

Background

- Adjuvant endocrine therapy recommendations for patients with invasive lobular carcinoma (ILC) are no different than for other breast cancer subtypes.
- Due to unique differences in estrogen pathway signaling of ILC, identifying biological markers of ET sensitivity or resistance could have a major impact on its clinical management.
- Pre-clinical studies suggest that fulvestrant may be more effective than anastrozole or tamoxifen for ILC.
- Here we test reduction in the proliferation marker Ki67 as a surrogate for treatment response to endocrine therapy.

Methods

TRIAL DETAILS:

- open label, randomized, controlled, multicenter phase 0 window of opportunity trial (NCT02206984)

INCLUSION CRITERIA:

- Postmenopausal women, previously untreated hormone receptor-positive, HER2 negative ILC measuring ≥ 1 cm, centrally histologically confirmed on diagnostic core needle biopsy

EXCLUSION CRITERIA:

- Stage IV, prior/concurrent HRT, endocrine therapy within the last 2 years, concurrent illness, thromboembolic disease, bleeding diathesis

TRIAL DESIGN

- Conducted at 12 TBCRC institutions in US between 10/8/15 and 7/28/23
- Patients were randomized 1:1:1 to:
 - **Fulvestrant (500 mg IM on days 1 and 15)**
 - **Anastrozole (1mg/day)**
 - **Tamoxifen (20 mg/day)**

- After 21-27 days of treatment, patients underwent operation (from which a core needle biopsy of residual tumor bed was taken) or a post-treatment image-guided core needle biopsy.

PRIMARY ENDPOINT:

- **Change in Ki67 proliferation index, post-treatment vs baseline**

STATISTICAL ANALYSIS:

- Given the log-normal distribution of Ki67 measurements generally observed in this population, values were log-transformed for statistical analysis [$\log(\text{post/pre})$]. A linear mixed model (glmmTMB R package) was fit that adjusted for institutional-level random effects and allowed for treatment level error variance. Post-hoc pairwise comparison of $\log(\text{post/pre})$ were performed using Tukey adjustment for multiple comparison.

Results

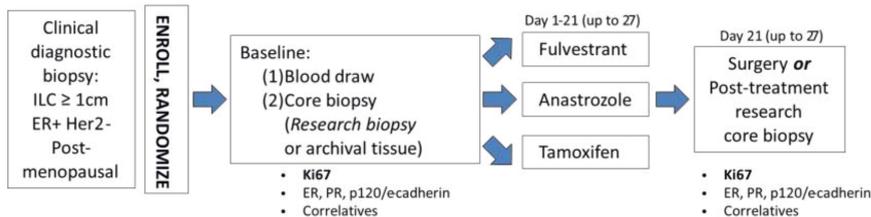


Figure 1. Study Schema.

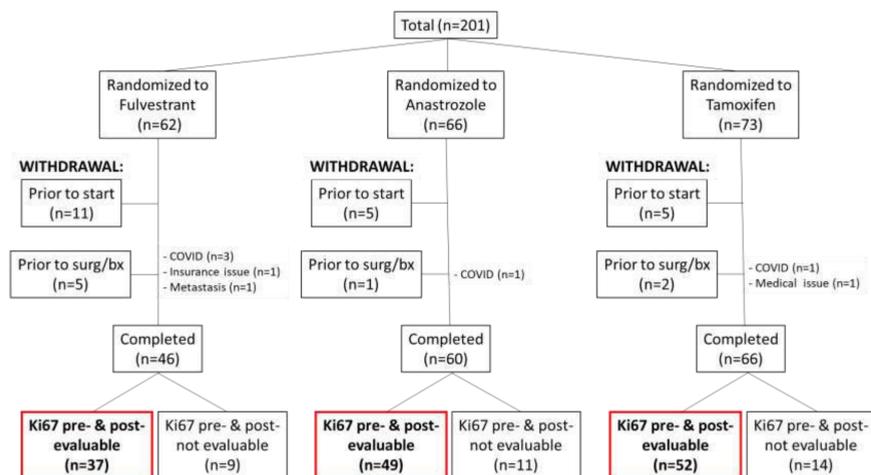


Figure 2. Consort Diagram. 201 women were randomized, 172 completed their assigned treatment, and 138 had evaluable pre- and post-treatment tissue.

Characteristics	Total cohort N=138	Fulvestrant N=37	Anastrozole N=49	Tamoxifen N=52
Age, median years (range)	67 (48-86)	70 (48-89)	66 (49-85)	66 (50-84)
Race				
Asian	2 (1.5%)	1	0	1
Black	15 (10.9%)	5	5	5
Other	4 (2.9%)	1	2	1
White	117 (84.8%)	30	42	45
Ethnicity				
Hispanic	8 (5.8%)	2	4	2
Non-Hispanic	123 (89.1%)	33	42	48
Unknown	7 (5.1%)	2	3	2
Presenting clinical stage				
IA	54 (39.1%)	10	22	22
IB	4 (2.9%)	0	2	2
IIA	51 (37%)	18	15	18
IIB	19 (13.7%)	5	7	7
IIIA	4 (2.9%)	1	1	2
IIIB	5 (3.6%)	3	1	1
IIIC	1 (0.7%)	0	1	0
H-score, median (IQR)				
Estrogen Receptor	260 (50)	270 (43)	248 (58)	263 (40)
Progesterone Receptor	140 (215)	120 (209)	125 (228)	140 (203)

Table 1. Pre-treatment demographic and tumor characteristics were well balanced between treatment groups.

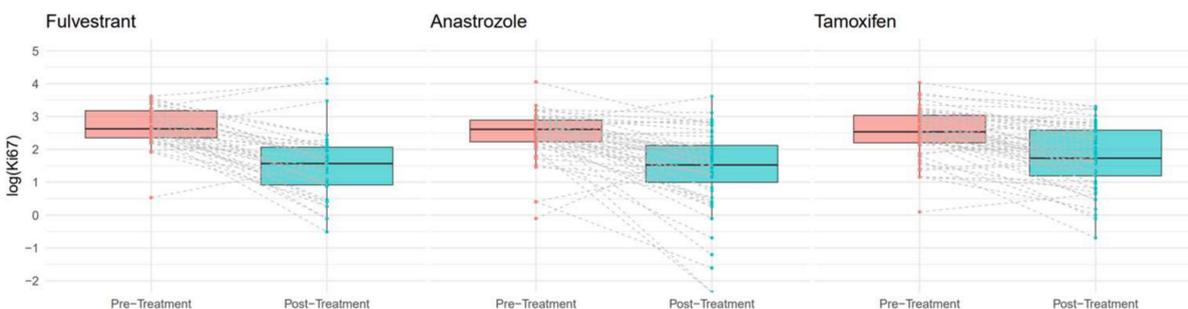


Figure 3. Log Ki67 pre- and post-treatment with Fulvestrant, Anastrozole or Tamoxifen and corresponding statistical result.

	Fulvestrant	Anastrozole	Tamoxifen
Mean log pre-Ki67 (SD)	2.69 (0.6)	2.45 (0.8)	2.50 (0.8)
Mean log post-Ki67 (SD)	1.47 (1)	1.43 (1.1)	1.79 (1)
Fixed paired differences with mean (SD) log (post/pre)	-1.22 (1.1)	-1.02 (1.1)	-0.72 (0.8)

	Log (post/pre)	Adjusted p-value
Fulvestrant vs Anastrozole		0.6643
Anastrozole vs Tamoxifen		0.2602
Fulvestrant vs Tamoxifen		0.0419

- No serious adverse events or deaths occurred.
- In the fulvestrant, anastrozole and tamoxifen groups respectively, median
 - pre-treatment Ki67 [IQR]: 13.8 [13.5], 13.6 [8.7], and 12.6 [11.8]
 - post-treatment Ki67 [IQR]: 4.8 [5.4], 4.5 [5.4], and 5.7 [10].

Conclusions

- A greater statistically significant post-treatment reduction in Ki67 was seen in ILC core needle biopsy of patients treated with Fulvestrant v tamoxifen.
- Interestingly, reductions in Ki67 were generally observed for tamoxifen, despite clinical concerns about its reduced efficacy in ILC. No significant differences between tamoxifen and anastrozole were found in the primary outcome of transformed log values of Ki67.
- Correlative studies are planned to determine whether Ki67 reduction is associated with alterations in expression of ER or ER-regulated genes and/or in other novel pathways, potentially opening avenues for improved treatment strategies in ILC.

Limitations

- Results of window of opportunity trials, while critical for studying drug effects on tumor tissue and for biomarker development, may not directly translate to patient outcomes.
- More withdrawals from Fulvestrant (injection) arm vs anastrozole and tamoxifen (pill) arms.
- Ki67 pre-/post- pairs were "not evaluable" if ILC was not confirmed on central review or if tissue block exhausted, tissue non-adhered to slide or outside case could not be retrieved. On review of clinical pathology report, no circumstance of insufficient tissue post-treatment was due to pCR.

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References

- Sikora MJ et al. Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. *Cancer Res.* 2014 Mar 1;74(5):1463-74. PMID: 24425047.
- Metzger Filho O, et al. Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial. *J Clin Oncol.* 2015 Sep 1;33(25):2772-9. PMID: 26215945.
- Smith I et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol.* 2020 Nov;21(11):1443-1454. PMID 33152284.

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