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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Abstract #647

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 liver 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.

TriSalus Infusion System

Pancreatic Retrograde Venous Infusion (PRVI™) System

The PRVI System with SmartValve technology is an FDA-cleared device for delivery of therapeutics to the peripheral vasculature. This device is being studied for the delivery of SD-101 via the PRVI approach into unresectable pancreatic tumors.

The PRVI System is positioned in the vasculature using standard interventional radiology procedures. The PRVI System isolates the tumor bed and enables pressure measurement during infusion for uniformity of procedural approach.

Pancreatic Retrograde Venous Infusion™ MOA

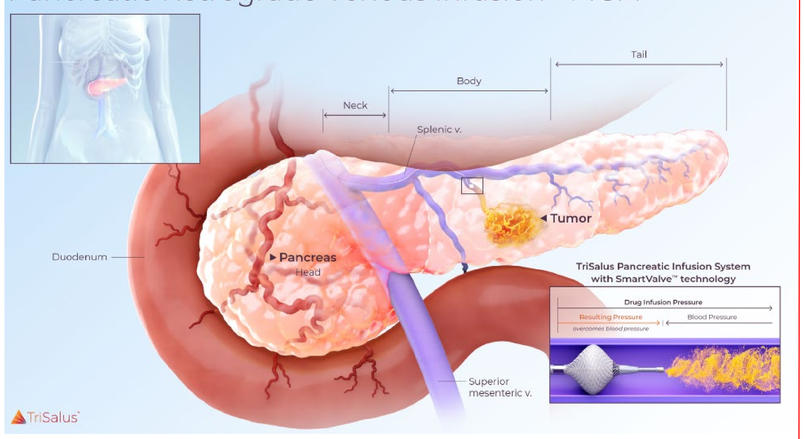
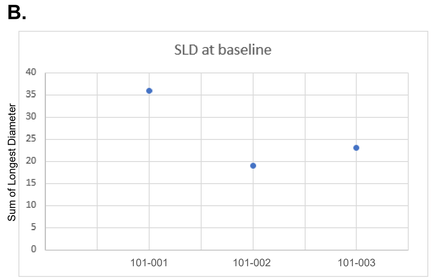


Table 1. Patient Characteristics and Sums of Longest Diameters (SLD) for Primary Pancreatic Lesions at Baseline

A.

Patient Characteristics	n= 3 (%)
Gender	
Female	0
Male	3 (100)
Age (years, range)	57-66
Prior Lines of Therapy	
0	0
1	0
2	0
≥3	3 (100)
N/A	
Number of Lesions at Baseline	
≤10	3 (100)
>10	0
N/A	0
Largest Lesion at BL	
≤50mm	3 (100)
>50mm	0
N/A	0

B.



Summary

- Three patients were enrolled at the lowest (0.5 mg) SD-101 dose.
- All PRVI procedures were successfully completed, with no safety events related to the infusions.
- Comparison of pre- and post-SD-101 infusion PDAC tumor specimens revealed decreases in expression of MDSC associated genes TGFβ, NT5E, ARG1, ROS1, and NOS2.
- NanoString analysis of peripheral WBCs demonstrated increases in pathway scores for lymphocyte activation, cytokine signaling, and chemokine signaling.
- Flow cytometry of peripheral WBCs revealed increases in Ki-67+ CD8 T cells, CD4 T cells, and NK Cells as well as CD69+ CD8 T cells.

Conclusions

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 ICI.

Results

Table 2. Safety Summary

Phase 1 – 0.5mg SD-101 Monotherapy: Adverse Events related to SD-101	
Preferred Term (MedDRA v24.0)	SD-101 0.5 mg n=3
All Grades (events in ≥ 5% of patients), n (%)	
AT LEAST ONE EVENT	3 (100)
Abdominal Pain	1 (33)
Fatigue	2 (67)
Nausea	1 (33)
Vomiting	1 (33)
Platelet Count Decreased	2 (67)
Alanine Aminotransferase Increased	2 (67)
Aspartate Aminotransferase Increased	2 (67)
Anemia	1(33)
Fever	1 (33)
Chills	1 (33)
Alkaline Phosphatase Increased	1 (33)
Hyperthyroidism	1 (33)
Grade ≥ 3 (Events in ≥1 patient), n (%)	
AT LEAST ONE EVENT	1 (33)
Alanine Aminotransferase Increased	1 (33)

Figure 1. Swimmers Plot and Spider Plot

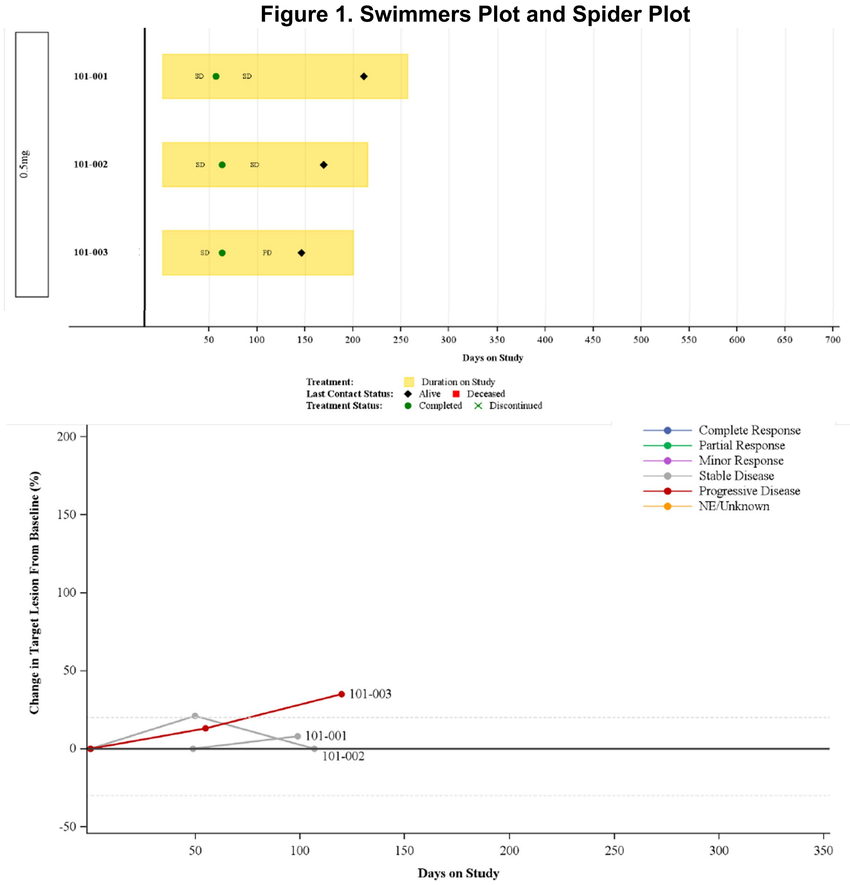


Figure 1. Best available radiographic response and survival times.

Figure 2. CT Scan with Intravenous Contrast Demonstrating Pseudoprogression following SD-101 Infusion Using PRVI and PEDD

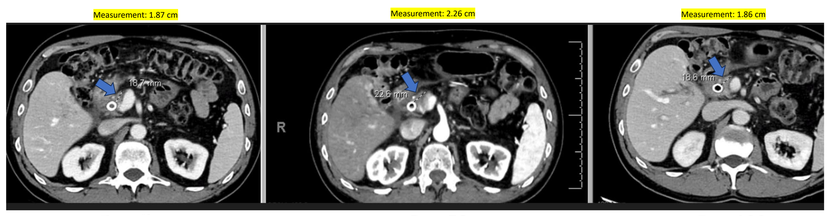


Figure 2. Sequential CT scans with intravenous contrast of patient 101-002

Figure 3. Myeloid Derived Suppressor Cell (MDSC)-Associated Gene Expression Patterns within Tumors

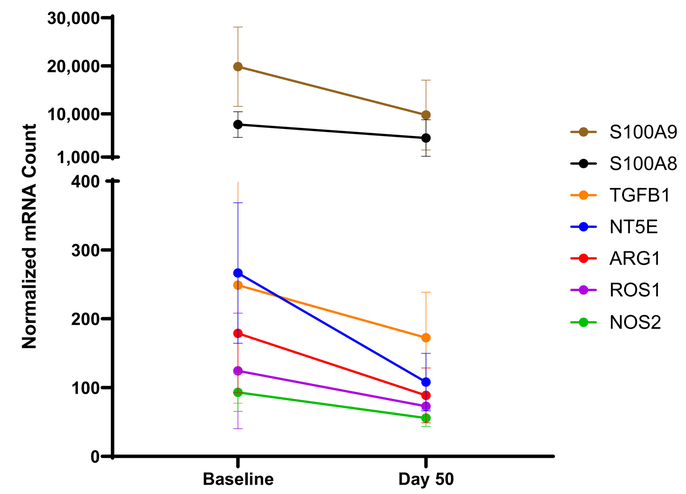


Figure 3. Gene expression levels within tumor biopsies collected at baseline and on Day 57 quantified by NanoString (n=3).

Figure 4. Changes in Pathway Scores for Peripheral WBCs

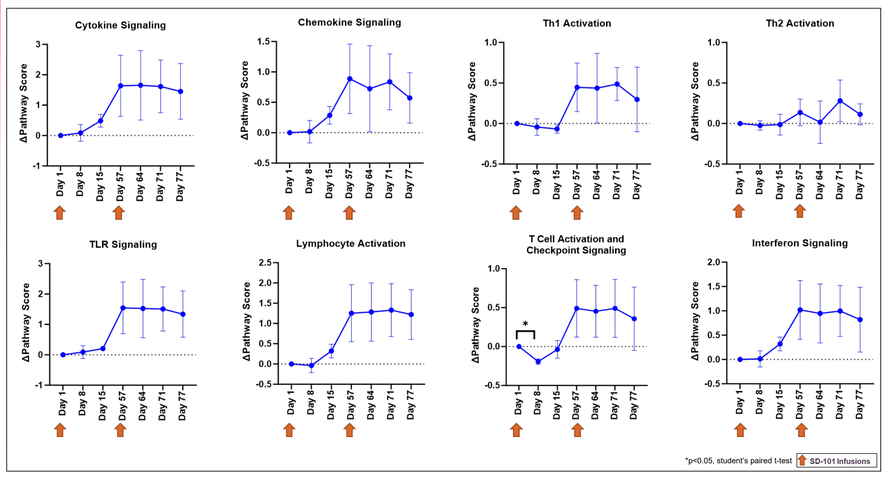


Figure 4. Pathway scoring determined by advanced analysis of NanoString gene expression data of peripheral WBCs (n=3).

Figure 5. Changes in Circulating Immune Markers

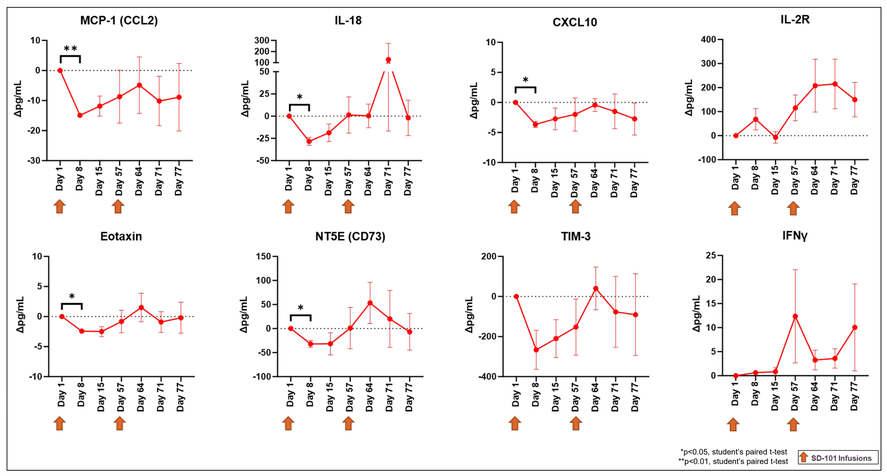


Figure 5. Changes in immune marker levels within plasma determined by Luminex (n=3).

Figure 6. Changes in Circulating WBC Immune Signals

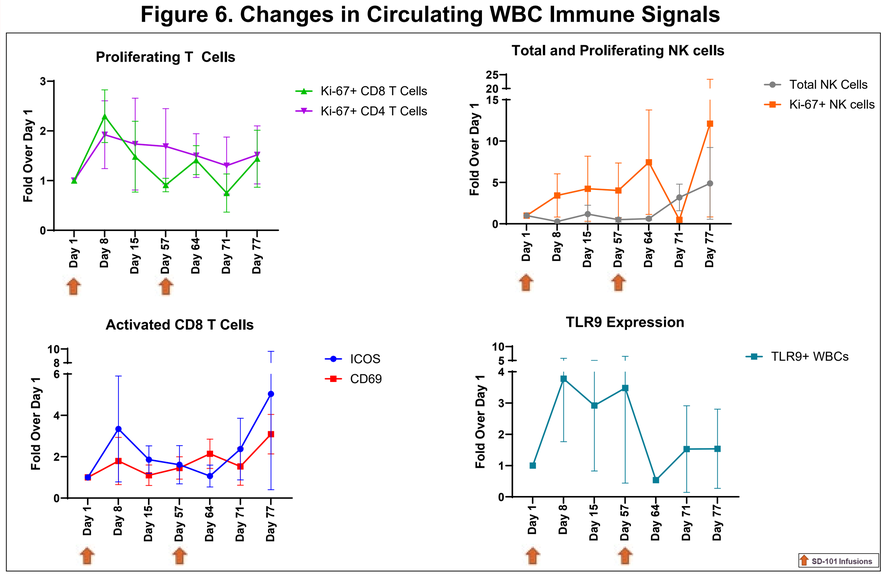


Figure 6. Changes in peripheral WBC protein expression patterns as determined by flow cytometry (n=3).