A Phase 2 Trial of (Z)-endoxifen + Goserelin as Neoadjuvant Treatment for Premenopausal Women with ER+/HER2- Breast Cancer (EVANGELINE)

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Matthew P. Goetz[1], Vera J. Suman[1], Janet Rea[2], Hayley Erickson[2], Lucia Beaulieu[2], Sandra S. Hammer[2], Lida Mina[3], Pooja Advani[4], Roberto Leon-Ferre[1], Karthik Giridhar[1], Felipe Batalini[3], Daniel Flora[5], Jason M. Jones[6], Nusayba A. Bagegni[7], Katie N. Hunt[1], James Jakub[4], Mara Piltin[1], Amy Degnim[1], James N. Ingle[1], Judy C. Boughey[1], Sarah A. Buhrow[1], Joel M. Reid[1], Matthew Schellenberg[1], Vandana Abramson[8], Vrushali Dabak[9], William Irvin Jr.[10], Sima Ehsani[11], Seema Khan[12], Ghassan Al-Jazayrly[13], Ahmed Elkhanany[14], Hannah Linden[15], Steven C. Quay[2]
[1]Mayo Clinic, Rochester, MN; [2]Atossa Therapeutics Inc., Seattle, WA; [3]Mayo Clinic, Phoenix, AZ; [4]Mayo Clinic, Jacksonville, FL; [5]St. Elizabeth Healthcare, Edgewood, KY; [6]Avera Health, Sioux Falls, SD; [7]Washington University, St. Louis, MO, [8]Vanderbilt Ingram Cancer Center, Nashville, TN; [9]Henry Ford Cancer Institute, Detroit, MI; [10]Bon Secours Cancer Institute, Midlothian, VA; [11]University of Arizona, Tucson, AZ; [12]Northwestern University, Chicago, IL; [13]California Research Institute, Los Angeles, CA; [14]Baylor University, Houston, TX; [15]Fred Hutchinson Cancer Research Center

BACKGROUND

Premenopausal women with ER+, HER2- breast cancer are often treated with Aromatase Inhibitors (AI) + Ovarian Function Suppression (OFS). Common adverse events associated with AI+OFS include musculoskeletal symptoms, hot flashes, night sweats, mood changes, and sexual dysfunction, limiting adherence to AI/OFS.

For patients who cannot tolerate AI + OFS, tamoxifen (alone or with OFS) is the only alternative endocrine therapy option. In pre- and post-menopausal women treated with short term neoadjuvant endocrine therapy (NET), reductions in Ki-67 (≤10% absolute value following 2- 4 weeks of therapy) results in 5-year distant disease-free survival >96%. Problematically, in pre-menopausal women, only 30-40% of patients reach this Ki-67 threshold with tamoxifen compared to 78% with AI+OFS (Nitz JCO 2022). Lower efficacy with Tamoxifen is attributed in part to resistance mechanisms involving signaling pathways such as Protein Kinase C beta (PKCβ), a known oncogenic protein that is not targeted by tamoxifen itself.

EVANGELINE is an ongoing phase 2 multicenter neoadjuvant study assessing (Z)-endoxifen (ENDX), a potent tamoxifen metabolite that dually targets ERα and PKCβ, in combination with OFS in premenopausal women with ER+/HER2- breast cancer.

TUMOR AND BLOOD BIOMARKERS

- Ki-67
- ERα and PR
- PKCβ1
- C-PARP
- Cyclin D1
- pAKT and total AKT
- Tumor transcriptome
- Whole genome sequencing
- Thymidine Kinase
- E1/E2
- ctDNA
- Lipid profile/bone biomarkers

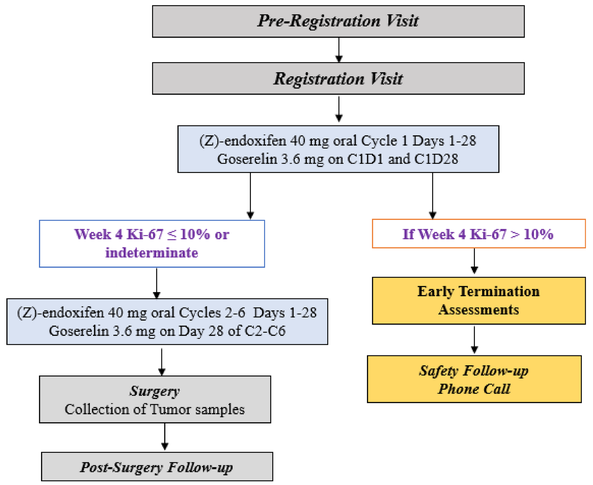
SAFETY AND TOLERABILITY

- Clinical labs (hematology, chemistry, lipid profile and bone biomarkers)
- Adverse events (CTC-CAE v5)
- ECGs
- Physical exams
- Drug levels
- MRI

KEY INCLUSION CRITERIA

- Premenopausal Female 18 + years
- cT2-3; cN0-1 Breast cancer
- ER ≥67% or Allred Score (6-8); HER2-
- Nottingham Grade 1 or 2
- Largest tumor diameter >2.0 cm

PART 3 SCHEMA



METHODS

EVANGELINE (NCT05607004) is a multicenter, open-label, Phase 2 study with a PK run-in examining the clinical activity and tolerability of ENDX 40mg daily + goserelin every 28 days in premenopausal women with invasive cT2-3 cN0-1 breast cancer.

- A Simon two stage Phase II design was chosen to assess whether the Week 4 Ki-67 ≤10% rate is at least 65%. If 9 or more of the first 20 patients enrolled have a Week 4 Ki-67 >10%, enrollment will be stopped due to futility. Otherwise, an additional 25 patients will be enrolled. If at least 25 patients have a week 4 Ki-67 ≤10% among the 45 patients enrolled, we would conclude Week 4 Ki-67 ≤10% rate is at least 65%.
  - Pre-NET Ki67 ≤10% Cohort: 20 patients will be enrolled to determine the objective tumor response rate by breast MRI at week 24.
  - Ki-67 levels will be determined by central laboratory testing.
- Secondary endpoints include: toxicity profile, Residual Cancer Burden (RCB), and PEPI score.

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STATISTICAL CONSIDERATIONS

- For patients with pre-NET Ki-67 >10%, based on ALTERNATE trial (65.5% achieving this threshold with anastrozole), a Week 4 Ki-67 ≤10% rate of ≥65% for ENDX + goserelin is considered promising in postmenopausal women.
- A Simon two stage design will be used to assess the null hypothesis that the week 4 Ki-67 ≤10% is at most 45% against the alternative hypothesis that the week 4 Ki-67 ≤10% is at least 65%.
- The Duffy-Santner approach will be used to construct a 90% confidence interval for the proportion of subjects whose Week 4 Ki-67 ≤10%. A 90% binominal confidence interval will be constructed for the proportion of subjects with a finding of PR or CR on central review of MRI scans using RECIST criteria 1.1.
- For patients with pre-NET Ki-67 ≤10, a point and interval estimate or objective tumor response rate at 24 weeks will be constructed. The maximum width of a 90% binomial confidence for the objective response rate at week 24 is +/- 18.4%.

PK Run In Results

The PK run-in (completed Fall 2024) enrolled 22 patients regardless of pre-NET Ki-67 level, and assessed ENDX doses at 40 and 80 mg daily (+/-OFS). The Week 4 Ki-67 ≤10% rate post ENDX was 86% (+/-OFS). Early safety, PK, and compliance data supported the selection of ENDX 40 mg daily + OFS.

Conclusions

- EVANGELINE is the first trial to evaluate ENDX + OFS as neoadjuvant therapy in premenopausal ER+/HER2– breast cancer.
- By targeting both ER and PKC pathways, ENDX may offer a well-tolerated alternative to AI-based regimens and expand endocrine therapy options for this population.

UPDATES

- All patients enrolled in PK run-in part have completed the study. A manuscript is being drafted.
- Phase II is open to enrollment at approved sites
- Clinical Trial Registration: **NCT05607004**

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