***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***

**Authors**: Sapna P. Patel[1], Richard Carvajal[2], Kamaneh Montazeri[3], Jose Lutzky[4], Bartosz Chmielowski[5], Sunil Reddy[6], Shailander Bhatia[7], Shaheer Khan[2], Theresa Medina[8], Cara Haymaker[1], Rahul Sheth[1], Joshua D. Kuban[1], Lindsay Thornton[4], Eric Wehrenberg-Klee[3], Paula Novelli[9], Anthony Lucci[1], Vanessa Sarli[1], Salyna Meas[1], Bryan Cox[10], Jason LaPorte[10], Prajna Guha[10], Chandra Ghosh[10], Ann-Marie Hulstine[10], Robert Knight[10], Ashley Moody[10], David Geller[9], Marlana Orloff[11], Steven C. Katz[10, 12], Diwakar Davar[9]

1. The University of Texas MD Anderson Cancer Center, Houston, TX

2. Northwell Health Cancer Institute, New Hyde Park, NY

3. Massachusetts General Hospital, Boston, MA

4. University of Miami, Miami, FL

5. University of California, Los Angeles, CA

6. Stanford Cancer Center, Stanford, CA

7. University of Washington, Seattle, WA

8. University of Colorado, Denver, CO

9. University of Pittsburgh Medical Center, Pittsburgh, PA, TX

10. TriSalus Life Sciences, Westminster, CO

11. Thomas Jefferson University, Philadelphia, PA

12. Department of Surgery, Brown University, Providence, RI

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***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$^{TM}$) 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 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.
***Results***: 53 patients received ≥1 dose of SD-101: 13 in Cohort A, 25 in Cohort B, and 15 in Cohort C. Median age was 65 and 45% were female. 70% received prior MUM-LM treatment, and 8 (15%) received tebentafusp. Fifteen participants (28%) had LM >5cm and 18 (44%) had >10 LMs. One patient experienced partial response (Cohort B 4 mg) that is ongoing at 258 days. Six additional patients had decreases in target lesion size (SD), 3 ongoing at a median follow-up of 168 days. Across dose levels, median PFS was highest in Cohort B (2 mg) at 11.7 months, with a disease control rate of 86% (6/7 SD). Serious grade 3/4 treatment-related AEs (TRAEs) to SD-101 or ICI were documented in 8% of subjects:

0% in Cohort A, 4% in Cohort B, and 20% in Cohort C, with an overall grade 3/4 TRAE rate of 21%. PEDD of SD-101 resulted in reductions in LM monocytic MDSC (mMDSC) by immunofluorescence, along with decreased expression of ARG1, CD163, and FASN. We also observed evidence of immune activation in LM with increased CD4+ and CD8+ T cells, decreased Treg, and increased IFNγ and IFNα2 gene expression. These were associated with evidence of systemic immune activation peripherally characterized by increased proliferating CD8+ T and NK cells, and increased IP-10, TNFα, IFNγ, IL-2R, and IL-18. Among 25 patients with evaluable ctDNA data, 68% had a decrease relative to peak, with complete clearance in 28%.

***Conclusion***: Delivery of SD-101 by PEDD plus systemic ICI in MUM-LM patients results in clinical activity with median PFS of 11.7 months, MDSC re-programming, and evidence of peripheral and intra-tumoral immune activation. Phase 2 of PERIO-01 is planned for expansion of the optimal dose.