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A Phase 1b study of PVX-410 Vaccine in Combination with Pembrolizumab in Metastatic Triple Negative Breast Cancer (mTNBC)

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Introduction

- The immune system plays an important role in triple negative breast cancer (TNBC) and is a validated therapeutic target.
- Several programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) checkpoint inhibitors show activity in mTNBC. Pembrolizumab and atezolizumab both are commercially available or PDL1+ mTNBC in combination with nab-paclitaxel. Pembrolizumab in combination with chemotherapy is approved for use as a neoadjuvant therapy for TNBC (Merck & Co., Inc., 2021).
- Vaccines may further induce host immune response and enhance therapeutic activity of checkpoint inhibitors. PVX-410 (OncoPep, Inc.) is a novel, HLA-A2 restricted, tetra-peptide vaccine targeting 4 tumor-associated antigens highly expressed in multiple myeloma (MM) and solid tumors (e.g., breast, colon, pancreatic, prostate): XBP1 (2 forms), CD138, and CS-1. XBP1 and CD138 are highly expressed and linked to poor prognostic outcomes in TNBC (Szekely 2018; Chen, 2014).
- In clinical studies, PVX-410 alone and in combination induced vaccine-specific immune responses and was safe with no significant toxicity observed. Data from a phase 1b study of PVX-410 + durvalumab as adjuvant therapy in early-stage HLA-A2+ TNBC showed that patients experienced a durable immune response to PVX-410, with immune response typically maintained for up to 6 months (Isakoff, 2019).
- Predicated on these data, we hypothesized that PVX-410 would stimulate a patient's cytotoxic T lymphocytes (CTLs) by presenting antigens critical to TNBC growth, while simultaneously, pembrolizumab would overcome tumor-mediated immune suppression.

Objectives

Primary:

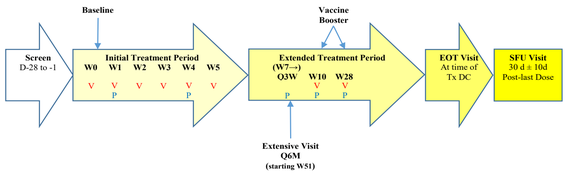
- Evaluate immune response to PVX-410 in combination with pembolizumuab, measured as the fold-change in CD8+ CTLs by intracellular staining (flow cytometry) of interferon (IFN -gamma) from baseline vs Week (W) 10.

Secondary:

- Evaluate immune response to PVX-410 in combination with pembrolizumab at W28.
- Assess and explore the safety and tolerability of PVX-410 in combination with pembrolizumab.
- Assess response rate; clinical benefit rate (CBR), disease control rate (DCR); duration of response (DoR); progression-free survival (PFS), 1- and 2-year survival rates, and overall survival (OS).
- Evaluate and characterize immune response to PVX-410 with pembrolizumab through a flow cytometry-based assay for correlative immune response indicators.
- Explore other potential biomarkers of immune response.

Study Design

- Phase 1b, multi-center (3 sites in US) open-label, non-randomized study in 20 HLA-A2+ females with mTNBC.
- PVX-410 (800 µg total peptide emulsified in 1.2 mL Montanide ISA 720 VG given by subcutaneous (SC) injection at W0, 1, 2, 3, 4, and 5 followed by 2 booster vaccine doses at W10 and 28 (8 doses total).
  - At each administration time point, Hiltonol® 0.5 mL (0.9 mg) was administered intramuscularly (IM) concurrently with PVX-410.
- Pembrolizumab 200 mg intravenously (IV) administered every 3 weeks starting at W1.
- Weekly study center visits from W0 to W5; additional study immunogenicity assessments at W10 and 28; after W28, comprehensive visits performed on an every-6-month basis.
- End-of-Treatment visit when PVX-410 and pembrolizumab permanently discontinued; Safety Follow-up visit 30 days thereafter.



Key: DC=Discontinuation; EOT=End–of-Treatment; M=Month; P=Pembrolizumab; Q3W=Every 3 weeks; Q6M=Every 6 months; SFU=Safety follow up; Tx=Treatment; V=Vaccine (+Montanide and Hiltonol); W=Week

Immunogenicity Assessments

- Flow cytometric (FACS)-based combination intracellular cytokine/tetramer binding assay used to detect PVX-410 vaccine specific CD3+CD8+ T cell responses.
- The assay was performed on the patient derived peripheral blood mononuclear cells after a 7-day in vitro stimulation with Interleukin (IL)-2, IL-15, and the PVX-410 peptides.
- "PVX-410 Responder" was defined as a minimum increase from baseline of 2-fold for CD3+CD8+ interferon-gamma (IFN-γ)+ cells and a minimum of 2-fold increase from baseline for CD3+CD8+ PVX-410 tetramer+ cells at any time point
- The primary analysis is the fold-change in CD3+CD8+ IFN-γ+ cells and CD3+CD8+ PVX-410 tetramer+ cells from baseline to W10.

Key Entrance Criteria

Key Inclusion Criteria

- Female aged ≥18 years on the day of signing informed consent.
- HLA A2+ by deoxyribonucleic acid (DNA) sequence analysis (by history with documentation or as part of this study).
- Histopathological diagnosis of metastatic or inoperable locally advanced TNBC.
- Measurable disease by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).
- Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1.
- No limit to the number of prior therapies.

Key Exclusion Criteria:

- Mucinous, tubal, or another good prognosis histology.
- Known active central nervous system metastases and/or carcinomatous meningitis.

Statistical Plan

- Twenty patients evaluable for immune response were planned. Accrual was paused, and a formal monitoring of safety conducted when 6 patients completed at least 1 dose of the combination of PVX-410+pembrolizumab treatment (i.e., when a patient reached W4).
- Descriptive statistics summarized baseline levels of expression and the observed fold-change from baseline to 5 weeks post-vaccine treatment at Week 10 (final analysis pending).
- Secondary exploratory endpoints including correlative studies evaluating immunohistochemical expression of markers on archived tumor samples were reported as descriptive results and estimation-only.
- Clinical secondary endpoints (response rate, clinical benefit rate [CBR], disease control rate [DCR], duration of response [DoR], progression-free survival [PFS], overall survival [OS]) were calculated using standard methods.
- Safety and tolerability were analyzed descriptively.

Demographics

- 19 patients were enrolled between March 2018 and August 2020. Demographic and baseline characteristics follow:

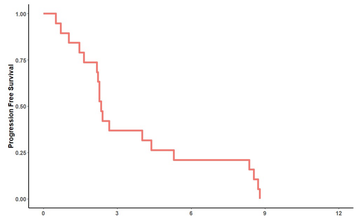
Parameter	Result
N	19
Female, n (%)	19 (100)
White, n (%)	19 (100)
Age at registration (years), median (range)	62 (46, 79)
ECOG Performance Status, n (%)	
0	14 (73.7)
1	5 (26.3)
Disease Stage at Primary Diagnosis, n (%)	
I	9 (47.4)
II	3 (15.8)
III	1 (5.3)
IV	3 (15.8)
Median lines of prior therapy for mTNBC	2 (0, 9)
Median disease-free interval for 16 patients with prior early TNBC (years)	3.3

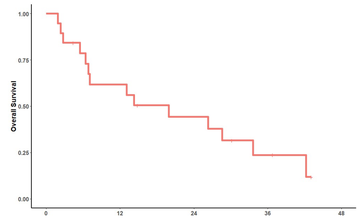
Safety and Tolerability

- All 19 patients were evaluable for safety.
- Common adverse events (AEs) attributable to PVX-410 (grade ≥2) included fatigue (21%), arthralgia (11%), injection site reaction (5%), pain (5%), lymphocyte count decreased (5%), maculopapular rash (5%), and skin infection (5%).
- Two grade 3 AEs (aspartate aminotransferase elevation, hyponatremia) and one grade 4 AE (alanine aminotransferase elevation) were attributed to pembrolizumab.
- No grade 5 AEs occurred.

Progression-free Survival and Overall Survival

- Median PFS (left panel) was 2.3 months (95% CI 2.2, 8.4 months). Through a median follow-up of 36.8 months, median OS (right panel) was 19.9 months (95% CI 6.9 months, not estimable).





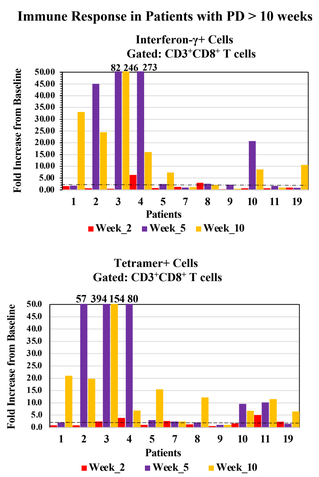
Clinical Response

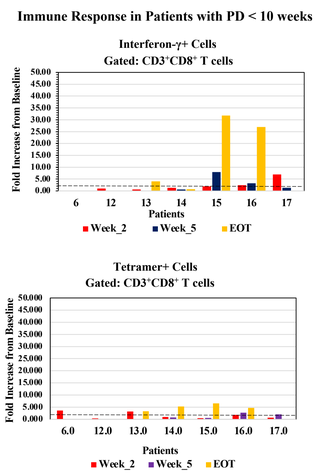
- Best overall response was stable disease in 9 (47%) patients.
- CBR (complete response [CR] + partial response [PR] + stable disease [SD]) for ≥16 weeks was 31.6%.
- No patient experienced CR or PR.

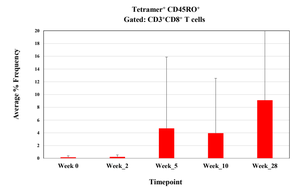
Immune Response

- 18 patients were evaluated for immune response; 11 patients were evaluable at W10.
- Vaccine-specific CD3+CD8+T cell responses detected in 8/11 patients (i.e., experienced a 2-fold increase over Baseline for CD3+CD8+ IFN gamma+ T cells and CD3+CD8+ Tetramer+ T cells).
  - The immune response persisted in the 4 patients evaluable for analysis at W28.
- Of the 7 patients who progressed prior to W10, 4/7 had a positive immune response.
- An increase in vaccine specific memory T cells (CD3+CD8+tetramer+CD45RO+ cells) was observed; the majority of these vaccine-specific peptide specific memory T cells were of the effector memory phenotype.

Immune response for patients with progressive disease (PD) after 10 weeks (top left panels) was greater than for patients with PD within 10 weeks (top right panels). The average of all patients' vaccine-specific memory T cells is presented in the lower panel.







Conclusions

- PVX-410+pembrolizumab is safe, with a manageable toxicity profile, in patients with mTNBC.
- No new unexpected AEs were identified.
- Immune response data show PVX-410 induces antigen-specific T cell expansion as observed by increases in CD3+CD8+ PVX-410 tetramer + and CD3+CD8+ IFN gamma positive T cells.
- Median PFS and OS were 2.3 and 19.9 months, respectively.
- Clinical disease control was observed, with a CBR (CR+PR+SD >16 weeks) of 31.6%.
- Based on these promising data in this pretreated population, a phase 2 study with PVX-410+pembrolizumab in combination with standard chemotherapy in treatment naïve, PD-L1+ mTNBC is underway (NCT04634747).

Acknowledgements

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