A randomized phase II study comparing monthly versus 3-monthly GnRH agonist for ovarian function suppression in premenopausal patients with HR-positive breast cancer: study design and rationale

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Background

- The SOFT and TEXT trials have shown substantial survival benefit from adding ovarian function suppression (OFS) with gonadotropin-releasing hormone agonists (GnRHa) to aromatase inhibitors (AI), compared with tamoxifen alone in premenopausal patients with hormone receptor (HR)-positive breast cancer.
- This benefit was particularly pronounced among women with a higher risk of recurrence, such as younger patients and those who received adjuvant chemotherapy.
- Although most pivotal trials used monthly GnRHa, many clinicians prescribe 3-monthly depot injections for convenience, despite limited prospective data supporting their efficacy.
- Retrospective data from a Brazilian cohort presented at the 2023 ASCO Annual Meeting [JCO 41, no. 16_suppl (June 1, 2023) 527-527] suggested fewer estradiol (E2) increases with 3-monthly compared to monthly GnRHa, prompting the need for a prospective randomized trial.
- The hypothesis of this present study is that GnRHa administered every three months is as effective as monthly administration for ovarian function suppression in premenopausal breast cancer patients.

Methods and Study Design

- Randomized phase II trial
- Premenopausal women with HR-positive breast cancer
- HER2 negative or positive
- Stage I-III
- Age ≤ 40 years
- **N = 50**

R 1:1

Cohort A
Leuprolide 22.5 mg IM q12w plus AI (N=25)

Cohort B
Leuprolide 7.5 mg IM q4w plus AI (N=25)

Stratification Factors:

Prior chemotherapy: yes vs no

Follow-up: 12 months

- E2 blood samples will be collected at baseline and thereafter at 3, 6, 9, and 12 months.
- E2 levels will be measured using liquid chromatography-tandem mass spectrometry.

Primary objective:

- To compare the proportion of patients in each treatment arm who experience at least one estradiol level above the threshold of 2.72 pg/mL.

Secondary objectives:

- To describe E2 levels at different timepoints during a 12-month follow up.
- To evaluate the association between baseline patient characteristics and E2 elevations.

Inclusion criteria

- Female premenopausal participants with a histologically confirmed diagnosis of breast cancer.
- Stage I-III HR-positive, HER2-negative or HER2-positive breast cancer (ER ≥1% and/or PR ≥1% per American Society of Clinical Oncology [ASCO]/College of American Pathologists [CAP] guidelines).
- Age 18 to 40 years (inclusive), with no impairment in decision-making capacity.
- Candidate for adjuvant endocrine therapy and ovarian function suppression.
- For patients scheduled to receive chemotherapy, premenopausal status will be defined by the presence of regular menses prior to initiation of chemotherapy.
- For patients not receiving chemotherapy, premenopausal status will be defined by regular menses prior to randomization.
- ECOG Performance Status (PS) of 0 to 1.
- Ability to provide written informed consent for the trial.

Preliminary data
2023 ASCO Annual Meeting

Current Status

- This investigator-initiated study is supported by the 2024 Long-term International Fellowship (LIFe) Award from Conquer Cancer, the ASCO Foundation.
- IRB approval was obtained in July 2025, and the study is currently in the activation phase.
- Patient enrollment is expected to begin shortly thereafter.

Conclusions

- OFS management remains a major challenge for oncologists worldwide, with limited evidence to guide optimal GnRHa dosing schedules.
- This study will generate prospective data comparing OFS using monthly versus 3-monthly GnRHa in combination with adjuvant endocrine therapy, addressing an important gap in clinical practice.
- The findings may contribute to future clinical guidelines for OFS, while also improving convenience, supporting treatment adherence, and enhancing quality of life for premenopausal breast cancer patients globally.

Disclosures

- The first and presenting author declares no conflicts of interest.
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