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

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AN OPEN-LABEL, MULTI-CENTER TRIAL OF INO-5401 AND INO-9012 DELIVERED BY ELECTROPORATION (EP) IN COMBINATION WITH CEMIPIMAB 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 ≥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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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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Background Checkpoint inhibitor (CPI) monotherapies, including pembrolizumab (KEYTRUDA®, pembro), avelumab and atezolizumab have demonstrated modest clinical benefit in chemotherapy-relapsed/refractory TNBC patients (pts) with ~5-10% response rate, median overall survival (mOS) of 7-9 months, and 1 year OS ~37-40%. TNBC, although more immunogenic relative to the other breast cancer subtypes, is also the most heterogenous, resulting in substantial variability in immune responses. There is a dire need for immunotherapeutic agents that could consistently induce anti-cancer immune responses.

Methods The primary analyses of our Phase 2 study (NCT02981303; collaboration with Merck & Co., Inc.) in 44 (intent-to-treat) chemotherapy-refractory/relapsed TNBC pts treated with Imprime PGG (Imprime), a novel yeast derived, Dectin-1 agonist β -glucan PAMP in combination with pembro has shown enhanced disease control rate (25%, N= 11; 1 CR, 6 PR and 4 SD>24 weeks), 12-month OS rate (57.3%) and increased mOS (16.6 months) vs the respective endpoints in Keynote086 pts treated with pembro alone. As part of exploratory translational objectives, peripheral blood from pts receiving the combination in 3-week cycles were collected at various time points. Results from serum and cellular immunopharmacodynamic (IPD) evaluations from 41 pts are presented.

Results Peak levels of serum circulating immune complexes (~3 to 22-fold) and complement protein SC5b-9 (~1.4 to 41-fold) in stage 1 pts provided evidence for Imprime-anti beta glucan antibody immune complex formation. A significant increase in the frequency of HLA-DR+ myeloid cells was observed in the overall population (up to 7.4-fold). In pts showing disease control (N=11), a significant increase in complement function (CH50, ~0.8-4 fold range), select chemokines such as MCP-1 production (up to 1000-fold), CD86 expression on monocyte (~0.5-6-fold) and DC subsets (~0.8-11-fold), and increased frequency of Ki-67+, HLA-DR/PD-1+ CD8 T cells (~0.4-14-fold) was observed. Some IPD responses were associated with the 12-month landmark OS analyses. Additionally, enhanced mPFS (HR 0.51; p=0.03) and mOS (HR 0.13; p=0.0013) was observed in 18 pts with >1.25-fold increase in CD86 expression on classical monocytes. Greater than 2-fold increase in the frequency of Ki-67+, HLA-DR/PD-1+ CD8 T cells in 16 pts was also associated with enhanced mPFS (HR 0.395; p=0.01) and mOS (HR 0.183; p=0.008). Additionally, the gene expression profile of these IPD-responders were similar to the RECIST responders with >2-fold upregulation of several genes including IFN γ , CD83, GZMA, GZMK, and CD3.

Conclusions Overall, the strong association of the innate/adaptive IPD responses to the clinical responses are suggestive of interplay between the therapeutic mechanisms of Imprime and pembro combination.

Ethics Approval The study was approved by central and local ethics committees depending on site requirements. The central IRB for the study is Western Institutional Review Board (WIRB), approval number 20162506; all sites received IRB approval before opening the study at the respective sites.

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RESULTS FROM A COMBINATION OF OX40 (PF-04518600) AND 4-1BB (UTOMILUMAB) AGONISTIC ANTIBODIES IN MELANOMA AND NON-SMALL CELL LUNG CANCER IN A PHASE 1 DOSE EXPANSION COHORT

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Background PF-04518600 (PF-8600) and utomilumab (uto) are humanized agonist IgG2 monoclonal antibodies for the tumor necrosis factor superfamily receptors OX40 and 4-1BB, respectively. In a phase I dose escalation study (NCT02315066), this antibody combination was tolerable at all dose levels and induced responses in patients with melanoma resistant to immune checkpoint inhibitors. We report results from a dose expansion cohort of this study of patients with melanoma and non-small cell lung cancer (NSCLC) treated with PF-8600 (OX40 antibody) in combination with uto. Efficacy, safety, and the association of baseline and pharmacodynamic biomarkers with efficacy were examined.

Methods In this expansion cohort, patients with locally advanced/metastatic melanoma (n=10) and NSCLC (n=20) who progressed on prior anti-PD1/PD-L1 treatment and/or anti CTLA4 treatment (melanoma only) were enrolled. Patients received OX40 antibody 30 mg IV every 2wks in combination with uto 20 mg IV every 28d. Tumor assessments were performed every 8wks using RECIST1.1. Paired biopsy samples collected at baseline and 6wks were analyzed by immunohistochemistry and RNA sequencing to evaluate the pharmacodynamic effects of the OX40 antibody in combination with uto. Whole blood samples were collected longitudinally, from which DNA was extracted and submitted for high-throughput sequencing of the T cell receptor β -chain.

Results One patient with NSCLC achieved a confirmed and ongoing partial response lasting at least 6 months; Based on analyses of a subset of baseline biopsies, this patient's tumor had the lowest FOXP3 expression. A total of 7 (70%) melanoma patients and 7 (35%) NSCLC patients achieved a best overall response of stable disease (SD). The median duration of SD was 16.3 weeks (melanoma: 16.0 weeks; NSCLC: 24.1 weeks), for a disease control rate of 50%. Among patients with a defined response, paired biopsy analyses showed that the greatest increase in CD8 occurred in the NSCLC patient with the longest duration of stable disease. The most frequent treatment related adverse events (TRAEs) reported in $\geq 10\%$ of patients were pruritis, anemia, fatigue, decreased appetite, and rash. Grade 3 TRAEs, rash and lymphocyte count decreased, were reported in 5 patients and a grade 4 TRAE of lipase increased (asymptomatic) was reported in 1 patient.