TPS1143 Poster Session

AXALAP: Phase Ib study of axatilimab in combination with olaparib in *BRCA1/2* and *PALB2*-associated metastatic HER2-negative breast cancer (BC).

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Background: Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have revolutionized the treatment of patients (pts) with germline *BRCA1/2* (gBRCA)-associated HER2-negative BC. However, resistance eventually occurs in almost all pts. Tumor-associated macrophages (TAMs), a key component of the BC tumor microenvironment, are highly immunosuppressive and associated with poor clinical outcomes. In preclinical immunocompetent models of BRCA-associated BC, PARP inhibition induces suppressive CSF-1R+ TAMs, contributing to resistance, so that combining anti-CSF-1R therapy with PARPi significantly enhances progression free survival (PFS) compared to PARPi monotherapy (190d vs 92d). Axatilimab (SNDX-6352; Ab969.g2), a humanized IgG4 monoclonal antibody targeting CSF-1R, reduces TAMs, potentially slowing tumor growth and enhancing anti-tumor immunity. 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. Axatilimab is FDA-approved for chronic graft-versus-host disease (cGVHD). **Methods:** AXALAP (NCT06488378) is a non-randomized open-label, proof-of-concept phase 1 study designed to evaluate axatilimab 1mg/kg or 3mg/kg every 2 weeks in combination with olaparib 300 mg twice daily in pts with somatic or germline *BRCA1/2*- and *PALB2*-associated HER2-negative metastatic BC. Patients must be PARPi naïve, or have not progressed on prior PARPi, and have received up to 2 prior lines of chemotherapy for metastatic disease. Pts will receive a two-week lead-in of olaparib monotherapy, followed by combined olaparib and axatilimab. Pts will undergo mandatory tumor biopsies pre-treatment, after the 2-week olaparib lead-in, and after 2 cycles of olaparib/axatilimab, with an optional biopsy at time-of-progression. Primary objectives are to establish the maximum tolerated dose (MTD) and recommended phase 2 dose and to assess the safety and tolerability of axatilimab and olaparib. Secondary objectives include assessment of changes in CSF-1R+ CD163+ macrophage levels after olaparib monotherapy and after 2 cycles of combination treatment at the MTD; to determine the objective response rate and the median PFS of the combination per RECIST 1.1 criteria. The MTD will be determined by Bayesian Optimal Interval (BOIN) design. Pts will be treated in cohorts of 3 with a maximum of 10 at each dose. If the MTD is identified as 3mg/kg, we will complete enrollment of 10 pts at 1 mg/kg to assess biological effectiveness and clinical efficacy of the lower dose. We expect to treat up to 20 pts, who will receive study treatment until development of unacceptable toxicity or disease progression. Enrollment began on 5/2024 at Dana-Farber Cancer Institute and the trial will also open at Beth Israel Deaconess Medical Center and Mayo Clinic-Rochester. Clinical trial information: NCT03604692. Research Sponsor: Incyte; U.S. National Institutes of Health; U.S. National Institutes of Health.