potency. TGF-beta signaling is highly immunosuppressive in the tumor microenvironment and has been associated with immune checkpoint inhibitor resistance.[1-4] TGF-beta1 and -beta3 are most closely associated with cancer progression whereas TGF-beta2 is required for normal cardiac function and hematopoiesis. Accordingly, selective targeting of TGF-beta1 and -beta3 by AVID200 may improve the efficacy of immunotherapy while avoiding toxicities associated with earlier generations of non-selective TGF-beta inhibitors.

Methods This open-label, multicenter Phase 1 study (NCT03834662) evaluated safety, tolerability and dose-limiting toxicities (DLTs) of sequential escalating doses of AVID200 (Q3W IV) to establish the recommended Phase 2 dose. Patients with documented, locally advanced or metastatic solid tumors without other treatment options were eligible. The primary objective was safety and tolerability; secondary objectives included preliminary anti-tumor activity, pharmacokinetics (PK), and assessment of pharmacodynamic biomarkers indicative of target modulation. PK was assessed by enzyme immunoassay. Ability of AVID200 to selectively sequester and neutralize its target was assessed by TGF-beta quantification per ELISA, as well as cell-based IL-11 release functional evaluation of TGF-beta signal inhibition. In addition, phosphorylation of SMAD2, a downstream target of TGF-beta, was assessed by immunohistochemistry in skin biopsies at screening and Cycle 1, Day 4 (C1D4).

Results Enrollment to all planned cohorts is complete: A total of 13 patients with ECOG 0-1 received AVID200 across the three planned dose levels of 180 (N=7), 550 (N=3), and 1100 mg/m2 (N=3) (~5, 15, and 30 mg/kg). The MTD was not reached. Grade 3 study drug-related AEs were reported in two patients (diarrhea, lipase elevation); no related Grade 4 or 5 AEs were observed. Serum exposure was dose-proportional. AVID200 sequestered circulating endogenous active TGF-beta at all dose levels. Moreover, AVID200 in patient plasma potently neutralized TGF-beta1- and -3 – but not -beta2 – mediated signaling. SMAD2 phosphorylation in skin biopsies was detectably reduced at C1D4 across all dose levels. Three of nine patients evaluated for response had a best response of stable disease (SD), including one prolonged SD which was ongoing at six months at time of writing.

Conclusions AVID200 has been well tolerated as monotherapy and engaged its target in patients providing proof-of-principle that selective and potent inhibition of TGF-beta1 and -beta3 is feasible in the clinic. The results warrant evaluation of AVID200 in combination with anti-PD(L)1 and other anti-cancer therapies.

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Trial Registration Clinicaltrials.gov NCT03834662

Ethics Approval The study was approved by START-Midwest's IRB (approval number STMW2018.19), University Health Network's Research Ethics Board (approval number 18-6104), and The University of Texas MD Anderson Cancer Center's IRB (approval number 2018-1079).

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Immune-stimulants and immune modulators

P857 ONM-500 – A NOVEL STING-ACTIVATING THERAPEUTIC NANOVACCINE PLATFORM FOR CANCER IMMUNOTHERAPY

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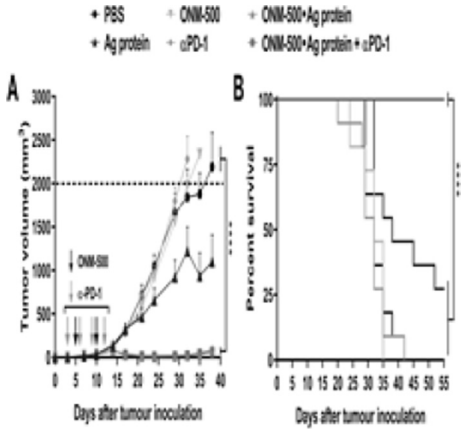
Background Efficacy of cancer vaccines requires the induction of tumor antigen-specific cytotoxic T-lymphocytes (CTL) to effectively clear established tumors. Orchestration of antigen presentation, co-stimulatory signaling, and innate cytokine signals are necessary steps for tumor-specific T-cell activation. The ONM-500 nanovaccine platform[1-2] utilizes a novel pH-sensitive polymer that forms an antigen-encapsulating nanoparticle and functions both as a carrier for antigen delivery of both peptide and protein antigens to dendritic cells and acts as an adjuvant, activating the stimulator on interferon genes (STING) pathway and generating a CD8+ CTL response. Peptide antigens have translational challenges due to complex formulations and/or HLA-type-specific antigen sequence recognition, processing and presentation. Full-length protein antigens alleviate HLA subtype limitation, allowing coverage of multi-immunogenic T cell epitopes in patients. Pairing ONM-500 adjuvant with the full-length E6 and E7 oncoproteins from human papillomavirus (HPV) cancers shows great potential to treat HPV-associated cancer in patients.

Methods Based on the previously demonstrated STING-dependent T cell activation by ONM-500 [1], the nanovaccine was formulated with full-length HPV16 E6 and E7 proteins (recombinant), and the nanoparticle properties and antigen loading were characterized. In vivo lymph node accumulation following subcutaneous administration was evaluated using fluorescent nanovaccines. Direct binding of ONM-500 to



Abstract P857 Figure 1

recombinant human STING (CTD) was evaluated using isothermal titration calorimetry (ITC) compared to the endogenous ligand 2',3'-cGAMP. Antitumor efficacy was evaluated in multiple syngeneic tumor models, including the TC-1 model which overexpresses HPV16 E6 and E7 with the ONM-500 vaccine in combination with anti-PD-1 checkpoint inhibitor. Long-term anti-tumor memory was evaluated in a follow-up rechallenge study after 60 days in tumor-free animals.

Results Characterization of ONM-500 nanovaccine shows reproducible particle chemi-physical properties and antigen loading. The nanoparticle size substantiates the effective lymph node accumulation for antigen cross-presentation in dendritic cells following subcutaneous administration. ITC studies with human STING demonstrated effective binding by ONM-500 adjuvant. The nanovaccine anti-tumor efficacy was previously demonstrated in melanoma, colorectal, and HPV-associated syngeneic tumor models. In TC-1 tumors, ONM-500 nanovaccine containing full-length E6/E7 protein showed 100% overall survival at 55 days (figure 1). Tumor growth inhibition was also improved over E7 antigen peptide formulated nanovaccine. A rechallenge study demonstrated long-term antigen-specific anti-tumor memory response.

Conclusions ONM-500 STING-activating nanovaccines effectively deliver antigens in vivo to lymph nodes to elicit antigen-specific CTL response. The anti-tumor efficacy in multiple tumor models demonstrates the potential of ONM-500 as a general STING agonist cancer vaccine platform, and full-length E6/E7 incorporated ONM-500 is being developed for HPV-associated cancers.

Ethics Approval All animal procedures were performed with ethical compliance and approval by the Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center (Protocol No. 2017-101954) and Pennsylvania State College of Medicine (Protocol No. 47682).

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In-Progress clinical trials

P858 AN OPEN-LABEL, MULTI-CENTER TRIAL OF INO-5401 AND INO-9012 DELIVERED BY ELECTROPORATION (EP) IN COMBINATION WITH CEMIPLIMAB IN SUBJECTS WITH NEWLY-DIAGNOSED GLIOBLASTOMA (GBM)

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Background GBM is one of the most deadly cancers and treatment is surgery, followed by radiation (RT) and temozolomide (TMZ) daily during RT followed by cycles of TMZ for select patients.[1] New immunotherapies, such as checkpoint inhibition, may benefit patients with GBM. T cell-enabling therapies, in combination with checkpoint inhibition, may improve overall survival (OS). In this study, a novel antigen-specific T cell-generating therapy, INO-5401 (synthetic DNA plasmids encoding for human telomerase [hTERT], Wilms Tumor-1 [WT-1] and prostate specific membrane antigen [PSMA]), plus INO-9012 (synthetic DNA plasmid encoding for IL-12), with the PD-1 checkpoint inhibitor, cemiplimab, was given to patients with newly-diagnosed GBM to evaluate tolerability, immunogenicity and clinical efficacy of the combination.

Methods Phase I/II, single arm, two cohort study (A: MGMT Promoter Unmethylated, B: MGMT Promoter Methylated). The primary objective is to evaluate the safety of INO-5401 and INO-9012 followed by EP with CELLECTRA® 2000 in combination with cemiplimab. Secondary objectives include the evaluation of preliminary clinical efficacy and immunogenicity. Treatment is with 9 mg INO-5401 with 1 mg INO-9012 every three weeks (Q3W) for four doses, then Q9W; and cemiplimab (350 mg IV Q3W). RT is given as 40 Gy over three weeks; TMZ is given concurrent with radiation (Cohorts A and B), followed by maintenance TMZ (Cohort B).

Results 52 patients were enrolled onto this study; 32 in Cohort A and 20 in Cohort B. 18 were women (35%) and 47 were white (90%). The median age was 60 years (range 19-78 years). The most common Grade $\geq$3 adverse events were elevations in alanine or aspartate aminotransferase (ALT/AST; 5 patients), and tumor inflammation/edema (5 patients); there was one Grade 5 unrelated event of urosepsis. The only related SAE reported in more than one patient was pyrexia. 22 patients (42%) reported immune-related AEs, with the most common being elevations in ALT or AST (8 patients), and were reported most commonly within the first nine weeks of treatment. The safety profile was consistent with that of patients with GBM and of checkpoint inhibitors. ELISpot assessments performed to date demonstrated the majority of patients have T cell responses to INO-5401. PFS6 was 75% (95% CI 56.6, 88.5) in Cohort A (preliminary; Cohort B pending).

Conclusions INO-5401 + INO-9012 with cemiplimab has an acceptable safety profile, is immunogenic and is potentially efficacious in patients with newly-diagnosed GBM. This combination is promising; survival results will be updated next year.

Trial Registration NCT03491683.

Ethics Approval This study was approved by New York University institution's Ethics Board; approval number i17-00764.

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P859 ASSOCIATION OF IMMUNOPHARMACODYNAMIC RESPONSES OF IMPRIME PGG PLUS PEMBROLIZUMAB WITH CLINICAL BENEFIT IN METASTATIC TRIPLE NEGATIVE BREAST CANCER (TNBC) SUBJECTS FAILING FRONT-LINE CHEMOTHERAPY

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