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Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12

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Background: Zoledronic acid (ZOL) plus adjuvant endocrine therapy significantly improved disease-free survival (DFS) at 48- and 62-month follow-up in the ABCSG-12 trial. We present efficacy results of a final additional analysis after 94.4 months.

Patients and methods: Patients were premenopausal women who had undergone primary surgery for stage I/II estrogen-receptor-positive and/or progesterone-receptor-positive breast cancer with <10 positive lymph nodes, and were scheduled for standard goserelin therapy. All 1803 patients received goserelin (3.6 mg every 28 days) and were randomized to tamoxifen (20 mg/days) or anastrozole (1 mg/days), both with or without ZOL (4 mg every 6 months) for 3 years. The primary end point was DFS; recurrence-free survival and overall survival (OS) were secondary end points.

Results: After 94.4-month median follow-up (range, 0–114 months), relative risks of disease progression [hazard ratio (HR) = 0.77; 95% confidence interval (CI) 0.60–0.99; $P = 0.042$] and of death (HR = 0.66; 95% CI 0.43–1.02; $P = 0.064$) are still reduced by ZOL although no longer significant at the predefined significance level. Overall, 251 DFS events and 86 deaths were reported. Absolute risk reductions with ZOL were 3.4% for DFS and 2.2% for OS. There was no DFS

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difference between tamoxifen alone versus anastrozole alone, but there was a pronounced higher risk of death for anastrozole-treated patients (HR = 1.63; 95% CI 1.05–1.45; $P = 0.030$). Treatments were generally well tolerated, with no reports of renal failure or osteonecrosis of the jaw.

Conclusion: These final results from ABCSG 12 suggest that twice-yearly ZOL enhances the efficacy of adjuvant endocrine treatment, and this benefit is maintained long-term.

ClinicalTrials.gov: NCT00295646 (http://www.clinicaltrials.gov/ct2/results?term=00295646).

Key words: bisphosphonates, early breast cancer, zoledronic acid, tamoxifen, anastrozol, LHRH agonists

introduction

Treatment of early breast cancer (BC) generally involves surgical resection, locoregional treatment (e.g. radiotherapy), and systemic therapy (chemotherapy, HER2-targeted therapy if applicable, endocrine therapy for hormone-responsive disease) [1]. Some adjuvant BC therapies can adversely affect bone health through decreased estrogen levels, accelerated bone loss [1–3], and increased fracture risk [4].

Bisphosphonates can delay the onset and reduce the risk of skeletal-related events in patients with bone-metastatic BC [5], and can prevent and treat cancer-treatment-induced bone loss [6, 7]. When the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) was initiated, evidence for the anticancer potential of bisphosphonates in early BC was just emerging. In patients with early BC, 2-year clodronate treatment improved disease-free survival (DFS) and overall survival (OS) [8]. Although long-term follow-up showed prolonged OS benefits in one trial, a meta-analysis of data from three trials did not find significant benefit with adjuvant clodronate. More recently, mounting evidence supports a potential anticancer role for bisphosphonates, especially zoledronic acid (ZOL) [9–18].

Within this historical context, the ABCSG-12 trial now has data for 8-year (94.4-month) median follow-up, 5 years after treatment completion. An additional 114 (251 versus 137; 83%) patients had DFS events, and 44 (86 versus 42; 105%) additional on-study deaths occurred since the initial 48-month follow-up report [11]. This final exploratory analysis allows further evaluation of the sustained benefits of ZOL combined with adjuvant endocrine therapy in the early BC setting.

methods

patient characteristics and study design

The patient population and trial design were described previously [11, 12] and are summarized in supplementary Methods, available at *Annals of Oncology* online.

statistical analysis

All prospective analyses were based on the intent-to-treat population (all randomized patients). DFS and OS were compared between treatment groups using Cox proportional hazards regression model. Details can be found in supplementary Methods, available at *Annals of Oncology* online.

results

Between June 1999 and May 2006, 1803 patients were enrolled and randomly assigned to treatment (supplementary Figure S1, available at *Annals of Oncology* online) [12]. Patient demographics and baseline disease characteristics were well balanced between treatment arms (supplementary Table S1, available at *Annals of Oncology* online) [12]. When the dataset was extracted from the database on 13 June 2012, the median follow-up duration was 94.4 months (range, 0–114 months). In all, 251 events [86 deaths, 65 locoregional relapses, 125 distant relapses (62 in bone), 26 contralateral BC, and 36 new primary tumors outside the breast] met the primary end point criteria (Table 1).

At 94.4-month median follow-up, adding ZOL to endocrine therapy strongly suggests improved DFS versus endocrine therapy alone [796/900 patients (88.4%) versus 768/903 (85.0%), respectively] for an absolute increase of 3.4%. The combination of ZOL plus endocrine therapy was consistent with a reduced risk of DFS events by 23% versus endocrine therapy alone [hazard ratio (HR) = 0.77; 95% confidence interval (CI) 0.60–0.99; Cox $P = 0.042$; Figure 1A]. There were fewer disease recurrences overall in the ZOL versus no-ZOL group (111 versus 140), with the greatest reductions in locoregional recurrences (25 versus 40), distant recurrences (58 versus 67), and bone metastases (27 versus 35; Table 1). DFS rates were consistently higher with ZOL versus no-ZOL regardless of endocrine therapy received (88.4% versus 85.6%, respectively, Cox $P = 0.203$ with tamoxifen; and 86.9% versus 83.4%, respectively, Cox $P = 0.110$ with anastrozole). DFS did not differ significantly between the tamoxifen and anastrozole groups (117 versus 134 events; HR = 1.13; 95% CI 0.88–1.45; Cox $P = 0.335$; Figure 1B). There was no significant interaction between endocrine therapy and ZOL ($P = 0.860$).

In these exploratory analyses at 94.4-month median follow-up, ZOL consistently suggests to reduce the relative risk of disease progression in node-positive ($n = 550$; HR = 0.74; 95% CI 0.52–1.05; Cox $P = 0.095$) and node-negative disease ($n = 1211$; HR = 0.78; 95% CI 0.55–1.11; Cox $P = 0.167$), and in T1-stage ($n = 1375$; HR = 0.77; 95% CI 0.56–1.05; Cox $P = 0.093$) and T2/3-stage disease ($n = 368$; HR = 0.73; 95% CI 0.47–1.12; Cox $P = 0.144$). However, because of small sample sizes, statistical significance was not achieved in these subgroups. Although the interaction between ZOL and age was not statistically significant ($P = 0.267$), prespecified exploratory subgroup analysis by age at study entry suggests that ZOL reduced the relative risk of disease progression in patients >40 years (Figure 2A) but not ≤40 years of age (Figure 2B).

Overall, adjuvant endocrine therapy plus ovarian function suppression produced a 7.9-year OS rate of 95.2%. There were 35 deaths (3.9% of 900 patients) in the ZOL group versus 51 deaths (5.6% of 903 patients) in the no-ZOL group (Table 1), corresponding with a consistent, but statistically nonsignificant relative reduction in risk of death for ZOL versus no-ZOL (HR = 0.66; 95% CI 0.43–1.02; Cox $P = 0.064$; Figure 1C). At the median follow-up, the OS rate was higher among the ZOL versus no-ZOL groups [870 of 900 (96.7%) versus 853 of 903 (94.5%), respectively], corresponding to an absolute 2.2% reduced risk of death. In spite of an indication for an

Table 1. Disease-free survival events (ITT population)[a]

Events	TAM ($N = 900$)	ANA ($N = 903$)	HR (95% CI)	Cox P value	No ZOL ($N = 903$)	ZOL ($N = 900$)	HR (95% CI)	Cox P value	Total ($N = 1803$)
Total events, *n*	117	134	1.13 (0.88–1.45)	0.335[b]	140	111	0.77 (0.60–0.99)	0.042[b]	251
Recurrences, *n*									
Locoregional	33 (35)	32 (33)	0.94 (0.59–1.51)		40 (41)	25 (27)	0.65 (0.40–1.05)		65 (68)
Distant	54 (58)	71 (73)	1.25 (0.89–1.76)		67 (71)	58 (60)	0.83 (0.59–1.18)		125 (131)
Bone metastases	26 (26)	36 (36)	1.38 (0.83–2.28)		35 (35)	27 (27)	0.76 (0.46–1.25)		62 (62)
Non-bone metastases	28 (32)	35 (37)	1.15 (0.71–1.84)		32 (36)	31 (33)	0.91 (0.57–1.46)		63 (69)
Contralateral breast cancer	14 (16)	12 (12)	0.74 (0.35–1.56)		13 (15)	13 (13)	0.86 (0.41–1.80)		26 (28)
Secondary malignancy, *n*	16 (16)	20 (21)	1.30 (0.68–2.48)		19 (20)	17 (17)	0.84(0.44–1.60)		36 (37)
All deaths, *n*	33	53	1.63 (1.05–2.52)	0.030	51	35	0.66 (0.43–1.02)	0.064	86
Without prior recurrence	1	3			4	0			4

Data are number of patients.

[a]In each subcategory, an event is counted only if it is the first (or first simultaneous) event per patient. The numbers of events in brackets refer to all events per category and provide the basis for the calculated hazard ratios (HR).

[b]The P values of the DFS comparisons have to be compared with an $\alpha = 0.025$ as originally defined to adjust for two primary end points in the 2×2-factorial design.

ANA, anastrozole; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; TAM, tamoxifen; ZOL, zoledronic acid.

improvement in OS in patients >40 years receiving Zol (Figure 2C), but not in younger patients (≤40 years; Figure 2D), the interaction between ZOL and age was not significant ($P = 0.378$). In the anastrozole group, OS was significantly worse versus the tamoxifen group (51 versus 35 events; HR = 1.63; 95% CI 1.05–2.52; Cox $P = 0.030$; Figure 1D).

The DFS and OS benefits observed in this final analysis have persisted throughout all of the follow-up analyses. Improved DFS for ZOL versus no-ZOL (first observed at 47.8-month follow-up) remained stable throughout the 5-year follow-up period after 3 years of treatment (Figure 3A). Similarly, the OS benefit consistently favored ZOL combination therapy throughout the 5-year follow-up period and remained statistically significant at the 76-month follow-up. After that point of follow-up, statistical significance was lost but the HR reduction remained in comparable magnitude (Figure 3B). Overall, the beneficial effect of ZOL was not different during the first 3 years (during treatment) when compared with the post-treatment period (HR = 0.75; 95% CI 0.48–1.17 versus HR = 0.78; 95% CI 0.58–1.06).

Among the 251 patients with disease recurrence, the relative risk of death was significantly higher in patients who received anastrozole compared with patients treated with tamoxifen (53 of 134 versus 33 of 117; HR = 2.0, 95% CI 1.28–3.13; Cox $P = 0.002$).

Adverse events were generally consistent with known safety profiles of each agent, and no safety concerns were evident 5 years after median treatment completion (supplementary Table S2, available at *Annals of Oncology* online). After 94.4-month median follow-up, there were still no confirmed cases of ONJ.

discussion

Final analyses of our study indicate that the benefits of ZOL reported at 48- and 62-month follow-up persist in premenopausal women with endocrine-responsive early-stage BC who underwent ovarian suppression with goserelin [11, 12]. Adding ZOL (4 mg every 6 months) to adjuvant endocrine therapy suggests persistent DFS benefit and a considerable improvement in OS, first observed at the 76-month analysis [21]. The between-group differences for DFS and OS favored adding ZOL to endocrine therapy versus endocrine therapy alone ($P = 0.042$ for DFS, $P = 0.064$ for OS). Regardless of treatment group, results from these overall outcomes (95.2% OS at 8 years of follow-up) are promising and support the efficacy of endocrine therapy without cytotoxic therapy in this patient population.

Locoregional recurrence or distant relapse occurs, even when there is no sign of residual disease following surgical resection and adjuvant therapy. At 94.4-month follow-up, fewer distant (58 versus 67) and locoregional recurrences (25 versus 40) occurred in patients receiving ZOL plus endocrine therapy compared with patients receiving endocrine therapy alone, indicating that the anticancer effects of treatment were not confined to bone. The potential mechanism for this benefit is likely related to the anticancer effect of ZOL on residual tumor cells residing within the bone marrow, which may prevent tumor cells from 're-seeding' locoregional or contralateral breast tissue at a later date [22]. Increased risks of disease recurrence and poorer outcomes have been correlated with DTCs in the bone marrow of BC patients, a likely source of future skeletal and extraskeletal metastases [23]. In other studies, ZOL treatment has been

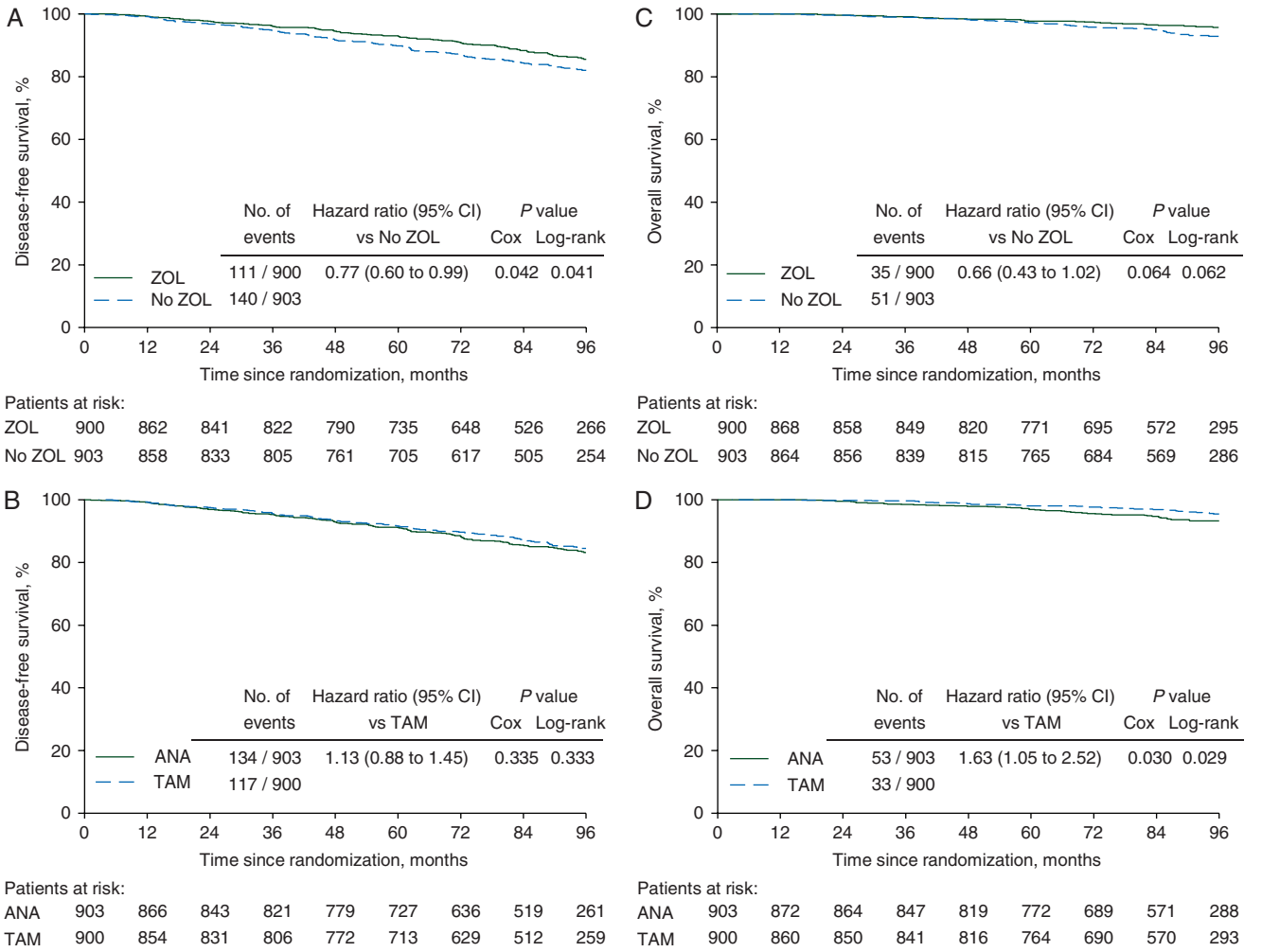

Figure 1. Kaplan–Meier estimates of disease-free survival (DFS) and overall survival (OS). DFS in all patients treated with (A) ZOL versus no-ZOL, (B) ANA versus TAM. OS in all patients treated with (C) ZOL versus no-ZOL, (D) ANA versus TAM. CI, confidence interval; ZOL, zoledronic acid; ANA, anastrozole; TAM, tamoxifen.

associated with a decrease in DTC levels in patients receiving adjuvant therapy for early BC [9, 19], supporting the anticancer potential of ZOL within and outside of bone demonstrated in our study.

Of particular note, the benefit for ZOL-treated patients arises early and remains persistent long after treatment cessation. This is consistent with prolonged DFS benefits seen with adjuvant endocrine therapy in patients with early BC. The exciting perspective of this final ABCSG-12 analysis is that early intervention for a limited duration can provide persistent benefits for $\geq$5 years. In fact, we did not find a numerical difference between the 'early' and the persisting benefit.

Of course, the half-life of aminobisphosphonates in bone is long, and metabolic effects can be seen for several years [20], but another possible explanation for this persistent anticancer effect lies in the putative anticancer activity of adjuvant ZOL on dormant tumor cells in the bone marrow [22]. Recently, a number of biochemical interactions between tumor and host cells within the bone marrow have been identified. Together with the activity of hematopoietic stem and lineage cells, these interactions appear to be of crucial importance for the survival of dormant tumor cells within the bone marrow, which are ultimately the source of metastasis, not only within, but also outside bone [24].

ABCSG-12 was the first large, prospective clinical trial to demonstrate an anticancer benefit with ZOL in the early BC setting [11]. Subsequently, other trials confirmed those results and contributed to the evolving understanding of the mechanisms underlying the anticancer potential of ZOL. Similar to ABCSG-12, AZURE was designed with DFS as the primary end point [15], whereas treatment effects on disease outcomes were assessed as a secondary end point in ZO-FAST [13]. Although ABCSG-12 in premenopausal women and ZO-FAST in postmenopausal women provided evidence of the anticancer potential of ZOL [11–13], AZURE results were more difficult to interpret [15]: there was significant improvement in disease outcomes in 1041 women who were postmenopausal for >5 years before enrollment, but not in pre- and perimenopausal patients [15]. Initially, these results appeared inconsistent with data from the premenopausal population of ABCSG-12; however, ovarian function suppression rendered all patients amenorrheic and, thus, estrogen levels of patients in ABCSG-12 were likely similar to the postmenopausal subset in AZURE. In contrast,

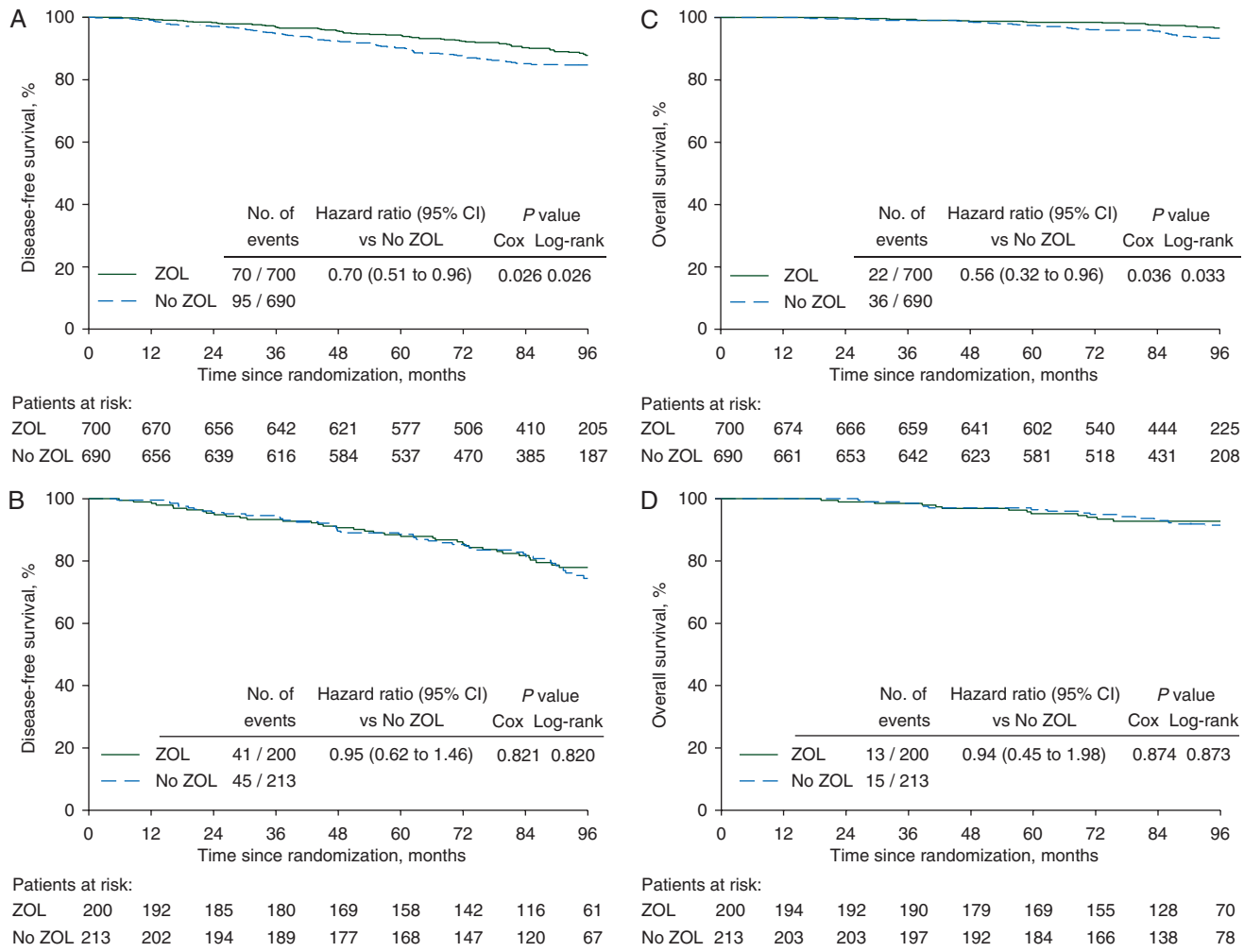

Figure 2. Kaplan–Meier estimates of disease-free survival (DFS) and overall survival (OS). DFS in patients treated with ZOL versus no-ZOL: (A) >40 years of age subgroup, (B) ≤40 years of age subgroup. OS in patients treated with ZOL versus no-ZOL: (C) >40 years of age subgroup, (D) ≤40 years of age subgroup. Interaction between ZOL and age was not statistically significant for DFS ($P = 0.267$) or OS ($P = 0.378$). CI, confidence interval; ZOL, zoledronic acid.

premenopausal patients in AZURE did not receive ovarian suppression (per prevailing local treatment practices). Moreover, predefined exploratory subgroup analyses by age at enrollment in ABCSG-12 demonstrate that DFS and OS benefits of ZOL were greatest in the 1390 women >40 years of age at study entry versus those ≤40 years of age, suggesting that patients >40 years at baseline may have achieved more complete estrogen deprivation. Together, these results suggest that the anticancer benefits of adjuvant ZOL might be greatest in patients achieving maximum estrogen blockade and that depriving the bone microenvironment of estrogen may play a substantial role in determining who benefits most from adjuvant ZOL therapy. This hypothesis is supported by recent data from the National Surgical Adjuvant Breast and Bowel Project B-34 trial (NSABP B-34), in which clodronate improved disease outcomes in women ≥50 years but not <50 years of age [25]. Similar beneficial effects in postmenopausal patients have been reported in other recent trials of bisphosphonates and a large meta-analysis [26], and a consistent pattern of benefit based on the complex interaction between reproductive hormones, bone marrow stem cell function, and dormant tumor cells seems to be emerging [10, 15].

However, not all trials of adjuvant bisphosphonates have demonstrated significant DFS benefits: In Z-FAST, there was a small but nonsignificant difference between DFS events in the immediate- versus delayed-ZOL groups at 36 months (5.0% versus 7.6%, respectively; $P = 0.3$) and 61 months (9.8% versus 10.5%, respectively; $P = 0.6283$) [6]. In the overall population of NSABP B-34, there was no difference in DFS from adding clodronate to adjuvant therapy ($P = 0.27$) [25]. In the GAIN trial, adjuvant ibandronate did not improve DFS overall (HR = 0.945; $P = 0.589$) or in the postmenopausal subset [27], and an oral pamidronate trial was also negative [28]. The reasons for these differences between trial results are unclear, but could be related to compliance with study medication, heterogeneous populations, and menopausal status. Recently, a large meta-analysis of all adjuvant bisphosphonate trials involving individual data from >22 000 patients confirmed outcome benefits in low-estrogen environments [26].

In our study, ZOL was generally well tolerated and associated with few side-effects versus endocrine therapy alone. There was no evidence of increased AE rates or unexpected toxicity when ZOL was combined with either tamoxifen or anastrozole. No

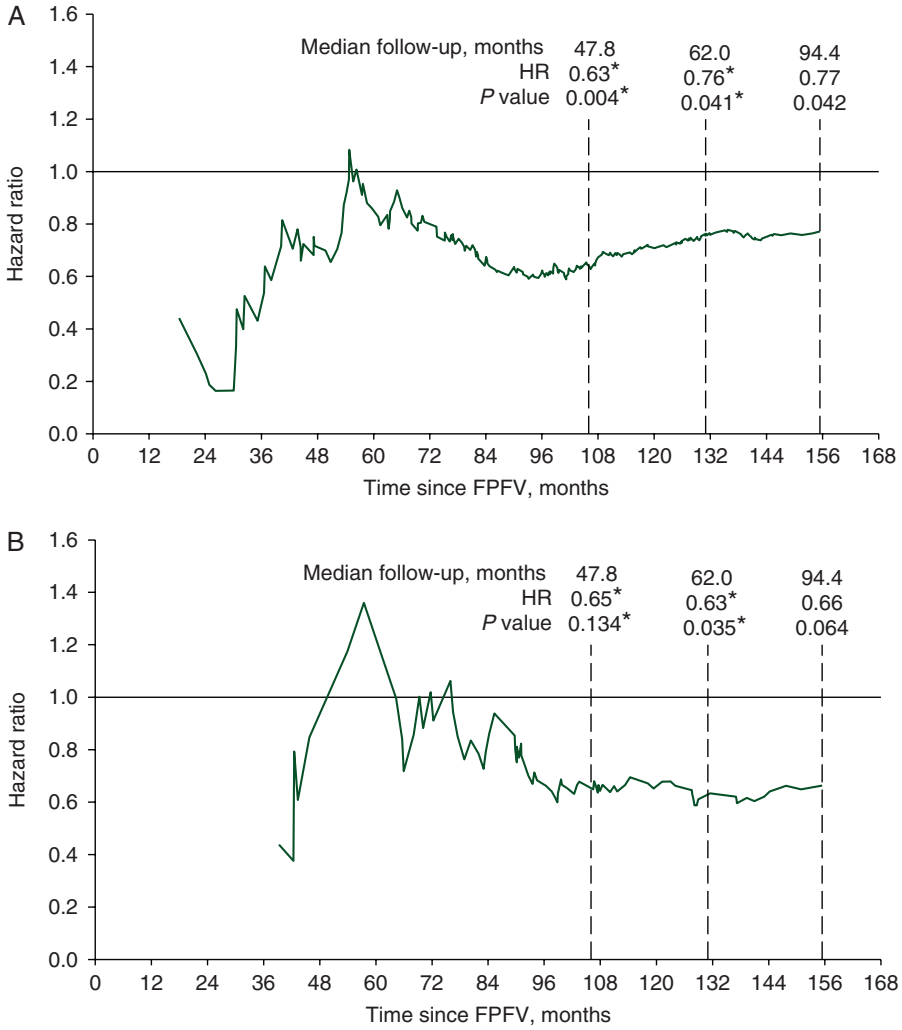

Figure 3. Hazard ratios over the duration of the trial for disease-free survival (A) and overall survival (B). The *x*-axis represents calendar time beginning with the first patient first visit (FPFV). *The hazard ratios and *P* values reported for this retrospective analysis at a median follow-up of 47.8 and 62.0 months may differ slightly from those reported in previous publications [19, 20], because documentation delays resulted in some events being missed in the previous reports.

confirmed cases of ONJ were reported despite extensive efforts undertaken after 2003 to identify potential cases. ONJ is a rare AE reported in patients receiving complex treatment regimens including bisphosphonates, and very few confirmed cases of ONJ have been reported in the adjuvant setting with twice-yearly ZOL dosing. There were four (0.6%) cases of ONJ in the ZO-FAST trial ($N = 1065$) and 26 (2.1%) cases in the ZOL arm of the AZURE trial ($n = 1681$) with more intensive ZOL dosing. Moreover, there were no signs of serious renal toxicity in our study, which is consistent with the renal AE profiles of ZO-FAST and AZURE (<0.5% in each study, regardless of treatment) [14, 24].

With respect to the ANA versus TAM comparison, we did not find a benefit for the aromatase inhibitor when compared with tamoxifen in combination with ovarian function suppression. To the contrary, there was an unfavorable trend for ANA with respect to OS. We have previously reported [7] that there was a slight imbalance in post-relapse AI treatment of these patients, but the concern remains that adjuvant AIs induce could induce resistance which makes post-relapse treatment more challenging [29]. In fact, even in the overall contrasting results of the combined SOFT/TEXT analysis [30], a similarly concern is indicated by a DFS HR of 0.72 favoring the AI and an OS HR of 1.14—unfortunately no post-relapse information was given in that paper. As a result of these conflicting reports, and with serious doubts about AI efficacy in overweight women [31], the optimal adjuvant endocrine treatment strategy for premenopausal women remains uncertain.

In conclusion, these final exploratory 94.4-month results from ABCSG-12 confirm that twice-yearly ZOL safely enhances the efficacy of adjuvant endocrine therapy. Combining ZOL with adjuvant endocrine therapy should be considered for premenopausal women undergoing ovarian function suppression for early-stage endocrine-responsive BC, and appears to be most beneficial in those >40 years of age. Tamoxifen together with Goserelin for now remains the endocrine standard of care. In general, OS of more than 95% at 8 years' median follow-up supports the efficacy of endocrine-only regimens in this premenopausal patient population.

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funding

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disclosure

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Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study

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Background: HannaH (NCT00950300) was a phase III, randomized, international, open-label study that compared pharmacokinetics (PK), efficacy, and safety of two different trastuzumab formulations [subcutaneous (s.c.) and intravenous (i.v.)] in HER2-positive, operable, locally advanced, or inflammatory breast cancer in the neoadjuvant/adjuvant setting. The co-primary end points, to show noninferiority of s.c. versus i.v. trastuzumab in terms of serum concentration (C_{trough}) and pathologic complete response (pCR) were met; safety profiles were comparable at 12 months' median follow-up. Secondary end points included safety and tolerability, PK profile, immunogenicity, and event-free survival (EFS). We now report updated safety and efficacy data after a median follow-up of 20 months.

Patients and methods: Patients ($N = 596$) were treated with eight cycles of neoadjuvant chemotherapy, administered concurrently with 3-weekly s.c. trastuzumab (fixed dose of 600 mg) or the standard weight-based i.v. method. Following surgery, patients continued trastuzumab treatment to complete 1 year of therapy. Updated analyses of PK, efficacy, safety, and immunogenicity data were carried out.

Results: s.c. trastuzumab was generally well tolerated and the incidence of adverse events (AEs), including grade 3 or 4 AEs, between treatment groups was comparable. A slightly higher incidence of serious AEs (SAEs), mainly due to infections, was reported with s.c. treatment {64 [21.5%; 95% confidence interval (CI) 17.0%–26.7%] versus 42 (14.1%; 95% CI 10.4%–18.6%) in the i.v. group}; however, the differences were small and often based on rare events, with no observable pattern across reported events. An early analysis of EFS showed rates of 95% in both groups 1 year postrandomization. Exploratory analyses did not reveal an association between toxicity and body weight or exposure.

Conclusions: Overall, the safety profile of s.c. trastuzumab was consistent with the previously published data from HannaH and the known safety profile of i.v. trastuzumab. EFS rates were comparable between the i.v. and s.c. groups.

Clinical trial number: NCT00950300.

Key words: breast cancer, chemotherapy, HER2/neu, neoadjuvant, subcutaneous, trastuzumab

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