Locoregional interventions combined with checkpoint inhibition from an oncologist's perspective

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SIR 2024 MARCH 23–28 SALT LAKE CITY
SIRpass the summit

Society of Interventional Radiology

Disclosures

Sapna P. Patel

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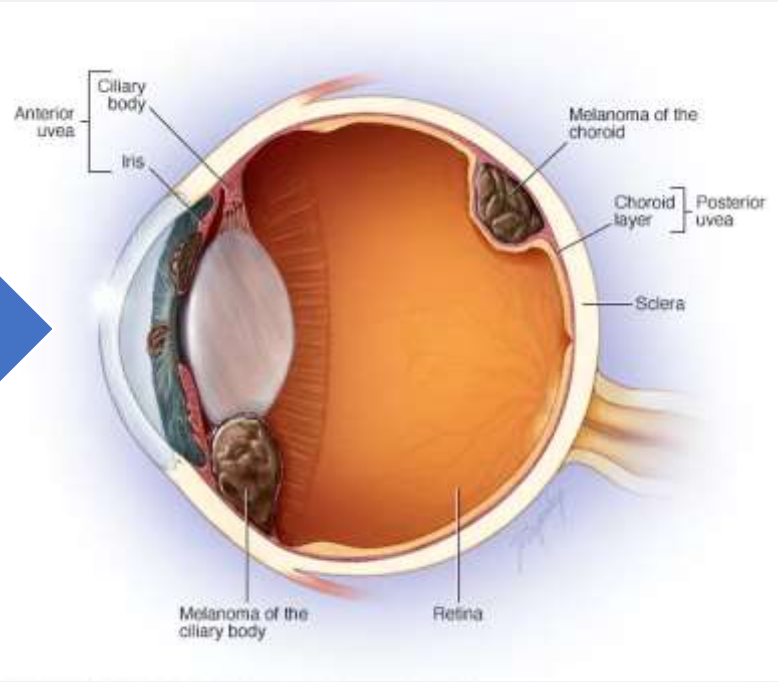
Speaker's honoraria (non-promotional): BMS, MSD

Uveal melanoma

Rare tumor → Liver predominance → SOC with low efficacy metrics (PFS, ORR, OS)



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Available at: https://www.mayoclinic.org/diseases-conditions/eye-melanoma/symptoms-causes/syc-20372371. Accessed April 10, 2023.

<u>Tebentafusp</u>
ORR 9%
mPFS 3.3 mo
mOS 21.7 mo
DOR 9.9 mo

<u>Percutaneous hepatic perfusion of melphalan</u>
ORR 36%
mPFS 9 mo
mOS 19.25 mo
DOR 14 mo

Sacco JJ, et al. Presented at: 20th International Congress of the Society for Melanoma Research (SMR); November 8, 2023; Philadelphia, PA.

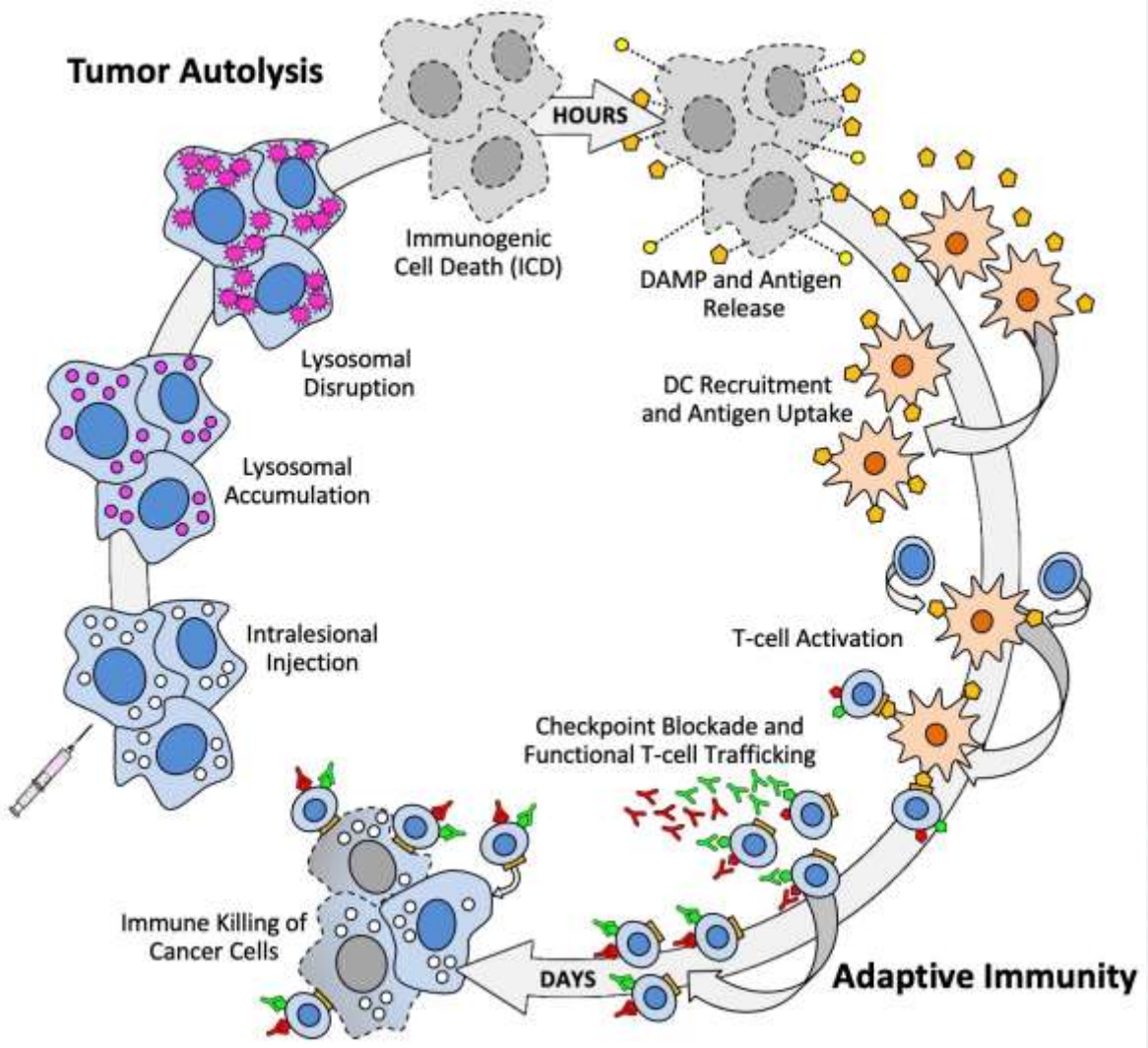
3 programs combining IR treatments with checkpoint inhibition

1. Intralesional PV-10

2. Intralesional RP2

3. Regional delivery PERIO-01

PV-10 (Rose Bengal)



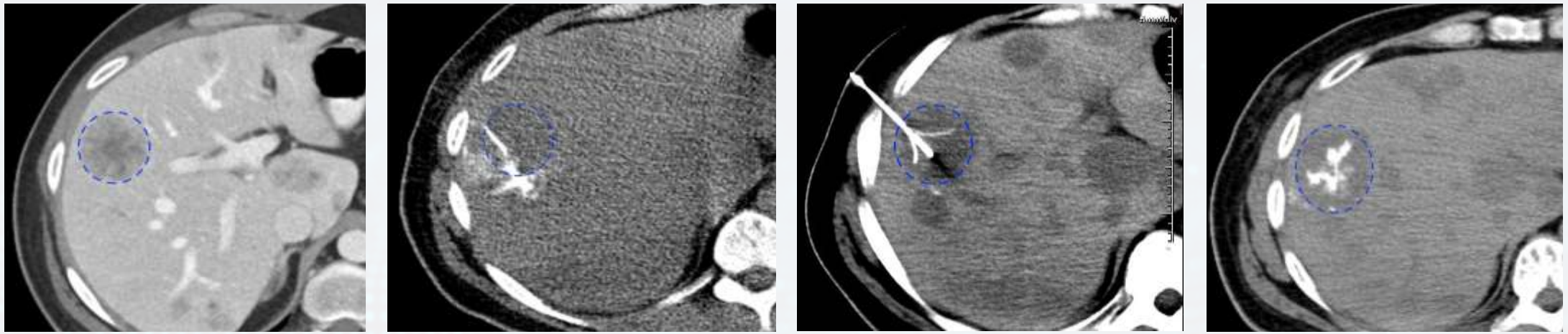
- **PV-10 (10% rose bengal sodium)** is a small molecule autolytic immunotherapy in clinical development for solid tumors
- Intralesional (IL) injection initiates tumor autolysis
  - Rapid accumulation of PV-10 in tumor lysosomes triggers lysosomal disruption and immunogenic cell death (ICD)
- ICD causes the release of damage-associated molecular pattern (DAMP) molecules (DAMPs), cytokines, and tumor antigens, leading to dendritic cell (DC) recruitment and antigen uptake
- Presentation of these antigens serves to educate and activate T cells, leading to maturation into functional T cells: primarily CD8 cytotoxic T cells, and also CD4 and NKT cells
- T cell function against tumor can be further augmented by addition of immune checkpoint blockade

Seminal references to date

(1) Wachter et al. Functional Imaging of Photosensitizers using Multiphoton Microscopy. Proceedings of SPIE 4620, 143, 2002.
(2) Liu et al. Intralesional rose bengal in melanoma elicits tumor immunity via activation of dendritic cells by the release of high mobility group box 1. Oncotarget 7, 37893, 2016.
(3) Qin et al. Colon cancer cell treatment with rose bengal generates a protective immune response via immunogenic cell death. Cell Death and Disease 8, e2584, 2017.
(4) Liu et al. T cell mediated immunity after combination therapy with intralesional PV-10 and blockade of the PD-1/PD-L1 pathway in a murine melanoma model. PLoS One 13, e0196033, 2018.

Intralesional PV-10 for uveal melanoma liver metastasis

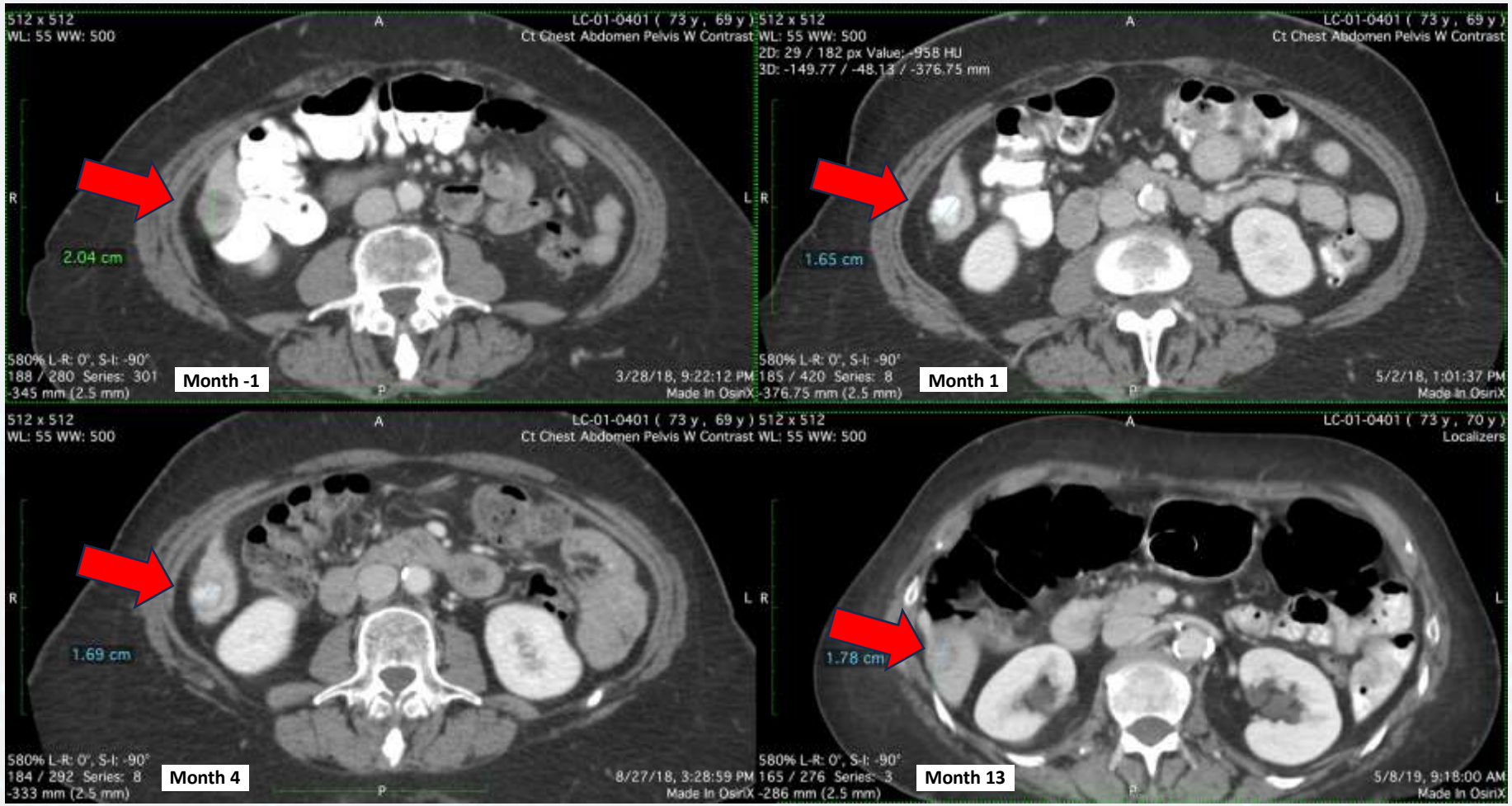
PV-10 contains 4 iodides and can be visualized during and after administration via CT or ultrasound



Subject 0412 (mUM), single lesion injected twice in repeat cycles. Initial injection with single end-holed needle resulted in extravasation and heterogeneous IL distribution of PV-10. Repeat injection with multi-pronged needle yielded improved retention and more uniform distribution within the injected tumor.

Source: Patel S. et al., SIR 2020

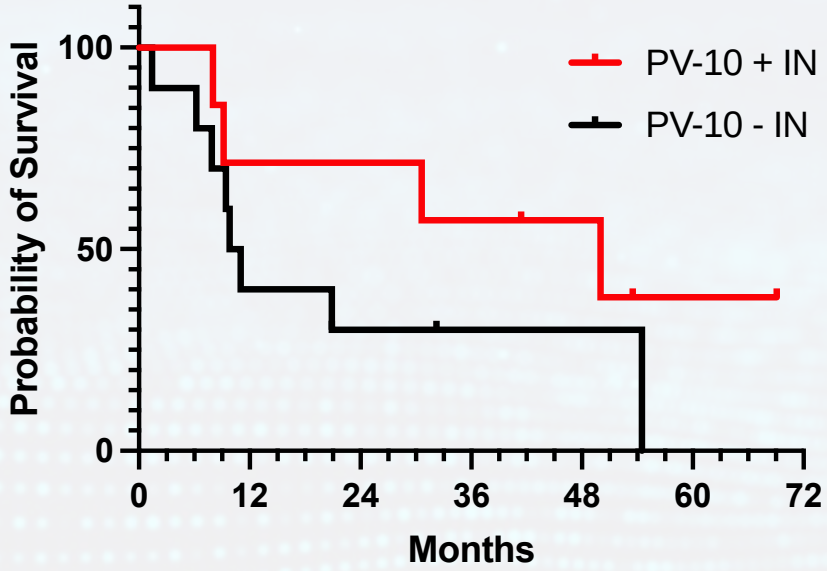
Another uveal melanoma case treated with intralesional PV-10



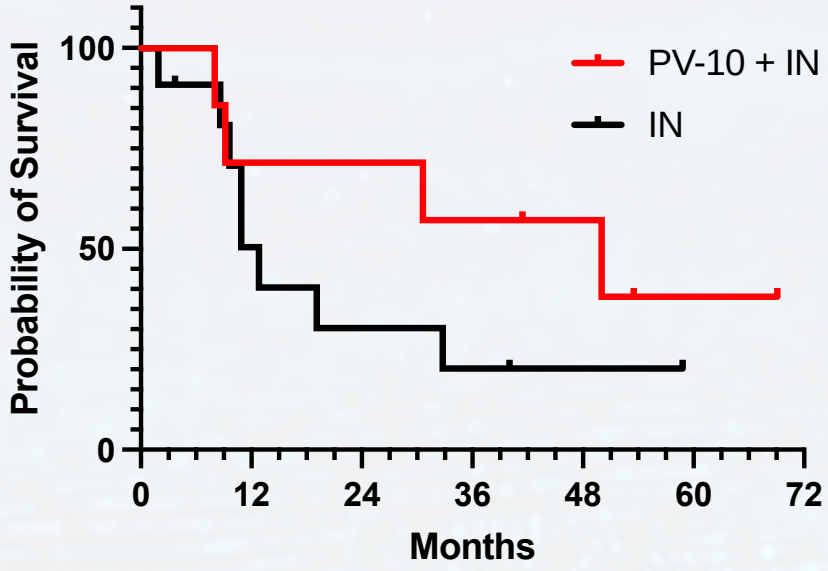
Subject 0401

Improved overall survival in uveal melanoma treated with PV-10 + checkpoint inhibitor compared to monotherapy

Metastatic uveal melanoma – M1a hepatic metastases



- mOS = 50.0 months (PV-10 + IN)
- mOS = 10.4 months (PV-10 - IN)



- mOS = 50.0 months (PV-10 + IN)
- mOS = 12.8 months (IN alone)

RP2 monotherapy and in combination with nivolumab

Tumor directed oncolytic immunotherapy mechanism of action

Attenuated potent new clinical isolate of HSV-1 modified to express a fusogenic glycoprotein and immune stimulating proteins

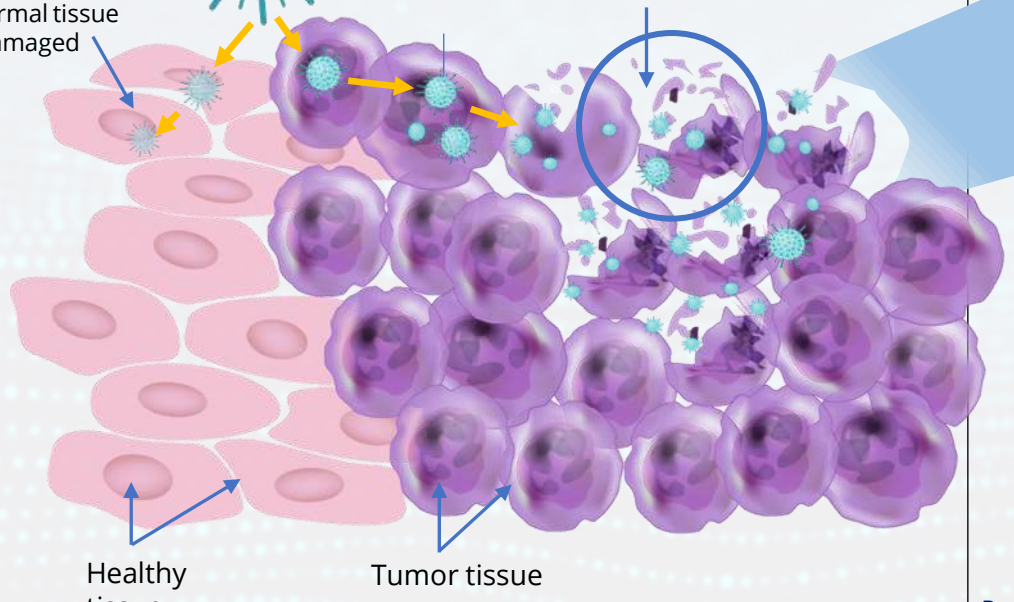
Oncolytic immunotherapy

Injected tumor

MECHANISM 1

Dysregulated host antiviral response allows robust virus replication and tumor lysis

Intact host antiviral response: Normal tissue remains undamaged

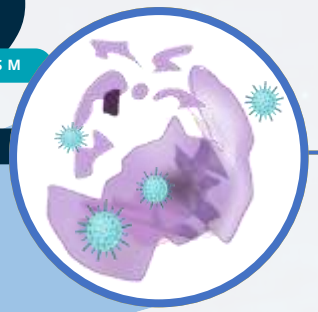


Healthy tissue

Tumor tissue

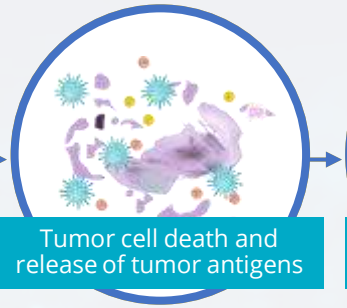
Immune response

MECHANISM 2



Release of virus progeny

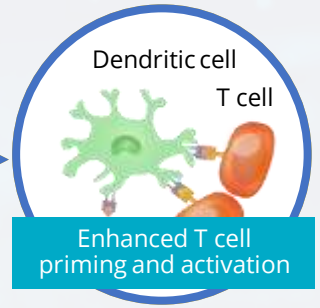
Infection of more tumor cells



Tumor cell death and release of tumor antigens

Local Inflammation

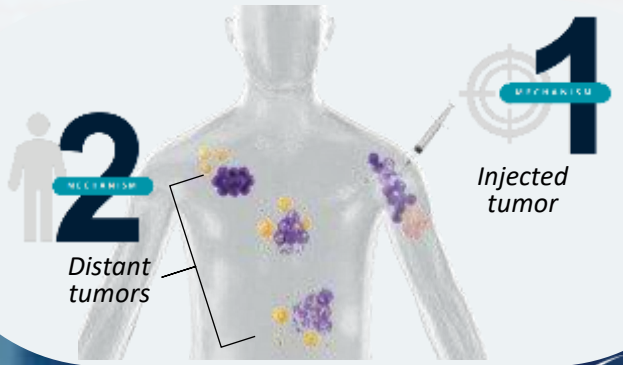
Altering of tumor microenvironment



Enhanced T cell priming and activation

T cell infiltration and killing of distant, uninjected tumors

Generating a strong and durable systemic anti-tumor immune response

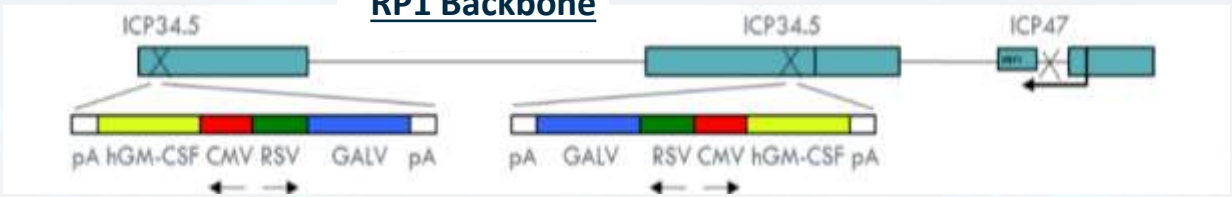


Bommareddy PK et al AJCD. 2016

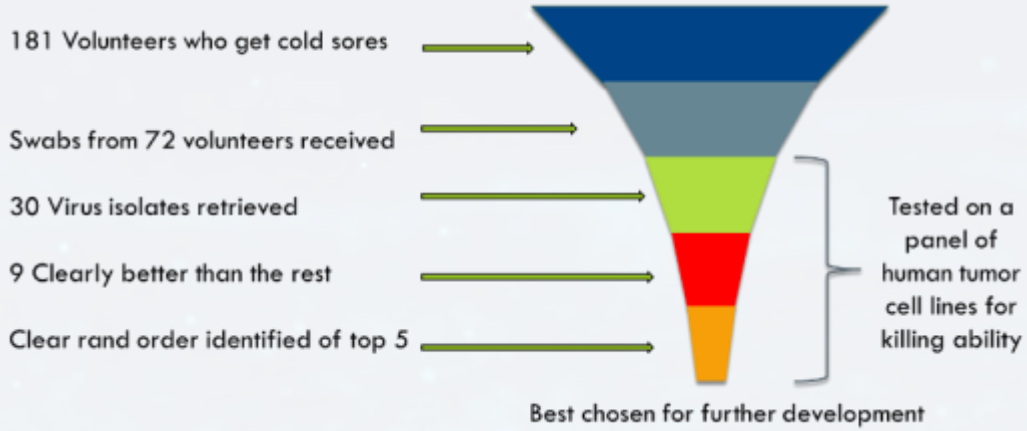
Replimune's investigational oncolytic immunotherapy platform

- The RPx family of OIs were developed from a potent new clinical strain of herpes simplex virus (HSV-1) selected for its ability to kill a panel of human cancer cell types

RP1 Backbone



RP platform Development



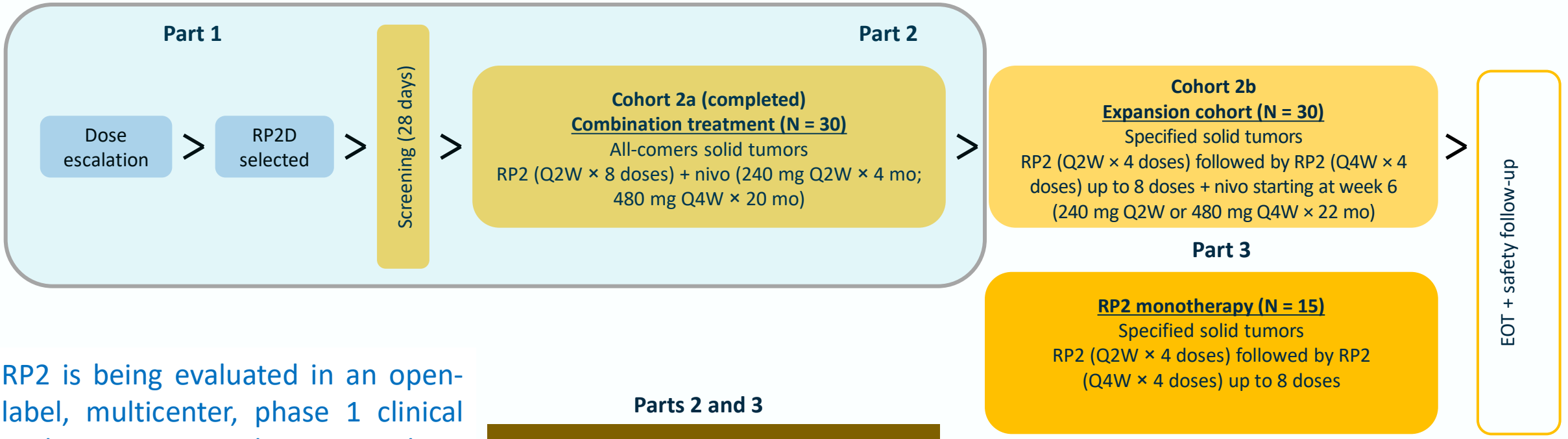
RPx Modifications	Rationale
Deletion of ICP34.5 (HSV-1 neurovirulence factor)	Render non-pathogenic/limit replication to tumors
Deletion of ICP47 • Early expression of US11	Improve antigen presentation • Improve tumor selective virus replication
Insertion of of fusogenic protein (GALV-GP R-)	**Improve direct tumor killing and increase immunogenic cell death**
Insertion of GM-CSF	Augment anti-tumor immunity through activation of dendritic cells
Anti-CTLA-4 antibody	**Improves Signal-2 / T-reg depletion**

RP1

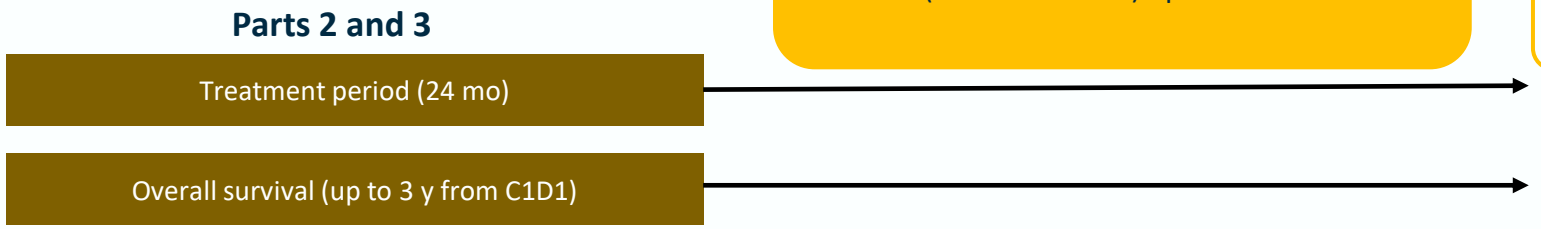
RP2

Thomas et al JITC. 2019

RP2 investigational oncolytic immunotherapy study design



RP2 is being evaluated in an open-label, multicenter, phase 1 clinical trial as a monotherapy and in combination with nivolumab (anti–PD-1; NCT04336241)



RP2 is administered via direct intratumoral injection into superficial/subcutaneous lesions or into deep/visceral lesions using image guidance (eg, ultrasound or CT)

The RP2D was identified as 1×10^6 PFU/mL once, followed by up to 7 doses of 1×10^7 PFU/mL per dosing day. A second course of up to 8 additional RP2 injections is permitted if prespecified criteria are met.

C1D1, cycle 1 day 1; CT, computed tomography; EOT, end of treatment; nivo, nivolumab; PD-1, programmed cell death protein 1; PFU, plaque-forming unit; Q2W, every 2 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose.

Sacco JJ, et al. Presented at: 20th International Congress of the Society for Melanoma Research (SMR); November 8, 2023; Philadelphia, PA.

RP2 response rates in patients with metastatic uveal melanoma

	RP2 monotherapy (n = 3)	RP2 + nivolumab (n = 14)	Total (N = 17)
Best overall response, n (%)			
CR	0	0	0
PR	1 (33.3)	4 (28.6)	5 (29.4)
SD	0	5 (35.7)	5 (29.4)
PD	1 (33.3)	4 (28.6)	5 (29.4)
ORR (CR + PR)	**1 (33.3)**	**4 (28.6)**	**5 (29.4)**
DCR (CR + PR + SD)	1 (33.3)	9 (64.3)	10 (58.8)

- **ORR:** 29.4% (all PRs)
- **DCR:** 58.8%
- **Median (range) DOR** at the data cutoff: 11.47 (2.78–21.22)[a] months

[a]Response is ongoing.
CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
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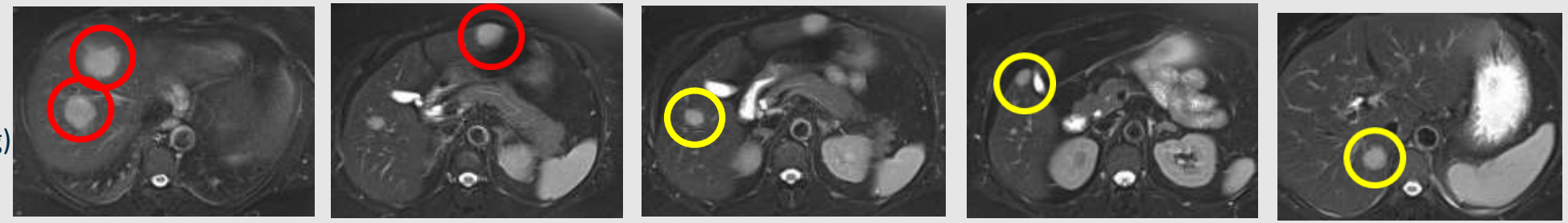
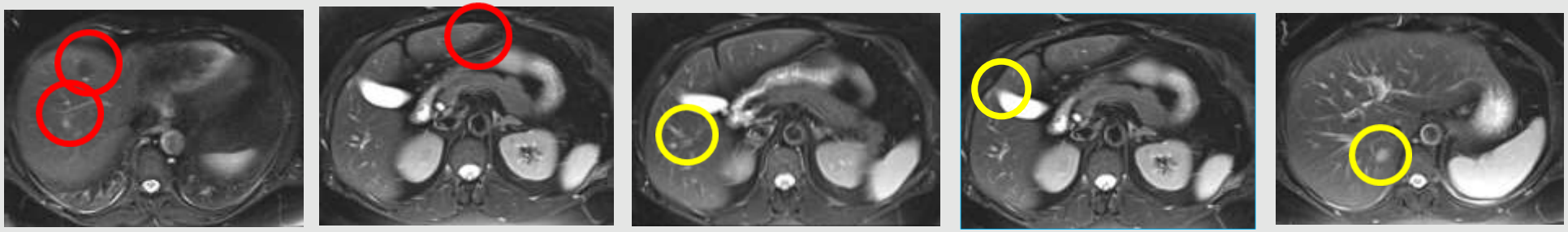
RP2 + nivolumab: partial response in patient with prior nivolumab + ipilimumab

Dec 24, 2021 (screening)



Aug 10, 2023



Patient 201-4403-0017:

- Liver metastases
- Prior therapy: ipilimumab/ nivolumab
- Patient has ongoing PR at 19 months

Injected

Uninjected

PR = partial response;

Sacco JJ, et al. Presented at: 20th International Congress of the Society for Melanoma Research (SMR); November 8, 2023; Philadelphia, PA

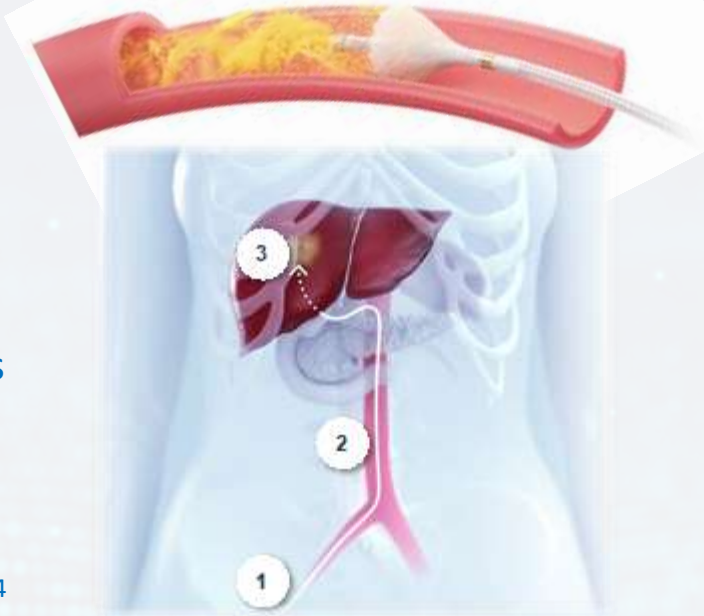
PERIO-01

PERIO-01 designed to address these barriers

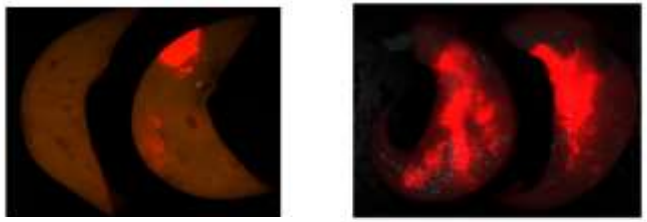
Overcoming pressure and immune suppression

Delivery Strategy (TriNav®)

- 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



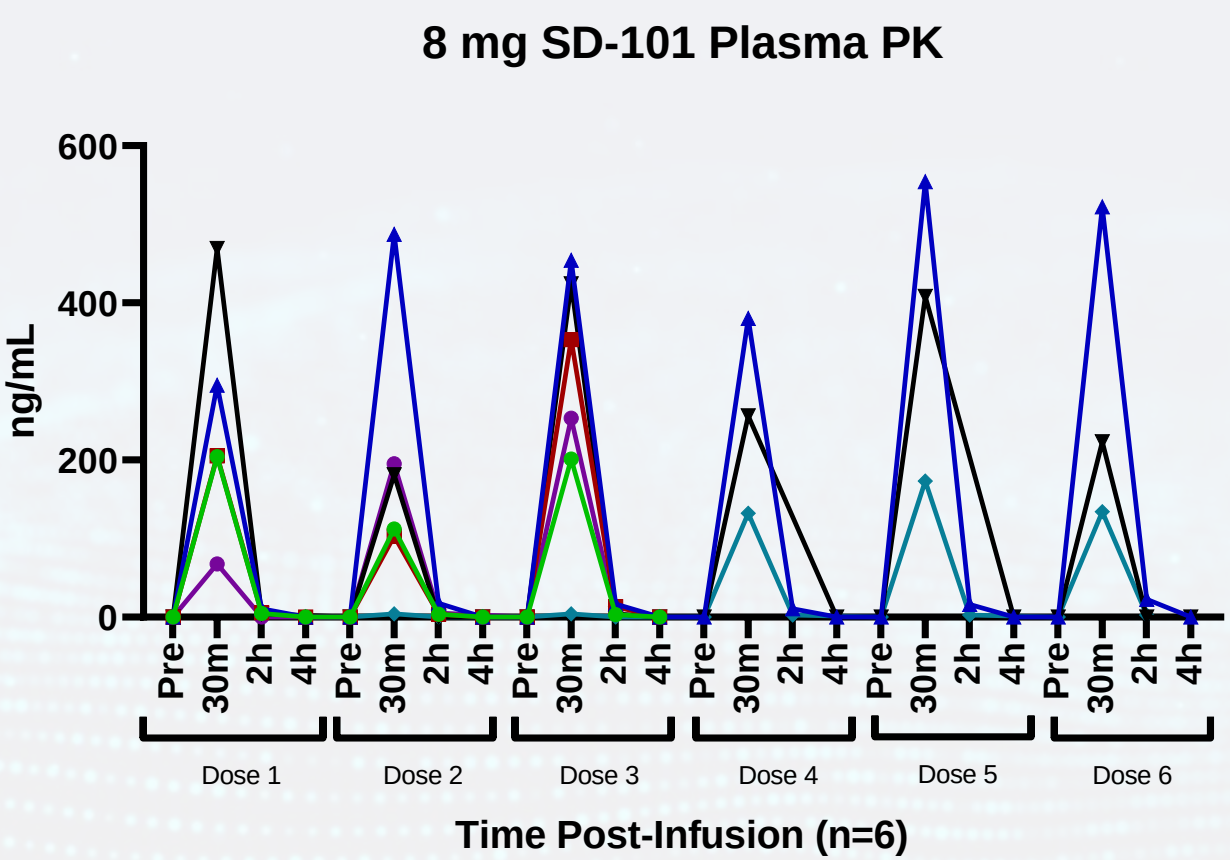
Needle Injection PEDD

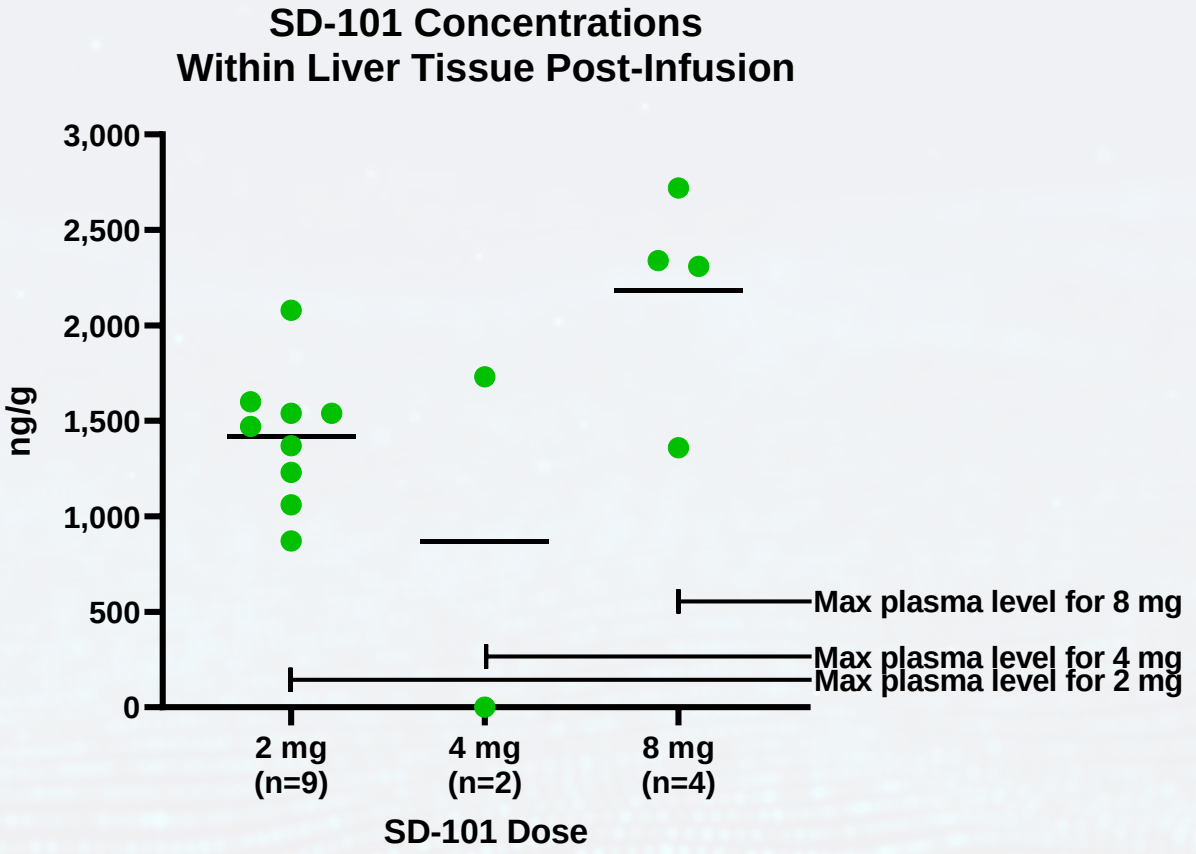
Drug Strategy (SD-101)

- 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

PERIO-01 PK Data

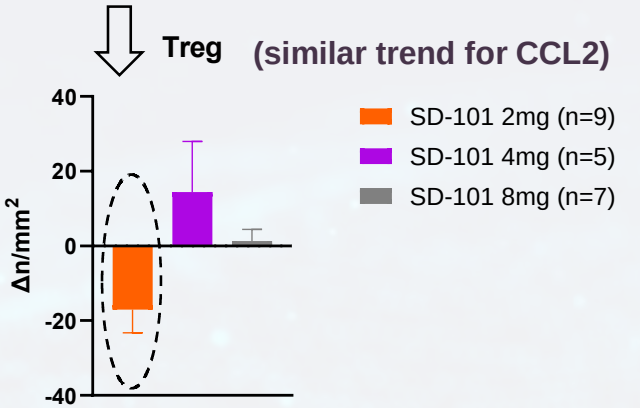


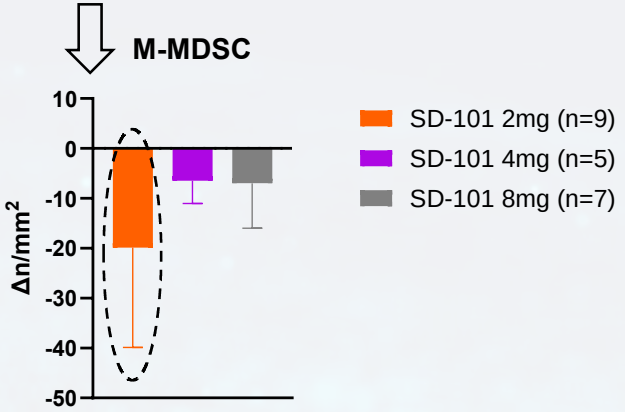


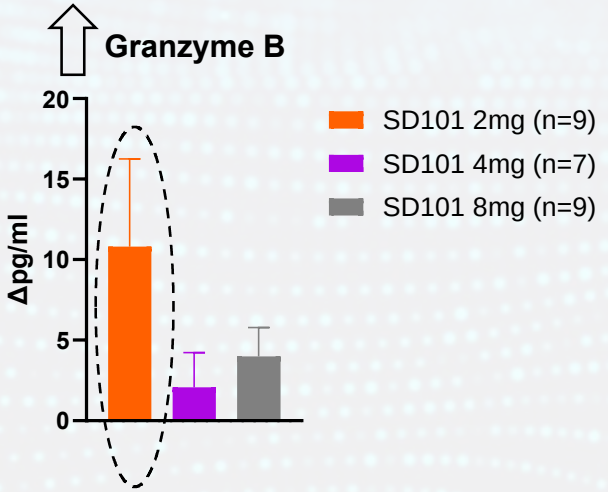
Regional delivery of SD-101 results in low, transient drug levels within the peripheral circulation, and high drug levels in the liver

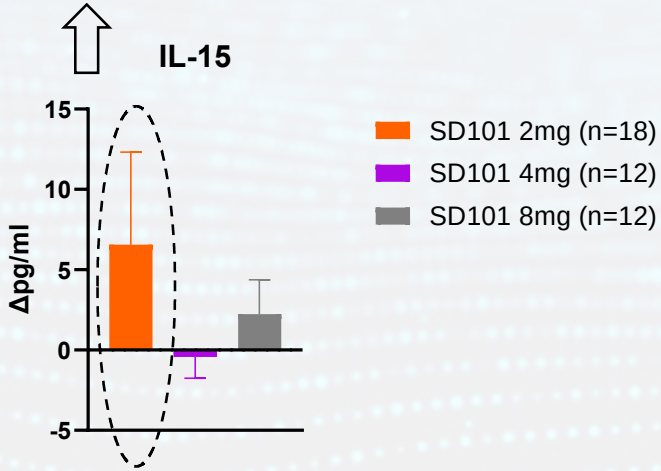
Optimal dose selection guided by clinical and immune signals

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









At 2 mg SD-101 via PEDD + nivolumab:

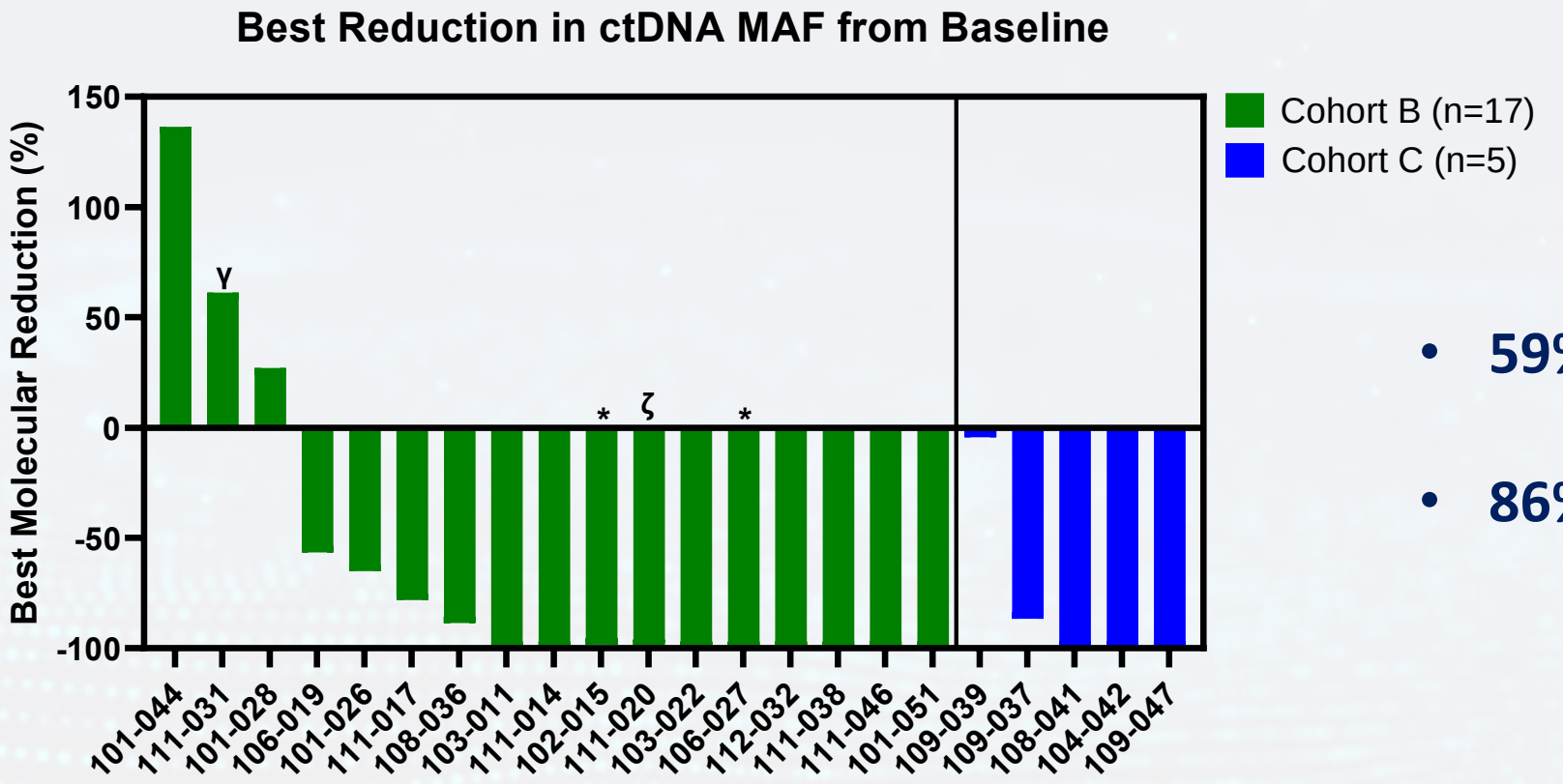
- ✓ >80% ctDNA response rate
- ✓ >80% disease control rate
- ✓ 11.7-month progression free survival (PFS)
- ✓ Immune signals correlate with clinical effect:

↑ Granzyme B – protein used by T cells to kill tumor cells

↑ IL-15 – Cytokine stimulating anti-tumor T + NK cell immune responses

↓ MDSC and Treg in liver tumors – Fewer cells that drive ICI failure

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

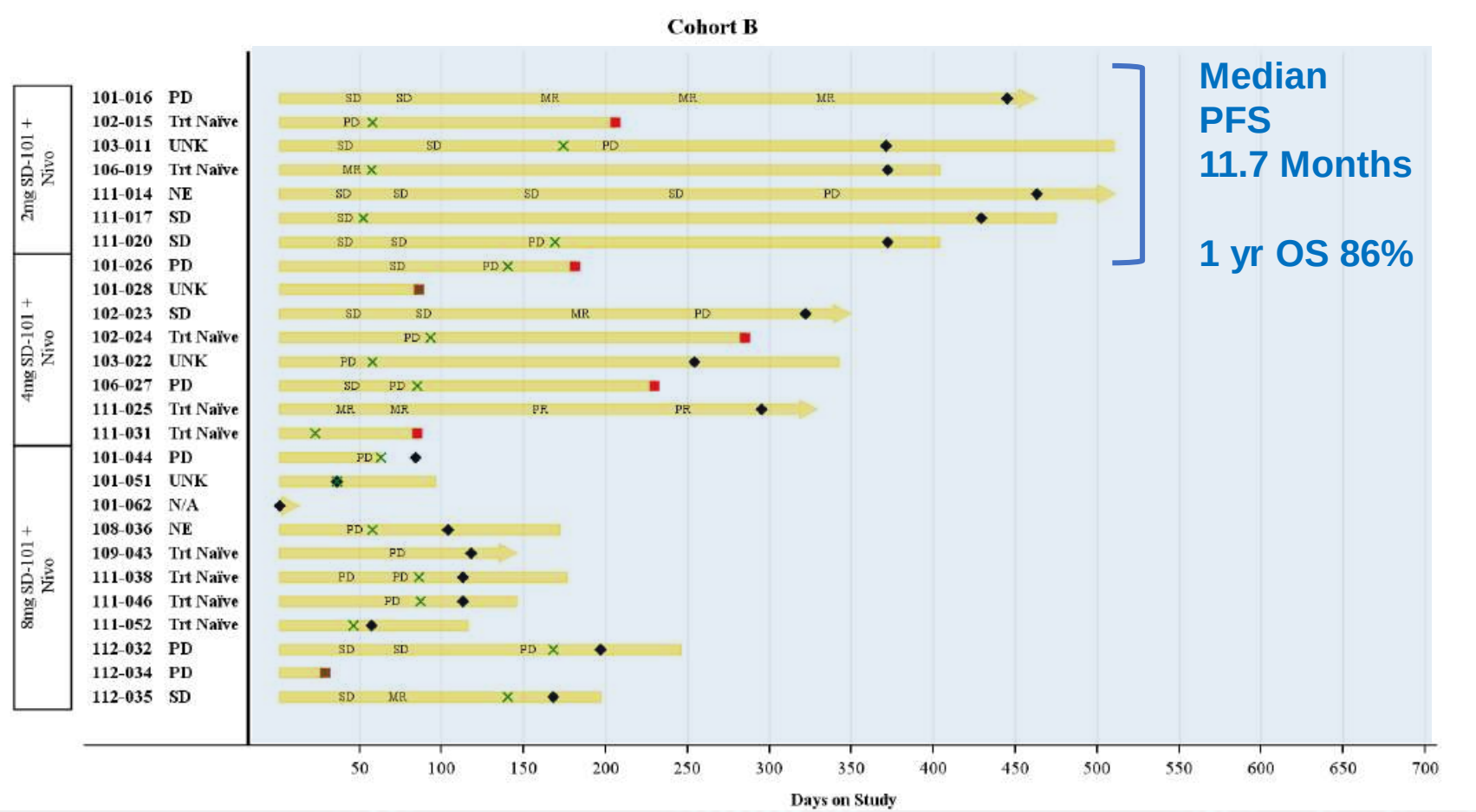
- **59%** ctDNA clearance
- **86%** reduction of any rate

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

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

Durable disease control and PFS in phase 1

2mg SD-101 + anti-PD-1 PFS aligns with immune signals and ctDNA data[1,2,3]



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

59% ctDNA clearance vs (13% with tebentafusp[1]) in naïve + pre-treated

ctDNA Reported as predictor of overall survival in stage IV uveal melanoma when imaging is unreliable[1]

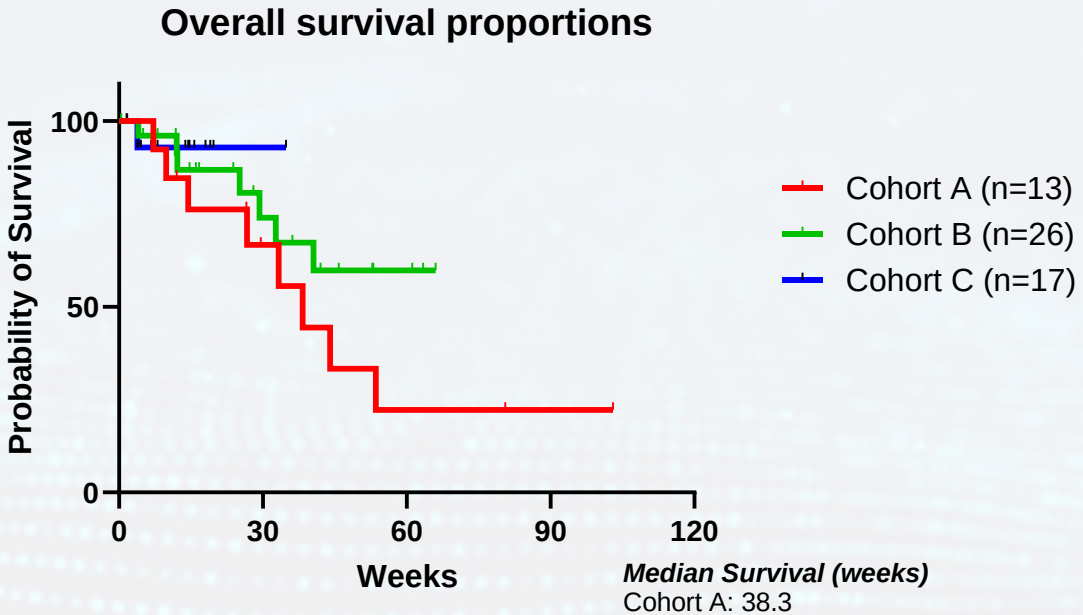
Even progressive disease patients with ↓ctDNA may survive long-term.

5 of 7 of 2mg + nivo patients with >50% decrease in ctDNA including 2 complete ctDNA responders

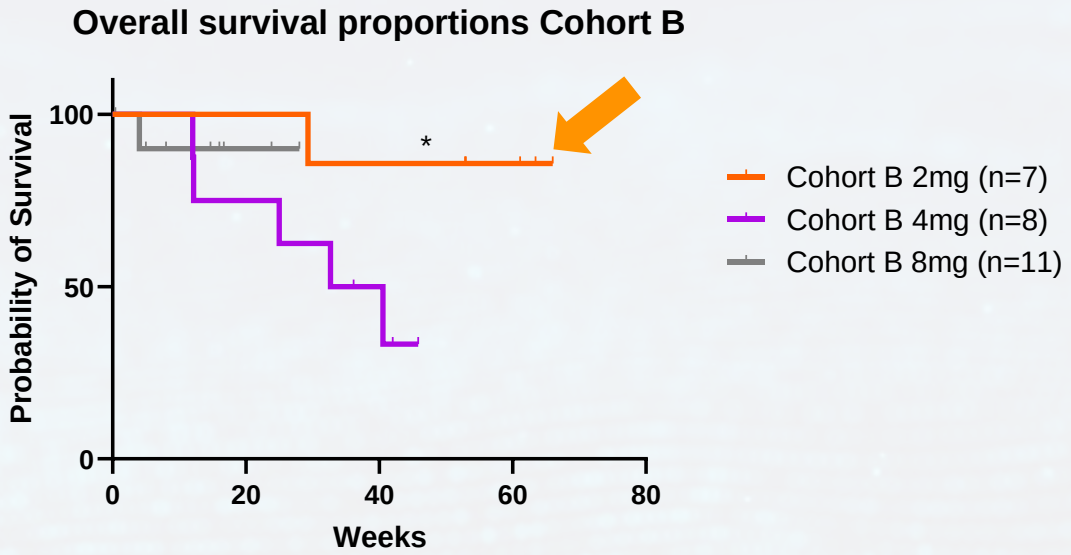
Note: the patient of the Cohort C 2mg PR would was not included in swim plot.

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

Early overall survival signal encouraging and supportive of optimal biologic dose of 2 mg SD-101 via PEDD + PD1 checkpoint inhibition



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 2 mg + nivo – 86%

Summary

- Tumor-directed approaches and regional delivery of therapy has a role in the treatment of metastatic uveal melanoma
- Intralesional therapy in combination with checkpoint inhibition demonstrates efficacy (injected & bystander tumors – ORR, OS)
- Regional delivery of TLR9 agonist using PEDD demonstrates efficacy at an optimal biologic dose

Thank you

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Tarin Hennegan
Mara Castaneda

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