TPS10628 **Poster Session**

Acolbifene vs tamoxifen for breast cancer prevention in premenopausal women at high risk for breast cancer.

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Background: The TAM01 trial of low dose (5 mg) tamoxifen (LDTAM) vs placebo was associated with significant improvement in risk for breast cancer in postmenopausal women with a hazard ratio of 0.30 along with a favorable side effect profile. Risk reduction in premenopausal women was less clear, with a non-significant hazard ratio of 0.73. Tamoxifen in premenopausal women can induce substantial increases in systemic estradiol and in preclinical studies upregulate endocrine resistance gene *AGR2*. Both phenomena may impact LDTAM efficacy in premenopausal women. A pilot study (NCT00853996) of 20 mg/d of the SERM acolbifene in premenopausal women was associated with reduction in mammographic density, benign breast tissue Ki-67, and estrogen response gene expression (Fabian et al; Cancer Prev Res 2015) with no increase in *AGR2* or vasomotor symptoms. Further studies of LDTAM and acolbifene in premenopausal women are warranted assessing change in imaging and benign breast tissue risk biomarkers with change in systemic hormones, ovarian reserve, and drug metabolites. **Methods:** NCT05941520 is a randomized, double-blind Phase II trial performed as part of the University of Michigan Early Phase Clinical Cancer Prevention (ClinCaP) Consortium part of the Cancer Prevention Clinical Trials Network (CP-CTNet) comparing 6 months of tamoxifen 5 mg and acolbifene 20 mg. Eligible participants are premenopausal women ≥35 without prior invasive breast cancer, but with ≥ 2-fold increased risk for the disease. The primary endpoint is difference in change in levels of *AGR2* mRNA between the two arms. Secondary endpoints are within-arm change in an endocrine response gene index (ERGI), mammographic density, and MENQOL. Exploratory endpoints include within-arm change in benign breast Ki-67, ER, PR and AGR2 protein, association of baseline Anti-Mullerian Hormone (a measure of ovarian reserve) with 6-month serum estradiol and change in tissue estrogen responsive gene expression and *AGR2*. Based on the preliminary data, mean log base2 (fold change, FC) of *AGR2* in the acolbifene arm is assumed to be -1, which is tantamount to a 50% reduction. The estimated SD of the log2(FC) is 2.25. Assuming a log2(FC) of +0.6 in the low dose tamoxifen arm (50% increase), and the same SD as in the acolbifene arm, 36 evaluable subjects per arm are required to detect, with 80% power at an alpha = 0.03 (two-sided), a difference in FC of this magnitude between the two arms. Secondary endpoints are assessed via paired samples t-test or Wilcoxon signed-rank test. Target enrollment in this 4-site trial is 80 over 2.5 years. The protocol opened for accrual at the University of Kansas Medical Center in October 2024 and as of January 2025 is pending activation at the other sites. Clinical trial information: NCT05941520. Research Sponsor: National Cancer Institute.