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


*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)

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<td>OS</td>
<td>21.7 months</td>
<td>16.0 months</td>
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<tr>
<td>ORR</td>
<td>9%</td>
<td>5%</td>
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<tr>
<td>DoR</td>
<td>9.9 months</td>
<td>9.7 months</td>
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<tr>
<td>G3/4</td>
<td>44%</td>
<td>17%</td>
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A significant unmet clinical need remains for 1L HLA-A*02:01-negative patients and ≥2L treatment

Presented by Sapna P. Patel, M.D.
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\(^3\)

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Presented by Sapna P. Patel, M.D.
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

TriSalus data on file from pre-clinical and clinical studies.

Presented by Sapna P. Patel, M.D.
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
- Optimized vascular pressure enhances perfusion → improved therapeutic delivery to tumor
- Flow redirection to improve concentration of drug in tumor tissue while allowing whole liver treatment
- Reduces reflux

**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
- Optimal dose may be lower than maximally tolerated dose
- Mechanism of SD-101 may limit utility of traditional RECIST assessment

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1. Data on file, TriSalus Life Sciences, 2019
2. Data on file, TriSalus Life Sciences, 2019

Presented by Sapna P. Patel, M.D.
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**

- **SD-101 Cycle 1**: Weekly x 3
- **SD-101 Off Period**: 5-week rest
- **SD-101 Cycle 2**: Weekly x 3

- Checkpoint Inhibitor (12 months)

ClinicalTrials.gov NCT04935229

Presented by Sapna P. Patel, M.D.
## TS-PERIO-01 Patient Characteristics

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<td>4 mg</td>
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<td>8 mg</td>
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Data cutoff: September 29, 2023

Presented by Sapna P. Patel, M.D.
### Safety Summary

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<td>Cohort A 2mg SD-101 n (%)</td>
<td>Cohort A 4mg SD-101 n (%)</td>
<td>Cohort A 8mg SD-101 n (%)</td>
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**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

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Presented by Sapna P. Patel, M.D.
# Safety Summary

## Phase 1: Cohorts A, B, C

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Data cutoff: September 29, 2023

Presented by Sapna P. Patel, M.D.
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

Presented by Sapna P. Patel, M.D.
Increased CD8\(^+\) T cell and NK cell infiltration in the tumors

**CD8\(^+\) T cells**

- Baseline
- D57

**NK cells**

- Baseline
- D57

**Change in CD8\(^+\) T cells**

- Cohort A (n=5)
- Cohort B (n=12)
- Cohort C (n=4)

**Change in CD4\(^+\) T cells**

- Cohort A (n=5)
- Cohort B (n=12)
- Cohort C (n=4)

**Change in NK cells**

- Cohort A (n=1)
- Cohort B (n=12)
- Cohort C (n=4)

Presented by Sapna P. Patel, M.D.

*Increased CD8\(^+\) T cells and NK cells were observed in tumors at Day 57*
Increased immune cell activation within liver metastases

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

ΔPathway Score (Baseline - Day 57)

Cohort: A (n=7)  B (n=13)  C (n=4)

Th1 activation
Th2 activation
TLR signaling
Interferon signaling
Cytokine signaling
Chemokine signaling
Lymphocyte activation
T cell activation and checkpoint signaling
Differentiation and maintenance of myeloid cells

Pathway scores generated with NanoString nSolver software and normalized mRNA data

Presented by Sapna P. Patel, M.D.
Peripheral immune signatures in PBMC

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

Cohort: A (n=10)  B (n=15)  C (n=7)

ΔPathway Score (Day 1 - Day 36)

Presented by Sapna P. Patel, M.D.
Optimal dose selection guided by clinical and immune signals
Dose within predicted range elicits expected immune signals within liver metastases from phase 1

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

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

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

Granzyme B

IL-15

At 2 mg SD-101 via PEDD + nivolumab:

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

Presented by Sapna P. Patel, M.D.
**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**

*5 SD subjects with 10-29% target lesion shrinkage*
Decreased ctDNA observed in heavily pretreated patients

cDNA response correlates with overall survival consistent with published data

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

- 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

Presented by Sapna P. Patel, M.D.
Progression-free survival (PFS) and durable disease control

Median PFS 11.7 Months

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

**Overall survival proportions**

- **Cohort A** (n=13)
- **Cohort B** (n=26)
- **Cohort C** (n=17)

*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

**Overall survival proportions Cohort B**

- **Cohort B 2mg** (n=7)
- **Cohort B 4mg** (n=8)
- **Cohort B 8mg** (n=11)

*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%**

Presented by Sapna P. Patel, M.D.
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**
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Abstract: 647:  
PERIO-03: Pancreatic adenoca

Abstract 1123:  
SD-101 with subcutaneous ICI

*Northwell Health Cancer Inst