Intergroup Exemestane Study mature analysis: overall survival data

Jacek Jassem on behalf of the International Exemestane Study Group

The findings of the Intergroup Exemestane Study (IES) challenge the standard adjuvant endocrine therapy consisting of 5 years of tamoxifen therapy in women with oestrogen receptor-positive breast cancer. The IES study confirmed that switching to an aromatase inhibitor (AI) such as exemestane after 2–3 years of tamoxifen therapy resulted in improved survival relative to women remaining on 5 years of tamoxifen therapy. Data from IES concur with the findings of other studies with AIs that support the rationale of switching from tamoxifen to an AI after 2–3 years of tamoxifen in postmenopausal women who remain disease-free.
***Anti-Cancer Drugs* 19 (suppl 1):S3–S7 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2008, **19 (suppl 1)**:S3–S7

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Tamoxifen has traditionally been recognized as the standard adjuvant endocrine therapy for oestrogen receptor-positive (ER +) breast cancer [1]. In postmenopausal women with hormone-sensitive advanced breast cancer resistant to tamoxifen, third-generation aromatase inhibitors (AI) have been effective. Early improvements in disease-free survival (DFS) have also been noted when an AI is given either instead of or sequentially following tamoxifen in postmenopausal women with ER + early breast cancer [1–4].

Little information, however, exists on the long-term effects of AIs after treatment, and whether these early improvements lead to real gains in survival. The global Intergroup Exemestane Study (IES) is the largest long-term double-blind trial ($n = 4724$) in the endocrine treatment setting using a switch strategy. The aim of IES was to determine whether switching to exemestane, a steroidal AI, after 2–3 years of tamoxifen treatment was more effective in terms of improving disease outcomes compared with continuing on 5 years of tamoxifen therapy. Investigators hypothesized that switching to exemestane would improve treatment efficacy and reduce adverse events; carry-over from early exposure to tamoxifen may minimize AI-associated excess loss of bone mineral density (BMD) and reductions in the incidences of thromboembolism and endometrial cancer associated with tamoxifen use were also anticipated [1].

In the IES study, postmenopausal women with unilateral invasive, ER + or ER-unknown breast cancer, who were disease-free on 2–3 years of tamoxifen therapy, were randomly assigned to switch to exemestane 25 mg/day ($n = 2352$) or to stay on tamoxifen 20–30 mg/day ($n = 2372$) for the remainder of the 5-year endocrine treatment period (Fig. 1) [5]. The primary study endpoint was DFS: breast cancer recurrence, new primary (ipsilateral or contralateral) breast cancer and intercurrent death (death without disease relapse). Secondary endpoints included overall survival, incidence of contralateral breast cancer and long-term tolerability and safety. Breast cancer-free survival and time to distant recurrence were also evaluated.

The patient demographics were similar in both treatment arms. Approximately 52% of women in each treatment arm had node-negative breast cancer, one-third had prior chemotherapy and the majority of patients had ER + and progesterone receptor-positive (PR +) status. The intention-to-treat population was used for all efficacy analyses along with a supplementary analysis excluding patients subsequently found to have had ER-negative (ER –) disease, who would otherwise not have been eligible for participation into the trial if their ER status had been known at randomization.

In this patient cohort, more than 95% of patients had a minimum of 3 years' follow-up or had died during the corresponding period [1]. A similar proportion of patients randomized to either exemestane or tamoxifen-completed treatment (1807 vs. 1832) or withdrew from treatment (513 vs. 506). Although there was a numerical increase of withdrawal due to adverse events or patient refusal in the exemestane arm (321 vs. 251 for tamoxifen), there was a smaller number withdrawing owing to breast cancer recurrence or death (133 vs. 194).

After a median follow-up of 55.7 months (range 0–89.7 months), 809 events contributing to the analysis of DFS had been reported (354 exemestane vs. 455 tamoxifen); unadjusted hazard ratio (HR) 0.76 (95% CI: 0.66–0.88; $P = 0.0001$) in favour of exemestane, absolute benefit 3.3% (95% CI: 1.6–4.9) by the end of treatment (i.e. 2.5 years after randomization) [1].

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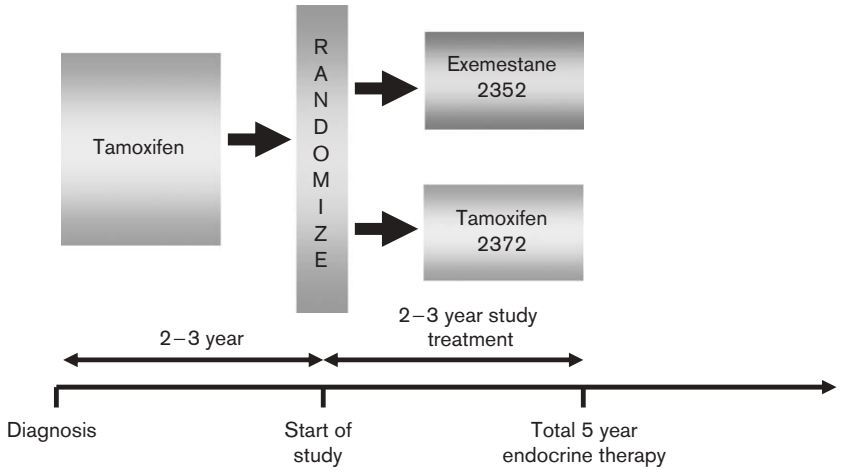
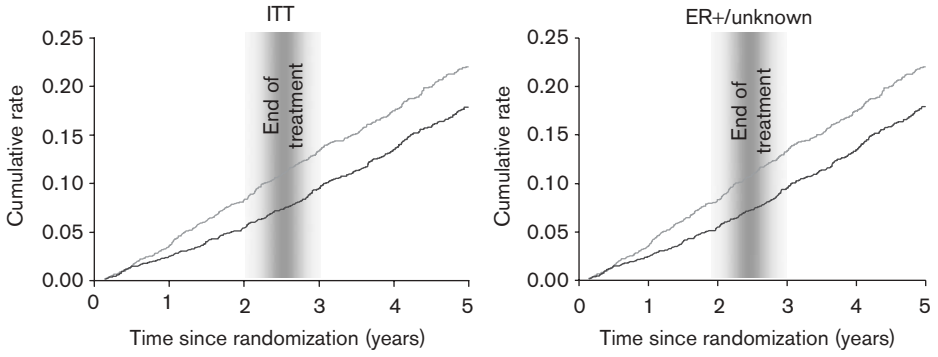
Fig. 1



Intergroup Exemestane Study trial design [2].

Fig. 2



Annual hazard rate, % (95% CI)

ITT	1	2	3	4	5
Exemestane	2.5 (2.0, 3.3)	3.0 (2.4, 3.8)	4.0 (3.2, 4.9)	4.0 (3.1, 5.0)	4.4 (3.4, 5.9)
Tamoxifen	3.6 (2.9, 4.5)	4.7 (3.9, 5.8)	5.0 (4.1, 6.1)	4.2 (3.3, 5.3)	4.6 (3.4, 6.0)

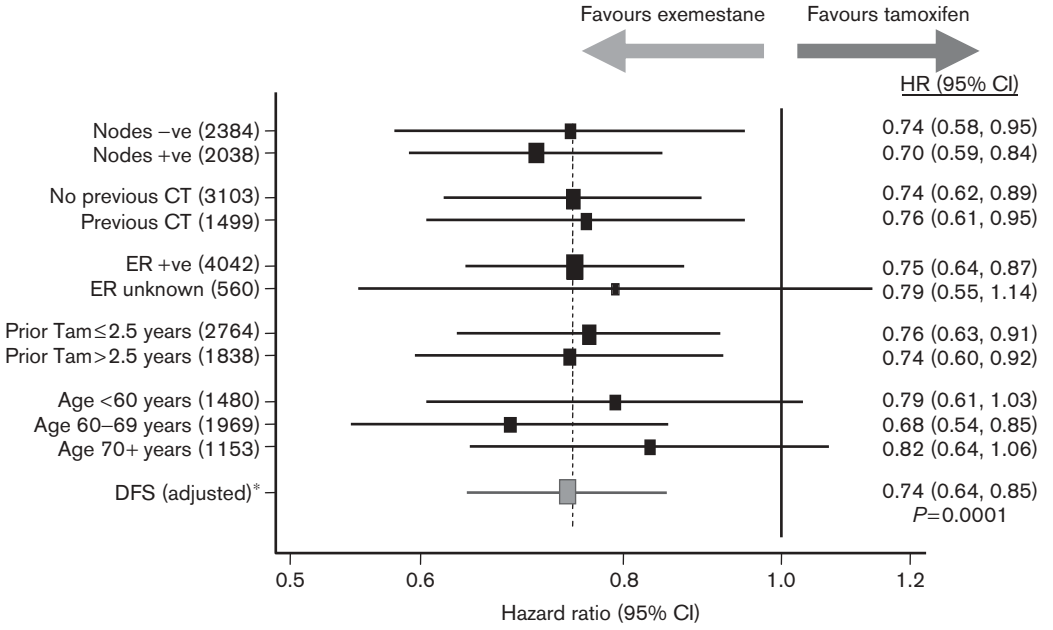
Cumulative hazard rate for disease-free survival in the intention-to-treat and ER+*/unknown populations.
*ER+, oestrogen receptor-positive.

Between the two treatment groups, an early divergence in terms of the cumulative HR was observed and this divergence was maintained at 5 years (Fig. 2).

In terms of events contributing to DFS, distant recurrence (216 vs. 257), local recurrence only (49 vs. 68), contralateral breast primary (18 vs. 35), and intercurrent deaths (71 vs. 95) all occurred with a lower incidence in the exemestane treatment arm. Subgroup analyses in ER+/unknown patients and adjustment for known prognostic factors indicate that the effects were consistent with the overall effect (Fig. 3).

A total of 222 deaths occurred in the exemestane group compared with 261 in the tamoxifen group; unadjusted HR 0.85 (95% CI: 0.71–1.02; $P = 0.08$); 0.83 (95% CI: 0.69–1.00; $P = 0.05$) when 122 patients with ER–

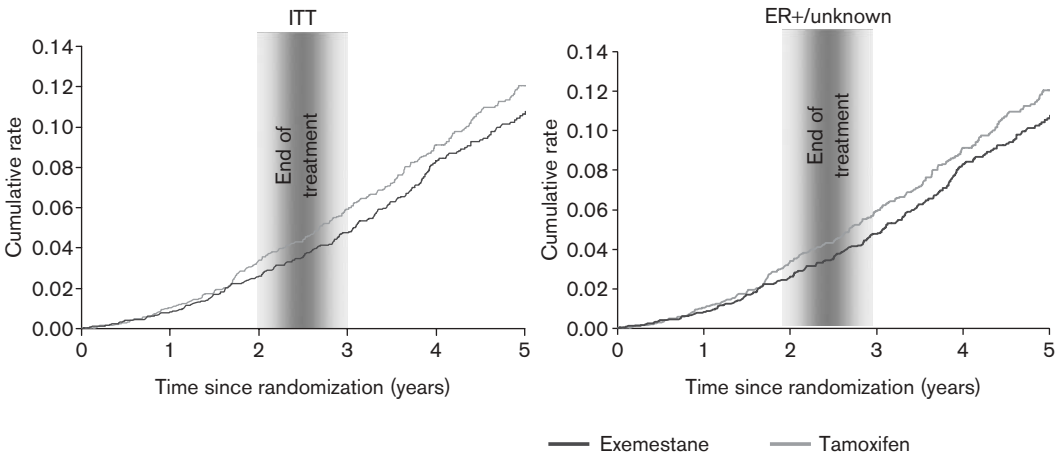
Fig. 3



*Adjusted for nodal status, chemotherapy use and HRT use

Disease-free survival subgroup analysis for patients with ER+*/unknown receptor status.
*ER+, oestrogen receptor-positive.

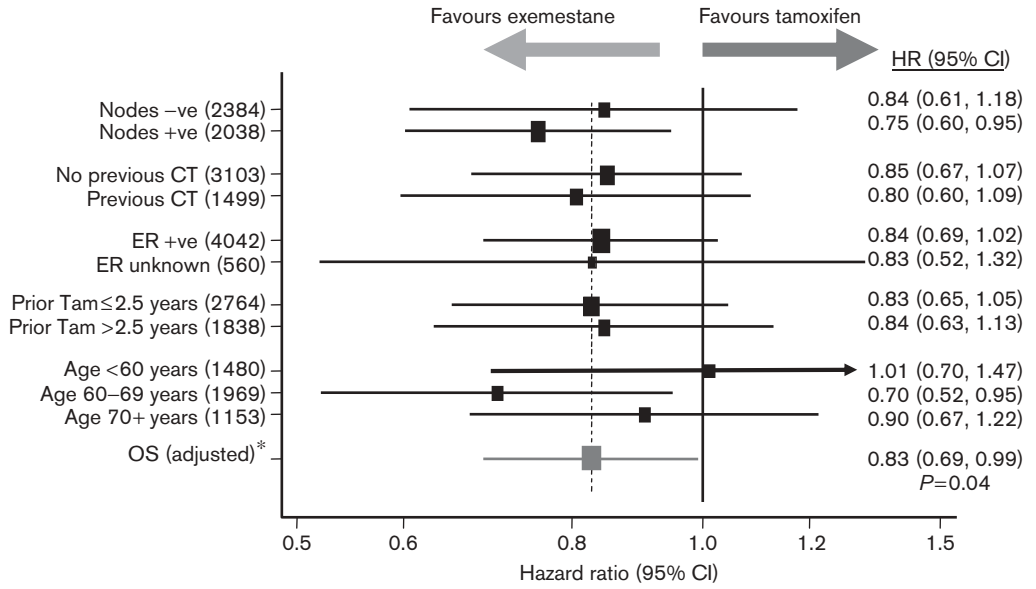
Fig. 4



Annual hazard rate, % (95% CI)					
ITT	1	2	3	4	5
Exemestane	0.8 (0.5, 1.2)	1.8 (1.3, 2.5)	2.2 (1.6, 2.9)	3.6 (2.8, 4.5)	2.3 (1.6, 3.4)
Tamoxifen	1.0 (0.7, 1.5)	2.4 (1.8, 3.1)	2.5 (2.0, 3.3)	3.2 (2.5, 4.1)	2.9 (2.1, 4.1)

Cumulative hazard rate for overall survival for the intention-to-treat and ER+*/unknown populations.
*ER+, oestrogen receptor-positive.

Fig. 5



Overall survival subgroup analysis for patients with ER+*/unknown receptor status.
*ER+, oestrogen receptor-positive.

disease were excluded. The Nelson Aalen cumulative hazard plot for overall survival demonstrates a modest but real benefit favouring the exemestane arm (Fig. 4). Again, subgroup analyses in ER+/unknown patients and adjustment for known prognostic factors indicate that the effects were consistent with the overall effect on overall survival (Fig. 5).

The proportion of secondary malignancies was lower in the exemestane treatment arm (70 vs. 105). Longer-term data may help to elucidate the reasons for this difference.

Serious cardiovascular adverse events were rare. Considering both on treatment only events and including post-treatment events, there was no evidence of a difference between the two groups with regard to the incidence of cardiovascular events (excluding venous thromboembolic events). Myocardial infarctions were also infrequent and not statistically different from tamoxifen, with 31 (1.3%) among exemestane-treated patients compared with 19 (0.8%) in tamoxifen-treated patients ($P = 0.08$). Fewer venous thromboembolic events, however, were reported with exemestane (28 vs. 54 for tamoxifen; $P = 0.004$).

As expected, and in line with other AI studies, there was a greater incidence of musculoskeletal adverse events in the exemestane group, including musculoskeletal pain ($E = 21.0\%$, $T = 16.1\%$; $P < 0.0001$), arthralgia ($E = 18.6\%$, $T = 11.8\%$; $P < 0.0001$) and joint stiffness ($E = 1.9\%$, $T = 1.0\%$; $P = 0.009$). Tamoxifen, however, was associated with a greater incidence of gynaecological adverse events, for example vaginal bleeding ($E = 4.6\%$, $T = 6.5\%$; $P = 0.008$), endometrial hyperplasia ($E = 0.1\%$, $T = 1.0\%$; $P < 0.0001$) and uterine polyps ($E = 1.2\%$, $T = 3.2\%$; $P < 0.0001$).

The results of the IES are in line with the findings of clinical trials employing a switching strategy from tamoxifen to anastrozole [6,7]. These studies support the rationale of switching from tamoxifen to an AI after 2–3 years of tamoxifen in postmenopausal women who remain disease free. IES, however, is the first double-blind study utilizing a switch strategy to show a modest but real improvement in survival.

In conclusion, switching to exemestane after 2–3 years of tamoxifen reduces the risk of dying in ER+/unknown postmenopausal women with early breast cancer. The switching strategy appears to minimize the risk of adverse events associated with both agents, particularly the long-term toxicities associated with the use of these agents, and serious adverse effects are rare. These results indicate that early improvements in DFS observed in patients who switch to exemestane after 2–3 years of tamoxifen persist after treatment, and translate into modest improvements in overall survival.

Conflicts of interest: Jacek Jassem lectured at the Pfizer symposium and received an honorarium.

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