Addressing Mechanical and Biologic Features of Immunotherapy Failure in Liver Metastases

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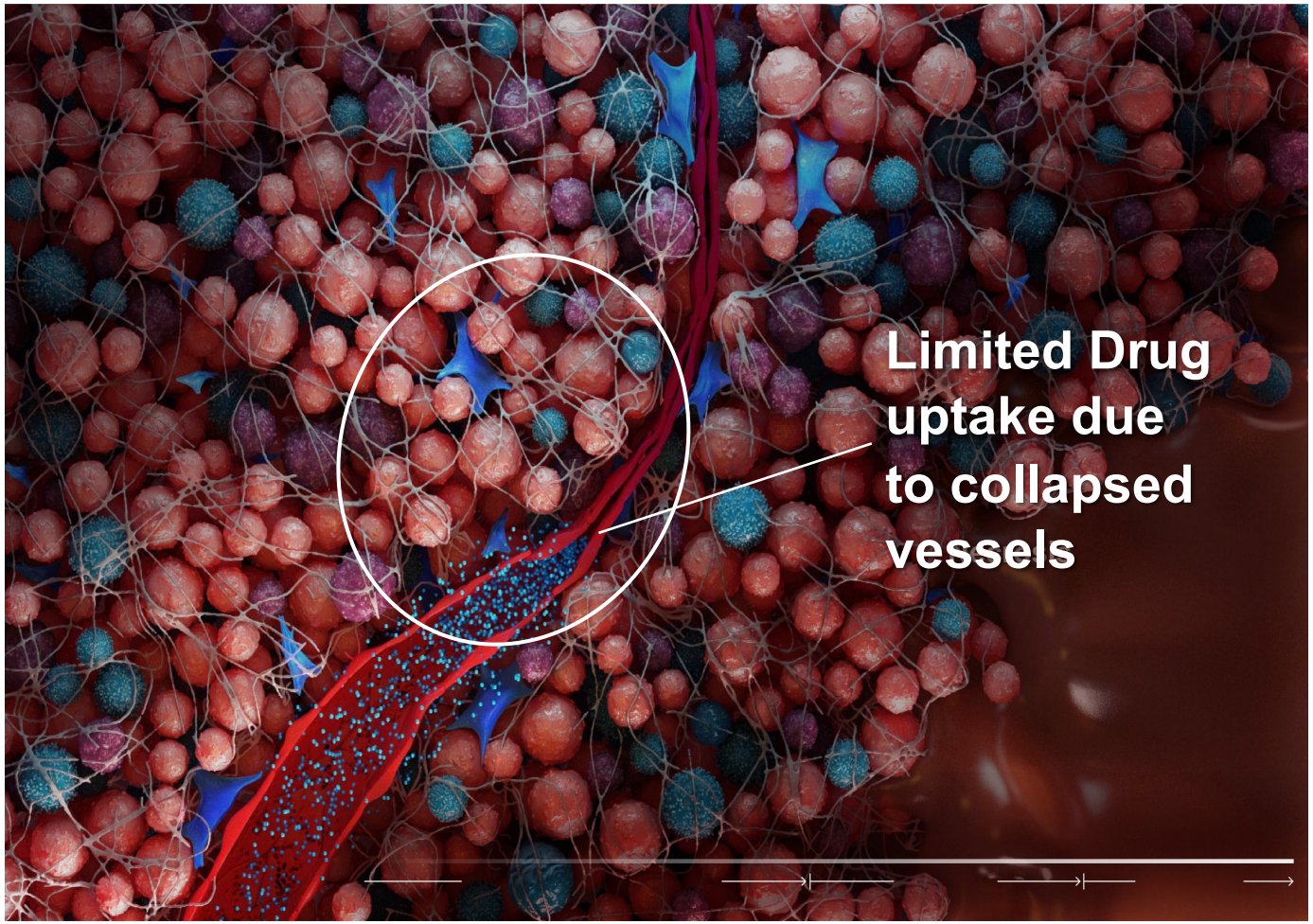
Two important barriers to immunotherapy success in liver tumors



1. Mechanical

The **pressure** within the tumor can be higher than the patient's blood pressure, limiting drug uptake

2. Biologic

MDSC orchestrate a complex **immunosuppression network** involving multiple cell types and soluble factors

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Guha, P., Reha, J. & Katz, S. C. Immunosuppression in liver tumors: opening the portal to effective immunotherapy. Cancer Gene Ther. 24, 114–120 (2017).

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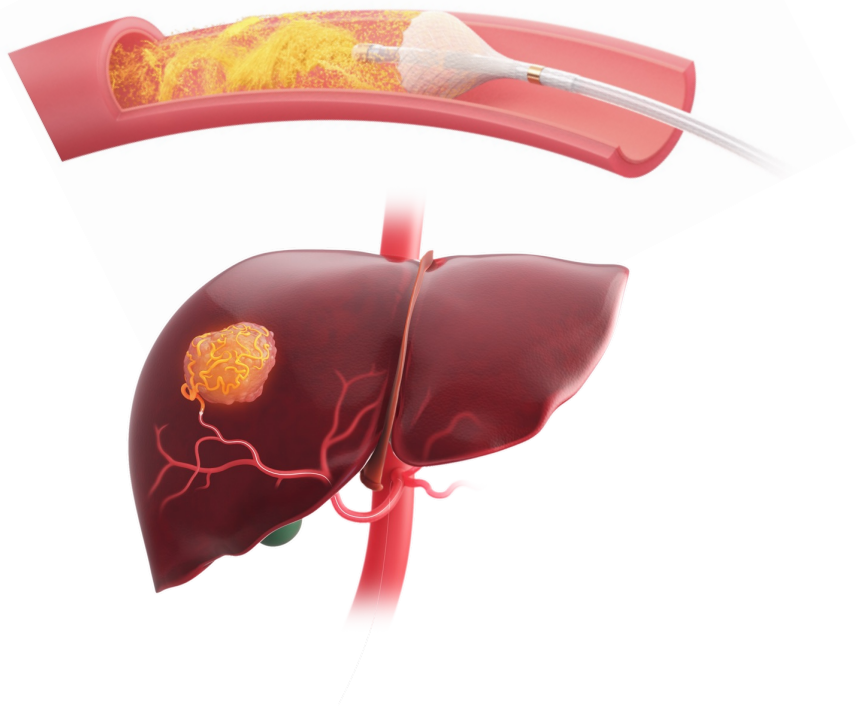
Pressure Enabled Drug Delivery (PEDD™) works in sync with the cardiac cycle to modulate pressure and flow to improve therapeutic delivery

PEDD has been demonstrated to

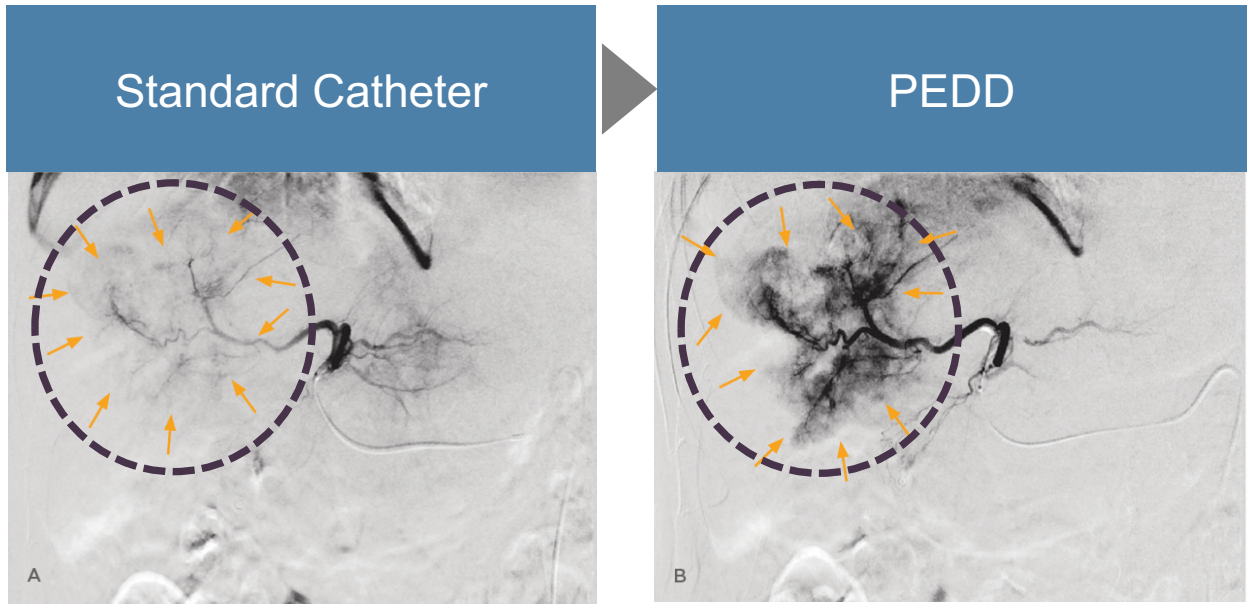
- Work in sync with the cardiac cycle[1*]
- Atraumatically increase local vascular pressure [2‡]
- Improve therapeutic delivery[3,4,5]
- Modulate of intravascular pressure gradient and flow[2]
- Improve T:N ratio for improved accuracy and predictability[3,4]



1. Data on file, TriSalus™ Life Sciences, 2019
*Study Design: Ultrasound was employed in a porcine model to image tip performance in relation to the cardiac cycle
2. Data on file, TriSalus™ Life Sciences, 2019
‡ Study Design: Pressure wire introduced during planning angiogram to measure pressure of PEDD with SmartValve tip collapsed, expanded and during high-pressure saline flush
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. “HITM-SURE: Phase Ib CAR-T hepatic artery infusion trial for stage IV adenocarcinoma using Pressure-Enabled Drug Delivery technology.” SITC (2018) Poster Presentation.

How Can we Get More Therapeutic Into High Pressure Tumors?

Same liver cancer patient treated with different devices.



Interventional radiologist injected contrast dye into tumor vessels.

Angiogram of tumor vessels demonstrated that PEDD

- ↑ Delivery of contrast dye into liver tumor
- ↑ Opening of collapsed tumor vessels
- ↓ Reflux of contrast dye into normal liver

1. TriSalus images and data on file.

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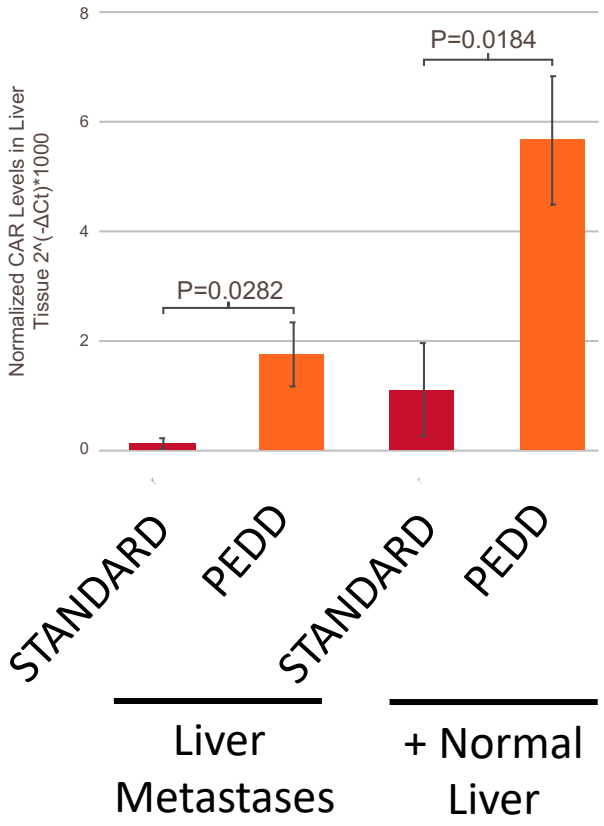
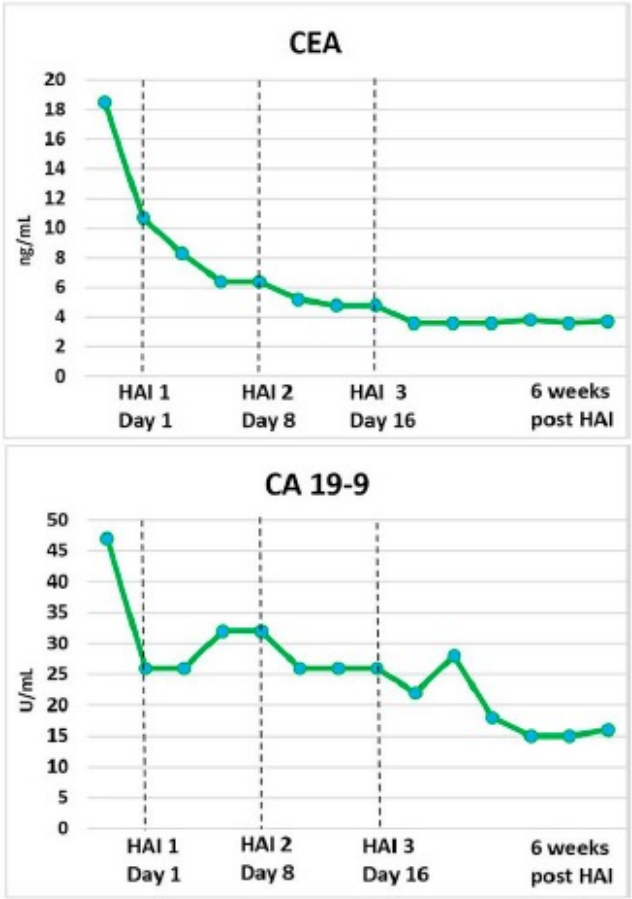
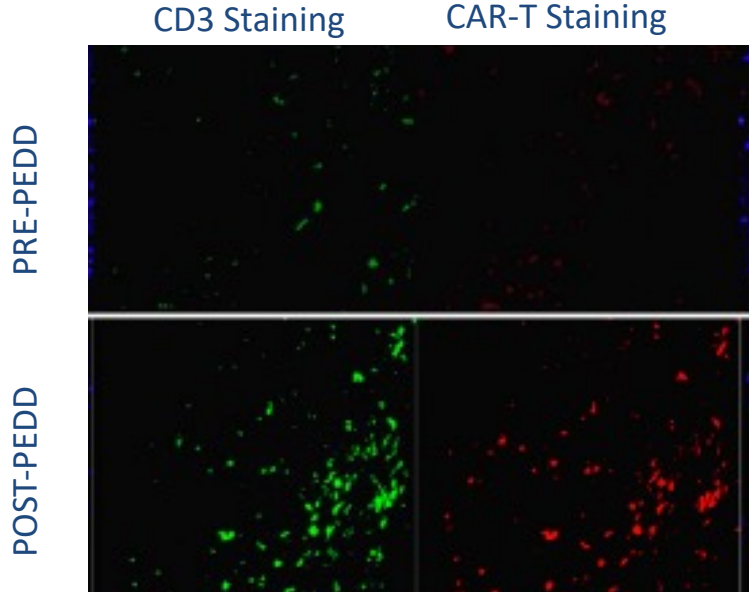
Addressing CAR-T Exclusion in Liver Metastasis Patient

5-fold Trafficking Improvement



Tumor Markers Normalized





Journal for ImmunoTherapy of Cancer

HITM-SURE: Hepatic immunotherapy for metastases phase Ib anti-CEA CAR-T study utilizing pressure enabled drug delivery

Steven C Katz,[1,2,3] Ashley E Moody,[1] Prajna Guha,[1] John C Hardaway ,[1] Ethan Prince,[4] Jason LaPorte,[1] Mirela Stancu,[5] Jill E Slansky,[6] Kimberly R Jordan,[6] Richard D Schulick,[6] Robert Knight,[7] Abdul Saied,[1] Vincent Armenio,[2] Richard P Junghans[8]

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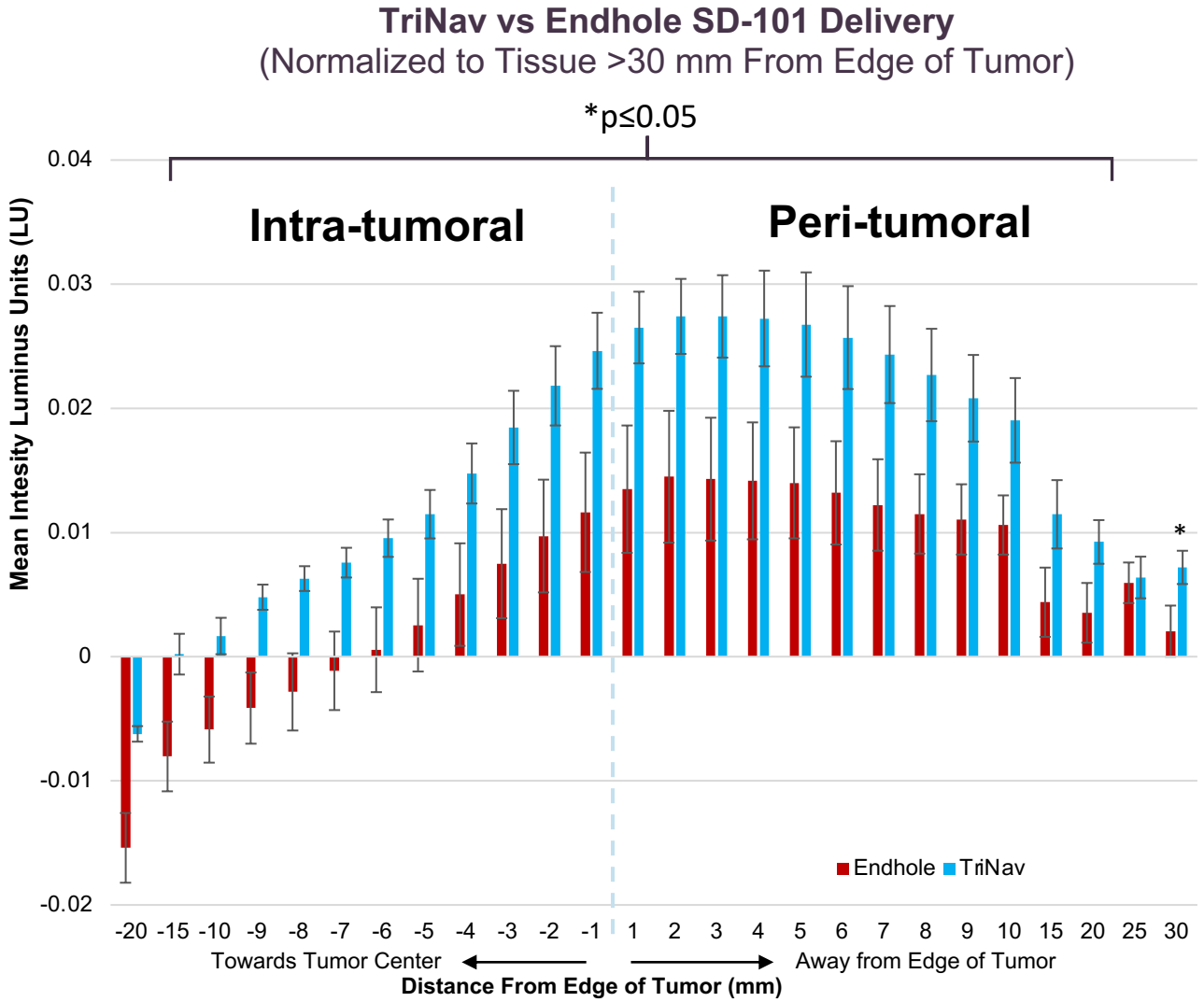
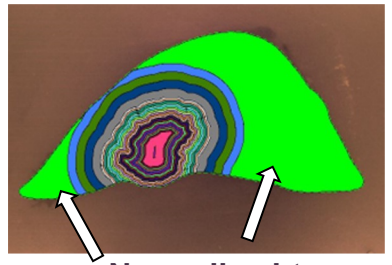
SITC 2018

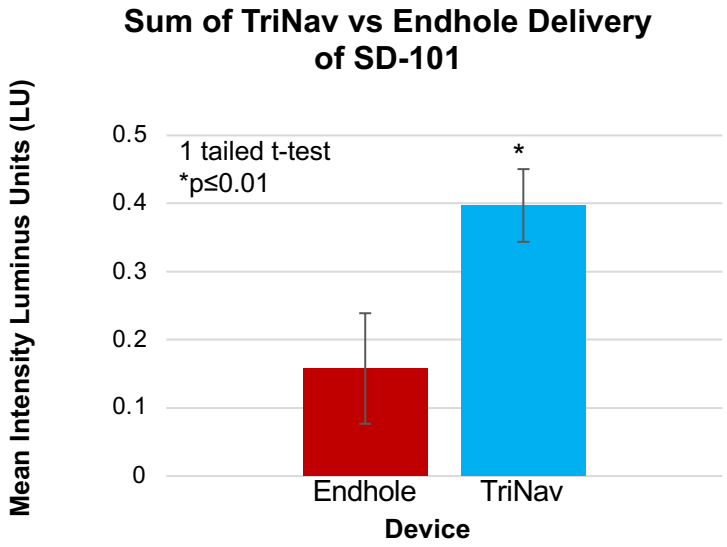
PEDD Enhanced TLR9 Agonist Delivery in Oncopig Liver Tumors





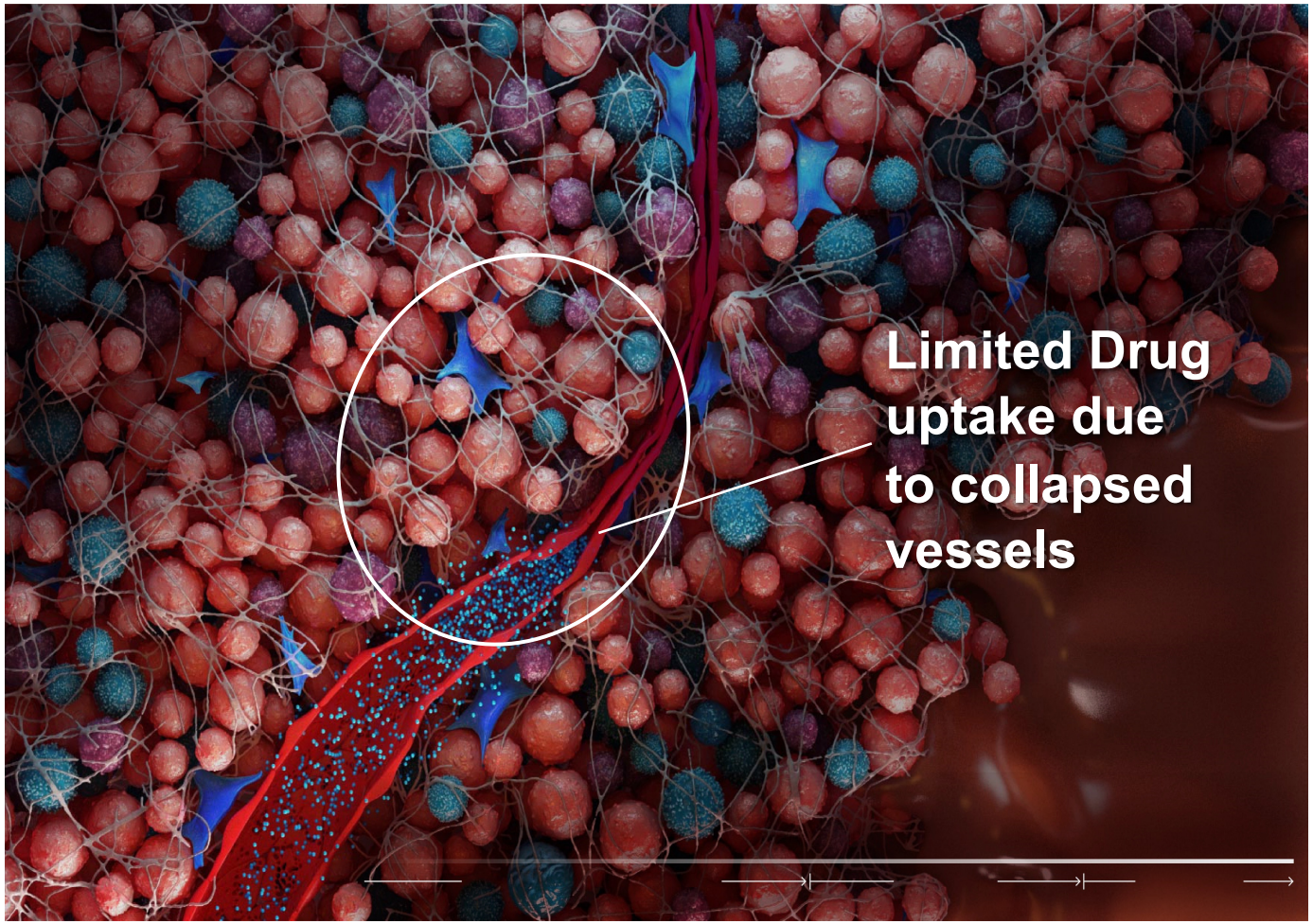
>30 mm from edge of tumor

Normalized to background signal



TriSalus™ Shown are means and standard errors for TriNav (N=9) and Endhole (N=9) intra arterial delivery of SD-101. 1 tailed t-test Hullinger SIO 2023.

Two important barriers to immunotherapy success in liver tumors



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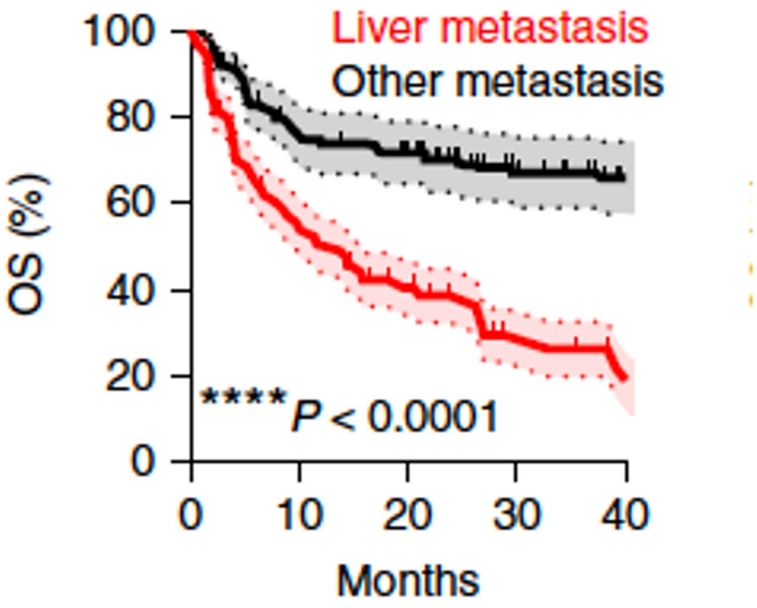
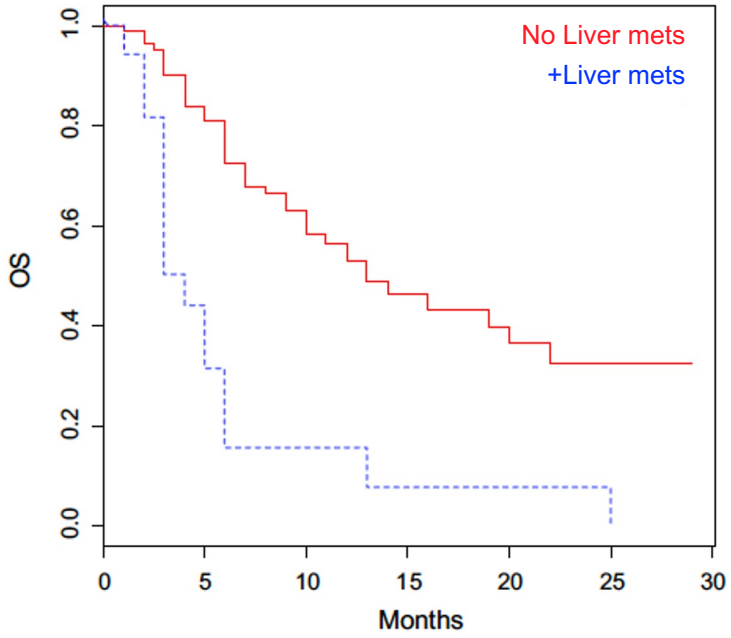
Do liver tumors drive immunotherapy failure?

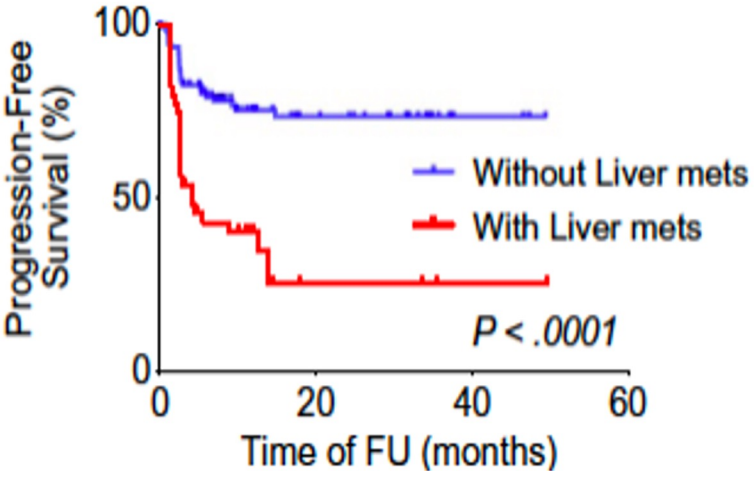
In **multiple indications**, liver mets predicted CPI failure **in association with myeloid cell driven suppressio**n[1]



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

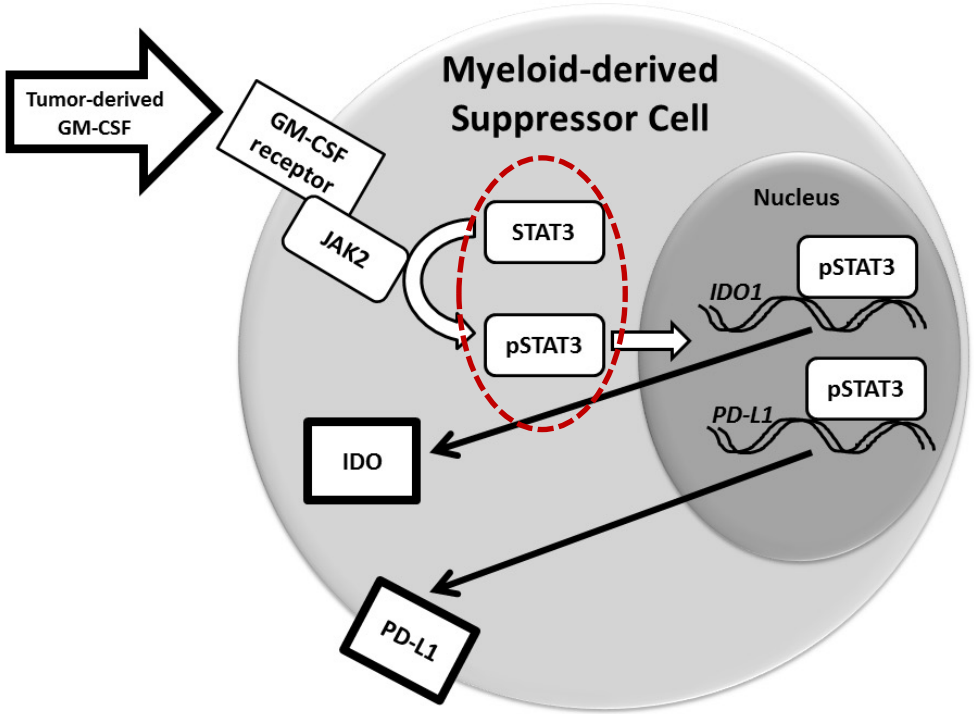


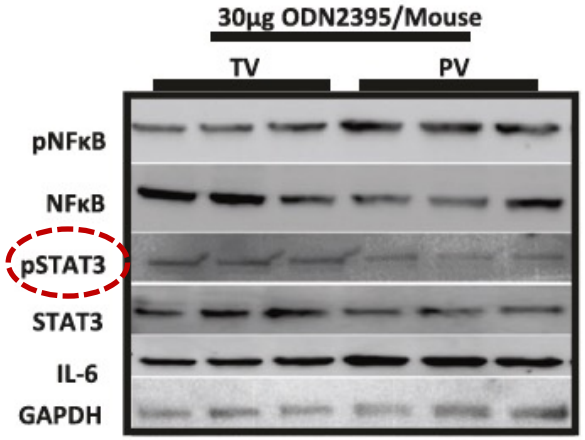
In **cutaneous melanoma** patients, liver mets predicted inferior PFS and OS[3]

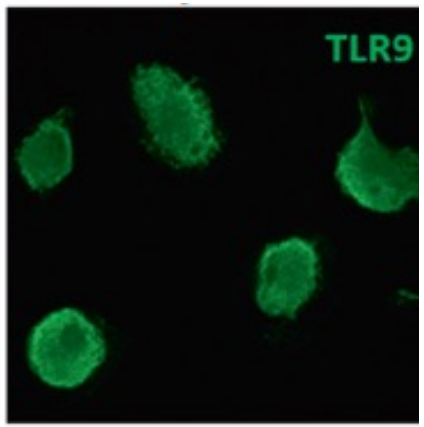


1. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med.* 2021;27:152-164. https://doi.org/10.1038/s41591-020-1131-x; 2. Botticelli A, Salati M, Di Pietro FR, et al. A nomogram to predict survival in non-small cell lung cancer patients treated with nivolumab. *J Transl Med. 2019;*17:99. https://doi.org/10.1186/s12967-019-1847-x; 3. Silva I, Lo S, Quek C, González M, Carlino M, Long G, and Menzies A. Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti–PD-1 therapy. *Cancer.* 2019;126: 10.1002/cncr.32522.

Rationale for targeting liver MDSC with SD-101







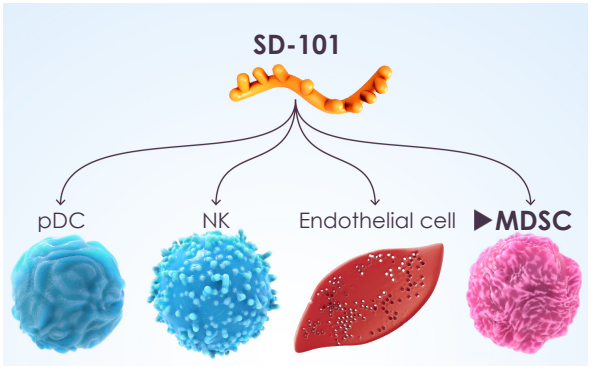
1. ***STAT3 drives liver MDSC expansion, survival, and function***
2. ***TLR9 signaling can deactivate STAT3***
3. ***MDSC express TLR9***

Ghosh 2023
Thorn 2016

SD-101 dual mechanism of action chosen for liver and pancreas

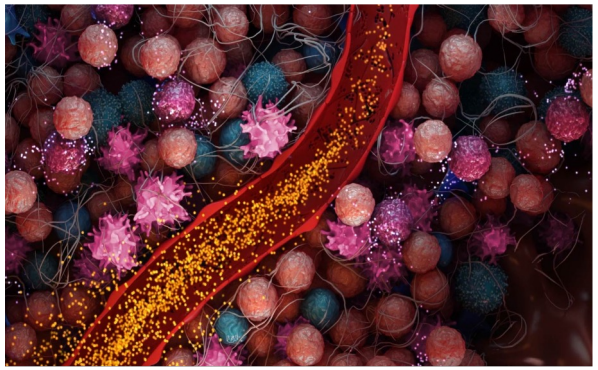
▶ **SD-101** reprograms the TME through multiple mechanisms

1. SD-101 binds to TLR9

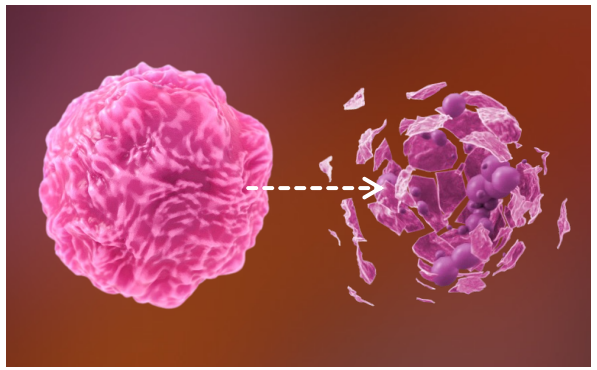


SD-101 acts on multiple cell types

2. Broad TME activation by SD-101 via PEDD

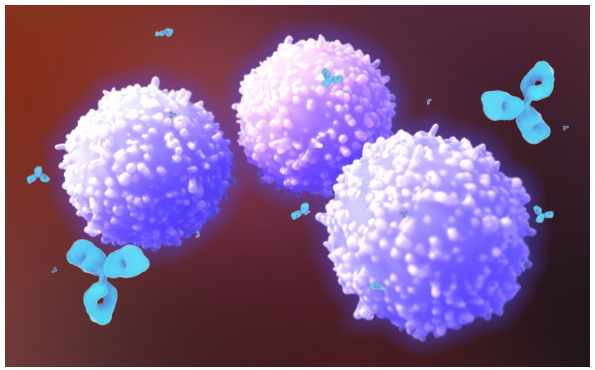


3. MDSC elimination



Dual mechanism of action

4. T cells accumulate in tumor for CPI binding



CPI molecules bind to T cells recruited to tumor

TME = tumor microenvironment
CPI = checkpoint inhibitor

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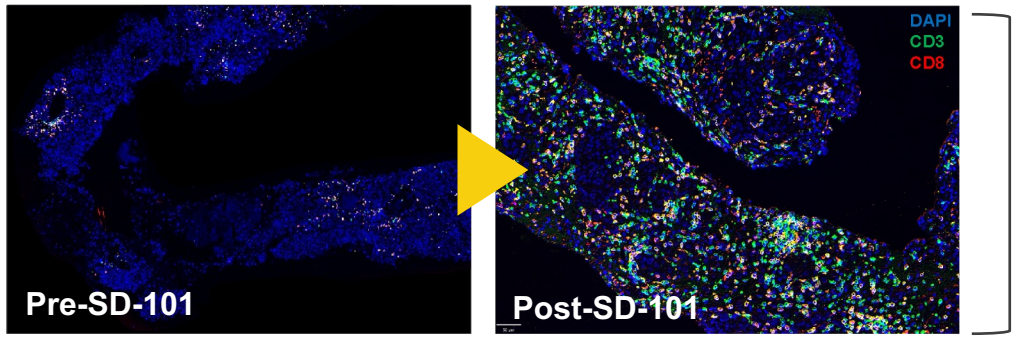
1. Ghosh. Cancer Gene Therapy 2023
2. Montazeri. ASCO 2023

SD-101's Dual MoA Well Suited for Liver and Pancreas Tumors



Increase in liver metastasis T cells following SD-101 treatment (PERIO-01)

1 Broad Immune Modulation of the Tumor[1,2,3]

- Stimulates multiple immune cell types
- Drives T-cell infiltration to enable checkpoint activity

2 MDSC Depletion[4,5]

- MDSC reduction in initial studies consistent with pre-clinical mechanism (deactivation of STAT3)[2,4]
- Attacks liver-specific MDSC pathways[4]

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1. TriSalus data on file; 2. Ghosh CC, et al. *Cancer Gene Ther*. 2022 Dec;29(12):1854-1865; 3. Journal of Clinical Oncology 2019;37(15):9534-9534; 4. Guha, et al. 2020 November 4 (online ahead of print); 5. Montezari ASCO 2023

PERIO-01 Study Regimen

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

COMPLETED

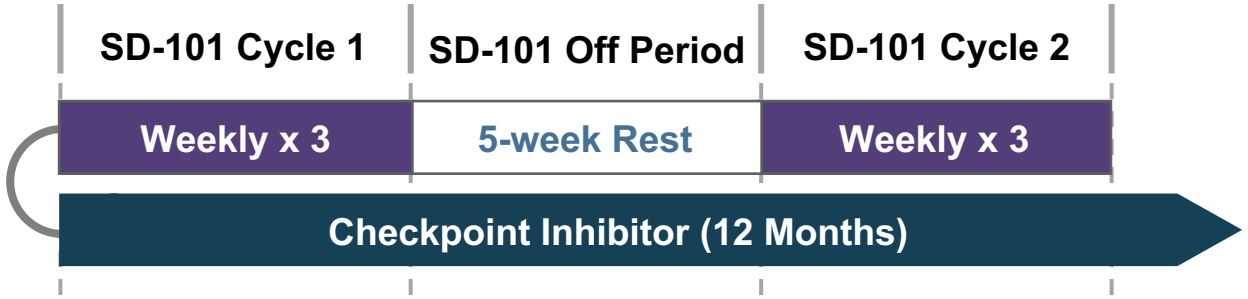
Cohort B
SD-101 + Anti-PD-1 Dose Escalation (n=6-12)

8 DOSE LEVELS OPEN

Cohort C
SD-101 + Anti-PD-1 + Anti-CTLA-4
Dose Escalation (n=6-12)

4 MG DOSE LEVEL OPEN

REGIMEN
SD-101 via PEDD
Checkpoint via
Systemic Infusion



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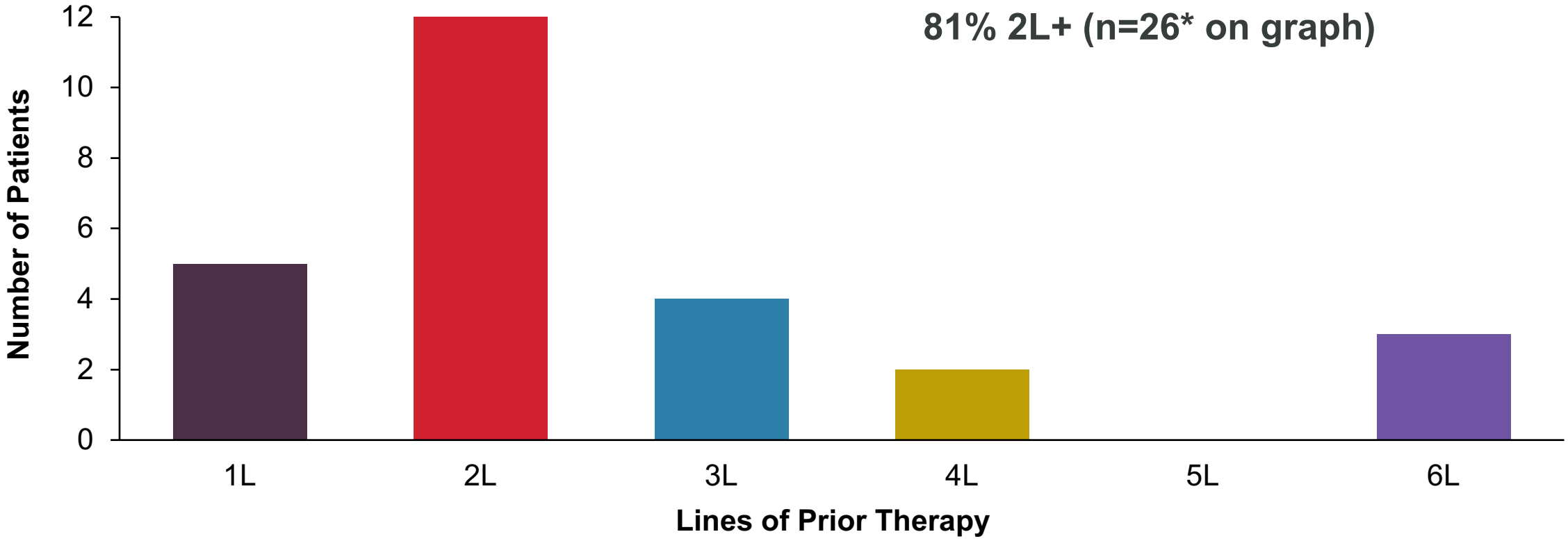
Montazeri. ASCO 2023

Phase 1 Uveal Melanoma Liver Metastasis Patient Characteristics



*Data not available for all patients

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SD-101 well tolerated with low level of Serious AE's

TS-PERIO-01 Phase 1 (1L if Kimmtrak ineligible; 2L+ if Kimmtrak eligible)			
	TriSalus (SD-101) N=39 (phase 1)	**Immunocore (Kimmtrak)** N=378 (2:1 RCT)	**Ideaya (Ph2 interim)** N=37
Stage IV UM LM population eligible	**100%**	~ 50% (HLA-0201+)	~ 50% (HLA-0201-)
Serious adverse event rate related to drug	**5%**	44%	>31% (one death)
Grade 2 or higher cytokine release syndrome	2%	76%	N/A

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PEDD concentrates SD-101 in liver with well-tolerated systemic immune effects

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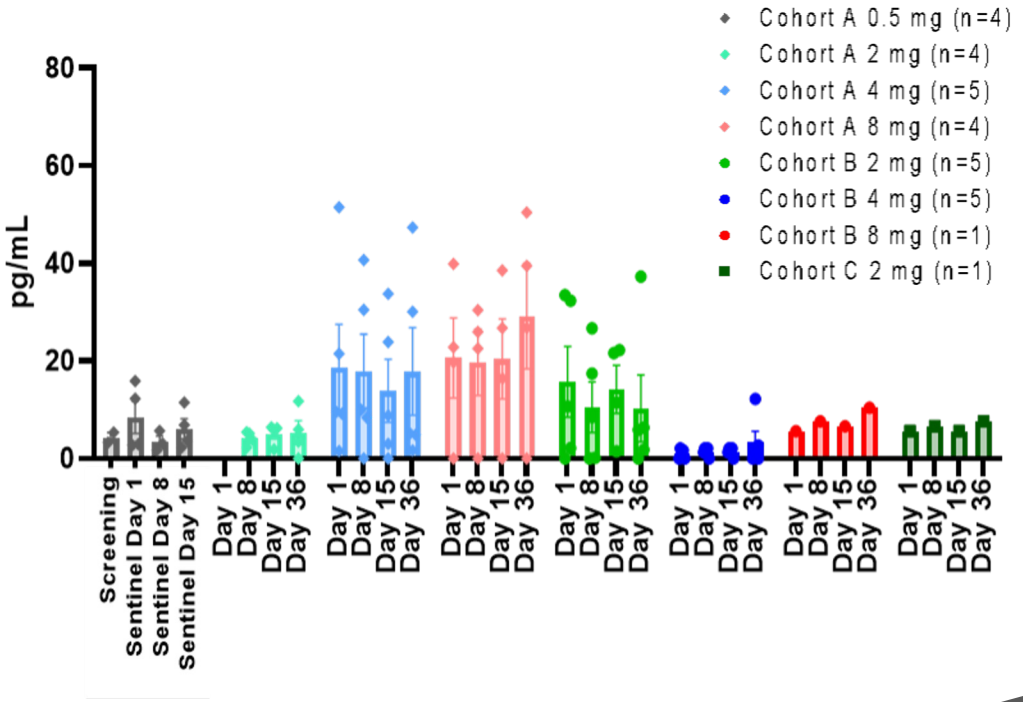
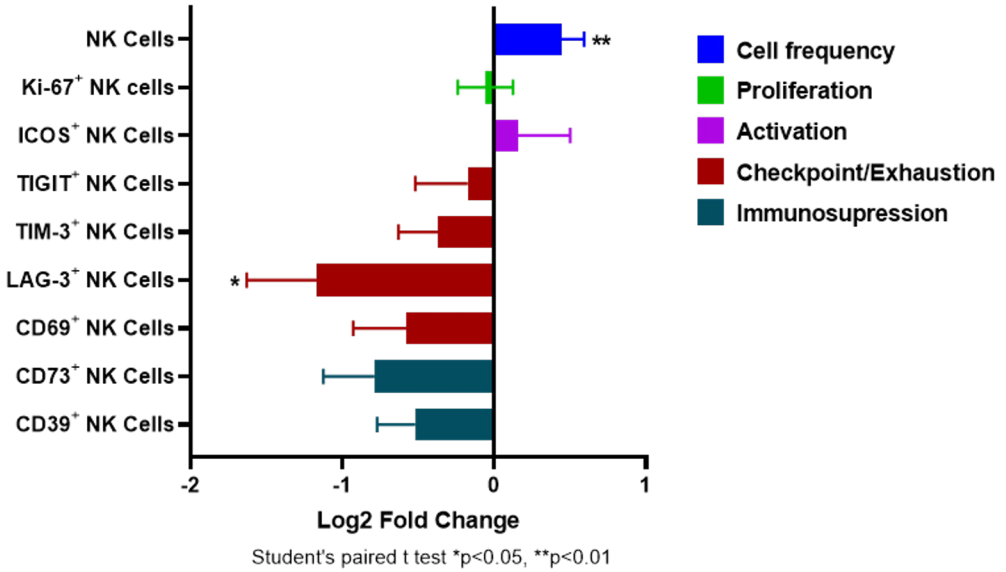
Montazeri et al. ASCO 2023

SD-101 Activity in Liver Associated with Well Tolerated Systemic Immune Effects

IFNγ



Change in Circulating NK Cell Protein Expression Patterns (Day 1–Day 36)



Student's paired t test *p<0.05, **p<0.01

Data represented as Mean ± SEM (n=19)

Serum IFNγ and peripheral blood natural killer cells

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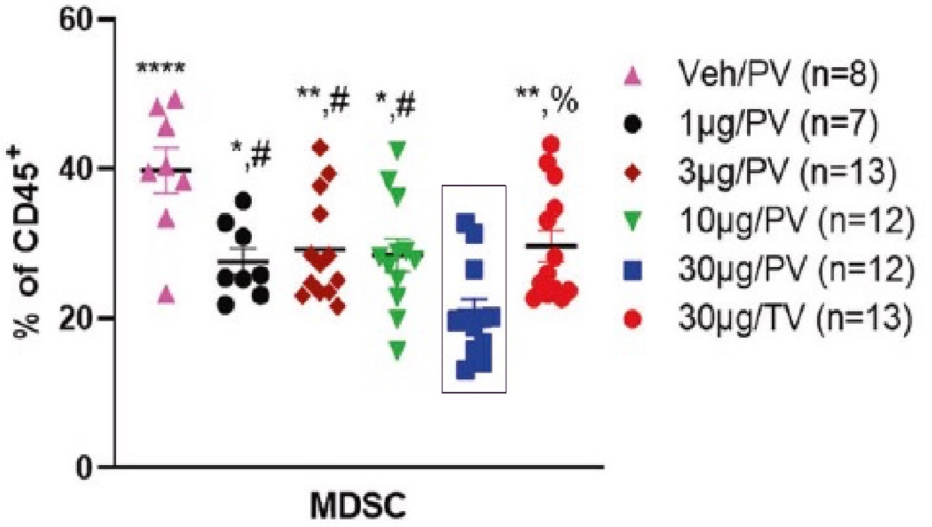
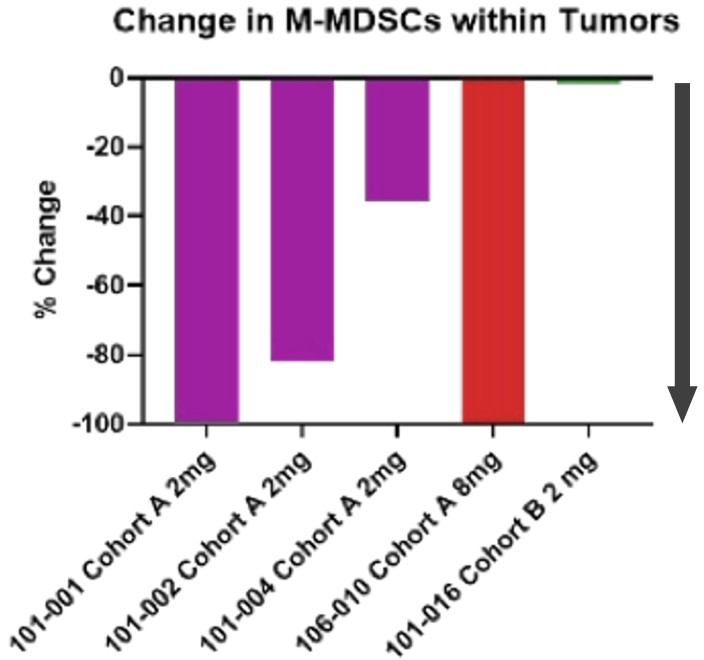
PEDD Pre-clinical Model and Clinical MDSC Depletion Data

↓ Liver MDSC in Pre-Clinical Model



*p<0.05, **p<0.01,****p<0.0001 (compared to 30µg/PV)
%p<0.05, #p<0.01 (compared to Veh/PV)

↓ Liver MDSC in PERIO-01 Patients



Reduction in liver metastasis MDSCs in 5 of 5 patients (PERIO-01)

Larger confirmatory data set to be released in Q4 2023

Ghosh CC, Heatherton KR, Connell KPO, et al. Regional infusion of a class C TLR9 agonist enhances liver tumor microenvironment reprogramming and MDSC reduction to improve responsiveness to systemic checkpoint inhibition. *Cancer Gene Ther.* 2022;29:1854-1865. https://doi.org/10.1038/s41417-022-00484-z

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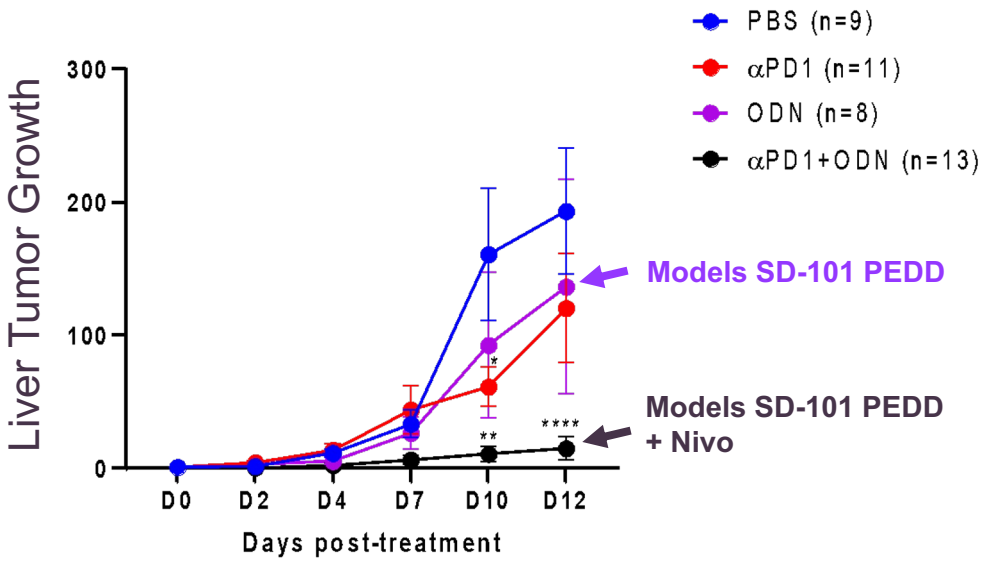
PEDD Pre-clinical Model and Clinical Data Compared

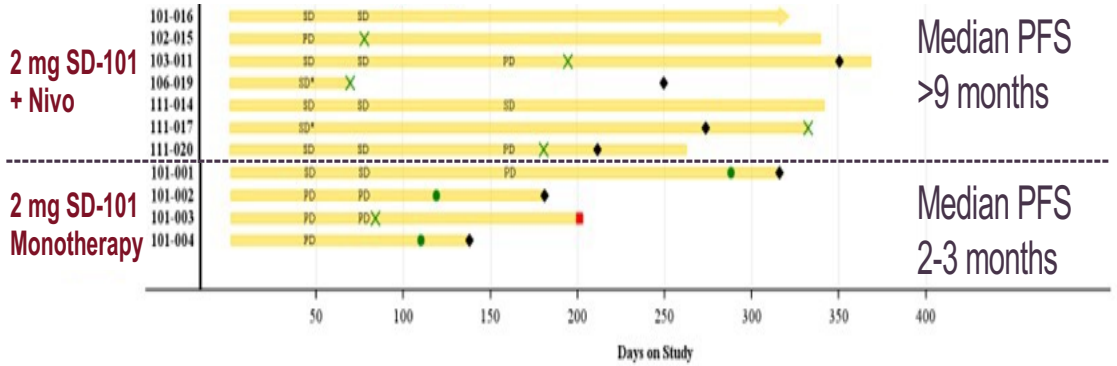
Enhancement of SD-101/PEDD Monotherapy Effect by CPI in Pre-Clinical Model



Two way ANOVA followed by Tukey's post-hoc test
*p<0.05, αPD vs. PBS; **p<0.01 αPD1+ODN vs. PBS group @ D10
****p<0.0001 αPD1+ODN vs. PBS group @ D12

ODN = TLR9 agonist tool compound with similar effect as SD-101

Enhancement of SD-101/PEDD Monotherapy Effect by CPI in PERIO-01



Immunocore median PFS
3.3 months in phase 1 1L

Ghosh CC, Heatherton KR, Connell KPO, et al. Regional infusion of a class C TLR9 agonist enhances liver tumor microenvironment reprogramming and MDSC reduction to improve responsiveness to systemic checkpoint inhibition. *Cancer Gene Ther.* 2022;29:1854-1865. https://doi.org/10.1038/s41417-022-00484-z

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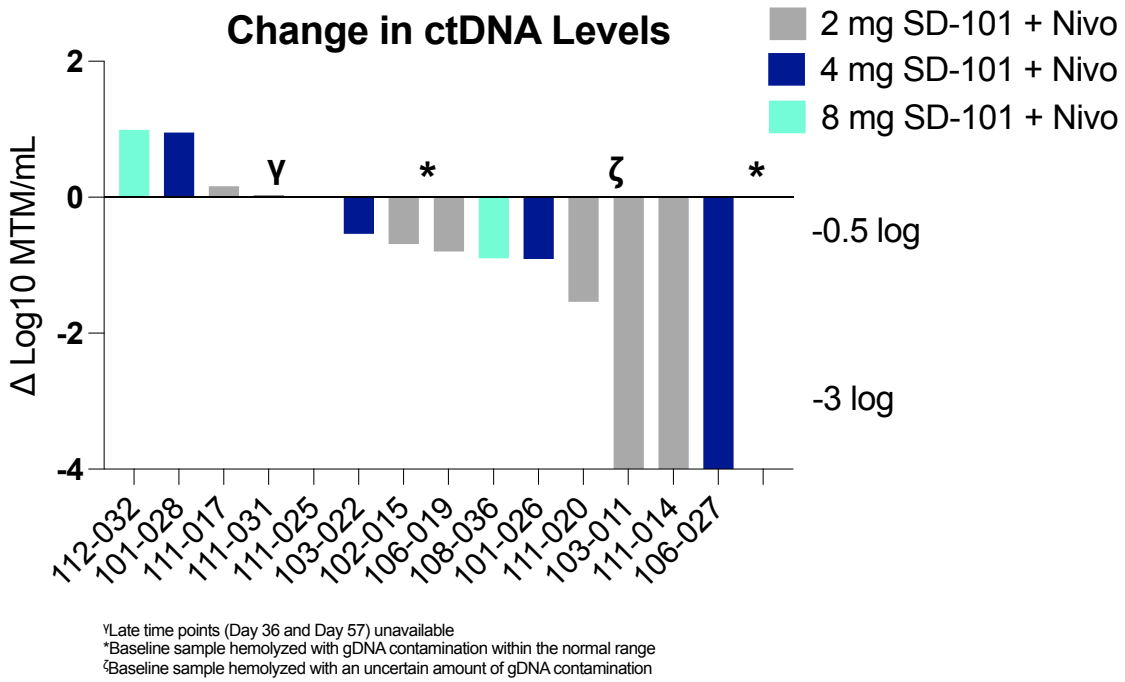
SD-101 + CPI resulted in ctDNA decreases

ctDNA reductions in 64% (n=14) patients –
81% in Phase 1 2nd line or beyond



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

21% ctDNA clearance

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Additional SD-101 cycles added with goal of further Enhancing clinical effect

ctDNA may enable clinical response assessment in the setting of delayed response kinetics or pseudoprogression

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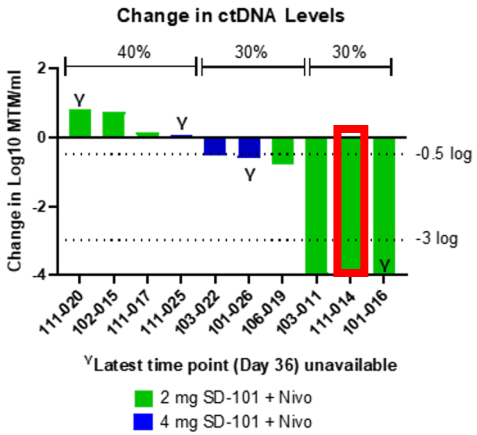
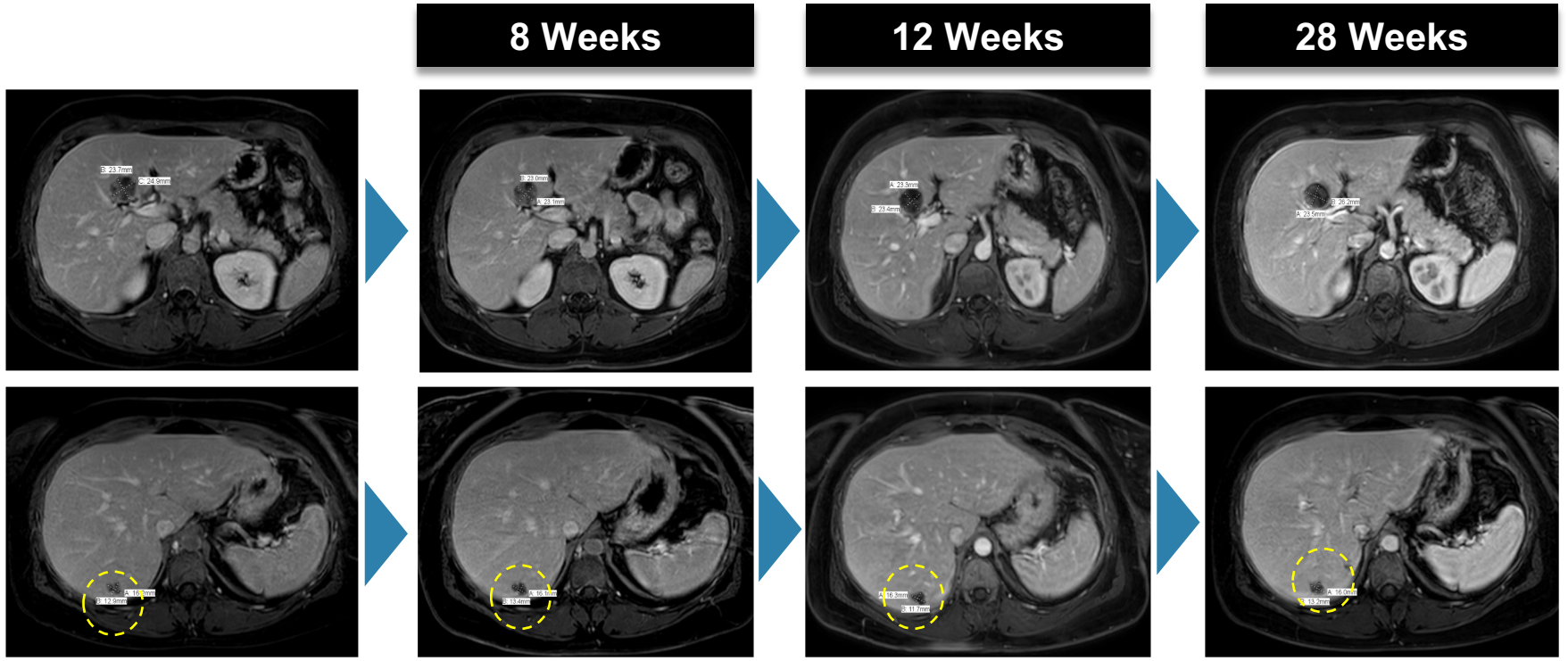
Example of favorable clinical response in PERIO-01

Stable disease for >11 months and complete ctDNA response

Age/Gender: 34 y.o. female **Diagnosed:** Oct 2020 **Surgery:** s/p Enucleation OS

Lines of Prior Therapy: 2 (ipi/nivo, nivo) **Liver Lesions at Baseline:** 1-3, nodular





Loss of enhancement in lesion

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Final Thoughts

1. Mechanical delivery barriers may promote immunotherapy failure
2. MSDC in liver are a critical component of immunosuppression
3. Addressing mechanical and biologic barriers to immunotherapy success may be required in certain solid tumor settings, including liver tumors

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