

Effect of (Neo)adjuvant zoledronic acid on disease-free and overall survival in clinical stage II/III breast cancer

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BACKGROUND: Despite neoadjuvant/adjuvant chemotherapy, women with resectable stage II/III breast cancer (BC) have high risk of recurrent disease. Recent data suggest that zoledronic acid (ZOL) therapy concurrent with adjuvant treatments may improve cancer-related outcomes in patients with BC.

METHODS: Disease-free survival (DFS; secondary end point) and overall survival (OS; tertiary end point) were evaluated in 119 women with stage II/III BC randomised to intravenous ZOL 4 mg every 3 weeks for 1 year or no ZOL (control) starting with the first chemotherapy cycle.

RESULTS: At 61.9 months' median follow-up, there was no significant difference in recurrence or survival between study arms. However, time to recurrence or death (DFS) was significantly different between subgroups defined by oestrogen receptor (ER) status (interaction $P=0.010$ for DFS and 0.025 for OS). Hazard ratios (HRs) for disease recurrence and death were significantly less among patients with ER-negative (ER⁻) tumours who received ZOL vs no ZOL (DFS: HR = 0.361, 95% confidence interval (CI) 0.148, 0.880; OS: HR = 0.375, 95% CI 0.143, 0.985).

CONCLUSION: ZOL administered with chemotherapy may improve DFS and OS in a subset of BC patients with ER⁻ tumours. This study was not powered to compare subgroups of patients; thus, these findings should be considered hypothesis generating.

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Breast cancer (BC) is the most commonly diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide (Ferlay *et al*, 2010). Despite the use of neoadjuvant and adjuvant therapies in patients with localised BC, recent trials report ~8% incidence of disease recurrence overall within the first few years after treatment, with even higher recurrence rates for patients with certain BC subtypes (Gnant *et al*, 2009; Eidtmann *et al*, 2010). The development of recurrent disease is thought to be the result of persistent micro-metastatic disease that is chemotherapy resistant (Pantel *et al*, 2009). The presence and persistence of disseminated tumour cells (DTCs), also known as bone marrow micro-metastases, have been associated with poor outcomes and recurrent disease in patients with early-stage BC, regardless of hormone receptor status and other established prognostic features such as nodal status (Braun *et al*, 2005). We and others have reported that the bone-targeted bisphosphonate, zoledronic acid (ZOL), which is currently used to treat osteoporosis and to reduce the risk of skeletal morbidity in patients with bone metastases, can also reduce the persistence of DTCs in the bone marrow of women with early BC (Lin *et al*, 2008; Solomayer *et al*, 2009; Aft *et al*, 2010; Rack *et al*, 2010).

Zoledronic acid has been reported to decrease tumour burden in the breast when administered with neoadjuvant chemotherapy (Coleman *et al*, 2010). In addition, we observed that subsets of patients with triple-negative BC were more likely to have a pathologic complete response (pCR) to neoadjuvant chemotherapy if they received concurrent ZOL, suggesting that bisphosphonates may provide potential anti-cancer benefits in addition to their established bone-protective activities (Neville-Webbe *et al*, 2010). Numerous studies have evaluated the impact of bisphosphonates on disease-free survival (DFS) and overall survival (OS) in localised BC. Although the results have been mixed, consensus is emerging that certain subsets of patients with early-stage BC may benefit from bisphosphonate therapy. Zoledronic acid administration increased DFS in premenopausal women with oestrogen receptor-positive (ER⁺) BC who were treated with ovarian suppression and endocrine-targeted therapies (Gnant *et al*, 2011a). Likewise, ZOL increased DFS in postmenopausal women with ER⁺ tumours who received endocrine-targeted therapies (Eidtmann *et al*, 2010; Coleman *et al*, 2011). The mechanisms of the anti-cancer effects of bisphosphonates are under intense investigation.

In this study, we report the effect of ZOL administered every 3 weeks for 1 year, beginning at the start of neoadjuvant chemotherapy, on DFS and OS outcomes in a phase II trial of 120 women with stage II/III BC, which included pre- and postmenopausal women and patients with ER⁺ and ER-negative (ER⁻) tumours (Aft *et al*, 2010).

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PATIENTS AND METHODS

Patients

Eligible patients had clinical stage II/III ($\geq T2$ and/or $\geq N1$) newly diagnosed BC with inclusion of all tumour biomarker subtypes, Eastern Cooperative Oncology Group performance status score of 0 or 1, and normal cardiac, renal and liver function. Menopausal status was defined as 1 year with no menstrual activity, previous bilateral oophorectomy, or age > 56 years. Inclusion criteria for this study were as previously described (Aft *et al*, 2010).

Study design and treatment

This single-centre, open-label, phase II trial evaluated the efficacy and safety of adding ZOL to standard therapy in women with stage II/III BC. This study is registered with ClinicalTrials.gov, NCT00242203. Eligible women were randomly assigned to receive either 4 mg intravenous ZOL every 3 weeks for 1 year (total 17 doses) commencing with the first dose of chemotherapy, or no ZOL (chemotherapy alone; Figure 1). The randomisation process was as previously described (Aft *et al*, 2010).

The primary end point was the number of patients with detectable DTCs in bone marrow, measured at baseline, 3 months (after four cycles of chemotherapy), and 12 months. These results have been reported earlier (Aft *et al*, 2010). Respective secondary and tertiary end points were DFS, defined as the time interval between surgery (the time point of all residual disease removal) and first detectable disease recurrence or death, and OS, defined as the time from diagnosis to death from any cause or to last follow-up.

The approved dosing schedule of ZOL (4 mg via 15-min intravenous infusion every 3 weeks) for bone metastasis was used (Hillner *et al*, 2003). All women received four cycles of intravenous neoadjuvant epirubicin (75 mg m^{-2}) plus docetaxel (75 mg m^{-2}) every 3 weeks, with granulocyte-stimulating factor support and oral dexamethasone premedication (20 mg), followed by surgery and two cycles of adjuvant epirubicin plus docetaxel administered every 3 weeks. Adjuvant radiation, endocrine, and trastuzumab therapies were administered when indicated. The recommended follow-up was every 3 months for years 1 and 2 after randomisation, then every 6 months for years 3–5 after randomisation. It was recommended that all radiological exams (i.e., mammogram, computed tomography, bone or positron emission tomography) be performed annually.

All patients were encouraged to take 1000 mg calcium with 800 IU vitamin D daily. Adverse events were assessed at each follow-up. Patients were removed from the study for safety reasons, progression during chemotherapy or recurrent disease development. The Internal Review Board of Washington University approved the study, and patients provided written consent.

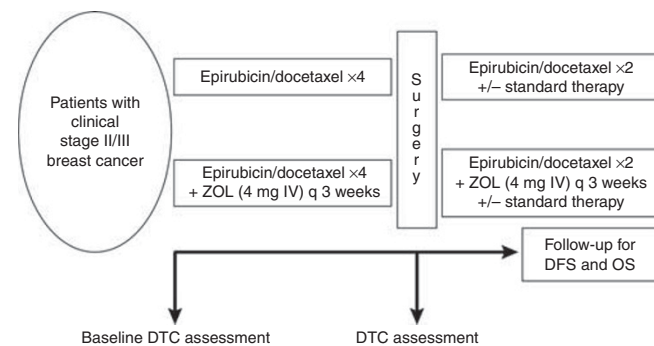


Figure 1 Study design. Abbreviations: DFS = disease-free survival; DTC = disseminated tumour cells; IV = intravenous; OS = overall survival; ZOL = zoledronic acid (4 mg every 3 weeks).

Study assessments

Immunostaining for ER, progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER2) was performed at Washington University. ER and PgR were considered positive if there was any detectable staining by immunohistochemistry (Ventana, Inc., Tucson, AZ, USA). HER2 was considered positive if HercepTest (Dako North America, Inc., Carpinteria, CA, USA) was 3^+ or if the fluorescence *in situ* hybridisation (FISH) score was > 2.0 . The FISH analysis was done for all specimens scored as 2^+ by HercepTest.

Pre-treatment tumour size was defined as the largest tumour dimension documented by mammogram, breast ultrasound, or magnetic resonance imaging. Pre-treatment lymph-node status was defined as any abnormal lymph nodes on computed tomography or ultrasound imaging, or on clinical exam, or by the presence of metastatic disease from fine-needle aspiration or sentinel lymph-node biopsy. Pathologic complete response was defined as no residual invasive tumour in the breast specimen at the time of surgery.

Statistical analysis

Kaplan–Meier estimates were generated for DFS and OS in each treatment arm, and patient subsets were defined by ER and HER2 status. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. A propensity score, adjusting for differences in age, race, menopausal status, ER, PgR, and HER2, was found to be a significant predictor of DFS and OS; thus, all reported analyses were adjusted using the propensity score. *P*-values < 0.05 were considered significant.

RESULTS

Patients

Of the 120 eligible women enrolled in this study, 119 were evaluated, and of those patients $\sim 55\%$ had ER⁺ tumours, 20% had HER2⁺ tumours, and 33% had ER⁻/HER2⁻ tumours (Table 1; Aft *et al*, 2010). One patient withdrew consent before receiving treatment, one patient did not have tumour biomarkers, and two patients did not undergo surgery for their cancer. Thirty-seven patients developed recurrent disease, of whom 27 died and 10 were alive with disease at last follow-up. There were 18 deaths among the 52 ER⁻ patients and 9 deaths among the 66 ER⁺ patients. The remaining 82 patients were alive without disease at last follow-up. No deaths were identified within this cohort as having a cause unrelated to BC.

Efficacy

After a median follow-up of 61.9 months, DFS ($P=0.92$) and OS ($P=0.92$) were similar in the ZOL and no-ZOL arms for the overall study population (Figure 2). ER status is an independent predictor of OS (Berry *et al*, 2006) and, as expected in our study, times to recurrence and death were significantly different between patient subgroups defined by ER status in the no-ZOL arm (interaction $P=0.010$ for DFS and 0.025 for OS; Table 2). However, in the ZOL treatment arm we failed to find a differences among the ER⁺ and ER⁻ patients. The hazards of disease recurrence and of death were significantly less among patients with ER⁻ tumours who received ZOL vs those who did not (DFS: HR = 0.361; 95% CI 0.148, 0.880; OS: HR = 0.375; 95% CI 0.143, 0.985). There was no evidence that ZOL treatment altered DFS or OS vs no ZOL in patients with ER⁺ tumours (Table 3). In Kaplan–Meier analyses, there were significant differences in DFS ($P=0.0007$) and OS ($P=0.0018$) based on treatment arms (Figure 3).

Table 1 Patient demographics and baseline disease characteristics

Characteristic	No ZOL (n = 59)	ZOL (n = 60)
Mean age, years (range)	49.1 (32–69)	50 (30–68)
Race, n (%)		
Caucasian	45 (76.3)	39 (65)
African American	11 (18.6)	20 (33)
Menopausal status, n (%)		
Premenopausal	33 (55.9)	31 (51.7)
Postmenopausal	26 (44.1)	29 (48.3)
Pathology, n (%)		
Ductal carcinoma	49 (83.1)	47 (78.3)
Lobular carcinoma	7 (11.8)	7 (11.7)
Other	3 (5.1)	6 (10)
Mean tumour size, cm (s.d.)	3.56 (2.41)	3.81 (2.03)
Lymph-node positive, n (%)	33 (55.9)	38 (63.3)
Grade, n (%)		
I	2 (3.4)	7 (11.7)
II	28 (47.5)	20 (33.3)
III	29 (49.2)	33 (55)
Receptor status, n (%)		
ER ⁺ /HER2 ⁺	5 (8.5)	6 (10)
ER ⁺ /HER2 ⁻	29 (49.2)	26 (43.3)
ER ⁻ /HER2 ⁺	5 (8.5)	7 (11.7)
ER ⁻ /HER2 ⁻	19 (32.2)	21 (35)
Unknown	1 (1.7)	—

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; s.d. = standard deviation; ZOL = zoledronic acid. Some of these patient data were previously published (Aft et al, 2010).

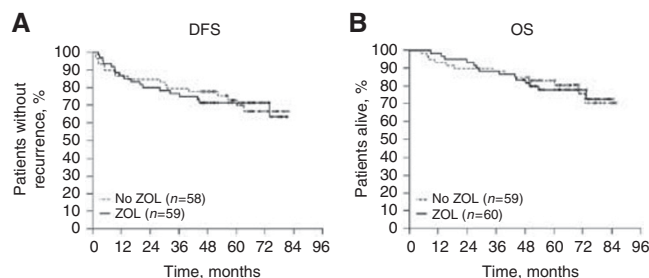


Figure 2 Disease-free survival (A) and overall survival (B) were similar between the ZOL and no-ZOL arms for the overall trial population. Abbreviations: DFS = disease-free survival; OS = overall survival; ZOL = zoledronic acid (4 mg every 3 weeks); ○ = censored.

Table 2 Proportional hazards by tumour subtype and treatment arm adjusted for propensity score

Parameter	P-value			
	Overall DFS (N = 119)	Overall OS (N = 119)	HER2 ⁻ DFS (N = 95)	HER2 ⁻ OS (N = 95)
Treatment, ZOL vs no ZOL	0.14	0.17	0.36	0.32
Propensity score	0.038	0.02	0.026	0.023
ER status, ER ⁺ vs ER ⁻	0.0012	0.0042	0.025	0.022
Treatment by ER status, interaction	0.01	0.025	0.064	0.052

Abbreviations: DFS = disease-free survival; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; OS = overall survival; ZOL = zoledronic acid.

Table 3 Risk of recurrence or death by tumour subtype and treatment arm

Parameter	Hazard ratio (95% confidence interval)			
	Overall DFS	Overall OS	HER2 ⁻ DFS	HER2 ⁻ OS
Treatment in ER ⁻	0.361 (0.148, 0.880)	0.375 (0.143, 0.985)	0.374 (0.125, 1.12)	0.306 (0.091, 1.04)
Treatment in ER ⁺	2.43 (0.748, 7.90)	3.07 (0.626, 15.1)	1.78 (0.512, 6.21)	2.32 (0.440, 12.2)
ER ⁻ vs ER ⁺ in ZOL	0.958 (0.377, 2.43)	1.12 (0.391, 3.18)	0.832 (0.262, 2.64)	0.835 (0.222, 3.14)
ER ⁻ vs ER ⁺ in no ZOL	6.45 (2.08, 20.0)	9.15 (2.01, 41.6)	3.96 (1.19, 13.2)	6.32 (1.31, 30.4)
Propensity score, per 0.01 increase	1.03 (1.002, 1.06)	1.04 (1.01, 1.08)	1.05 (1.01, 1.09)	1.06 (1.01, 1.11)

Abbreviations: DFS = disease-free survival; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor-2; OS = overall survival; ZOL = zoledronic acid. Treatment is ZOL vs no ZOL.

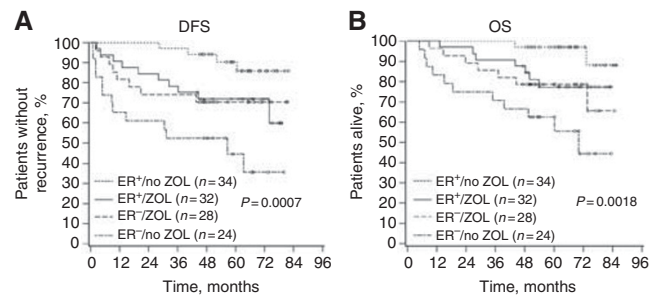


Figure 3 Kaplan-Meier estimates of (A) disease-free survival and (B) overall survival in all patients according to the ER status of their tumours. Abbreviations: DFS = disease-free survival; ER = oestrogen receptor; ZOL = zoledronic acid (4 mg every 3 weeks); ○ = censored.

As HER2⁺ status has significant effects on DFS and OS, especially with the recent adoption of HER2-targeted therapy, and to analyse more uniform subsets of BC patients, we analysed the effects of ER status on DFS and OS in the subset of patients with HER2⁻ tumours (n = 95). In the subset of HER2⁻ tumours, the effect of ZOL on OS and DFS was not shown to be significantly different in ER⁺ and ER⁻ patients (DFS interaction P = 0.052 and OS interaction P = 0.064; Table 2). However, among patients with ER⁻/HER2⁻ tumours, only 58% were alive at last follow-up in the no-ZOL arm compared with 81% in the ZOL arm. The corresponding DFS rates were 47% (no ZOL) and 71% (ZOL).

Safety

As previously reported, ZOL was generally well tolerated; toxicities were similar in the two treatment groups, with no observed cases of nephrotoxicity resulting in dose modifications. One of the 60 patients (1.7%) developed osteonecrosis of the jaw after receiving 11 infusions of ZOL (Aft et al, 2010).

DISCUSSION

With a median follow-up of 62 months, the addition of neoadjuvant ZOL to standard therapy did not significantly change median DFS or OS in women with stage II/III BC treated in this study. This is consistent with our earlier report in which we

did not observe significant differences in the 1- and 2-year disease recurrence and survival rates (Aft *et al*, 2010). Analysis of survival rates stratified according to BC subtype revealed significant improvements in DFS and OS in women with ER⁻ tumours randomised to receive ZOL. Our data are consistent with a recent report demonstrating a survival benefit of bisphosphonates in ER⁻ patients with metastatic disease (Park *et al*, 2009). In most adjuvant trials with bisphosphonates in non-metastatic BC, the predominant tumour type is ER⁺. Our trial was intentionally geared to patients at high risk of metastasis; >40% of patients treated in our trial had ER⁻ tumours and were premenopausal at diagnosis.

Three recently reported large phase III trials, which included women with all tumour subtypes, did not demonstrate an overall DFS or OS benefit from bisphosphonate treatment in women receiving adjuvant chemotherapy. These trials were the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34 trial, which compared clodronate *vs* placebo in women with early BC treated with adjuvant chemotherapy or endocrine therapy, the German Adjuvant Intergroup Node-positive (GAIN) study, which compared ibandronate *vs* placebo in women receiving adjuvant chemotherapy, and the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) study, which compared ZOL *vs* placebo in women receiving adjuvant chemotherapy or endocrine therapy (Coleman *et al*, 2011; Mobus *et al*, 2011; Paterson *et al*, 2011). In contrast, other trials evaluating the addition of ZOL (4 mg every 6 months) to endocrine therapy demonstrated significant improvement in DFS compared with adjuvant endocrine therapy alone in premenopausal women with ovarian suppression in phase III trials ($N=1803$; DFS HR = 0.64; $P=0.01$; Gnant *et al*, 2009) and postmenopausal ($N=1065$; DFS HR = 0.59; $P=0.03$; Eidtmann *et al*, 2010) women with stage I to III BC. However, clinical data indicate that ER status may be a variable for clinical benefit from bisphosphonates in this setting.

In a subset analysis of the AZURE trial in patients who were unequivocally postmenopausal at the time of starting the trial, ZOL provided a benefit for DFS to those patients with ER⁺ tumours (Coleman *et al*, 2011). We await OS data from the planned subgroup analysis by tumour subtype of the NSABP B-34 and GAIN trials. Meanwhile, in the ABCSG-12 trial, those women who derived the greatest benefit from the addition of ZOL were >40 years of age at study entry (Gnant *et al*, 2011b). These studies suggest that women with ER⁺ tumours and low oestrogen levels (postmenopausal, or premenopausal women with ovarian suppression) experience a survival benefit when ZOL is administered in the adjuvant setting. In this study, we did not observe any DFS benefit with the addition of ZOL to standard therapy in the subset of patients with ER⁺ tumours. The lack of DFS benefit in ER⁺ patients may be related to the small number of events in this subgroup with a more favourable prognosis compared with ER⁻ patients. The ER⁺ patients in this study were relatively young (median age, 47 years) and may have benefitted from upfront neoadjuvant chemotherapy because of their high-risk status (tumour size and other risk factors). As 60% of the patients with ER⁺ tumours in this trial were premenopausal at diagnosis, in contrast to the AZURE population, and were not given ovarian suppression, in contrast to the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) population, it is difficult to extrapolate the results of our trial to others (Gnant *et al*, 2009).

Many bisphosphonate trials have focused on patients with ER⁺ disease or have not included a large population of patients with ER⁻ disease. Few studies have examined the effects of bisphosphonates on ER⁻ BCs. In a retrospective study, Park *et al* (2009) found significantly prolonged survival in ER⁻ stage IV BC patients who received bisphosphonate treatment. In our trial, we found a significant decreased risk of recurrent disease development and death in patients with ER⁻ disease who received ZOL (HR = 0.361

and 0.375, respectively). We observed 21 recurrences among the 50 ER⁻ patients. This population was composed of predominantly premenopausal (55%) and African American (45%) women. Thus, in contrast to ER⁺ tumours, the effect does not seem to be dependent on a low oestrogen environment and may be the result of a more direct anti-tumour effect of ZOL on ER⁻ tumour cells.

In the primary report of this study, it was shown that adding ZOL to neoadjuvant chemotherapy was associated with increased rates of pCR *vs* no ZOL, although this difference was not significant (Aft *et al*, 2010). For Luminal B, HER2⁺, and ER⁻/HER2⁻ BC subtypes, response in the breast correlates with OS, which is thought to reflect the response of systemic micro-metastatic disease (Von Minckwitz *et al*, 2011). Thus, patients who achieve a pCR in the breast with chemotherapy have a better prognosis than patients who have residual breast disease (Chavez-MacGregor and Gonzalez-Angulo, 2010). Pathologic complete response in the breast has been used as a surrogate for response to therapy. As previously reported, in our patient population the between-group differences in the pCR rate were most pronounced in the triple-negative subset (ER⁻/PgR⁻/HER2⁻; ZOL group = 28%; no-ZOL group = 10%), although, as with the overall population, this difference was not statistically significant (Aft *et al*, 2010). These data are consistent with previous clinical data from the neoadjuvant therapy subset ($n=205$) of the ongoing AZURE trial, wherein the addition of ZOL (4 mg every 3 to 4 weeks) to 6 cycles of neoadjuvant chemotherapy improved pCR rates approximately two-fold in a multivariate analysis of the entire neoadjuvant cohort and significantly reduced the residual invasive tumour size at surgery (relative decrease of 43%; $P=0.006$) *vs* chemotherapy alone (Coleman *et al*, 2010).

As previously reported, among patients without detectable DTCs at baseline, a larger proportion of ZOL-treated patients (87%) remained DTC⁻ at 3 months compared with patients receiving chemotherapy alone (60%; $P=0.03$; Aft *et al*, 2010). Similarly, among patients who were DTC⁺ at baseline, a larger proportion of patients transitioned to DTC⁻ status in the ZOL group (48%) compared with chemotherapy alone (43%; $P=0.05$ *vs* no ZOL; Aft *et al*, 2010). Emerging data suggest that there is a complex interaction between the tumour and bone marrow (McAllister and Weinberg, 2010). Primary tumours release cytokines that are thought to prime the bone marrow for receipt of micro-metastasis disease, interrupt the delicate balance between bone formation and destruction with the release of growth factors, and recruit bone marrow-derived cells to enhance tumour growth and invasion. Similarly, bone marrow-derived myeloid cells can promote tumour growth at primary and distant sites (Weilbaecher *et al*, 2011). It is possible that drugs such as ZOL affect this interaction with the observed results of tumour growth inhibition and reduction of DTCs and metastases formation (Aft, 2011).

Although multiple statistical models used in the current study show a trend of increased clinical benefit in ER⁻ patients treated with ZOL, our findings are limited in that time to relapse (i.e., DFS) and OS were secondary and tertiary end points, respectively, and the study was not designed or powered to compare subgroups of patients. Thus, our findings should be regarded as hypothesis generating, and interpretation should be regarded with appropriate caution.

In summary, in this study, adding ZOL (4 mg every 3 weeks) to neoadjuvant chemotherapy reduced DTC persistence (Aft *et al*, 2010), improved pCR rates in specific patient subsets (Aft *et al*, 2010), and improved DFS and OS *vs* chemotherapy alone in the patient subset with ER⁻ tumours. These observations in the ER⁻ subset suggest that neoadjuvant or adjuvant ZOL may be a beneficial addition to current treatment paradigms in patients with ER⁻ tumours, and may warrant further investigation in larger clinical trials in this high-risk patient population with few targeted therapy options.

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Conflict of interest

R Aft and M Naughton have received honoraria from Novartis. The remaining authors have no conflict of interest.

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