ASCO abstract # TPS1143

AXALAP: Phase Ib study of AXAtilimab in Combination with OLAParib in *BRCA1/2* and *PALB2*-associated metastatic HER2-negative breast cancer

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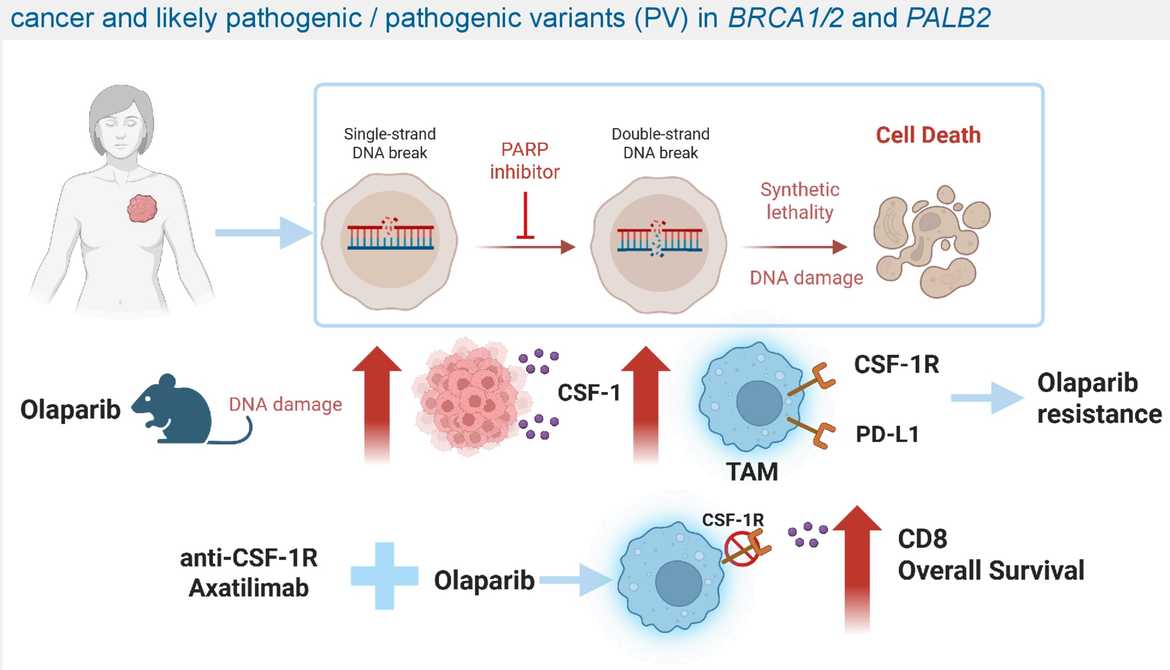
BACKGROUND & RATIONALE

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have revolutionized the treatment of patients with germline *BRCA1/2* (*gBRCA*)-associated HER2-negative breast cancer (Robson, M.E et al. 2019). However, resistance eventually occurs in almost all patients.

FIGURE 1. Rationale for the combination of Olaparib and Axatilimab in patients with breast cancer and likely pathogenic / pathogenic variants (PV) in *BRCA1/2* and *PALB2*



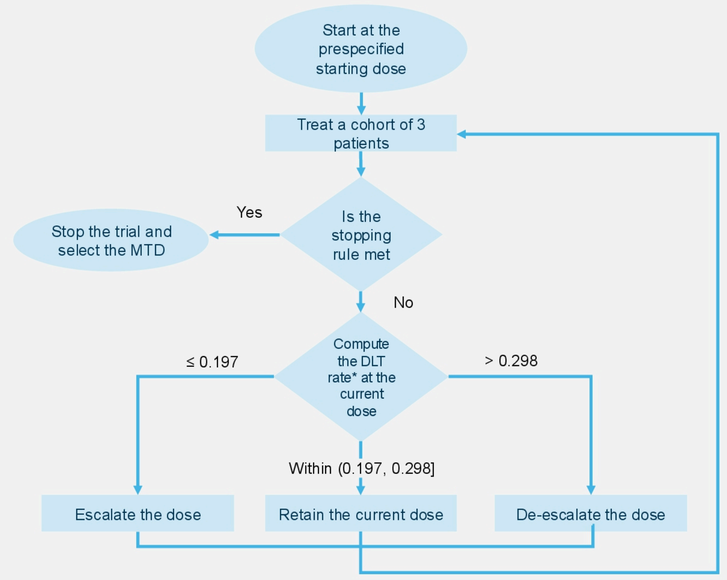
CSF-1: colony stimulating factor-1**; TAM:** Tumor-associated macrophages; **CSF-1R:** colony stimulating factor-1 receptor

- Tumor-associated macrophages (TAMs), a key component of the breast cancer tumor microenvironment, are highly immunosuppressive and associated with poor clinical outcomes (Cassetta, L. et al, 2019).
- In preclinical immunocompetent models of *BRCA*-associated breast cancer, PARP inhibition induces suppressive CSF-1R+ TAMs, contributing to resistance, so that combining anti-CSF-1R therapy with PARPi (**Figure 1**) significantly enhances overall survival (Mehta et al., 2021).
- In the Phase I SNDX-6352-0502 study for advanced solid tumors, axatilimab showed tolerability at the highest dose (6 mg/kg), with biomarker modulation observed at doses as low as 1 mg/kg (Nilo Azad, 2021).
- Axatilimab is FDA-approved for chronic graft-versus-host disease (cGVHD) (FDA 2024).

STUDY DESIGN

Non-randomized, open-label, proof-of-concept, phase 1 study to evaluate the safety and tolerability of the CSF-1R antibody, axatilimab 1 mg/kg (DL1) or 3mg/kg (DL2) every 2 weeks in combination with olaparib at 300 mg, twice daily, in patients with *BRCA1/2*- and *PALB2*-associated HER2-negative metastatic breast cancer. Patients will be treated until unacceptable toxicity or progression as defined by RECIST 1.1 criteria.

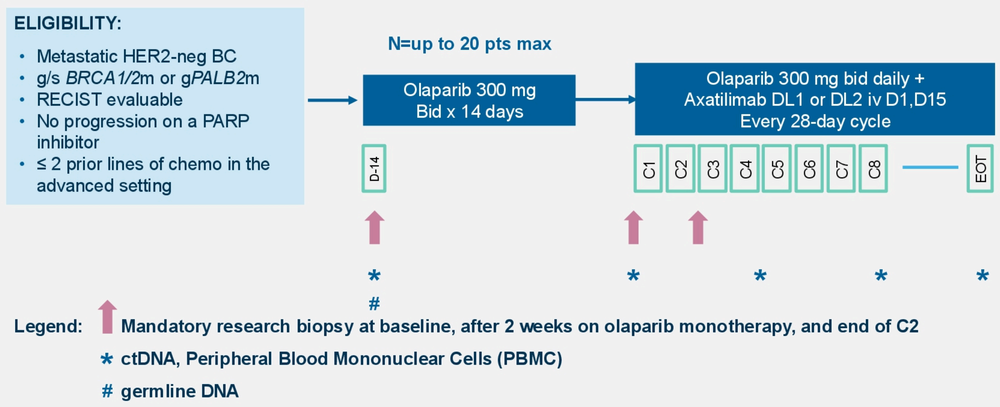
FIGURE 2. Flowchart for trial conduct using the BOIN design



DLT: Dose-Limiting Toxicity

$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

FIGURE 3. Study schema



OBJECTIVES

PRIMARY OBJECTIVE:
To establish the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D), and to evaluate the safety and tolerability of the combination of axatilimab and olaparib.

SECONDARY OBJECTIVES:
- To assess changes in CSF-1R$^+$ CD163$^+$ macrophage levels following olaparib monotherapy and after two cycles of combination therapy at the MTD.
- To determine the objective response rate (ORR) of the combination.
- To evaluate progression-free survival (PFS) according to RECIST v1.1 criteria.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA
- Any hormone receptor (HR) expression is permitted, HER2-negative breast cancer.
- Received up to 2 prior lines of cytotoxic chemotherapy for metastatic disease.
- *BRCA1/2 and* PALB2 germline and/or somatic PV.
- CNS involvement is allowed if stable.

EXCLUSION CRITERIA
- Prior PARPi within 12 months or progression on PARPi.
- History of Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).

CURRENT STATUS

We expect to treat up to 20 patients. Enrollment began on 5/2024 at Dana-Farber Cancer Institute, is currently open at Beth Israel Deaconess Medical Center and is expected to open at Mayo Clinic-Rochester.

CONTACT & FUNDING

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