squamous carcinoma=1, OS 3+yrs; MET-exon14+ NSCLC=1, OS 9 mos.), 1 PR (7.7%, OS 6 mos), and 2 SDs (15.4%) in the CNS. Median CNS-PFS and OS were 2.9 mos (95% CI: 1.3-NR) and 4.9 mos (95% CI: 3.7-NR), respectively. There were no unacceptable safety signals. Sensitivity for LMM detection by t-DNA was 84.6% (95% CI: 54.6-98.1%), and 46.2% (95%CI: 19.2-74.9%) by cytopathology. Pre and on-therapy CSF cytokine analysis showed complete responders clustered together, while progressors clustered differently.

Conclusions Patients with LMM from solid tumors have a dismal prognosis and limited treatment options. In this phase 2 trial, we identified an impressive 38% CNS response rate for pembrolizumab in patients with LMM, deep and durable responses in selected patients with ICI-responsive tumors, and that pembrolizumab was well-tolerated. CSF t-DNA may be more sensitive for detection of LMM than cytopathology, and immunologic subsets of ICI-response based on cytokine profiles warrant further study. These data support investigation of pembrolizumab in larger populations with LMM.

Trial Registration NCT03091478

Ethics Approval The study was approved by John's Hopkins University's Institututional Ethics Board, approval number J1655

Consent All participants provided informed consent as per the study protocol

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789 INTRATUMORAL PLASMID IL-12 EXPANDS CD8+ T CELLS AND INDUCES A CLINICALLY VALIDATED CXCR3 SIGNATURE IN TRIPLE-NEGATIVE BREAST CANCER

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Background Triple-negative breast cancer (TNBC) is an aggressive disease with limited therapeutic options. Immune checkpoint inhibitors (ICI) have entered the therapeutic landscape in TNBC, but only a minority of patients benefit. Interleukin-12 (IL-12) is a pro-inflammatory cytokine involved in the generation of an inflammatory tumor microenvironment and is critical in eliciting a productive anti-tumor immune response. It has been investigated as an anti-cancer therapeutic using various delivery routes, but intratumoral injection of plasmid IL-12 (tavokinogene telseplasmid; tavo) followed by electroporation is a gene therapy approach with minimal systemic immune-related toxicity.

Methods Intratumoral injection of tavo was tested in several preclinical models of TNBC and single cell RNA sequencing (scRNAseq) was used to evaluate changes in the tumor microenvironment following treatment. These findings were then applied to the analysis of patient samples from a single arm, prospective clinical trial of tavo monotherapy (OMS-I140; NCT02531425).

Results A comprehensive analysis of cellular networks using ligand-receptor interactions identified CXCR3 (expressed by APCs) to be positively correlated with CXCL9/10/11 secreted by CD8 T cells. Further investigation of tavo treated murine tumors resulted in a 50-gene CXCR3 gene expression signature that is associated with a decrease in granulocytes, enhanced antigen presentation, increased T cell infiltration, and induction of PD-1/PD-L1. A deeper look at paired TCR alpha and beta chains on tumor infiltrating T cells (TILs) demonstrated a dramatic shift in TIL clonality and frequency following tavo treatment. There was a significant increase in not only the number of expanded (>10) clones, but also a robust activation signature that was absent in control tumors. Treatment of mice with tavo prior to anti-PD1 therapy led to complete tumor regression and long-term survival in a significant proportion of mice, while none of the mice treated with anti-PD1 alone exhibited this therapeutic efficacy. As a proof of concept, we utilized nanostring data from OMS-I140 to show a significant enhancement in this signature in patients who demonstrated a greater than 2-fold increase in CD8 TILS by IHC post-treatment. Further, we show a single patient who had previously been non-responsive to ICI that went on to receive anti-PD1 as their immediate next treatment after participating in OMS-I140, and demonstrated a significant clinical response.

Conclusions Together these data identify a clinically relevant CXCR3-associated gene signature that represents both a potential biomarker for response to ICIs and a potentially targetable pathway for therapeutic intervention in TNBC.

Ethics Approval All animal studies described were approved by the Duke University Medical Center Institutional Animal Care & Use Committee (A198-18-08) and performed in accordance with established guidelines.

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790 A PHASE II STUDY (TACTI-002) OF EFTILAGIMOD ALPHA (A SOLUBLE LAG-3 PROTEIN) WITH PEMBROLIZUMAB IN PD-L1 UNSELECTED PATIENTS WITH METASTATIC NON-SMALL CELL LUNG(NSCLC) OR HEAD AND NECK CARCINOMA(HNSCC)

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Background Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment may lead to stronger anti-tumor responses in combination with pembrolizumab than observed with pembrolizumab alone. We report results from stage 1 of all parts of the study (NCT03625323).

Methods Patients (pts) with unselected PD-L1 expression were recruited into 3 cohorts: part A; 1st line, immunotherapy naïve NSCLC; part B; 2nd line, immunotherapy refractory NSCLC and part C; 2nd line immunotherapy naive HNSCC. The study uses a Simon's 2-stage design, with objective response rate (ORR) by iRECIST as the primary endpoint (EP). Secondary EPs include tolerability, disease control rate (DCR), progression free survival (PFS), overall survival (OS), PK, PD and immunogenicity. Fifty-eight (58) pts were recruited into stage 1. Up to additional 51 pts will be recruited if a pre-specified ORR threshold is met for the respective part. Efti is administered as 30 mg subcutaneous injection every 2 wks for 8 cycles and then every 3 wks for 9 cycles; pembrolizumab is administered at 200 mg intravenous infusion every 3 wks for up to 2 yrs. The study was approved by ethic committees and institutional review boards.

Results Between Mar 2019 and Jul 2020 88 pts were enrolled. The median age was 67 yrs (range 53-84) and 70% were male. ECOG PS 0:1 was 42% and 58% respectively. Pts from all PD-L1 tumor expression subgroups were recruited. Pts received a median of 4 (1-25) pembrolizumab and 5.5 (1-22) efti administrations. The most common (≥ 15%) treatment emergent adverse events (TEAEs) were asthenia (28%), cough (27%), decreased appetite (22%), dyspnea (21%), fatigue (18%) and diarrhea (15%). Three (3) pts discontinued due to treatment related AEs. The ORR (acc. to iRECIST) of the 58 patients enrolled into stage 1 is shown in (table1). PK profiles after the first or repeated efti dosing were in line with previous studies, with a mean Cmax at7 ng/ml reached ≤ 24h. Circulating TH1 biomarkers 2 weeks after the last efti administration were increased (3 months vs. baseline) by a mean 61% and 209% for CXCL10 (Student paired t-test, p=0.02, n=31) and IFN-γ(p= 0.02, n=19), respectively.

Abstract 790 Table 1
ORR (acc. to iRECIST) of the 58 patients enrolled into stage 1

Response parameter	Part A (1st line NSCLC, PD-X-naive) N=17	Part B (2nd line NSCLC, PD-X refractory) N=23	Part C (2nd line HNSCC; PD-X-naive) N=18
Median follow-up, months	16.4	5.5	9.5
ORR (n, (%)); [95 %CI]	9 (52.9) [27.8 – 77.0]	1 (4.4 %) [0.1 – 21.9]	7 (38.9) [17.3 – 64.3]
CR (n, (%))	1 (5.9)	0 (0)	2 (11.1)
DCR (n, (%))	14 (76.5)	7 (30.4)	9 (50.0)
Responses with low PD-L1, (n, (%))	4 (44.4), < 50 % PD-L1 TPS	(0)	1 (25.0), 1-19 % PD-L1 CPS
Median PFS, months [95 % CI]	11.8 [3.0;16.6]	2.1 [1.8;3.0]	4.26 [1.48; NE]
OS rate at 9 / 12 / 15 months	85 % / 71 % / 64 %	not yet reached	67 % / 60 % / not yet reached

Conclusions Efti plus pembrolizumab is safe and shows encouraging antitumor responses in NSCLC and HNSCC patients

Trial Registration NCT03625323

Ethics Approval The study was approved by relevant ethic committees and institutional review boards.

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791 A PHASE II STUDY OF THE ANTI-PROGRAMMED CELL DEATH-1 (PD-1) ANTIBODY PENPULIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSIC HODGKIN LYMPHOMA (CHL)

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Background Penpulimab is a humanized IgG1 mAb that blocks PD-1 binding to PD-L1. Penpulimab was engineered to eliminate Fc?R binding and ADCC/ADCP completely, as compared to majority of marketed IgG4 PD-1 antibodies with ADCC/ADCP activity. ADCC/ADCP effects can induce T-cell apoptosis and clearance and then compromise anti-tumor activity. The removal of Fc?R binding eliminates Fc receptor mediated immune-cell recruitment and activation and could potentially reduce immune-related adverse reactions. Penpulimab demonstrated a slower PD-1 antigen binding off-rate than marketed PD-1 antibodies, which result in better cellular activity and higher receptor occupancy. Penpulimab also showed numerous contacts with N58 glycosylation on the BC loop of PD-1 which could be an advantage to facilitate interaction of PD-1 antibody and may contribute to slower binding off-rate. These structural differentiations offer more robust biological effect and enhance anti-tumor activity of penpulimab.

Methods AK105-201 (NCT03722147) is a multicenter, single-arm, open-label study of penpulimab in R/R cHL. All pts received penpulimab 200 mg q2w until progression or unacceptable toxicity. Eligible pts had R/R cHL after ASCT, or at least 2 lines of prior chemotherapy. The primary endpoint was ORR based on the Lugano 2014 criteria as assessed by an independent review committee (IRC). Key secondary endpoints included CR rate, DCR, PFS, duration of response (DoR), safety, and tolerability.

Results As of 10 January, 2020, the median follow-up was 6.3 months (range, 3.5 to 17.0). The anti-tumor activity of penpulimab in the 73 pts evaluable for efficacy (defined as pts who had