

Nonhormonal Treatments for Menopause-Associated Symptoms in Breast Cancer Survivors: Emerging Therapies

A review centered on elinzanetant and other novel approaches for managing hot flashes and vasomotor symptoms.

Introduction [Header]

A. The burden of vasomotor symptoms (VMS) in breast cancer survivors (BCS)

- Vasomotor symptoms (VMS)—hot flashes and night sweats—are among the most common and distressing adverse effects experienced by BCS, with substantial impacts on quality of life (QOL).^{1–6}
- The prevalence of VMS ranged from 50% (127 of 253) to 85% (170 of 200) of women in some cohorts, with variation based on severity.^{5–10}
- **Endocrine therapies (ET)-induced VMS:** In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, hot flashes occurred in 35.7% of women receiving anastrozole (an aromatase inhibitor) and 40.9% receiving tamoxifen (a selective estrogen receptor modulator [SERM]).⁷
- **Care gap:** Only a subset of women experiencing VMS pursue interventions.^{4–6,8}
- Impact on oncologic adherence: VMS are a common reason for discontinuation of curative-intent ET.^{9–14}

B. The therapeutic gap: Hormone Replacement Therapy (HRT) is contraindicated.

- Two randomized controlled trials— Hormonal Replacement Therapy After Breast Cancer—Is It Safe (HABITS)¹⁵($n=434$) and Stockholm¹⁶($n=378$) —of combined estrogen–progestin therapy showed increased recurrence risk (Hazard Ratio [HR] 3.50; 95% CI, 1.50–8.10, and HR, 1.80; 95% CI, 1.03–3.10, respectively); both trials were stopped early for harm.
- The Livial Intervention Following Breast Cancer: Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) trial ($n=3,148$; 2009) of tibolone showed an increased recurrence overall (HR, 1.40; 95% CI, 1.14–1.70; $P = .0009$).¹⁷
- Nonhormonal pharmacologic options provide only low to moderate efficacy^{18–21}, and adverse effects plus drug-drug interactions with adjuvant ET limit their use^{22,23}, highlighting the need for effective, durable, hormone-free alternatives that do not compromise ET.

Mechanism-Targeted Pharmacologic Interventions [Header]

A. Neurobiological pathophysiology of VMS

- VMS arise from dysregulation within the hypothalamic thermoregulatory center.²⁴
- KNDy neurons—co-expressing kisspeptin, neurokinin B, dynorphin, and the neurokinin-1 (NK1R) and neurokinin-3 receptors (NK3R)—are central to thermoregulatory control.^{24,25}
- Figure 1. Role of the KNDy Neuron Signaling Pathway in VMS.

B. The neurokinin pathway: mechanism of novel non-hormonal therapies

- **Fezolinetant:** An FDA-approved selective NK3R antagonist for the treatment of moderate-to-severe VMS.²⁶ Pivotal phase 3 studies excluded women with a history of breast cancer²⁶; consequently, the use of fezolinetant in BCS is off-label.
- **Elinzanetant:** An FDA-approved dual antagonist that blocks both NK1R and NK3R.

Elinzanetant: A Dual-Targeted Solution for Breast Cancer Survivors [Header]

A. Clinical efficacy: Pivotal phase 3 data in BCS for Overall Assessment of efficacy and Safety of elinzanetant In patients with vasomotor Symptoms (OASIS)-4 trial.

- **Trial design:** OASIS-4 (NCT05587296) is a phase 3 study evaluating elinzanetant in women aged 18–70 years with moderate-to-severe ET-associated VMS.^{27,28}
- **Primary end points:** Elinzanetant 120 mg once daily produced statistically significant reductions in the frequency of moderate-to-severe VMS vs. placebo at weeks 4 and 12.²⁸
- **Secondary end points:** Reductions in VMS severity at weeks 4 and 12, with overall improvements in health-related quality of life (QOL).²⁸

B. Safety profile and pharmacovigilance

- In OASIS-4 (BCS population) trial, the safety profile was consistent with that observed in the general population of menopausal women (data from OASIS-1, -2, and -3 trials).^{29,30}
- OASIS-3 showed no meaningful changes in bone mineral density or turnover markers and no hepatotoxicity or endometrial hyperplasia over 52 weeks—key considerations for BCS.²⁹
- **Drug-drug interactions:** Strong cytochrome P450 3A4 (CYP3A4) inducers (e.g., carbamazepine) can markedly reduce elinzanetant exposure and may compromise efficacy.³¹
- Table 1: Critical Drug-Drug Interactions with Elinzanetant.
- **Regulatory status:** The FDA has approved elinzanetant (Lynkuet) for the management of moderate-to-severe VMS for BCS.³² Regulators in the UK and Canada have also approved elinzanetant.

Other Novel Therapies (latest to oldest) [Header]

- **Peripheral thermoregulatory modulation —wrist cooling device:** In BCS with VMS, a wrist-worn cooling device (KÜLKUF) reduced severe hot flashes by 41% from baseline (95% CI, 18–74; $P < .02$), demonstrating clinical and statistical significance.³³
- **Other nonhormonal options** include Cognitive Behavioral Therapy (CBT),³⁴ hypnosis.^{35,36} Drugs such as venlafaxine (serotonin-norepinephrine reuptake inhibitors [SNRI]),^{20,37} oxybutynin (anticholinergic),²¹ and gabapentin,^{18,35,37} have also shown some efficacy in randomized trials for BCS.
- **Table 2: Summary of Key Clinical Trials.**

Conclusions [Header]

Elinzanetant specifically establishes a new clinical benchmark for safety and efficacy in this critically underserved group, provided that forthcoming detailed pharmacokinetic data confirm minimal interference with the metabolism of concomitant endocrine therapies.

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