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Review Article

Does estrogen play a role in response to adjuvant bone-targeted therapies?

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ABSTRACT

Bone remains the most common site of breast cancer recurrence. The results of population studies, preclinical research and clinical studies in patients with metastatic disease provided a rationale for testing bone-targeted agents in the adjuvant setting. Despite the initial optimism, results from eight prospectively designed, randomized control studies powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting. Data have shown that, where benefit exists, it tends to be in women with a "low estrogen environment", either through menopause or suppression of ovarian function. In this manuscript, we review clinical data supporting the hypothesis that estrogen levels may play a part in explaining the response of patients to bone-targeted agents in the adjuvant setting. The results presented to date suggest that there may be data supporting a unifying role for estrogen in adjuvant trials. However, in the absence of any prospective randomized trials in which estrogen data has been systematically collected we cannot specifically answer this question. We await the results of the Oxford overview analysis of individual patient data with interest.

1. Introduction

In recent years there has been increasing interest in the role of bone-targeted agents, such as bisphosphonates (BP) and denosumab, as adjuvant therapies for breast cancer. The results of large randomized trials with BPs have been variable showing either; benefit [1–3], no benefit [4–7] or harm [8]. However, subgroup analyses have consistently shown that, where benefit exists, it is in women with a "low estrogen environment" either through menopause or suppression of ovarian function. In this manuscript, we review the link between estrogen and breast cancer risk and the hypothesis that estrogen levels may in part explain the response of patients to bone-targeted agents in the adjuvant setting.

2. Estrogen and breast cancer link

The pivotal role of cyclical estrogens in breast cancer risk is well recognized. This has been shown in epidemiological studies where risk is related to earlier age at menarche, later age at first birth and menopause, and parity [9,10]. Breastfeeding is protective and is theorized to be secondary to increased prolactin secretion and subsequent suppression of estrogen production [11–13]. Studies on hormone replacement therapy (HRT) have shown increased risk of breast cancer while receiving combined estrogen and progesterone hormone replacement [14,15] and, interestingly, a fall in risk on discontinuation [15–17]. Obesity has also been shown to increase breast cancer risk in postmenopausal women, which is likely due to adipose tissue facilitating the conversion of adrenally secreted dehydroepiandrosterone (DHEA) into estrogen, leading to elevated estrogen levels [18].

In addition, several studies note that higher serum levels of estrogen in postmenopausal women are associated with increased breast cancer risk [19–23]. A meta-analysis of nine prospective studies, with data on 2428 predominantly postmenopausal women, 663 with breast cancer, demonstrated a roughly twofold higher risk of breast cancer in women with higher serum estrogen (2nd–4th quartiles) compared to those with lower levels (1st quartile) [24].

3. Estrogen and bone

The importance of estrogen is maintaining bone health is well recognized [25,26]. The bone microenvironment is dynamic with

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on-going remodeling through the activity of both osteoclasts (bone resorption) and osteoblasts (bone formation). Osteoclastogenesis is tightly regulated by the receptor activator of nuclear factor kappa B ligand (RANKL), receptor activator of nuclear factor kappa B (RANK) and osteoprotegerin (OPG) system. RANKL is a protein synthesized by preosteoblast cells. When these proteins bind to their receptors (RANK) on osteoclast precursor cells, they stimulate osteoclast differentiation and activation, resulting in bone resorption [27,28]. Preosteoblast cells also express OPG, a soluble decoy receptor that binds to RANKL and blocks the interaction between RANKL and its receptor RANK, thereby inhibiting osteoclastogenesis [29,30]. OPG is also known to induce apoptosis in mature osteoclasts, further limiting bone resorption [31].

The amount of bone resorption is dependent on the balance between RANKL and OPG. Many cytokines and hormones are involved in regulation of the RANKL/RANK/OPG system, including sex steroids [27,30]. Estrogen is known to inhibit RANKL production [27,30], and stimulate the production of OPG [32,33]. Thus, estrogen deficient states result in increased RANKL production, which in turn overwhelms the OPG decoy receptors. This results in greater osteoclastogenesis and excessive bone resorption, which may eventually lead to reduced bone density. Throughout this process, growth factors are released into the bone microenvironment, which is hypothesized to result in tumor cell proliferation and survival [34,35]. Thus, in estrogen deficient states, increased release of growth factors driven by increased osteoclastic resorption activity may provide a favorable environment for tumor growth and progression. As such, bone-targeted therapies such as BPs that inhibit osteoclast activation, should in theory limit growth factor release and hence tumor cell proliferation.

4. Bisphosphonate use and breast cancer risk

BPs are commonly used in the management of postmenopausal osteoporosis. They consist of two phosphate groups, which give them a high affinity to bone. They attach to bone at exposed calcium hydroxyapatite binding sites, which are most accessible at sites of bone resorption. During bone turnover, BPs are released causing inhibition of osteoclast-mediated bone resorption [36,37]. In addition, BPs are known to decrease osteoclast development and recruitment as well as promote osteoclast apoptosis [38,39]. Through these mechanisms, BPs have shown to both increase bone mineral density (BMD) and decrease osteoporotic fractures [40–43].

Several studies also suggest that postmenopausal women on oral BPs for osteoporosis have a reduced risk of breast cancer incidence [44–46]. In theory, the reduction in osteoclast-resorption limits growth factor release into the bone microenvironment, which may limit cancer cells from proliferating and developing into malignant tumors. Furthermore, there are data which suggest BPs have direct anti-tumor effects [47,48].

A large study, the Woman's Health Initiative (WHI), included 154,768 women, 2816 of whom were taking oral BPs for osteoporosis at the time of enrollment. After 7.8 years of follow-up, multivariate analysis demonstrated a 32% risk reduction ($P<0.01$) in the incidence of invasive breast cancer and a 30% reduction ($P=0.02$) in the risk of estrogen receptor (ER) positive breast cancer in postmenopausal women on oral BPs compared to those not on BP therapy [44].

Rennert et al. observed similar results in their population-based, case-control study of 4039 postmenopausal women taking oral BPs, 1832 who were diagnosed with breast cancer [46]. A 28% relative risk reduction in the incidence of breast cancer was observed with the use of BPs for greater than one year. A significantly greater number of breast cancers were ER positive and were less frequently poorly differentiated tumors. Newcomb et al.'s population based, case-cohort study ($N=5911$) yielded comparable results [45]. Multivariate analysis demonstrated a significant reduction in the risk of breast cancer with BP use (OR 0.67; 95% CI 0.51–0.89). There was increased benefit with increasing duration of BP therapy. Interestingly, benefit was only observed in non-obese women (BMI < 30 kg/m^2).

5. Pre-clinical studies

In pre-clinical studies, BPs have shown anti-tumor effects directly through inhibition of tumor proliferation and induction of apoptosis, and indirectly, through their ability to inhibit tumor cell adhesion and invasion of the extra-cellular bone matrix, and their anti-angiogenic and immunomodulatory effects [48–51]. Pre-clinical animal studies have demonstrated a reduction in the development of new bone metastases with preventative and therapeutic dosing of BPs [52–58], as well as inhibition of the progression of existing bone metastases with therapeutic dosing [54,56,58].

6. Advance disease clinical trials

In patients with bone metastatic disease, studies have shown BPs to decrease the incidence of skeletal related events, delay the onset of these complications, and reduce bone pain [59–61]. There is also evidence that they may improve overall survival in subgroups of patients with advanced cancers [62].

7. Adjuvant bisphosphonate trials

These studies provided a rationale for testing bone-targeted agents in the adjuvant setting. Despite the initial optimism, results from eight large prospective randomized control studies powered to assess the value of adjuvant bone-targeted therapy in early breast cancer are conflicting (Table 1) [1–8,63]. These studies results are outlined below. However, subgroup analyses from these studies have shown that women with a “low estrogen environment,” either through menopause or suppression of ovarian function, tend to derive greater benefit from adjuvant BP treatment [64].

7.1. Powles study

Powles et al. were the first to show a survival benefit with the use of adjuvant BP in early breast cancer patients [1]. A total of 1069 women with stages I–III breast cancer were randomized to either two years of oral clodronate or placebo following surgery, radiotherapy and adjuvant chemotherapy. Results from this study showed that patients treated with two years of clodronate had a 41% reduction in the risk of developing bone metastases at five years ($P=0.043$). Additionally, there was a survival advantage in the clodronate arm with a 23% risk reduction in death with a median follow-up of 5.6 years ($P=0.048$). These benefits appear to be limited to postmenopausal patients or those with positive ER status. Results of subgroup analyses demonstrated a significant reduction in bone metastases at two-years ($P=0.017$) and a trend towards significance at five-years ($P=0.056$) in postmenopausal patients treated with two years of adjuvant clodronate therapy versus the premenopausal subgroup, which showed no benefit with clodronate on the risk of bone metastases either at two-years ($P=0.448$) or five-years ($P=0.334$).

Table 1
Summary of adjuvant bisphosphonate studies. Adapted from Clemons M, Russell K, Costa L, Addison CL, with permission [58].

Trial	Treatment arm	Bisphosphonate/ dosing used	Cohort size	Hormone receptor			Menopausal status			Trial outcome
				Positive	Negative	Unknown	Pre	Post	Unknown	
Powles et al. [1]	Bisphosphonate	Clodronate, 1600 mg daily orally for 2 yr	530	46%	26%	28%	50%	50%	-	**Positive**—reduced incidence of bone metastases and trend for better OS at 5 yr
	Placebo	Yes	539	45%	25%	30%	49%	51%	-	
Coleman et al. [5,60]	Bisphosphonate	4 mg zoledronic acid IV every 3–4wk for 6 cycles, then every 3–6 m for 5 yr	1681	79%	21%	0.8%	45%	46%†	10%	**Negative**—no differences in OS, DFS at 5 yr - increased invasive-disease-free survival and OS in woman postmenopausal at least 5 yr
	Placebo	No	1678	78%	21%	0.4%	45%	46%†	9%	
Paterson et al. [6]	Bisphosphonate	Clodronate, 1600 mg orally daily for 3 yr	1662	75%#	NR	NR	NR	65%#	NR	**Negative**—no differences in OS or DFS at 8 yr
	Placebo	Yes	1661	75%#	NR	NR	NR	65%#	NR	
Gnant et al. [2]	Bisphosphonate	4 mg zoledronic acid IV every 6 m for 3 yr	900	94.6%	3.3%	2.1%	NR	NR	-	**Positive**—increased DFS and OS at 8 yr in patients > 40 yr of age
	Placebo	No	903	93.3%	3.9%	2.6%	NR	NR	-	
Diel et al. [3]	Bisphosphonate	Clodronate, 1600 mg daily orally for 2 yr	157	75%	25%*		36%	39%	-	**Positive**—increased OS at 8.5 yr
	Placebo	No	145	71%	20%*		64%	61%	-	
Kristensen et al. [4]	Bisphosphonate	Pamidronate, 150 mg orally twice a day for 4 yr	460	14%	60%	26%	67%	33%	0%	**Negative**—no differences in OS, DFS or incidence of metastases at 5 yr
	Placebo	No	493	17%	53%	30%	66%	34%	0.2%	
Mobus et al. [7]	Bisphosphonate	Ibandronate, 50 mg daily orally for 2 yr	1873	75%*	NR	NR	50%#	NR	NR	**Negative—**no differences in OS or DFS at 5 yr
	Placebo	No	998	75%*	NR	NR	50%#	NR	NR	
Saarto et al. [8]	Bisphosphonate	Clodronate, 1600 mg orally daily for 3 yr	139	61%	35%	4%	48%	52%	-	**Negative**—no significant differences in OS or frequency of metastases at 10 yr - decreased DFS and increased extraskeletal metastases in clodronate group at 10 yr
	Placebo	No	143	68%	23%	9%	57%	43%	-	

NR – Not Reported.

* Not originally reported therefore may contain Negative and Unknown categories.

† Originally reported as postmenopausal < 5 yr and > 5 yr but here is represented as combined for total percentage of post-menopausal patients.

Values taken from meeting abstract/presentation so need final publication to confirm values.

7.2. AZURE

The AZURE trial, although a negative study overall, did show benefit with adjuvant BP therapy in women who had been in menopause for at least five years [5]. A total of 3360 women were randomized to either five years of adjuvant zoledronic acid (ZA) or control in addition to standard adjuvant treatment. After a median follow-up of 59 months, no significant differences in the DFS or OS were seen between the ZA and control arms. However, subgroup analyses did show that women postmenopausal for greater than five years, had a superior invasive-disease-free survival (IDFS) when treated with adjuvant ZA in addition to standard adjuvant therapy (HR 0.75, 95% CI 0.59–0.96, $P=0.02$). The five-year survival rate in postmenopausal women was also superior in the ZA arm at 84.6% compared to 78.7% in the control group, with a 26% reduced risk of death (82 vs. 111 deaths; $P=0.04$). A follow-up biomarker analysis using serum collected and stored on 872 AZURE patients for use in future translational research showed a trend towards benefit with the use of ZA in biochemically postmenopausal women [65]. Women with an estradiol level < 50 pmol/l had a 21% risk reduction in time to distant recurrence compared to a 56% increased risk in women with estradiol levels ≥50 pmol/l ($P=0.056$). These results further substantiate the theory that benefits from BPs are dependent on a "low estrogen environment".

7.3. NSABP B-34

Similar to the AZURE trial, data from the National Surgical Adjuvant Breast and Bowel Project protocol B-34 (NSABP-34) demonstrated superior benefit with adjuvant BP in the postmenopausal patient population [6]. Over three thousand patients with operable, stages I–III breast cancer were randomized to three years of oral clodronate or placebo. With a median follow-up of 90.7 months, no differences were seen between the groups for DFS, OS, recurrence-free interval or bone metastasis-free interval. A 26% ($P=0.047$) increase in the non-bone metastasis-free interval was seen in the clodronate group compared to placebo. Although benefit with adjuvant BP therapy was limited to NBMFI, subgroup analyses showed women 50 years or older treated with adjuvant BP therapy had superior recurrence-free interval ($P=0.045$), bone metastasis-free interval ($P=0.027$) and non-bone metastasis-free interval ($P=0.014$) compared to placebo which, similar to other studies, suggests greater derived benefit from BPs in "low estrogen states".

7.4. ABCSG-12

Benefit of adjuvant BPs in a "low estrogen" patient population was also demonstrated in the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) [2]. This large randomized, open-label, two-by-two factorial trial enrolled 1803 pre-menopausal women with early stage (stage I–II), ER and/or PR positive breast cancers. All patients were treated with goserelin, a luteinizing hormone releasing hormone (LHRH) agonist, with the intent of achieving castrate estrogen levels. They were then randomized to receive either tamoxifen or anastrozole with or without ZA for three years. After a 62-month follow-up, a 32% improvement in DFS ($P=0.009$) was observed in patients treated with ZA in addition to adjuvant hormonal therapy compared to adjuvant tamoxifen or anastrozole alone. No difference was seen in overall survival (OS).

7.5. DIEL study

Diel et al. demonstrated benefit with adjuvant BP treatment [3]. In this trial, 302 women with operable breast cancer who had evidence of disseminated tumor cells on bone marrow aspirate and hence were at high risk of relapse were enrolled and randomized to adjuvant clodronate or to the control arm. After 36 months of follow-up, there was a significant reduction in the incidence of distant metastases, bone metastases, visceral metastases, as well as a significant survival advantage in patients treated with adjuvant BP therapy. At the 103 month follow-up, benefit was limited to improved OS with a 20.3% reduction in mortality ($P=0.049$) in the BP arm. Although no subgroup analyses to evaluate pre- versus post-menopausal status were performed, the majority of patient enrolled were postmenopausal (61–64%).

7.6. KRISTENSEN study

In contrast, no benefit from adjuvant BP therapy was observed by Kristensen et al. in which 953 women with node negative, operable breast cancer were randomized to four years of oral pamidronate or control after surgery, adjuvant chemotherapy, +/− radiotherapy [4]. Interestingly, adjuvant hormonal therapy was avoided in this trial. Both pre- and postmenopausal women were enrolled; however ER positive, post-menopausal women were excluded from the study. Postmenopausal women accounted for approximately one third of patients in both groups. After ten years of follow-up, there were no differences in incidence of bone metastases or OS between groups.

7.7. GAIN study

Similarly, the phase III, German Adjuvant Intergroup Node Positive (GAIN) study failed to show any survival advantage with adjuvant BPs, even subgroup analyses of the postmenopausal population. In this trial, 3023 node positive, breast cancer patients were initially randomized to intense dose-dense epirubicin, paclitaxel and cyclophosphamide (iddETC) or conventionally dosed epirubicin and paclitaxel (ET) [7]. Patients then underwent a second randomization to two years of adjuvant ibandronate or control. Approximately 52% of patients were postmenopausal. Results from this study failed to show benefit from adjuvant BPs. No significant differences between the ibandronate and observation groups were evident in the three-year DFS or OS. Subgroup analyses failed to show any benefit in three-year DFS with adjuvant BP treatment in the postmenopausal cohort ($P=0.462$). These results suggest that the efficacy of adjuvant BPs may be dependent on more than just a “low estrogen environment,” or that different BPs are differentially affected by low estrogen.

7.8. SAARTO study

Saarto et al.'s trial was the only one to demonstrate harmful effects with adjuvant BP treatment [8]. This study enrolled 299 women with axillary node positive breast cancer and randomized them to either oral adjuvant clodronate for three years or control. Premenopausal women were treated with chemotherapy, whereas postmenopausal women were treated with adjuvant hormonal therapy with tamoxifen or toremifene. Baseline characteristics revealed a greater proportion of ER positive patients in the control group at 68% compared to 61% in the clodronate group, as well as fewer postmenopausal patients in the control arm (43%) versus the clodronate arm (52%). At ten-year follow-up, there was no significant difference in bone metastases between treatment arms, however those treated with BPs were found to do worse with increased extra-skeletal metastases and a reduced DFS. Extra-skeletal metastases were significantly higher in the treatment cohort ($P=0.004$), with 50% of patients on clodronate therapy developing local or visceral recurrence compared to only 36% of the control patients.

Ten-year DFS was also significantly lower in the clodronate arm (50%) versus patients in the control arm (64%; $P=0.004$). Subgroup analyses interestingly demonstrated that postmenopausal, ER positive women were the only subgroup not to have a negative effect from three years of adjuvant clodronate therapy, again raising the question of the importance of the patient's “estrogen environment.” All other subgroups including ER positive and negative premenopausal patients and ER negative postmenopausal patients did worse when treated with adjuvant clodronate. It is unclear whether the imbalance in ER status and menopausal status between the treatment and control arms played a role in the final results. Furthermore, treatment varied between premenopausal (adjuvant chemotherapy) and post-menopausal patients (adjuvant hormonal therapy), which may have also impacted these findings [66–68].

8. Predictors of benefit from bisphosphonates

Randomized control studies of adjuvant BP therapy in early breast cancer show benefit related to “low estrogen states” [1,2,5,6]. Unfortunately, thus far, only one study has assessed systemic estrogen levels to substantiate these results. This is clearly going to remain an issue as accurate assays for estradiol measurement in postmenopausal women [69–71] and women on aromatase inhibitors in particular are not widely available [72]. We therefore have to explore the literature for evidence to support this hypothesis. It is known that postmenopausal women go through two phases of bone loss: an initial accelerated phase in early menopause, followed by a more gradual, continuous phase [26]. The greatest loss of bone mineral density (BMD) has been shown to occur within the first five years of menopause during the early phase, when estrogen levels dramatically decline compared to premenopausal levels [73,74]. Bone turnover markers are highest in perimenopausal women and significantly decrease with increasing age [75]. This suggests that early postmenopausal women would be at the highest risk of breast cancer recurrence to the bone during this period given the rate of bone turnover and increased release of growth factors, creating a fertile environment for tumor growth. Contrary to expectations, subgroup analysis from the AZURE trial only showed a significant improvement in IDFS and OS at 5-years in women treated with adjuvant zolendronic acid who where postmenopausal for five years or more compared to the control arm. This suggests that the benefit of adjuvant BPs in early breast cancer patients may depend on more than simply a “low estrogen environment”.

9. Biomarker studies

Studies on predictive markers for developing bone metastases have been done to identify those early breast cancer patients at highest risk for disease recurrence [76–78]. The bone microenvironment is constantly in flux through continuous resorption and formation (bone turnover). This process releases bone turnover markers (BTM) into the serum, such as C-terminal telopeptide (CTx), which can be measured giving an estimate of the rate of bone turnover [79]. Growth factors are also mobilized through this process, which is hypothesized to provide a favorable environment for tumor cells to proliferate [34,35]. In theory, elevated levels of BTMs may predict the risk of early breast cancer patients developing bone metastases and would be clinically useful.

The MA.14 phase III clinical trial, set out to explore this question. Pre-treatment serum CTx concentrations were collected from 621 primary breast cancer patients who were treated with adjuvant tamoxifen with or without octreotide with the aim of testing the ability of this marker at predicting disease recurrence [78]. After a median 7.9 years of follow-up, 123 of 621 (19.8%) patients developed breast cancer recurrence and of those, 19 had isolated bone metastases. Analysis of patients with bone-only disease showed a significantly shorter recurrence-free survival (RFS) in those with elevated pretreatment serum CTx concentrations. This suggests that increased bone turnover provides a favorable environment for breast cancer and that CTx may be a good predictive marker for developing bone metastases in patients with early breast cancer.

Recent research has explored the utility of the BTMs procollagen type I N-terminal propeptide (P1NP), osteocalcin, IL-6 and CTx, as markers to predict bone metastases in stage I-III breast cancer patients [76]. This study showed that elevated serum P1NP levels (≥75 ng/ml) predicted a 2.7 fold increase in the risk of bone metastases ($P=0.031$) and a significant decrease in OS ($P=0.031$) in this patient population. CTx surprisingly did not demonstrate any correlation with bone metastases despite the MA.14 results [78] and other studies showing elevated CTx levels in patients with bone metastases [77,80].

In contrast, data from a follow-up biomarker analysis from the AZURE trial presented at the 2012 San Antonio Breast Cancer Symposium showed that vitamin D levels and not BTMs predict risk of breast cancer relapse in women with early breast cancer [65]. In the study, patient with high baseline levels of 25-OH vitamin D (30 ng/ml) had a significantly lower risk of developing bone metastases (HR 0.11; $P=0.0257$). Both P1NP and CTx levels however, failed to demonstrate any association with bone relapse. These findings demonstrate that predicting risk of breast cancer recurrence is clearly complex and a single predictor marker may not be an effective strategy.

Further complicating matters is that although menopause can increase serum BTMs, other normal physiological conditions, certain disease states, and drugs are also associated with elevated BTM concentrations [81–83]. Low body-mass index (BMI) is a risk factor for low bone density [84] and evidence has shown that women with low BMIs have higher BTM levels consistent with elevated bone resorption under these conditions [82]. Alcoholism and smoking are also associated with elevated BTMs [81,82]. There is a diurnal variation in bone turnover too, with peak rates of turnover in the early morning with subsequent elevated serum BTMs at these times [83].

10. Conclusion

Overall, despite extensive pre-clinical and clinical rationale for the benefits of adjuvant bone-targeted therapies, the results of the adjuvant trials have not met expectations. Indeed, the multiple deficiencies of the animal models used in this setting have led authors to question their validity as pre-clinical models for patient studies [85]. Given the thousands of patients enrolled on these studies this is clearly disappointing and the results from studies prospectively designed and powered to show adjuvant benefit on the whole have been resoundingly negative. Similar to the situation with any targeted agent such as endocrine therapy or trastuzumab-based studies, it is important to identify whether or not a population of patients exists within the main study population that might derive greater benefit from the treatment. Although the data presented to date suggest enhanced benefit in post-menopausal patients or those with a so called “low estrogen environment”, definitive studies supporting this are lacking. Linking bone, adjuvant BPs and the estrogen environment could lead to the development of a unifying hypothesis to explain the results of different trials and to help us target appropriate patients in the future.

In this review we have highlighted data supporting the importance of estrogen in normal bone physiology. We have looked at adjuvant BP trials in early breast cancer patients and shown that one study and subgroup analyses from three other trials demonstrate a benefit of adjuvant BP in postmenopausal women as well as one trial showing harm in premenopausal and ER negative postmenopausal women. Trying to link estrogen and cancer treatment is however complex in the absence of prospectively collected serum estrogen levels.

Unfortunately, no randomized control studies in this population are currently planned, and anticipated results from the remaining studies SWOG 0307, D-CARE study and NATAN trial will not be able to formally answer the question of the role of estrogen in response to adjuvant bone-targeted therapy. While groups will likely continue to publish meta-analyses of the published data [64] we eagerly await the results of the Oxford overview analysis of individual patient data to see if we can tease out whether estrogen levels play a role in the efficacy of bone-targeted therapies in adjuvant breast cancer treatment.

Conflict of interest

The authors declare that there are no conflicts of interest.

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