least one adverse event (AE), with the most common being fatigue, liver function test increases, and decreased platelet count (all minor). The only grade 3-4 AE noted was a single subject with grade 3 hypertension. Two patients had decreased circulating monocytic MDSCs by flow cytometry following SD-101 infusion, and LAG-3 expression increased in 2 of 3 patients among circulating CD8+ T cells. Nanostring analysis of PBMCs demonstrated decreases in genes associated with MDSCs, including NOS2, IL10, and IDO1. Increases in IL2, IL12, and IL15 gene expression were noted. Comparison of pre- and post-SD-101 infusion PDAC tumor specimens revealed decreases in expression of MDSC associated genes including TGFb, ARG1, NOS2, and IL10.

Conclusion: SD-101 PRVI infusions with PEDD were well tolerated in the initial 3 patients. Infusions were associated with potentially favorable immune changes in the periphery and tumors. These findings support continuing with single-agent dose escalation and subsequent combination with systemic CPI.