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

Sapna P. Patel* , Richard Carvajal, Kamaneh Montazeri, Jose Lutzky, Bartosz Chmielowski, Sunil Reddy, Shailander Bhatia, Shaheer Khan, Theresa Medina, Cara Haymaker, Rahul Sheth, Joshua D. Kuban, Lindsay Thornton, Eric Wehrenberg-Klee, Paula Novelli, Brinda Rao, Anthony Lucci, Vanessa Sarli, Salyna Meas, Bryan Cox, Jason LaPorte, Prajna Guha, Chandra Ghosh, Ann-Marie Hulstine, Robert Knight, Ashley Moody, David Geller, Marlana Orloff, Steven C. Katz, Diwakar Davar

*Chair, SWOG Melanoma Committee
Assoc Professor, Director of the Uveal Melanoma Program
The University of Texas MD Anderson Cancer Center

Late Breaking Abstract #1534

Presenting Author Disclosures

- Advisory board, steering committee, data safety monitoring board, consulting:
  BMS, Cardinal Health, Castle Biosciences, Delcath, Ideaya, Immatics, Immunocore, MSD, Novartis, OncoSec, Pfizer, Replimune, ***TriSalus Life Sciences***

- Clinical trial support (institutional):
  BMS, Foghorn Therapeutics, Ideaya, InxMed, Lyvgen Biopharma, Novartis, Provectus Biopharmaceuticals, Seagen, Syntrix Bio, ***TriSalus Life Sciences***

- Speaker's honoraria (non-promotional):
  BMS, MSD

Uveal melanoma

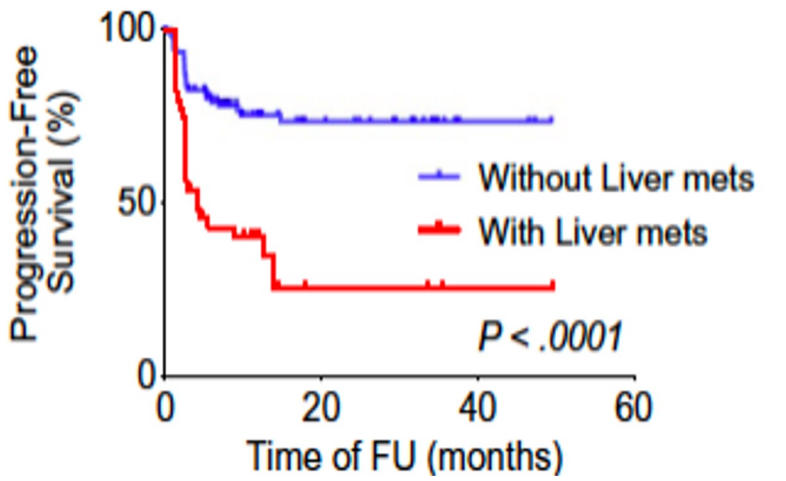
- Uveal melanoma is the most common primary eye tumor in adults with an incidence of 6 per million
- Half of patients will develop metastatic disease, 90% with liver involvement
- One approved immunotherapy treatment for metastatic uveal melanoma
  - Tebentafusp: T-cell redirection molecule restricted to HLA-A*02:01 (January 2022)
- And one approval for a cytotoxic regimen
  - Percutaneous hepatic perfusion (PHP): Melphalan (August 2023)

	Tebentafusp	Control
PFS	3.3 months	2.9 months
OS	21.7 months	16.0 months
ORR	9%	5%
DoR	9.9 months	9.7 months
G3/4	44%	17%

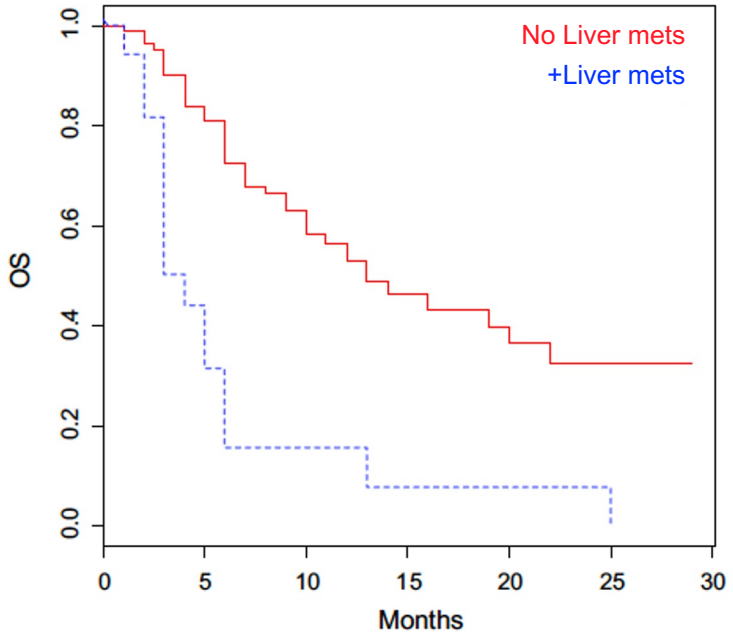
A significant unmet clinical need remains for 1L HLA-A*02:01-negative patients and ≥2L treatment

The presence of liver metastases promotes checkpoint inhibitor failure

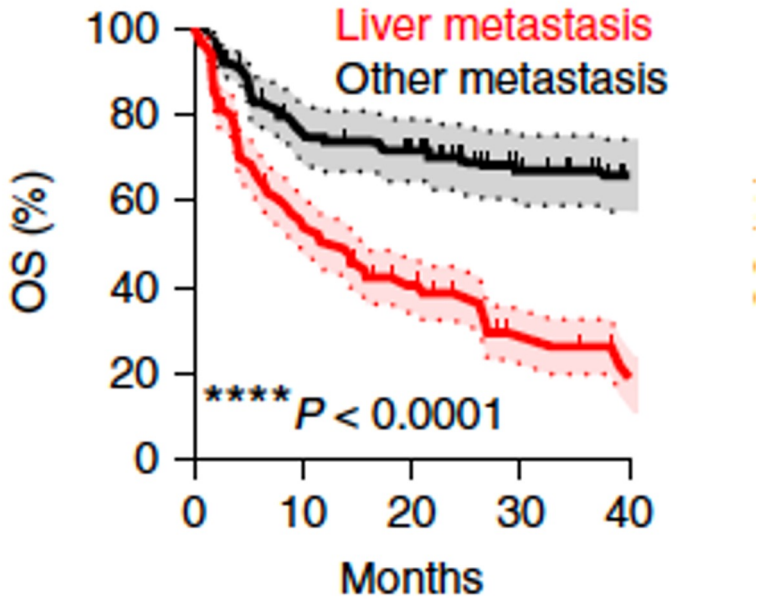
In **cutaneous melanoma** patients, liver mets predicted inferior PFS and OS[1]



In **lung carcinoma** patients, the presence of liver mets was an independent predictor of ICI failure[2]

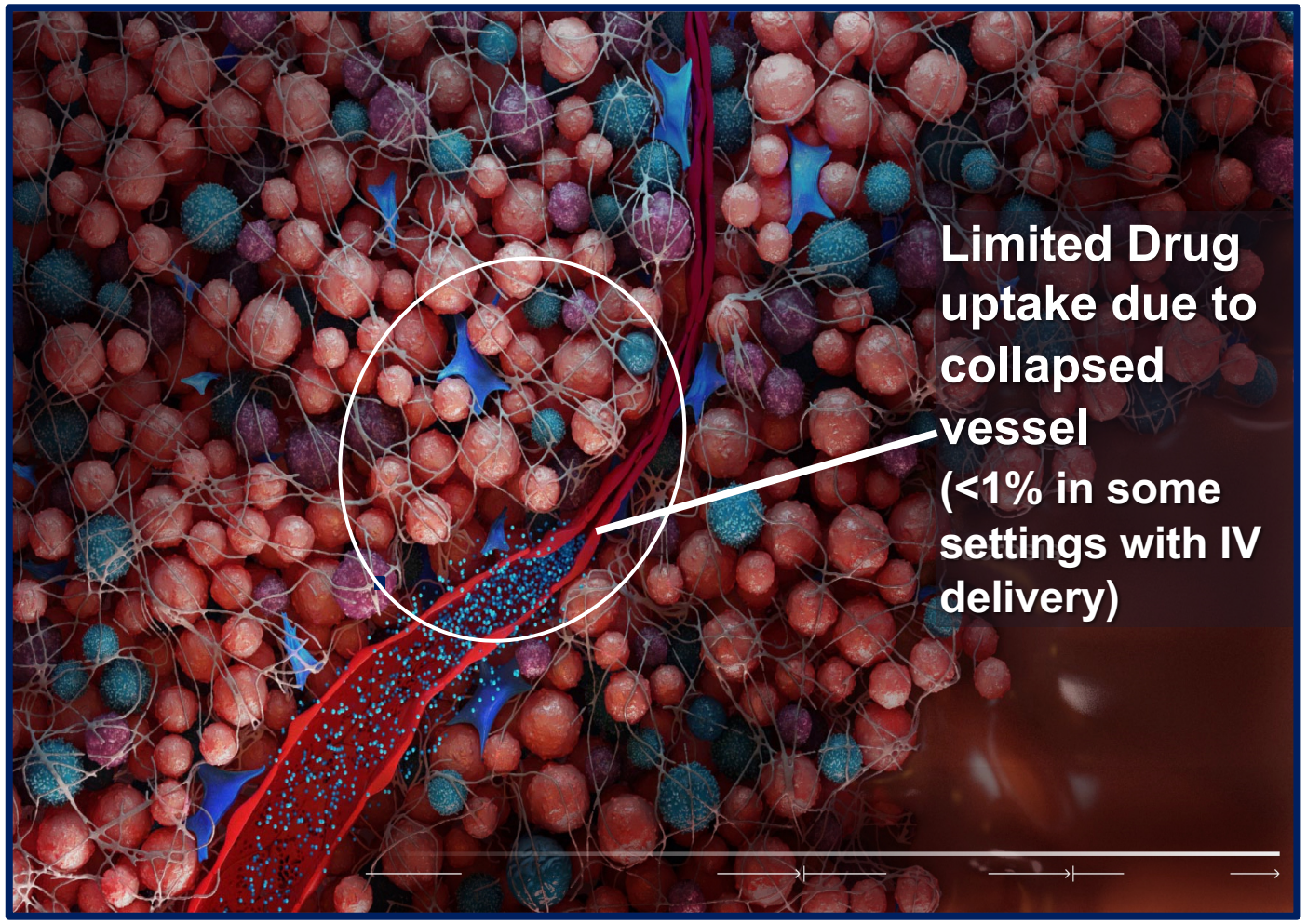


In **multiple indications**, liver mets predicted ICI failure **in association with myeloid cell driven suppression**[3]



1. Silva I, Lo S, Quek C, González M, Carlino M, Long G, and Menzies A. *Cancer.* 2019;126
2. Botticelli A, Salati M, Di Pietro FR, et al. *J Transl Med. 2019;*17:99.
3. Yu J, Green MD, Li S, et al. *Nat Med.* 2021;27:152-164

Two important barriers to immunotherapy success for liver metastases



1. Pressure

High intra-hepatic and intra-tumoral pressure produce a **mechanical barrier** limiting efficient drug delivery via intravenous or regional hepatic infusion

2. Immune suppression

Myeloid-derived suppressor cells (MDSCs) create a **suppressive tumor microenvironment** (TME) limiting activity of therapeutic agents

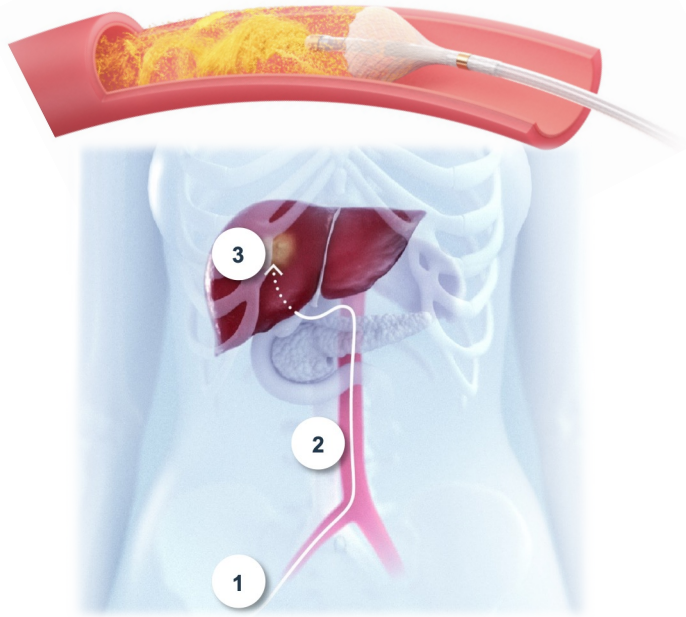
Wilhelm et al. (2016) Analysis of nanoparticle delivery to tumours. Nature Reviews Materials 1.5:16014.
Sheth, Rahul A., Robin Hesketh, David S. Kong, Stephan Wicky, and Rahmi Oklu. 2013. "Barriers to Drug Delivery in Interventional Oncology." Journal of Vascular and Interventional Radiology 24 (8): 1201–7.
TriSalus data on file from pre-clinical and clinical studies.
Guha, P., Reha, J. & Katz, S. C. Immunosuppression in liver tumors: opening the portal to effective immunotherapy. Cancer Gene Ther. 24, 114–120 (2017).

PERIO-01 study addresses these barriers

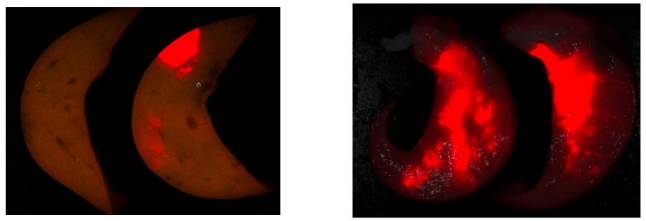
Overcoming pressure and immune suppression

Delivery Strategy

- Pressure-enabled drug delivery (PEDD) catheter works in sync with the cardiac cycle[1]
- Optimized vascular pressure[2] enhances perfusion → improved therapeutic delivery to tumor[3,4,5]
- Flow redirection to improve concentration of drug in tumor tissue[3,4] while allowing whole liver treatment
- Reduces reflux



Porcine Model – SD-101 Delivery



Needle Injection **PEDD**

Drug Strategy

- SD-101 is a Class C toll-like receptor 9 agonist
- Impacts multiple cell types to prime TME for checkpoint inhibitor treatment
- SD-101 leads to MDSC depletion, T-cell recruitment and activation[6]
- Optimal dose may be lower than maximally tolerated dose
- Mechanism of SD-101 may limit utility of traditional RECIST assessment

1. Data on file, TriSalus Life Sciences, 2019
2. Data on file, TriSalus Life Sciences, 2019
3. Titano JJ, et al. Cardiovasc Intervent Radiol. 2019;42:560-568.
4. Pasciak AS, et al. J Vasc Interv Radiol. 2015;26:660-669.
5. Katz et al. SITC (2018) Poster Presentation.
6. Ghosh. Cancer Gene Therapy 2023

TS-PERIO-01 Trial Design

COHORTS*

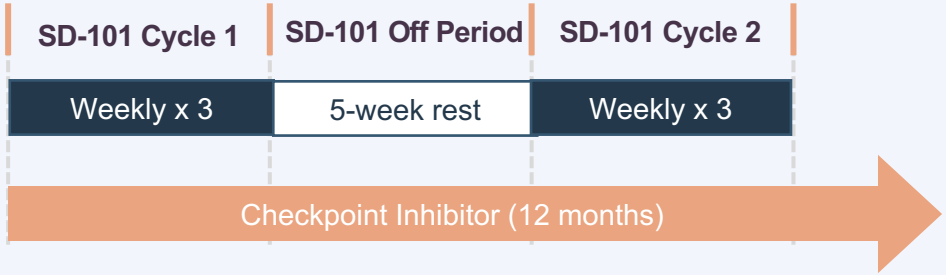
Cohort A
SD-101 Single Agent Dose Escalation
(n=9)

Cohort B
SD-101 + Anti-PD-1 Dose Escalation
(n=6)

Cohort C
SD-101 + Anti-PD-1 + Anti-CTLA-4
Dose Escalation (n=6)

*Patient numbers indicate planned minimum

REGIMEN
SD-101 via PEDD
Checkpoint via Systemic Infusion



ClinicalTrials.gov NCT04935229

TS-PERIO-01 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)

	N = 56 (%)
Cohort A	13 (23)
2 mg	4
4 mg	5
8 mg	4
Cohort B	26 (46)
2 mg	7
4 mg	8
8 mg	11
Cohort C	17 (30)
2 mg	10
4 mg	7

Safety Summary

Phase 1: Cohort A

	N=13	N=4	N=5	N=4
All listed events are related to SD-101, ipi, and/or nivo	**Cohort A Summary n (%)**	**Cohort A 2mg SD-101 n (%)**	**Cohort A 4mg SD-101 n (%)**	**Cohort A 8mg SD-101 n (%)**
Treatment-related AEs (TRAE) (any grade)	**5 (38)**	0	3 (60)	2 (50)
DLTs	**0**	0	0	0
SAEs	**1 (8)**	0	0	1 (25)
≥G3 events (%)	**1 (8)**	0	1 (20)	0
Serious G3/G4 TRAEs	**0**	0	0	0
Most common AEs				
-Gastrointestinal Disorders	**3 (23)**	0	2 (40)	1 (25)
-Fatigue	**2 (15)**	0	2 (40)	0
-Skin Disorders	**0**	0	0	0
-Fever	**2 (15)**	0	1 (20)	1 (25)
-Administration Site Conditions	**1 (8)**	0	0	1 (25)
-Increased ALT	**0**	0	0	0
-Increased AST	**0**	0	0	0

Safety Summary

Phase 1: Cohorts A, B

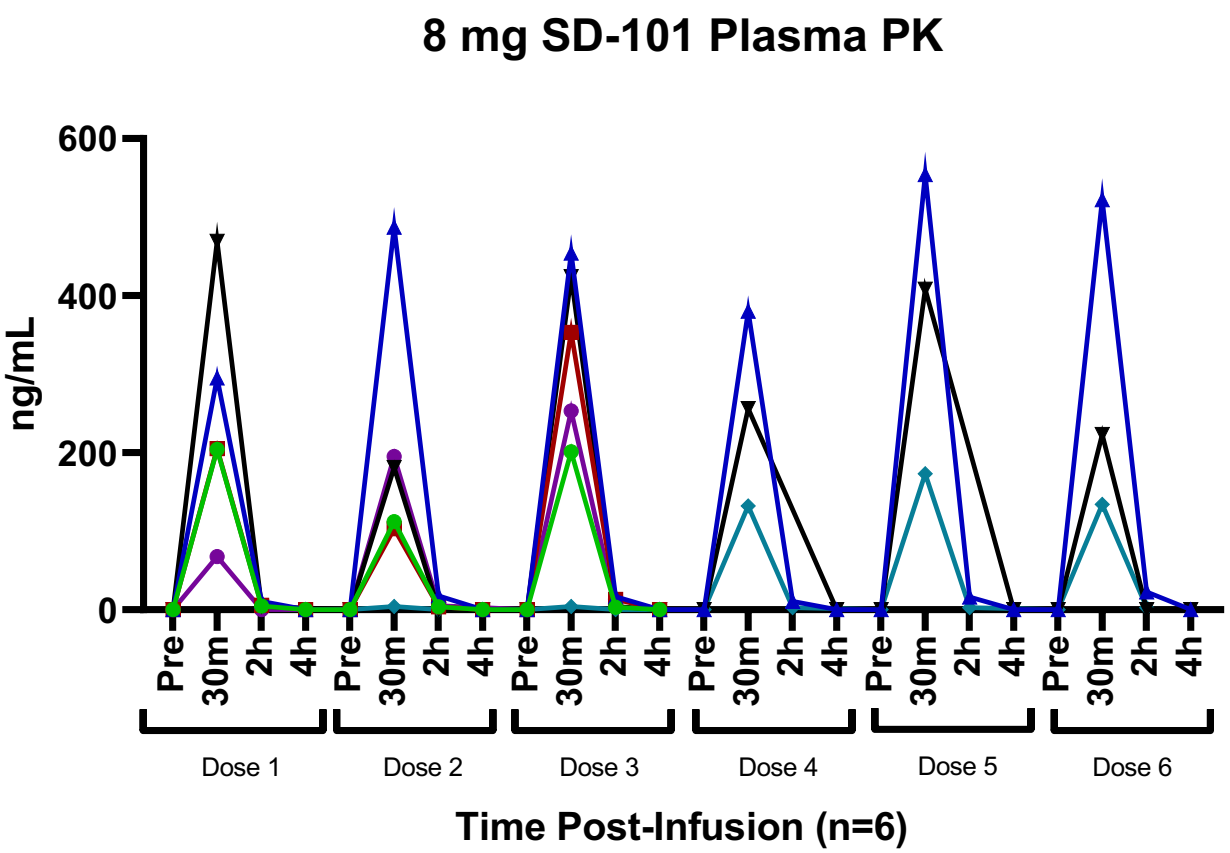
	N=13	N=4	N=5	N=4	N=26	N=7	N=8	N=11
All listed events are related to SD-101, ipi, and/or nivo	**Cohort A Summary n (%)**	**Cohort A 2mg SD-101 n (%)**	**Cohort A 4mg SD-101 n (%)**	**Cohort A 8mg SD-101 n (%)**	**Cohort B Summary n (%)**	**Cohort B 2mg SD-101 + Nivo n (%)**	**Cohort B 4mg SD-101 + Nivo n (%)**	**Cohort B 8mg SD-101 + Nivo n (%)**
Treatment-related AEs (TRAE) (any grade)	**5 (38)**	0	3 (60)	2 (50)	**19 (73)**	5 (71)	6 (75)	8 (73)
DLTs	**0**	0	0	0	**2 (8)**	1 (14)	0	1 (9)
SAEs	**1 (8)**	0	0	1 (25)	**1 (4)**	0	1 (13)	0
≥G3 events (%)	**1 (8)**	0	1 (20)	0	**5 (19)**	1 (14)	2 (25)	2 (18)
Serious G3/G4 TRAEs	**0**	0	0	0	**1 (4)**	0	1 (13)	0
Most common AEs								
-Gastrointestinal Disorders	**3 (23)**	0	2 (40)	1 (25)	**8 (31)**	2 (29)	3 (38)	3 (27)
-Fatigue	**2 (15)**	0	2 (40)	0	**5 (19)**	2 (29)	2 (25)	1 (9)
-Skin Disorders	**0**	0	0	0	**7 (27)**	3 (43)	1 (13)	3 (27)
-Fever	**2 (15)**	0	1 (20)	1 (25)	**1 (4)**	0	0	1 (9)
-Administration Site Conditions	**1 (8)**	0	0	1 (25)	**4 (15)**	2 (29)	0	2 (18)
-Increased ALT	**0**	0	0	0	**4 (15)**	1 (14)	2 (25)	1 (9)
-Increased AST	**0**	0	0	0	**4 (15)**	1 (14)	2 (25)	1 (9)

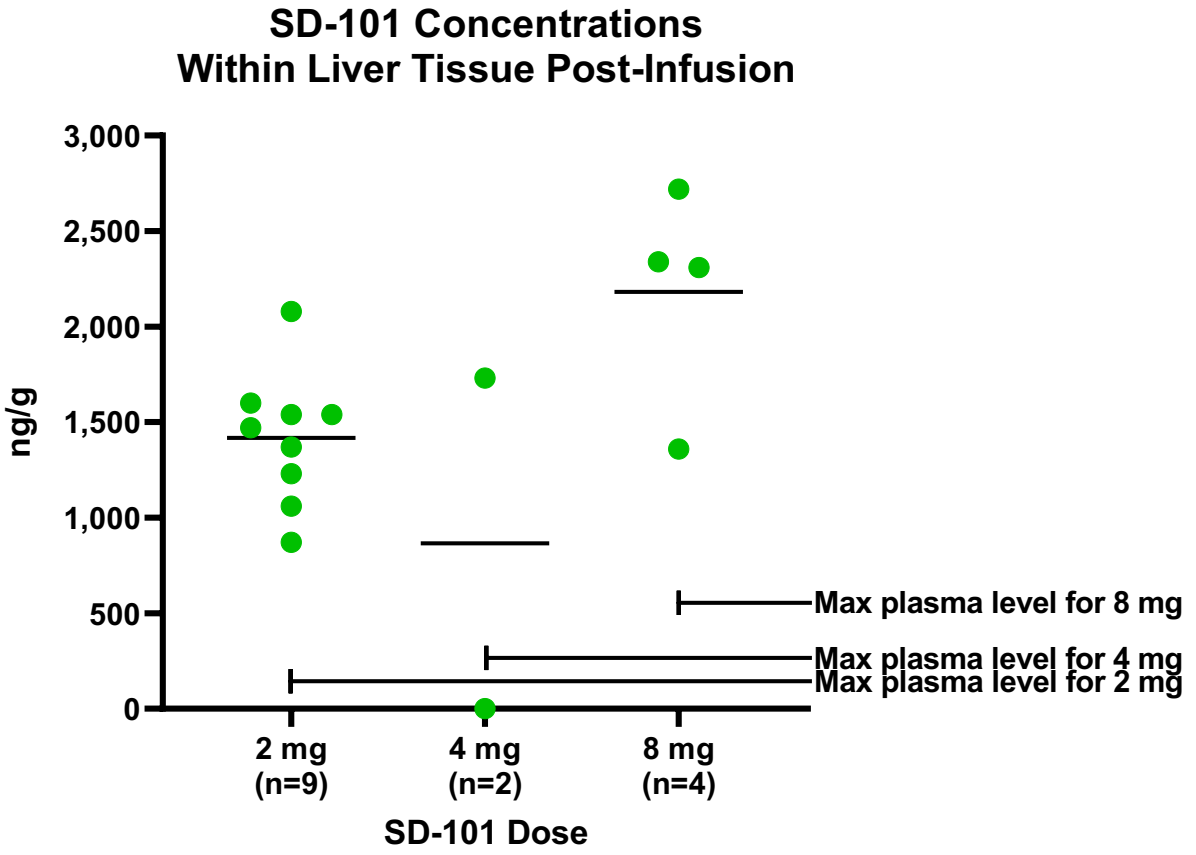
Safety Summary

Phase 1: Cohorts A, B, C

	N=13	N=4	N=5	N=4	N=26	N=7	N=8	N=11	N=17	N=10	N=7	N=56
All listed events are related to SD-101, ipi, and/or nivo	**Cohort A Summary n (%)**	**Cohort A 2mg SD-101 n (%)**	**Cohort A 4mg SD-101 n (%)**	**Cohort A 8mg SD-101 n (%)**	**Cohort B Summary n (%)**	**Cohort B 2mg SD-101 + Nivo n (%)**	**Cohort B 4mg SD-101 + Nivo n (%)**	**Cohort B 8mg SD-101 + Nivo n (%)**	**Cohort C Summary n (%)**	**Cohort C 2mg SD-101 + Ipi/Nivo n (%)**	**Cohort C 4mg SD-101 + Ipi/Nivo n (%)**	**All cohorts n (%)**
Treatment-related AEs (TRAE) (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)**
Serious G3/G4 TRAEs	**0**	0	0	0	**1 (4)**	0	1 (13)	0	**5 (29)**	4 (40)	1 (14)	**6 (11)**
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)**

SD-101 PK Data

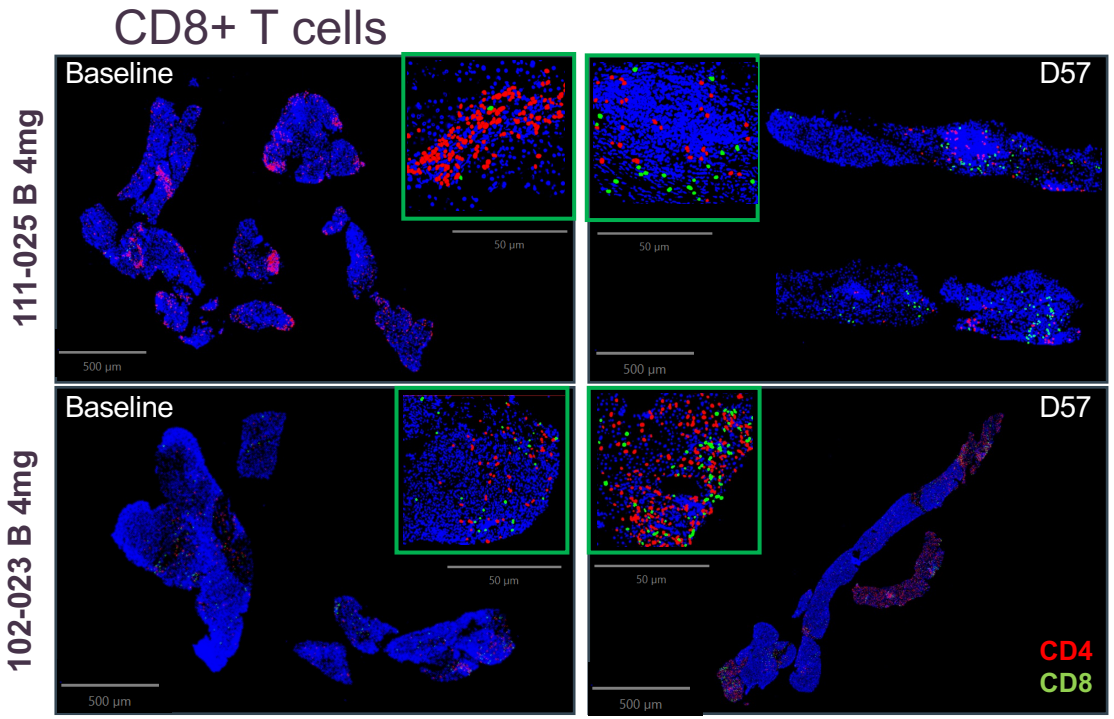


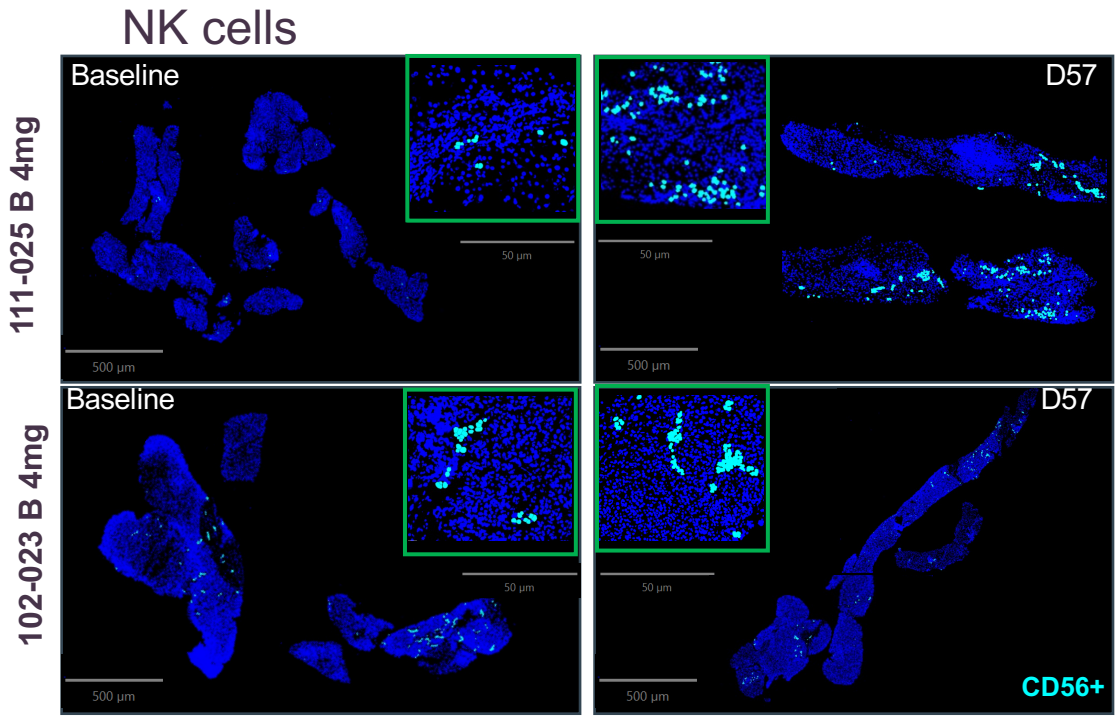


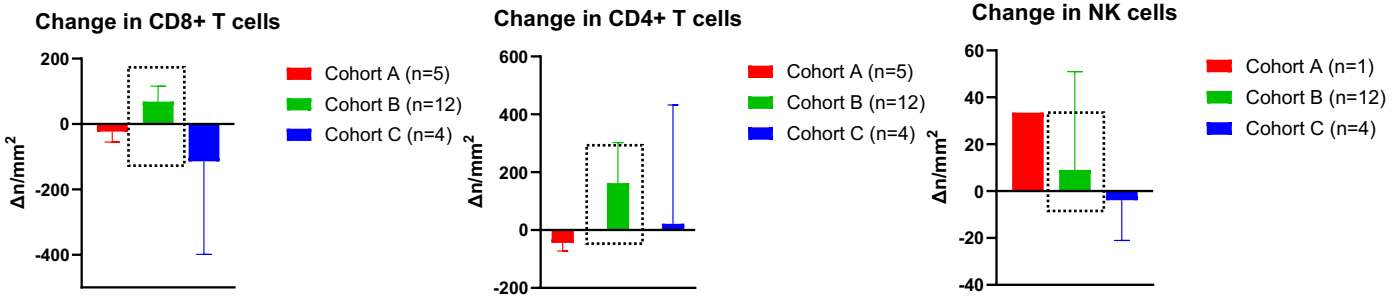
Regional delivery of SD-101 results in low, transient drug levels within the peripheral circulation, and high drug levels in the liver

Montazeri, K. et al. ASCO 2023

Increased CD8+ T cell and NK cell infiltration in the tumors



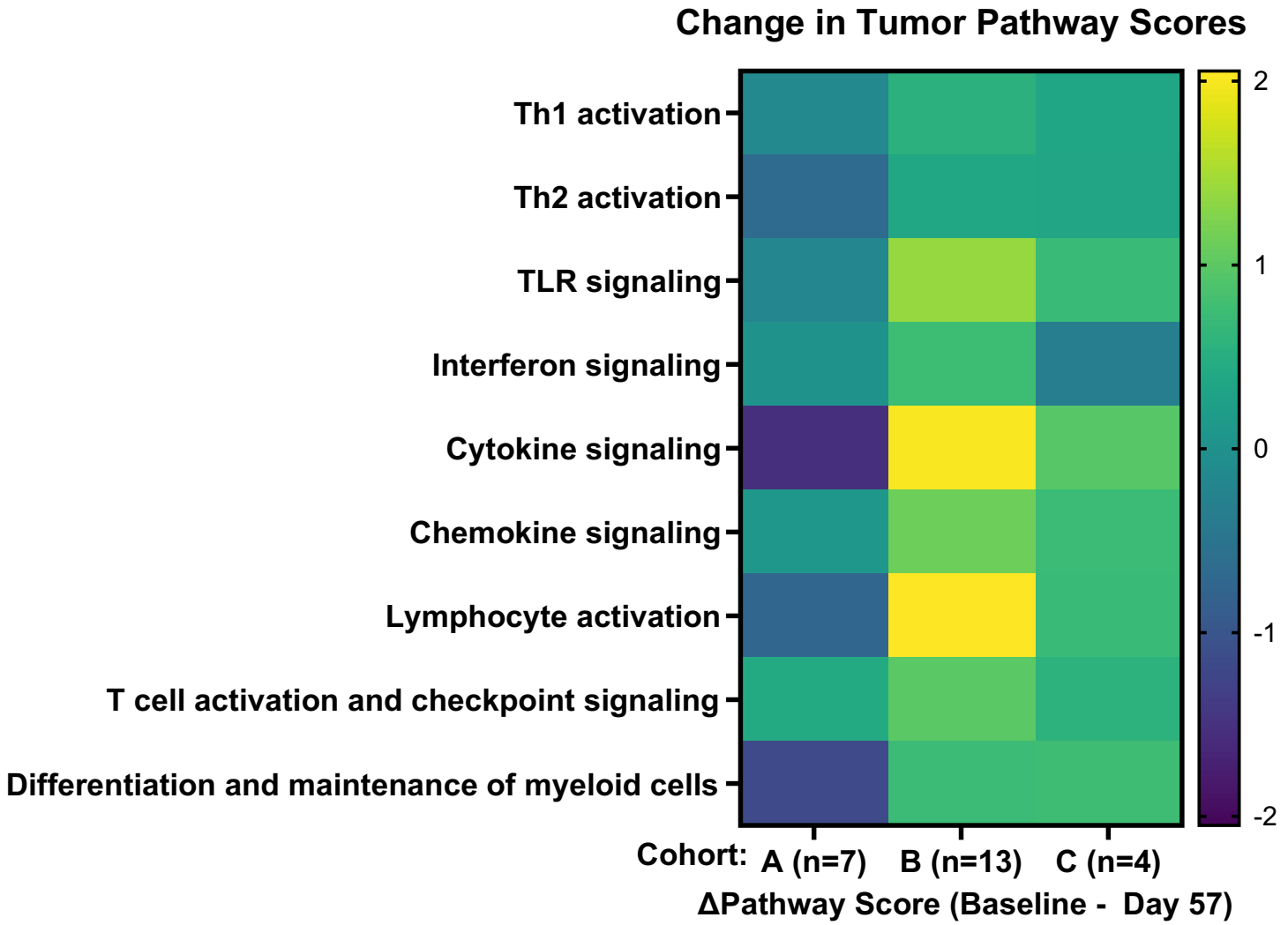




Increased CD8+ T cells and NK cells were observed in tumors at Day 57

Imaged with Phenocycler Fusion
Analyzed with Qupath-0.4.3

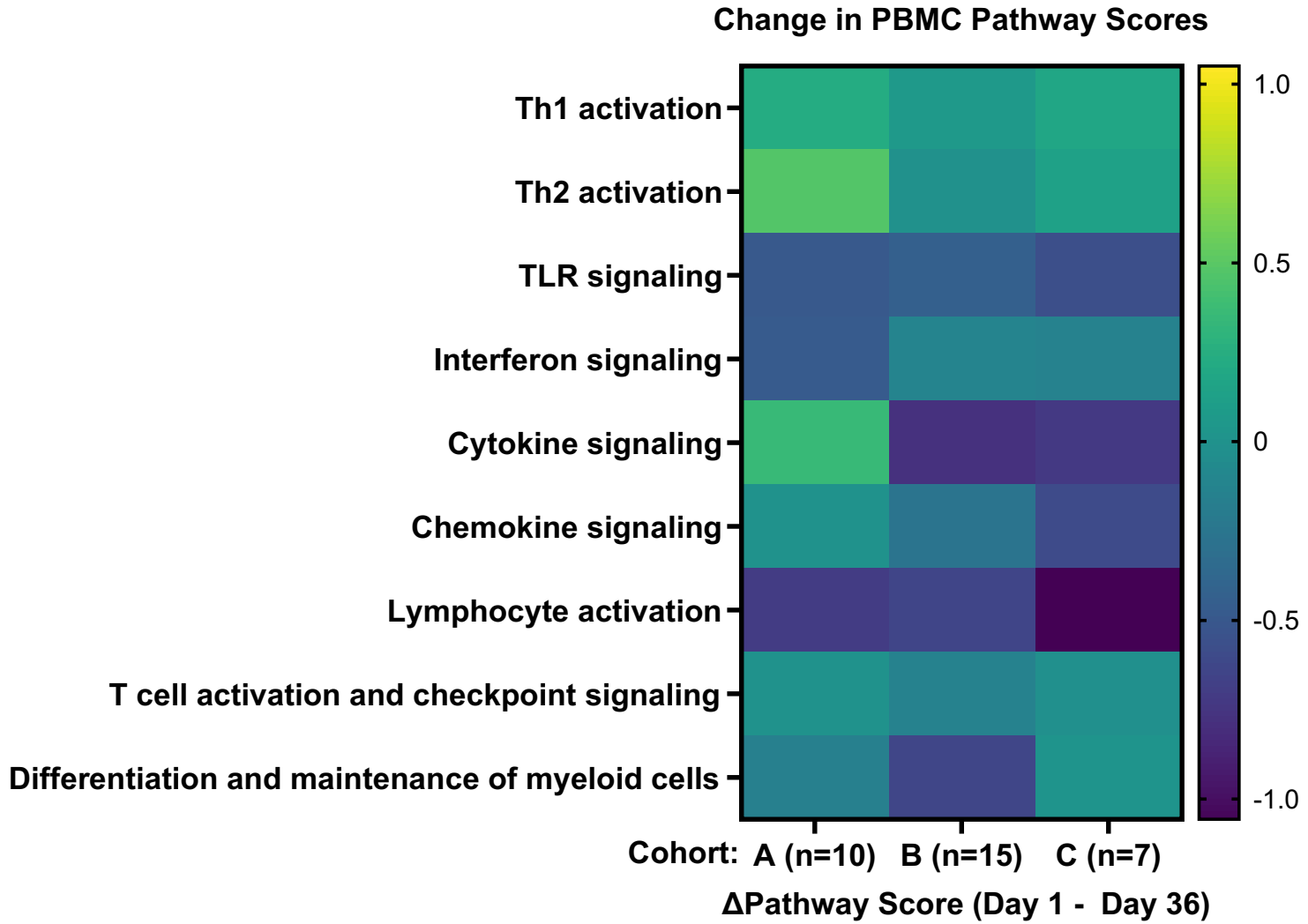
Increased immune cell activation within liver metastases



Pathway scores generated with NanoString nSolver software and normalized mRNA data

Hepatic artery infusion of SD-101 via PEDD associated with induction of T cell activation and cytokine signaling ***in liver metastases***

Peripheral immune signatures in PBMC

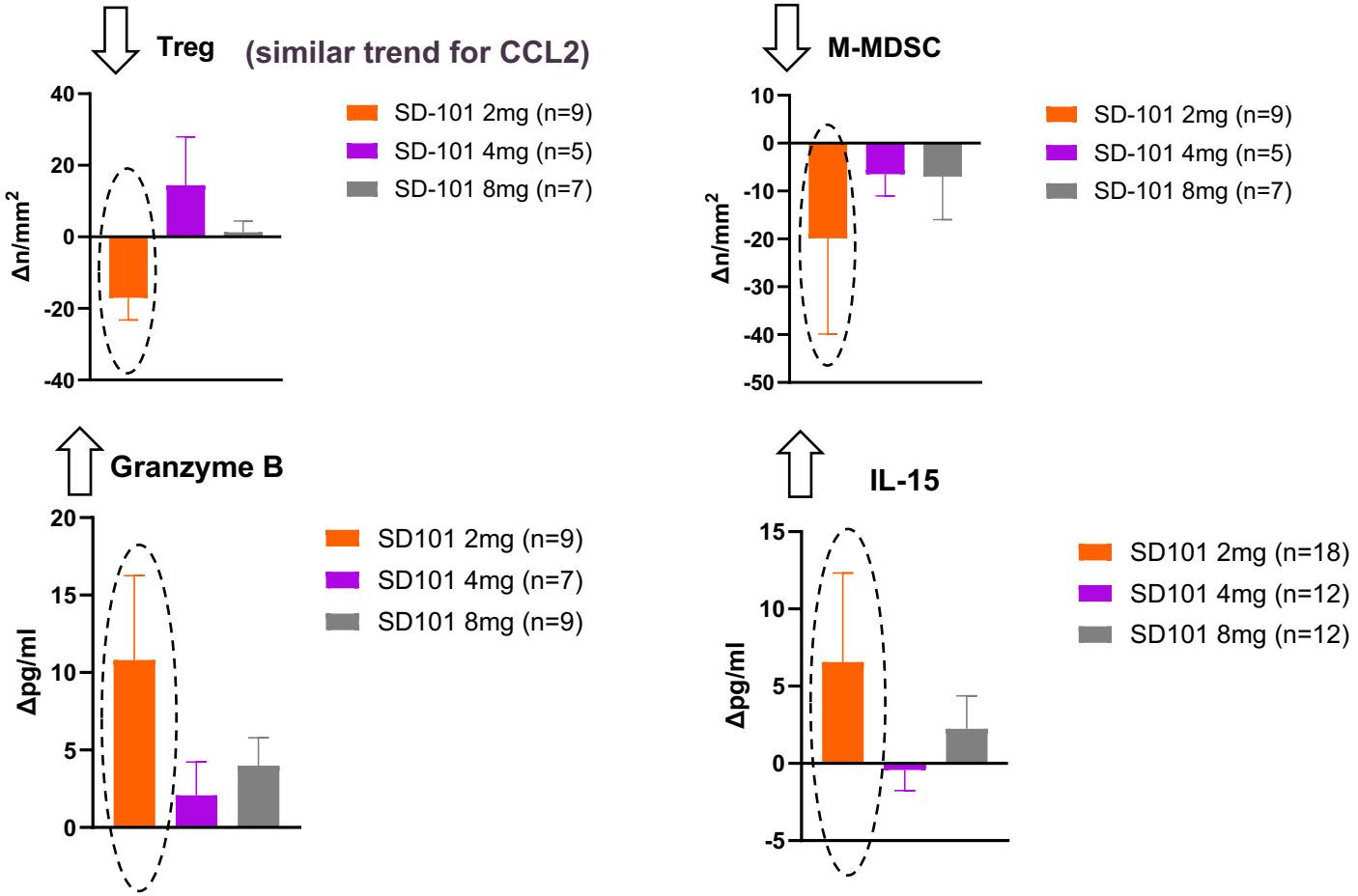


Pathway scores generated with NanoString nSolver software and normalized mRNA data

Hepatic artery infusion of SD-101 via PEDD associated with induction of T cell activation and cytokine signaling ***in the blood*** despite low levels of SD-101 outside of the liver

Optimal dose selection guided by clinical and immune signals

Dose within predicted range elicits expected immune signals within liver metastases from phase 1

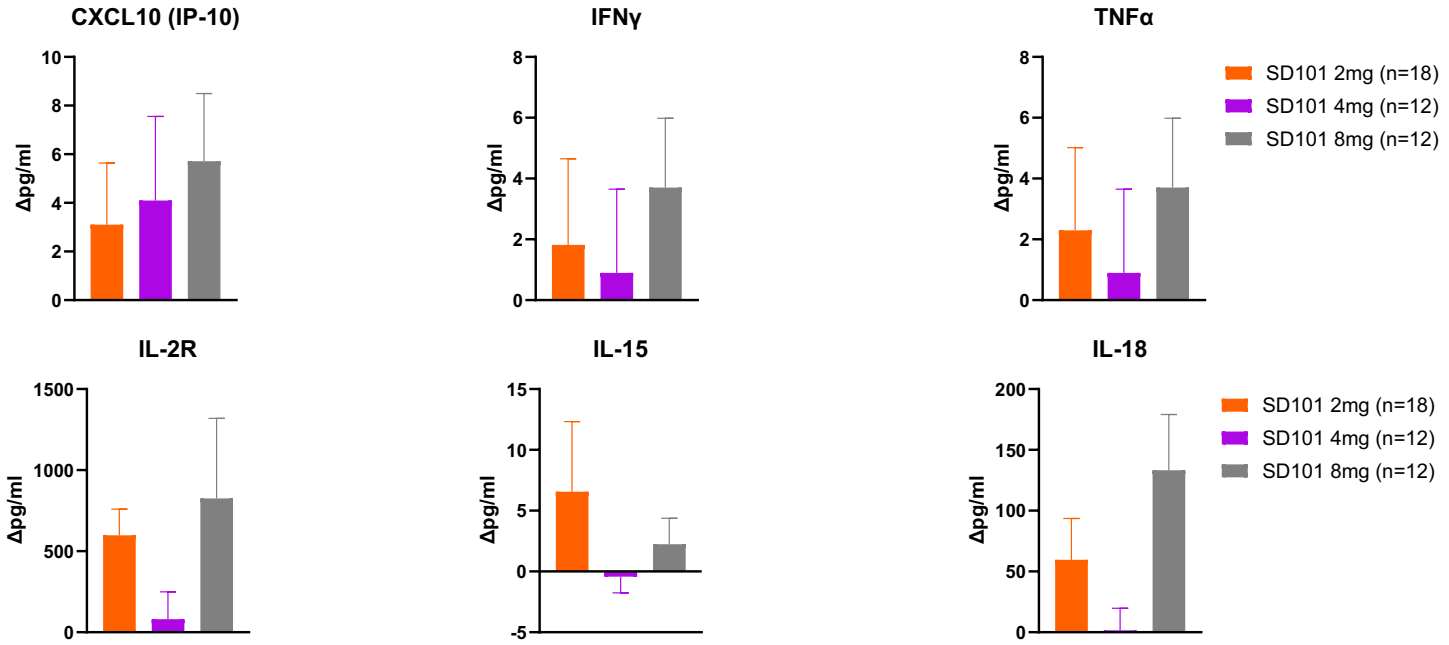


At 2 mg SD-101 via PEDD + nivolumab:

- ⇩ Treg and MDSC in liver tumors – Fewer cells that drive ICI failure
- ⇧ Granzyme B – protein used by T cells to kill tumor cells
- ⇧ IL-15 – Cytokine stimulating anti-tumor T + NK cell immune responses

Further enrollment at 2 mg SD-101 + nivolumab planned

Peripheral immune signatures induced by SD-101 delivered via PEDD

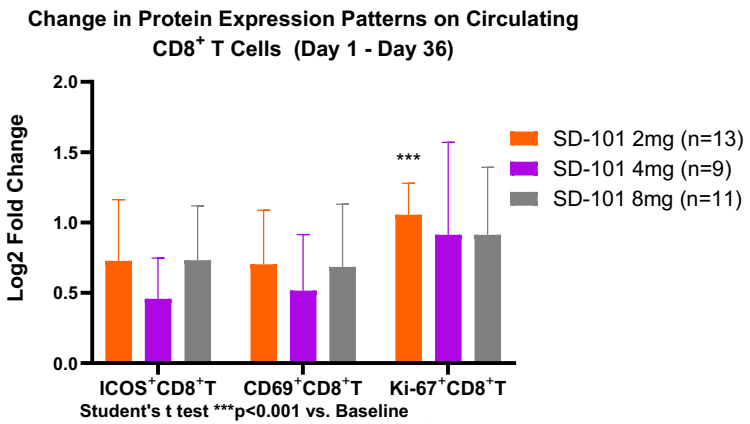


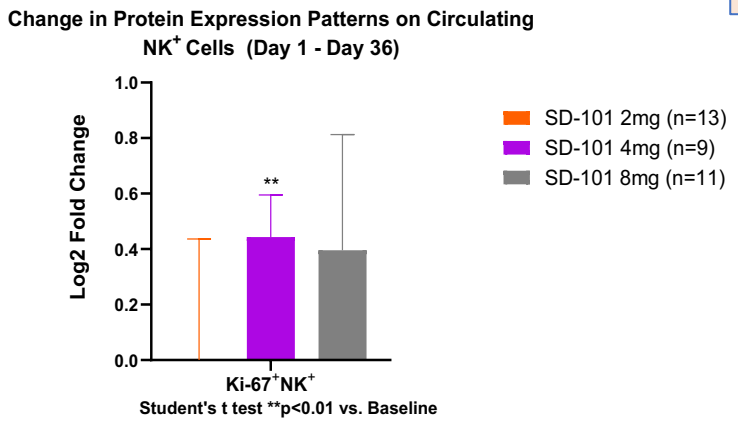
↑Systemic immune activation despite limited SD-101 systemic exposure

↑Pro-inflammatory cytokines

↑$CD8^+$ T cell activation in blood

↑NK cell activation in blood

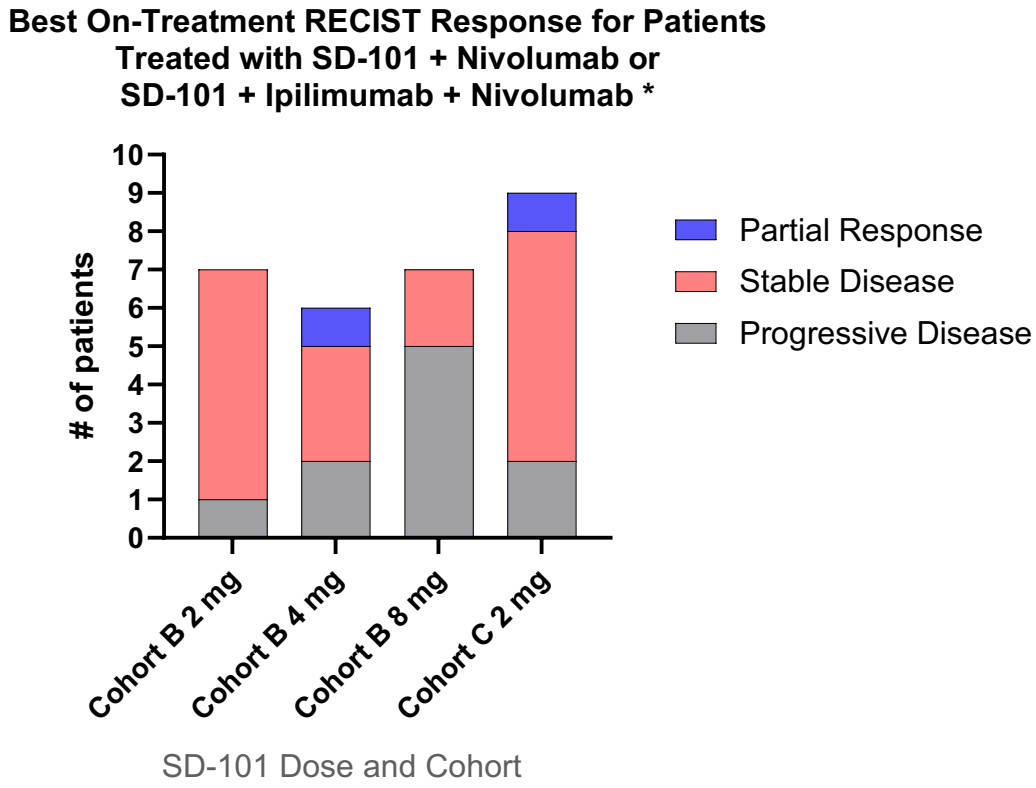




RECIST 1.1 assessment consistent with disease control

Potential for favorable clinical outcomes in absence of tumor shrinkage

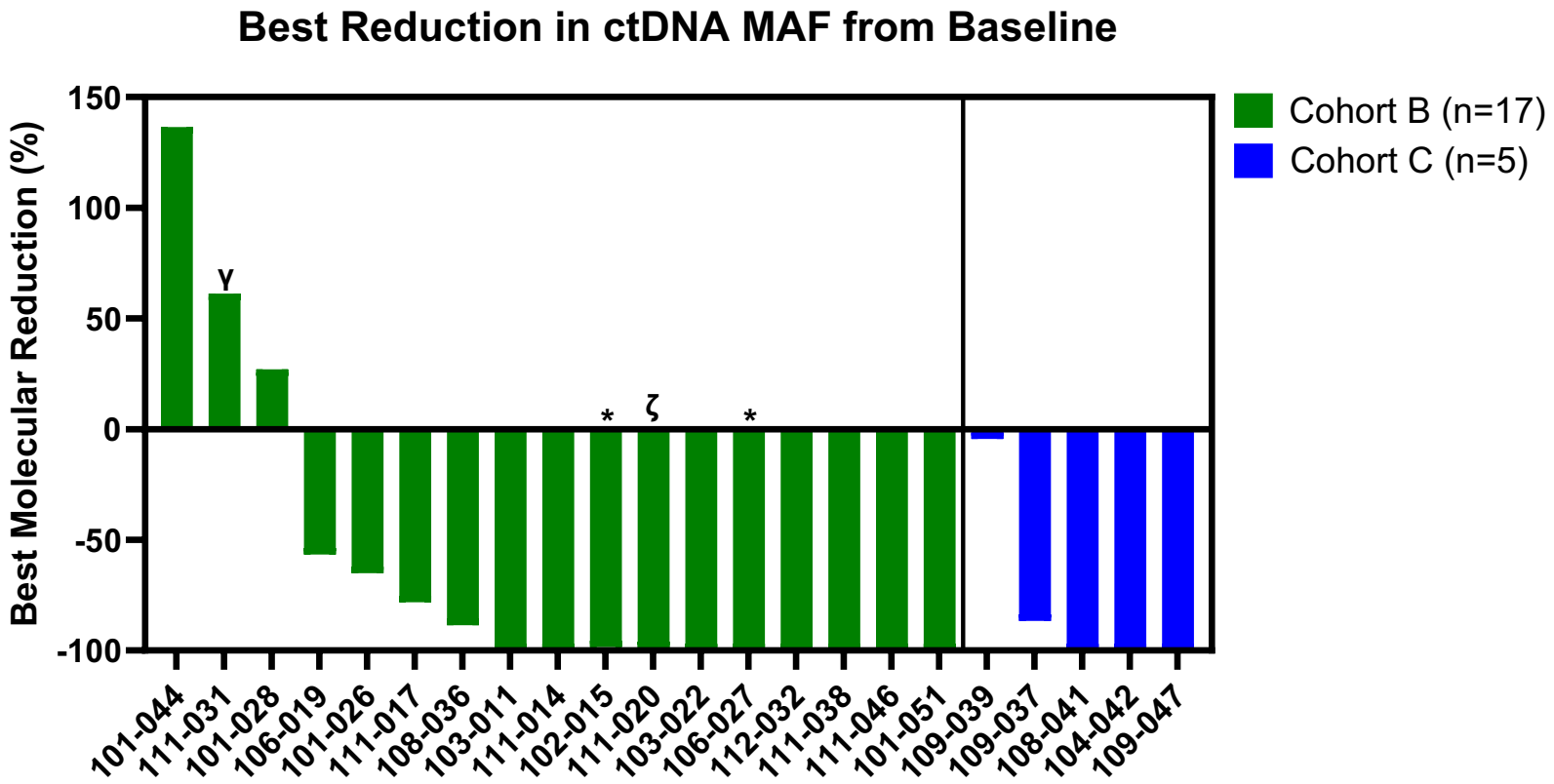
- **58% DCR across all SD-101 doses** in combination with ICI
- Delayed responses noted in some subjects
- ***81% DCR at 2 mg***



DCR: Disease Control Rate
ICI: Immune Checkpoint Inhibitor
SD: Stable Disease

5 SD subjects with 10-29% target lesion shrinkage

Decreased ctDNA observed in heavily pretreated patients



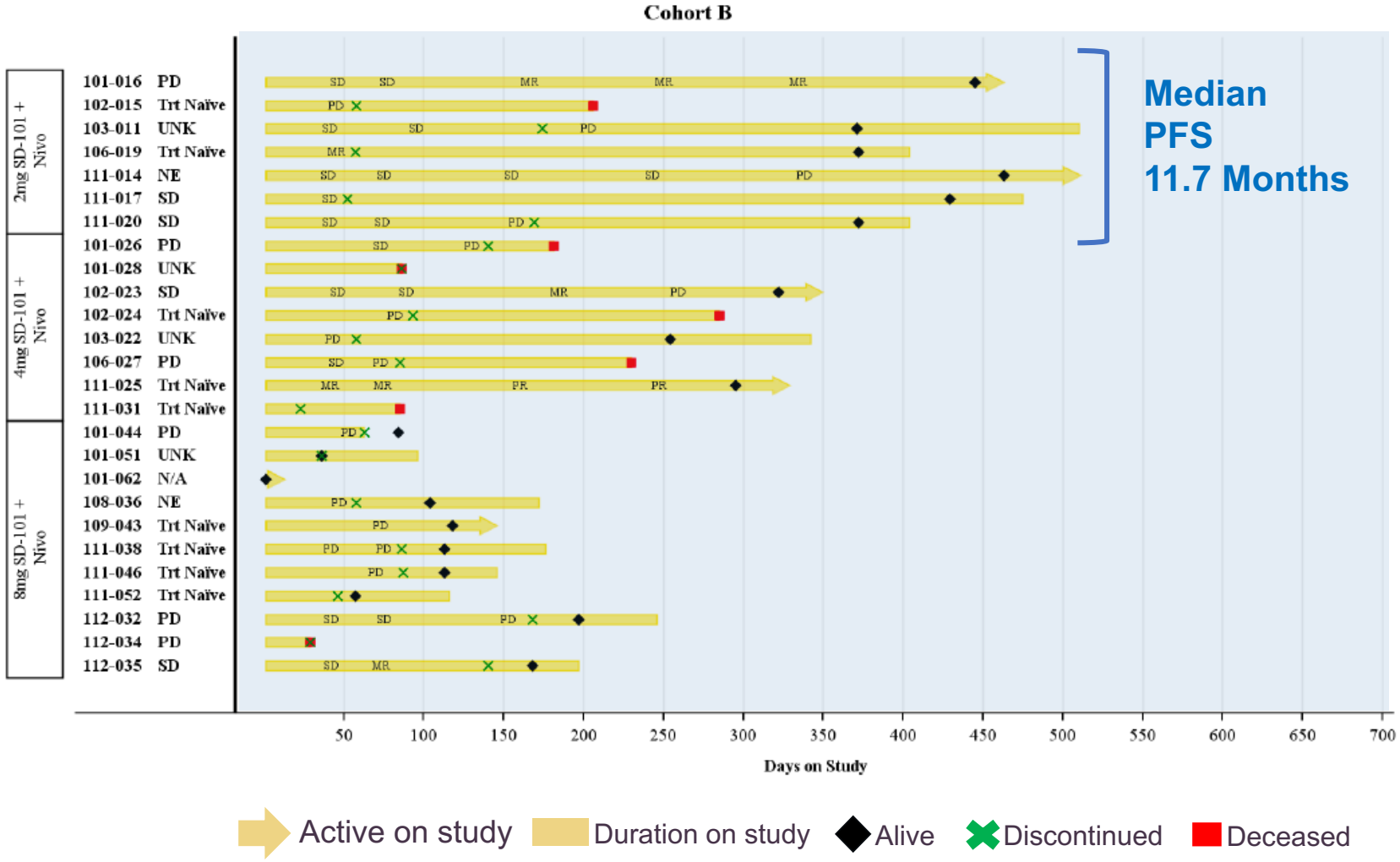
γLate time points (Day 36 and Day 57) unavailable
*Baseline sample hemolyzed with gDNA contamination within the normal range
ζBaseline sample hemolyzed with an uncertain amount of gDNA contamination

- **59%** ctDNA clearance
- **86%** reduction of any rate
- At 2 mg + nivo:
  - **5 of 7 with >50%** decrease in ctDNA
  - 2 patients with ctDNA clearance

ctDNA response correlates with overall survival consistent with published data[1,2,3]

1. Carvajal Nat Med 2022
2. Dawson NEJM 2013
3. Al-Showbaki JITC 2023

Progression-free survival (PFS) and durable disease control



71% 2L and beyond, including 4L and 6L patients

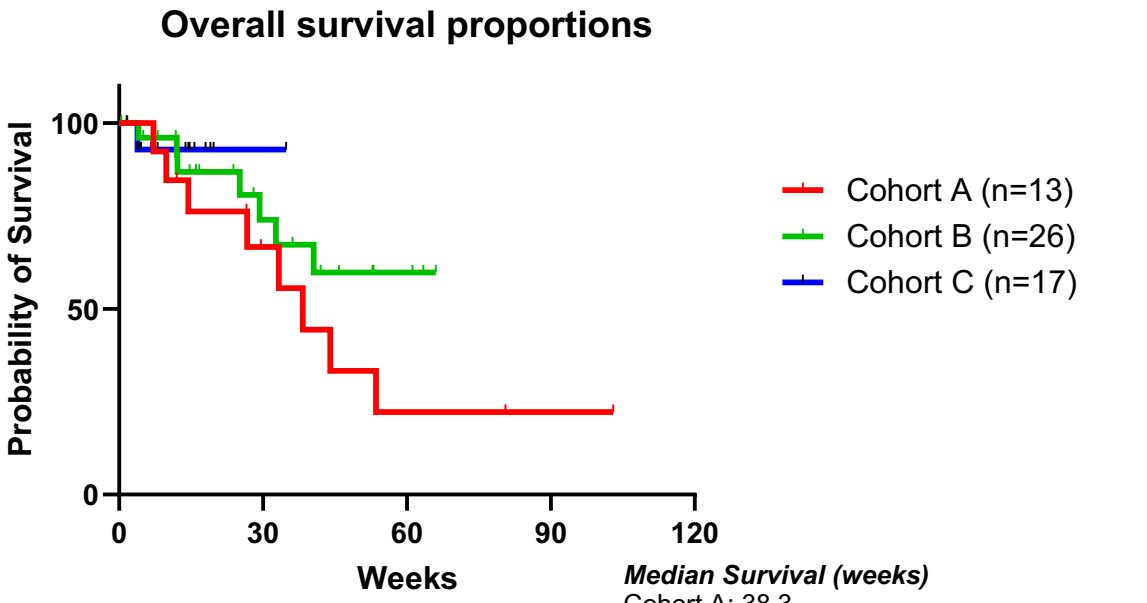
59% ctDNA clearance in naïve + pre-treated patients

Prolonged PFS in the setting of mainly SD objective responses suggests imaging underestimates clinical activity of therapy

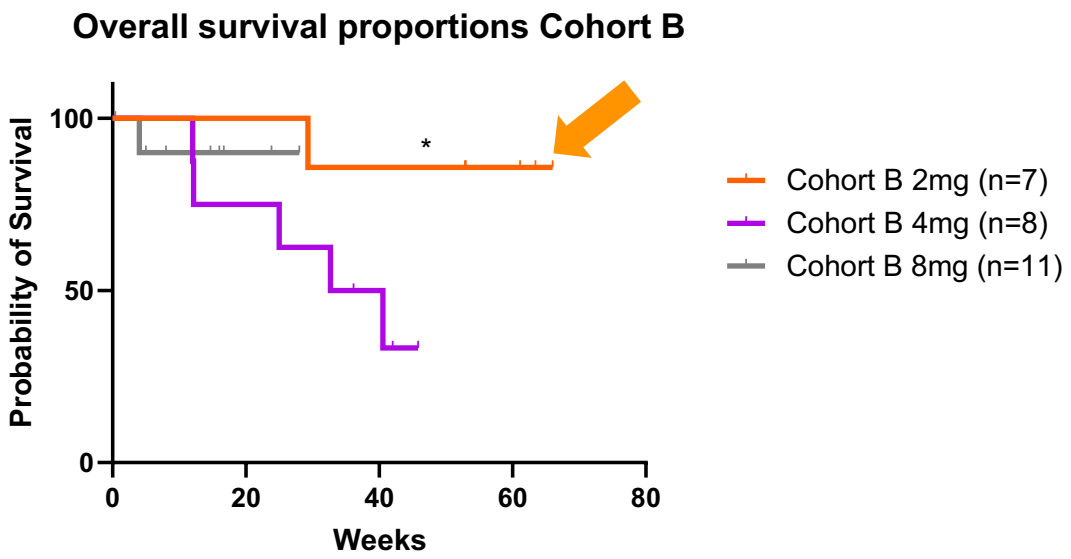
SD = Stable Disease (+19% to -29%) **MR** = Minor Response (10-29% decrease) **PR** = Partial Response (≥30% decrease)

Due to the timing of the Cohort C 2mg PR, result was not included in swim plot.

Overall survival (OS) by cohort and dose level



Median Survival (weeks)
Cohort A: 38.3
Cohort B and C: Undefined (survival > 50%)



Log-rank (Mantel-Cox) test
*p=0.057 vs. Cohort B 4mg

Median Survival (weeks)
Cohort B 4mg: 36.6
Cohort B 2 and 8 mg: Undefined (survival > 50%)

1-year OS at 2 mg SD-101 + nivo – 86%

Comprehensive review of biologic effects points to 2 mg SD-101 + nivolumab

- ↓**Treg** in liver metastases
- ↓Monocytic **MDSC** in liver metastases
- Median **PFS** 11.7 months
- 1 year **OS** 86%
- 5 of 7 with >50% decrease in **ctDNA**
- No Grade 3/4 **TRAEs**

TS-PERIO-01 Summary

- Promising approach for **addressing barriers to success** in treating liver metastasis in uveal melanoma
- SD-101 in combination with ICI well tolerated with limited peripheral exposure
- Expected immune effects, including **liver MDSC depletion** consistent with SD-101 mechanism of action
  - Augmentation of Treg and M2 macrophage populations also documented in liver metastasis
  - Peripheral cytokine changes suggest CD8 and NK cell activation
- **ctDNA molecular response rates encouraging**
  - 86% of patients experienced ctDNA reduction from baseline
  - 59% complete clearance
- **2 mg SD-101 + nivolumab**
  - Median PFS of 11.7 months
  - Most favorable augmentation of tumor microenvironment
  - Disease control rate of 81%

SD-101 via pressure-enabled drug delivery (PEDD) + ICI has the potential to address a significant unmet clinical need for uveal melanoma liver metastasis

Acknowledgements

Massachusetts General Hospital (Kamaneh Montazeri)
University of Pittsburgh Medical Center (Diwakar Davar)
University of Miami (Jose Lutzky)
Stanford Cancer Center (Sunil Reddy)
Columbia University (Alexander Wei / Richard Carvajal*)
UCLA Jonsson Comprehensive Cancer Center (Bartosz Chmielowski)
University of Washington (Shailender Bhatia)
University of Colorado (Theresa Medina)
Thomas Jefferson University (Marlana Orloff)
MD Anderson Cancer Center (Sapna Patel)

*Northwell Health Cancer Inst

Abstract: 647:
PERIO-03: Pancreatic adenoca

Abstract 1123:
SD-101 with subcutaneous ICI

NCT04935229 PERIO-01 is sponsored by TriSalus Life Sciences