TPS1124 Poster Session

LITESPARK-029: A phase 2, randomized, open-label study of belzutifan plus fulvestrant in participants with estrogen receptor–positive, HER2-negative unresectable locally advanced or metastatic breast cancer after progression on previous endocrine therapy.

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Background: Endocrine-based therapy (ET), with or without cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), prolongs PFS and OS in participants (pts) with metastatic hormone receptor–positive (HR+) and human epidermal growth factor receptor 2–negative (HER2–) breast cancer. After PD on first-line therapy, next-line therapy options provide limited PFS gains, in part due to resistance mechanisms (eg, hyperactive FOXA1). The transcription factor hypoxia-inducible factor 2α (HIF-2α), a major target of FOXA1, regulates key components of angiogenesis and subsequent development of metastasis. Preclinical studies show suppression of tumor growth with an HIF-2α antagonist, particularly when combined with fulvestrant. Belzutifan, an HIF-2α inhibitor, is approved for the treatment of pts with advanced renal cell carcinoma following a PD-(L)1 inhibitor and vascular endothelial growth factor tyrosine kinase inhibitor. LITESPARK-029 (NCT06428396) evaluates belzutifan + fulvestrant vs everolimus + fulvestrant or exemestane in pts with estrogen receptor–positive (ER+)/HER2– unresectable locally advanced or metastatic breast cancer. **Methods:** This phase 2, randomized, active-controlled, open-label, multicenter study is enrolling pts (≥18 y) with locally confirmed ER+/HER2– unresectable, locally advanced or metastatic disease who have had radiographic PD on ≥12 mo of ET + CDK4/6i therapy in the noncurative setting or received ≥2 lines of ET in the noncurative setting including CDK4/6i where the CDK4/6i was discontinued due to intolerance (not due to progression). Pts must also be eligible for additional ET with everolimus plus either fulvestrant or exemestane per local investigator assessment, have an ECOG PS of 0 or 1, and provide a new or recent core biopsy for central determination of ER and HER2 status. Prior treatment with chemotherapy, antibody-drug conjugates, or PARP inhibitors in the noncurative setting is prohibited. Pts are randomized 1:1 to receive oral belzutifan 120 mg once daily + fulvestrant 500 mg on days 1 and 15 of cycle 1 and on day 1 of all subsequent 28-day cycles or oral everolimus 10 mg once daily + fulvestrant (as above) or oral exemestane 25 mg once daily until PD or unacceptable toxicity. Randomization is stratified by treatment with prior ET + CDK4/6i therapy ($<$ 18 mo duration before PD vs ≥18 mo duration before PD or no PD). Tumor imaging is performed at screening, Q8W from randomization through week 56, and Q12W thereafter. The primary endpoint is PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints include PFS rate per RECIST v1.1 by BICR at 6 and 12 mo, OS, ORR per RECIST v1.1 by BICR, clinical benefit (CR, PR, or stable disease for ≥24 weeks), and safety. The study start date was July 2024. Clinical trial information: NCT06428396. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.