Intratumoral tavokinogene telseplasmid and electroporation in pre-treated inoperable locally advanced or recurrent triple-negative breast cancer

Melinda L. Telli[1], Kaitlin Zablotsky[1], Bernard A. Fox[2], Mai H. Le[3], Erica Browning[3], Donna Bannavong[3], David A. Canton[3], Kellie Malloy Foerter[3], Lauren Svenson[3], Irene Wapnir[1]

[1]Stanford University School of Medicine, Stanford, CA; [2]Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR; [3]OncoSec Medical Incorporated, San Diego, CA

Poster P2-09-11 / Abstract 851874
San Antonio Breast Cancer Symposium®
December 4–8; San Antonio, Texas, USA

INTRODUCTION

- Triple-negative breast cancer (TNBC), which constitutes ~15% of breast cancer diagnoses in the United States,[1] is associated with an increased risk of recurrence and a more aggressive course in the metastatic setting compared with other breast cancer subtypes.[2]
- Patients with advanced and recurrent TNBC have limited treatment options. The only current standard of care is cytotoxic chemotherapy, which leads to a median survival of ~13 months from the time of recurrence.[3-5]
- Recent data suggest that some patients benefit from therapies targeting the anti-programmed cell death protein 1 (PD-1)/PD-1 ligand 1 (PD-L1) axis.[6-9] However, this treatment has shown limited success in poorly immunogenic tumors.
- Thus, combination therapies that promote the presence of CD8$^+$ tumor-infiltrating lymphocytes (TILs) and/or upregulate PD-L1 expression are required to increase response rates to these therapeutics.
- Intratumoral injection of plasmid interleukin (IL)-12 (tavokinogene telseplasmid; tavo) followed by electroporation (collectively, TAVO™) is a gene therapy approach that drives local expression of the pro-inflammatory cytokine IL-12, with minimal systemic immune-related toxicity.
  - Via this mechanism, TAVO™ can convert poorly immunogenic/low-TIL TNBC tumors into highly inflamed, immunologically active lesions

OBJECTIVES

PRIMARY OBJECTIVE

- Evaluate the potential of intratumoral treatment with TAVO™ to promote a proinflammatory molecular and histologic signature.

SECONDARY OBJECTIVE

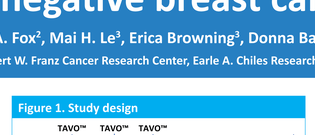
- Evaluate safety and tolerability of TAVO™.

METHODS

STUDY DESIGN AND INTERVENTION

- OMS-I140 is a phase 1 non-randomized, open-label study of TAVO™ in patients with inoperable locally advanced, metastatic and/or treatment-refractory TNBC (NCT02531425).
- Eligible patients had pre-treated TNBC and at least 2 anatomically distinct cutaneous or subcutaneous lesions accessible for injection and electroporation, with or without other regional or distant metastases.
- TAVO™ was administered intratumorally on days 1, 5, and 8 of a single 28-day cycle into accessible tumor lesions (**Figure 1**). At least 1 lesion remained untreated.
- One tumor biopsy was obtained at screening and 2 biopsies were obtained post-treatment on day 28 of both treated and untreated lesions.
- A subset of patients went on to receive anti-PD–1 monotherapy as their immediate next treatment.

Figure 1. Study design



Key eligibility criteria
- Adult patients (≥18 years) with histologically confirmed diagnosis of locally advanced, inoperable, metastatic and/or treatment-refractory TNBC (ER/PR <10%)
- At least 2 anatomically distinct lesions accessible for biopsy
- Eastern Cooperative Oncology Group performance status 0–1
- Life expectancy ≥6 months

Primary endpoint: Evaluation of pre- and post-treatment changes in the molecular and histologic signature in patients treated with TAVO™

One patient was retreated with TAVO™ following completion of the study endpoints and completed 3 additional retreatment cycles.
C, cycle; D, day; EOS, end of study; ER, estrogen receptor; PR, progesterone receptor; TAVO™, intratumoral interleukin-12 plasmid administration followed by electroporation; TNBC, triple-negative breast cancer.

- Tavo was injected intratumorally at a concentration of 0.5 mg/mL at a dose volume of ~¼ of the calculated lesion volume with a minimum dose volume/lesion of 0.1 mL for lesions of volume <0.4 cm^3.
- An applicator tip containing either a 1.0-cm or 0.5-cm diameter array of 6 stainless-steel needles was co-localized at the site(s) and depth of plasmid injection and 6 pulses at a field strength of 1500 volt/cm and pulse width of 100 µs at 300-msec intervals were delivered.

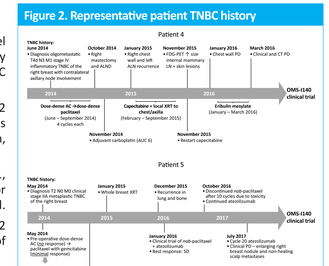
ASSESSMENTS

- For changes in the proportion of intratumoral lymphocyte subsets, paired tumor biopsy samples were quantitatively analyzed using a multi-spectral quantitative immunohistochemistry (IHC) method with PerkinElmer's Vectra® IHC platform, as well as chromogenic IHC.
- Analysis of NanoString-based gene expression profiles was performed using NanoString's nCounter® Immunology Panel (Human V2). Plasma cytokine levels were detected using the Luminex® MAGPIX® platform (Human High Sensitivity T Cell Magnetic Bead Panel; 15-plex).
- Changes in peripheral immune subsets were assessed using flow cytometry.
- Adverse events (AEs) were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Pain assessment was performed using a 0–10 numeric pain-rating scale.

PATIENT VIGNETTES

- Representative TNBC histories of 2 patients enrolled in the study are shown in **Figure 2**.

Figure 2. Representative patient TNBC history



AC, anthracycline-cyclophosphamide; ALN, axillary lymph node; ALND, axillary lymph node dissection; AUC, area under the curve; BID, twice daily; CT, computed tomography; D, day; FDG-PET, fluorodeoxyglucose (18F) positron emission tomography; LN, lymph node; PD, progressive disease; po, orally; q, every; SD, stable disease; TNBC, triple-negative breast cancer; XRT, radiotherapy.

RESULTS

PATIENTS

- As of November 1, 2018, ten patients have completed study therapy. Demographics and baseline characteristics are summarized in **Table 1**.
- The TAVO™ dose delivered per patient per day ranged between 0.3–20 mL.

Table 1. Demographics and baseline characteristics

Characteristic	All patients (N = 10)
Age, years	
Mean	61
Min–max	35–84
Age group, n (%)	
<65 years	5 (50)
≥65 years	5 (50)
Sex, n (%)	
Male	0 (0)
Female	10 (100)
Race, n (%)	
Caucasian	6 (60)
Asian	4 (40)
Distant metastases at enrollment, n (%)	7 (70)

max, maximum; min, minimum.

- Representative images of Patients 4 and 5 pre- and post-treatment with TAVO™ and nivolumab are presented in **Figure 3**.

Figure 3. Representative patient images pre- and post-treatment with TAVO™ and nivolumab

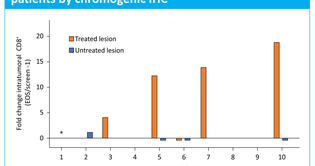
Figure 3 (cont). Representative patient images pre- and post-treatment with TAVO™ and nivolumab

Bx, biopsy post-chemoradiation; D/C, discontinued; IV, intravenous; PD-1, programmed cell death protein 1; q, every; TAVO™, intratumoral interleukin-12 plasmid administration followed by electroporation; XRT, radiotherapy.

PROINFLAMMATORY MOLECULAR AND HISTOLOGIC SIGNATURE

- From screening to end of study (EOS), changes were detected by chromogenic IHC in the proportion of intratumoral CD8$^+$ lymphocytes in the treated lesions (**Figure 4**).

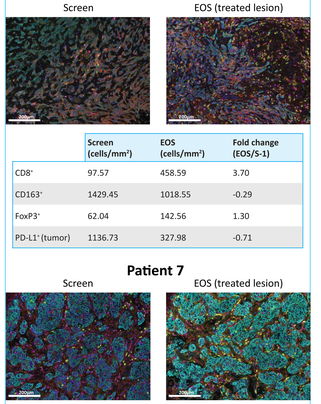
Figure 4. Enumeration of intratumoral CD8$^+$ lymphocytes at screening and at EOS in all treated patients by chromogenic IHC



*Patient 1: value at screen = 0%.
EOS, end of study; IHC, immunohistochemistry.

- Changes in the proportion of intratumoral lymphocyte subsets were also recorded by multispectral IHC (**Figure 5**).

Figure 5. Representative multispectral IHC images of intratumoral immune subsets at screening and at EOS in 3 patients (inset tables show quantitation of images)



Patient 5

	Screen (cells/mm^2)	EOS (cells/mm^2)	Fold change (EOS/S-1)
CD8$^+$	97.57	458.59	3.70
CD163$^+$	1429.45	1018.55	-0.29
FoxP3$^+$	62.04	142.56	1.30
PD-L1$^+$(tumor)	1136.73	327.98	-0.71

Patient 7

	Screen (cells/mm^2)	EOS (cells/mm^2)	Fold change (EOS/S-1)
CD8$^+$	159.44	589.23	2.70
CD163$^+$	1736.01	1985.05	0.14
FoxP3$^+$	158.59	182.48	0.15
PD-L1$^+$(tumor)	0.70	302.06	430.51

Patient 10

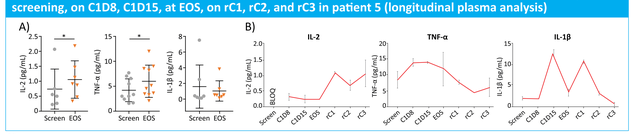
	Screen (cells/mm^2)	EOS (cells/mm^2)	Fold change (EOS/S-1)
CD8$^+$	0	1759.03	≥1759.03*
CD163$^+$	2310.30	5257.87	1.28
FoxP3$^+$	2.52	689.44	272.59
PD-L1$^+$(tumor)	4472.80	374.58	-0.92

Stains: PD-L1, CD8, FoxP3, CD3, CD163, Tumor, DAPI

*Divide by zero.
DAPI, 4′,6-diamino-2-phenylindole; EOS, end of study; FoxP3, forkhead box P3; IHC, immunohistochemistry; PD-L1, programmed cell death protein 1 ligand 1; S, screening.

- Plasma analysis of cytokines involved in the differentiation, intratumoral accumulation, and activation of T cells and other immune cells revealed a subtle increase in their levels during treatment with TAVO™ in treated patients (**Figure 6**).

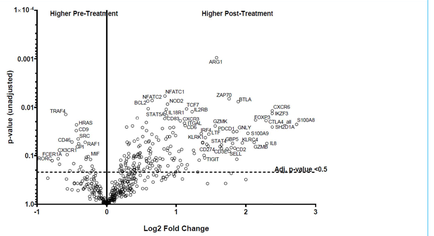
Figure 6. Plasma levels of antitumoral cytokines A) at screening and EOS in all evaluable patients, and B) at screening, on C1D8, C1D15, at EOS, on rC1, rC2, and rC3 in patient 5 (longitudinal plasma analysis)



*p <0.05.
BLOQ, below limit of quantification; C, cycle; D, day; EOS, end of study; IL, interleukin; r, retreatment; TNF, tumor necrosis factor.

- A treatment-related upregulation of immune-based transcripts in the tumor microenvironment was observed in matched biopsies of treated tumors (**Figure 7**).

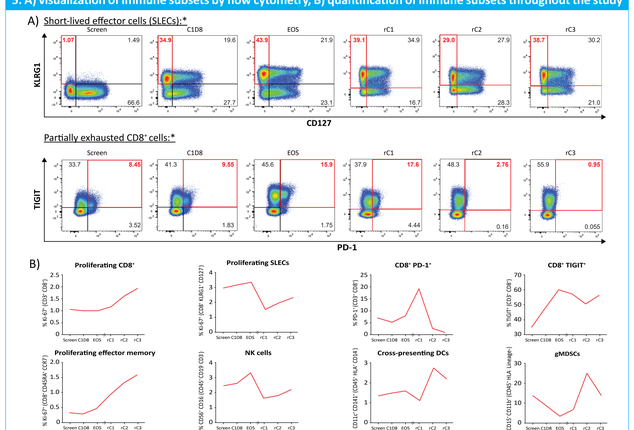
Figure 7. Volcano plot depicting results from transcriptional analyses of lesion-matched biopsies collected at screening and treated EOS lesions (n = 5)



A matched lesion represents the same lesion pre- and post-treatment with TAVO™.
AIM2, ezrin; IL-2 Rβ2, IL-2 receptor subunit beta; IRF4, interferon regulatory factor 4; ITGAL, integrin subunit alpha L; KLRC4, killer cell lectin like receptor C4; KLRK1, killer cell lectin like receptor K1; LTF, lactotransferrin; MIF, macrophage migration inhibitory factor; NFATC, nuclear factor of activated T cells; NOD2, nucleotide binding oligomerization domain containing 2; PDCD1, programmed cell death 1; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; RORC, RAR related orphan receptor C; S100A8, S100 calcium binding protein A8; S100A9, S100 calcium binding protein A9; SELL, selectin L; SH2D1A, SH2 domain containing 1A; SRC, SRC proto-oncogene, non-receptor tyrosine kinase; STAT, signal transducer and activator of transcription; TAVO™, intratumoral interleukin-12 plasmid administration followed by electroporation; TCF7, transcription factor 7; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TRAF4, TNF receptor associated factor 4; ZAP70, zeta chain of T-cell receptor associated protein kinase 70.

- Longitudinal analysis of changes in levels of various peripheral immune subsets showed an increase in antitumoral immune subsets following treatment in a representative patient (**Figure 8**).

Figure 8. Longitudinal analysis of changes in levels of peripheral immune cell subsets throughout the study in patient 5: A) visualization of immune subsets by flow cytometry, B) quantification of immune subsets throughout the study



*Gating: Singlets>Live/CD56/CD19/CD14>CD3+CD8+.
C, cycle; D, day; DC, dendritic cell; EOS, end of study; HLA, human leukocyte antigen; gMDSC, granulocytic myeloid-derived suppressor cell; Ig, immunoglobulin; ITIM, immunoreceptor tyrosine-based inhibitory motif; KLRG1, killer cell lectin-like receptor subfamily G member 1; NK, natural killer; PD-1, programmed cell death protein 1; r, retreatment; TIGIT, T-cell immunoreceptor with Ig and ITIM domains.

SAFETY

- Treatment-emergent AEs are shown in **Table 2**.

Table 2. TEAEs recorded in all treated patients (N = 10)

MedDRA preferred term, n (%)	Grade 1	Grade 2	Grade 3
Abdominal pain upper	1 (10)		
ALT increased	1 (10)		
Anemia	1 (10)		
Application site pain	1 (10)		
AST increased*	1 (10)	1 (10)	
Axillary pain	1 (10)		
Blood ALP increased		1 (10)	
Blood LDH increased			1 (10)
Bone pain	1 (10)		
Breast pain	1 (10)		
Contusion	1 (10)		
Decreased appetite	1 (10)		
Diarrhea	1 (10)		
Dizziness	1 (10)		
Fall		1 (10)	
Fatigue	1 (10)	1 (10)	
Headache	1 (10)		
Hypercalcemia	1 (10)		
Hypoalbuminemia		2 (20)	
Neck pain*	1 (10)	1 (10)	
Neuropathy peripheral	1 (10)		
Oropharyngeal pain	1 (10)		
Pain	8 (80)		
Pruritus	1 (10)		
Tremor	1 (10)		
Vision blurred	1 (10)		

*The same patient experienced both a grade 1 and grade 2 event.
Only TEAEs that started after the first study drug administration are included.
Patients experiencing multiple events under the same grading are only counted once.
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

- Reported treatment-related AEs included pain associated with electroporation (grade 1) in 9 patients and fatigue (grade 1), pruritus (grade 1), and tremors/involuntary shaking (grade 1) in 1 patient each. The AE of tremors was experienced 3 times by the same patient.
- Median pain score (range 0–10) immediately after treatment was 2 (range 0–10) and 5 minutes post-treatment was 1 (range 0–7).

CONCLUSIONS

- Treatment-related increases in CD8$^+$ TIL density were observed in 4 of 10 heavily pre-treated patients.
- Following 1 cycle of TAVO™, a modest post-treatment increase of effector cytokines was detected in plasma; upregulation of immune-related gene expression was also observed in treated lesions.
- Treatment-related increases of cross-presenting dendritic cells and short-lived effector cells were observed in some patients. Levels of antitumoral immune subsets increased by EOS.
- Our data suggest that TAVO™ is a safe and tolerable TIL-stimulating therapy in TNBC.
- Responses to anti–PD–1 monotherapy were observed following TAVO™ treatment. Notably, 1 patient who had no objective response to atezolizumab and chemotherapy responded to nivolumab following TAVO™ treatment.
- A phase 2 study of TAVO™ in combination with pembrolizumab in pretreated metastatic TNBC has been initiated (poster #OT2-06-03).

REFERENCES: 1. American Cancer Society. *Breast Cancer Facts & Figures 2017–2018.* Atlanta: American Cancer Society, Inc. 2017; 2. Lin NU, et al. *Cancer.* 2012;118(22):5463–72; 3. Cardoso F, et al. *Ann Oncol.* 2017;28(1):16–33; 4. Kassam F, et al. *Clin Breast Cancer.* 2009;9(1):29–33; 5. Steponaviciene L, et al. *Adv Med Sci.* 2011;56(2):285–90; 6. Juric D, et al. *J Clin Oncol.* 2017;35(15 suppl): abstract TPS3104; 7. Kok M, et al. *Ann Oncol.* 2017;28(suppl 5): abstract LBA14; 8. Cortes Castan J, et al. *Ann Oncol.* 2017;8(suppl 5): abstract 234TiP; 9. Emens LA, et al. *J Clin Oncol.* 2016;34(15 suppl): abstract TPS1104.

DISCLOSURES: MLT: Advisory role: Aduro, Celldex, Genentech, G1 Therapeutics, Immunomedics, Merck, Pfizer, Tesaro. Research funding (to my institution): Biothera, Calithera, Genentech, Medivation, Merck Serono, OncoSec, PharmaMar, Pfizer, Tesaro, Vertex. **KZ:** No disclosures. **BAF:** Multiplex, SAB Perkin/Elmer, SAB Definiens/AstraZeneca. Research support from BMS, MedImmune, OncoSec, NanoString, Definiens, Viralytics, Merck, and MacroGenics. **IW:** Advisory boards to Cardinal Health, Tolmar, and Genomic Health. **MHL, EB, DB, DAC, KMF, LS:** Employees of OncoSec Medical Inc.
ACKNOWLEDGEMENTS: Editorial and medical writing assistance was provided by Shilu Amin, PhD, and Oana Draghiciu, PhD, CMPP, from Aptitude Health, The Hague, The Netherlands, funded by OncoSec Medical Inc. The authors are fully responsible for all content and editorial decisions for this poster.

A phase 2 study of intratumoral tavokinogene telseplasmid (tavo) plus electroporation with pembrolizumab in patients with inoperable locally advanced or metastatic triple-negative breast cancer

Poster OT2-06-03 / Abstract 850997
San Antonio Breast Cancer Symposium®
December 4–8; San Antonio, Texas, USA

Melinda L. Telli[1], Irene Wapnir[1], Shaveta Vinayak[2], Hatem Soliman[3], Katharine Cuff[4], Bianca Devitt[5,6], Christopher Twitty[7], Kellie Malloy Foerter[7], Rohit Joshi[8]

[1]Stanford University School of Medicine, Stanford, CA, USA; [2]University of Washington, Seattle, WA, USA; [3]Moffitt Cancer Center, Tampa, FL, USA; [4]Princess Alexandra Hospital, Woolloongabba, QLD, AU; [5]Department of Medical Oncology, Box Hill Hospital, Box Hill, VIC, AU; [6]Eastern Health Clinical School, Monash University, VIC, AU; [7]OncoSec Medical Incorporated, San Diego, CA; [8]Adelaide Oncology and Haematology, Adelaide, SA, AU

INTRODUCTION

- Triple-negative breast cancer (TNBC) accounts for 10–20% of breast cancer diagnoses in the United States[1] and is associated with an increased risk of recurrence and a more aggressive course in the metastatic setting.[2,3]
- Emerging studies show that TNBC tumors with a proinflammatory environment are associated with better outcomes[4-6] and suggest that some patients with TNBC could benefit from the addition of immune therapy.
  - Reports show that patients with early stage TNBC and at least 50% tumor-infiltrating lymphocytes (TILs) have a longer disease-free survival[4-6]
- Additionally, immune-modulating therapies, like the anti-programmed cell death protein 1 (PD-1)/PD-1 ligand 1 monoclonal antibodies, have demonstrated modest activity as monotherapy in pretreated patients with metastatic TNBC, with objective response rates (ORR) <10%.[2]
  - These therapies appear to require an immunogenic tumor to be effective
- Local intratumoral administration of tavo (interleukin-12 [IL-12] plasmid) followed by electroporation (collectivelly, TAVO™) of accessible lesions is hypothesized to enhance tumor immunogenicity.
  - Preliminary results of an ongoing phase 1 study in patients with locally advanced or recurrent TNBC showed that TAVO™ is a safe and tolerable TIL-stimulating therapy for skin and subcutaneous TNBC tumors[7]
- Combining TAVO™ with an anti–PD-1 antibody, such as pembrolizumab, may further improve responses in patients with TNBC by potentially converting poorly immunogenic/low-TIL tumors into immune-responsive/high-TIL tumors.

MECHANISM OF ACTION

- IL-12 is a well-characterized, potent proinflammatory cytokine.
- Intratumoral delivery of plasmid IL-12 followed by electroporation yields sustained expression of the proinflammatory cytokine IL-12 and stimulates a proinflammatory immune response (**Figure 1**), without leading to systemic immune-related toxicities.[8,9]

Figure 1. Mechanism of action of TAVO™

Note: The DNA plasmid pUMVC3-hIL-12-NGVL331 (IL-12 plasmid) contains the sequences coding for the human IL-12 p35 and p40 subunits, separated by an internal ribosomal entry site and are driven by a single CMV promoter.
bp, base pairs; CITE, cap-independent translation enhancer; CMV, cytomegalovirus; IL-12, interleukin-12; TAVO™, IL-12 plasmid administration followed by electroporation; tavo, IL-12 plasmid.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

- To assess the ORR, by blinded independent central review (BICR), of TAVO™ in combination with pembrolizumab in patients with inoperable locally advanced/metastatic TNBC.

SECONDARY OBJECTIVES

- To evaluate safety and tolerability of the combined therapy.
- To assess duration of response (DOR), investigator-assessed ORR, immune ORR, progression-free survival (PFS), immune PFS, and overall survival (OS) of the combined therapy.

EXPLORATORY OBJECTIVE

- To evaluate correlations between changes in immune cell subsets and response to treatment.

STUDY DESIGN AND INTERVENTION

- OMS-I141 is a nonrandomized, open-label, single-arm, multicenter phase 2, Simon 2-stage study (NCT03567720) of TAVO™ with intravenous (IV) pembrolizumab in patients with inoperable locally advanced/metastatic and/or treatment-refractory TNBC.
- The study is estimated to enroll approximately 25 patients; key patient eligibility criteria are described in **Table 1**.

Table 1. Key patient eligibility criteria

Key inclusion criteria
Aged ≥18 years
Histologically confirmed inoperable locally advanced/metastatic TNBC and ≥1 prior line of approved systemic therapy/immunotherapy
Measurable disease based on RECIST v1.1, and at least 1 anatomically distinct lesion of ≥0.3 cm involving EP-accessible skin/subcutaneous tissue (lesion must be accurately measured in ≥1 dimensions)
At least 1 lesion on a computed tomography scan that is measurable as defined by RECIST v1.1
Estrogen and progesterone receptor staining <10% and HER2 negative as defined by IHC 0 to +1 or HER2 FISH negative
ECOG PS 0–1 and life expectancy ≥6 months
Adequate hematologic, renal, and hepatic functions
• Male: surgically sterile or using contraception during the study • Female: negative serum pregnancy test, or postmenopausal, surgically sterile, or using ≥1 acceptable contraceptive method (eg, intrauterine devices, double-barrier methods, sexual abstinence, or a vasectomized partner)

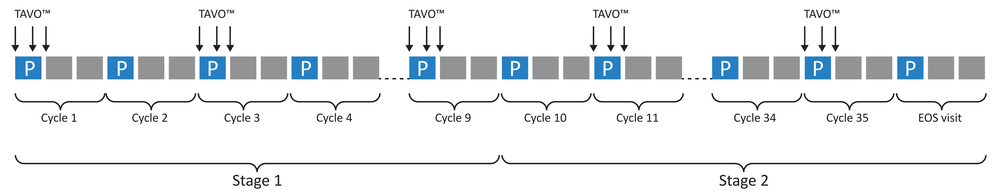
Table 1. Key patient eligibility criteria (cont.)

Key exclusion criteria
Additional malignancy that is progressing or requires active treatment (except basal or squamous cell carcinoma of the skin or in situ cervical cancer)
Clinically active CNS metastases or any nonmeasurable bone-only metastases
Use of electronic pacemakers and defibrillators
Known history of HIV (HIV 1/2 antibodies), active hepatitis B or C, or interstitial lung disease
Diagnosis of immunodeficiency, active infection requiring systemic therapy, use of chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
Live-virus vaccination within 30 days of first treatment dose, active infection requiring systemic therapy, or severe hypersensitivity (grade ≥3) to anti–PD-1 therapies
Known psychiatric or substance abuse disorders that would interfere with cooperation in the study
Participation in another clinical study of an investigational agent or usage of an investigational device within 30 days of screening

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EP, electroporation; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; IHC, immunohistochemistry; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria In Solid Tumors; TNBC, triple-negative breast cancer.

- In Stage 1 of the study, patients will be treated with 0.5 mg/mL TAVO™ to the accessible lesions on days 1, 5, and 8 every 6 weeks, and with 200 mg IV pembrolizumab on day 1 of each 3-week cycle for 27 weeks (**Figure 2**). The effect of the combined therapy will be evaluated at the end of 24 weeks of treatment on day 1 of cycle 9.
  - Intratumoral tavo will be injected at a dose volume of approximately ¼ of the calculated lesion volume, with a minimum dose volume per lesion of 0.1 mL for lesions of volume <0.4 cm^3
  - The OncoSec Medical Electroporation Therapy System (OMS) will be placed into or around the injected tumor. The applicator tip containing either a 1.0-cm or a 0.5-cm diameter array of 6 stainless-steel needles will be co-localized at the site(s) and depth of plasmid injection. The applicator will be connected to the power supply and 6 pulses at a field strength (E+) of 1500 volt/cm and pulse width of 100 µs at 1-second intervals will be delivered
  - Pembrolizumab will be administered using a 30-minute (–5/+10 min) infusion
  - All accessible lesions (each ≥0.3 cm × 0.3 cm) may be treated, except 1 lesion (≥1.0 cm) that will be left untreated for the duration of the study, if feasible
- In Stage 2 of the study, patients completing Stage 1 will continue to receive the combined treatment for up to 17 cycles of TAVO™ and 35 cycles of pembrolizumab from baseline (~2 years) or until subsequent disease progression.

Figure 2. Study design



EOS, end of study; P, pembrolizumab; TAVO™, intratumoral administration of interleukin-12 plasmid followed by electroporation.

  - Patients will not be able to continue treatment in Stage 2 if they withdraw from the study or have intercurrent illness, unacceptable adverse event(s) (AE[s]), significant noncompliance with the protocol, or general/specific changes in their condition that render them unacceptable for further treatment in the judgment of the investigator
- All patients will be followed long-term (through 90 days from last dose of study drug) after the end-of-study (EOS) visit for serious AEs (SAEs) and long-term survival. The EOS visit will occur 4 weeks after last study treatment administration.
- Throughout the study, the independent data and safety monitoring board will monitor safety and efficacy parameters at approximately semi-yearly intervals.

ASSESSMENTS

- ORR, DOR, and PFS will be assessed by investigator review on the basis of Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 within 24 weeks and over the course of the study.
- ORR, DOR, and PFS will also be assessed by BICR within 24 weeks.
- Immune ORR and immune PFS will be assessed by investigator review on the basis of immune RECIST v1.1 within 24 weeks and over the course of the study, as well as by BICR within 24 weeks.
- OS will be measured as the time from diagnosis until death from any cause. Patients without a confirmed date of death will be censored at the last date when the patient was known to be alive.
- Safety will be assessed by: frequency and severity of AEs and SAEs, as well as their relation to study drug; number of patients with events of clinical interest; and number of patients who discontinued due to AEs.
  - Further evaluations will include: incidence and shifts of clinically significant laboratory abnormalities, laboratory assessments (eg, complete blood count, blood biochemistry, and urinalysis), physical examination, vital signs, procedural pain, and concomitant medications
  - AEs and laboratory abnormalities will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
- For multispectral IHC assessments, tumor biopsies may be acquired from any accessible treated or nontarget lesions >1.0 cm and untreated cutaneous lesions >5 mm (accessible lesions are defined as cutaneous/subcutaneous lesions that can be reached from the surface with the EP needle array [up to 1.5-cm depth]).
  - Fresh and fixed tumor biopsies may be collected at screening, on day 1 of cycles 2, 4, 9, 12, 18, 22, 26, 30, and 34, and at EOS
- For monitoring changes in immune subsets during treatment by multicolor flow cytometry, blood samples may be collected at screening, on day 8 of cycle 1, and on day 1 of cycles 2, 4, 9, 11, 12, 18, 22, 26, 30, and 34, and at the EOS visit.

STATISTICAL ANALYSES

- The statistical power calculations are based on the Simon's two-stage minmax design.[10]
  - From the 25 eligible patients planned for enrollment, 15 will be accrued in Stage 1
  - If the number of responders in Stage 1 meets the prespecified number (n ≥1/15), then the enrollment for Stage 2 will proceed, and include an additional 10 patients
  - If ≥6 responders are observed in the group of 25 patients, the conclusion will be that the therapy is worthy of further investigation
- The summary statistics for continuous variables are sample size, mean, and standard deviation, and for categoric variables, frequencies and percentages. Time-to-event variables will be analyzed using Kaplan-Meier methods. All statistical tests will be performed at the 0.05 level of significance unless otherwise specified.
- Statistical analyses will be performed using SAS v9.4 or higher (SAS Institute, Cary, NC, USA).

SUMMARY

- This phase 2 study is evaluating the efficacy and safety of TAVO™ in combination with pembrolizumab in patients with inoperable locally advanced/metastatic TNBC.
- To date, 4 patients have been enrolled and received the study treatment.

REFERENCES: 1. American Cancer Society. *Breast Cancer Facts & Figures 2017–2018*. Atlanta: American Cancer Society, Inc. 2017; 2. Dua I, et al. *Am J Hematol Oncol.* 2017;13(4):20–7; 3. Polk A, et al. *Cancer Treat Rev*. 2017;63:122–34; 4. Adams S, et al. *J Clin Oncol.* 2014;32(27):2959–66; 5. Loi S, et al. *Cancer Res*. 2016;76(4 suppl): abstract S1-03; 6. Loi S, et al. *Ann Oncol.* 2014;25(8):1544–50; 7. Telli ML, et al. *Cancer Res.* 2018;78(13 suppl):Abstract nr. CT022; 8. Daud AI, et al. *J Clin Oncol.* 2008;26(36):5896–903; 9. Pierce RH, et al. *Hum Vaccin Immunother*. 2015;11(8):1901–9; 10. Simon R. *Control Clin Trials.* 1989;10(1):1–10.
DISCLOSURES: **MLT:** Advisory role: Aduro, Celldex, Genentech, G1 Therapeutics, Immunomedics, Merck, Pfizer, Tesaro. Research funding (to my institution): Biothera, Calithera, Genentech, Medivation, Merck Serono, OncoSec Medical Inc, PharmaMar, Pfizer, Tesaro, Vertex. **IW:** Advisory board: Cardinal Health, Tolmar, and Genomic Health. **SV:** Advisory board for nirapanib: Tesaro; advisory board: OncoSec Medical Inc. **HS:** Consulting role: Eli Lilly, Astrazeneca, Novartis, Celgene, Eisai, Pfizer. **KC, BD**, and **RJ:** No conflicts of interest to disclose. **CT** and **KMF:** Employees of OncoSec Medical Inc.
ACKNOWLEDGEMENTS: Editorial and medical writing assistance was provided by Oana Draghiciu, PhD, CMPP, from Aptitude Health, The Hague, The Netherlands, funded by OncoSec Medical Inc. The authors are fully responsible for all content and editorial decisions for this poster.