VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Follow-Up of the Intergroup Exemestane Study

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Published at jco.org on May 3, 2017.

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Clinical trial information: ISRCTN11883920.

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0732-183X/17/3522w-2507w/$20.00

ABSTRACT

Purpose

The Intergroup Exemestane Study, an investigator-led study of 4,724 postmenopausal patients with early breast cancer (clinical trial information: ISRCTN11883920), has previously demonstrated that a switch from adjuvant endocrine therapy after 2 to 3 years of tamoxifen to exemestane was associated with clinically relevant improvements in efficacy. Here, we report the final efficacy analyses of this cohort.

Patients and Methods

Patients who remained disease free after 2 to 3 years of adjuvant tamoxifen were randomly assigned to continue tamoxifen or switch to exemestane to complete a total of 5 years of adjuvant endocrine therapy. Given the large number of non–breast cancer–related deaths now reported, breast cancer–free survival (BCFS), with censorship of intercurrent deaths, was the primary survival end point of interest. Analyses focus on patients with estrogen receptor-positive or unknown tumors (n = 4,599).

Results

At the time of the data snapshot, median follow-up was 120 months. In the population that was estrogen receptor positive or had unknown estrogen receptor status, 1,111 BCFS events were observed with 508 (22.1%) of 2,294 patients in the exemestane group and 603 (26.2%) of 2,305 patients in the tamoxifen group. The data corresponded to an absolute difference (between exemestane and tamoxifen) at 10 years of 4.0% (95% CI, 1.2% to 6.7%), and the hazard ratio (HR) of 0.81 (95% CI, 0.72 to 0.92) favored exemestane. This difference remained in multivariable analysis that was adjusted for nodal status, prior use of hormone replacement therapy, and prior chemotherapy (HR, 0.80; 95% CI, 0.71 to 0.90; $P < .001$). A modest improvement in overall survival was seen with exemestane; the absolute difference (between exemestane and tamoxifen) at 10 years in the population that was estrogen receptor positive or had unknown estrogen receptor status was 2.1% (95% CI, −0.5% to 4.6%), and the HR was 0.89 (95% CI, 0.78 to 1.01; $P = .08$). For the intention-to-treat population, the absolute difference was 1.6% (95% CI, −0.9% to 4.1%); the HR was 0.91 (95% CI, 0.80 to 1.03, $P = .15$). No statistically significant difference was observed in the proportion of patients who reported a fracture event in the post-treatment period.

Conclusion

The Intergroup Exemestane Study and contemporaneous studies have established that a strategy of switching to an aromatase inhibitor after 2 to 3 years of tamoxifen can lead to sustained benefits in terms of reduction of disease recurrence and breast cancer mortality.

J Clin Oncol 35:2507-2514. © 2017 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2016.70.5640

Data Supplement
DOI: https://doi.org/10.1200/JCO.2016.70.5640

DOI: https://doi.org/10.1200/JCO.2016.70.5640

INTRODUCTION

Despite improvements in adjuvant treatment, breast cancer remains the most frequent cause of cancer-related death in women; approximately 508,000 deaths were reported worldwide in 2011.[1] For patients diagnosed with estrogen receptor (ER)–positive disease, risk of disease relapse remains for more than 15 years after initial diagnosis; and recent research has demonstrated that patients who received chemotherapy had a cumulative risk of relapse at 15 years comparable to that of patients with ER-negative disease.[2] Aromatase inhibitors reduce recurrence rates and 10-year breast cancer mortality rates compared

with tamoxifen. However, the optimal way to schedule aromatase inhibitors is still debated.[3]

The Intergroup Exemestane Study (IES) was an investigator-led, Pfizer-sponsored trial to assess the affect on disease-related outcome, adverse events, and quality of life of a switch to exemestane after 2 to 3 years of tamoxifen compared with continuation up to 5 years of tamoxifen.[4-11] The most recent update of efficacy analyses published in 2012 (data snapshot on December 7, 2009) after a median follow-up of 91 months demonstrated that the highly statistically significant benefit of a switch to exemestane on disease-free survival (DFS) observed at initial publication was maintained, and this translated to a modest improvement in overall survival (OS).[6]

IES was the first trial published to describe the benefits of a switch from tamoxifen to an aromatase inhibitor (exemestane) at 2 to 3 years, and it was one of the pivotal trials to assess the role of aromatase inhibitors in combination with or as a replacement for standard tamoxifen treatment.[3] Whether the strategy results in long-term sustained improvement in DFS or OS remains controversial, although our previous report suggested that this was the case.[6]

Recent analyses of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial have sought to identify clinical and biologic factors associated with disease relapse after completion of endocrine therapy.[12,13] Nodal involvement and tumor size are the most important clinical factors for prediction of relapse both during and after treatment completion in patients with ER-positive breast cancer.[14,15] The other aim of this study, therefore, was to establish which prognostic features were important in the IES trial, which used a switching strategy, especially after the end of endocrine therapy.

Here, we present the final efficacy analysis of the IES, along with exploratory analyses to investigate clinical factors that affect the risk of distant relapse after completion of endocrine therapy.

PATIENTS AND METHODS

Patients

Details of trial design, eligibility criteria, and study procedures have been presented previously.[4-6] Briefly, eligible patients were postmenopausal women with ER-positive/unknown primary invasive breast cancer who remained disease free and on treatment after 2 to 3 years of tamoxifen. At random assignment, women were allocated to continue tamoxifen (20 mg [or 30 mg in Denmark] daily) or to switch to exemestane (25 mg daily) for the remainder of the 5-year endocrine therapy period. Timing of analyses was preplanned and triggered according to the last patient randomly assigned to reach her 10-year follow up. This analysis includes all data received as of September 4, 2013.

Efficacy analyses presented here were performed on the main IES analysis population, which included patients whose tumors were ER positive (n = 4,052; 85.8%) plus those whose ER status was unknown (n = 547; 11.6%). Analyses excluded patients who had ER-negative disease (n = 125; 2.6%) who would not have been eligible for the trial had their receptor statuses been known at trial entry. Intention-to-treat (ITT) analysis of overall survival is included for completeness.

Statistical Analysis

The primary end point of the IES was DFS, defined as time from random assignment to local or distant breast cancer recurrence, new primary breast cancer, or death without disease relapse (intercurrent death). As reported previously,[6] the proportion of patients who experienced intercurrent death increased as the IES population aged, which decreased the sensitivity of DFS to detect differences between treatments in breast cancer outcome. Therefore, breast cancer–free survival (BCFS), in which intercurrent deaths are censored, is now regarded as a more direct estimate of the treatment effect on breast cancer outcome in the long term. Other secondary end points presented include OS (defined as time from random assignment to death as a result of any cause), breast cancer–specific survival (BCSS; defined as time from random assignment to breast cancer death, including death as a result of unknown cause and other cause after recurrence), time to contralateral breast cancer (CLB; defined as time to contralateral breast cancer with patients censored at time of nonbreast second primary cancer), and time to distant recurrence (TTDR; defined as time to distant recurrence or death as a result of breast cancer or unknown cause without prior recurrence).

Kaplan-Meier plots, log-rank tests, and Cox proportional hazards analyses were used to compare survival end points between randomly assigned treatment groups. Multivariable analysis that was adjusted for known prognostic factors of nodal status, chemotherapy use, and hormone replacement therapy (HRT) use also was conducted.

Sites of first distant recurrence were grouped as either visceral, bone, or soft tissue/nodal. Patients were assigned to multiple groups, when relevant. Progression of metastatic disease subsequent to the initial distant recurrence was ignored. Events in which the site of recurrence was unknown were excluded from this part of the analysis.

The overall and age-related incidences of non–breast cancer second primary cancers were investigated to confirm the observation in previous reports of a differential pattern according to randomly assigned treatment.[5,6] When patients reported more than one nonbreast second primary cancer (n = 6), the first reported event was included. Second primaries reported with no confirmed date of diagnosis were excluded (n = 8).

Competing-risks analyses were undertaken to assess the impact of the randomly assigned treatment on breast cancer events (local recurrence, distant recurrence, CLB, ipsilateral breast cancer, and death as a result of breast cancer or an unknown cause) allowing for competing risks of intercurrent death and nonbreast second primary cancer. Patients were included on the basis of which event occurred first: breast cancer event or competing risk event. Gray's test was used to compare the two treatment groups with respect to breast cancer event in the presence of competing risks.[16]

Landmark analyses were performed to investigate the factors related to distant recurrence after the end of endocrine therapy. TTDR was the end point of interest, and survival time was partitioned at 2.5 years, which represented the approximate end of endocrine therapy in IES. The effect of randomly assigned treatment and of a number of patient and tumor characteristics on TTDR after 2.5 years were assessed, both as single variables and together in a multivariable Cox proportional hazards model.

Full adverse event[4-7,11] and quality of life[9,10] data have been reported previously and, therefore, are not included in this article, but an updated estimate of post-treatment fracture incidence by treatment received is presented. This estimate includes all fractures that occurred > 6 months after treatment completion in patients who received at least 1 day of treatment, and events were censored after recurrence or new second primary cancer.

Analyses were performed with STATA, version 13.2 (STATA Corp, College Station, TX). All statistical tests were two sided, and $P < .05$ was considered statistically significant.

RESULTS

Between 1998 and 2003, 4,724 evaluable patients were randomly assigned from 366 sites in 37 countries. Of these, 4,599 patients were ER positive or had an unknown ER status (Fig 1).

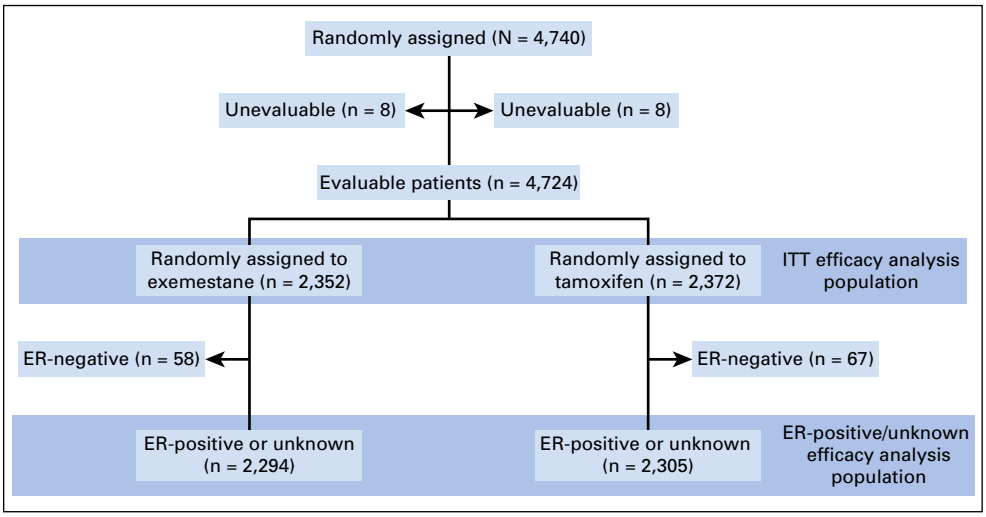

Fig 1. CONSORT diagram. ER, estrogen receptor; ITT, intention to treat.

Patient characteristics have been reported previously; patients were well balanced between treatment groups.[5,6] In summary, 2,089 (44.2%) of 4,724 patients had node-positive disease, and 1,542 (32.6%) of 4,724 patients had received adjuvant chemotherapy. The mean age at random assignment was 64.2 years (standard deviation, 8.2 years). At the time of the data snapshot (September 4, 2013), the median follow-up in patients still known to be alive was 120.0 months (interquartile range, 114.8 to 122.0 months; range, 2.9 to 164.1 months); the analysis was based on more than 39,000 woman-years of follow-up. A total of 74.7% of patients had at least 10 years of follow-up or had previously died.

Efficacy

In the ER-positive/unknown population, 1,111 of 4,599 patients experienced a BCFS event (508 [22.1%] of 2,294 in the exemestane group and 603 [26.2%] of 2,305 in the tamoxifen group). A reduction in the risk of breast cancer–related events was observed; the absolute difference at 10 years was 4.0% (95% CI, 1.2% to 6.7%), and the hazard ratio (HR) was 0.81 (95% CI, 0.72 to 0.92) in favor of a switch to exemestane (Fig 2A).

In the ER-positive/unknown population, 940 of 4,599 patients died (445 [19.4%] of 2,294 in the exemestane group and 495 [21.5%] of 2,305 in the tamoxifen group). A modest improvement in OS was seen with exemestane; the absolute survival difference at 10 years was 2.1% (95% CI, −0.5% to 4.6%), and the HR was 0.89 (95% CI, 0.78 to 1.01), in favor of a switch to exemestane (Fig 2B). The numerical difference in deaths was observed mainly in deaths as a result of breast cancer, and rates of intercurrent deaths were similar between randomly assigned treatment groups (Table 1). Results were similar when the ITT population was considered, with 467 (19.9%) of 2,352 patients in the exemestane group dying, and 510 (21.5%) of 2,372 patients in the tamoxifen group dying (HR, 0.91; 95% CI, 0.80 to 1.03; Fig 2C).

In the ER-positive/unknown population, 659 of 4,599 patients reported a BCSS event (303 [13.2%] of 2,294 patients in the exemestane group, and 356 [15.4%] of 2,305 patients in the tamoxifen group). The absolute BCSS difference at 10 years was 2.3% (95% CI, −0.0% to 4.6%), and the HR was 0.84 (95% CI, 0.72 to 0.98) in favor of a switch to exemestane (Fig 2D).

A total of 1,392 DFS events have been reported in only the patients with ER-positive/unknown disease (650 [28.3%] of 2,294 in the exemestane group, and 742 [32.2%] of 2,305 in the tamoxifen group). The highly significant improvement in DFS associated with a switch to exemestane that was noted previously remained, and no convergence of survival curves was seen (Fig 2E). This sustained benefit translated to an absolute difference in the proportion who remained alive and disease free at 10 years of 3.8% (95% CI, 0.9% to 6.6%). This difference remained in multivariable analyses that adjusted for nodal status, prior HRT use, and prior chemotherapy; the HR of 0.83 favored a switch to exemestane (95% CI, 0.75 to 0.93; $P = .001$).

With competing risks methodology, in which all outcomes were investigated in a single analysis, the cumulative incidence of intercurrent deaths increased steadily throughout the follow-up period and was comparable between randomly assigned treatment groups (Fig 3). In consideration of breast cancer events (after adjustment for competing risks), the early benefit from a switch to exemestane was maintained throughout follow-up (Gray's test $P = .002$).

No statistically significant difference was seen between the randomly assigned groups in the number of patients who reported a new primary CLB (exemestane [n = 56] and tamoxifen [n = 75]; HR, 0.73; 95% CI, 0.52 to 1.03; Table 1), although the observed HR was consistent with that of other trials that have explored the additional preventive benefits of aromatase inhibitors compared with tamoxifen.[17] Numerically, fewer nonbreast second primary cancers were reported with exemestane (n = 143) than with tamoxifen (n = 191; Table 1). Analyses of incidence of distant recurrence and nonbreast second primary cancer by age at random assignment reflect data presented previously; there was a suggestion that second primary cancer incidence increases with age, but

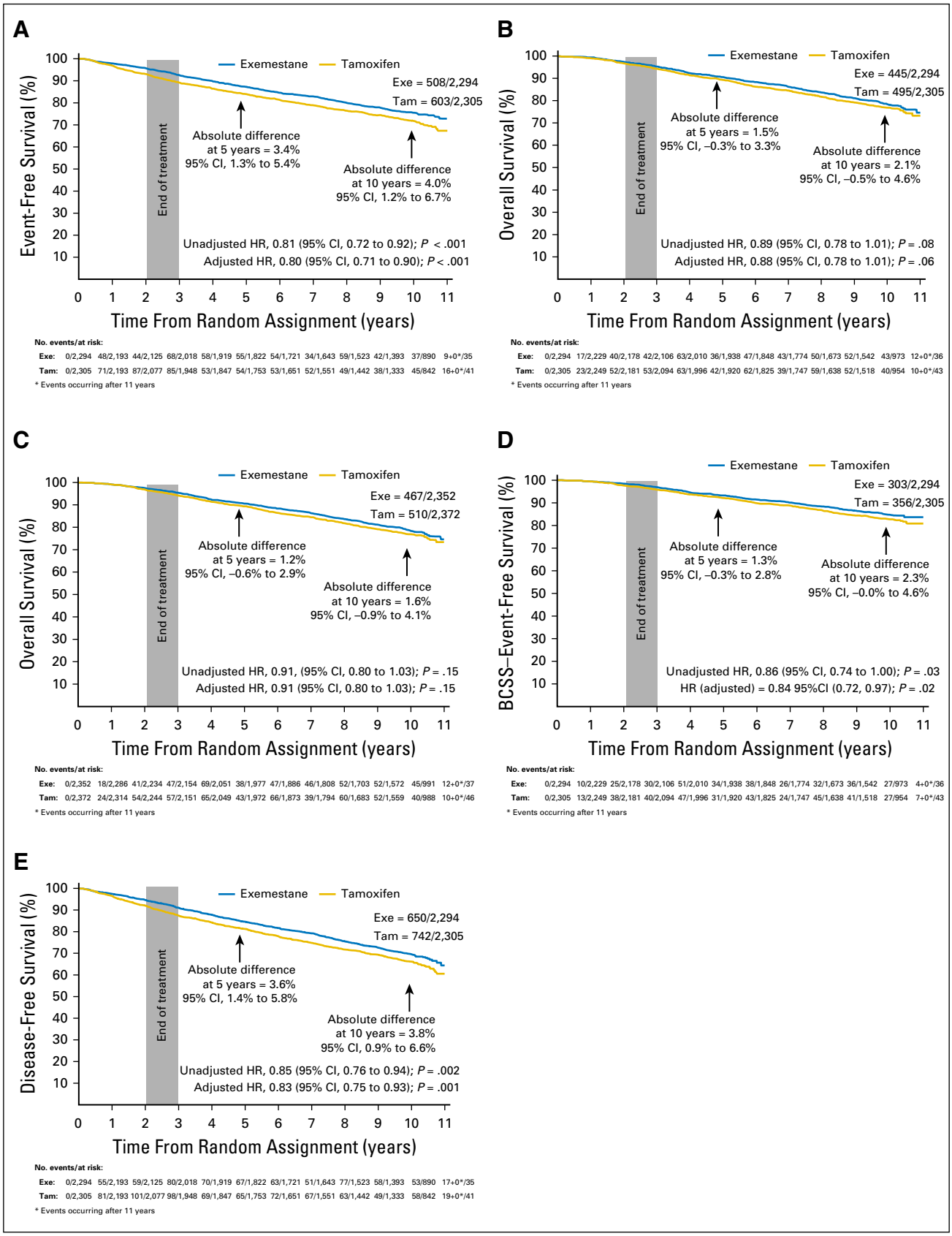

Fig 2. Survival results in study populations: estrogen receptor–positive/unknown (n = 4,599) and intention to treat (n = 4,724). (A) Breast cancer–free survival in the ER–positive/unknown population. (B) Overall survival (OS) in the ER-positive/unknown population, and (C) in the intention-to-treat population. (D) Breast cancer–specific survival (BCSS) in the ER-positive/unknown population. (E) Disease-free survival (DFS) in the ER-positive/unknown population. Exe, exemestane; HR, hazard ratio; Tam, tamoxifen.

Table 1. Efficacy Events by Treatment Group in the ER-Positive/Unknown Population

Event	No. (%) of Events in ER-Positive/Unknown Population		
	Exemestane (n = 2,294)	Tamoxifen (n = 2,305)	Total (N = 4,599)
DFS first event	650 (28.3)	742 (32.2)	1,392 (30.3)
Total BCFS events	508	603	1,111
Distant recurrence	369	420	789
Local recurrence	81	109	190
Second primary breast cancer	58	74	132
Intercurrent death	142	139	281
All deaths	445 (19.4)	495 (21.5)	940 (20.4)
Breast cancer	263	310	573
Unknown cause	40	46	86
Other known cause	142	139	281
Other cancer	40	60	100
Vascular	36	23	59
Cardiac	30	23	53
Other	36	33	69
Distant recurrence	403 (17.6)	469 (20.4)	872 (19.0)
To known site	346	393	739
Visceral only	129	130	259
Soft tissue/nodal only	29	25	54
Visceral and soft tissue/nodal	15	18	33
Total sites not including bone	173	173	346
Bone only	87	127	214
Visceral and bone	60	63	123
Visceral, bone, and soft tissue/nodal	15	18	33
Bone and soft tissue/nodal	11	12	23
Total sites including bone	173	220	393
Breast cancer death with no previous recurrence	17	28	45
Death as a result of unknown cause	40	48	88
Contralateral breast cancer	56 (2.4)	75 (3.3)	131 (2.8)
Nonbreast second primary cancer	143 (6.2)	191 (8.3)	334 (7.3)
Uterus	15	28	43
GI, upper	24	20	44
GI, lower	20	28	48
Lung	14	29	43
Melanoma	10	9	19
Ovary	10	8	18
Hematologic	15	17	32
Kidney	5	8	13
Other	30	44	74

NOTE. Events were those that contributed to end points of interest.
Abbreviations: BCFS, breast cancer–free survival; DFS, disease-free survival; ER, estrogen receptor.

no association was observed between age and distant recurrence incidence (trend test $P = .08$ and .22, respectively; Appendix Table A1 and Fig A1, online only).

Results of TTDR analyses across the entire follow-up period reflected other efficacy end points. The absolute difference in the rate of distant recurrence or breast cancer death at 10 years was 2.6% (95% CI, 0.2% to 5.1%), and the HR was 0.84 (95% CI, 0.74 to 0.96) in favor of a switch to exemestane. Analyses of TTDR after completion of endocrine therapy—equivalent to approximately 5 years after diagnosis—included 4,147 patients known to be event free at 2.5 years after random assignment (exemestane [n = 2,091] and tamoxifen [n = 2,056]; Table 2). No statistically significant difference in TTDR during this period was observed between randomly assigned treatment groups (HR, 0.94; 95% CI, 0.80 to 1.10; $P = .41$), which reflects the observation that the initial difference in disease outcome observed during the treatment period was maintained throughout the follow-up period. After inclusion in a multivariable Cox proportional hazards model, age at random assignment, nodal status, hormone receptor status, previous HRT use, and tumor size but not grade, had a significant effect on the risk of TTDR event after completion of endocrine therapy (ie, of late relapse). Of note, risk of late distant recurrence in patients with tumor sizes $>$ 5 cm at diagnosis was almost double that of patients with tumors $<$ 2 cm (HR, 1.92; 95% CI, 1.28 to 1.90), and the risk was more than six times greater in patients who had $\geq$10 nodes involved than in patients who were node-negative at random assignment (HR, 6.10; 95% CI, 4.41 to 8.44) after adjustment for other factors.

Fractures

No statistically significant difference was observed in the proportion of patients who reported at least one fracture event in the post-treatment period with 196 (9.3%) of 2,105 patients in the

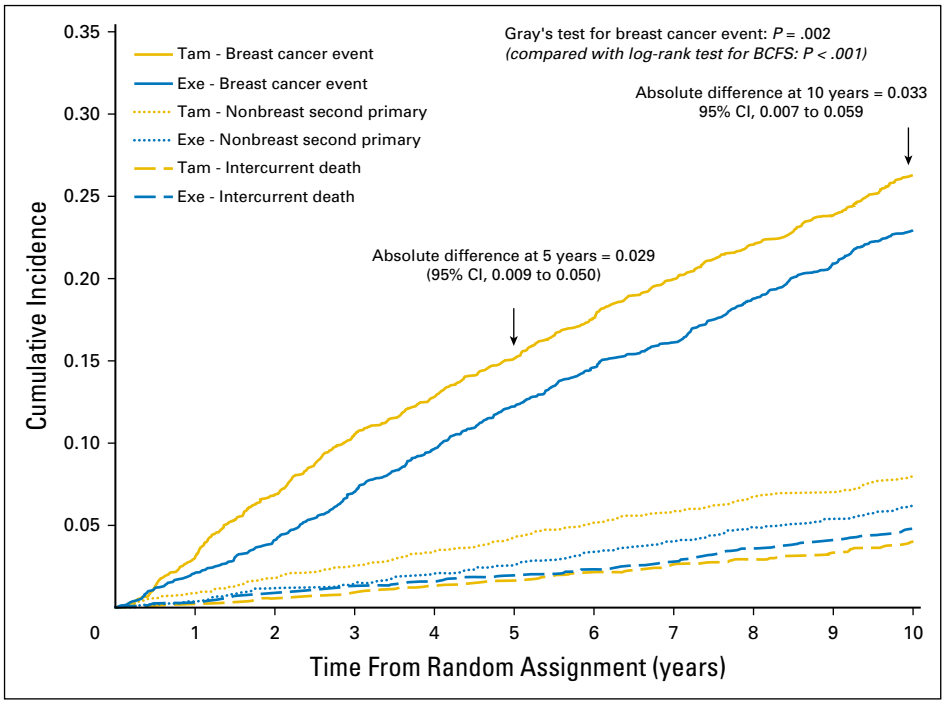

Fig 3. Cumulative incidence of breast cancer event in the presence of competing risks (intercurrent death and nonbreast second cancer). BCFS: breast cancer–specific survival; Exe, exemestane; Tam, tamoxifen.

exemestane group and 163 (8.0%) of 2,036 patients in the tamoxifen group ($P = .14$).

DISCUSSION

This updated and final analysis of IES demonstrates that the benefit associated with a switch to exemestane observed early in the follow-up period remained undiminished by additional follow-up. As the IES population aged, incidences of non–breast cancer deaths and nonbreast second primary cancers have increased, which has led to a dilution of OS results. However, a modest benefit from the switch to exemestane can still be seen, with an absolute difference in OS at 10 years after random assignment of 1.6%. As suggested previously, BCFS (which does not include non–breast cancer deaths) remains the most appropriate measure of treatment efficacy in this setting; an absolute benefit of 4.0% from the switch to exemestane was observed at 10 years. Analyses that account for competing events of intercurrent death and nonbreast second primary cancer showed an absolute difference in breast cancer event at 10 years of 3%.

The IES trial compared treatments for a duration of up to 5 years. Recent large, randomized controlled trials[18-20] have demonstrated an improvement in disease-related outcomes associated with continuation of tamoxifen or aromatase inhibitor treatment past the standard 5 years of treatment. However, long-term use of endocrine therapy is associated with many adverse effects, some of which substantially affect patient well-being, such as osteoporosis, vasomotor problems, and musculoskeletal conditions.[21] There remains great clinical need to identify patients who remain at high risk of disease relapse after completion of 5 years of endocrine therapy who may benefit from additional treatment and, conversely, patients who may be spared this treatment because of low residual risk.

Results of analyses partitioned at 2.5 years after random assignment support conclusions made previously that the difference in disease-related outcome observed at 10 years between treatment groups is due to maintenance of the initial on-treatment divergence between groups rather than any emerging post-treatment effect. Multivariable analyses of clinical factors that affect the time to late distant recurrence identified age at random assignment, nodal involvement, hormone receptor status, previous HRT use, and tumor size, although the relationship between HRT use and late distant recurrence is confounded by geographic region. The observation that tumor grade no longer retains prognostic significance in this setting after adjustment for other factors reflects previous analyses of retrospective case series[22] and comparable analyses of the ATAC trial.[12] The authors of this analysis also demonstrated the value of the PAM50-based risk of recurrence score as an independent predictor of late distant recurrence; other molecular scores studied (eg, IHC4, Oncotype DX) did not add prognostic information when added to clinical data.[13]

In summary, the IES and other contemporaneous studies have established that a strategy of a switch to an aromatase inhibitor after 2 to 3 years of tamoxifen can lead to sustained benefits in terms of reduction of disease recurrence and breast cancer mortality. The identification of patients who remain at higher risk of disease recurrence after the completion of 5 years of endocrine therapy (whether tamoxifen, an aromatase inhibitor, or a combination of the two) according to clinical factors, such as nodal involvement and tumor size, will aid decision making about the administration of additional endocrine therapy or additional therapeutic agents.

Table 2. Factors That Affect Risk of TTDR Event After 2.5 Years

Factor	No. of Patients	Unadjusted Analysis				Adjusted Analysis					
						Without Geographic Region			With Geographic Region		
		No. (%) With TTDR Event	HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
Random assignment											
Tamoxifen	2,056	311 (15.1)	1	—	.41	1	—	.29	1	—	.32
Exemestane	2,091	300 (14.3)	0.94	0.80 to 1.10		0.92	0.78 to 1.08		0.92	0.79 to 1.08	
Age at random assignment, years											
< 60	1,352	187 (13.8)	1	—	< .001	1	—	.008	1	—	.004
60-69	1,548	248 (16.0)	1.01	0.84 to 1.22		1.03	0.85 to 1.25		1.05	0.86 to 1.27	
≥ 70	999	176 (17.6)	1.43	1.17 to 1.76		1.36	1.09 to 1.70		1.41	1.13 to 1.76	
Nodal status											
Negative	2,227	183 (8.2)	1	—	< .001	1	—	< .001	1	—	< .001
1-3	1,256	220 (17.5)	2.22	1.83 to 2.70		2.11	1.72 to 2.59		2.09	1.70 to 2.56	
4-9	386	131 (33.9)	4.8	3.84 to 6.01		4.41	3.45 to 5.63		4.28	3.35 to 5.46	
≥ 10	119	57 (47.9)	7.57	5.63 to 10.21		6.10	4.41 to 8.44		6.07	4.38 to 8.40	
Unknown	159	20 (12.6)	1.59	1.01 to 2.53		1.63	1.02 to 2.60		1.82	1.14 to 2.92	
Previous chemotherapy											
Yes	1,305	248 (19.0)	1	—	< .001	1	—	.48	1	—	.58
No	2,842	363 (12.8)	0.66	0.56 to 0.77		1.07	0.89 to 1.30		1.06	0.87 to 1.28	
Hormone receptor status											
ER- and PgR-positive	2,474	331 (13.4)	1	—	.008	1	—	.01	1	—	.006
ER-positive and PgR-negative/unknown	1,204	206 (17.1)	1.3	1.09 to 1.55		1.29	1.08 to 1.54		1.33	1.11 to 1.60	
ER- and PgR- unknown	469	74 (15.8)	1.24	0.96 to 1.59		1.22	0.94 to 1.58		1.22	0.93 to 1.61	
Histologic type											
Ductal	3,157	450 (14.3)	1	—	.02	1	—	.30	1	—	.29
Lobular	578	108 (18.7)	1.32	1.07 to 1.62		1.16	0.93 to 1.45		1.17	0.94 to 1.46	
Other/unknown	412	53 (12.9)	0.87	0.65 to 1.16		0.93	0.69 to 1.24		0.93	0.70 to 1.25	
Previous HRT use											
Yes	1,021	115 (11.3)	1	—	< .001	1	—	.006	1	—	.09
No	3,035	473 (15.6)	1.47	1.20 to 1.80		1.35	1.10 to 1.67		1.20	0.97 to 1.49	
Unknown	91	23 (25.3)	2.38	1.52 to 3.72		1.74	1.10 to 2.74		1.59	1.00 to 2.52	
Tumor size, cm											
≤ 2	2,537	277 (10.9)	1	—	< .001	1	—	< .001	1	—	< .001
> 2 but ≤ 5	1,431	292 (20.4)	2.03	1.72 to 2.39		1.51	1.28 to 1.80		1.51	1.27 to 1.79	
> 5	94	26 (27.7)	3.05	2.04 to 4.56		1.92	1.28 to 1.90		1.96	1.30 to 2.96	
Unknown	85	16 (18.8)	1.76	1.07 to 2.92		1.35	0.80 to 2.25		1.28	0.77 to 2.15	
Tumor grade											
1	737	73 (9.9)	1	—	< .001	1	—	.40	1	—	.69
2	1,785	263 (14.7)	1.52	1.17 to 1.97		1.16	0.89 to 1.51		1.14	0.88 to 1.49	
3/undifferentiated	756	120 (15.9)	1.66	1.24 to 2.22		1.16	0.86 to 1.56		1.13	0.84 to 1.53	
Unknown	869	155 (17.8)	1.91	1.45 to 2.52		1.29	0.96 to 1.72		1.20	0.89 to 1.61	
Region											
United States	325	26 (8.0)	0.53	0.35 to 0.79	< .001				0.67	0.45 to 1.02	.02
United Kingdom	512	54 (10.5)	0.63	0.47 to 0.84					0.69	0.51 to 0.94	
Central and Eastern Europe	754	134 (17.8)	1.20	0.98 to 1.46					1.15	0.93 to 1.44	
Rest of Europe	2,351	367 (15.6)	1	—					1	—	
Southern hemisphere and Hong Kong	205	30 (14.6)	1.01	0.70 to 1.47					0.96	0.66 to 1.40	

NOTE. The 2.5-year time point was approximately 5 years after diagnosis.
Abbreviations: ER, estrogen receptor; HR, hazard ratio; HRT, hormone replacement therapy; PgR, progesterone receptor; TTDR, time to distant recurrence.
**P* value represents likelihood ratio test. *P* values are calculated with unknown categories included.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Pfizer; also supported by Cancer Research UK (to the trial coordinating units at Imperial College London and The Institute of Cancer Research).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Follow-Up of the Intergroup Exemestane Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Research Funding: Roche, Novartis, Celgene, AstraZeneca, Pfizer
Expert Testimony: Roche, Novartis, AstraZeneca
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Acknowledgment

We thank the women who took part in this study; the doctors, nurses, and support staff at local sites; and the monitors, data managers, trial coordinators, and study managers from the Argentine Breast Cancer Group, the Australian New Zealand Breast Cancer Trials Group, the Central and Eastern European Oncology Group, the Danish Breast Cancer Group, the Dutch Breast Cancer Research Group, the European Organisation for Research and Treatment of Cancer, the Grupo Espanol De Investigacion Del Cancer De Mama, the Gruppo Oncologico Nord Ovest, the Gruppo Oncologico Italiano di Ricerca Clinica, the International Breast Cancer Study Group, the International Collaborative Cancer Group, the Israeli Clinical Oncology Group, Italian Trials in Medical Oncology, the North West England Group, the Norwegian Breast Cancer Group, the Yorkshire Breast Group, the Federation Nationale Des Centres De Lutte Contre Le Cancer, the German Exemestane Adjuvant Group, the Wales Cancer Trials Network, US Oncology, the Swedish Breast Cancer Group, and Pfizer. We also thank the Breast International Group for their support, the members of the study steering committee, and the members of the independent data monitoring committee.

Appendix

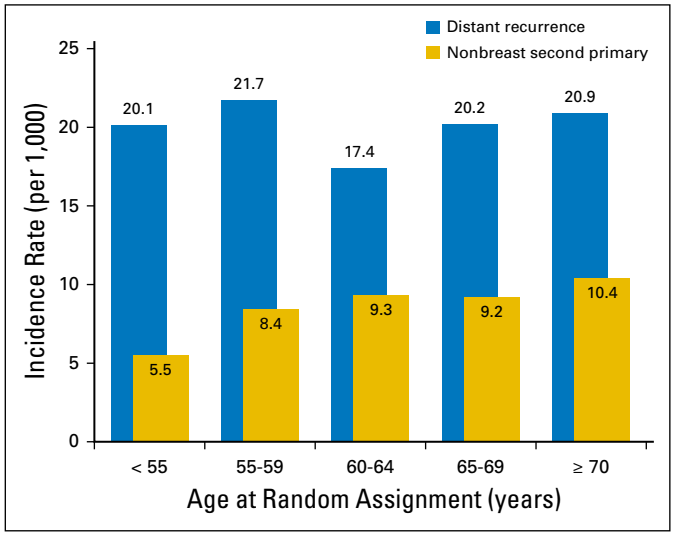

Fig A1. Distant recurrence and nonbreast second primary incidence by age.

Table A1. Distant Recurrence and Nonbreast Second Primary Incidence by Age

Age at Random Assignment (years)	Distant Recurrence			Nonbreast Second Primary		
	No. of Events	Incidence Rate (per 1,000)	95% CI	No. of Events	Incidence Rate (per 1,000)	95% CI
< 55	88	20.1	16.3 to 24.8	25	5.5	3.7 to 8.2
55-59	172	21.7	18.7 to 25.1	68	8.4	6.6 to 10.6
60-64	154	17.4	14.9 to 20.4	83	9.3	7.5 to 11.5
65-69	149	20.2	17.2 to 23.7	69	9.2	7.3 to 11.7
≥ 70	176	20.9	18.0 to 24.2	89	10.4	8.5 to 12.9
Total	739	20.0	18.6 to 21.5	334	8.9	8.0 to 9.9
Nonparametric test for trend		$P = .223$			$P = .079$	