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BACKGROUND

- Triple negative breast cancer (TNBC) is an aggressive subtype accounting for 15% of all breast cancer cases. Treatment with immunotherapy in combination with chemotherapy is of benefit only in PD-L1 positive tumors, which represents a minority of patients.
- Pelareorep**, a proprietary isolate of the unmodified, replication competent reovirus type 3 Dearing (T3D), has been shown to upregulate PD-L1 expression in tumor and inflammatory cells and downregulate intra-tumoral regulatory T-cells in the tumor microenvironment in pre-clinical and early clinical studies. **Retifanlimab** is a PD-1 inhibitor currently in development.
- The rationale for this clinical study is that the administration of pelareorep will prime the tumor microenvironment for enhanced tumor response to PD-1 inhibitor retifanlimab.

TRIAL DESIGN

- This is a phase II multi-site single-arm investigator-initiated clinical trial.
- Eligible patients will receive pelareorep 4.5×10^{10} TCID₅₀ /day IV, on Days 1, 2, 15 and 16 and retifanlimab 500mg IV on day 3 of every 28-day cycle until disease progression or unacceptable toxicity.
- Tumor tissue, stool and blood samples will be collected while on treatment to evaluate changes in PD-L1 expression, gut microbiome and inflammatory cells induced by the study drugs. (ClinicalTrials.gov Identifier: **NCT04445844**)

ELIGIBILITY CRITERIA

Inclusion Criteria

- Metastatic TNBC who have previously received 1-2 prior lines of chemotherapy in the metastatic setting
- Measurable disease based on RECIST v1.1
- Age > 18 year with ECOG performance status of 0 or 1 with life expectancy ≥ 3 months with adequate organ function.
- Subjects with CNS metastases treated with radiation therapy (WBXRT or SRS) are eligible if stable, > 28 days following completion of XRT.

Exclusion Criteria

- Subjects who have received 3 or more lines prior treatment in the metastatic setting
- Prior therapy with Pelareorep.
- History of immunodeficiency, interstitial lung disease, active pneumonitis or receiving chronic systemic steroids.
- Known history of HIV, hepatitis B or Hepatitis C infection.

ENDPOINTS

Primary Endpoints:

- Objective Response Rate (ORR) per RECIST v1.1
- Safety, tolerability and feasibility, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0;

Secondary Endpoints:

- Progression Free survival (PFS)
- Overall Survival (OS)
- Duration of Response (DOR)

Exploratory Endpoints:

- Assess changes in PD-L1 expression pre and post treatment and correlate with treatment response.
- Assess the role of TCR sequencing in predicting treatment response.

STATISTICAL DESIGN

- Simon's optimal 2-stage design will be used to calculate sample size. In the first stage, 14 patients will be accrued. If there are 1 or fewer responses in these 14 patients, the study will be stopped. Otherwise, 11 additional patients will be accrued for a total of 25 patients. The null hypothesis will be rejected if 4 or more responses are observed in 25 patients. The first 6 patients will be enrolled in a staggering interval for the safety run-in phase of the study.

ACCRUAL

- The study has enrolled 5 patients. There have not been any safety concerns noted so far with the combination. The study will continue to enroll patients at Rutgers Cancer Institute of New Jersey and Ohio State University Comprehensive Cancer Center.

