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Prognostic and predictive value of ERβ1 and ERβ2 in the Intergroup Exemestane Study (IES)—first results from PathIES†

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Background: Intergroup Exemestane Study (IES) was a randomised study that showed a survival benefit of switching adjuvant endocrine therapy after 2–3 years from tamoxifen to exemestane. PathIES aimed to assess the potential prognostic and predictive value of ERβ1 and ERβ2 expression in primary tumours in order to determine benefit in the two treatment arms.

Patients and methods: Primary tumour samples were available for 1256 patients (27% IES population). ERβ1 and ERβ2 expression was dichotomised at the median IHC score (high if ERβ1 ≥ 191, ERβ2 ≥.164). Hazard ratios (HRs) were estimated by multivariable Cox proportional hazards models adjusting for clinicopathological factors. Treatment effects with biomarker expressions were determined by interaction tests. Analysis explored effects of markers both as a continuous variable and with dichotomised cut-offs.

Results: Neither ERβ1 nor ERβ2 were associated with disease-free survival (DFS) or overall survival (OS) in the whole cohort. In patients treated with continued tamoxifen, high ERβ1 expression compared with low was associated with better DFS [HR = 0.38:95% confidence interval (CI) 0.21–0.68, $P = 0.001$]. DFS benefit of exemestane over tamoxifen (HR = 0.40:95% CI 0.22–0.70) was found in the low ERβ1 subgroup (interaction $P = 0.01$). No significant difference with treatment was observed for ERβ2 expression in either DFS or OS.

Conclusion: In the PathIES population, exemestane appeared to be superior to tamoxifen among patients with low ERβ1 expression but not in those with high ERβ1 expression. This is the first trial of its kind to report a parameter potentially predicting benefit of an aromatase inhibitor when compared with tamoxifen and an independent validation is warranted.

Key words: breast cancer, oestrogen receptor beta, aromatase inhibitor, tamoxifen, prognosis, biomarker

introduction

Several studies have established utility of using aromatase inhibitors (AIs) within the adjuvant setting, either upfront or sequentially with tamoxifen [1–5]. Considerable uncertainty exists as to whether such treatment is necessary for all patients and which patients should be treated solely with either tamoxifen or AI alone or switched to AI following tamoxifen treatment. Oestrogen receptor alpha (ERα) expression in primary breast cancer is an established predictor of benefit from adjuvant endocrine treatment [6, 7]. While women with breast cancer can acquire resistance to endocrine treatment, it remains uncertain how resistance occurs, and whether mechanisms of resistance differ between the two treatment types [8].

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Compared with ERα, the potential prognostic and predictive value of oestrogen receptor beta (ERβ) in breast cancer has been controversial, mainly due to variations in specificity of primary antibodies and to small patient numbers in many reports. Conflicting results were reported in particular, in patients with ERα-positive breast cancer. In a recent review by Murphy et al. [9], high levels of nuclear ERβ1 were found to be associated with a good response to tamoxifen and better prognosis, although in ERα-negative breast cancers, ERβ1 has a different role and could be considered a target for therapy. Furthermore, a review by Leung et al. [10, 11] described seven studies in which ERβ1 was associated with good prognostic parameters, but six studies found no association.

Of 11 studies addressing the impact of ERβ2, two linked ERβ2 expression to good prognosis, two to poor prognosis and the remainder showed no association [10]. Some studies indicated that sub-cellular location was critical suggesting that cytoplasmic ERβ2 appeared to be associated with poor survival, high-grade tumours and recurrence. Nuclear ERβ2 appeared to predict for favourable tamoxifen response and better survival [12–14]. Lack of appreciation of the different ERβ isoforms has also contributed to confusion in the literature. Emerging data from large-scale studies using well-validated isoform-specific primary antibodies points to a potential role for ERβ1 and ERβ2 in breast carcinogenesis [13, 15–18].

We established a translational group (PathIES) as part of the Intergroup Exemestane Study (IES) and investigated the potential role of markers postulated as having a role in distinguishing effectiveness of tamoxifen and AI. We report here on the role of ERβ1 and ERβ2 in determining the relative sensitivity to either tamoxifen or sequential treatment with tamoxifen and the AI exemestane.

patients and methods

design and samples

IES was a randomised, double-blind phase III study comparing exemestane 25 mg/day to tamoxifen 20 mg/day (30 mg in Denmark) for 2–3 years in post-menopausal women with ER+/unknown primary breast cancer, who remained disease free after receiving adjuvant tamoxifen therapy for 2–3 years. The IES study design, eligibility criteria and treatment schedules have been previously described [3, 19, 20]. PathIES is a retrospective translational study that aims to identify markers predictive of response or resistance to tamoxifen or an AI. Sample collection was carried out in accordance with institutional guidelines, ethical requirements and national laws. Clinical data used were based on the snapshot taken for the most recent IES publication (median follow-up time: 91 months) [19]. REMARK criteria were employed for data reporting [21]. Additional information on Design and Samples is in the supplementary Data, available at *Annals of Oncology* online.

immunohistochemistry

Q2 FFPE tissue blocks were stained with haematoxylin and eosin to identify areas of invasive carcinoma. Four 0.6 mm cores were extracted from these areas and placed in two replicate tissue microarrays, except where lesions were of insufficient size. Full information on immunohistochemistry is in the supplementary Data, available at *Annals of Oncology* online.

statistical analysis

Continuous and dichotomised ERβ expression was explored. Dichotomisation of the ERβ variants was based at the median value: ERβ1 histoscore of 191 and ERβ2 of 164. Dichotomisation of Ki67 was based on the median cut-off 11%. Full information on statistical analysis is in the supplementary Data, available at *Annals of Oncology* online.

results

characteristics of patients included in PathIES

Of the 4724 post-menopausal women with ER-positive/unknown primary breast cancer included in the IES trial, 1483 were recruited into PathIES. Of those, material was available for 1256 women, 27% of the IES population. After accounting for attrition due to e.g. insufficient tumour, core loss, missing data, ERβ1 and ERβ2 data were assessable from 718 (57%) and 689 (55%) patients, respectively (supplementary Figure S1, available at *Annals of Oncology* online).

The characteristics of the patients in which at least one of the markers could be reliably assessed ($n = 1050$) were similar within the patients with and without a determined ERβ score or available tissue (supplementary Table S1, available at *Annals of Oncology* online).

association of ERβ variants with clinicopathological factors

The correlations between centrally assessed ERα, PR, HER2 and Ki67 with the ERβ variants were moderate (supplementary Table S2, available at *Annals of Oncology* online). PR was 'weakly' positively correlated with ER-β1 $\rho = 0.1$, and negatively correlated with Ki67 $\rho = -0.21$ (supplementary Table S2, available at *Annals of Oncology* online). ERα was correlated positively with both ERβ1 (correlation coefficient = 0.26, $n = 669$, $P < 0.001$) and ERβ2 (correlation coefficient = 0.17, $n = 645$, $P < 0.001$). PR expression was 'very weakly' positively correlated with ERβ1 ($\rho = 0.10$).

Overall, patient characteristics in the ERβ1 or ERβ2 high subgroups—as defined by the median value—were similar to those in the low ERβ subgroups (Table 1 and supplementary Tables S3 and S4, available at *Annals of Oncology* online). The only variables that demonstrated a trend were tumour grade and size. Patients with high ERβ1 expression (histoscore ≥ 191) had on average a higher proportion of grade 3 tumours and a smaller tumour size compared with the low ERβ1 subgroup.

association of ERβ variants with disease-free and overall survival

There were no statistically significant associations between ERβ variants and either disease-free survival (DFS) or overall survival (OS) in the whole cohort (Figure 1A and B). Evaluating the prognostic value of ERβ expression within the exemestane and tamoxifen cohorts separately, the univariate analysis also demonstrated no significant difference in DFS [tamoxifen hazard ratio (HR) 0.71 (0.48–1.04), $P = 0.08$ and exemestane HR 0.94 (0.63–1.41), $P = 0.79$] or OS [tamoxifen HR 0.64 (0.41–1.01), $P = 0.06$ and exemestane HR 0.99 (0.61–1.60), $P = 0.96$ (Figure 1C and D)]. However, following a multivariable Cox regression analysis (Table 2)—adjusting for nodal status, age, grade, tumour size, ERα, PR, Ki67 and HER2—a significant interaction was detected between ERβ1 and treatment group (interaction test $P = 0.01$). There was also a significant interaction effect when ERβ1 was analysed as a continuous variable (Table 3).

Due to the significant interaction observed, we explored treatment effect within ERβ1 low and high subgroups, as defined by

Table 1. Association of ERβ variants with clinicopathological factors

	ERβ1				Total		ERβ2				Total	
	Low		High				Low		High			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age group												
<60	112	34	133	34	245	34	123	36	120	34	243	35
60–69	136	41	169	44	305	42	145	43	149	42	294	43
70+	83	25	85	22	168	23	70	21	82	23	152	22
Total	331	100	387	100	718	100	338	100	351	100	689	100
	Test for trend $P = 0.52$						Test for trend $P = 0.39$					
Grade												
G1	66	20	60	16	126	18	65	19	57	16	122	18
G2	153	46	162	42	315	44	158	47	148	42	306	44
G3	59	18	94	24	153	21	74	22	69	20	143	21
Undifferentiated	1	0	2	1	3	0	1	0	2	1	3	0
Not assessable	4	1	4	1	8	1	2	1	5	1	7	1
Unknown/missing/not assessed	48	15	65	17	113	16	38	11	70	20	108	16
Total	331	100	387	100	718	100	338	100	351	100	689	100
	Test for trend $P = 0.02$[a]						Test for trend $P = 0.76$[a]					
Tumour size												
≤2 cm	168	51	226	59	394	55	176	53	204	59	380	56
>2–5 cm	145	44	145	38	290	41	150	45	128	37	278	41
>5 cm	15	5	11	3	26	4	9	3	13	4	22	3
Total	328	100	382	100	710	100	335	100	345	100	680	100
	Test for trend $P = 0.02$						Test for trend $P = 0.20$					
Nodal status												
Negative	145	44	171	44	316	44	154	46	144	41	298	43
1–3 N+	116	35	132	34	248	35	120	36	121	34	241	35
4–9 N+	33	10	47	12	80	11	36	11	47	13	83	12
≥10 N+	10	3	18	5	28	4	13	4	17	5	30	4
Total	304	100	368	100	672	100	323	100	329	100	652	100
	Test for trend $P = 0.32$						Test for trend $P = 0.16$					
Histology type												
Infiltrating ductal	252	76	308	80	560	78	258	76	279	79	537	78
Infiltrating lobular	37	11	51	13	88	12	46	14	36	10	82	12
Other	42	13	28	7	70	10	34	10	36	10	70	10
Total	331	100	387	100	718	100	338	100	351	100	689	100
	χ^2 $P = 0.04$						χ^2 $P = 0.40$					

[a] χ^2 calculations include only grades 1, 2, 3/undifferentiated.

the median. The superiority of exemestane over tamoxifen was confirmed in the low ERβ1 subgroup of patients [DFS HR 0.40 (0.22–0.70), OS HR 0.35 (0.17–0.69)] after adjusting for variables (Figure 2A and B, and Tables 2 and 3). Effect of ERβ1 seemed to be independent of ERα expression. The interaction P value remained significant in a multivariable model adjusted for ERα expression. In the high ERβ1 subgroup of patients, there was no significant difference between the two treatment groups [DFS HR 1.16 (0.63–2.15), OS HR 1.50 (0.73–3.07)]. ERβ2 expression showed no significant association with DFS or OS.

discussion

This study suggests that, in patients with ERα-positive breast tumours, the benefit of switching from adjuvant tamoxifen to exemestane is confined to a subgroup of patients with low ERβ1 expression. Gene profiling studies indicated that a greater number of genes are repressed by tamoxifen bound ERβ than with tamoxifen bound ERα [22] while ERα/β heterodimers appear to regulate different genes compared with the respective homodimers [23]. We are not certain as to the exact mechanism by which co-expression of ERα and ERβ1 is associated with good prognosis in patients treated with tamoxifen, with no additional benefit from exemestane. This may be due to the fact that AIs block oestrogen biosynthesis and thereby prevent, for the most part, regulation of gene expression by either receptor.

An alternative explanation could be that co-expression of ERβ1 is necessary for the optimal tamoxifen effect. This is supported by recent findings showing that ERβ sensitises breast cancer cells to endoxifen, the main metabolite of tamoxifen. It was also shown that endoxifen exerts its effects in part by stabilising ERβ1, thus favouring ERα/β heterodimer formation [24].

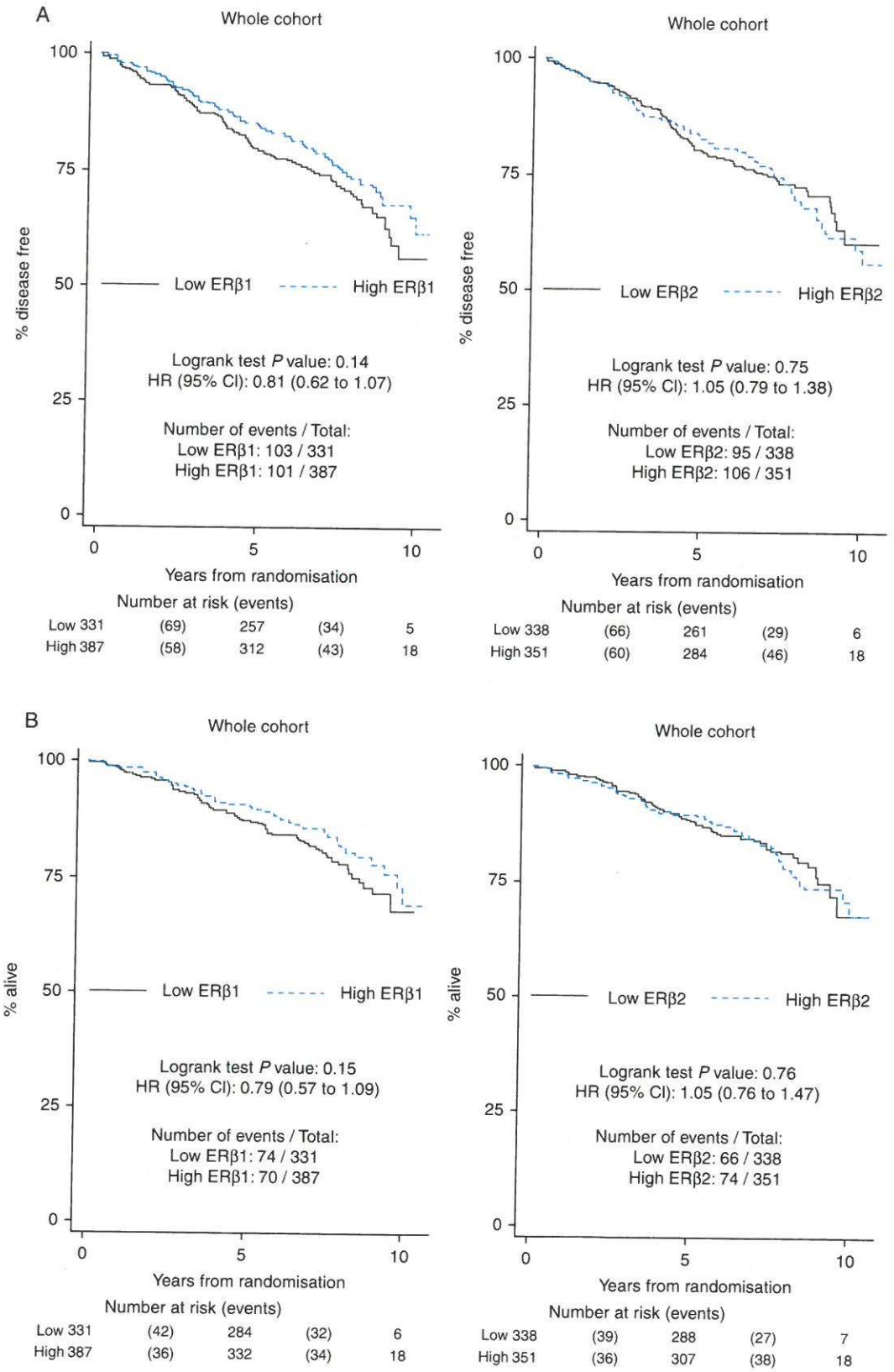

Figure 1. (A) Kaplan–Meier estimate of disease-free survival in the whole cohort according to ERβ1 and ERβ2 nuclear expression. (B) Kaplan–Meier estimate of overall survival in the whole cohort according to ERβ1 and ERβ2 nuclear expression. (C) Kaplan–Meier estimate of disease-free survival according to ERβ1 nuclear expression within each treatment arm. (D) Kaplan–Meier estimate of overall survival according to ERβ1 nuclear expression within each treatment arm. Q7

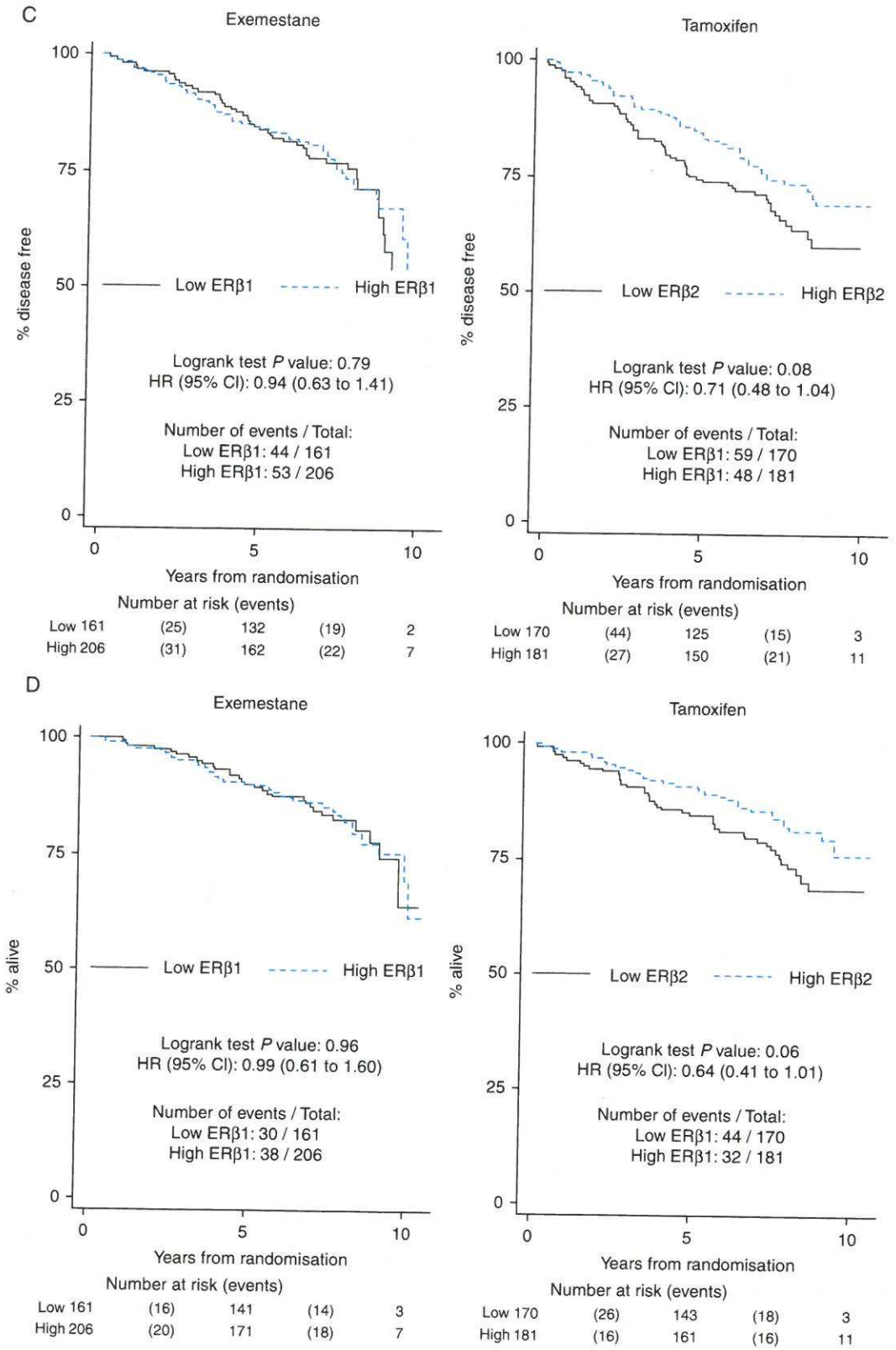

Fig. 1 *Continued*

Table 2. Multivariable analysis of disease-free and overall survival, with ERβ1 low and high

	DFS			OS		
	HR (95% CI)	95% CI	*P* value	HR (95% CI)	95% CI	*P* value
Treatment × ERβ1 interaction	2.96	1.30–6.71	0.01	4.31	1.61–11.54	0.004
Treatment (exemestane versus tamoxifen)						
Within ERβ1 low	0.40	0.22–0.70	0.001	0.35	0.17–0.69	0.003
Within ERβ1 high	1.16	0.63–2.15	0.63	1.50	0.73–3.07	0.27
ER B1 (low versus high)						
Within tamoxifen	0.38	0.21–0.68	0.001	0.36	0.18–0.73	0.005
Within exemestane	1.12	0.62–2.04	0.71	1.55	0.76–3.16	0.23
Age						
<60 versus 60–69	1.38	0.84–2.28	0.21	1.15	0.62–2.10	0.66
<60 versus 70+	1.70	0.98–2.95	0.06	1.94	1.03–3.68	0.04
ER (−ve versus +ve)	1.02	0.46–2.26	0.97	0.67	0.28–1.63	0.38
PgR (−ve versus +ve)	0.59	0.31–1.10	0.10	0.54	0.26–1.11	0.09
HER2 (−ve versus +ve)	0.73	0.34–1.60	0.44	0.75	0.31–1.82	0.53
Ki67 (−ve versus +ve)	1.50	0.95–2.38	0.08	1.19	0.70–2.03	0.52
Tumour size						
≤2 versus 2–5 cm	1.07	0.70–1.64	0.76	0.86	0.51–1.44	0.57
≤2 versus 5+ cm	0.89	0.30–2.69	0.84	0.82	0.23–2.94	0.76
Nodal status						
Negative versus 1–3N+	1.46	0.89–2.40	0.13	1.54	0.85–2.77	0.15
Negative versus >3N+	3.18	1.82–5.54	<0.001	3.27	1.67–6.39	0.001
Negative versus unknown	0.50	0.17–1.50	0.22	0.38	0.08–1.70	0.21
Grade						
G1 versus G2	1.09	0.55–2.13	0.81	1.05	0.45–2.45	0.90
G1 versus G3/undifferentiated	1.37	0.62–3.02	0.44	1.76	0.68–4.51	0.24
G1 versus not assessable/unknown	1.52	0.68–3.39	0.31	1.51	0.57–3.95	0.41

Table 3. Multivariable analysis of disease-free and overall survival, with continuous ERβ1

	DFS			OS		
	HR (95% CI)	95% CI	*P* value	HR (95% CI)	95% CI	*P* value
Treatment × ERβ1 interaction	1.01	1.00–1.01	0.03	1.01	1.00–1.01	0.02
Treatment (exemestane versus tamoxifen)	0.23	0.08–0.67	0.007	0.18	0.05–0.64	0.008
ER B1 (continuous)						
Within tamoxifen	1.00	0.99–1.00	0.04	1.00	0.99–1.00	0.06
Within exemestane	1.00	1.00–1.00	0.89	1.00	1.00–1.00	0.21
Age						
<60 versus 60–69	1.31	0.79–2.17	0.29	1.09	0.59–2.00	0.79
<60 versus 70+	1.73	0.99–3.00	0.05	1.97	1.04–3.73	0.04
ER (−ve versus +ve)	0.99	0.44–2.24	0.99	0.66	0.27–1.62	0.37
PgR (−ve versus +ve)	0.58	0.30–1.11	0.10	0.55	0.27–1.15	0.12
HER2 (−ve versus +ve)	0.74	0.34–1.60	0.44	0.77	0.33–1.85	0.57
Ki67 (−ve versus +ve)	1.54	0.97–2.43	0.07	1.21	0.71–2.06	0.48
Tumour size						
≤2 versus 2–5 cm	1.01	0.66–1.56	0.95	0.81	0.48–1.36	0.42
≤2 versus 5+ cm	0.97	0.32–2.92	0.96	0.90	0.25–3.20	0.87
Nodal status						
Negative versus 1–3N+	1.46	0.89–2.42	0.14	1.60	0.88–2.92	0.12
Negative versus >3N+	3.08	1.77–5.37	<0.001	3.25	1.66–6.35	0.001
Negative versus unknown	0.51	0.17–1.51	0.22	0.39	0.09–1.74	0.22
Grade						
G1 versus G2	0.98	0.51–1.91	0.96	0.98	0.43–2.27	0.97
G1 versus G3/undifferentiated	1.20	0.55–2.62	0.64	1.61	0.64–4.07	0.31
G1 versus not assessable/unknown	1.41	0.64–3.11	0.40	1.50	0.57–3.91	0.41

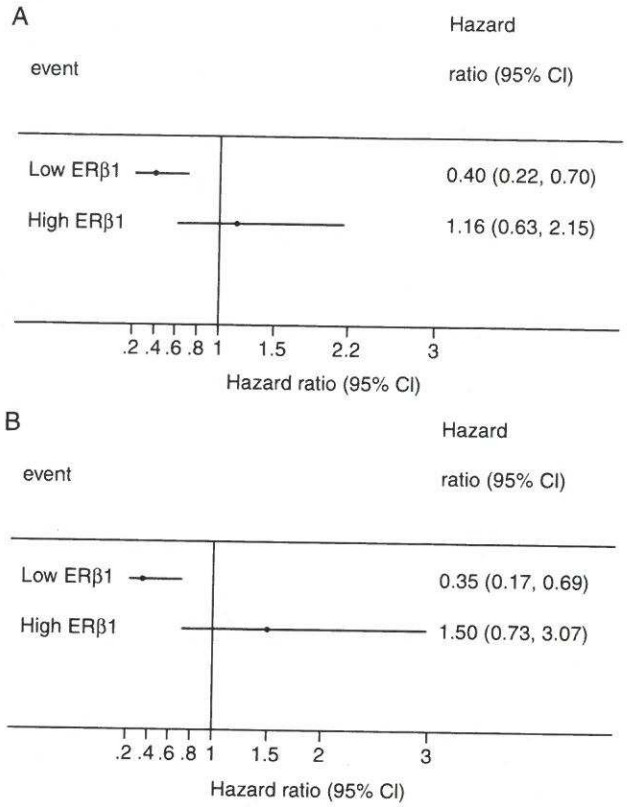

Figure 2. Treatment effect within ERβ1 subgroups (adjusted for known prognostic variables) by disease-free survival (A) and overall survival (B).

A further possibility is that ERβ1 has a restraining action on ERα-mediated growth and cell survival. This would be additive to the tamoxifen effect, thus leading to improved outcome, similar to that observed with aromatase inhibition. Contrary to this view, there is evidence that tamoxifen acts as an agonist of ERβ at AP-1 sites, and thus could oppose the anti-proliferative effects of the tamoxifen-ERα complex [25]. There is evidence in cell lines suggesting a relationship between ERβ expression and endocrine sensitivity by reduction of HER2/HER3 signalling [26]. A further factor that could contribute to this effect is that exemestane has androgenic metabolites. Activation of the AR pathway inhibits breast cancer cell growth by up-regulation of ERβ expression [27].

There is emerging evidence that the cellular location of ERβ2 may be critical in determining outcome [12–14], with cytoplasmic location associated with a poor prognosis [13]. However, apart from being associated with reduced tumour size, neither nuclear nor cytoplasmic expression of ERβ2 influenced outcome in the present study (data not shown). While ERβ2 itself is incapable of ligand binding [11], data from cell line models indicate a negative regulation of ERα function through heterodimerisation [28].

In our study, tissue samples were not randomly selected and this might have introduced bias in the results. Centre selection was limited by local laws and regulations, and within centres only a proportion of samples were provided. This was either because there was no available tissue or because the patient had their primary surgery at hospitals not participating in the IES. Although the characteristics of patients who did and did not provide tissue within each centre were similar, some unavoidable inherent bias cannot be excluded. The reduced sample size, low number of events and potentially biased selection of available samples requires cautious interpretation of the results.

Our results suggest that in patients whose primary breast cancers express ERα switching to exemestane may be beneficial principally in a subset with low ERβ1 expression. This finding may allow better selection of post-menopausal patients to adjuvant endocrine therapies and a safe switch back to tamoxifen in the case of poor AI tolerance. However, due to the exploratory nature of this study, prospective validation is required before advising change in practice.

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disclosure

The authors have declared no conflicts of interest.

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