



LANDMARKS

EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 31st San Antonio Breast Cancer Symposium (SABCS), held December 10–13, 2008.

Leading Canadian experts offer commentary and clinical interpretations.

Reporting will continue in the next issue of *Oncology Exchange*.

Contributors were selected by Joseph Ragaz, MD, FRCPC, McGill University, Montreal, QC.

Hormonal therapy in early postmenopausal breast cancer

Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital, Winnipeg, MB.

Jones SE, Seynaeve C, Hasenburger A et al. **Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer.** SABCS 2008, Abstract 15.

TRIAL SUMMARY: The open-label, multinational TEAM study randomized postmenopausal women with invasive, endocrine receptor-positive early breast cancer to receive either exemestane 25 mg/day or tamoxifen 20 mg/day as initial adjuvant endocrine therapy. Enrollment began in 2001, and the protocol was modified in 2004 such that patients initially randomized to tamoxifen switched to exemestane after 2.5 to 3 years of tamoxifen, based on the results of the Intergroup Exemestane Study (IES). These patients who switched were compared with the exemestane-alone arm (5 years of exemestane) of the original trial design. The current analysis focuses on exemestane monotherapy vs tamoxifen at 2.75 years, which marked the average time of crossover to exemestane. In this planned interim report, based on data from October 2008, 9766 women of the 9775 accrued had been followed for 2.75 years. Of these, all had estrogen and/or progesterone receptor-positive tumours, 50% had no lymph node involvement, 44% had mastectomy, 68% had radiotherapy and 36% had chemo-

therapy; 1434 of the 4874 (29.5%) patients randomized to receive tamoxifen stopped their allocated treatment before 2.75 years, compared to 928 of the 4901 (19%) of the women randomized to exemestane. The hazard ratio (HR) for disease-free survival (DFS) was 0.89 (95% CI 0.77 to 1.03; $p = 0.12$); and for relapse-free survival (RFS) it was 0.85 (95% CI 0.72 to 1.00; $p = 0.05$). The HR for time to distant metastases was 0.81 (95% CI 0.67 to 0.98; $p < 0.03$). A pre-switch analysis that excluded the 96 patients who did not receive the study drug showed a HR for DFS of 0.83 (95% CI 0.71 to 0.97; $p = 0.02$). As shown in **Table 1**, rates of adverse events were low except for hot flushes and arthralgia. Gynecologic events were more frequent in the tamoxifen group and musculoskeletal events were more frequent in the exemestane group. Cardiac disorders were equivalent in the 2 groups. The authors concluded that these results are consistent with those of other trials showing improved rates of DFS, RFS and time to distant metastasis with aromatase inhibitors vs tamoxifen, with no unexpected adverse events.

Mouridsen H, Giobbie-Hurder A, Mauriac L et al. **BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** SABCS 2008, Abstract 13.

TRIAL SUMMARY: The primary core analysis of the 4-arm phase of the BIG 1-98 trial randomized 6182 postmenopausal women with endocrine receptor-positive breast cancer

to 1 of 4 treatment arms for adjuvant endocrine therapy: tamoxifen for 5 years ($n = 1548$), letrozole for 5 years ($n = 1546$), tamoxifen for 2 years followed by letrozole

for 3 years (n = 1548), or letrozole for 2 years followed by tamoxifen for 3 years (n = 1540) (see **Figure 1**, page 14). An earlier 2-arm monotherapy phase of the trial enrolled 1828 women, randomizing them to 2 treatment arms: 5 years of tamoxifen (n = 911) or letrozole (n = 917). Results reported in 2005 of the primary core analysis and monotherapy analyses (both 2 and 4-arm phases) showed longer DFS — the primary endpoint — and lower risk of distant metastases for patients taking letrozole monotherapy compared to those taking tamoxifen monotherapy. After release of these results, the patients randomized to tamoxifen were unblinded.

As planned in the protocol, the current report focused on both monotherapy (n = 4922) and the “sequential therapy vs letrozole” results (n = 4634). The monotherapy results were confounded by the large number of patients (619 out of a total 2459, 25%), randomized to tamoxifen monotherapy, who switched from tamoxifen to letrozole after the 2005 results were released, which complicates comparisons with tamoxifen alone. Therefore, the comparison of tamoxifen vs letrozole was performed by 2 methods: intent-to-treat (ITT) and with censoring at crossover.

Table 2 shows the monotherapy update with a median followup of 76 months. By ITT, there was a nonsignificant trend for improved overall sur-

vival (OS) for patients treated with letrozole vs tamoxifen (HR 0.87; 95% CI 0.75 to 1.02; p = 0.08). DFS significantly favoured letrozole (HR 0.88; 95% CI 0.78 to 0.99; p = 0.03).

Table 3 (page 14) shows comparisons between the 3 blinded treatment arms of the “sequential therapy vs letrozole” phase of the trial (the primary core analysis) after median followup of 71 months. There was no difference in DFS between patients on letrozole vs those on letrozole → tamoxifen or vs those on tamoxifen → letrozole (5-year DFS 87.9%, 87.6% and 86.2%, respectively). The investigators suggest a trend favouring upfront letrozole vs tamoxifen → letrozole, although none of the outcome results were statistically different between these 2 groups. Adverse events were as expected for both tamoxifen and letrozole. The authors concluded that the sequential treatment regimes did not improve DFS compared to letrozole alone, that trends support initial use of letrozole in women at higher risk of relapse, and that patients who begin treatment on letrozole can switch to tamoxifen.

TABLE 1. Selected adverse event in the TEAM trial

Type of event	exemestane	tamoxifen	p-value
gynecologic			
vaginal discharge	2.3%	6.8%	p < 0.0001
vaginal hemorrhage	1.6%	3.1%	p < 0.0001
vaginal infection	0.7%	2.2%	p < 0.0001
uterine polyp	0.1%	0.5%	p < 0.0001
endometrial hyperplasia	0.0%	2.0%	p < 0.0001
endometrial cancer	0.1%	0.2%	p = NS
cardiac disorders			
myocardial ischemia or infarction	0.8%	0.6%	p = NS
cardiac deaths	0.4%	0.2%	p = NS
vascular disorders			
hot flush or flushing	28.5%	33.3%	p ≤ 0.001
hypertension	3.3%	2.1%	p ≤ 0.001
thromboembolic events	0.9%	2.3%	p ≤ 0.001
musculoskeletal events			
arthralgia	17.9%	9.2%	p ≤ 0.001
arthritis	3.0%	1.7%	p ≤ 0.001
osteoporosis (reported)	4.7%	2.1%	p ≤ 0.001
fractures (reported)	2.7%	2.3%	p = NS

TABLE 2. The BIG 1-98 trial: analysis of the monotherapy arms letrozole (n= 2463) vs tamoxifen (n=2459) after a median follow-up of 76 months

endpoint	intent-to-treat	censored
Disease-free survival	HR 0.88 95% CI 0.78–0.99 p = 0.03	HR 0.84 95% CI 0.74–0.95 p = n/a
Overall survival	HR 0.87 95% CI 0.75–1.02 p = 0.08	HR 0.81 95% CI 0.69–0.94 p = n/a
Time to distant recurrence	HR 0.85 95% CI 0.72–1.00 p = 0.05	HR 0.81 95% CI 0.68–0.96 p = n/a

Hazard ratios (HR) with 95% confidence intervals (CI)

COMMENTARY: Aromatase inhibitors (AIs) are integral drugs in the treatment of postmenopausal, hormone-sensitive breast cancers. Several large, adjuvant Phase III randomized controlled trials have now reported results using all 3 commercially available third-generation AIs, namely, anastrozole, letrozole and exemestane. Compared to the previous gold standard, the selective-estrogen receptor modulator tamoxifen, AIs appear to confer modest improvement in DFS and reduced distant recurrences.¹⁻³

Exemestane vs tamoxifen

At the 2008 SABCs meeting, the TEAM trial investigators presented results of upfront adjuvant treatment with the steroidal AI exemestane. This trial showed a trend for improved DFS with exemestane for 5 years compared to upfront tamoxifen, with a nonsignificant HR of 0.89. It also showed improved RFS and reduced time to distant metastases (TTDM) with exemestane. Unfortunately, these results are affected by the significant proportion (29%) of patients randomized to tamoxifen who discontinued the drug prior to the switch, compared to only 19% in the exemestane arm having discontinued treatment. Because of concerns about compliance, a separate analysis looked at endpoints only in pre-switch patients who were confirmed to be taking their assigned drug regimen, and excluded 96 of the 9766 patients available for efficacy analysis who never started their assigned therapy (51 assigned to tamoxifen and 45 to exemestane). This analysis reported a significant

TABLE 3. The BIG 1-98 trial: analysis comparing sequential therapy (tamoxifen → letrozole or letrozole → tamoxifen) vs letrozole alone; hazard ratios (HR) with 99% confidence intervals (CI) to account for multiple comparisons

Endpoint	T→L vs L ¹ (n = 3094)	L→T vs L ² (n = 3086)
disease-free survival (all patients)	HR 1.05 99% CI 0.84–1.32	HR 0.96 99% CI 0.76–1.21
node-negative patients (n = 1760)	HR 0.96 99% CI 0.67–1.38	HR 0.97 99% CI 0.67–1.39
node-positive patients (n = 1280)	HR 1.13 99% CI 0.84–1.53	HR 0.98 99% CI 0.72–1.33
overall survival	HR 1.13 99% CI 0.83–1.53	HR 0.90 99% CI 0.65–1.24
time to distant recurrence	HR 1.22 99% CI 0.88–1.69	HR 1.05 99% CI 0.75–1.47

¹ tamoxifen for 2 years followed by letrozole for 3 years vs letrozole for 5 years

² letrozole 2 for years followed by tamoxifen for 3 years vs letrozole for 5 years

improvement in DFS with a HR of 0.83 (p = 0.02) with upfront exemestane. However, in the ITT population, the higher noncompliance rates with tamoxifen should favour outcomes in patients taking exemestane by comparison. These data attest to a possibly higher rate of side effects affecting quality of life in the tamoxifen arm — one of the main reasons for noncompliance. It is also unclear whether

those patients opting to discontinue tamoxifen may have actually started exemestane off-protocol, a concern in this open-label trial. One might conclude that despite these issues, the results of the TEAM trial are consistent with the ATAC and BIG 1-98 results showing advantage of AIs over tamoxifen, although the TEAM results appear less robust.^{1,2}

Letrozole vs tamoxifen

The BIG 1-98 investigators provided an updated analysis of the adjuvant monotherapy arms of tamoxifen vs letrozole after median followup of more than 6 years. These results in the ITT population confirmed significantly improved DFS favouring letrozole and nonsignificant improvements in time to distant recurrences (TTDR) and OS, also in favour of letrozole. The OS results are unfortunately affected by the fact that approximately a quarter of the patients randomized to tamoxifen alone opted to switch to letrozole once initial results of BIG 1-98

FIGURE 1. BIG 1-98 trial design as reported at SABCs 2008

		treatment arm	number of patients	
2-arm phase	A	tamoxifen	n = 911	enrolled 1998-2000
	B	letrozole	n = 917	
	C	total	n = 1828	
4-arm phase	D	tamoxifen	n = 1548	enrolled 1999-2003
	E	letrozole	n = 1546	
	F	tamoxifen → letrozole	n = 1548	
	G	letrozole → tamoxifen	n = 1540	
	H	total	n = 6182	D+E+F+G
monotherapy comparison		tamoxifen vs letrozole	n = 4922	A+D vs B+E
sequential comparisons		letrozole vs tamoxifen → letrozole	n = 3094	E vs F
		letrozole vs letrozole → tamoxifen	n = 3086	E vs G

were released in 2005. The investigators suggest an OS and TTDR benefit with upfront use of letrozole compared to tamoxifen in patients censored at crossover but the robustness of this analysis is unclear.

Remaining questions

In summary, based on results from BIG 1-98, ATAC and now the TEAM trial, upfront use of an AI vs tamoxifen confers reduced breast cancer recurrences and distant recurrences, and whether an overall survival benefit emerges remains to be determined. Three questions remain.

First, what is the best strategy for incorporating AIs into adjuvant treatment of early breast cancer in postmenopausal women: upfront or sequentially with tamoxifen? The BIG 1-98 data suggest that all 3 strategies are potentially equivalent, with a trend favouring outcomes in women taking letrozole for 5 years compared to those taking tamoxifen for 2 years followed by letrozole. The TEAM results exploring 5 years of exemestane vs tamoxifen followed by exemestane will not be available until perhaps later this year. The sequential strategy has potential benefits in decreasing the incidence of toxicities associated with each class of drug and lower overall treatment cost. One approach is to use an upfront AI in patients at highest risk of an early breast cancer recurrence. The BIG 1-98 investigators previously reported prognostic factors for early relapse (within 2 years). These were node positivity, low level of hormone receptor expression, high tumour grade, HER2 overexpression, large tumour size and vascular invasion.⁴ Data from the British Columbia Agency Cancer Agency suggests that women with positive lymph nodes, high-grade tumours or low estrogen receptors have a higher risk (> 10%) for relapse within the first 2.5 years.⁵ However, it is unknown if these adverse prognostic factors will also be predictive for upfront use of an AI in ultimately conferring an overall survival benefit vs tamoxifen.

Second, what is the optimal duration of endocrine treatment that initially included an AI? The NSABP B.42 trial (NCT00382070) randomizes postmenopausal women to 5 more years of the AI letrozole or to placebo after 5 initial years of hormonal therapy that included an AI. The Canadian-led NCIC MA.17R (NCT00754845) is also exploring endocrine therapy duration. Both trials are actively recruiting in Canada with results not expected for many years. Neither BIG 1-98, ATAC nor TEAM explore this issue.

Finally, which AI? Because all 3 agents now have trial data in the upfront setting as well as in a switching or sequencing strategy,^{1-3,6,7} women have many choices. In terms of upfront use, the longest median followup is in the ATAC trial of anastrozole, with 100 months. No direct comparisons of the 3 AIs are available but results are anticipated from the NCIC MA.27 trial (NCT00066573, closed) of adjuvant anastrozole vs exemestane and the ongoing Femara versus Anastrozole Clinical Evaluation (FACE) trial.⁸ All AIs are not equivalent in terms of potency of estrogen suppression but it remains to be seen whether the minute differences in levels of hormone suppression will lead to meaningful differences in clinical efficacy.

In brief

Already known

- The aromatase inhibitors anastrozole and letrozole used as initial hormonal adjuvant therapy in postmenopausal women with hormone-sensitive breast cancer have been shown in large randomized Phase III trials to improve rates of disease-free survival, relapse-free survival and time to distant metastasis compared to tamoxifen.

What these studies showed

- This analysis from the TEAM trial showed improved relapse-free survival and time to distant metastasis with the aromatase inhibitor exemestane vs tamoxifen as initial adjuvant hormonal therapy in postmenopausal women with hormone-sensitive breast cancer, with no unexpected adverse events, at 2.75 years median followup. Results were complicated by non-compliance, and disease-free survival was significantly different only when patients who received the study drug were analyzed.
- These results from BIG 1-98 at median followup of 76 months confirmed significantly improved disease-free survival, favouring letrozole over tamoxifen, and nonsignificant improvements in time to distant recurrence and overall survival, also in favour of letrozole. Results were confounded by a large number of the patients randomized to tamoxifen switching to letrozole when earlier results were released.
- Upfront letrozole appeared to be as efficacious as letrozole → tamoxifen or tamoxifen → letrozole.

Next steps

- It is hoped that results of ongoing studies will answer the 3 questions of whether aromatase inhibitors are most effective given upfront or sequentially with tamoxifen, the optimal duration of endocrine treatment and which aromatase inhibitor has the best efficacy and safety profile.

Clinical implications

The strategy of an AI upfront is effective in reducing breast cancer recurrences compared to tamoxifen alone, but for the time being, survival remains the same. Switching to an AI after 2–3 years of tamoxifen is also effective, as is switching to tamoxifen after 2 years of letrozole. The optimal strategy remains unknown but it is reasonable to start an AI in patients at high risk for an early breast cancer recurrence. All 3 AIs have now reported data in the adjuvant setting but the duration of treatment remains unknown and clinical trial enrollment is encouraged. Ultimately, after detailed

discussion, the patient will choose her treatment. Notwithstanding the controversies, these incremental, albeit modest, improvements in breast cancer outcomes are vital.

References

1. Forbes JF, Cuzick J, Buzdar A et al, Arimidex, Tamoxifen; Alone or in Combination (ATAC) Trialists' Group. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9(1):45-53.
2. Mouridsen H, Giobbie-Hurder A, Mauriac L et al. BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. SABCS 2008, Abstract 13.
3. Jones SE, Seynaeve C, Hasenburg A et al. Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer. SABCS 2008, Abstract 15.
4. Mauriac L, Keshaviah A, Debled M et al; BIG 1-98 Collaborative Group; International Breast Cancer Study Group. Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial. *Ann Oncol* 2007;18(5):859-67.
5. Kennecke H, McArthur H, Olivetto IA et al. Risk of early recurrence among postmenopausal women with estrogen receptor-positive early breast cancer treated with adjuvant tamoxifen. *Cancer* 2008;112(7):1437-44.
6. Coombes RC, Hall E, Gibson LJ et al; Intergroup Exemestane Study. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *NEJM* 2004;350(11):1081-92.
7. Jakesz R, Gnani M, Griel R et al. Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: updated data from the Austrian breast and colorectal cancer study group trial 8.. SABCS 2008, Abstract 14.
8. O'Shaughnessy J. A decade of letrozole: FACE. *Breast Cancer Res Treat* 2007;105 (Suppl 1):67-74.

Zoledronic acid and bone loss in women receiving letrozole

Sunil Verma, MD, MSED, FRCPC, Medical Oncologist, Odette Cancer Centre, and Danny Robson, MD, FRCPC, Breast Oncology Fellow, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON.

H. Eidtmann et al. **The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST.** SABCS 2008, Abstract 44.

TRIAL SUMMARY: The Zometa Other Femara Adjuvant Synergy Trial (ZO-FAST) enrolled 1074 postmenopausal women with hormone receptor-positive early breast cancer and bone mineral density (BMD) T-scores of not less than -2 (i.e. not osteoporotic). Patients were randomized to receive the aromatase inhibitor letrozole 2.5 mg for 5 years plus either immediate zoledronic acid 4 mg intravenously every 6 months (i.e. regardless of BMD), or delayed zoledronic acid at the same dose, if their BMD T-score declined below -2 or if they had a clinical or asymptomatic fracture. This followup report at 36 months showed that immediate zoledronic acid improved the outcome with a 9.29% gain in BMD ($p < 0.0001$) at the lumbar spine and 5.41% ($p < 0.0001$)

at the hip, compared to delayed zoledronic acid. However, the difference in number of patients experiencing clinical fractures was not significant, with 24 (4.6%) in the immediate group and 26 (4.9%) in the delayed group ($p = 0.502$). Adverse events did not change from previous reports. Interestingly, the difference in rate of DFS was significant, with 22 recurrence events in the immediate group vs 37 in the delayed group (HR 0.588; 95% CI 0.361 to 0.959; $p = 0.0314$). The authors concluded that these results continue to demonstrate that zoledronic acid prevents bone loss in postmenopausal women receiving adjuvant endocrine therapy for breast cancer, and that the beneficial effect on disease events needs further followup.

COMMENTARY: ZO-FAST was originally designed as a companion trial to the Z-FAST and E-ZO-FAST trials, but with a larger, more international patient accrual. Data from 36 months of followup were presented at SABCS 2008, adding to previous reports of both 12 and 24 months of followup.^{1,2} The benefit between upfront and delayed zoledronic acid (ZA) in lumbar BMD, the primary endpoint, continued to be statistically significant. Similar results were evident in the 36-month update of the Z-FAST trial presented at SABCS 2007³ and the 12-month dataset from E-ZO-FAST at ECCO 2007.⁴

Despite these significant results, the bone health benefit has yet to translate into a significant reduction in fractures. The incidence of clinical and radiographic fractures was 4.6% and 0.6% vs 4.9% and 1.5% in the upfront and delayed arms, respectively. Combining data from both the Z-FAST and ZO-FAST trials, representing 1667 patients, still yielded

no benefit in fracture reduction (2.2% vs 2.1%).⁵ The most recently published ASCO guidelines (2003) mandate use of bisphosphonates, either oral or intravenous, only when BMD falls into the osteoporotic range or for patients with osteopenia and significant risk factors for fractures.⁶ Indeed, when ZA is measured against an oral bisphosphonate such as risedronate, no significant difference in improving bone health is seen.⁷

More importantly, however, intravenous ZA may have profound antitumour properties: ZO-FAST is yet another adjuvant bisphosphonate trial to support a benefit in DFS. The original adjuvant clodronate trial was the first to show a reduction in both skeletal and visceral relapse,⁸ although subsequent clodronate studies have failed to definitively support this association.⁹ More recently, the updated Austrian Breast & Colorectal Cancer Study Group (ABCSG)-12 trial, which reported survival endpoints at ASCO 2008,

demonstrated a 36% reduction in breast cancer recurrence due to zoledronic acid, with reductions of both local and distant relapse events.¹⁰ This benefit is comparable to that seen with the addition of adjuvant taxanes: another SABCS 2008 presentation showed that the number needed to treat (NNT) to prevent 1 breast cancer recurrence event is 28 patients for paclitaxel, 31 for docetaxel and 31 for ZA.¹¹ A combined analysis of the Z-FAST and ZO-FAST trials also revealed similar improvement in 12-month DFS with the addition of upfront vs delayed ZA, with a 59% reduction of events (absolute: 98.9% vs 97.7%; $p = 0.0396$).⁵

Zoledronic acid is not yet approved in Canada for the adjuvant care of women with early invasive breast cancer. While some maintain that results are too immature and that further study is warranted, this is the second adjuvant trial to support the benefit of ZA in the adjuvant setting. After the release of the ABCSG results, there were some initial concerns about the strict inclusion criteria for that study and whether its data can be extrapolated to patients who have received adjuvant chemotherapy and to postmenopausal patients in general. The ZO-FAST trial results help confirm a benefit in these other populations, further supporting the hypothesis that this drug likely has a therapeutic role beyond improvement in bone health.

Results of other upcoming adjuvant bisphosphonate trials are eagerly awaited. The large, Phase III AZURE trial (BIG-1-04, NCT00072020) investigating the effect of adding ZA to neoadjuvant or adjuvant chemotherapy has now completed accrual, with results expected next year. The role of adjuvant clodronate will be better defined once final results of the NSABP B-34 (NCT00009945) trial of adjuvant clodronate vs placebo are available. Other key trials include the German Adjuvant Intergroup Node-positive (GAIN) study (NCT00196872) evaluating adjuvant ibandronate vs placebo and the MAC-12 trial (NCT00310180) of adjuvant clodronate vs ibandronate vs ZA. Some preliminary results in the neoadjuvant setting also presented at the SABCS 2008 conference indicate that ZA may work synergistically with chemotherapy, with improvement in pathologic complete response rates.¹² In addition to the efficacy results, there will be increased focus on the toxicity observed in these trials, in particular the rates of osteonecrosis of the jaw. In the meantime, while some clinicians are considering this class of drugs in the adjuvant setting for patients at high risk of recurrence, we do need the final results from the aforementioned adjuvant trials before use of these bisphosphonates becomes routine in the adjuvant setting.

References

1. Bundred NJ, Campbell ID, Davidson N et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008;112(5):1001-10.
2. De Boer R, Eidtmann H, Lluch A et al. The ZO-FAST trial: zoledronic acid effectively inhibits aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 24 month BMD results. SABCS 2007, Abstract 501.
3. Brufsky A, Bosserman L, Caradonna R et al. The effect of zoledronic acid on aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: the Z-FAST study 36-month follow-up. SABCS 2007, Abstract 27.

In brief

Already known

- Earlier data from this study and smaller prior studies had shown that the intravenous bisphosphonate zoledronic acid prevents bone loss in postmenopausal women receiving adjuvant endocrine therapy for breast cancer.
- Differences in disease-free survival (DFS) in breast cancer patients, favouring use of bisphosphonates over no bisphosphonate, had been reported.

What this study showed

- At 36 months median followup, this study continues to support the bone density benefit seen previously; however, even when combined with results of 2 similar studies of zoledronic acid, no difference in fracture rates was seen.
- DFS was significantly prolonged in women receiving zoledronic acid early compared to those receiving it later.

Next steps

- Efficacy and toxicity results of other adjuvant bisphosphonate trials are needed before adopting routine use of bisphosphonates in adjuvant treatment of early breast cancer.

4. Schenk N, Lombart A, Frassoladti A et al. The EZO-FAST trial: Zoledronic acid (ZA) effectively inhibits aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (EBC) receiving adjuvant Letrozole (Let). *European Journal of Cancer Supplements* 2007;5(4):186. ECCO 2007, Abstract 2008.
5. Brufsky A, Bundred N, Coleman R et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008;13(5):503-14.
6. Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;21(21):4042-57.
7. Van Poznak C, Hannon R, Clack G, et al. Managing cancer treatment-induced bone loss: 24-month results from the study of Anastrozole with the bisphosphonate Resedronate (SABRE). SABCS 2007, abstract 1137.
8. Diel IJ, Solomayer EF, Costa SD et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *NEJM* 1998;339(6):357-63.
9. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007;96(12):1796-801.
10. Gnant M, Mlineritsch B, Schippinger W et al. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. SABCS 2008, Abstract LBA4.
11. Gnant M, Mlineritsch B, Schippinger W et al. The number needed to treat (NNT) as a measure of drug efficacy: the case of zoledronic acid for early hormone-responsive breast cancer in the ABCSG-12 trial. SABCS 2008, Abstract 2113.
12. Winter MC, Thorpe HC, Burkinshaw R et al. The addition of zoledronic acid to neoadjuvant chemotherapy may influence pathological response – exploratory evidence for direct anti-tumor activity in breast cancer. SABCS 2008, Abstract 5101.

Lapatinib added to endocrine therapy in metastatic breast cancer

Sunil Verma, MD, MSc, FRCPC, Medical Oncologist, Odette Cancer Centre, and Danny Robson, MD, FRCPC, Breast Oncology Fellow, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON.

S. Johnston et al. **Lapatinib combined with letrozole vs. letrozole alone for front line postmenopausal hormone receptor positive (HR+) metastatic breast cancer (MBC): first results from the EGF30008 Trial.** SABCs 2008, Abstract 46.

TRIAL SUMMARY: The Phase III EGF30008 trial randomized 1286 postmenopausal women with hormone receptor-positive untreated metastatic breast cancer (219 of whom were HER2-positive by IHC 3+ and/or FISH amplification) to receive letrozole 2.5 mg plus either lapatinib 1500 mg or placebo, once per day. Median PFS, the primary endpoint, was significantly higher in the HER2-positive women who received lapatinib compared to those on placebo, at 8.2 months vs 3.0 months respectively (HR 0.71; 95% CI 0.53 to 0.96; $p = 0.019$). Median PFS in the intent-to-treat population, a secondary endpoint, was 19.9 months vs 10.9 months, respectively (HR 0.86; 95% CI 0.76 to 0.98; $p = 0.026$). Overall response rate in the HER2-positive patients

was 27.9% in the lapatinib group vs 14.8% in the placebo group (odds ratio 0.4; 95% CI 0.2 to 0.9; $p = 0.021$), and the clinical benefit rate (definition not given) was 47.7% vs 28.7% (odds ratio 0.4; 95% CI 0.2 to 0.8; $p = 0.003$). No differences were seen in overall response or clinical benefit rates in the HER2-negative women. The HER2-positive women also showed a possible trend towards improved overall survival (HR 0.74; 95% CI 0.5 to 1.1; $p = 0.113$). Patients tolerated the combination therapy well and no new safety concerns were identified. The authors concluded that adding lapatinib to the aromatase inhibitor letrozole significantly improved clinical efficacy in women with hormone receptor-positive, HER2-positive metastatic breast cancer.

COMMENTARY: Although the EGF30008 trial design was a simple 2-arm randomization to lapatinib + letrozole vs letrozole alone as first-line therapy in women with advanced breast cancer, the heterogeneity of the trial population and analyses suggest that this was 3 trials in one.

HER2-positive and hormone receptor-positive disease

The first analysis focused on the women with HER2-positive and hormone receptor-positive breast cancer, representing around 17% of the entire trial population. The addition of lapatinib to letrozole in this cohort nearly doubled the overall response rate (ORR), from 15% to 28%, and almost tripled PFS (3.0 months to 8.2 months). This is the second confirmatory trial of dual receptor blockade. It confirms the results seen from the TAnDEM trial, presented at SABCs 2006, where adding trastuzumab to anastrozole doubled PFS from 2.4 months to 4.8 months in women with HER2-positive, estrogen receptor-positive metastatic breast cancer.¹

Both the EGF30008 and the TAnDEM trials highlight the limited benefit of aromatase inhibitor therapy alone for such patients. An alternative approach, using chemotherapy in combination with lapatinib, was evaluated in another poster at SABCs 2008.² This Phase 2 trial reported on the combination of lapatinib with weekly paclitaxel in 57 patients with advanced breast cancer. Despite the poor prognosis of the patient population (86% with visceral disease) the reported PFS of 12 months (47.9 weeks) seems more robust than with the combination of targeted HER2 and endocrine inhibition (32.8 weeks).

HER2-negative disease

The second analysis was done on the HER2-negative cohort, the remaining 83% of the trial participants. Only 15% of

these women had bone metastases (limited), and approximately 85% had visceral involvement — figures similar to their HER2-positive counterparts. There was no incremental benefit in ORR (32% vs 33%) or PFS (13.4 to 13.7 months) with the addition of lapatinib to letrozole. Similar results have been found in the recently reported Phase III trial of lapatinib + paclitaxel in women with HER2-negative or unknown advanced breast cancer.³ Breast cancer event-free survival was similar (22.6 weeks vs 25.1 weeks) despite the addition of lapatinib.

Lapatinib is a dual HER2 and EGFR antagonist, and although there is often an inverse relationship between estrogen receptor expression and EGFR overexpression, the EGFR pathway may be important in the development of hormone therapy resistance. Osborne et al previously confirmed the benefit of adding gefitinib (an EGFR inhibitor without anti-HER2 activity) to tamoxifen in tamoxifen-resistant disease,⁴ with a 2-month improvement in PFS (although without statistical significance) seen for women with combined estrogen receptor and EGFR blockade (HR 0.84; 95% CI 0.59 to 1.18).

Hormone therapy-resistant disease

In the third analysis of the EGF30008 trial, a preplanned exploratory stepwise Cox proportional hazard analysis for PFS, the group of women who relapsed within 6 months of completing 5 years of adjuvant tamoxifen (21% of HER2-negative patients) had improved PFS (3.1 vs 8.3 months) with the addition of lapatinib, similar to the benefit seen in the HER2-positive cohort. Lapatinib offered no benefit to women who relapsed more than 6 months after completing adjuvant tamoxifen, or who had never received adjuvant endocrine therapy.

Clinical implications

So how best to integrate such data into our own practice? First, we are still awaiting the approval of lapatinib in Canada. The SABCS 2008 data along with the TAnDEM results suggest that endocrine therapy alone for patients with estrogen receptor-positive and HER2-positive disease is not sufficient. One has to consider either combination therapy with chemotherapy and an anti-HER2 agent, or endocrine therapy with an anti-HER2 agent. The addition of anti-HER2 therapy to endocrine therapy might be appropriate in women with advanced but indolent hormone receptor-positive and HER2-positive disease. In the remaining patients with non-indolent disease, chemotherapy combined with an anti-HER2 agent is still the mainstay for the majority. Direct comparison between lapatinib and trastuzumab in the advanced setting awaits completion of the National Cancer Institute of Canada (NCIC)-sponsored MA-31 randomized trial (NCT00667251). Second, more evidence is required to validate EGFR blockade in hormone receptor-positive disease. Cristofanilli et al have already reported PFS improved by 6 months with the addition of gefitinib to anastrozole in a Phase II clinical trial presented ASCO 2008.⁵ Data on further studies examining the ideal EGFR inhibitor (gefitinib vs lapatinib) and the optimal setting and timing (e.g. hormone-resistant vs biopsy-proven EGFR overexpression) will be forthcoming.

References

1. Mackey JR, Kaufman B, Clemens M et al. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2006;100 (suppl 1). SABCS 2006, Abstract 3.
2. Jagiello-Gruszfeld A, Tjulandin Sergei S, Dobrovolskaya N et al. Lapatinib (L) with weekly paclitaxel (P) as first-line therapy for patients (pts) with HER2+ metastatic breast cancer (MBC). SABCS 2008, Abstract 3145.
3. Di Leo A, Gomez HL, Aziz Z et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol* 2008;26(34):5544-52.
4. Osborne C, Neven P, Dirix L et al. Randomized Phase II study of gefitinib (IRESSA) or placebo in combination with tamoxifen in patients with hormone receptor positive metastatic breast cancer. SABCS 2007, Abstract 2067.
5. Cristofanilli M, Valero V, Mangalik A et al. A phase II multicenter, double-blind, randomized trial to compare anastrozole plus gefitinib with anastrozole plus placebo in postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer (MBC). *J Clin Oncol* 2008;26(May 20 suppl) ASCO 2008, Abstract 1012.

In brief

Already known

- Adding the HER2-inhibitor trastuzumab to the aromatase inhibitor anastrozole had been shown to double progression-free survival (PFS) in women with HER2-positive, estrogen receptor-positive metastatic breast cancer.
- Adding the EGFR-inhibitor gefitinib to tamoxifen provided no statistically significant improvement in PFS in women with tamoxifen-resistant breast cancer.

What this study showed

- In women with HER2-positive and hormone receptor-positive disease, adding lapatinib to letrozole nearly doubled the overall response rate and almost tripled PFS.
- In women with HER2-negative disease, no benefits in overall response rate or PFS were seen.
- Among women with hormone therapy-resistant disease, those who relapsed within 6 months of completing adjuvant tamoxifen had improved PFS, similar to the women with HER2-positive disease, with the addition of lapatinib.

Next steps

- Await approval of lapatinib by Health Canada.
- Meanwhile, women with disease that is both estrogen receptor-positive and HER2-positive should consider treatment with either chemotherapy combined with an anti-HER2 agent (e.g. trastuzumab) or endocrine therapy combined with an anti-HER2 agent.

Using breast density to predict tamoxifen efficacy in breast cancer prevention

Joseph Ragaz, MD, FRCPC, Medical Oncologist; Clinical Professor and Senior Oncology Researcher, McGill University, Montreal, QC.

Cuzick J, Warwick J, Pinney L et al. et al. **Change in breast density as a biomarker of breast cancer risk reduction; results from IBIS-I.** SABCS 2008, Abstract 61.

STUDY SUMMARY: This analysis aimed to determine whether the change in breast density observed in the International Breast Cancer Intervention Study (IBIS-I)¹ predicted the impact of tamoxifen on subsequent breast cancer development in high-risk women. IBIS-I participants received

60 months of tamoxifen given as prophylactic therapy to prevent breast cancer, or placebo. The present re-analysis examined mammograms at study entry and at 12–18 months in women who developed breast cancer and 943 controls who did not. A consultant radiologist visually assessed

LANDMARKS

mammographic density as a percentage of the total breast area. Multivariate analysis showed significant preventive effects of mammographic density at entry, body mass index (BMI), breast cancer risk by the Cuzick-Tyrer model and change in density during the first 12–18 months of tamoxifen. In the tamoxifen patients (n = 504, 48 with breast cancer and 456 without), at 95.6 months median followup, only change in mammographic density was a significant predictor (p = 0.05) of subsequent breast cancer development. As shown in **Table 4**, the 46% of women receiving tamoxifen whose density declined by 10% or more had a 63% relative reduction in the risk of breast cancer compared to the control group (p = 0.002) while no risk reduction was seen in the 54% of women whose density was not reduced by at least 10%. The authors suggested that changes in breast density

TABLE 4. Effect of tamoxifen on breast cancer risk according to breast density reduction at 12–18 months in the IBIS-I trial

	relative risk	95% CI	p-value
> 10% density change	0.37	0.20–0.69	p = 0.002
< 10% density change	1.03	0.66–1.61	
all patients	0.73	0.58–0.91	p = 0.004

after 12–18 months of prophylactic tamoxifen may predict the impact of tamoxifen in preventing breast cancer, but that this needs to be confirmed by other studies.

COMMENTARY: This study, based on the IBIS-I trial,¹ aimed to examine the impact of breast density dynamics on the risk of future breast cancer, as assessed by conventional mammography done within 12–18 months after the start of tamoxifen. Cuzick et al’s SABCs 2008 presentation, summarized above, identified a subgroup of women who may derive more benefit from hormonal chemoprevention — for whom the benefits are likely to offset the side effects. For the first time, results imply that change in breast density could be a strong predictive factor for the effectiveness of tamoxifen in preventing breast cancer. Because the preventive effect can be monitored in the early stages of treatment, patients who benefit can be identified early and the others can cease treatment, thus avoiding side effects.

Earlier research on tamoxifen’s role in breast cancer prevention

In IBIS-I, a mostly UK-based trial, a population of women at high risk for developing breast cancer was randomized to tamoxifen 20 mg/day for 60 months (n = 3579) vs placebo (n = 3575). The first analysis in 2002² already confirmed a significant reduction of breast cancers and hazards, and was

included in a meta-analysis of 5 randomized trials published soon afterwards.³ The updated analysis at 96 months¹ confirmed a 27% significant reduction of breast cancer risk due to tamoxifen (p = 0.004), with benefit restricted to estrogen receptor-positive cancers, and no ability to reduce estrogen receptor-negative tumours. These findings were congruent with those described by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of tamoxifen’s effect in adjuvant treatment of breast cancer,⁴ with a tamoxifen competing-cause mortality model,⁵ and with the 2003 meta-analysis of all the tamoxifen prevention trials.³

Notably, the reduction of estrogen receptor-positive breast cancers was almost 3-fold higher in the 10-year compared to the 5-year analysis, while the side effects including rates of uterine cancer, thromboembolism and gynecologic symptoms were lower in years 5–10 than in years 1–5. These data indicated an improved cost-benefit ratio with longer followup. Similar observations will probably not be available from The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 tamoxifen prevention trial — the only other randomized trial with sufficient sample size and followup duration — due to crossover to tamoxifen of women initially assigned to placebo soon after the first publication showing tamoxifen benefit.⁶ Thus, the IBIS-I data indicated that estrogen receptor-positive breast cancers can be prevented, and that if patients are carefully selected for, the long-term risks may be more acceptable. They highlighted the need for new approaches to prevent estrogen receptor-negative breast cancers. Biologics that interrupt the impact of carcinogenic signal molecules, implemented in the early stages of hormone-refractory carcinogenesis, are the obvious candidate agents.

The IBIS-I data also highlight the need to optimize the cost-benefit ratio of tamoxifen given in the preventive setting to high-risk women who are otherwise in good health. One direction highlighted by Cuzick’s SABCs 08 presentation is to identify a subgroup that may derive more benefit from hormonal chemoprevention — in whom the benefits are more likely to offset the hazards.

TABLE 5. Correlation of mammographic breast density with breast cancer risk rates from a meta-analysis including more than > 14,000 cases and 226,000 noncases⁵

breast percentage density category	relative risk	95% CI
I (5% to 24%)	1.79	1.48–2.16
II (25% to 49%)	2.11	1.70–3.63
III (50% to 74%)	2.92	2.49–3.42
IV (75% to 100%)		

Breast density and breast cancer

That mammographic density is an important risk factor for breast cancer was first recognized by Wolfe in the 1970s.⁷ His pioneering observation has since been confirmed in a recent meta-analysis of more than 42 studies (> 14,000 cases and 226,000 noncases),⁸ the vast majority of which have shown a positive association between increased mammographic density and increased risk of breast cancer. **Table 5** shows breast cancer risk rates relative to breast density of less than 5% in the woman's most recent mammogram.⁸ Incident breast cancer rates were significantly increased in parallel with increasing breast density categories, with the lowest relative risk (RR) rates in category I (breast density 5% to 24%; RR = 1.79) and highest in the category IV (breast density 75% to 100%, RR = 4.64). Boyd et al have shown the importance of breast density, independent of age, in multiple studies, as a risk factor for breast cancer.⁹ A recent *New England Journal of Medicine* editorial¹⁰ states that only 2 other prognostic factors would increase the risk more substantially than mammographic density: age and mutations in the breast cancer-susceptibility genes BRCA1 and BRCA2.

Cuzick et al's SABCS 2008 analysis

The current report by Cuzick et al at SABCS 08 examined whether mammographic breast density (MBD) of women participating in the IBIS-I trial had both prognostic and predictive significance for breast cancer. The mammograms were assessed using conventional mammography at 12–18 months after randomization. Results, shown in **Table 4**, confirmed that the reduction of breast density in women allocated to tamoxifen was associated with significantly more benefit in reducing the risk of future breast cancer (RR 0.37; $p = 0.002$) than in the tamoxifen-treated cases without breast density changes (RR 1.03). It is of great interest that breast density reductions among controls who did not receive tamoxifen had no impact on breast cancer occurrence ($p = 0.62$): the authors suggest this may represent physiologic involutory changes not related to any therapeutic effect, at least in the short term. In multivariate analysis, the reduction in breast density in the tamoxifen group was more significantly associated with reduced breast cancer risk than either baseline breast density at diagnosis or BMI — both well-established risk factors for breast cancer. In the placebo arm, breast density change was not more significant than these other factors.

The study makes several important observations. It highlights that tamoxifen does work in the setting of breast cancer prevention, and that it works best in those whose breast density changes the most. Thus, MBD is emerging as a potentially important biomarker. If this concept is confirmed by other studies and widely adopted, many patients could discontinue tamoxifen after the first round of 12–18 months, instead of the planned 60 months, and be spared unnecessary side effects. A focus on logistic and cost issues will be needed to improve image quality for assessing breast density, with easy reproducibility, maximum objectivity and accuracy.

Cuzick et al's study offers a glimpse into the natural history of breast cancer, with breast density changes emerging as a potentially unique biomarker. If these data are confirmed,

In brief

What we already knew


- Several trials had shown that in women at high risk of developing breast cancer, tamoxifen reduces the risk of estrogen receptor-positive disease.

What this study showed

- In the randomized, controlled IBIS-I trial, women receiving tamoxifen as preventive treatment for developing breast cancer whose breast density declined by 10% or more at 12–18 months were less likely to develop breast cancer compared to tamoxifen-treated patients with breast density reduction less than 10%. Also, no risk reduction was seen among controls, even in those with breast density reduction greater than 10%.
- The reduction in breast density in the women receiving tamoxifen was more significantly associated with reduced breast cancer risk than either baseline breast density at diagnosis or body mass index — other well established risk factors.

Next steps

- Await confirmation from ongoing studies of the predictive effect of breast density reduction in response to selective estrogen receptor modulators (SERMs, e.g. tamoxifen and raloxifene) used in breast cancer prevention.
- If confirmed, breast density change in response to SERM treatment could be implemented as part of breast cancer prevention clinical practice guidelines.
- Improvements in image quality for assessing breast density will be needed to implement such decision-making based on changes in breast density.
- Continue to seek chemopreventive approaches with an improved side effect profile over tamoxifen and raloxifene for estrogen-positive breast cancers, and with better efficacy for estrogen-negative cancers.

then women with more significant reduction of breast density as a result of tamoxifen would benefit to a much higher degree. For them, the tamoxifen-associated hazards may be more acceptable — and chance for cure much higher — at a lower societal cost. 

References

1. Cuzick J, Forbes JF, Sestak I et al; International Breast Cancer Intervention Study I Investigators. Long-term results of tamoxifen prophylaxis for breast

LANDMARKS

- cancer--96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007;99(4):272-82.
2. Cuzick J, Forbes J, Edwards R et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet* 2002;360(9336):817-24.
 3. Cuzick J, Powles T, Veronesi U et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003;361(9354):296-300.
 4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(9472):1687-717.
 5. Ragaz J, Coldman A. Survival impact of adjuvant tamoxifen on competing causes of mortality in breast cancer survivors, with analysis of mortality from contralateral breast cancer, cardiovascular events, endometrial cancer, and thromboembolic episodes. *J Clin Oncol* 1998;16(6):2018-24.
 6. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90(18):1371-88.
 7. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* 1976;37(5):2486-92.
 8. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006 Jun;15(6):1159-69.
 9. Boyd NF, Guo H, Martin LJ, Sun L et al. Mammographic density and the risk and detection of breast cancer. *NEJM* 2007;356(3):227-36.
 10. Kerlikowske K. The mammogram that cried Wolfe. *NEJM* 2007;356(3):297-300.

Disclosure

Drs. Ragaz and Robson report having no potential conflicts of interest related to this article. Dr. Grenier reports being on advisory boards of AstraZeneca and GlaxoSmithKline. Dr. Verma reports receiving research support from and being a consultant and on advisory boards and speakers' bureaus for Amgen, Novartis and Roche.

You're not receiving *Oncology Exchange*?

If you or someone you know would like to receive *Oncology Exchange*, please send an email to circulation@parkpub.com or fill out the online subscription form at www.oncologyex.com.