Original Article

Fatigue and Endocrine Symptoms Among Women With Early Breast Cancer Randomized to Endocrine Versus Chemoendocrine Therapy: Results From the TAILORx Patient-Reported Outcomes Substudy

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BACKGROUND: TAILORx (Trial Assigning Individualized Options for Treatment) prospectively assessed fatigue and endocrine symptoms among women with early-stage hormone receptor–positive breast cancer and a midrange risk of recurrence who were randomized to endocrine therapy (E) or chemotherapy followed by endocrine therapy (CT+E). **METHODS:** Participants completed the Functional Assessment of Chronic Illness Therapy–Fatigue, the Patient-Reported Outcomes Measurement Information System–Fatigue Short Form, and the Functional Assessment of Cancer Therapy–Endocrine Symptoms at the baseline and at 3, 6, 12, 24, and 36 months. Linear regression was used to model outcomes on baseline symptoms, treatment, and other factors. **RESULTS:** Participants (n = 458) in both treatment arms reported greater fatigue and endocrine symptoms at early follow-up in comparison with the baseline. The magnitude of change in fatigue was significantly greater for the CT+E arm than the E arm at 3 and 6 months but not at 12, 24, or 36 months. The CT+E arm reported significantly greater changes in endocrine symptoms from the baseline to 3 months in comparison with the E arm; change scores were not significantly different at later time points. Endocrine symptom trajectories by treatment differed by menopausal status, with the effect larger and increasing for postmenopausal patients. **CONCLUSIONS:** Adjuvant CT+E was associated with greater increases in fatigue and endocrine symptoms at early time points in comparison with E. These differences lessened over time, and this demonstrated early chemotherapy effects more than long-term ones. Treatment arm differences in endocrine symptoms were more evident in postmenopausal patients. *Cancer* **2022;128:536-546**. © *2021 American Cancer Society*.

LAY SUMMARY:
• Participants in TAILORx (Trial Assigning Individualized Options for Treatment) with early-stage hormone receptor–positive breast cancer and an intermediate risk of recurrence were randomly assigned to endocrine or chemoendocrine therapy.
• Four hundred fifty-eight women reported fatigue and endocrine symptoms at the baseline and at 3, 6, 12, 24, and 36 months.
• Both groups reported greater symptoms at early follow-up versus the baseline.
• Increases in fatigue were greater for the chemoendocrine group than the endocrine group at 3 and 6 months but not later.
• The chemoendocrine group reported greater changes in endocrine symptoms in comparison with the endocrine group at 3 months but not later.

KEYWORDS: breast neoplasms, drug therapy, fatigue, hormones, patient-reported outcomes.

INTRODUCTION

Breast cancer remains the most common cancer in women,[1] but mortality rates are declining, partially because of widespread adjuvant therapy.[2] Hormone receptor–positive (HR+) cases account for roughly two-thirds of breast cancers and can be treated with chemotherapy and/or endocrine therapy.[3] Although less toxic than chemotherapy, long-term endocrine therapy[4,5] can produce symptoms (arthralgias, vasomotor symptoms, and sexual dysfunction) that affect health-related quality of life (HRQOL)[6] and medication nonadherence,[7,8] which in turn decrease treatment efficacy.[9]

Beyond being acutely toxic, chemotherapy may also result in future health consequences, including persistent fatigue.[10] After the Early Breast Cancer Trialists Group meta-analysis,[11] adjuvant chemotherapy became standard for most localized breast cancers.[12,13] The ensuing overtreatment led to the development of the 21-gene assay[4,14,15] to predict the risk of distant recurrence more accurately than classic clinicopathologic features in patients with HR+ breast cancer[14,16] and the benefit of adding adjuvant chemotherapy to endocrine therapy in that population.[5,7]

TAILORx (Trial Assigning Individualized Options for Treatment) randomized women with early HR+, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer and intermediate recurrence scores (RSs) of 11 to 25 to chemotherapy followed by endocrine therapy (CT+E) or endocrine therapy (E).[17,18] TAILORx demonstrated highly favorable outcomes for patients with RSs of 0 to 25 receiving endocrine therapy, and this indicates that women with intermediate or low RSs can be spared chemotherapy.[16,19] TAILORx provided an unparalleled opportunity to prospectively evaluate the trajectory of HRQOL among women randomized to CT+E versus E for breast cancer.

Patient-reported outcome (PRO) measures are ideal for assessing subjective symptoms and can inform treatment.[20,21] TAILORx allowed us to examine the unique contributions of chemotherapy to fatigue[22] and endocrine symptoms.[6] The substudy's primary objective was to compare those longitudinal patient-reported symptoms among women with early HR+ breast cancer randomized to adjuvant CT+E versus E.

MATERIALS AND METHODS

Design and Participants

The ECOG-ACRIN Cancer Research Group coordinated TAILORx (ClinicalTrials.gov identifier NCT00310180),[17,18] which enrolled patients from April 2006 to October 2010. In January 2010, a PRO substudy was approved by participating institutions' human investigation committees. Eligibility was consistent with TAILORx[17,18]: women 18 to 75 years old diagnosed with HR+, HER2-negative, axillary node–negative breast cancer meeting the guidelines for adjuvant chemotherapy. Participants provided informed consent and completed PRO measures at the baseline (before randomization) and 3, 6, 12, 24, and 36 months afterward. Given that menopausal status was among the TAILORx stratification factors, we conducted subset analyses to examine its relationships with fatigue and endocrine symptoms. We retrieved data in February 2016.

Measures

The Patient-Reported Outcomes Measurement Information System–Fatigue Short Form (PROMIS Fatigue 7) is a 7-item measure of fatigue using a 5-point Likert response scale.[23] PROMIS measures are reported on a T-score metric, with higher scores indicating greater symptomatology. It has demonstrated good precision and reliability.[24] Here, Cronbach's α was 0.874.

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scale is a 13-item measure using a 5-point Likert scale,[25] with higher scores indicating less fatigue (ie, higher HRQOL). It has demonstrated reliability and validity in clinical trials. Cronbach's α was 0.956.

The Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) is a 19-item measure using a 5-point Likert response scale, with higher scores indicating less symptomatology. It has demonstrated suitability for clinical trials.[26] Cronbach's α was 0.844.

Trial participants completed additional PROs (Functional Assessment of Cancer Therapy–Cognitive Function [FACT-Cog],[27,28] Functional Assessment of Cancer Therapy–General,[29] and Assessment of Survivor Concerns[30]), with the results reported separately.[31]

Analysis

Our primary analysis compared TAILORx participants who received the treatments to which they were randomized. These per-protocol analyses excluded patients on the basis of postrandomization treatment decisions, which may introduce bias. To examine their robustness, we also performed intention-to-treat (ITT) analyses. Our primary end points were fatigue and endocrine symptom score differences between the treatment arms at 3 months, with controlling for baseline scores. Most women on CT+E received 12-week regimens and were expected to experience maximum chemotherapy side effects at 3 months. We also examined treatment differences at subsequent time points. The PRO substudy was designed to have 90% power for a 4.5-point difference in the mean change from the baseline to 3 months in FACT-Cog (the primary PRO end point) between CT+E and E[31]; a sample of 235 women per arm was required. We expected comparable power for differences of similar magnitude in the 3 PRO measures examined here.

We computed means and SDs by using all cases at a time point. When comparing treatment arms at time points, the analysis fit a linear model with arm (binary covariate) and baseline levels (continuous linear covariate), with the test and estimated effect based on the coefficient of treatment effect. We also computed mean changes

from the baseline and standard errors. We included only cases with assessments at the baseline and the follow-up time point. We excluded cases with baseline assessments more than 7 days after treatment initiation. We conducted analyses with R 3.5.1.[32]

RESULTS

Sample

Seven hundred thirty-four women enrolled in the PRO substudy (Fig. 1). They had characteristics generally similar to those of the larger TAILORx sample.[31] Participants were eligible to continue on the PRO substudy if they experienced a recurrence or new primary breast cancer while enrolled in TAILORx. Table 1 presents the demographic and clinical characteristics for patients (n = 458) in the per-protocol analysis with data on at least 1 of the PRO measures at the baseline and 3 months. As previously reported, the characteristics of participants in the PRO study, in comparison with the larger trial sample randomized to treatment, were generally very similar, with slightly higher proportions of postmenopausal patients, low RSs, and very small (<1-cm) tumors in the PRO study.[31] The per-protocol data set had slightly lower proportions of older patients, lower RSs, and low-grade and very small tumors in the CT+E arm (such patients may have been more likely to refuse chemotherapy).

Treatment Arm–Related Differences

In the per-protocol analysis, women in CT+E reported significantly greater increases in PROMIS Fatigue 7 scores from the baseline to 3 and 6 months in comparison with women in E; change scores were comparable between the treatment arms at later time points (Table 2). The trajectories of longitudinal PROMIS Fatigue 7 change scores by treatment arm converged more over time because the CT+E arm reported decreased fatigue after a sharp increase after the baseline (while receiving chemotherapy). However, both arms reported more fatigue at all follow-up assessments in comparison with the baseline (Fig. 2A).

Women receiving CT+E reported significantly greater increases in FACIT-Fatigue scale scores from the baseline to 3 months, and approached significantly greater increases in fatigue at 6 months in comparison with women on E; change scores were comparable between treatment arms at later time points (Table 2). Change scores in a negative direction indicated more fatigue. Change scores by treatment arm converged over time because the CT+E arm reported decreased fatigue after chemotherapy (Fig. 2B). However, scores for the

CT+E arm remained worse than baseline scores at all follow-up time points.

Women randomized to CT+E reported significantly greater increases in FACT-ES scores from the baseline to 3 months in comparison with women randomized to E; change scores were not significantly different between the treatment arms at later time points (Table 2). Change scores in a negative direction indicated more symptomatology. Both arms reported significantly more endocrine symptoms at all follow-up assessments in comparison with the baseline (Fig. 2C). For all 3 PROs, we observed similar result patterns in ITT analysis (see Supporting Table 2). Supporting Table 1 presents descriptive statistics for all 3 PROs across time points, and by treatment arm and menopausal status.

Meaningful Change

We calculated the percentages of per-protocol participants whose symptoms meaningfully changed across assessments (Fig. 3). Using a prior approach,[33] we conservatively used 0.5 SD as the threshold for meaningful change. The estimated SD of the baseline PROMIS Fatigue 7 scores was 8.2, so we defined *better* as a decrease of >4.1 points, *same* as a change within ±4.1, and *worse* as an increase of >4.1. At 3 months, 59% of the women receiving CT+E reported worse fatigue, whereas 34% receiving E did; at 6 months, the values were 47% (CT+E) and 33% (E). The magnitude of difference between the arms was lower later (eg, 40% for CT+E vs 36% for E at 12 months). Nevertheless, a sizable proportion of women in both arms reported worsened fatigue at long-term follow-up (35%-44% at 24 and 36 months). We observed similar results with the Functional Assessment of Chronic Illness Therapy–Fatigue. Using an estimated SD of 9.4 for FACT-ES baseline scores (defining: better, an increase of >4.7 points; same, within ±4.7 points; worse, a decrease of >4.7 points), women randomized to CT+E had worsened endocrine therapy–related symptoms at 3 and 6 months (50% and 52%, respectively) in comparison with women randomized to E (39% and 44%, respectively).

Differences by Menopausal Status

We examined symptom change scores by menopausal status. Fatigue trajectories by treatment appeared to be different for premenopausal women and postmenopausal women (Fig. 2A,B), with the effect larger and more persistent for postmenopausal women. Postmenopausal women appeared to have had a larger influence on the overall treatment arm differences in fatigue changes from the baseline to 3 months. Postmenopausal women in
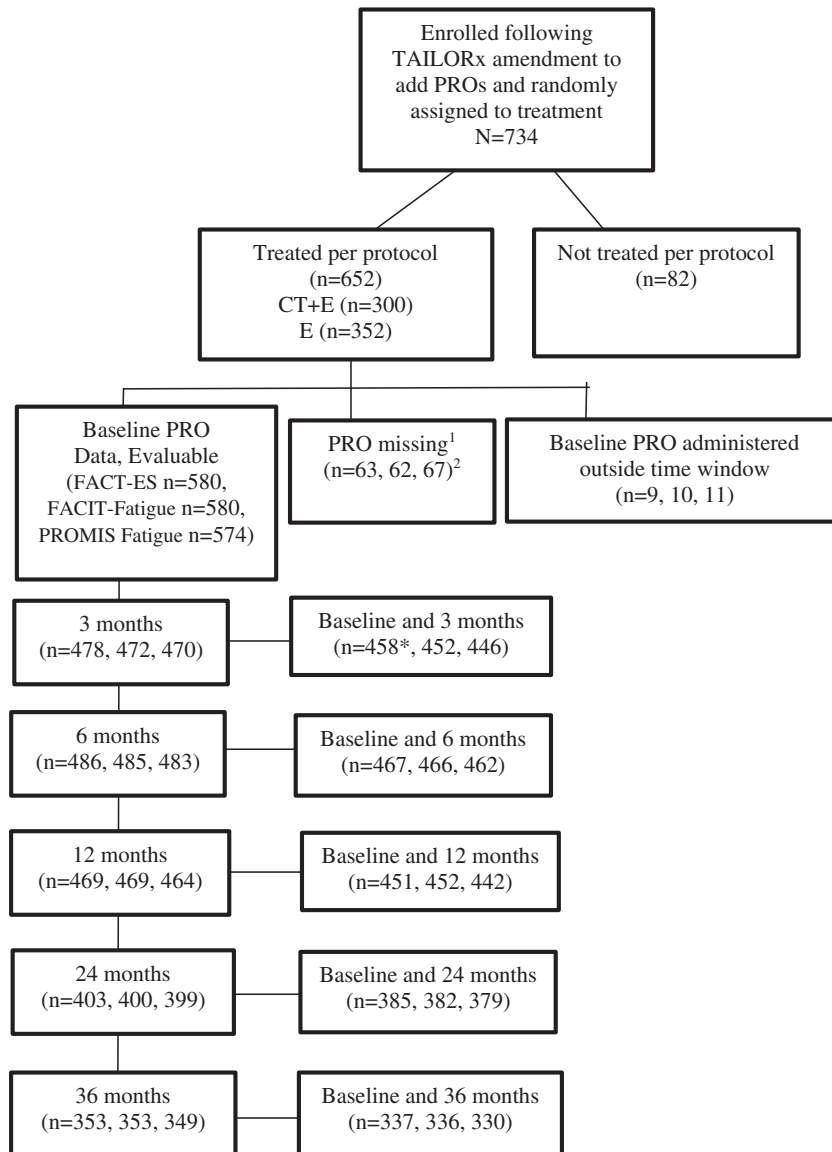
Figure 1. Consolidated Standards of Reporting Trials diagram: TAILORx PRO substudy. [1]The reasons for missing baseline data were as follows: patient not given the PRO form (n = 15), refusal (n = 15), language or disability (n = 14), other (n = 8), and site did not provide reason (n = 11) for FACT-ES; patient not given the PRO form (n = 13), refusal (n = 15), language or disability (n = 14), other (n = 8), and site did not provide reason (n = 12) for FACIT-Fatigue; and patient not given the PRO form (n = 17), refusal (n = 16), language or disability (n = 14), other (n = 9), and site did not provide reason (n = 11) for PROMIS Fatigue. [2]Numbers are presented in the order of FACT-ES, FACIT-Fatigue, and PROMIS Fatigue. *Characteristics of this sample of 458 per-protocol participants, the largest with data on at least 1 of the PRO measures at the baseline and 3 months, are presented in Table 1. CT+E indicates chemotherapy followed by endocrine therapy; E, endocrine therapy; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Symptoms; PRO, patient-reported outcome; PROMIS Fatigue, Patient-Reported Outcomes Measurement Information System–Fatigue; TAILORx, Trial Assigning Individualized Options for Treatment.

the CT+E arm reported significantly higher increases in fatigue in comparison with those in the E arm at 24 months. However, menopause-by-treatment interactions were nonsignificant at all time points for both fatigue measures (Table 2).

Endocrine symptom trajectories by treatment were also different for premenopausal women versus post-menopausal women (Fig. 2C), with the effect larger and increasing over time for postmenopausal women. Menopause-by-treatment interactions were significant at

TABLE 1. Demographic and Clinical Characteristics (n = 458)

Characteristic	E (n = 238)	CT+E (n = 220)
Age, mean (SD), y	56 (9)	55 (8)
Age, No. (%)		
≤50 y	78 (33)	68 (31)
51-65 y	115 (48)	126 (57)
>65 y	45 (19)	26 (12)
Race, No. (%)		
White	196 (82)	181 (82)
Black	15 (6)	13 (6)
Asian	16 (7)	8 (4)
Other/unknown	11 (5)	18 (8)
Ethnicity, No. (%)		
Hispanic	12 (5)	18 (8)
Non-Hispanic	210 (88)	183 (83)
Unknown	16 (7)	19 (9)
Menopause, No. (%)		
Pre	74 (31)	80 (36)
Post	164 (69)	140 (64)
Recurrence score, No. (%)		
11-15	101 (42)	82 (37)
16-20	81 (34)	80 (36)
21-25	56 (24)	58 (26)
Tumor size, No. (%)		
≤1.0 cm	37 (16)	21 (10)
1.1-2.0 cm	149 (63)	140 (64)
2.1-3.0 cm	40 (17)	50 (23)
3.1-4.0 cm	11 (5)	5 (2)
>4.0 cm	1 (0)	4 (2)
Unknown	0	0
Histology grade, No. (%)		
Low	75 (32)	59 (27)
Medium	123 (53)	127 (58)
High	33 (14)	32 (15)
Unknown	7	2
Estrogen receptor, No. (%)		
Negative	0 (0)	0 (0)
Positive	238 (100)	220 (100)
Progesterone receptor, No. (%)		
Negative	14 (6)	18 (8)
Positive	216 (94)	195 (92)
Unknown	8	7
Surgery, No. (%)		
Tumorectomy	175 (74)	152 (69)
Mastectomy	63 (26)	68 (31)
Initial endocrine therapy, No. (%)		
Aromatase inhibitor	139 (58)	127 (58)
Tamoxifen	87 (37)	83 (38)
Tamoxifen and aromatase inhibitor	3 (1)	5 (2)
Ovarian function suppression	7 (3)	0 (0)
Other	1 (0)	0 (0)
None reported	1 (0)	5 (2)
Changed endocrine therapy, No. (%)		
Tamoxifen to aromatase inhibitor	31 (13)	41 (19)
Aromatase inhibitor to tamoxifen	14 (6)	21 (10)
Chemotherapy, No. (%)		
Taxane and cyclophosphamide	—	153 (70)
Anthracycline ± taxane	—	44 (20)

TABLE 1. *Continued*

Characteristic	E (n = 238)	CT+E (n = 220)
Cyclophosphamide, methotrexate and fluorouracil	—	18 (8)
Other	—	5 (2)
None	238 (100)	0 (0)
Comorbidities, No. (%)		
Hypertension		
No	140 (59)	134 (62)
Yes	97 (41)	83 (38)
Unknown	1	3
Hyperlipidemia		
No	165 (70)	164 (76)
Yes	71 (30)	51 (24)
Unknown	2	5
Depression		
No	186 (79)	172 (80)
Yes	50 (21)	43 (20)
Unknown	2	5
Diabetes		
No	210 (89)	192 (89)
Yes	25 (11)	23 (11)
Unknown	3	5
Osteoarthritis		
No	214 (90)	191 (88)
Yes	23 (10)	25 (12)
Unknown	1	4
Osteopenia/osteoporosis		
No	199 (85)	201 (94)
Yes	36 (15)	13 (6)
Unknown	3	6

Abbreviations: CT+E, chemotherapy followed by endocrine therapy; E, endocrine therapy.
The per-protocol analytic data set was specified a priori and consisted of patients (n = 458) with data on at least 1 of the patient-reported outcome measures at the baseline and 3 months.

24 and 36 months (Table 2). Postmenopausal women in the CT+E arm reported significantly higher increases in endocrine symptoms than those in the E arm.

DISCUSSION

Women receiving treatment for early-stage breast cancer commonly report fatigue and endocrine symptoms. Chemotherapy-related fatigue is expected because of known mechanisms of action,[34] and it is often assumed to be reversible a sufficient time from completion. However, long-term data to demonstrate resolution have been lacking and complicated by the receipt of radiation and endocrine therapy. Chemotherapy may also produce endocrine symptoms by inducing transient or persistent ovarian failure in premenopausal patients.[35] Similarly, tamoxifen and aromatase inhibitor (AI) side effects[36] differ by menopausal status.[37]

TAILORx allowed an examination of the unique contribution of chemotherapy to fatigue and endocrine symptoms as well as symptom trajectories extending into

TABLE 2. Per-Protocol Analysis: Changes From the Baseline

Subset	Time Point	No.	E	CT+E	Raw Diff	LM Diff	P for LM
FACT-ES[a]							
All	3 mo	458	–3.61 (0.59)	–5.56 (0.60)	–1.95 (0.84)	–1.62 (0.79)	.04
All	6 mo	467	–4.24 (0.60)	–5.63 (0.55)	–1.39 (0.81)	–0.97 (0.76)	.20
All	12 mo	451	–5.62 (0.67)	–6.96 (0.68)	–1.34 (0.95)	–1.08 (0.90)	.23
All	24 mo	385	–5.31 (0.75)	–6.81 (0.68)	–1.50 (1.02)	–1.05 (0.96)	.27
All	36 mo	337	–5.17 (0.80)	–7.14 (0.85)	–1.97 (1.17)	–1.69 (1.10)	.13
Premenopausal	3 mo	154	–5.96 (1.14)	–7.62 (1.02)	–1.65 (1.53)	–1.44 (1.47)	.33
Premenopausal	6 mo	151	–6.19 (1.15)	–8.34 (1.03)	–2.15 (1.54)	–1.63 (1.45)	.26
Premenopausal	12 mo	148	–8.95 (1.16)	–7.94 (1.28)	1.01 (1.73)	1.06 (1.64)	.52
Premenopausal	24 mo	118	–10.39 (1.53)	–8.29 (1.27)	2.09 (1.99)	2.27 (1.84)	.22
Premenopausal	36 mo	102	–10.84 (1.70)	–8.96 (1.66)	1.88 (2.38)	2.18 (2.25)	.34
Postmenopausal	3 mo	304	–2.55 (0.66)	–4.39 (0.72)	–1.83 (0.98)	–1.49 (0.92)	.11
Postmenopausal	6 mo	316	–3.41 (0.69)	–4.19 (0.61)	–0.78 (0.93)	–0.45 (0.87)	.60
Postmenopausal	12 mo	303	–4.10 (0.79)	–6.45 (0.78)	–2.34 (1.12)	–2.04 (1.06)	.06
Postmenopausal	24 mo	267	–3.23 (0.80)	–6.10 (0.80)	–2.87 (1.13)	–2.39 (1.06)	.03
Postmenopausal	36 mo	235	–2.87 (0.82)	–6.28 (0.97)	–3.41 (1.26)	–3.17 (1.18)	.008
FACIT-Fatigue[b]							
All	3 mo	452	–2.48 (0.66)	–8.77 (0.74)	–6.29 (0.99)	–5.32 (0.94)	.00000002
All	6 mo	466	–1.97 (0.64)	–4.37 (0.61)	–2.40 (0.88)	–1.55 (0.83)	.06
All	12 mo	452	–2.14 (0.70)	–4.01 (0.64)	–1.86 (0.95)	–1.01 (0.87)	.25
All	24 mo	382	–1.49 (0.74)	–4.27 (0.82)	–2.77 (1.11)	–1.76 (1.03)	.09
All	36 mo	336	–1.83 (0.81)	–3.67 (0.88)	–1.84 (1.19)	–0.90 (1.07)	.40
Premenopausal	3 mo	152	–3.87 (1.41)	–8.01 (1.13)	–4.14 (1.79)	–3.11 (1.64)	.06
Premenopausal	6 mo	150	–1.66 (1.19)	–3.26 (0.96)	–1.60 (1.51)	–0.82 (1.43)	.57
Premenopausal	12 mo	149	–1.32 (1.51)	–2.99 (1.14)	–1.67 (1.88)	–1.12 (1.64)	.50
Premenopausal	24 mo	116	–2.52 (1.60)	–2.45 (1.44)	0.07 (2.16)	1.02 (2.07)	.62
Premenopausal	36 mo	102	–2.11 (1.76)	–1.60 (1.71)	0.51 (2.45)	1.46 (2.12)	.49
Postmenopausal	3 mo	300	–1.87 (0.72)	–9.22 (0.96)	–7.35 (1.18)	–6.42 (1.14)	.00000004
Postmenopausal	6 mo	316	–2.10 (0.76)	–4.97 (0.77)	–2.87 (1.09)	–1.99 (1.02)	.05
Postmenopausal	12 mo	303	–2.52 (0.75)	–4.55 (0.76)	–2.03 (1.07)	–1.16 (1.02)	.26
Postmenopausal	24 mo	266	–1.09 (0.82)	–5.14 (1.00)	–4.05 (1.28)	–3.02 (1.17)	.01
Postmenopausal	36 mo	234	–1.71 (0.89)	–4.67 (1.00)	–2.95 (1.34)	–2.01 (1.22)	.10
PROMIS Fatigue[c]							
All	3 mo	446	1.70 (0.44)	6.10 (0.50)	4.39 (0.67)	3.68 (0.63)	.00000001
All	6 mo	462	1.26 (0.44)	3.51 (0.50)	2.25 (0.66)	1.52 (0.62)	.01
All	12 mo	442	1.45 (0.50)	2.76 (0.53)	1.31 (0.73)	0.60 (0.67)	.37
All	24 mo	379	1.34 (0.58)	3.35 (0.61)	2.01 (0.85)	1.11 (0.77)	.15
All	36 mo	330	1.42 (0.61)	2.86 (0.64)	1.44 (0.89)	0.93 (0.80)	.25
Premenopausal	3 mo	150	1.66 (0.85)	7.34 (0.83)	5.69 (1.19)	4.18 (1.13)	.0003
Premenopausal	6 mo	147	1.12 (0.74)	3.50 (0.89)	2.38 (1.16)	0.85 (1.11)	.44
Premenopausal	12 mo	144	0.41 (0.93)	2.92 (0.95)	2.51 (1.33)	1.28 (1.18)	.28
Premenopausal	24 mo	117	1.90 (1.12)	2.68 (1.16)	0.78 (1.61)	–0.74 (1.53)	.63
Premenopausal	36 mo	98	0.73 (1.26)	2.36 (1.06)	1.63 (1.66)	0.41 (1.52)	.79
Postmenopausal	3 mo	296	1.72 (0.52)	5.41 (0.62)	3.69 (0.80)	3.33 (0.76)	.00002
Postmenopausal	6 mo	315	1.32 (0.55)	3.52 (0.60)	2.19 (0.81)	1.83 (0.75)	.02
Postmenopausal	12 mo	298	1.92 (0.59)	2.67 (0.64)	0.75 (0.87)	0.25 (0.82)	.76
Postmenopausal	24 mo	262	1.10 (0.69)	3.68 (0.72)	2.57 (1.00)	1.97 (0.88)	.03
Postmenopausal	36 mo	232	1.70 (0.70)	3.09 (0.81)	1.39 (1.06)	1.21 (0.94)	.20

Abbreviations: ACFB, average change from baseline; LM Diff, linear model difference (estimated treatment difference [CT+E – E] from the linear regression of the score at the time point on treatment and the baseline score); P for LM, P value for the treatment difference from the linear model; Raw Diff, raw difference (arm CT+E ACFB – arm E ACFB).
[a]FACT-ES menopause-by-treatment interactions: $P = .97$, $P = .41$, $P = .11$, $P = .02$, and $P = .02$ at 3, 6, 12, 24, and 36 months, respectively.
[b]FACIT-Fatigue menopause-by-treatment interactions: $P = .13$, $P = .49$, $P = .85$, $P = .06$, and $P = .17$ at 3, 6, 12, 24, and 36 months, respectively.
[c]PROMIS Fatigue menopause by treatment interactions: $P = .42$, $P = .48$, $P = .34$, $P = .08$, and $P = .60$ at 3, 6, 12, 24, and 36 months, respectively.

posttreatment. Symptoms were greater at follow-up time points in comparison with the baseline for both arms. Women on CT+E reported significantly greater increases in fatigue and endocrine symptoms during chemotherapy in comparison with those on E. Although endocrine therapy is assumed to be well tolerated, a considerable proportion of women in both arms reported fatigue at long-term follow-up that exceeded a conservative threshold for meaningful worsening. At 12 to 36 months, increases in fatigue and endocrine symptoms were not significantly different between arms; the trajectories of women on CT+E converged with those of women on E. That there was some fatigue resolution in the chemoendocrine arm should be reassuring to women who may benefit from chemotherapy on the basis of clinicopathologic features and RSs. For women who can safely skip chemotherapy,
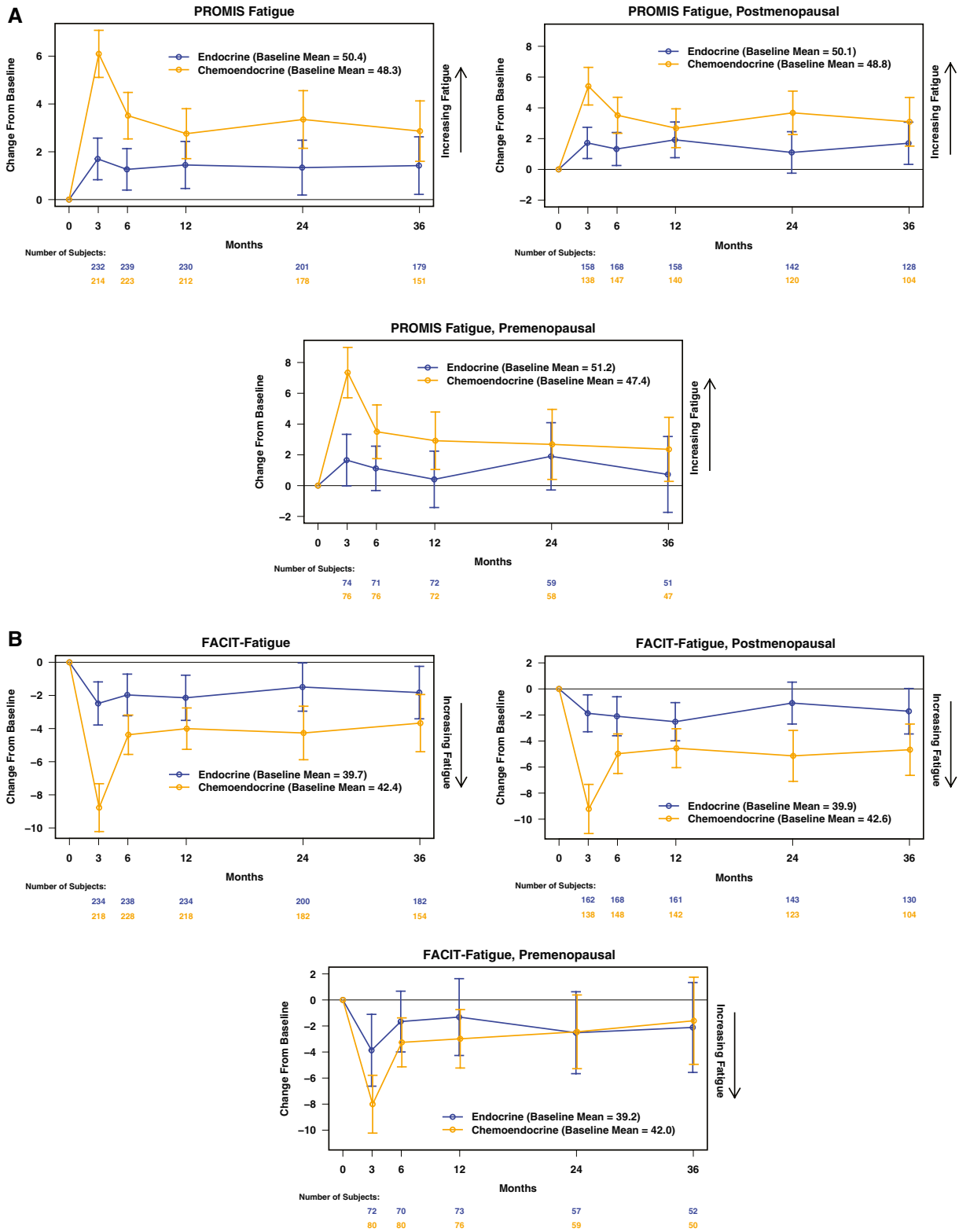
Figure 2. Endocrine and chemoendocrine arms: changes over 36 months. FACIT-Fatigue indicates Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-Endocrine, Functional Assessment of Cancer Therapy–Endocrine Symptoms; PROMIS Fatigue, Patient-Reported Outcomes Measurement Information System–Fatigue.
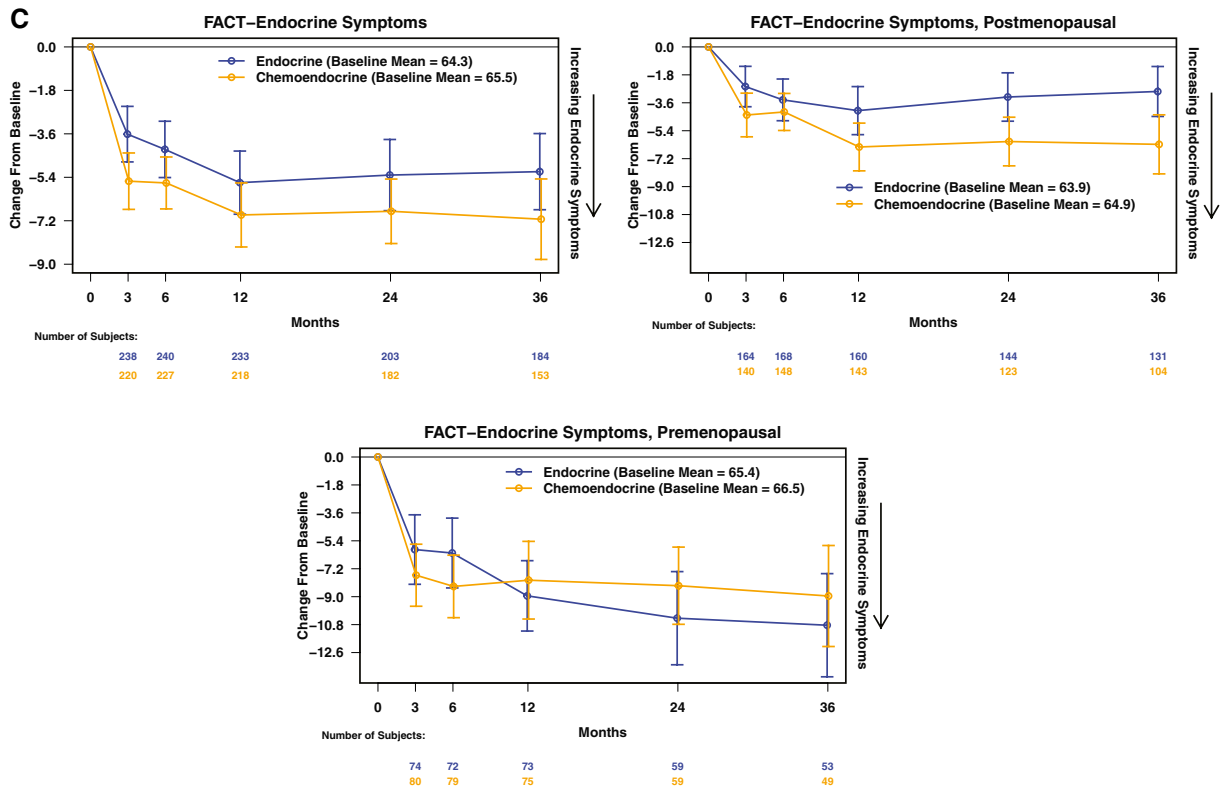
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Figure 2. (Continued).

our findings on the significant, acute chemotherapy-related symptoms support the value of precision-guided therapy sparing unnecessary toxicity.

Treatment arm fatigue trajectories appeared different for pre- and postmenopausal women, with the effect larger and more persistent in the latter, although the differences did not reach statistical significance. The trajectories of endocrine symptoms by treatment also appeared different by menopausal status, with the effect larger and increasing over time for postmenopausal patients, and menopause-by-treatment interactions were significant at later time points. Patients randomized to CT+E began endocrine therapy after completing chemotherapy. Therefore, endocrine symptoms would not develop in the CT+E arm until later time points.

These findings suggest that earlier results demonstrating that prior chemotherapy is associated with greater treatment side effect bother (which predicted a higher risk of early AI discontinuation[38]) may be explained by more endocrine symptoms among women on CT+E. Yet, TAILORx demonstrated a significantly lower risk of early endocrine therapy discontinuation among women on CT+E.[39] Although we speculated that the chronic symptom burden

may diminish endocrine therapy's tolerability,[40] the results indicate that further study is needed. Endocrine therapy adherence remains a complex challenge; interventions must be comprehensive,[41] and PROs have predictive value in identifying women at risk for early discontinuation.[38,42]

This study's strengths include the randomized prospective design, long-term follow-up, and well-validated measures. Limitations include missing data, including some attrition, which may have introduced bias (although we observed overall good retention). Sample characteristics were similar to those of the overall trial, and this supported generalizability. The per-protocol analysis may have introduced bias; however, our ITT analysis yielded similar results. Therapy regimens were selected via clinician judgment, which introduced variability. The majority of women randomized to chemotherapy received docetaxel and cyclophosphamide, so it is possible that we underestimated the symptom burden associated with other regimens. The number of patients receiving particular endocrine treatments was not assessed at all time points. We were unable to evaluate the impact of tamoxifen versus AI treatment in our analyses of menopausal status subgroups. Lastly, we were unable to define the contribution of radiation or surgery.
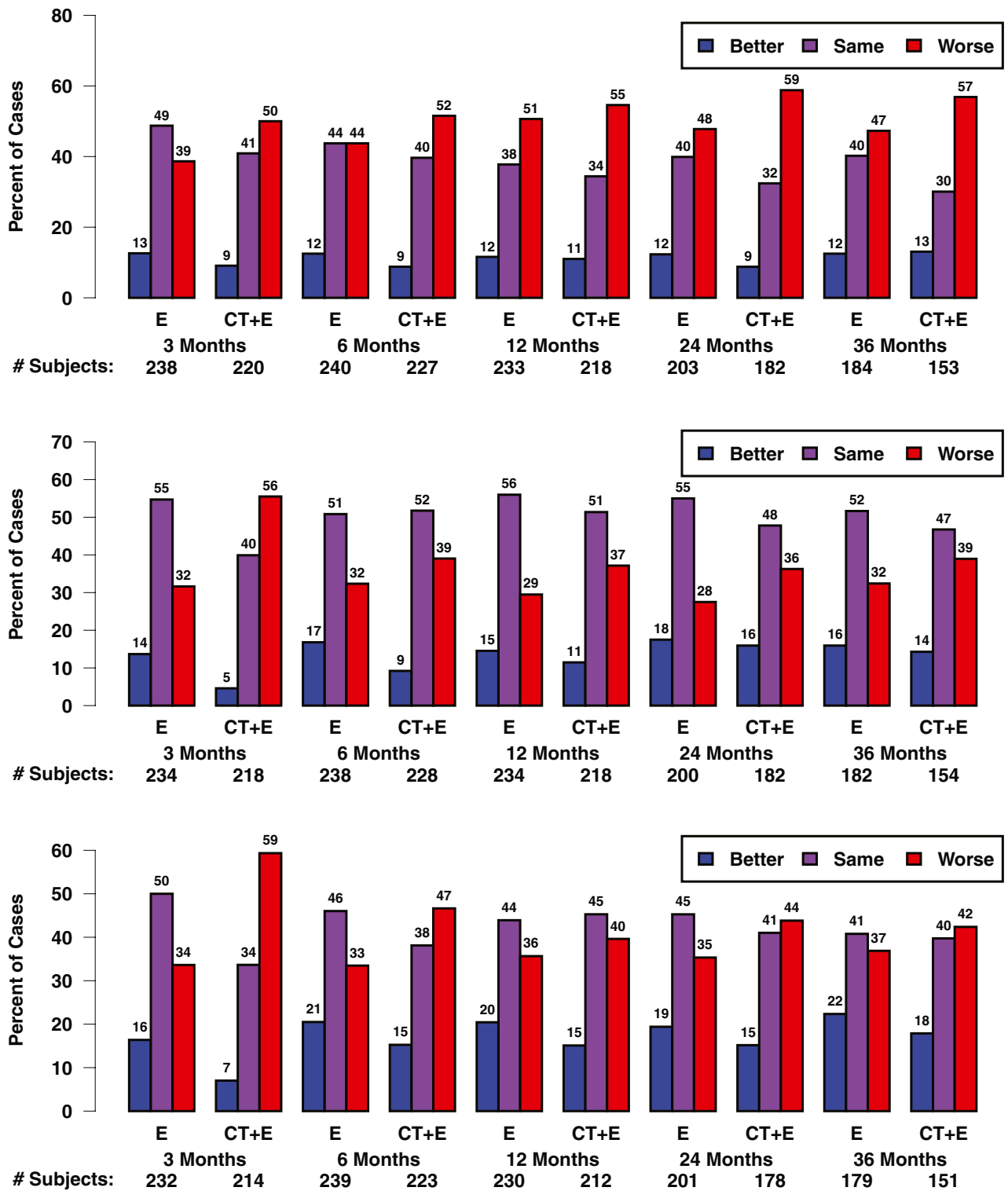
Figure 3. Endocrine and chemoendocrine arms: meaningful changes. CT+E indicates chemotherapy followed by endocrine therapy; E, endocrine therapy.

The results demonstrate the fatigue experienced acutely during chemotherapy and decreasing afterward, long-term endocrine symptom trajectories, and significant proportions of women with persistent symptoms. Our findings support the importance of providing long-term symptom assessment and management. In quantifying the unique contributions of chemotherapy to fatigue and endocrine symptoms, the study results add to the research identifying women with breast cancer unlikely to benefit substantially from chemotherapy with respect to its associated HRQOL impact. The findings illustrate the symptom burden that women with early-stage HR+ breast cancer and intermediate RSs can be spared when they elect to receive endocrine versus chemoendocrine therapy. This study's results also provide valuable longitudinal data on the trajectories of common, distressing symptoms from the patient's perspective.

CONFLICT OF INTEREST DISCLOSURES
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AUTHOR CONTRIBUTIONS
Sofia F. Garcia: Conceptualization, methodology, visualization, writing–original draft, and writing–editing and review. **Robert J. Gray:** Conceptualization, methodology, formal analysis, data curation, visualization, writing–original draft, and writing–editing and review. **Joseph A. Sparano:** Conceptualization, methodology, funding acquisition, and writing–editing and review. **Amye J. Tevaarwerk:** Writing–original draft and writing–editing and review. **Ruth C. Carlos:** Conceptualization, writing–original draft, and writing–editing and review. **Betina Yanez:** Writing–original draft and writing–editing and review. **Ilana F. Gareen:** Writing–editing and review. **Timothy J. Whelan:** Writing–editing and review. **George W. Sledge:** Writing–editing and review. **David Cella:** Conceptualization, writing–original draft, and writing–editing and review. **Lynne I. Wagner:** Conceptualization, methodology, investigation, funding acquisition, writing–original draft, and writing–editing and review.

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