TPS1142 Poster Session

TBCRC 058: A randomized phase II study of enzalutamide, enzalutamide with mifepristone, and treatment of physician's choice in patients with androgen receptor-positive metastatic triple-negative or estrogen receptor-low breast cancer (NCT06099769).

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Background: Triple-negative breast cancer (TNBC) refers to a heterogenous group of breast cancers (BC) that lack expression of ER, PR, and HER2. Despite recent advances with immunotherapy (IO) and antibody-drug conjugates (ADCs), TNBC remains the most aggressive subtype, characterized by a high risk of recurrence and a short overall survival in the metastatic setting. BCs with low levels of ER and PR expression (1-10%) clinically behave like TNBC, and clinical management follows the TNBC treatment (tx) paradigm. We and others have identified a subset of ER/PR/HER2 negative breast cancers (BC) that express the androgen receptor (AR). Enzalutamide (enza), an AR-antagonist, has demonstrated activity in AR+ metastatic TNBC (Traina et al, JCO 2018). Activation of the glucocorticoid receptor (GR) has been implicated as a mechanism of resistance to AR inhibition in prostate and BC (Kach et al, Sci Transl Med 2015). Advanced TNBC remains an area of unmet need, particularly in patients who are ineligible for or progress following a checkpoint inhibitor. This randomized study will evaluate the efficacy of enza or enza plus the GR antagonist mifepristone (mif) as compared to physician's choice chemotherapy (TPC). **Methods:** This is a randomized phase II trial; 201 patients (pts) will be randomized 1:1:1 to enza, enza with mif, or TPC (carboplatin, paclitaxel, eribulin, or capecitabine). The primary endpoint (endpt) is progression free survival (PFS), and the trial is designed to test the hypothesis that PFS in the pooled enzalutamide arms is superior to TPC; there is 80% power to detect a hazard ratio (HR) of 0.70, corresponding to increase in PFS from 3.5 months (mos) with TPC to 5.0 mos with enza-based tx. Secondary endpts include pairwise comparisons of PFS among the 3 arms and evaluation of response rate, clinical benefit rate, duration of response, overall survival, safety/toxicity, and patient-reported outcomes by arm. Exploratory endpts include correlation of tumor and circulating markers (constitutively active AR variants in circulating tumor cells and circulating tumor cell DNA) with tx response. Eligible pts must have: ECOG 0-2, metastatic ER/PR low or negative, HER2 0-2+ (FISH not amplified) (BC), measurable or evaluable disease (dz) per RECIST v1.1, $<$ 3 prior lines of chemotx, any # prior endocrine txs, no prior anti-AR tx or CYP17 inhibition, no prior mif. Pts with PD-L1+ BC must have received prior IO if not contraindicated. Tumors must have AR $>$10%, normal organ function, no history of brain mets. As of 1/23/25, 11 of 201 pts have begun protocol-specified tx. Clinical trial information: NCT06099769. Research Sponsor: Breast Cancer Research Foundation; TBCRC; Astellas; Corcept; The TaTa Sisterhood Foundation; Pfizer.