Pregnancy and Menopausal symptoms in Breast Cancer Survivors

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Pregnancy after breast cancer

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Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer

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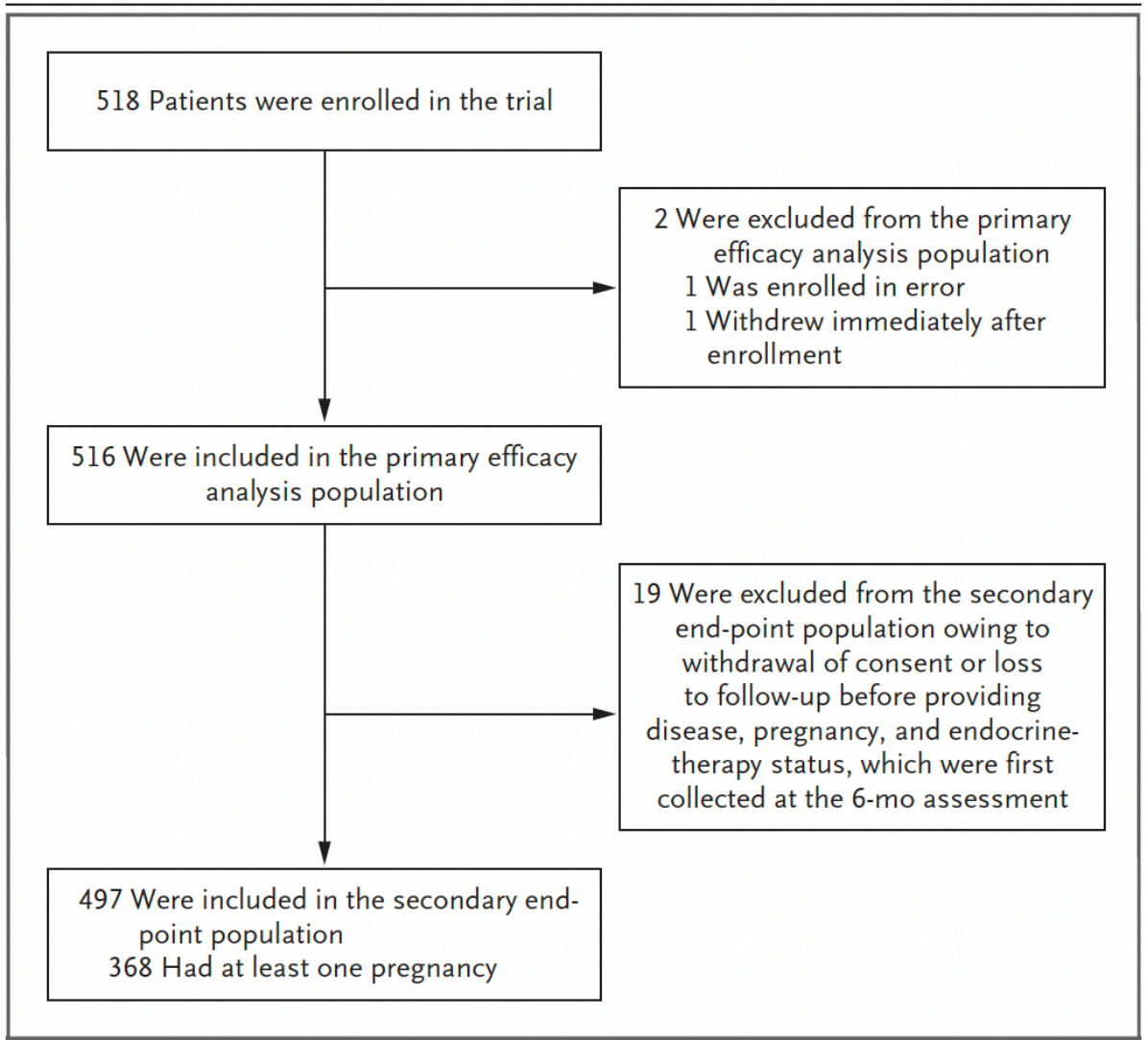


Figure 1. Trial Enrollment and Analysis Populations.

Eligibility / Procedures / End Points

- Women aged 42 years or younger
- Stage I-III HR+ breast cancer, received adjuvant endocrine therapy for 18-30 months
- Wished to temporarily discontinue endocrine therapy to attempt pregnancy
- Could have received previous chemotherapy, with or without fertility preservation
- No clinical evidence of recurrence

- Discontinued endocrine therapy within 1 month before enrollment
- 3-month washout period before attempting pregnancy
- Duration interruption: up to 2 years to allow for attempting pregnancy, conception, delivery, and breast-feeding
- Assisted reproductive technology was allowed, strongly encouraged If pregnancy did not occur after 1 year
- After pregnancy and breast-feeding or after unsuccessful conception, resumption of endocrine therapy to complete the planned 5-10 years was strongly recommended.

- Primary end point: number of breast cancer events: ipsilateral or locoregional invasive disease, distant recurrence, or contralateral invasive breast cancer during the total patient-years of follow-up.
- Prespecified time-to-event end points: freedom from a breast cancer event and freedom from distant breast cancer recurrence
- Secondary end points: ability to become pregnant, pregnancy outcomes, birth outcomes, breast-feeding, use of assisted reproductive technology, resumption of endocrine therapy

Statistical Analysis

- 2% annual risk of a breast cancer event was acceptable (4% was unacceptable) based on SOFT/TEXT
- Planned sample of 500 patients
- Primary analysis planned after 1600 patient-years of follow-up. If 46 or less breast cancer events were observed the interruption of endocrine therapy to attempt pregnancy would be considered safe

External control cohort 1499 patients from SOFT/TEXT who would have been eligible for the POSITIVE trial.

Three methods to compare proportion of patients who were free from breast cancer events and free from distant recurrence of breast cancer in the POSITIVE trial with those in the control cohort.

1) bootstrap matching method
2) direct-comparison method of results in the treatment-interruption group with the results in the unadjusted control cohort
3) Use of multivariable Cox proportional- hazard models, estimated hazard ratios

Table 1. Demographic and Clinical Characteristics in the Treatment-Interruption Group and the Matched Control Cohort.*

Variable	Unadjusted Cohorts		Bootstrap-Matched Cohorts†	
	Treatment-Interruption Group (N=516)‡	Control Cohort (N=1499)	Treatment-Interruption Group	Control Cohort
	number of patients (percent)		*percent*	
Age group — yr§				
<35	177 (34.3)	286 (19.1)	34.3	34.3
35–39	221 (42.8)	573 (38.2)	42.8	42.8
40–42	118 (22.9)	640 (42.7)	22.9	22.9
Race¶				
White	397 (76.9)	1246 (83.1)	76.9	83.9
Non-White	118 (22.9)	236 (15.7)	22.9	14.6
Black	7 (1.4)	—	1.4	—
Asian	90 (17.4)	—	17.4	—
Other	21 (4.1)	—	4.1	—
Unknown	1 (0.2)	17 (1.1)	0.2	1.5
Body-mass index‖				
<25 or unknown	377 (73.1)	905 (60.4)	73.1	73.1
≥25	139 (26.9)	594 (39.6)	26.9	26.9
Previous births				
None	387 (75.0)	415 (27.7)	75.0	33.3
At least one	129 (25.0)	1068 (71.2)	25.0	65.7
Unknown	0	16 (1.1)	0	1.0
Tumor size — cm				
≤2	331 (64.1)	847 (56.5)	64.2	62.3
>2 to ≤5	161 (31.2)	541 (36.1)	31.2	31.2
>5	21 (4.1)	64 (4.3)	4.1	3.5
Unknown	3 (0.6)	47 (3.1)	0.6	3.1
No. of positive lymph nodes				
0	342 (66.3)	794 (53.0)	66.3	66.3
1–3	151 (29.3)	523 (34.9)	29.2	29.3
4–9	23 (4.5)	175 (11.7)	4.4	4.5
Unknown	0	7 (0.5)	0	0
Tumor histologic grade**				
1	89 (17.2)	223 (14.9)	17.3	17.7
2	252 (48.8)	770 (51.4)	48.9	51.2
3	172 (33.3)	478 (31.9)	33.3	29.5
Unknown	3 (0.6)	28 (1.9)	0.6	1.5
Adjuvant endocrine therapy††				
SERM alone	215 (41.7)	315 (21.0)	41.7	24.5
SERM and OFS	184 (35.7)	578 (38.6)	35.7	53.0
AI and OFS	82 (15.9)	495 (33.0)	15.9	18.4
Other	35 (6.8)	111 (7.4)	6.8	4.1
Previous neoadjuvant or adjuvant chemotherapy	320 (62.0)	1140 (76.1)	62.0	63.9

* Data for some characteristics of the control cohort have not been included owing to a lack of comparable data collection or relevance. Percentages may not total 100 because of rounding. AI denotes aromatase inhibitors, OFS ovarian function suppression, and SERM selective estrogen-receptor modulator.

† For each bootstrap iteration, the treatment-interruption group was sampled with replacement. In addition, the control cohort was sampled with replacement to match the bootstrap treatment-interruption group on the basis of the proportional frequencies of the relevant patient, disease, and treatment characteristics of the bootstrap treatment-interruption group. This process was repeated 5000 times (see Section 3.3.2 in the Supplementary Appendix). The percentages shown are the percentages of all patients across all bootstrap iterations according to group and cohort.

‡ Among the 516 patients in the primary efficacy analysis population, 316 (61.2%) were enrolled at a European site, 116 (22.5%) at a North American site, and 84 (16.3%) at a site in the Asia Pacific region. Among the 134 patients who had human epidermal growth factor receptor 2 (HER2)–positive disease, 131 received HER2-targeted treatment.

§ The age used in the analysis in the treatment-interruption group was the age at enrollment. The age used in the analysis in the control cohort was the age after 2 years of adjuvant endocrine therapy.

¶ Race was determined by the investigator.

‖ The body-mass index was unknown in 1.2% of the patients in the treatment-interruption group, in 2.3% of the patients in the control cohort, and in 2.7% of the bootstrap-matched samples.

** Tumor grade was assessed locally as histologic grade 1 (well differentiated), 2 (moderately differentiated), or 3 (poorly differentiated).

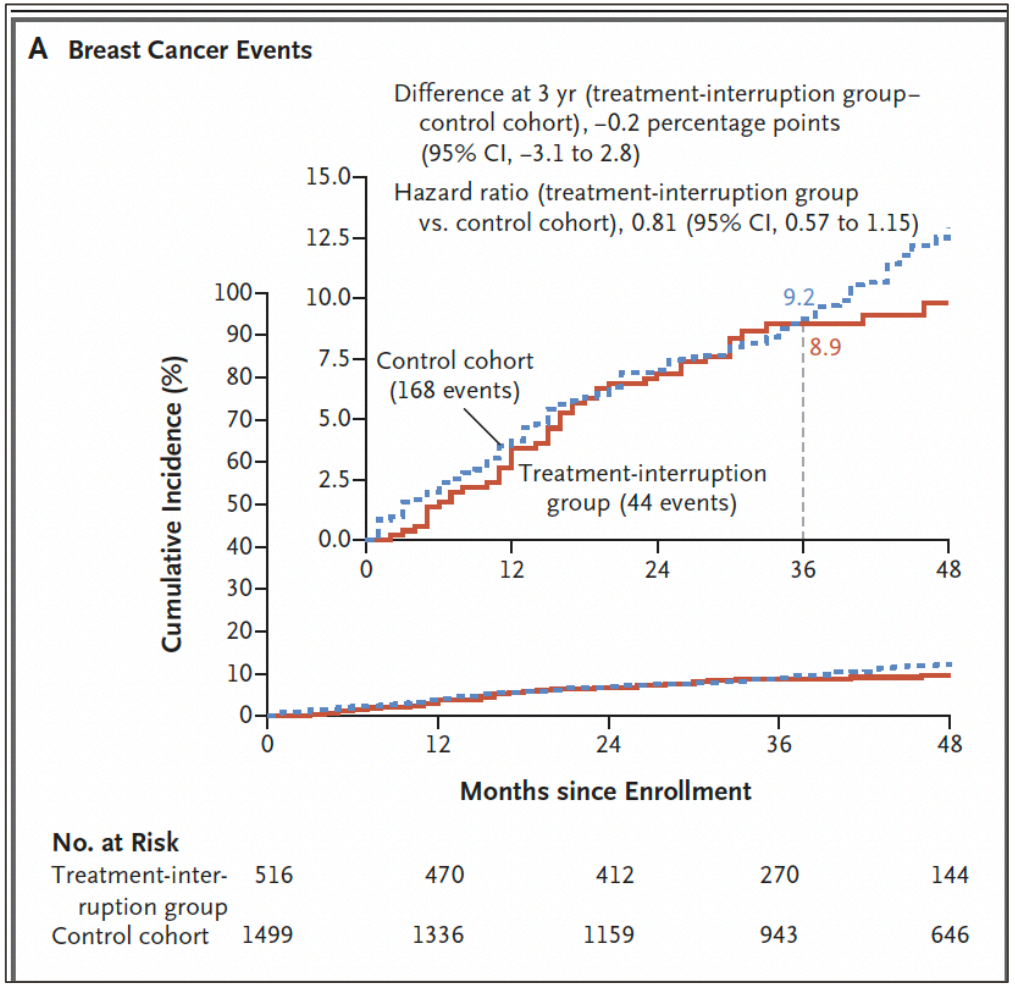
†† Adjuvant endocrine therapy for the treatment-interruption group refers to the adjuvant endocrine therapy that patients had received before enrollment. Patients in the control cohort had received adjuvant endocrine therapy for up to 2 years.

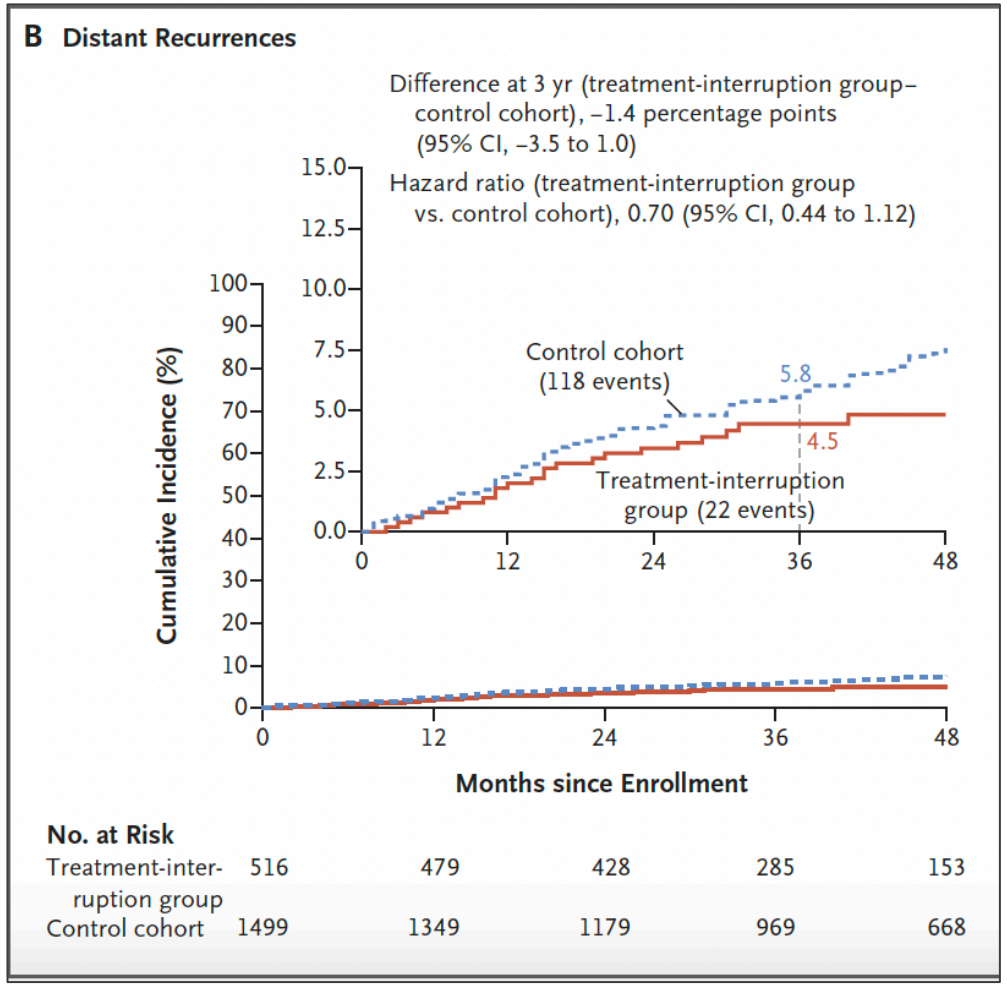
Results

- Median follow up: 41 months
- Median time from breast cancer DX to enrollment: 29 months
- Median age at enrollment: 37 years (range, 27-43), 34% <35 years
- 93% stage I-II disease; 29% had 1-3+LNs, 4.5% had 4-9 +LNs
- 62% had received chemotherapy
- 73% had resumed endocrine therapy at some point after interruption (50% within 26 months)

- 44 patients in the treatment-interruption group had a breast cancer event, (safety threshold 46 events)
- 3-year incidence of breast cancer events 8.9% (95%CI, 6.3 to 11.6) compared to 9.2% (95%CI, 7.6 to 10.8) in the external control cohort
- 22 distant recurrences, 3-year incidence of 4.5% (95% CI, 2.7 to 6.4) compared to 5.8% (95% CI, 4.5 to 7.2) in the control cohort
- Nothing outstanding in the subgroup analysis

Figure 2. Cumulative Incidence of Breast Cancer Events and Distant Recurrences





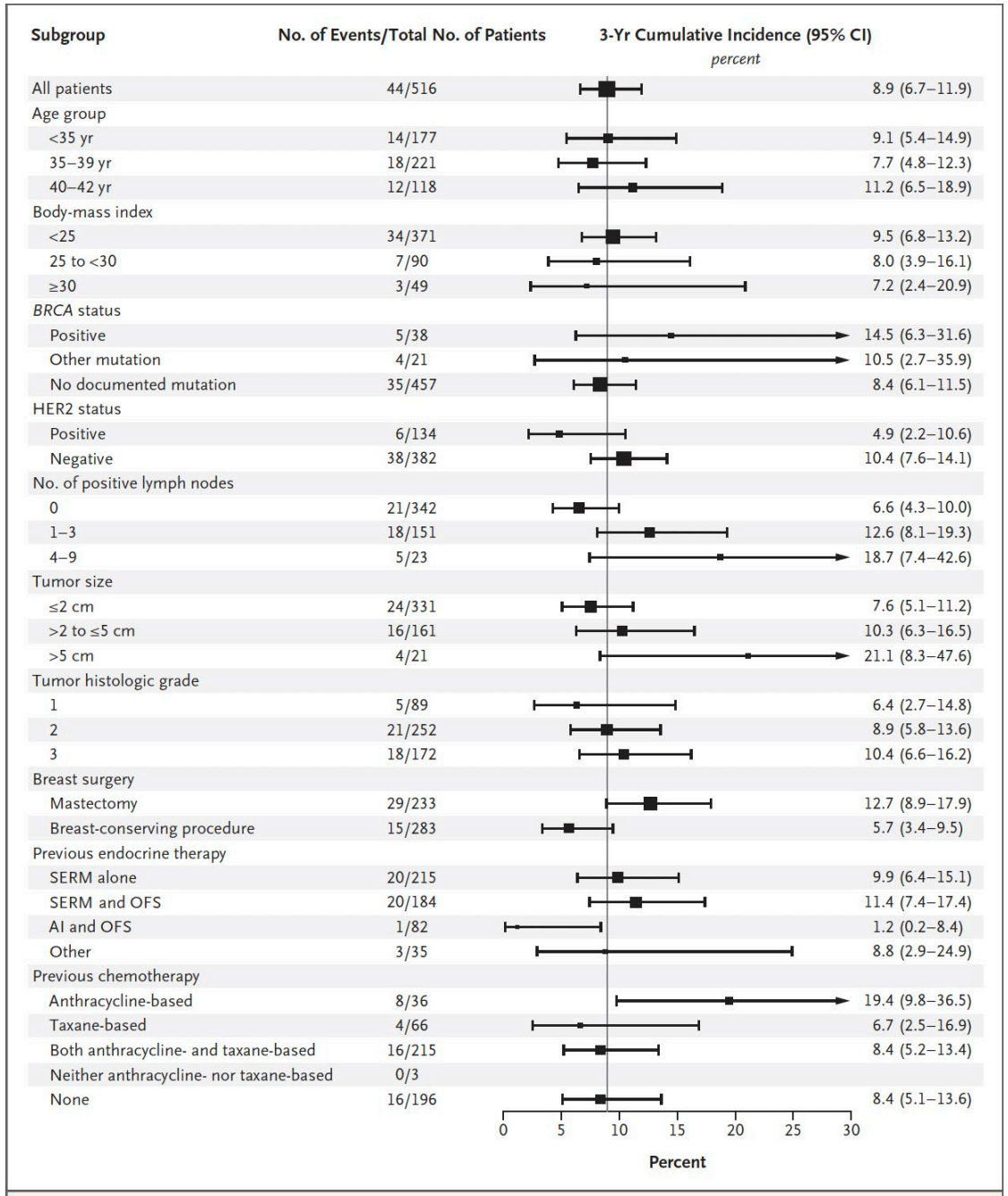


Figure 3. Cumulative Incidence of Breast Cancer Events at 3 Years, According to Demographic and Disease Characteristics and Previous Treatment.

Pregnancy outcomes

Table 2. Pregnancy Outcomes in Patients with at Least One Pregnancy during the Trial.*

Outcome That Occurred at Least Once	Patients with ≥1 Pregnancy (N=368)
	no. (%)
Live birth, full-term or preterm	317 (86.1)†
Full-term live birth	292 (79.3)
Preterm live birth	27 (7.3)
Miscarriage	93 (25.3)
Elective abortion	16 (4.3)
Stillbirth	1 (0.3)
Neonatal death	1 (0.3)

- Younger age was the only factor that was substantially related to successful pregnancy: 86% of <35 y/o becoming pregnant; 76% 35-39 y/o; 53% 40-42 y/o
- 43% used assisted reproductive technology
- Cumulative incidence of first pregnancy: 29% at 6 months from enrollment, 54% at 12 months, and 71% at 24 months
- 317/497 (64%) had a least one live birth
- 11% of pregnant patients reported at least one pregnancy complication

Discussion

- Although endocrine therapy for 5-10 years substantially improves disease outcomes in patients with HR+ early breast cancer, a temporary interruption to attempt pregnancy does not appear to have an appreciable negative short-term effect.
- Women were enrolled at least 18 months after initiation of chemotherapy, the proportion of women with pregnancy complications are consistent with those of populations of women of a similar age who did not have breast cancer.
- Incidence of birth defects was low (2.2% of 365 offspring) and consistent with general population estimates.
- The proportion of patients who had not resumed therapy (15.4%) appears similar to reported among young patients in previous trials.

Menopausal symptoms in breast cancer survivors

Menopausal symptoms

- Many breast cancer survivors may experience symptoms whether they have ovarian function or not.
- Peri- or premenopausal survivors who have become amenorrheic and later develop vaginal bleeding, serial estradiol, FSH, LH levels can be useful to determine return of ovarian function.
- Survivors who have become amenorrheic and are sexually active should be counseled on the need for contraception to prevent unintended pregnancy if they do not meet the definition of menopause.
- Definition of Menopause: no menses for 1-year in the absence of prior chemotherapy or tamoxifen use, or no menses after BSO.

Menopausal Signs and Symptoms

- Vasomotor symptoms (hot flashes/night sweats)
- Vaginal dryness
- Urogenital complaints
- Sexual dysfunction
- Sleep disturbance
- Mood disturbance and depression
- Cognitive dysfunction
- Arthralgias/myalgias
- Fatigue
- Related health risks: Osteoporosis, CV disease, cognitive changes

Hormone-Related Symptoms

Assessment

- Rule out other etiologies (i.e., thyroid disease, diabetes)
- Assess serial estradiol, testosterone, FSH, LH, and/or prolactin levels as clinically indicated
- For vaginal dryness, consider pelvic evaluation to assess for vaginal atrophy

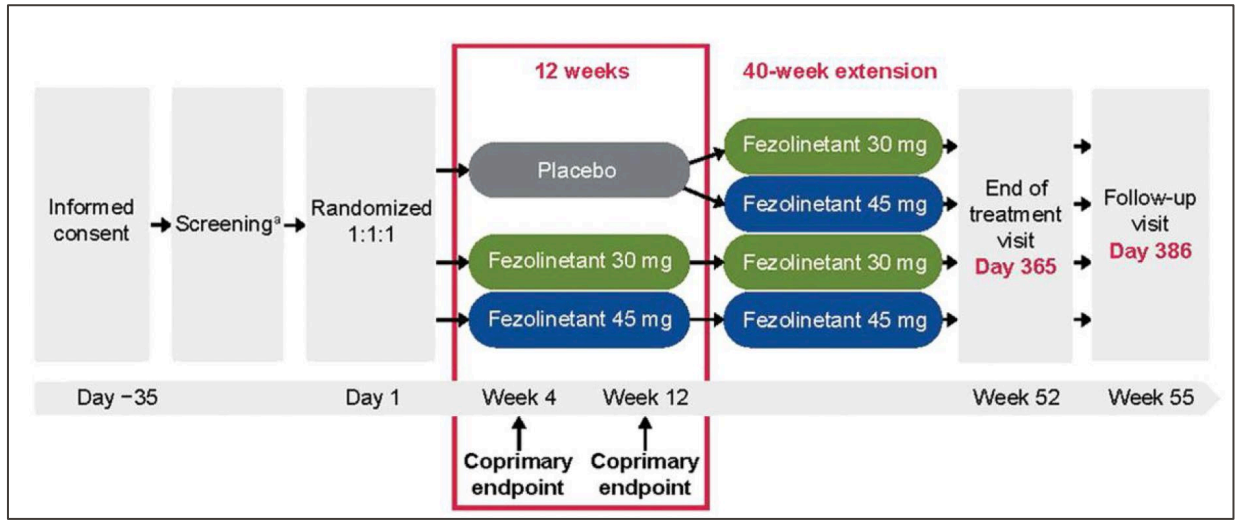
Principles

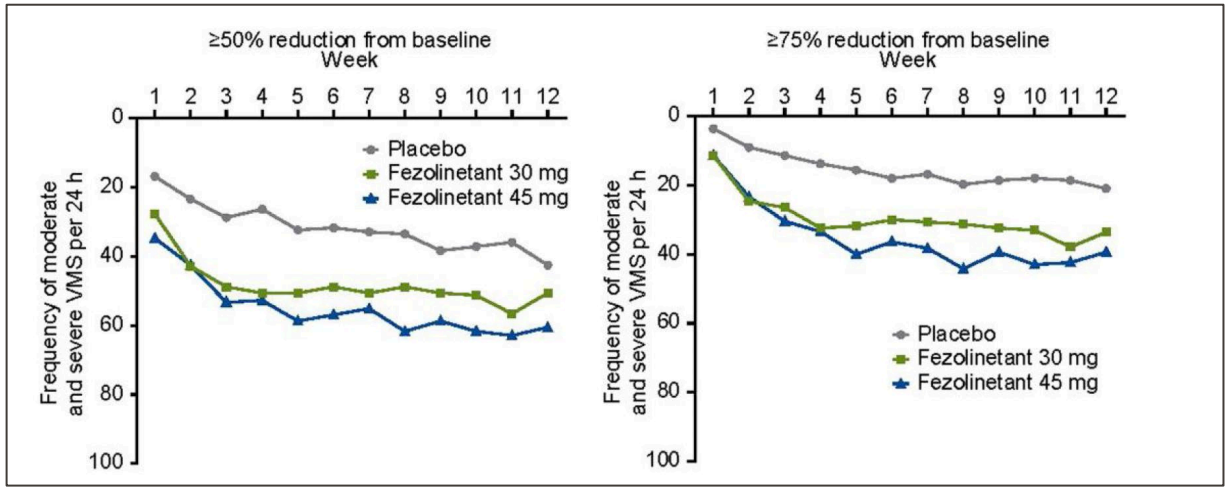
- Hormone systemic therapy is contraindicated in breast cancer survivors of HR+ disease
- Non-hormonal pharmacological treatments include antidepressants, neuropathic pain relievers (gabapentin), clonidine, oxybutynin, fezolinetant (selective neurokinin-3 NK3 receptor antagonist)
- Non-pharmacologic treatments include weight loss, exercise, acupuncture, decrease alcohol intake, integrative therapies (yoga, CBT, hypnosis)

Vaginal dryness

- Non-hormonal treatments: Vaginal moisturizers, vaginal gels, hyaluronic acid, oils; recommended as first line.
- Local estrogen treatment (i.e., rings, suppositories, creams): Limited data in breast cancer survivors suggest minimal systemic absorption with rings and suppositories. Therefore, if estrogen-based treatment is warranted, rings and suppositories are preferred over creams for survivors of HR+ breast cancer.
- Vaginal estrogen and vaginal testosterone preparations can be used in managing vaginal atrophy, but safety has not been established for use in patients with or survivors of HR+ breast cancers.

Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: 2 Phase 3 RCT (SKYLIGHT 1 and 2)





- Declining estrogen levels alters the activity of the thermoregulatory center in the hypothalamus.
- Fezolinetant is a nonhormonal selective neurokinin-3 receptor (NK3R) antagonist that blocks NKB binding restoring normal sensitivity of the thermoregulatory center
- Double-blind, placebo controlled, phase 3, two doses (30-mg, 45-mg)
- Both doses significantly reduced VMS
- Common AEs: elevated LFTs (1.8%), nausea (2.4%), dry mouth (2.4%), headache (3%)
- No breast cancer survivors

Discussion

- Many breast cancer survivors may experience symptoms whether they have ovarian function or not.
- Definition of Menopause: no menses for 1-year in the absence of prior chemotherapy or tamoxifen use, or no menses after BSO.
- There are multiple menopausal signs and symptoms and related health risks.
- Rule out other etiologies
- Hormone systemic therapy is contraindicated in breast cancer survivors of HR+ disease
- Consider non-hormonal pharmacological or non-pharmacological treatments
- Vaginal estrogen preparations can be used in vaginal atrophy, but safety has not been established for use in patients with or survivors of HR+ breast cancers
- New medication Fezolinetant: breast cancer survivors were not included in the clinical trials; financial toxicity