PERIO-02: Phase 1b Pressure Enabled Regional Immuno-oncology Trial of nelitolimod (SD-101), a Class C TLR9 agonist, delivered via hepatic artery infusion +/- checkpoint inhibition in intrahepatic cholangiocarcinoma and hepatocellular carcinoma

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Abstract # 2622

BACKGROUND

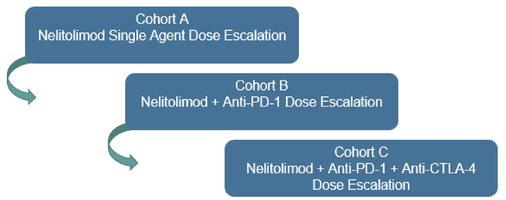
Immune checkpoint inhibitors (ICI) has shown limited survival benefit in patients (pts) with advanced HCC and intrahepatic cholangiocarcinoma (ICC). Nelitolimod (SD-101), a Class C toll-like receptor-9 (TLR-9 agonist), depletes MDSCs while broadly stimulating the tumor microenvironment. Given safety challenges with IV infusion and distribution limitations of needle injection, we studied hepatic arterial infusion (HAI) of nelitolimod with Pressure-Enabled Drug Delivery (PEDD) to enhance ICI responsiveness.

METHODS

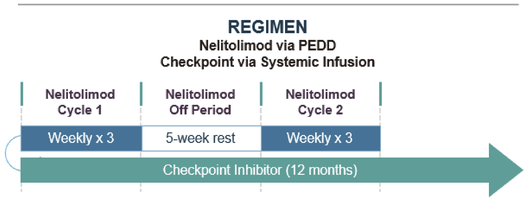
PERIO-02 is an open-label phase 1 trial of nelitolimod given by HAI in HCC and ICC (NCT05220722). The study consists of dose-escalation cohorts of nelitolimod alone (Cohort A), with pembrolizumab (Cohort B), or nivolumab + ipilimumab (Cohort C). Nelitolimod is delivered over 2 cycles, with 3 weekly doses per cycle. Blood, liver tumor, and normal liver biopsies are collected for immune monitoring.

Figure 1. Schema

A.



B.



2-4 mg dose range predicted based on murine orthotopic liver metastasis PEDD model

Figure 1. **(A)** Overall study design. **(B)** Treatment regimen.

Table 1. Patient Characteristics

Patient Characteristics	n=23 (%)
Gender	
Female	8 (35)
Male	15 (65)
Age (years, range)	45-75
HCC	7 (30)
ICC	16 (70)
Prior Lines of Therapy	
0	0
1	4 (17)
2	5 (22)
≥3	14 (61)
N/A	1(<1)
Number of Lesions at Baseline	
≤10	16 (70)
>10	6 (26)
N/A	1 (4)
Nodular	14 (61)
Infiltrative	8 (35)
N/A	1 (4)
Largest Lesion at BL	
≤50mm	18 (78)
>50mm	5 (22)
N/A	0

SUMMARY

- At the 4 mg dose in cohort C, 3 of 3 patients had disease control, with one CR in the liver (5L ICC), one PR (-31%), and 1 SD. For patient 101-017 (CR), decreases were noted in the target liver lesion (31.3 to 17.5 mm), non-target liver lesion, and extra-hepatic lymph nodes on days 53 and 84 with complete response of target liver lesions and stability of extra hepatic nodal lesions reported on day 154.
- Median PFS in the cohort C 4 mg dose level is > 120 days. Median OS for this group has not been reached (range 120-170 days).
- Immune effects of nelitolimod included increases in liver tumor CD4 and CD8 T cells and an increase in the CD8 T cell:MDSC ratio.
- Gene expression changes revealed increased Th1 programming as well as increased expression of granzyme A, IFNγ, and CXCL10 in both liver tumor and surrounding normal liver.
- Changes among plasma marker levels included increased IL-2R and CXCL10 expression, with decreased IL-17A, IDO, and NT5E (CD73).

CONCLUSION

HAI of nelitolimod via PEDD has been well tolerated and associated with encouraging immunologic activity in HCC and ICC. Clinical and biologic activity in cohort C at 4 mg is supportive of further enrollment in this cohort.

Figure 2. Adverse events and treatment responses

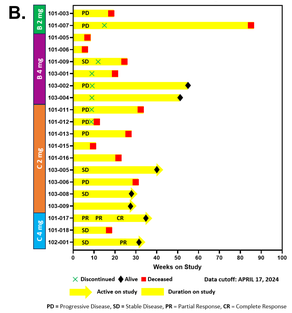
A.

*All listed events are related to nelitolimod, pembro, ipi, and/or nivo	N=3 Cohort A 4 mg Nelitolimod Monotherapy n (%)	N=8 Cohort B Summary n (%)	N=4 Cohort B 2 mg Nelitolimod + Pembro n (%)	N=4 Cohort B 4 mg Nelitolimod + Pembro n (%)	N=12 Cohort C Summary n (%)	N=9 Cohort C 2 mg Nelitolimod + Ipi/Nivo n (%)	N=3 Cohort C 4 mg Nelitolimod + Ipi/Nivo n (%)	N=23 All Cohorts n (%)
Treatment-related AEs (any grade)	**2 (67)**	**6 (75)**	4 (100)	2 (50)	**10 (83)**	7 (78)	3 (100)	**18 (78)**
DLTs	**0**	**0**	0	0	**1 (8)**	1 (11)	0	**1 (4)**
SAEs	**0**	**0**	0	0	**3 (25)**	1 (11)	2 (67)	**3 (13)**
≥G3 events (%)	**0**	**1 (13)**	1 (25)	0	**3 (25**	1 (11)	2 (67)	**3 (13)**
Most common AEs								
- Fever	**0**	**2 (25)**	2 (50)	0	**3 (25)**	3(33)	0	**5 (22)**
- Decrease in appetite	**1 (33)**	**1 (13)**	0	1 (25)	**0**	0	0	**2 (9)**
- Adbominal Pain	**0**	**2 (25)**	1 (25)	1 (25)	**4 (33)**	2 (22)	2 (67)	**6 (26)**
- Chills	**0**	**0**	0	0	**3 (25)**	2 (22)	1 (33)	**3 (13)**
- Fatigue	**0**	**0**	0	0	**3 (25)**	2 (22)	1 (33)	**3 (13)**

* 1 Patient from Cohort C 2 mg and 1 patient from Cohort C 4 mg each had 2 SAEs

Safety data comparable to PERIO-01 in patients with underlying liver disease[1]

B.



C.

Patient 101-017: Cohort C 4 mg Nelitolimod + Ipi/Nivo

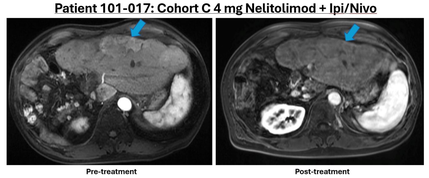
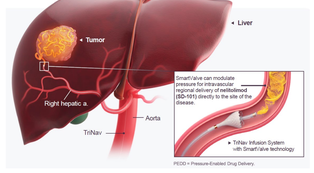


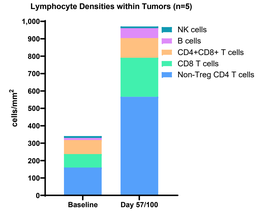
Figure 2. (A) Adverse events. **(B)** Best available radiographic response and survival times. **(C)** Arterial phase imaging for patient 101-017.

Figure 3. PEDD of nelitolimod via HAI induced a favorable immunologic shift in the TME as well as the surrounding normal liver tissue

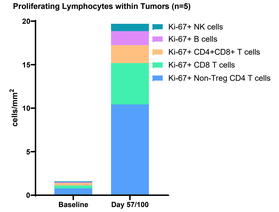
A. Delivery approach for nelitolimod



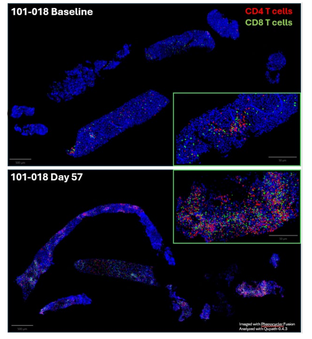
B. Lymphocyte Densities within Tumors (n=5)



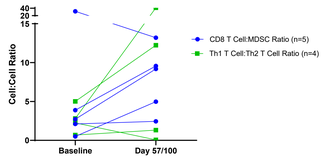
C. Proliferating Lymphocytes within Tumors (n=5)



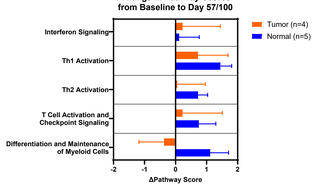
D. CD4+ and CD8+ T cells within tumors



E. Change in Immune Cell Density Ratios within Tumors



F. Change in Pathway Scores from Baseline to Day 57/100



G. Change in Gene Expression Levels from Baseline to Day 57/100

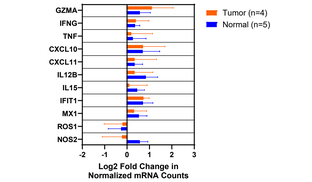
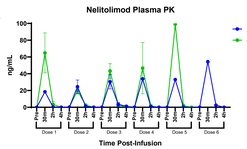


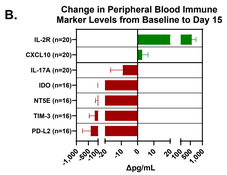
Figure 3. **(A)** PEDD approach for nelitolimod. **(B)** Cumulative lymphocyte densities within tumors at Baseline and Day 57 or Day 100 quantified by multiplex immunofluorescence (mIF). **(C)** Cumulative proliferating lymphocyte densities within tumors at Baseline and Day 57 or Day 100 quantified by mIF. **(D)** Representative mIF images of T cell infiltration within tumors at Baseline and Day 57. **(E)** Change in immune cell densities from Baseline to Day 57 or Day 100 determined by mIF. **(F)** Change in pathway scores from Baseline to Day 57 or Day 100 for tumor and normal liver tissue determined by advanced analysis of NanoString gene expression data. **(G)** Change in gene expression levels from Baseline to Day 57 or Day 100 for tumor and normal liver tissue determined by NanoString.

Figure 4. Peripheral immune cell activation and signaling increased following treatment despite low and transient systemic exposure of nelitolimod when delivered via PEDD

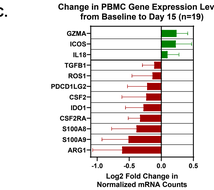
A. Nelitolimod Plasma PK



B. Change in Peripheral Blood Immune Marker Levels from Baseline to Day 15



C. Change in PBMC Gene Expression Levels from Baseline to Day 15 (n=19)



D. Change in Cell Densities within Peripheral Blood from Baseline to Day 15 (n=14)

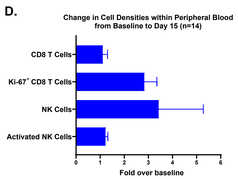
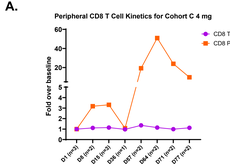


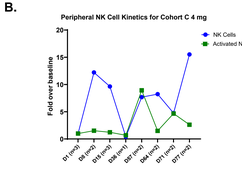
Figure 4 (A) Plasma levels of nelitolimod determined by LC-MS. **(B)** Change in peripheral blood immune marker levels from Baseline to Day 15 determined by Luminex. **(C)** Change in PBMC gene expression levels from Baseline to Day 15 determined by NanoString. **(D)** Change in peripheral immune cell levels from Baseline to Day 15 determined by flow cytometry (FC).

Figure 5. Immune response kinetics for Cohort C 4 mg

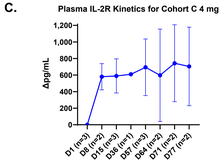
A. Peripheral CD8 T Cell Kinetics for Cohort C 4 mg



B. Peripheral NK Cell Kinetics for Cohort C 4 mg



C. Plasma IL-2R Kinetics for Cohort C 4 mg



D. Plasma IFNγ Kinetics for Cohort C 4 mg

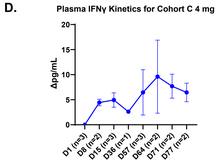


Figure 5. **(A, B)** Change in peripheral immune cell levels from Baseline determined by FC. **(C, D)** Change in peripheral blood immune marker levels from Baseline 15 determined by Luminex.

Figure 6. Similar immune effects observed for regional delivery of nelitolimod into both liver and pancreatic tumors

Pre-treatment to Post-treatment Trend

		PERIO-01[1] MUM-LM	PERIO-02 HCC + ICC	PERIO-03[2] PDAC
Tumor	Anti-tumor immunity genetic signature	↑	↑	TBD
	T cell infiltration	↑	↑	TBD
	MDSC effect	MDSC density ↓	MDSC:CD8 T cell ratio ↓	MDSC gene signature ↓
Systemic	Circulating proliferating T cells	↑	↑	↑
	Circulating NK cells	Proliferation ↑	Activation ↑	Proliferation ↑
	WBC proinflammatory gene expression pattern	↑	↑	↑
	Proinflammatory cytokines	↑	↑	↑
	Immunosuppressive cytokines	↓	↓	↓

Figure 6. Trends observed for changes in mean biomarker levels from pre-treatment to post-treatment

References

1. Clinical activity of SD-101 with immune checkpoint inhibition (ICI) in metastatic uveal melanoma liver metastasis (MUM-LM) from the PERIO-01 Phase 1 trial. SITC 2023
2. PERIO-03: Pressure Enabled Intrapancreatic Delivery of SD-101 With Checkpoint Blockade for Locally Advanced Pancreatic Adenocarcinoma – Initial Safety and Feasibility Experience. SITC 2023