TPS1126 **Poster Session**

Integrating gene signatures to guide HR+/HER2- MBC therapy in a diverse cohort (INSIGHT).

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Background: Black women with breast cancer (BC) have a 40% higher mortality rate compared to Non-Hispanic White (NHW) women. Worse outcomes have been observed among Black women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) BC despite comparable systemic therapies. Gene expression profiling has been used in early-stage BC to provide prognostic and predictive information beyond standard immunohistochemical classifications. BluePrint, an 80-gene molecular subtype signature, and MammaPrint (Agendia), a 70-gene risk of distant recurrence signature, further classify HR+/HER2- BC into luminal A, luminal B, HER2-enriched, and basal-type tumors. Non-Luminal A (Luminal B, HER2-enriched, and Basal-type) tumors are more aggressive and are associated with worse survival compared to Luminal A tumors. Our preliminary data demonstrate that non-Luminal A tumors are overrepresented in Black women (11% Black vs. 5% White). The role of molecular subtyping in guiding therapy for patients with HR+/HER- MBC is not defined. Retrospective studies have shown that non-Luminal A HR+/HER2- tumors derive less benefit from endocrine therapy (ET). We hypothesize that patients with non-Luminal A, HR+/HER2- MBC progressing on ET +/- CDK4/6 inhibition derive more benefit from chemotherapy than ET in the second line. Furthermore, the impact of the intervention will be more pronounced in Black women compared to NHW women. INSIGHT is a randomized phase II study evaluating the anti-tumor effect of capecitabine versus physician's choice ET as second line for patients with non-Luminal A HR+/HER2- MBC (NCT05693766). **Methods:** In this study, patients progressing on 1st line ET +/- a CDK4/6i are enrolled. Archival primary or metastatic tumor samples are analyzed using MammaPrint and BluePrint. Patients with non-Luminal A tumors are randomized (1:1) to receive physician's choice ET versus capecitabine, stratified by molecular subtype and race. Disease assessments are performed every three months. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall response rate, clinical benefit rate, overall survival, and patient reported outcomes. The study has 80% power to detect a minimal hazard ratio of 0.5 in 5-year PFS with one-sided α = 0.05. Exploratory correlative studies are planned. This trial enriches for racial/ethnic minority patients through collaborations with the University of Texas Southwestern and the University of Alabama at Birmingham, health systems that serve large minority populations. Seven of the 64 planned patients have been enrolled. Clinical trial information: NCT05693766. Research Sponsor: Susan G. Komen.