Background MEM-288 is a conditionally replicative oncolytic adenovirus expressing human IFNβ and a recombinant membrane-stable form of CD40L (MEM40). Preclinical studies show MEM-288 induces robust dendritic cell (DC)-mediated systemic T-cell responses capable of inhibiting injected and abscopal tumor growth.

Methods 14 patients with metastatic NSCLC refractory to anti-PD(L)1 and platinum chemotherapy (median 4 prior lines of treatment) received MEM-288 intratumoral treatment every 3 weeks in the same lesion for up to 6 cycles (NCT05076760). We collected peripheral blood at serial time-points and obtained tumor biopsies prior to the 1st and 2nd injections. We evaluated associations (t-test) between clinical outcomes in injected and non-injected tumors with pre- and on-treatment tumor microenvironment (TME) immune cell composition, plasma cytokines, T-cell clonotypes, and neoantigen-reactive T-cells.

Results Intervventional radiologists successfully injected MEM-288 into superficial tumors (n=7) and deep visceral tumors (n=7), including liver (n=4) and lung (n=2). Treatment-related AEs (all ≤13%) were limited to grade 1–2 injection site reactions and flu-like symptoms. We collected matched pre- and on-treatment biopsies of the injected lesion from 12 patients. Pre-treatment presence of T-cells and conventional DC1 in tumors significantly associated (p < 0.05) with subsequent shrinkage of injected tumors (n=5 of 11 (45%)). MEM-288 generated systemic anti-tumor T-cell immunity in responding patients as demonstrated by cytokine, T-cell clonotype, and tumor neoantigen analysis. Patient 002-001 (53% tumor shrinkage) showed both a marked increase in T-cell clonotypes present in the injected tumor and increases in tumor neoantigen-reactive peripheral T-cells. Remarkably, this patient has a subsequent ongoing complete response in multiple extracranial tumors 14 months after taxane/anti-VEGF rechallenge. Patient 002-005 (40% tumor shrinkage) showed increased plasma cytokines on-treatment, including IFNγ (131-fold increase; p < 0.05), and subsequently developed a partial response (7 months) to carboplatin/etoposide rechallenge. Patient 002-012 (28% tumor shrinkage) had pseudo-progression with initial increase in a non-injected distant tumor lymph node followed by subsequent shrinkage and meaningful disease control (ongoing SD at 4 months). Tumor shrinkage was limited to the 5 patients with ≤3 prior lines of treatment.

Conclusions MEM-288 injection shrunk tumors in 45% of evaluable NSCLC patients. Although no RECIST responses were yet met, tumor shrinkage associated with an immune-active TME in the injected tumors, systemic immune response activation, and strong benefit to chemotherapy rechallenge and long-term disease control. These proof-of-concept results guided the design of an expansion study of MEM-288 with nivolumab for second-line treatment of metastatic NSCLC refractory to anti-PD(L)1 ± chemotherapy.