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CLINICAL TRIAL

A randomized trial exploring the biomarker effects of neoadjuvant sequential treatment with exemestane and anastrozole in post-menopausal women with hormone receptor-positive breast cancer

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Abstract Several adjuvant endocrine strategies exist for postmenopausal women with breast cancer. This study compared the effect of two sequences of aromatase inhibitor use [steroidal (exemestane) and non-steroidal (anastrozole)] on serological and pathological biomarkers when given in the neoadjuvant setting to postmenopausal women with breast cancer. Thirty women were assigned to receive exemestane 25 mg or anastrozole 1 mg each given for 8 weeks in a randomized sequence. The effect of this treatment on serum estrone sulfate and estradiol levels, as well as tumor changes in the proliferation biomarker Ki67 were evaluated at baseline, 8 weeks and 16 weeks. WHO clinical response criteria, patient preference, and quality of life were also assessed. Assessable data was available from 28 patients. There were no differences in concentration changes of serum estradiol or Ki67 between patients in the two arms. Overall clinical response rate was 68% (19/28 assessable patients) and clinical benefit was 93% (26/28 assessable patients). There was no significant difference in toxicity or quality of life scores. The majority of patients expressed a personal preference for anastrozole over exemestane. Results suggest that the order of steroidal and non-steroidal aromatase inhibitors has little effect on outcome. The majority of patients express clear preferences for drug treatments.

Keywords Aromatase inhibitor · Endocrine treatment · Locally advanced breast cancer

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Introduction

Several adjuvant endocrine strategies exist for postmenopausal women with breast cancer. Despite thousands of women being enrolled in trials, questions still remain regarding optimal endocrine effectiveness, safety, sequencing, and combination. In general, testing agents in the neoadjuvant setting appears to be more efficient than the adjuvant setting. For instance, the P024 trial [1] compared letrozole and tamoxifen in the neoadjuvant setting in 337 patients, while the BIG (Breast International Group) 1-98 trial conducted a similar comparison in about 8,000 adjuvant patients [2]. The neoadjuvant study successfully predicted the superiority of letrozole over tamoxifen 5 years before the adjuvant result, while needing only 3% of the study population. Similarly, the IMPACT trial [3] compared

the neoadjuvant use of tamoxifen, anastrozole, and the combination of tamoxifen with anastrozole in 330 women. Despite not showing superiority of anastrozole to tamoxifen in the full study population, the trial did show that the aromatase inhibitor was significantly more effective than tamoxifen in downstaging large breast cancers and suppressing the surrogate biomarker of effectiveness, Ki67. This superiority mirrored the results of the adjuvant sister study (ATAC) [4], which required over 9,300 women to meet its endpoint. Moreover, had the IMPACT study been carried out before the ATAC trial, there may have been a priori evidence of the potential lack of additional efficacy of combining tamoxifen and anastrozole.

Consequently, this has led some investigators to suggest that hormonal agents could first be tested in smaller, neoadjuvant populations prior to being formally tested in larger adjuvant studies [5]. This is particularly important given the increasing interest in prolonged sequential aromatase inhibitor therapy. A number of ongoing trials (summarised in Table 1) will address the utility of steroidal and non-steroidal aromatase inhibitors either in head-to-head comparisons or as sequence comparisons. At present, the only interim data comes from the Italian Gruppo Oncologico Nord Ovest (GONO) MIG8 trial which evaluated the efficacy of switching between steroidal and non-steroidal aromatase inhibitors on detection of progressive disease in a cohort of patients with metastatic patients. This trial concluded that switching between steroidal and non-steroidal aromatase inhibitors was efficacious, but noted that this efficacy appeared to be independent of the order in the sequence [6]. As yet, no study has been designed specifically to explore the efficacy of switching between steroidal and non-steroidal aromatase inhibitors in the adjuvant or neoadjuvant setting.

This study aimed to compare the effects of a randomized sequence of a steroidal aromatase inhibitor (exemestane) and a non-steroidal aromatase inhibitor (anastrozole) on biological (plasma estrone sulfate and estradiol), and cell proliferation (tumor Ki67 expression) biomarkers when given in the neoadjuvant setting to a cohort of post-menopausal patients with locally advanced breast cancer (LABC).

Patients and methods

Patients

Eligible patients included women with newly diagnosed breast cancer (with or without concurrent metastases) who were either:

(1) Marginal candidates for breast conserving surgery,
(2) Definitely ineligible for breast conserving surgery, or
(3) Definitively inoperable.

Patients had to be postmenopausal (defined as $\geq$12 months amenorrhea), tumor size had to be >2 cm by clinical examination, and patients had to have core-cut biopsy confirmation of ER and/or PgR positivity defined as at least 10% nuclear staining. All patients had to have an estimated life expectancy of 6 months or more as determined by the treating physician. Due to the potential confounding effects of certain drugs on estrogen metabolism, the use of all liver enzyme inducing and inhibiting drugs was an exclusion criterion. Furthermore, patients with any prior or concomitant use of hormonal therapy (e.g. tamoxifen, or hormone replacement therapy taken less than 1 month prior to entry into the trial, or extended use of systemic glucocorticoids) were also excluded.

Table 1 Ongoing and completed trials evaluating the utility of steroidal and non-steroidal aromatase inhibitors

Assessment	Trial	Agents	Setting	Sample Size
Head-to-head	MA27	Anastrozole versus Exemestane	Adjuvant	6,830
	ExCel	Anastrozole versus Exemestane	Prevention	5,100
	IBIS II	Anastrozole versus Exemestane	Prevention	10,000
Sequencing	GONO MIG8	Exemestane then Anastrozole or Letrozole or Anastrozole or Letrozole then Exemestane	Metastatic	56
	NSABP B42	Any combination of tamoxifen and AI including Exemestane) then Letrozole	Extended Adjuvant	3,840
	ABCSG16: SALSA	Adjuvant AI (including Exemestane) then Anastrozole	Extended Adjuvant	3,500

AI aromatase inhibitor, *MA27* National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), *MA-ExCel* NCIC CTG MAP3, IBIS II: International Breast Cancer Intervention Study, *GONO MIG8* Gruppo Oncologico Nord Ovest (GONO) MIG8, *NSABP B42* National Surgical Adjuvant Breast and Bowel Project (NSABP) B42, *ABCSG6-SALSA* Austrian Breast and Colorectal Cancer Study Group trial 16: Secondary Adjuvant Long-term Study with Anastrozole

Study endpoints

The primary objectives of this prospective study were to evaluate the changes in serum estrone sulfate, and estradiol levels, as well as intra-tumor Ki67. Secondary objectives included clinical response to treatment, patient preference, quality of life and toxicity. Clinical response was assessed by measuring the palpable tumor using two diagonal measurements 90° apart. WHO criteria were used to define responses into: complete response (defined as no residual disease palpable), partial response (defined as a greater than 50% reduction in tumor size), stable disease (defined as any change between 50% reduction and 25% increase in tumor size) and disease progression (defined as greater than 25% increase in tumor size). Patient preference was determined by a patient preference questionnaire, quality of life by the Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) questionnaire and toxicity of treatment by the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Trial design

A prospective, randomized, multi-centre, single-blinded, sequential trial evaluating objective changes in biological and molecular biomarkers before and after neoadjuvant therapy with steroidal (exemestane, Aromasin®; Pfizer Inc, New York, NY) and non-steroidal (anastrozole, Arimidex®, Astra-Zeneca Pharmaceuticals, Macclesfield, UK) aromatase inhibitors given in a randomized sequence for post-menopausal breast cancer was performed. The Research Ethics Board of Princess Margaret Hospital, and Sunnybrook and Women's College Health Sciences Centre approved the study protocol.

After patients provided written informed consent to participate in the study, all subjects underwent a core biopsy prior to randomization to ensure eligibility and to record baseline tumor molecular biomarkers (Ki67, ER, PgR, and HER2/neu). Once eligibility was confirmed, patients were randomized to receive either anastrozole 1 mg orally daily, or exemestane 25 mg orally daily for a total of 8 weeks. At the completion of this time period, subjects underwent a second core biopsy. Those taking anastrozole were switched to exemestane 25 mg/d orally for a total of a further 8 weeks. Those taking exemestane switched to anastrozole 1 mg orally daily for a further 8 weeks. At the end of the second 8-week period (i.e., after a total of 16 weeks of treatment), patients underwent a third biopsy, following which the appropriate surgical intervention was carried out. Patients were stratified based on operability (marginal for breast conservation, ineligible for breast conservation and inoperable) and HER2/neu status. Measures of clinical and radiological response as well as serological assessment for endocrine biomarkers were carried out at 0, 8, and 16 weeks of the study.

Assessment of plasma estrogens was done using tandem mass spectrometry (Taylor Technology, Inc., Sparks, MD). This method is a specific and sensitive bioanalytical method has been validated to quantitate low levels (pg/ml) of natural steroids [7]. Pathological assessment for Ki67 was carried out on paraffin embedded biopsy samples. The primary antibody, a mouse monoclonal MIB-1 antibody (The Binding Site Ltd., Birmingham, UK) was applied to each slide in a 1:50 dilution as per manufacturer's instructions. The avidin–biotin complex horseraddish peroxidase (ABC/HRP) detection method was utilized. Ki67 was assessed as a continuous variable without a particular cutoff and the pathologist was blinded to the previous ki67 results and treatment arm. Estrogen receptor was assessed by immunohistochemistry using Clone SP1 (Ventana) or Clone 6F11 (Novacastra) (rabbit monoclonal) antibody. Progesterone receptor was determined by immunohistochemistry using Clone IE2 (Ventana) Clone 16PG-312 (Novacastra) or PgR-1292 (Rabbit Monoclonal) antibody. HER2/neu was assessed immunohistochemically using 4B5 or CB11 (Ventana) (Rabbit Monoclonal), SP3 (Labvision) (Rabbit Monoclonal), or AO485(DAKO) with TAB 250(Zymed)/CB11 (Vector) cocktail. HER2 equivocal tumors (2+) were tested using fluorescence in situ hybridization (FISH-Vysis) with the threshold for positive HER2:CEP17 ratio of >2.2. Clinical assessment of response in the breast was based on investigator evaluation of response/progression according to WHO criteria.

Statistical analysis

The study aimed to enrol 30 patients in order to have 12 patients in each randomized arm after assuming a 20% dropout rate. Twelve patients per arm were required to achieve an 80% power to detect a 20 pmol/l difference in estrone sulfate levels between exemestane and anastrozole at 8 and 16 weeks. The alpha error for the sample size calculation was reduced to 2.5% (compared to the standard 5%) to allow for two statistical comparisons at 8 and 16 weeks. Consequently a Bonferroni adjustment was carried out. The primary population was the intent-to-treat (ITT) population, which was defined as all randomly assigned patients who received ≥1 dose of study medication. For statistical analysis, the worst care scenario was used for biochemical assay results below the threshold for detection. Such values were defined as the next lowest point (e.g. a value was <0.625 was defined as 0.624). All outcomes data were presented descriptively, using parametric measures (e.g. means) for normally distributed data and non-parametric measures (e.g. medians) elsewhere. Generalized estimating equations (GEE) were used in a

repeated measures analysis to compare estrone sulfate, estradiol levels, intra-tumor Ki67 as well as the quality of life scores between groups over the 16 week period after an adjustment for baseline values. Overall differences between drug sequences were evaluated via interaction effects between "group" and "time".

Visual inspection of all data was carried out and if this inspection revealed skewing by extreme values, normalization by log transformation was applied. The adequacy of the procedure was verified by examination of the probability plots and the co-efficient of skewness. All of the statistical analyses were performed using Stata, release 9.0 (Stata Corp., College Station, Texas, USA).

Results

Patient characteristics

Thirty patients gave initial consent for the study. One patient was withdrawn from the study prior to receiving any study medication since she was unable to undergo a breast biopsy due to a wound infection. Another patient was withdrawn from the study prior to receiving any medication due to rapidly progressive metastatic disease. Subsequently, a total of 28 patients completed the trial with 14 patients completing treatment with anastrozole followed by exemestane (A → E), and 14 patients receiving exemestane followed by anastrozole (E → A) (see Fig. 1). Groups were balanced with respect to patient characteristics and demographics (Table 2). Tumors were confirmed as ER positive (ER ≥ 10%) in all but one patient who was ER-negative, but PgR positive. There were 2 HER2 positive patients (14.3%) in the E → A group, but none in the A → E group. There were seven (50%) metastatic patients in the A → E group and 3 (21%) in the E → A.

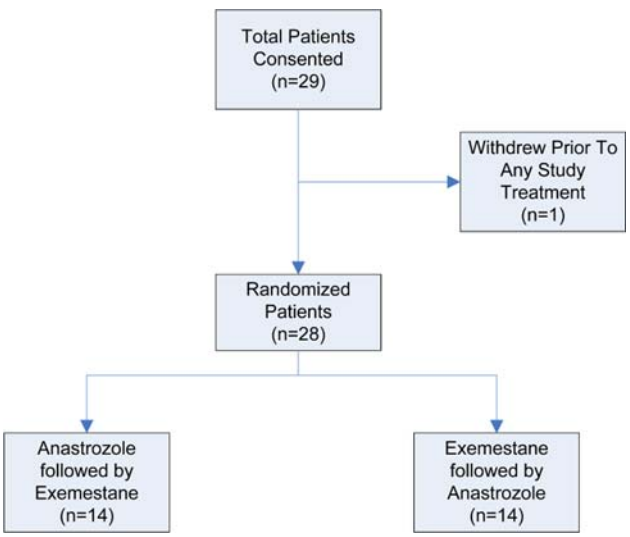

Fig. 1 CONSORT diagram

Table 2 Patient Demographics

	Anastrozole then exemestane	Exemestane then anastrozole
Age (years)		
Median	67	62.5
Range	56–87	51–84
Calliper tumor size (cm)		
Median	7.5	7.5
Range	0–12	3–11
Clinical tumor stage (*n* (%))		
T4	6 (43%)	3 (21%)
T3	5 (36%)	9 (64%)
T2	2 (14%)	2 (14%)
T1	0 (0%)	0 (0%)
T0	1 (7%)	0 (0%)
Clinical node stage (*n* (%))		
N3	4 (29%)	6 (43%)
N2	4 (29%)	3 (21%)
N1	4 (29%)	4 (29%)
N0	2 (14%)	1 (7%)
Metastatic staging (*n* (%))		
M1	7 (50%)	3 (21%)
M0	5 (36%)	10 (71%)
Mx	2 (14%)	1 (7%)
Baseline ER (%)		
Median	95	97.5
Range	70–100	5–100
Baseline PgR (%)		
Median	70	47.5
Range	0–100	0–100
Baseline HER2/neu		
Positive	0/14 (0%)	2/14 (14.3%)
Negative	14/14 (100%)	12/14 (85.7%)

Biomarker changes

At baseline, no patient in either treatment group had serum estradiol or estrone sulfate concentrations below the threshold of detection for the method. There was no significant difference in the mean baseline estradiol and estrone sulfate levels between the two treatment groups. Estradiol levels were 6.47 pg/ml in the A → E group and 5.25 pg/ml in the E → A group (Student t-test, $p = 0.34$). Estrone sulfate levels in the A → E group were 333 pg/ml and 272 pg/ml in the E → A group (Student *t* test, $P = 0.34$). At week 8, the proportion of patients in the A → E group with undetectable estradiol and estrone

sulfate levels were 78.6 and 0%, respectively while in the E → A group, these values were 69.2% and 7.7%. By week 16, these values were 64 and 7.7% for the A → E group and 69.2 and 7.7% for the E → A group. Both treatment arms were associated with significant reductions in serum estradiol and estrone sulfate. For estradiol, the repeated measures analysis over time showed that there were no significant differences in this reduction between the two treatment arms ($P = 0.76$, see Fig. 2). In the case of estrone sulfate, the difference between the two groups was of borderline statistical significance ($P = 0.056$, see Fig. 3). Biopsy material was available from 16, 13, and 13 patients at baseline, 8, and 16 weeks, respectively. Analysis of this material showed that the percentage of malignant cells staining for the biomarker Ki67 fell by 66% from a median of 29% at baseline to a median of 10% at week 16. Once again repeated measures analysis revealed no significant difference between the two treatment arms ($P = 0.83$; see Fig. 4).

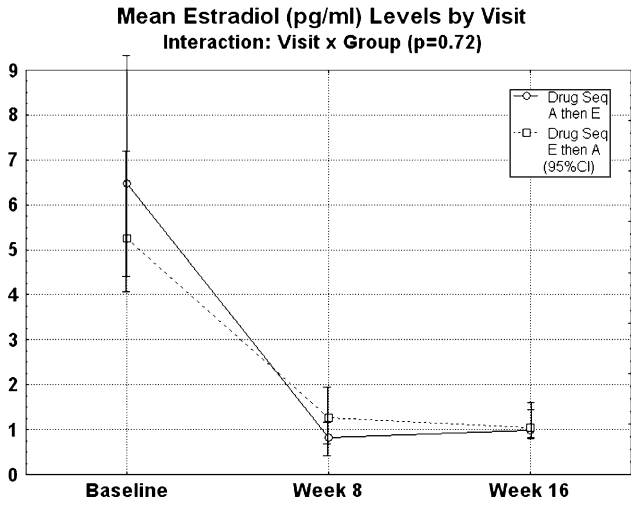

Fig. 2 Changes in serum estradiol

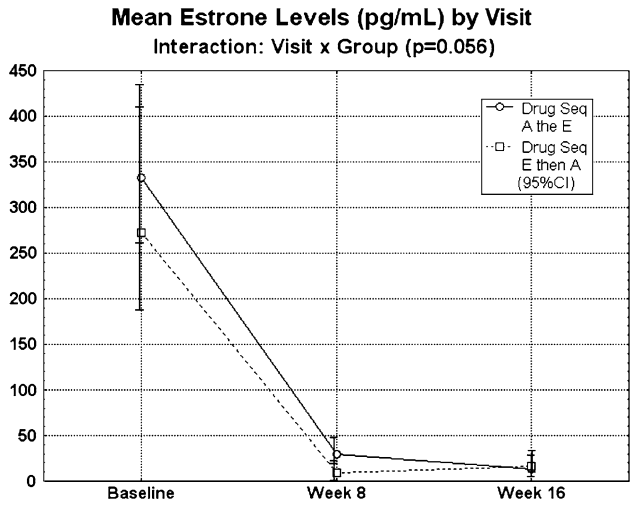

Fig. 3 Changes in serum estrone sulfate

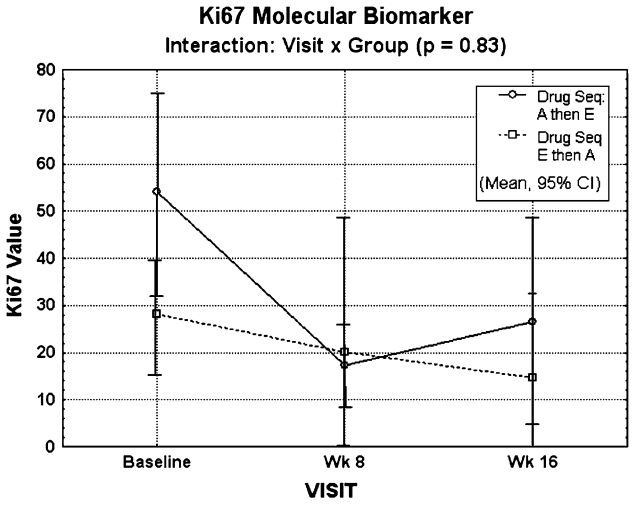

Fig. 4 Changes in tumor ki67

Clinical response

At 16 weeks of treatment, 4 patients (14%) experienced a complete clinical response, 15 (54%) a partial clinical response, seven (25%) had stable disease, and two (7%) had progressive disease (at 12 weeks). Of the two patients who were HER2+, one had a partial response and one had progressive disease. The overall response rate was therefore 68% (19 patients). Patients treated with A → E were more likely to have partial response to therapy than patients in the E → A group. Partial responses were seen at 22 evaluation points in the A → E arm compared to just 5 evaluation points in the E → A arm (Chi^2, $p = 0.001$).

Toxicities

In the A → E group, there were 136 adverse events of all grades documented compared with 134 such events in the E → A arm. The mean event count per patient in the A → E arm was 9.7 compared with 9.6 in the E → A group. Very few National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) of grade 3–4 were documented. In the A → E group two such toxicities occurred (diverticulitis and bowel obstruction, both thought to be unrelated to the trial medication) while in the E → A arm there were no grade 3–4 toxicities.

Patient preferences

Patient preference data was available from 23 patients (82%). Of these, 19 (83%) stated a preference for one of the drugs, and 19 (83%) stated that patients should be able to

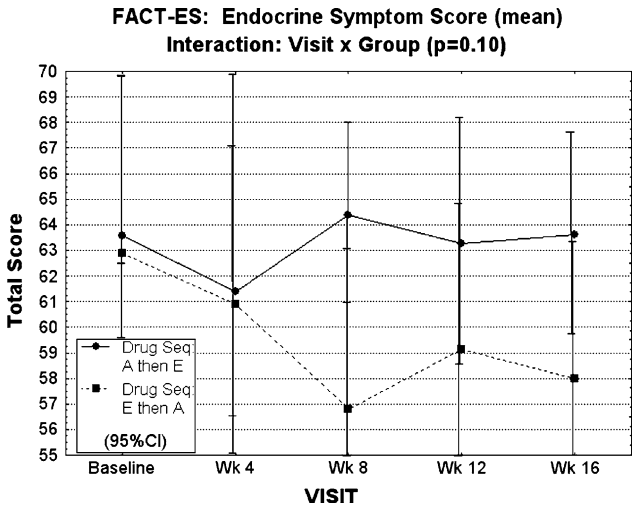

Fig. 5 Changes in quality of life

choose their treatment preference. Fourteen of 23 patients (61%) preferred anastrozole to exemestane. Among those patients in the A → E group, eight out of 13 (61%) preferred anastrozole, while in the E → A arm, two out of 10 (20%) preferred exemestane. Therefore, it appears that the sequence of agents did not affect patient preference data.

Quality of life

There were no differences between the two treatment groups in the quality of life scores. Repeated measures analysis of the total score was not significantly different ($P = 0.70$, see Fig. 5) nor were individual category scores: endocrine symptoms ($P = 0.10$), physical well-being ($P = 0.44$), emotional subscale ($P = 0.78$), functional score ($P = 0.73$) or trial outcome index ($P = 0.42$).

Discussion

The routine application of neoadjuvant endocrine therapy is acceptable in the setting of an ER-rich tumor in an older patient who is clearly not a candidate for chemotherapy. Although initial trials of tamoxifen as neoadjuvant therapy in LABC showed inferiority in comparison to chemotherapy [8], the advent of newer endocrine agents such as aromatase inhibitors has revolutionized the role of endocrine therapy in the neoadjuvant setting. In fact, the administration of aromatase inhibitors preoperatively has now been shown to be effective in hormone receptor-positive postmenopausal women in a number of studies comparing different aromatase inhibitors to tamoxifen [1, 3, 9–11]. Neoadjuvant endocrine therapy studies also provide an opportunity to develop insights into the biological basis for the efficacy of estrogen receptor-targeting agents. Given that there is increasing interest in sequential steroidal and non-steroidal aromatase inhibitor therapy (Table 1) [12–16], the rationale of this study was to compare the effects of a randomized sequence of a steroidal aromatase inhibitor (exemestane) and a non-steroidal aromatase inhibitor (anastrozole) on biological (plasma estrone sulfate and estradiol), and tumor (Ki67 expression) biomarkers when given in the neoadjuvant setting to a cohort of post-menopausal patients with locally advanced breast cancer.

There are several important findings worth noting in this study. First, the fact that 19 patients (68%) had clinical complete or partial response, and 26 patients (93%) had clinical benefit, strongly supports the utility of 16 weeks of neoadjuvant endocrine therapy in ER positive postmenopausal women. In this study, there was little appreciable difference in serological and pathological biomarkers between patients treated with A → E versus those treated with E → A. Furthermore, there was no difference observed in quality of life scores of patients in the two arms. This is consistent with previous data [17].

Despite no statistical difference in quality of life, the majority of patients expressed a preference for one drug over the other. Evidence for patient preference of one aromatase inhibitor over another has been shown in at least one other study [18]. In addition, many studies have demonstrated that participation in active decision making in itself may be beneficial for patients: patients who are offered options in their care demonstrate lower rates of anxiety and depression [19, 20], and greater perception of involvement in decision making heightens patient satisfaction with their decision and improves physician loyalty [21]. Therefore, in view of the fact that there is no data to support the use of one aromatase inhibitor ahead of another, it would appear appropriate for patients to be involved in decision-making regarding the choice of agent and in those that poorly tolerate one agent results of this study could support the utility of switching to another agent.

This study has a number of limitations. First, there were only a small number of patients enrolled in this trial. These patients who chose to receive endocrine therapy may be systematically different than those who chose to immediately proceed with chemotherapy. In addition, there was a number of missing biomarker data points. This was especially acute with ki67 as the availability of biopsy material was only around 50% of patients at all the three time points (baseline, week 8 and week 16). The extent of missing data in such a small dataset may have led to a diminution of statistical power and therefore to potentially erroneous results.

In summary, this study has shown that the sequencing of aromatase inhibitors is effective, and that the effect is

independent of the sequence employed. The majority of patients had a clear preference for one drug compared to the other, and the majority felt that patient choice should be incorporated into these treatment decisions. A trend towards better clinical response rates seen in patients treated with A → E needs to be confirmed in larger studies.

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