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Phase II Trial of Neoadjuvant Exemestane in Combination With Celecoxib in Postmenopausal Women Who Have Breast Cancer

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Abstract

Purpose—Within breast tissue, aromatase expression and activity is increased by prostaglandin E2, providing a rationale for combining the COX-2 inhibitor celecoxib with an aromatase inhibitor. To evaluate the effect of these drugs on aromatase and other biomarkers, a phase II trial of neoadjuvant exemestane followed sequentially by celecoxib plus exemestane was performed.

Methods—Postmenopausal women with estrogen receptor (ER) and/or progesterone (PR) positive stages II-III breast cancers received 8 weeks of exemestane 25 mg daily, followed by 8 weeks of exemestane 25 mg daily and celecoxib 400 mg twice daily. Core biopsies were collected pretreatment, after 8 weeks of exemestane, and at definitive breast cancer surgery. A tissue microarray was constructed and immunohistochemistry (IHC) for aromatase, ER, PR, HER-2, Ki-67, and COX-2 was performed.

Results—Twenty-two women were enrolled. Celecoxib was discontinued in 4 (18%) women for toxicity (all grade 1 and 2) and 2 (9%) developed serious cardiac events occurring at 1 and 4 months after completing treatment. By US, there were 8 (36%)-partial responses and 12 (55%)-stable disease. There were no pathological complete responses (pCR). There were statistically significant decreases in ER ($P = .003$), PR ($P = .002$), Ki-67 ($P < .001$), and COX-2 ($P = .004$) expression. No significant differences in aromatase or HER-2 expression were observed ($P = .13$ and $P = .39$, respectively).

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Disclosure

The authors have no conflicts of interest to report.

Conclusion—The addition of celecoxib to exemestane was tolerated by the majority of women and anti-tumor response was observed. Additional studies, including gene expression, are required to more fully understand the basis for the decreased expression of ER, PR, Ki-67, and COX-2.

Keywords

Celecoxib; COX-2 inhibitor; Estrogen receptor; Exemestane; Ki-67; Neoadjuvant

Introduction

The response to neoadjuvant aromatase inhibitors ranges between 37% and 70%^{1–6} with improved rates of breast-conserving surgery relative to tamoxifen.³ However, pathological complete responses are low ranging between 0 and 4%.^{1–7} Aromatase, a key enzyme in estrogen biosynthesis, is expressed in normal breast tissue with higher expression in breast tumors.^{8, 9} Aromatase is modulated by prostaglandins in the cyclooxygenase pathway.¹⁰ In breast tissue, prostaglandin E2 (PGE2), produced by cyclooxygenase-2 (COX-2), increases intracellular cyclic adenosine monophosphate levels, which in turn cause activation of aromatase promoters I.3 and PII.¹⁰ Breast cancers have higher PGE2 relative to normal breast tissue,¹¹ and higher COX-2 levels are associated with increased aromatase expression in human breast cancer tissues.¹²

Selective COX-2 inhibitors decrease aromatase expression and activity in breast cancer cell lines,¹⁰ and the combination of COX-2 inhibitor plus exemestane is synergistic in animal models.¹³ These findings, along with the clinical data described above, led to the hypothesis that a selective COX-2 inhibitor, celecoxib, may improve anti-tumor efficacy of an aromatase inhibitor in the neoadjuvant setting. To test this hypothesis, a phase II trial of neoadjuvant exemestane (EXE) followed sequentially by celecoxib plus EXE was performed with the primary objective to assess changes in the expression of aromatase, as well as estrogen receptor (ER), progesterone receptor (PR), HER-2, Ki-67, and COX-2 in sequential biopsy specimens of primary breast tumors before, during, and after treatment.

Materials and Methods

Eligibility Criteria

Women with the following characteristics were eligible: histologically confirmed with clinical stage II, III breast cancer; ER and/or PR positive (> 10% by immunohistochemistry [IHC]); residual breast cancer following the initial core needle biopsy measurable by physical examination or ultrasound (US); Eastern Cooperative Oncology Group (ECOG) performance status 0–1; postmenopausal as defined as 3 or more months of amenorrhea when patient was older than 55 years, follicle-stimulating hormone >30 MIU/mL when patient was younger than 55 years; or surgical menopause with bilateral oophorectomy. The following laboratory values were required: absolute neutrophil count > 1500; hemoglobin > 9 g/dL; platelet count > 100, 000/mm³; creatinine < 1.5 times upper limit of normal (ULN); total bilirubin < 1.5 x ULN, and aspartate transaminase/alanine transaminase <3 x ULN. Patients were excluded for the following reasons: any prior treatment for breast cancer; inflammatory breast cancer; documented allergy to aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or sulfonamides; history of myocardial infarction or unstable angina. Women who were being administered hormone replacement therapy, celecoxib, other COX-2 inhibitors or NSAIDs were required to stop these drugs for 4 weeks before study entry. Aspirin 81 mg daily was permitted. All patients provided written informed consent before enrollment in this Institutional Review Board approved study.

Pretreatment Assessment and Follow-Up Studies

Histories, physical examinations, and routine laboratory studies, including complete blood cell counts with differential and complete metabolic panel, were performed before initiation of treatment and repeated every 4 weeks. All tumors were measured using US and by physical examination at baseline, at 8 weeks, and at 16 weeks (before definitive breast cancer surgery). A baseline chest x-ray was obtained and additional staging imaging studies were completed as determined by the treating physician.

Treatment Plan

After the baseline core biopsy, patients received 8 weeks of exemestane 25 mg/d and then had a second core biopsy. Subsequently, they received celecoxib 800 mg/d in divided doses in combination with exemestane 25 mg/d for 8 additional weeks. After 16 weeks, they had definitive breast cancer surgery and a third core biopsy was obtained. Tumor measurements were obtained using US and physical examination at baseline, 8 weeks, and 16 weeks.

Toxicity

Toxicity was graded according to Common Toxicity Criteria (CTC version 3.0). There were no planned dose reductions or holding parameters for either drug. Removal from study because of toxicity was at the discretion of the treating physician. After the enrollment of 13 patients, the trial was temporarily suspended in December 2004 because of reports of increased cardiovascular (CV) risk with COX-2 inhibitors. The trial resumed in March 2005 after an amendment to patient consent forms detailing increased CV risk. The accrual period was extended until July 2007 and only 9 additional patients were enrolled for a total of 22.

Local Treatment

After completion of neoadjuvant therapy with exemestane and celecoxib, the type of definitive breast cancer surgery, either lumpectomy or mastectomy, was based on preoperative imaging studies, response to neoadjuvant therapy, and by the treating surgeon. All women had a sentinel node evaluation or level I/II axillary node dissection. Anthracycline-based adjuvant chemotherapy was recommended to those who had positive nodes after surgery; HER-2 over-expressing tumors received trastuzumab for a total duration of 1 year. Radiation treatment conformed to standard treatment guidelines with whole breast irradiation with a boost to the tumor bed after lumpectomy. Chest wall radiation after mastectomy was based on the initial tumor size greater than 5 cm and/or involvement of four or more axillary nodes. An aromatase inhibitor or tamoxifen, with a planned duration of at least 5 years, was administered after chemotherapy or radiation was completed.

Response Assessment

Clinical response was determined by physical examination and breast US at baseline and repeated at 8 weeks and 16 weeks, and pathological response by histopathological examination of the primary tumor and axillary nodes after definitive breast cancer surgery. Complete clinical response (CR) was defined as the complete disappearance of the breast tumor by US; partial clinical response (PR) and clinical stable disease (SD) were defined as the reduction of the size of tumor area by more or less than 50%, respectively. An increase of more than 25% in area was defined as progressive disease (PD). Pathological complete response (pCR) was defined according to the National Surgical Adjuvant criteria as no histological evidence of invasive tumor cells in the breast.¹⁴

Assessment of Aromatase, Er, Pr, Her-2, Ki-67, and Cox-2 Expression

Core biopsy specimens were obtained at baseline (within 21 days of study entry and starting exemestane), at 8 weeks (within 7 days of starting celecoxib), and at the time of definitive

surgery. For each interval, two core biopsy specimens were collected, fresh frozen, and stored in -80°C and two core biopsy specimens were paraffin-fixed. A tissue microarray was constructed from the paraffin-fixed specimens by the Ohio State University Pathology Core Facility. IHC staining was conducted with commercially available antibodies for ER (1:50 Dako clone 1D5), PR (1:800 Dako clone 1A6), HER-2 (1:200 clone c-erbB2), Ki-67 (1:150, clone MIB-1 Dako), and COX-2 (1:50, clone SP21 Neomarkers). IHC staining for aromatase was performed with aromatase antibody A677 (1:500), a gift from Dr. Dean B. Evans, Novartis Pharma AG (Basel, Switzerland). Per the Allred scoring system, the score obtained from the proportion of cells staining positive was added to the score obtained from the intensity of the staining.¹⁵ Scores could range from 0 (ie, 0 positive with 0 intensity) to 8 (ie, 76% to 100% staining positive with strong intensity). An independent pathologist calculated the Allred scores and was blinded to treatment and timing of the specimen acquisition.

Statistical Methods

The primary objective was to evaluate if the combination of exemestane with celecoxib resulted in significant changes in aromatase and other proteins including ER, PR, HER-2, Ki-67, and COX-2 in tumor tissue with therapy. IHC data were collected for these markers using Allred scoring. The largest changes in expression levels were expected to occur between 0 and 16 weeks with changes to a lesser degree between 0 and 8 weeks when only exemestane was administered. A two-sided nonparametric Wilcoxon signed rank test was used to test for a change in aromatase expression between 0 and 16 weeks. If significant at $\alpha = 0.05$, then a significant change in expression occurring earlier between 0 and 8 weeks would be tested. This analysis was repeated for the other biomarkers listed above. Here, the Holm's step-down procedure was used to obtain P values and control the family-wise error rate at $\alpha = 0.05$.

Results

Patient Characteristics

Between January 2003 and July 2007, 22 postmenopausal women were enrolled. Baseline characteristics are described in Table 1. The median age was 63 years (range, 49 to 87 years). The median tumor size was 4 cm (range, 2.5 to 6.0 cm) by physical examination and 2.6 cm (range, 1.5 to 3.8 cm) by US. The majority of women were clinical stage II (77%) and 7 (32%) had clinically palpable lymph nodes. Of the 22 enrolled, 2 (9%) were not evaluable for final pathological staging because they had received neoadjuvant chemotherapy before definitive breast cancer surgery.

Treatment Summary

Sixteen patients (73%) completed all 8 weeks of planned exemestane therapy followed by 8 weeks of planned combination therapy with exemestane and celecoxib. An additional 5 patients received all exemestane therapy, but discontinued celecoxib for the following reasons: toxicity ($n = 4$), progressive disease ($n = 1$), and temporary suspension of the trial in December 2004 to evaluate safety concerns while the CV data were evaluated ($n = 1$). Only one (5%) patient stopped exemestane after 4 weeks because of rapidly progressive disease and was started on neoadjuvant chemotherapy.

Toxicity

Table 2 describes treatment-related toxicities during the first 8 weeks of therapy (exemestane-only) and the second 8 weeks of therapy (combination of exemestane with celecoxib). There were no hematological or grade 4 toxicities. During the course of the trial,

the most common toxicities were arthralgias (41%), fatigue (45%), and hot flashes (41%), all grade 2 or less. The only grade 3 toxicity was hypertension developing in 2 (9%) patients during treatment with exemestane and celecoxib. As expected during celecoxib treatment, grades 1 and 2 gastric reflux symptoms and abdominal pain were increased relative to exemestane alone. Celecoxib was discontinued in 4 women for grade 2 rash ($n = 1$), grade 1 creatinine elevation ($n = 1$), grade 1 guaiac-positive stools ($n = 1$), and grade 1 edema ($n = 1$). No upper gastrointestinal (GI) bleeding occurred during study treatment. The one woman with guaiac-positive stools was found to have three polyps on colonoscopy. Another woman had lower GI bleeding after undergoing definitive breast cancer surgery when she was not on celecoxib; she was subsequently diagnosed with rectal cancer.

During the enrollment period, reports of CV complications of COX-2 inhibitors were first publicized. In our study, 2 women (9%) developed grade 3 hypertension while on celecoxib and were medically managed with antihypertensive drugs. These women had a history of hypertension and were on anti-hypertensive drugs. Two CV complications occurred after study treatment was completed. One woman developed a new left bundle branch block postoperatively after definitive breast cancer surgery and had an indeterminate stress test; the other had a myocardial infarction with congestive heart failure 4 months after treatment with celecoxib. All patients with complications from celecoxib therapy were older than 60 years and had hypertension before enrolling on trial.

Efficacy

Table 3 describes anti-tumor efficacy. There were no patients with clinical CR, 5 (23%) with PR and 8 (36%) with SD. One patient (5%) had PD and was taken off trial to receive neoadjuvant chemotherapy after 4 weeks of exemestane. Twenty women had definitive surgery with 12 (60%) having mastectomy, 7 (35%) lumpectomy, and 1 (5%) with an occult primary had axillary node dissection alone. There were no pCRs in the breast. One woman delayed definitive breast cancer surgery to receive neoadjuvant chemotherapy after completion of neoadjuvant endocrine therapy to attempt breast conserving surgery. Of the 13 women with node-positive disease after surgery, 10 (77%) went on to receive anthracycline-based chemotherapy. With a median follow-up duration of 38 months (range, 17 to 62 months), 20 women (91%) remain disease-free. Two (9%) developed distant metastasis at 13 and 26 months, respectively, and both subsequently died of metastatic disease.

IHC Results

Median differences in Allred scores at 16 and 8 weeks, respectively, versus baseline are presented in Table 4 for each biomarker. No significant difference in aromatase expression at 16 weeks compared to baseline was observed (median difference = 0; $P = .13$). The variability in aromatase was large, with 6 (43%) showing decreased expression of aromatase, 6 (43%) with no change, and 2 (14%) with an increased expression after treatment.

Both PR and Ki-67 scores significantly decreased after 16 weeks of treatment ($P = .002$ and $P < .001$, respectively) and also showed decreased scores after only 8 weeks of treatment ($P = .04$ and $P = .004$, respectively). Although both ER and COX-2 scores showed significant decreases at 16 weeks ($P = .003$ and $P = .004$, respectively), neither had statistically significant decreases at 8 weeks ($P = .19$ and $P = .27$, respectively); this result for COX-2 was expected because celecoxib was not administered during the first 8 weeks of treatment. No significant difference in HER-2 scores was observed after treatment ($P = .39$). Figure 1 shows representative tissue microarray images of biomarker changes in COX-2 and Ki-67 with the top panel showing the hematoxylin and eosin stain.

Discussion

To our knowledge, this phase II neoadjuvant trial is the first to investigate changes in aromatase expression and other protein markers with the addition of the selective COX-2 inhibitor celecoxib to exemestane. In this study, no significant differences in aromatase expression were detected with treatment. There were statistically significant decreases in ER, PR, Ki-67, and COX-2 expression. The decrease in ER and COX-2 expression was evident only after the addition of celecoxib to exemestane, but not with exemestane alone.

The hypothesis that this trial was designed to test, namely that aromatase expression would decrease with the addition of celecoxib to exemestane, was not observed. There are several possible explanations. Protein expression as measured by IHC did not change. However, the trial was initially intended to measure gene expression and fresh frozen tissue cores were collected with each biopsy expressly for this purpose. When the RNA was isolated and real time polymerase chain reaction for the genes of interest was performed the results suggested that the RNA was significantly degraded causing highly variable results in expression of both genes of interest as well as β -actin and other housekeeping genes used for standardization. These experiments were repeated in different laboratories using different machines with the same result. Thus, we have no information on gene expression of aromatase.

The combination of celecoxib with aromatase inhibitor therapy has been previously investigated in several trials in postmenopausal patients who had hormone receptor-positive metastatic breast cancer. One of the earliest feasibility studies of the combination reported clinical benefit rates of 74% in metastatic patients who were treated with a combination of exemestane and celecoxib.¹⁶ A randomized phase II study of exemestane versus exemestane plus celecoxib showed similar time to progression in both groups, but duration of clinical benefit was significantly longer in the combination group. A double-blind placebo-controlled phase III study (GINECO) of exemestane plus celecoxib versus placebo was terminated early because of CV complications and was underpowered to detect a difference between the two arms.¹⁷ The Celecoxib Anti-Aromatase Neoadjuvant (CAAN) trial evaluated exemestane alone, letrozole alone, and exemestane combined with celecoxib showing similar response rates between arms with greater tumor marker CA15.3 reductions in the celecoxib containing arm.⁶ Biomarker studies were not reported with these studies. Most recently, a neoadjuvant study of single-agent celecoxib for 14 days before surgery did not show significant changes in ER, PR, Ki-67, or COX-2.¹⁸ The only placebo-controlled randomized trial comparing exemestane and placebo to exemestane and celecoxib was conducted in patients who had ductal carcinoma in situ. In that trial, there were significant reductions in Ki-67 and PR expression after 14 days of exemestane and there was no additional expression level decreases with the addition of celecoxib.¹⁹

Several other trials have reported biomarker changes with single-agent neoadjuvant tamoxifen and an aromatase inhibitor as summarized in Table 5. Consistent with other trials in Table 5, Ki-67 and PR levels decreased in the current trial. In addition, there was a significant decrease in ER expression when celecoxib was added to exemestane. Possibly, a non-steroidal may affect the ER pathway differently than the non-steroidal aromatase inhibitors such as letrozole or anastrozole that were tested in other neoadjuvant studies. Because the decrease in ER expression was observed only after the addition of celecoxib, possibly the inhibition of the COX-2 pathway signaling may have been responsible. Estrogen biosynthesis is stimulated by PGE2 production that is modulated by COX-2 inhibition.²⁰ Additional studies are required to validate the decrease in ER expression and to elucidate the possible mechanisms.

The addition of celecoxib did not change the toxicity profile of exemestane in most women. However, in this small study, higher rates of hypertension were observed than in previously reported combination studies with aromatase inhibitors and celecoxib.⁶ Grade 3 hypertension was only observed in two women older than 60 years who had pre-existing hypertension. In addition, two women had CV toxicity at 1 and 4 months after exposure to celecoxib, and it is uncertain in this small non-randomized trial if celecoxib exposure was a potential contributor to this toxicity. In a recent pooled analysis of six placebo-controlled trials there was a dose-response relationship between celecoxib and CV toxicity with highest risk at 400 mg twice a day and with underlying CV risk factors.²¹

The small sample size limited the evaluation of the biomarker changes that could be detected in this trial. Originally, 34 patients were to be enrolled, but reports of increased CV complications with celecoxib in the Adenoma Prevention Trial in December 2004 led to suspension of the trial.²² Even after re-opening this trial in March of 2005 after an amendment that detailed the CV risks of celecoxib, physicians were reluctant to enroll women. In addition, for those women who were enrolled in the trial, physicians had a lower threshold for removing them from trial for toxicities attributed to celecoxib. This explains, in part, why grade 2 rash, grade 1 edema, and grade 1 creatinine elevations led to 3 women being removed from this trial. Eventually the trial closed with only 22 women enrolled because of low accrual. Also contributing to small numbers was the difficulty in procuring mid-treatment biopsy specimens that some women refused, and the fact that some core biopsy specimens did not have adequate tumor tissue for analysis. The latter highlights the difficulty of conducting small trials with multiple sequential biopsy specimens.

Conclusions

There were statistically significant decreases in ER, PR, Ki-67, and COX-2 expression with neoadjuvant combination therapy with exemestane and celecoxib. Additional studies are necessary to understand the biologic mechanism for decreased ER expression related to celecoxib shown in this trial and to determine possible long-term therapeutic implications.

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Figure 1.
Tissue Microarray Images of Biomarker Changes in COX-2 and Ki-67

Table 1Patient Characteristics^{ab}

Characteristic	N = 22 (%)
Median Age, Years (Range)	63 (49–87)
Race (W:AA:A)	20:1:1
Performance Status	
0–1	22 (100)
Menopausal Status	
Postmenopausal	22 (100)
Estrogen Receptor	
Positive	22 (100)
Progesterone Receptor	
Positive	16 (73)
Negative	6 (27)
Her-2 Status (IHC)	
0	12 (55)
1	1 (5)
2	8 (36)
3	1 (5)
Her-2 FISH	
Positive	4 (18)
Negative	8 (36)
Not available	10 (45)
Histology	
Invasive	15 (68)
Lobular	5 (23)
Mixed invasive and lobular	2 (9)
Grade	
1	1 (5)
2	14 (64)
3	7 (32)
Median Tumor Size, cm (Range)	
Clinical (largest diameter)	4 (2.5–6) ²
Ultrasound (largest diameter)	2.6 (1.5–3.75) ³
Clinical Axillary Status	
Positive	7 (32)
Negative	15 (68)
Axillary Nodal Evaluation	
Fine needle aspiration	2 (9)
Sentinel	1 (5)

Characteristic	N = 22 (%)
Clinical Stage	
I	1 (5)
IIA	14 (64)
IIB	3 (14)
IIIA	3 (14)
Occult primary	1 (5)

Abbreviations: A =Asian-American; AA =African-American; FISH =fluorescent in situ hybridization; IHC = immunohistochemistry; W = white.

^aFour patients, including one with an occult tumor, did not have tumor measurements at physical examination.

^bOne patient had an an occult primary tumor.

Table 2

Toxicity With Exemestane Alone and With Exemestane Plus Celecoxib

Toxicity ^a	Grade 1	Grade 2	Grade 3
exemestane alone	n (%)	n (%)	n (%)
exemestane + celecoxib	n (%)	n (%)	n (%)
Myalgias	1 (5)	0 (0)	0 (0)
	0 (0)	0 (0)	0 (0)
Arthralgias	7 (32)	2 (9)	0 (0)
	2 (9)	3 (14)	0 (0)
Heartburn	0 (0)	0 (0)	0 (0)
	3 (14)	1 (5)	0 (0)
Nausea	1 (5)	0 (0)	0 (0)
	3 (14)	0 (0)	0 (0)
Abdominal Pain	0 (0)	1 (5)	0 (0)
	4 (18)	1 (5)	0 (0)
Constipation	3 (14)	0 (0)	0 (0)
	2 (9)	0 (0)	0 (0)
Diarrhea	1 (5)	0 (0)	0 (0)
	0 (0)	0 (0)	0 (0)
Fatigue	6 (27)	4 (18)	0 (0)
	3 (14)	3 (14)	0 (0)
Hot Flashes	7 (32)	2 (9)	0 (0)
	5 (23)	1 (5)	0 (0)
Rash	0 (0)	0 (0)	0 (0)
	1 (5)	0 (0)	0 (0)
Edema	0 (0)	0 (0)	0 (0)
	2 (9)	0 (0)	0 (0)
Renal Insufficiency	0 (0)	0 (0)	0 (0)
	1 (5)	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)	0 (0)
	2 (9)	0 (0)	2 (9)
Sensory Neuropathy	0 (0)	0 (0)	0 (0)
	1 (5)	0 (0)	0 (0)
Lower GI Bleeding	0 (0)	0 (0)	0 (0)
	2 (9)	0 (0)	0 (0)

Abbreviation: GI = gastrointestinal.

^a n = 22; The same patient could be counted more than once if the same toxicity occurred during treatment with exemestane alone and again when exemestane was combined with celecoxib.

Table 3

Antitumor Efficacy

Best Response	n (%)
Physical Exam	
Complete	0 (0)
Partial	5 (23)
Stable Disease	1 (5)
Progressive Disease	1 (5)
Non-measurable	15 (68)
Ultrasound	
Complete	0 (0)
Partial	8 (36)
Stable Disease	12 (55)
Progressive Disease	1 (5)
Non-measurable	1 (5)
pCR	0 (0)
Nodal Status^a	
Positive	13 (65)
Negative	7 (35)

Abbreviation: pCR = pathological complete responses.

^a n=20, Two patients were excluded because they had chemotherapy before surgery.

Table 4

Comparison of IHC Allred Differences With Neoadjuvant Therapy

Marker	Exemestane + celecoxib (16 wks) vs. Baseline	<i>P</i>	Exemestane (8 wks) vs. Baseline	<i>P</i>
Aromatase				
Number of Pairs	14	.13	9	NA ^a
Median (Range)	0 (−4, +1)		0 (−2, +1)	
ER				
Number of Pairs	19	.003	15	.19
Median (Range)	−1 (−7, 0)		0 (−2, +1)	
PR				
Number of Pairs	19	.002	15	.04
Median (Range)	−5 (−8, +4)		−3 (−8, +5)	
HER-2				
Number of Pairs	19	.39	14	NA ^a
Median (Range)	0 (−3, +6)		0 (−2, +7)	
Ki-67				
Number of Pairs	18	< .001	13	.004
Median (Range)	−2.5 (−6, 0)		−4 (−5, +1)	
COX-2				
Number of Pairs	19	.004	14	.27
Median (Range)	−1 (−6, +1)		0 (−3, +1)	

Abbreviations: ER = estrogen receptor; IHC = immunohistochemistry; NA = not available; PR = progesterone receptor.

^aNA because a statistical test for differences in Allred scores between 8 wks and baseline would only be performed if the statistical test between 16 wks and baseline showed significance at $\alpha=0.05$.

Table 5

Biomarker Changes in Neoadjuvant Endocrine Trials

Trial	Treatment	Clinical Response (%)	Aromatase	ER	PR	Ki-67	COX-2
Current Trial	EXE + celecoxib	36	NoΔ	Dec	Dec	Dec	Dec
IMPACT¹²³	LET	38	ND	NoΔ	Dec	Dec	NA
	TAM	36		Dec	Inc/NoΔ ^a	Dec	
	LET + TAM	40		Dec	NR	Dec	
PROACT²	ANA	40	ND	NoΔ	Dec	ND	NA
	TAM	35					
P024³²⁴	LET	55	Baseline	NoΔ	Dec	Dec	NA
	TAM	36					
CAAN⁶	EXE + celecoxib	62	ND	ND	ND	ND	ND
	EXE	58					
	LET	56					
Tubiana-Hulin²⁵	EXE	73	ND	NoΔ	Dec	Dec	NA
Mustacci⁵	EXE	70	ND	NoΔ	Dec	Dec	NA

Abbreviations: ANA = anastrozole; Dec > significant decrease; ER = estrogen receptor; EXE = exemestane; LET = letrozole; NA = not done; NoΔ = no significant difference; PR = progesterone receptor; TAM = tamoxifen.

^aEarly increase in PR, then return to baseline.