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 (PEDDTM) 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 at least one 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, and 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 is delivered over 2 outpatient cycles, with 3 weekly doses/cycle.

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Conclusions 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. Trial Registration NCT04935229

Ethics Approval The study was IRB approved at all sites and participants signed written informed consent

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