Trial in progress: Phase 2 study of intratumoral plasmid interleukin-12 (tavokinogene telseplasmid; TAVO™) plus electroporation in combination with pembrolizumab with or without chemotherapy in patients with inoperable locally advanced or metastatic triple-negative breast cancer (KEYNOTE-890/OMS-I141)

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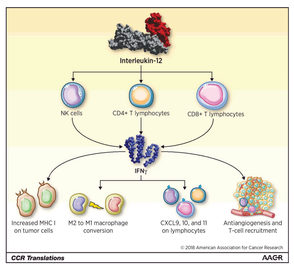
Background

- A proinflammatory environment in triple-negative breast cancer (TNBC) tumors, indicated by tumor-infiltrating lymphocytes (TIL), are associated with better outcomes.[1,2]
- Pembrolizumab monotherapy has demonstrated modest activity in patients with previously-treated TNBC. Objective response rates (ORR) have ranged from 5% to 18%,[3,4] and KEYNOTE-119 demonstrated no significant improvement in overall survival (OS) with pembrolizumab compared with chemotherapy.[5]
- KEYNOTE-355 demonstrated that pembrolizumab + chemotherapy resulted in a statistically significant and clinically meaning improvement in PFS and OS vs chemotherapy alone for the treatment of 1st-line PD-L1 positive mTNBC.[6]
- Interleukin-12 (IL-12) is a potent immunoregulatory cytokine that plays a key role in the crosstalk between the innate immune response (dendritic, macrophage, and natural killer cells) and the adaptive immune response (T cells and B cells). Through this activity, IL-12 promotes anti-tumor immune responses.[7,8]
- DNA plasmid-based IL-12, tavokinogene telseplasmid (TAVO™), delivered to accessible tumors by intratumoral injection and combined with electroporation (TAVO-EP) has been shown to induce activation of innate and adaptive tumor-infiltrating and peripheral immune cells, regression of treated and distant untreated lesions (abscopal effect), and expression of PD-L1 in patients with melanoma or TNBC, without the systemic toxicity that has historically limited therapeutic use of IL-12.[9-11]
- The combination of TAVO-EP and pembrolizumab has demonstrated durable responses in melanoma patients with immunologically "cold" tumors or with prior progression on anti-programmed cell death protein 1 (anti-PD1) therapy.[12]
- A phase 1 study demonstrated the safety and tolerability of TAVO-EP in patients with locally advanced or recurrent TNBC cutaneous and subcutaneous tumors.[13]
- Combining TAVO-EP with an anti-PD-1 antibody, such as pembrolizumab, is thought to further improve responses in patients with mTNBC by converting poorly-immunogenic/low TIL tumors into immune-responsive/high TIL tumors.
- KEYNOTE-890/OMS-I141 is a phase 2 study in patients with mTNBC that is evaluating the safety and efficacy of TAVO-EP in combination with pembrolizumab in the 2nd-line or later treatment setting (Cohort 1) or TAVO-EP in combination with pembrolizumab plus chemotherapy in the 1st-line setting (Cohort 2).
- Preliminary data from Cohort 1 indicate the potential for the combination of TAVO-EP plus pembrolizumab to elicit strengthened immunogenic responses in TNBC.10 Updated Cohort 1 data are presented in a separate abstract.
- The study design for Cohort 2 is presented herein.

Mechanism of Action of TAVO-EP



- IL-12 is a potent proinflammatory cytokine with the following antitumor mechanisms:
  - Increasing MHC I antigen presentation
  - Attracting additional NK, Th1, and CD8+ T cells into TME
  - Reversing tumor-induced immunosuppression

Clinical translation of IL-12 immunotherapies experienced setbacks in 1990s/2000s due to severe toxicities associated with systemic IL-12 injections. Intratumoral delivery of plasmid IL-12 (TAVO) followed by electroporation yields sustained expression of IL-12 and stimulates a systemic proinflammatory immune response, without systemic immune-related toxicities.

References

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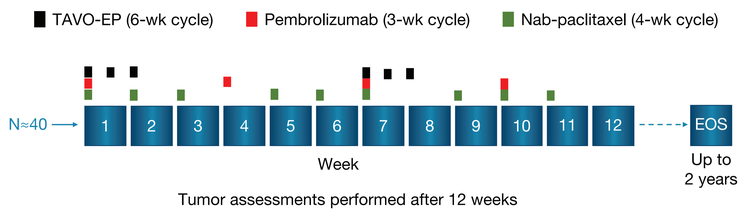
Study Objective

- KEYNOTE-890/OMS-I141 Cohort 2 will evaluate the safety and efficacy of first-line TAVO-EP in combination with pembrolizumab plus chemotherapy in patients with metastatic TNBC.

Study Design

- KEYNOTE-890/OMS-I141 (NCT03567720) is a phase 2, open-label, multicenter study.
- Patients in Cohort 2 will receive the following treatments:
  - TAVO-EP: days 1, 5, and 8, every 6 weeks, for up to 18 cycles.
    - TAVO dose is 0.5 mg/mL at dose volume of ~1/4 lesion volume, injected intratumorally.
    - EP is 6 pulses at a field strength of 1500 volt/cm and pulse width of 100 µs at 300-msec intervals, co-localized with TAVO injection.
  - Pembrolizumab: 200 mg IV, every 3 weeks, for up to 35 cycles.
  - Nab-paclitaxel: 100 mg/m2 IV on days 1, 8, and 15 every 4 weeks, for up to 25 cycles.
    - Additional chemotherapy options may be introduced in future protocol amendments.
- Imaging for tumor assessment will be completed every 12 weeks.
- On-study biopsies will be collected at baseline, approximately 3 weeks after the start of treatment, and at disease progression.

Study Schema



Endpoints

PRIMARY ENDPOINT

- ORR by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[14]

SECONDARY ENDPOINTS

- Safety and tolerability
- ORR by investigator review based on RECIST v1.1
- Duration of response (DOR), progression-free survival (PFS), and disease-control rate by BICR and investigator review based on RECIST v1.1
- iORR and iPFS by BICR and investigator review based on iRECIST[15]
- OS

EXPLORATORY ENDPOINTS

- Immune monitoring correlates with responders and non-responders
- Estimate of preliminary ORR in PD-L1–negative patients

Cohort 2 Patient Eligibility

KEY INCLUSION DATA

- Age ≥18 years old
- Histologically confirmed inoperable locally advanced or metastatic TNBC (ER and PR staining <10%, HER2 IHC 0 to 1+ or FISH-negative)
- No prior systemic therapy for advanced disease (neo/adjuvant therapy allowed if at least 6-month disease-free interval from last treatment)
- Measurable disease by RECIST v1.1
- At least 1 lesion accessible for intratumor injection/EP (≥0.3 cm diameter and up to 1.5 cm depth)
- Biopsy tissue available at screening (or archival tissue within 6 months without intervening treatment) for post-hoc central determination of PD-L1 expression
- Disease not amenable to curative treatment
- ECOG PS 0-1
- Adequate organ function
- Life expectancy of at least 6 months

KEY EXCLUSION DATA

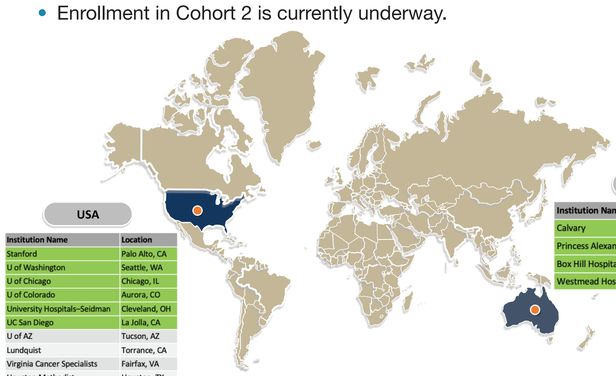
- Clinically active central nervous system metastases (radiologically and clinically stable, previously treated brain metastases permitted)
- Electronic pacemakers or defibrillators
- Additional malignancy that is progressing or requires active treatment, except basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer
- Human immunodeficiency virus, hepatitis B, or hepatitis C
- Immunodeficiency or immunosuppressive therapy
- Severe hypersensitivity to any study drugs

Statistical Analysis

- The planned sample size of Cohort 2 is 40 patients and is based on the ability to detect a clinically meaningful response rate.
  - Assuming the ORR of the combination therapy is 55%, the 95% confidence interval (CI) as calculated by the Clopper Pearson exact method from 40 patients is 38.5% to 70.7% with the lower bound excluding ORR <35%.
- Disease response will be assessed using RECIST v1.1.
- The estimates of the ORR and immune ORR will be accompanied by a 2-sided 95% exact binomial CI. Time-to-event endpoints such as DOR, PFS, immune PFS, and OS will be analyzed using the Kaplan-Meier method.
- Adverse events will be classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.

Current Status

- Enrollment in Cohort 2 is currently underway.



USA

Institution Name	Location
Stanford	Palo Alto, CA
U of Washington	Seattle, WA
U of Chicago	Chicago, IL
U of Colorado	Aurora, CO
University Hospitals–Seidman	Cleveland, OH
UC San Diego	La Jolla, CA
U of AZ	Tucson, AZ
Lundquist	Torrance, CA
Virginia Cancer Specialists	Fairfax, VA
Houston Methodist	Houston, TX
Massachusetts General	Boston, MA

Australia

Institution Name	Location
Calvary	Elizabeth Vale, SA
Princess Alexandra Hospital	Woolloongabba, QLD
Box Hill Hospital	Box Hill, VIC
Westmead Hospital	Westmead, NSW

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