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ORIGINAL REPORT

Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence Score

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ABSTRACT

Purpose
We have previously shown that the PAM50-based risk of recurrence (ROR) score is significantly correlated with distant recurrence in both the translational research cohort within the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial (TransATAC) and Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG 8) randomized trials. Here, we focus on the ROR score for predicting distant recurrence after 5 years of follow-up in a combined analysis of these two randomized trials.

Methods
Long-term follow-up data and tissue samples were obtained from 2,137 postmenopausal women with hormone receptor–positive early-stage breast cancer from the ABCSG 8 and TransATAC trials. We used Cox proportional hazard regression models to determine the prognostic value of ROR for distant recurrence beyond 5 years in the combined data set.

Results
A total of 2,137 women who did not have a recurrence 5 years after diagnosis were included in the combined analyses. The Clinical Treatment Score (CTS) was the strongest prognostic factor 5 years after diagnosis (univariable: likelihood ratio [LR] $\chi^2 = 94.12$, bivariable: LR $\chi^2 = 61.43$). The ROR score was significantly prognostic by itself in years 5 to 10. In the node-negative/human epidermal growth factor receptor 2–negative subgroup, more prognostic value for late distant recurrence was added by the ROR score compared with the CTS.

Conclusion
The ROR score added clinically meaningful prognostic information to the CTS in all patients and all subgroups in the late follow-up period. These results suggest that the ROR score may be helpful for separating patients into risk groups who could be spared or potentially benefit from extended hormonal therapy beyond 5 years of treatment.

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INTRODUCTION

Women with estrogen receptor (ER) –positive tumors remain at risk for late recurrences, with the annual rate in excess of 2% for at least 15 years, even after 5 years of tamoxifen therapy.[1] Currently, it is not possible to identify a group of women who can be considered as cured after the initial 5 years of endocrine therapy.[2,3] Most of the studies of prevention of late relapse have been performed with women who received tamoxifen as initial endocrine therapy,[4,5] and there are only a few reports with women who initially received an aromatase inhibitor.

It has been reported that women with highly proliferative tumors (a high mitotic kinase score) and a high estrogen-related score were at greater risk of late recurrence.[6] The Breast Cancer Index (BCI) showed prognostic ability to assess early and late distant recurrence.[7] Sgroi et al[8] reported on the comparative performance of the BCI versus immunohistochemical 4 markers and Oncotype Dx recurrence score (RS) for

late recurrence and found that the BCI is a strong prognostic factor in predicting late recurrence. Dubsky et al[9] reported on the EndoPredict test, which stratifies patients into low- and high-risk groups for late recurrence (Appendix Table A1, online only).

The risk of recurrence (ROR) score has previously been shown to add prognostic information not found in standard markers.[10,11] In the translational research cohort within the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial (TransATAC),[12] the performance of the ROR score was compared with that of the RS and immunohistochemical 4 for distant recurrence in 1,007 postmenopausal women, and results showed that the ROR added more prognostic information in endocrine-treated women with node-negative disease than the RS. Similarly, the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG 8) trial[13] showed that the ROR score predicted the risk of distant recurrence in 1,478 postmenopausal women with ER-positive early-stage breast cancer. It is important to determine to what extent the ROR score can help predict late recurrence, specifically beyond 5 years after diagnosis. Here, we combine the data from the TransATAC and ABCSG 8 trials and investigate the extent to which the ROR score predicts for distant recurrence exclusively in years 5 to 10 after diagnosis.

METHODS

The ATAC trial evaluated the efficacy and safety of anastrozole versus tamoxifen given for 5 years in postmenopausal women with localized breast cancer.[14] The TransATAC substudy collected formalin-fixed, paraffin embedded blocks from hormone receptor–positive breast cancers in a subset of women randomly assigned to the monotherapy arms of the ATAC trial.[15] The ABCSG 8 trial was a randomized, open-label trial comparing 5 years of tamoxifen with 2 years of tamoxifen followed by 3 years of anastrozole in postmenopausal women with hormone receptor–positive breast cancer, for whom formalin-fixed, paraffin embedded blocks from the original tumors were collected to extract RNA and for use in a subsequent PAM50 analysis.[16] Both trials were performed in accordance with the Declaration of Helsinki (1996 revision), under the principles of good clinical practice. The ATAC trial is registered as an International Standard Randomized Controlled Trial (ISRCTN18233230) and the ABCSG 8 trial is registered under the Clinical Trial Registry (NCT00291759).

The Clinical Treatment Score (CTS) contains information on nodal status, tumor size, grade, age, and treatment and was developed on the TransATAC data set.[17] The laboratory methods for the original ROR score have been described in detail previously.[10,17,18] Briefly, the expression levels for 50 classifier genes and eight housekeeping genes were measured by using the nCounter platform (NanoString Technologies, Seattle, WA), which gives a ROR score between zero and 100 that is indicative of the probability of distant recurrence. After normalization, the expression profile of the 50 classifier genes for each sample was used to determine the intrinsic subtype of the tumor. A 46-gene subset of the PAM50 genes plus tumor size was used to calculate a predefined ROR score, which performed as well as the ROR score that was based on the 50-gene set.[18] Risk stratification by using the ROR score was based on the predicted distant recurrence risk at 10 years ($<$ 10%: low-risk group, ROR 0 to 26; 10% to 20%: intermediate-risk group, ROR 26 to 68; $>$ 20%: high-risk group, ROR $>$ 68).

The primary objective of this study was to determine whether the ROR score provides prognostic information in the period beginning 5 years after diagnosis. The time from 5 years after diagnosis to the first distant recurrence after 5 years was the prospectively defined primary end point. Death before distant recurrence was treated as a censoring event. The association between ROR score and distant recurrence after 5 years of follow-up was assessed by using hazard ratios (HRs) derived from Cox proportional hazards regression models with associated 95% CIs. For bivariable analyses, the ROR score was added separately to the CTS to determine the added prognostic information in that score. Changes in likelihood ratio χ^2 (LR χ^2) values were used to measure and compare the relative amount of information of one score compared with the other. Survival curves were estimated by using the Kaplan-Meier method. All curves were truncated at 10 years of follow-up because differential follow-up was available for the two trials thereafter. However, overall HRs are presented for all events in both trials. The Net Reclassification Index (NRI) was used to determine the prognostic improvement by ROR beyond that of the CTS.[19,20] *P* values were two-sided based on normal approximation, and all CIs were at the 95% level. Analyses were performed by using STATA version 12.1 (STATA, College Station, TX).

RESULTS

The two trials were combined in this analysis and baseline characteristics are shown in Table 1, and further prognostic baseline factors according to ROR risk group are shown in Appendix Table A2 (online only). For this analysis, women who had a recurrence in the first 5 years were excluded; thus, data from both trials included only postmenopausal women with hormone receptor–positive breast cancer who received 5 years of endocrine treatment and who did not have a recurrence in the first 5 years (N = 2,137 [1,275 from ABCSG 8; 862 from TransATAC]). The mean ROR score for those women who were excluded from this analysis (who had a recurrence during the first 5 years) was significantly higher compared with the scores for those who did not have a recurrence in the first 5 years (53.57 [standard deviation, 20.4] *v* 41.89 [standard deviation, 19.5]; $P < .001$). The median follow-up for this analysis was 10 years.[21,22] There were 148 distant recurrences beyond 5 years of follow-up. This analysis focuses only on the prognostic information obtained for 5 years after diagnosis. Data are presented for all patients, node-negative patients, node-positive patients, and human epidermal growth factor receptor 2 (HER2) –negative patients.

There was a significantly higher rate of distant recurrence in years 5 to 10 in the TransATAC trial when compared with the ABCSG 8 trial ($P < .001$). The TransATAC trial had significantly more women with large tumors ($P < .001$), poorly differentiated tumors (none in the ABCSG 8 trial), and four or more positive nodes. Additional baseline characteristics for both populations have been described in detail previously.[16,17] An analysis has been performed excluding grade 3 tumors from the TransATAC data set. The omission of these tumors did not substantially change the results (data not shown). A total of 1,530 women (73.8%) had a luminal A breast cancer subtype and 542 women (26.2%) had a luminal B breast cancer subtype; those with a luminal B subtype had a 2.9 times higher risk of distant recurrence (HR, 2.89; 95% CI, 2.07 to 4.02; $P < .001$).

In the overall population, CTS added more prognostic information for distant recurrence 5 years after diagnosis in the univariable analysis (LR $\chi^2 = 94.12$) and when added to the ROR score (LR $\chi^2 = 61.43$; Table 2). The ROR score also added significant prognostic information for this time period but somewhat less than the CTS (univariable LR $\chi^2 = 67.94$; bivariable LR $\chi^2 = 35.25$). Figure 1 shows Kaplan-Meier curves for the separation of ROR scores into low-, intermediate-, and high-risk groups based on the 10-year distant recurrence risk of less than 10%, 10% to 20%, and more than 20%. Women categorized into the high-risk group had 16.6% (95% CI, 13.1% to 20.9%) risk of distant recurrence in years 5 to 10, those in the intermediate-risk group had a risk of 8.3% (95% CI, 6.1% to 11.2%), and those in the low-risk group had a risk of 2.4% (95% CI, 1.6% to

Table 1. Baseline Characteristics According to Trial

Characteristic	TransATAC (n = 862) No.	TransATAC (n = 862) %	ABCSG 8 (n = 1,275) No.	ABCSG 8 (n = 1,275) %	*P*
Treatment (tamoxifen *v* anastrozole)	412 *v* 450		629 *v* 646		.5
Nodal status (negative *v* positive)	647 *v* 215	75.1 *v* 24.9	933 *v* 342	73.2 *v* 26.8	.3
Node positive (one to three nodes)	180	20.9	307	24.1	
Node positive (four or more nodes)	35	4.1	35	2.8	
Tumor size, mm					< .001
Mean	19.0		16.7		
Standard deviation	10.1		8.3		
≤ 10	128	14.8	239	18.7	
10-20	459	53.3	699	54.8	
20-30	210	24.4	283	22.2	
> 30	65	7.5	54	4.2	
Age (≤ 65 *v* > 65 years)	504 *v* 358	58.5 *v* 41.5	774 *v* 501	60.7 *v* 39.3	.3
Differentiation					
Well	195	22.6	242	19.0	.04
Moderate	519	60.2	1033	81.0	< .001
Poor	148	17.2	—		—
Distant recurrence (years 5 to 10)	80	9.3	68	5.3	< .001

Abbreviations: ABCSG 8, Austrian Breast and Colorectal Cancer Study Group 8; TransATAC, translational research cohort within the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial.

3.5%; Fig 1). Women in the ROR high-risk group had a 6.9 times higher risk of late distant recurrence (HR, 6.90; 95% CI, 4.54 to 10.47), and those in the intermediate-risk group had a 3.3 times higher risk of late distant recurrence (HR, 3.26; 95% CI, 2.07 to 5.13) compared with those in the low-risk group. Figure 2 shows annual hazard rate curves with corresponding 95% CIs for the three risk groups. Those in the low-risk group showed stable annual hazard rates under 1% per year between 5 and 10 years, whereas those in the intermediate-risk group showed an increase from 1% up to 2% at year 8 (Fig 2). Women in the high-risk group had an increasing annual hazard rate peaking at 4% at 6.9 years of follow-up and then stabilized at around 3% per year thereafter.

Results for the main subgroups according to nodal and HER2 status are shown in Table 2 and Appendix Table A3 (online only). In node-negative patients (n = 1,580), the ROR score added more prognostic information than the CTS in both the univariable and the bivariable analyses (univariable LR $\chi^2 = 30.95$ *v* LR $\chi^2 = 21.48$; bivariable LR $\chi^2 = 17.25$ *v* LR $\chi^2 = 7.79$). A similar picture was seen for the node-negative/HER2-negative subgroup for which more prognostic value for late distant recurrence was added by the ROR score. Women in the ROR low-risk group had a 2% (95% CI, 1.3% to 3.2%) risk of distant recurrence by 10 years compared with similar 10-year distant recurrence rates for those in the intermediate-risk group (9.0%; 95% CI, 6.3% to 13.0%) and high-risk group (11.5%; 95% CI, 6.8% to 19.0%; Fig 3 and Appendix Table A3). In all, 557 women had

Table 2. HR for Univariable and Bivariable Models According to Subgroups and Scores

Subgroup	No. of Patients	No. of Distant Recurrences	Univariable HR	Univariable 95% CI	Bivariable* HR	Bivariable* 95% CI
All	2,137	148				
CTS			1.96	1.73 to 2.21	1.80	1.57 to 2.06
ROR			2.69	2.12 to 3.43	2.07	1.63 to 2.64
Node negative	1,580	76				
CTS			1.96	1.50 to 2.57	**1.56**	1.15 to 2.12
ROR			2.56	1.83 to 3.56	2.11	1.48 to 3.00
Node positive	557	72				
CTS			1.84	1.52 to 2.23	1.74	1.42 to 2.13
ROR			2.52	1.80 to 3.53	2.15	1.52 to 3.03
Node negative/ HER2 negative	1,455	70				
CTS			2.12	1.61 to 2.79	**1.65**	1.21 to 2.24
ROR			3.00	2.11 to 4.27	2.41	1.65 to 3.50

NOTE. *P* values < .001 for all HRs except those in bold.
Abbreviations: CTS, Clinical Treatment Score; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ROR, risk of recurrence.
*Each variable added to the other variable.

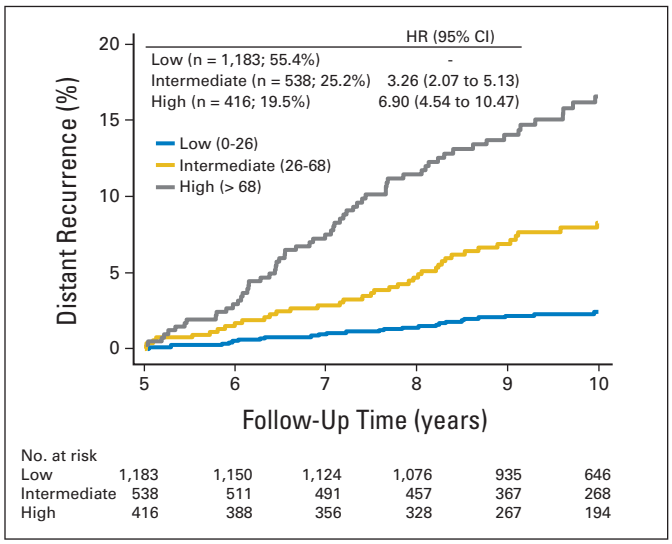

Fig 1. Kaplan-Meier curve for distant recurrence in years 5 to 10 in all patients according to risk of recurrence risk groups. HR, hazard ratio.

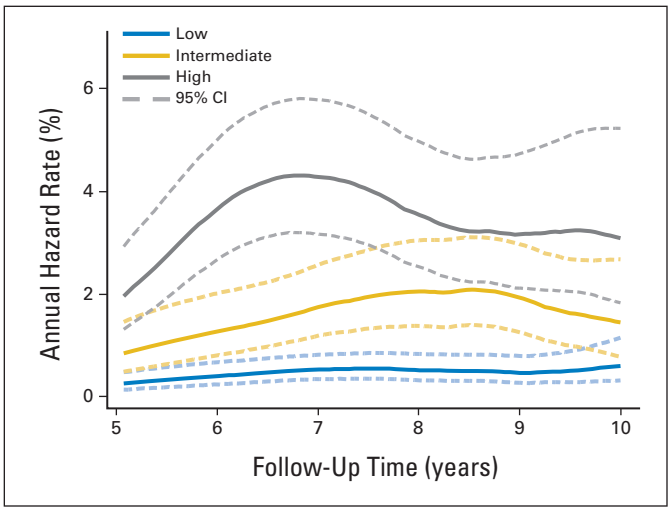

Fig 2. Annual hazard rate curve for all patients according to risk of recurrence groups.

a node-positive tumor, and in those, CTS added most prognostic information univariately (LR $\chi^2 = 35.60$) and when added to the ROR score (LR $\chi^2 = 25.67$). The ROR score added somewhat less but still significant prognostic information for distant recurrence in this subgroup (Table 2). 24.6% of women with node-positive disease were categorized into the low-risk ROR group with a distant recurrence risk of only 3.3% in the late follow-up period (Appendix Table A3). Overall, the effect size for the ROR score in the bivariable analyses was similar across all subgroups (Table 2).

The correlation between the CTS and ROR was weak ($r = 0.36$). Agreement between the ROR score and CTS for separating patients into low-, intermediate-, and high-risk groups is shown in Table 3. The number of women categorized into the low-risk group was similar for the two scores (55.4% *v* 53.3%). However, the CTS categorized overall more women into the intermediate-risk group (32.4%) than the ROR score (25.2%), which categorized more women as high risk (19.5% ROR *v* 14.3% CTS; Table 3). Furthermore, Appendix Fig A1 (online only) shows the reclassification of distant recurrence and nonevents by ROR or CTS plus ROR versus CTS alone. For those with distant recurrence, the ROR score classified 32 women into higher-risk and 21 into lower-risk categories compared with the CTS alone. This translates into a net reclassification of 7.4% for women with distant recurrence. For nonevents, the reclassification by ROR was small (1.5%). The overall NRI for ROR versus CTS was 5.97%, which was not significant ($P = .3$). The addition of ROR to the CTS improved the classification for distant recurrence (14 women into higher-risk *v* 3 women into lower-risk groups; net reclassification of 7.4%) compared with CTS alone, but a net loss was observed for women with nonevents (123 women into higher-risk *v* 161 into lower-risk groups; net reclassification, 1.9%). For this comparison, a significant NRI of 9.34% was observed ($P = .001$; Appendix Fig A1). Similar results were seen for women with node-negative disease (data not shown).

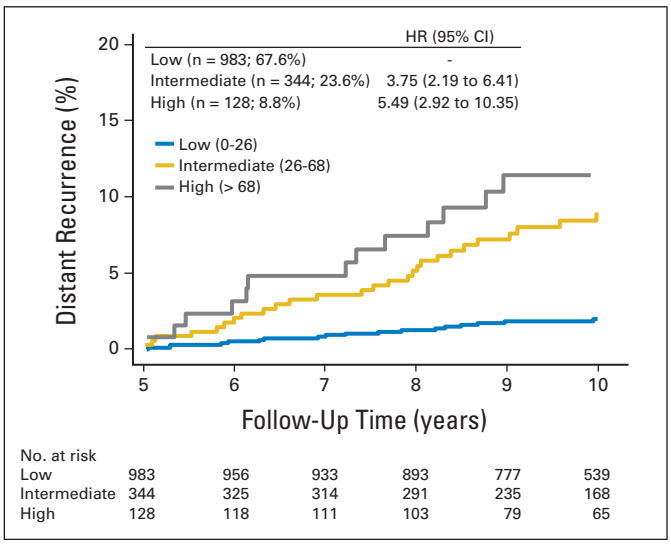

Fig 3. Kaplan-Meier curve for distant recurrence in years 5 to 10 in node-negative/human epidermal growth factor receptor 2–negative patients according to risk of recurrence risk groups. HR, hazard ratio.

DISCUSSION

It is well known that recurrence risk extends for at least 20 years in women with hormone receptor–positive early-stage breast cancer treated with 5 years of endocrine therapy.[23] Continued (extended) adjuvant treatment beyond 5 years reduces recurrence rates but is unlikely to be significantly beneficial to all patients individually. It is therefore crucial to identify molecular markers that predict late recurrence. The analyses of combined data from the TransATAC and ABCSG 8 trials showed that the ROR score added significant prognostic information for late distant recurrence in women with hormone receptor–positive early-stage breast cancer who did not receive chemotherapy. Predefined risk stratification showed significant differences between ROR-defined risk groups with respect to 10-year late distant recurrence.

The ROR score has previously been shown to add prognostic information for recurrence in the two trials of endocrine-treated patients.[11,18] The ROR score was able to predict the risk of distant recurrence in postmenopausal women with early hormone receptor–positive early-stage breast cancer.[22] In the TransATAC trial, the ROR score added more prognostic information than the Oncotype RS.[18] In this combined analysis, the CTS was the stronger prognostic score for late distant recurrence overall and for the node-positive subgroup. In contrast, the ROR score was the stronger predictor of late distant recurrence for patients with node-negative and node-negative/HER2-negative disease, who may be spared further endocrine therapy, specifically those who were categorized into the low-risk group by the ROR score.

The ROR score provided clinically useful prognostic information, predicting risk of late distant recurrence beyond that of classical clinical markers in all subgroups. Of note is that 24.6% of women with node-positive disease were categorized into the ROR low-risk group with a distant recurrence risk of only 3.3% in years 5 to 10. Given this low risk of distant recurrence at both early and late follow-up periods, the indication for adjuvant chemotherapy and the extension of endocrine therapy beyond 5 years are both questionable. Concerning the node-negative population with HER2-negative disease, large tumor size and premenopausal status at diagnosis have been suggested as factors to select women for extended adjuvant endocrine treatment.[24-26]

Table 3. Reclassification of Risk Groups by ROR *v* CTS and ROR Plus CTS *v* CTS Alone for All Patients

	CTS							
	Low		Intermediate		High		Total	
Risk Group	No.	%	No.	%	No.	%	No.	%
ROR								
Low	855		287		41		1,183	55.4
Intermediate	216		252		70		538	25.2
High	68		154		194		416	19.5
Total	1,139	53.3	693	32.4	305	14.3	2,137	
CTS plus ROR								
Low	1,055		139		0		1,194	55.8
Intermediate	84		501		25		610	28.5
High	0		53		280		333	15.6
Total	1,139	53.3	693	32.4	305	14.3	2,137	

NOTE. Cutoffs according to 10-year distant recurrence risk: low, < 10%; intermediate, 10% to 20%; high, > 20%.
Abbreviations: CTS, Clinical Treatment Score; ROR, risk of recurrence.

Our results show that women with node-negative disease categorized into the ROR low-risk group have an extremely low rate of late distant recurrence despite some of them having large tumors, which challenges the indication for additional therapy. In contrast, women with node-negative disease categorized into the high-risk group by the ROR score might benefit from additional endocrine therapy, but this needs further confirmation because the ROR score is a prognostic and not predictive marker.

Strengths of this analysis included its large sample size (N = 2,137), long follow-up with a median of 10 years, and a patient population that came from two well-characterized registration clinical trials using tamoxifen and anastrozole. One limitation was that none of these women received chemotherapy as part of their initial treatment, and therefore we are unable to analyze the prognostic value of the ROR score for late distant recurrence in this group of patients. Baseline characteristics were somewhat different between the two trials. Women in the ABCSG 8 trial had an overall low-to-intermediate risk of late distant recurrence, whereas those in the TransATAC trial showed an increased risk, which is explained by larger tumor size, the inclusion of grade 3 tumors (none in the ABCSG 8 trial), and the presence of more women with more than four positive nodes. Analyses with exploratory exclusion of grade 3 tumors from the TransATAC trial showed similar results. The combined analysis offered a unique opportunity to investigate the prognostic value of the ROR score in this clinically relevant population.

In summary, we showed that the ROR score provided additional clinically meaningful prognostic information for late distant recurrence beyond standard clinical variables (CTS) and was able to discriminate patients into low- and high-risk groups in this large combined data set. The ROR score has been validated in several trials,[11,12,18] and the results presented here may help to identify women who are at high risk of late distant recurrence and who may benefit from extended endocrine treatment beyond 5 years. Conversely, the results show that the ROR score is able to identify women who are at sufficiently low risk of late distant recurrence, even in women with node-positive disease, so that they may be spared prolonged and/or additional endocrine treatment and, therefore, overtreatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Manuscript writing: All authors
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GLOSSARY TERMS

anastrozole: a third-generation nonsteroidal aromatase inhibitor that prevents the conversion of androgen to estrogen in the peripheral tissues in postmenopausal women. Because hormone-dependent breast cancer progresses with estrogen, anastrozole has been used in the treatment of breast cancer in postmenopausal women. See *aromatase inhibitors*.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function. ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

prognostic factor: a measurable patient characteristic that is associated with the subsequent course of disease (whether or not therapy is administered). The identification of a prognostic factor does not necessarily suggest a cause-and-effect relationship. However, within a suitable outcome model, the measurement of a prognostic factor contributes to an estimate of an outcome probability (eg, the probability of disease-free survival within a given time interval).

recurrence score: a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of initial diagnosis. The score is derived from a mathematical function combining the expression values of 16 breast cancer related genes and five reference genes.

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Appendix

Table A1. Description of Clinical and Multigene Scores

Score	Abbreviation	Details	Reference
Clinical Treatment Score	CTS	Includes information on nodal status, grade, tumor size, age, and treatment. Score developed on TransATAC data.	Cuzick et al[17]
Immunohistochemical Score 4	IHC4	Includes information on ER, PgR, Ki-67, and HER2. Score developed on TransATAC data. FFPE blocks used to extract RNA to perform IHC for ER, PgR, Ki-67, HER2.	Dowsett et al,[15] Cuzick et al,[17] Zabaglo et al: J Clin Pathol 63:800-804, 2010
Oncotype Dx Recurrence Score	RS	Twenty-one-gene–based expression profile score using qRT-PCR (16 cancer genes, five housekeeping genes). FFPE blocks used to extract RNA.	Paik et al: N Engl J Med 351: 2817-2826, 2004
Prosigna Risk of Recurrence Score	ROR	Fifty gene–based expression profile score using qRT-PCR. FFPE blocks used to extract RNA to perform analysis on nCounter system.	Dowsett et al[12]
Breast Cancer Index	BCI	Multigene assay using qRT-PCR. Combination of two biomarkers: HOXB13/IL17BR and molecular grade index.	Zhang et al,[7] Sgroi et al[8]
EndoPredict	EPClin	Twelve gene–based expression profile score using qRT-PCR (eight cancer genes, four housekeeping genes). FFPE blocks used to extract RNA to perform analysis.	Dubsky et al[9]

Abbreviations: ER, estrogen receptor; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; TransATAC, translational research cohort within the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial.

Table A2. Prognostic Baseline Factors According to ROR Risk Groups

	ROR (%)		
Factor	Low	Intermediate	High
Grade			
Low	28.6	13.4	6.5
Intermediate	68.6	77.4	78.1
High	2.8	9.5	15.4
Negative nodal status	88.4	70.3	37.5
Tumor size > 2 cm	16.7	35.1	53.6
Age > 65 years	34.1	44.4	52.2

Abbreviation: ROR, risk of recurrence.

Table A3. HR and 10-Year Distant Recurrence Risk According to Patient Subgroups and ROR Risk Groups

Variable	No. of Patients	HR	95% CI	10-Year Risk (%)	95% CI
All patients					
Low	1,183	Reference		2.4	1.6 to 3.5
Intermediate	538	3.26	2.07 to 5.13	8.3	6.1 to 11.2
High	416	6.90	4.54 to 10.47	16.6	13.1 to 20.9
Node negative					
Low	1,046	Reference		2.3	1.5 to 3.5
Intermediate	378	3.22	1.93 to 5.37	8.5	5.9 to 12.1
High	156	4.26	2.33 to 7.78	9.3	5.5 to 15.5
HER2 negative					
Low	1,117	Reference		2.2	1.4 to 3.3
Intermediate	498	3.70	2.31 to 5.95	8.7	6.4 to 11.9
High	359	7.23	4.61 to 11.32	16.2	12.5 to 20.9
Node negative/HER2 negative					
Low	983	Reference		2.0	1.3 to 3.2
Intermediate	344	3.75	2.19 to 6.41	9.0	6.2 to 13.0
High	128	5.49	2.92 to 10.35	11.5	6.8 to 19.0
Node positive					
Low	137	Reference		3.3	1.2 to 8.6
Intermediate	160	3.16	1.04 to 9.61	7.8	4.4 to 13.8
High	260	7.94	2.87 to 21.92	20.9	16.1 to 26.9
Node positive with one to three nodes					
Low	137	Reference		3.3	1.2 to 8.6
Intermediate	154	3.04	0.99 to 9.32	7.5	4.1 to 13.5
High	196	7.37	2.63 to 20.65	19.6	14.4 to 26.5
Node positive with four or more nodes					
Low	0	—		—	
Intermediate	6	Reference		16.7	2.5 to 72.7
High	64	1.67	0.17 to 83.68	24.7	15.3 to 38.3

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ROR, risk of recurrence.

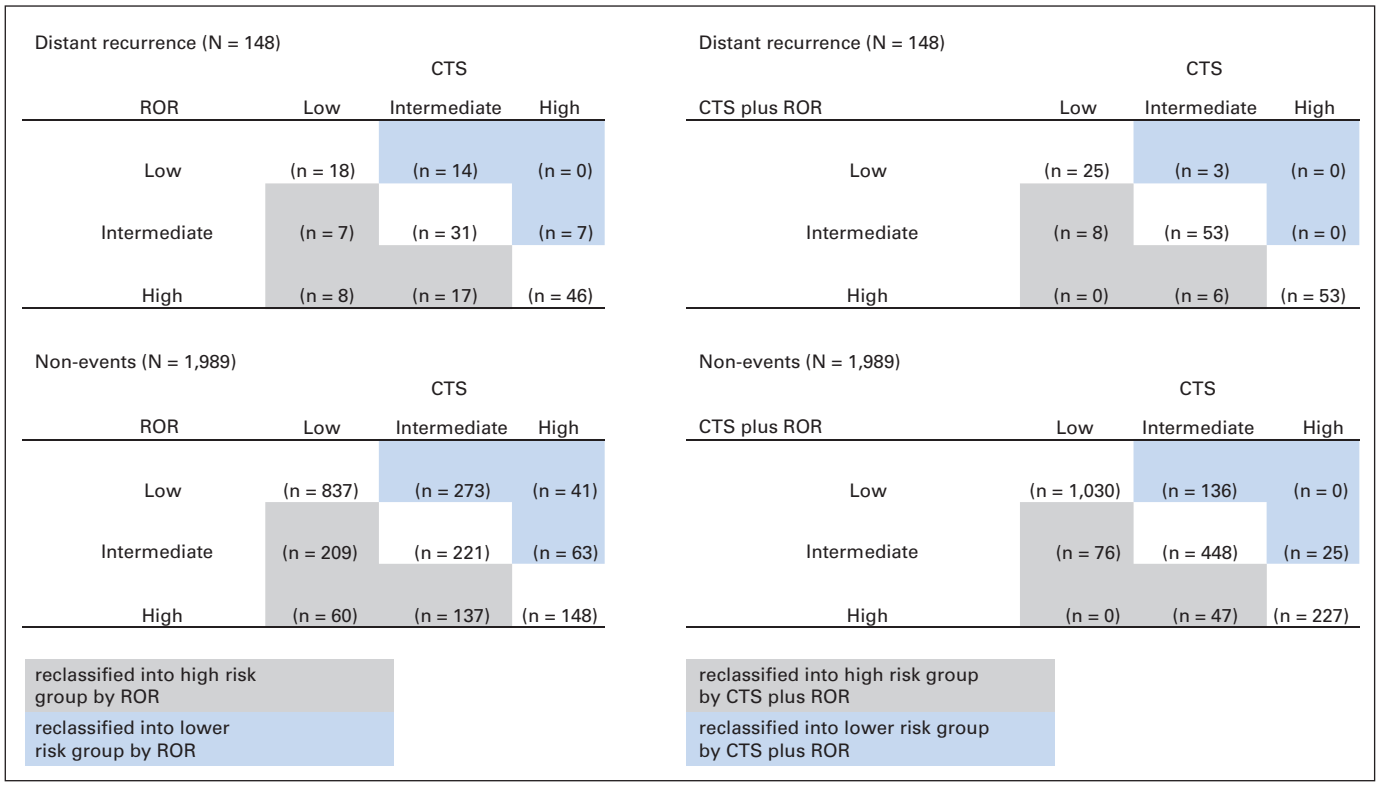

Fig A1. Net Reclassification Index (NRI) for distant recurrence (N = 148) versus nonevents (N = 1,989) for all patients. Left panel: gray-shaded area represent patients reclassified into high-risk group by risk of recurrence (ROR); blue-shaded area represents patients reclassified into lower-risk group by ROR. Right panel: gray-shaded area represents patients reclassified into high-risk group by Clinical Treatment Score (CTS) plus ROR; blue-shaded area represents patients reclassified into lower risk group by CTS plus ROR. NRI = [distant recurrence (% upward − % downward)] – [nonevents (% upward − % downward)]. NRI for ROR/CTS = [(32/148) − (21/148)] – [(406/1,989) − (377/1,989)] = 5.97%. NRI for ROR/CTS plus ROR = [(14/148) − (3/148)] – [(123/1,989) − (161/1,989)] = 9.34%.