TPS1125 Poster Session

ALISertib in combination with endocrine therapy in patients with hormone receptor-positive (HR+), HER2-negative (HER2–) recurrent or metastatic breast cancer: The phase 2 ALISCA-Breast1 study.

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Background: Despite the many available treatments for patients (pts) with HR+, HER2– recurrent/metastatic breast cancer (MBC), optimal treatment after progression on CDK4/6 inhibitors (CDK4/6i) is unclear. One possible CDK4/6i resistance mechanism is increased expression of Aurora kinase A (AURKA), a key mitosis regulator associated with poor prognosis. Further implicated in CDK 4/6i resistance, high c-Myc or RB1 loss of function (LOF) are associated with transcriptional co-regulation or synthetic lethality, respectively, with AURKA. Alisertib is a highly selective, reversible, ATP-competitive, orally administered, small-molecule AURKA inhibitor with antiproliferative activity in HR+ BC-derived cell lines and BC xenograft models. Models with elevated AURKA or c-Myc expression, or RB1 LOF show greater alisertib sensitivity. Alisertib had activity in phase 1 and 2 trials, including objective response rates (ORRs) of 19.6–20% and median progression-free survival (PFS) of 5.4–5.6 months alone or with fulvestrant in pts with HR+/HER2–, endocrine-resistant MBC. The most common treatment-related grade ≥3 adverse events (AEs) were neutropenia, anemia, and leukopenia. **Methods:** ALISCA-Breast1 (NCT06369285) is a randomized phase 2 study. Primary objective: to determine the optimal alisertib dose administered with endocrine therapy (ET) based on AEs and serious AEs per CTCAE v5.0 and efficacy (ORR, duration of response, disease-control rate, PFS, overall survival). Secondary objectives: to identify biomarkers of efficacy and alisertib pharmacokinetics (PK). Key inclusion criteria: ≥18 years; ECOG performance status 0 or 1; confirmed HR+, HER2–, recurrent/metastatic breast adenocarcinoma not amenable to curative therapy; available tumor tissue for biomarker analyses; progression on or after ≥2 prior ET lines in recurrent/metastatic setting; prior CDK4/6i with ET in recurrent/metastatic setting. Key exclusion criteria: prior chemotherapy in recurrent/metastatic setting; prior AURKA-specific or pan-Aurora-targeted agents; unstable brain metastases. Eligible pts will be randomized 1:1:1 to alisertib 30 mg, 40 mg, or 50 mg orally twice daily on days 1–3, 8–10, and 15–17 every 28 days, plus physician's choice of anastrozole, letrozole, exemestane, fulvestrant, or tamoxifen not previously used in recurrent/metastatic setting or progressed upon in adjuvant setting; ≤50 pts will be enrolled per arm in the USA and Europe. All pts will undergo sparse PK sampling. Tumor tissue will be centrally assessed for biomarkers, including *RB1, MYC, TP53, ESR1,* PI3K/AKT pathway, *HER2* and *AURKA* genomic alterations/expression levels. The study will determine the optimal alisertib dose to combine with ET and may identify biomarker(s) defining pts with the greatest benefit from alisertib-based therapy. Clinical trial information: NCT06369285. Research Sponsor: Puma Biotechnology Inc.