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).
PATIENTS AND METHODS

Patients

Eligible patients had clinical stage II/III (≥T2 and/or ≥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.

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 ~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 with 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); O = censored.

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

| Parameter                          | 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−              | 0.012                 | 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.

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 compared with chemotherapy alone (Coleman et al., 2010). Similar improvements in DFS and OS were also observed in premenopausal women with ovarian suppression in phase III trials (N = 1803; DFS HR = 0.63; P = 0.01; Gnant et al., 2009) and postmenopausal (N = 1065; DFS HR = 0.59; P = 0.03; Eichmann 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 benefited from upfront neoadjuvant chemotherapy because of their high-risk status (tumour size and other risk factors). As 60% of the patients with ER\(^+\) disease 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 (ABCGS-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 median time between pCR and local recurrence was 15.2 months in the ZOL group and 12.5 months in the chemotherapy-alone group (Aft et al., 2010). A Closer look at this population revealed no significant difference in DFS or OS for pCR tumours vs no pCR tumours in the ZOL-alone, chemotherapy-alone, and placebo arms (Aft et al., 2010). These data suggest that the ZOL benefit is related to the pCR rate and not the time to pCR. Thus, pCR alone may not be a valid surrogate for DFS or OS in the neoadjuvant setting.
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REFERENCES

Aft R (2011) Bisphosphonates in breast cancer: clinical activity and implications of preclinical data. *Clin Adv Hematol Oncol* 9(3): 194–205

Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-Macgregor M, Zhai J, Kuo S, Shannon W, Diemer K, Herrmann V, Dietz J, Ali A, Ellis M, Weiss P, Eberlein T, Ma C, Fracasso PM, Zoberi I, Taylor M, Gillanders W, Pluard T, Mortimer J, Weiβbaecher K (2010) Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. *Lancet Oncol* 11(5): 421–428

Berry DA, Gironcimino C, Henderson IC, Citron ML, Budman DR, Goldstein A, Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-Macgregor Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein A, Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-Macgregor Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein A, Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-Macgregor Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein A, Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-Macgregor

Breast cancer with complete endocrine blockade: long-term results from ABCSG-12 randomised trial. *Ann Oncol* 22(7): 1658–1667

Braun S, Vogl FD, Naume B, Janni W, Osborne MP, Coombes RC, Schlimok G, Dierl J, Gerber B, Gebauer G, Perga JT, Martich C, Broazd D, Wiedswang G, Solomayer EF, Kundt G, Strobl B, Fehm T, Wong GY, Bliss J, Vincent-Salomon A, Pantel K (2005) A pooled analysis of bone marrow micrometastasis in breast cancer. *N Engl J Med* 353(8): 793–802

Chavez-Macgregor M, Gonzalez-Angulo AM (2010) Breast cancer, neoadjuvant chemotherapy and residual disease. *Clin Transl Oncol* 12(7): 461–467

Coleman RE, Marshall H, Cameron D, Dodwell D, Burkanshaw R, Keane M, Gil M, Houston SL, Grieve BJ, Barrett-Peel J, Ritchie D, Pugh J, Gaunt J, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R (2011) Breast cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 365(15): 1396–1405

Coleman RE, Winter NC, Cameron D, Bell R, Dodwell D, Keane MM, Gil M, Ritchie D, Passos-Coelho JL, Wheatey D, Burkanshaw R, Marshall SL, Thorpe H (2010) The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer* 102(7): 1099–1105

Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Coleman RE, Winter NC, Cameron D, Bell R, Dodwell D, Keane MM, Gil M, Ritchie D, Passos-Coelho JL, Wheatey D, Burkanshaw R, Marshall SL, Thorpe H (2010) The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer* 102(7): 1099–1105

Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Coleman RE, Winter NC, Cameron D, Bell R, Dodwell D, Keane MM, Gil M, Ritchie D, Passos-Coelho JL, Wheatey D, Burkanshaw R, Marshall SL, Thorpe H (2010) The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. *Br J Cancer* 102(7): 1099–1105

Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 21(21): 4042–4057

Lin AY, Park JW, Scott J, Melisko M, Goga A, Moasser MM, Moore DH, Rugo HS (2008) Zoledronic acid as adjuvant therapy for women with early stage breast cancer and disseminated tumor cells in bone marrow (abstract). *J Clin Oncol* 26(S15): 559

McAllister SS, Weinberg RA (2010) Tumor-host interactions: a far-reaching impact of preclinical data. *Clin Adv Hematol Oncol* 9(3): 194–205

Mobus V, Diel IJ, Elling D, Harbeck N, Jackisch C, Thomssen C, Untch M, Conrad B, Schneeveiss A, Kreienberg R, Huober J, Muller V, Luck HJ, Bauerfeind L, Sloibl S, Niekjudova V, von Minckwitz G (2011) GAIN study: a phase III trial to compare ETC vs EC-TX and ibandronate vs observation in patients with node-positive primary breast cancer – 1st interim efficacy analysis (abstract), 34th Annual San Antonio Breast Cancer Symposium. 6–10 December, 2011; San Antonio, TX. Abstract S2–4

Neville-Webbe HL, Grant N, Coleman RE (2010) Potential anticancer properties of bisphosphonates. *Semin Oncol* 37(Suppl 1): S53–S65

Pantel K, Alix-Panabieres C, Riethdorf S (2009) Cancer micrometastases. *Nat Rev Clin Oncol* 6(6): 339–351

Park IH, Ro J, Nam BH, Kwon Y, Lee KS (2009) Potential antitumor effects of nitrogen-containing bisphosphonate in hormone receptor negative breast cancer patients with bone metastases. *BMCCancer* 9: 154

Paterson AHG, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, Weir LM, Bruksmy AJ, Dakhil S, Lad T, Baer-Diaz L, Gralow JR, Robidoux A, Perez EA, Zheng P, Geyer CE, Swain SM, Costantino JP, Mamounous EP, Wolmark N (2011) NSABP protocol B-34: a clinical trial comparing adjuvant clodronate vs placebo in early stage breast cancer patients receiving systemic chemotherapy and/or tamoxifen or no therapy—final analysis. 34th Annual San Antonio Breast Cancer Symposium. 6–10 December, 2011; San Antonio, TX. Abstract S2–3

Rack B, Jackstock J, Genss EM, Schobert A, Schindlbuch C, Strobl B, Heinrigs M, Ramml B, Zwingers T, Sommer H, Friese K, Jannin W (2010) Effect of zoledronic acid on persisting isolated tumour cells in patients with early breast cancer. *Anticancer Res* 30(5): 1807–1813

Solomayer E, Gebauer G, Hirnle P, Janni W, Lück H-J, Becker S, Huober J, Krammer B, Wackwitz B, Fehm T (2009) Influence of zoledronic acid on disseminated tumour cells (DTC) in primary breast cancer patients (abstract). *Cancer Res* 69(2 Suppl 1): 170s–171s. Abstract 2048

Von Minckwitz G, Kaufmann M, Kueimmel S, Fasching PA, Eiermann W, Blohm JU, Costa SD, Hilfrich J, Jackisch C, Gerber B, Du Bois A, Huober J, Hanusch CA, konceny GE, Fett W, Stickeler E, Harbeck N, Mehta K, Loibl S, Untch M (2011) Correlation of various pathologic complete response (pCR) definitions with long-term outcome and the prognostic value of pCR in various breast cancer subtypes: results from the German neoadjuvant meta-analysis. *J Clin Oncol* 29(S15): 1028

Weiβbaecher KN, Guise TA, McCauley LD (2011) Cancer to bone: a fatal attraction. *Nat Rev Cancer* 11(6): 411–425

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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.