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. Three of nine patients evaluated for response had a best response of stable disease (SD), including one prolonged SD. Three of nine patients evaluated for response had a best response of stable disease (SD), including one prolonged SD.

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.

Acknowledgements We would like to thank all participating patients, their families and caretakers as well as staff members at the clinical sites.

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).

REFERENCES


Immune-stimulants and immune modulators

P857

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

Jason Miller,1 Min Luo,2 Hua Wang,2 Zhaozhi Wang,3 Xinliang Ding,3 Ashley Campbell,1 Jonathan Almazan,1 Zhijian Chen,1 Jinnong Gao,1 Tian Zhao*.1 OncoNano Medicine Inc., Dallas, TX, USA; 2Institutes of Biomedical Sciences, Fudan University, Shanghai, China; 3UT Southwestern Medical Center, Dallas, TX, USA

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 platform1-2 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 iso-
thermal titration calorimetry (ITC) compared to the endoge-
nous 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 chemophysical 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 nanovac-
cine 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 nanovac-
cine. A rechallenge study demonstrated long-term antigen-spe-
cific anti-tumor memory response.

Conclusions ONM-500 STING-activating nanovaccines effec-
tively deliver antigens in vivo to lymph nodes to elicit anti-
gen-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 South-
western Medical Center (Protocol No. 2017-101954) and
Pennsylvania State College of Medicine (Protocol No. 47682).

REFERENCES
Porembka MR, Lea J, Frankel AE, Fu YX, Chen ZJ, Gao J. A STING-activating
2. Luo M, Liu Z, Zhang X, Han C, Samandi LZ, Dong C, Sumer BD, Lea J, Fu YX,
Gao J. Synergistic STING activation by PC7A nanovaccine and ionizing radiation

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 GLOBLASTOMA (GBM)

Jeffrey Skolnik, David Reardon, Steven Brem, Arati Desai, Stephen Bagley,
Sylvia Kurz, Macedo de la Fuente, Seema Nagpal, Mary Welch, Brian Sacchetta,
Sarah Barra, Amy Lee Bredlau, Israel Lowy, Kimberly Kraynyak, Matthew Morrow,
Trevor McMullan, Jean Boyer.

Background GBM is one of the most deadly cancers and
treatment is surgery, followed by radiation (RT) and temozolo-
mide (TMZ) daily during RT followed by cycles of TMZ for
select patients. 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 CELLEC-
TRA® 2000 in combination with cemiplimab. Secondary objectives include the evaluation of preliminary clinical effi-
cacy and immunogenicity. Treatment is with 9 mg INO-
5401 with 1 mg INO-9012 every three weeks (Q3W) for
d four doses, then Q9W; and cemiplimab (350 mg IV Q3W).
RT is given as 40 Gy over three weeks; TMZ is given con-
current 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 (5 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 com-
bination is promising; survival results will be updated next
year.

Trial Registration NCT03491683.

Ethics Approval This study was approved by New York Uni-
versity institution’s Ethics Board; approval number i17-00764.

REFERENCES

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

Nadine Ottoson, Maridita Bose*, Anisa Chan, Xiaohong Qi, Ben Harrison,
Richard Walsh, Paulette Mattson, Michele Gargano, Joanna Cox, Michael Chisamore,
Mark Uhlik, Jeremy Graff, Biothera Pharmaceuticals, Eagan, MN, USA; Merck and Co.,
Inc., Rahway, NJ, USA

Background GBM is one of the most deadly cancers and
treatment is surgery, followed by radiation (RT) and temozolo-
mide (TMZ) daily during RT followed by cycles of TMZ for
select patients. 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 CELLEC-
TRA® 2000 in combination with cemiplimab. Secondary objectives include the evaluation of preliminary clinical effi-
cacy and immunogenicity. Treatment is with 9 mg INO-
5401 with 1 mg INO-9012 every three weeks (Q3W) for
d four doses, then Q9W; and cemiplimab (350 mg IV Q3W).
RT is given as 40 Gy over three weeks; TMZ is given con-
current 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 (5 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 com-
bination is promising; survival results will be updated next
year.

Trial Registration NCT03491683.

Ethics Approval This study was approved by New York Uni-
versity institution’s Ethics Board; approval number i17-00764.

REFERENCES