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

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Abstract #1534

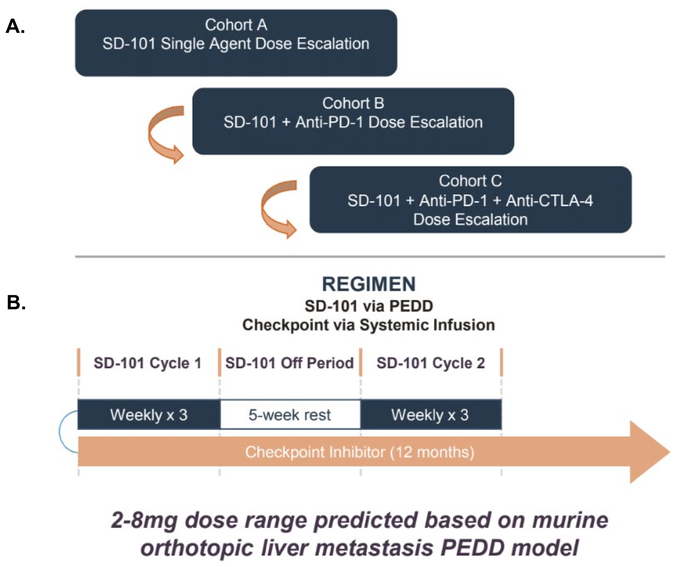
Background

- MUM-LM are resistant to ICIs for several reasons including the prevalence of myeloid-derived suppressor cells (MDSCs)
- PFS has been limited, even with approved therapies such as tebentafusp (median 3.3 months) with grade 3/4 AE rates typically >30%
- TLR9 agonists are capable of MDSC polarization but drug delivery has historically been limited using an intra-tumoral approach
- Pressure-enabled drug delivery (PEDD™) of SD-101, a TLR9 agonist, has the potential to overcome these barriers to improve outcomes

Methods

- PERIO-01 is a phase 1 trial of hepatic arterial infusion of SD-101 via PEDD™ in MUM-LM (NCT04935229), with dose-escalation cohorts as monotherapy (Cohort A), with nivolumab (Cohort B), or nivolumab + ipilimumab (Cohort C)
- SD-101 is delivered over 2 outpatient cycles, with 3 weekly doses/cycle.
- Plasma was analyzed for SD-101 levels by LC-MS and cytokine levels by Luminex
- NanoString was used to analyze gene expression levels within PBMCs and LM. The nSolver advanced analysis was performed for pathway scoring.
- FFPE tissue sections were analyzed by multiplex IF using the Akoya Bioscience PhenoCycler-Fusion system staining for DAPI, CD14, HLA-DR, CD163, CD68, CD11b, CD8, CD15, CD56, CD3e, CD4, CD20, FOXP3, gp100, & CD45. Quantitative cell density data was generated using QuPath 0.4.3
- Flow cytometry was performed to evaluate $CD8^+$ T cell proliferation ($CD45^+CD3^+CD8^+Ki67^+$), activation ($CD45^+CD3^+CD8^+ICOS^+$) and NK cell proliferation ($CD45^+CD3^-CD56^+Ki67^+$), using CytoFlex

Figure 1. Schema



2-8mg dose range predicted based on murine orthotopic liver metastasis PEDD model

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

Table 1. Patient Characteristics

Patient Characteristics	N=56 (%)
Age (median, range)	64 (35-86)
Gender	
Female	26 (46)
Male	30 (54)
LDH	
>ULN	27 (48)
Normal	27 (48)
N/A	2 (4)
Performance Status	
0	45 (80)
1	11 (20)
# prior lines therapy	
0	16 (29)
1	17 (30)
2	12 (21)
≥3	8 (14)
N/A	3 (5)
Prior tebentafusp	9 (16)

Results

Figure 2. PEDD of SD-101 via HAI reduced ctDNA

Specified time points (A.): 27% ctDNA clearance and 65% response rate
Best response on treatment (B.): 59% ctDNA clearance and 86% response rate

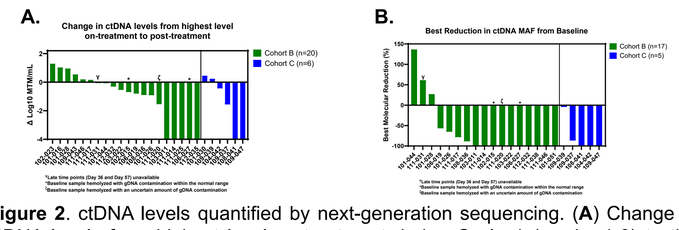


Figure 2. ctDNA levels quantified by next-generation sequencing. (**A**) Change in ctDNA levels from highest level on-treatment during Cycle 1 (weeks 1-3) to the latest available post-treatment time point following Cycle 1 (week 6 or 9). (**B**) Change in ctDNA levels from baseline to any time point with the lowest ctDNA level.

Figure 3. Overall Survival Kaplan-Meier Curves

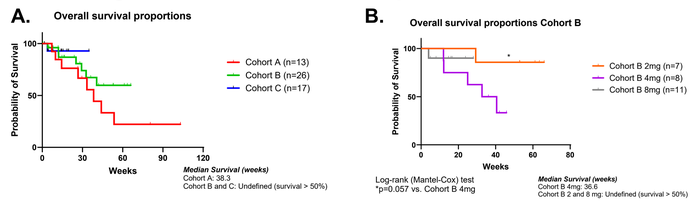


Figure 3. Kaplan–Meier curves showing overall survival for patients in different Cohorts (**A**) and in Cohort B (**B**).

Summary

- Regional delivery of SD-101 by PEDD results in high drug levels within the liver and transient serum exposure
- Median PFS of 11.7 months in patients receiving 2 mg + nivolumab is promising (median OS not reached)
- Increased $CD8^+$ T cell, NK cell and M1 macrophage infiltration in the tumors
- Decreased immunosuppressive Tregs, M-MDSCs and M2 macrophages in liver metastases
- Gene expression analysis in LM and in PBMCs revealed increased signals related to $CD8^+$ cytotoxic T lymphocyte activity, Th1 activation, cytokine and chemokine signaling
- Systemic immune activation observed by an increase in pro-inflammatory cytokines
- Systemic increase in NK cell proliferation and $CD8^+$ T cell activation

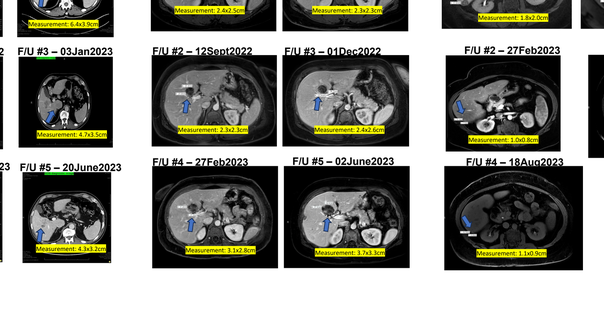
Conclusions

Delivery of SD-101 by PEDD plus systemic ICI in MUM-LM patients results in clinical activity with median PFS of 11.7 months, ctDNA molecular responses, MDSC re-programming, and evidence of peripheral and intra-tumoral immune activation.

Table 2. Safety Summary

*All listed events are related to SD-101, ipi, and/or nivo	N=13 Cohort A Summary n (%)	N=4 Cohort A 2mg SD-101 n (%)	N=5 Cohort A 4mg SD-101 n (%)	N=4 Cohort A 8mg SD-101 n (%)	N=26 Cohort B Summary n (%)	N=7 Cohort B 2mg SD-101 + Nivo n (%)	N=8 Cohort B 4mg SD-101 + Nivo n (%)	N=11 Cohort B 8mg SD-101 + Nivo n (%)	N=17 Cohort C Summary n (%)	N=10 Cohort C 2mg SD-101 + Ipi/Nivo n (%)	N=7 Cohort C 4mg SD-101 + Ipi/Nivo n (%)	N=56 All cohorts n (%)
Treatment-related AEs (any grade)	**5 (38)**	0	3 (60)	2 (50)	**19 (73)**	5 (71)	6 (75)	8 (73)	**15 (88)**	10 (100)	5 (71)	**39 (70)**
DLTs	**0**	0	0	0	**2 (8)**	1 (14)	0	1 (9)	**0**	0	0	**2 (4)**
SAEs	**1 (8)**	0	0	1 (25)	**1 (4)**	0	1 (13)	0	**6 (35)**	4 (40)	2 (29)	**8 (14)**
≥G3 events (%)	**1 (8)**	0	1 (20)	0	**5 (19)**	1 (14)	2 (25)	2 (18)	**8 (47)**	5 (50)	3 (43)	**14 (25)**
Most common AEs												
-Gastrointestinal Disorders	**3 (23)**	0	2 (40)	1 (25)	**8 (31)**	2 (29)	3 (38)	3 (27)	**12 (71)**	8 (80)	4 (57)	**23 (41)**
-Fatigue	**2 (15)**	0	2 (40)	0	**5 (19)**	2 (29)	2 (25)	1 (9)	**10 (59)**	7 (70)	3 (43)	**17 (30)**
-Skin Disorders	**0**	0	0	0	**7 (27)**	3 (43)	1 (13)	3 (27)	**8 (47)**	6 (60)	2 (29)	**15 (27)**
-Fever	**2 (15)**	0	1 (20)	1 (25)	**1 (4)**	0	0	1 (9)	**6 (35)**	3 (30)	3 (43)	**9 (16)**
-Administration Site Conditions	**1 (8)**	0	0	1 (25)	**4 (15)**	2 (29)	0	2 (18)	**4 (24)**	3 (30)	1 (14)	**9 (16)**
-Increased ALT	**0**	0	0	0	**4 (15)**	1 (14)	2 (25)	1 (9)	**4 (24)**	2 (20)	2 (29)	**8 (14)**
-Increased AST	**0**	0	0	0	**4 (15)**	1 (14)	2 (25)	1 (9)	**4 (24)**	2 (20)	2 (29)	**8 (14)**

Figure 4. Swimmer Plot of patients



MR = minor response (10-29% decrease) **PR** = partial response (≥30% decrease)

Objective RECIST 1.1 response rates

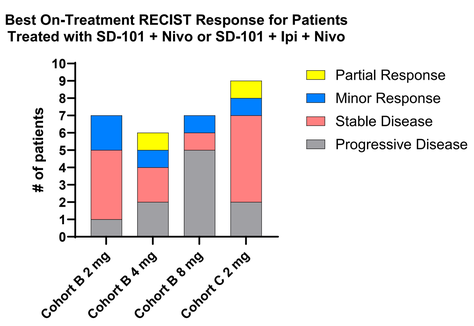


Figure 5. Sequential MRI/CT scans

Figure 6. Plasma levels of SD-101 are transient and remain low following PEDD

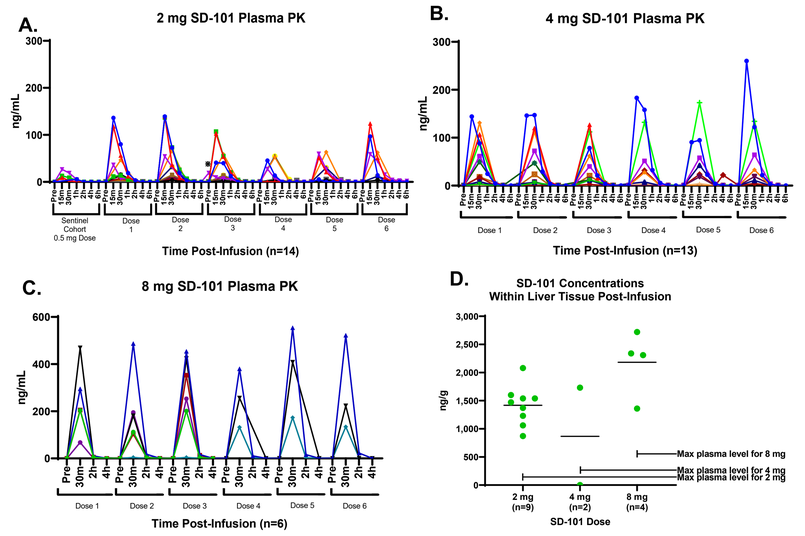


Figure 6. Plasma was collected on infusion days at the indicated time points and analyzed for SD-101 levels by LC-MS. **A.** 2mg dose **B.** 4mg dose, **C.** 8mg dose and **D.** in liver tissue post-infusion.

Figure 7. Improved immune cell infiltration in the tumor microenvironment

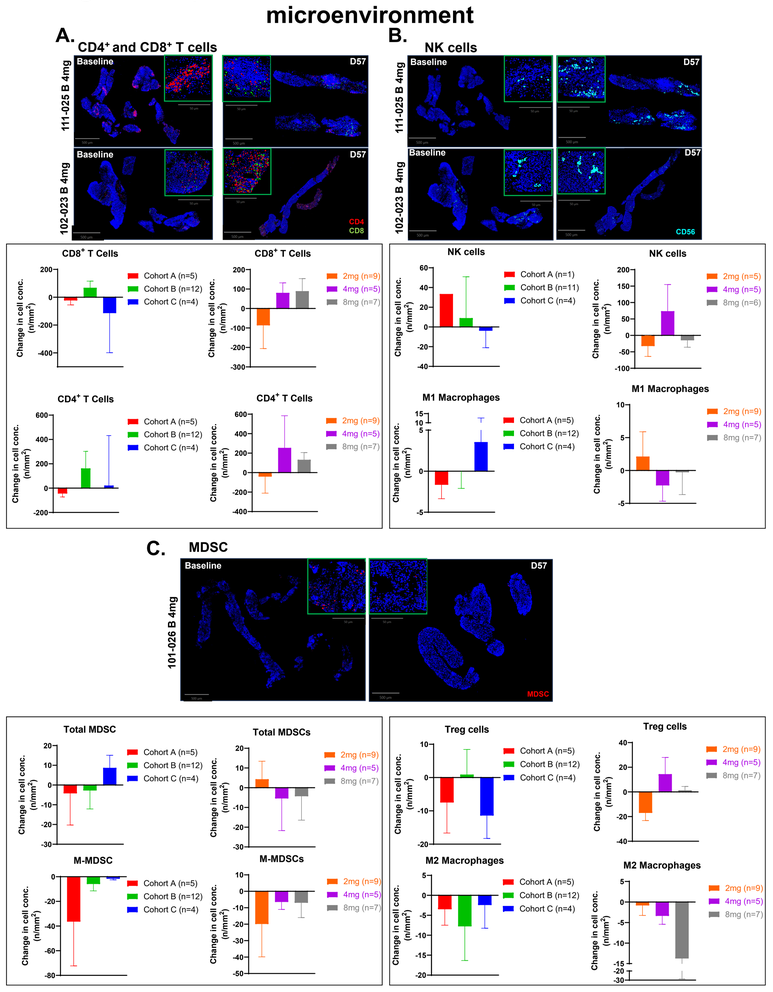


Figure 7. Multiplex immunofluorescence images of immune cell infiltration in baseline and Day 57 LM. $CD4^+$ and $CD8^+$ T cell infiltration in LM from patients 111-025 (top panel) and 102-023 (bottom panel) (**A**), NK cells ($CD3^-CD56^+$) (**B**) and MDSC ($CD45^+CD11b^+HLA\text{-}DR^-CD68^-$) for patient 101-026 (**C**). Images were quantified with QuPath. Change in cell concentration from baseline data represented as mean ± SEM.

Figure 8. Gene expression patterns in tumors and in circulation associated with tumor regression

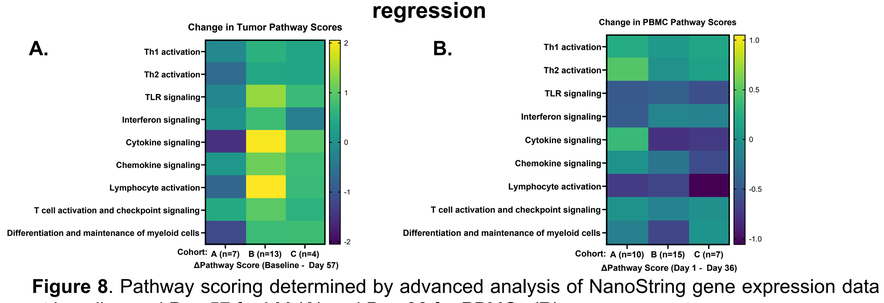


Figure 8. Pathway scoring determined by advanced analysis of NanoString gene expression data at baseline and Day 57 for LM (**A**) and Day 36 for PBMCs (**B**).

Figure 9. Immune signatures in circulation associated with tumor regression

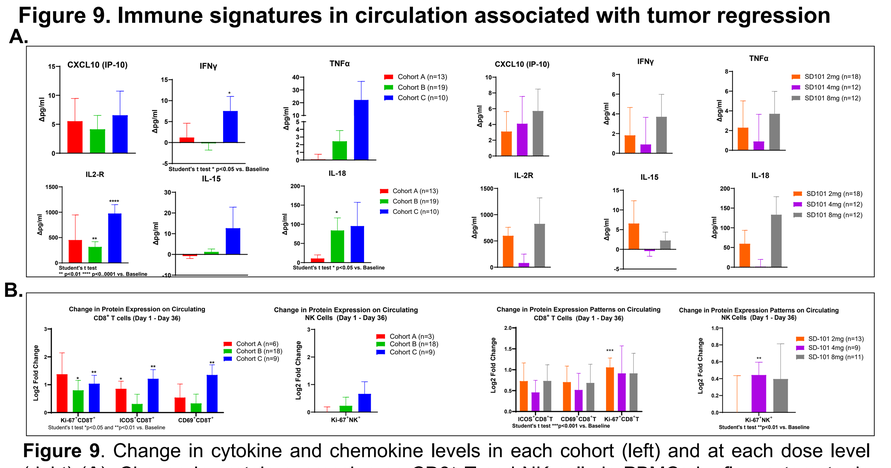


Figure 9. Change in cytokine and chemokine levels in each cohort (left) and at each dose level (right) (**A**). Change in protein expression on $CD8^+$ T and NK cells in PBMCs by flow cytometry in each cohort (left) and at each dose level (right) (**B**). Data presented as mean ± SEM.