JAMA Network Open

Original Investigation | Oncology

Selection of Patients With Early-Stage Breast Cancer for Extended Endocrine Therapy

A Secondary Analysis of the IDEAL Randomized Clinical Trial

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Abstract

IMPORTANCE There is a need for biomarkers that predict late recurrence risk and extended endocrine therapy (EET) benefit among patients with early-stage breast cancer (EBC). MammaPrint, a 70-gene expression risk-of-recurrence assay, has been found to project significant EET benefit in patients with assay-classified low-risk tumors.

OBJECTIVE To determine the test's utility in identifying which patients with EBC in the IDEAL (Investigation on the Duration of Extended Adjuvant Letrozole) trial could benefit from 5-year vs 2.5-year letrozole treatment.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of the IDEAL randomized clinical trial evaluated postmenopausal women with hormone receptor–positive EBC who were assigned to either 2.5 or 5 years of EET, with 10 years of follow-up after randomization. A 70-gene assay was used to classify tumors as high, low, or ultralow risk. Adverse event (AE) frequency and treatment compliance were evaluated. Statistical analyses were performed from April 2022 to September 2024.

INTERVENTIONS After 5 years of endocrine therapy, patients were randomized to 2.5 or 5 years of EET with letrozole.

MAIN OUTCOMES AND MEASURES Primary end point was distant recurrence (DR). Cox proportional hazard regression models and likelihood ratios tested the interaction between treatment and gene expression assay.

RESULTS Among 515 women included (mean [SD] age at randomization, 59.9 [9.5] years), 265 were in the 2.5-year treatment arm and 250 in the 5-year treatment arm. Of these patients, 223 (43.3%) patients with 70-gene assay–classified low-risk tumors had a significant absolute benefit of 10.1% for DR (hazard ratio, 0.32; 95% CI, 0.12-0.87; $P = .03$). Treatment interaction was not significant for DR. Of patients with either 70-gene assay–classified high-risk tumors (259 [50.3%]) or ultralow risk tumors (33 [6.4%]), 5 years vs 2.5 years of EET was not associated with improved benefit for DR. As expected, rates of AEs and treatment discontinuation were comparable among the different 70-gene assay risk groups in each treatment arm.

CONCLUSIONS AND RELEVANCE This secondary analysis of the IDEAL trial found that the 70-gene assay identified patients with low-risk tumors who could benefit from 5-year vs 2.5-year EET. These findings suggest that this gene expression assay could go beyond guiding neoadjuvant and adjuvant chemotherapy decisions to informing the optimal duration of adjuvant endocrine therapy.

(continued)

Key Points

Question Can a 70-gene expression risk-of-recurrence assay, identify which patients with hormone receptor–positive, early-stage breast cancer could benefit from extended endocrine therapy (EET)?

Findings In this secondary analysis of a randomized clinical trial involving 515 patients, 5 years of EET was associated with a significant reduction in late recurrences for patients with assay-classified low-risk tumors, whereas patients with ultralow- and high-risk tumors did not significantly benefit and could avoid EET-related adverse events.

Meaning Findings of this study suggest that a 70-gene expression risk-of-recurrence assay can project extended endocrine response and can identify a subset of patients with EET-improved outcomes.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

TRIAL REGISTRATION EU Clinical Trials Register Eudra CT: 2006-003958-16

JAMA Network Open. 2024;7(11):e2447530. doi:10.1001/jamanetworkopen.2024.47530

Introduction

Patients with hormone receptor (HR)–positive breast cancer have 10% to 40% risk of distant metastasis, which persists beyond the initial 5 years of adjuvant endocrine therapy.[1,2] Extended tamoxifen duration demonstrated reduced late recurrence risk in the ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) and aTTom (Adjuvant Tamoxifen—To Offer More?) trials.[3,4] The benefits and optimal duration of aromatase inhibitor therapy beyond 5 years after initial endocrine therapy have been evaluated in several clinical trials, including the NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) MA-17, NSABP (National Surgical Adjuvant Breast and Bowel Project) B-42, ABCSG-16 (Austrian Breast and Colorectal Cancer Study Group Trial-16), and IDEAL (Investigation on the Duration of Extended Adjuvant Letrozole).[5-9]

In the IDEAL trial, postmenopausal patients with HR-positive early-stage breast cancer (EBC) were randomized to receive 2.5 years or 5 years of letrozole treatment after 5 years of standard adjuvant endocrine therapy.[9] After a median follow-up of 6.5 years, extended endocrine therapy (EET) showed no significant benefit on the primary end point of disease-free survival or secondary end points of overall survival and distant metastasis–free survival. For postmenopausal patients with a high risk of late recurrence, the NCCN (National Comprehensive Cancer Network) Guidelines[10] recommend up to 10 years of adjuvant endocrine therapy. However, the IDEAL trial and similar trials report a modest EET benefit along with increased adverse events (AEs) and financial costs, which are associated with treatment noncompliance.[6,7,9,11,12] These findings underscore a critical need for biomarkers, or genomic classifiers, that can be used to accurately identify patients who could benefit from EET.

Widely used gene expression assays personalize adjuvant treatment for HR-positive, *ERBB2* (formerly *HER2*)–negative EBC and have been proven to allow chemotherapy de-escalation for patients with clinically high risk but genomically low risk.[13-16] The 70-gene expression assay classifies EBC as having a high risk or low risk of distant metastasis.[17,18] In the MINDACT (Microarray In Negative or Up to Three Nodes Disease May Avoid ChemoTherapy) trial, patients with 70-gene–classified low-risk tumors had excellent 9-year outcomes without chemotherapy despite clinical high-risk features.[15,16] Within the low-risk category, a threshold was established to detect indolent tumors in patients, referred to as having ultralow risk, who have excellent 20-year outcome with little to no endocrine therapy.[19-23] Conversely, patients with 70-gene assay–classified high-risk tumors had substantially improved survival with chemotherapy, confirming this test's value in guiding adjuvant chemotherapy decisions.[24,25]

The utility of gene expression assays has been evaluated for projecting risk of late relapse and EET benefit. Secondary analyses of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) and NSABP B-14 trials demonstrated that one assay did not predict late (years 5-10) distant recurrence (DR).[26,27] However, integration of clinicopathologic features with a recurrence score (using RSClin tool) improved late recurrence risk estimates.[28] No studies have shown this assay to be predictive of EET benefit. Breast Cancer Index, consisting of a 5-gene molecular grade index panel and a 2-gene *HOXB13/IL17BR* (H/I) ratio, has been shown to be a prognostic biomarker to predict late recurrence in HR-positive EBC in the ATAC and TEAM (Tamoxifen and Exemestane Adjuvant Multinational) trials,[26-30] and some randomized clinical trials have suggested prediction of EET benefit by the H/I ratio component.[31-33]

In the STO-5 (Stockholm tamoxifen) trial, patients with high-risk tumors were shown to have the majority of recurrence risk in the first 5 years, whereas patients with low-risk tumors continued to

be at risk of recurrence beyond 10 to 15 years.[34] A study found that the 70-gene expression risk-of-recurrence assay predicted EET benefit in a translational cohort of the NSABP B-42 trial.[35] Specifically, 5 additional years of letrozole therapy compared with placebo was associated with improved DR, disease-free survival, and breast cancer–free interval (BCFI) in patients with 70-gene assay–classified low-risk tumors but not among patients with high-risk or ultralow-risk tumors.[35] Therefore, in the IDEAL trial translational cohort, we hypothesized that the 70-gene assay would identify a subgroup of patients who could benefit from EET. The primary objective of this secondary analysis was to determine the assay's utility in identifying which patients with EBC could benefit from a 5-year vs 2.5-year letrozole treatment.

Methods

Patients and Study Design

The IDEAL trial was a prospective phase 3 trial that randomized postmenopausal patients with HR-positive EBC in a 1:1 ratio to 2.5 or 5 years of letrozole after 5 years of endocrine therapy, as described in the trial protocol (Supplement 1) and original report.[9] The study was conducted in compliance with the guidelines of the Declaration of Helsinki,[36] International Conference on Harmonisation, and Good Clinical Practice in the 73 participating hospitals in the Netherlands. All patients provided written informed consent, including for the use of biospecimens in further studies; patients who withdrew their consent were excluded from analysis. Central ethical approval was provided by the Medical Ethical Committee of the Leiden University Medical Center, including biomarker studies. This Medical Ethical Committee also approved the secondary analyses.

Patients with follow-up and available primary tumor tissue were included (eFigure in Supplement 2). Median (IQR) follow-up after randomization was 10.2 (9.4-10.8) years (data locked on April 19, 2022). Both groups received letrozole for the first 2.5 years after randomization. The original IDEAL trial was powered to show a difference in event rate starting at 2.5 years after randomization for EET, when 1 treatment arm continued letrozole for another 2.5 years, whereas the other treatment arm discontinued letrozole. Additionally, including or excluding patients with an event or treatment time less than 2.5 years after randomization did not affect the results.[9] This study followed the original IDEAL trial analysis plan, excluding events or treatment time less than 2.5 years.

The primary end point—freedom from DR—was defined as time starting 2.5 years after randomization to DR. Secondary end points were recurrence-free interval (RFI; time to local recurrence, regional recurrence, or DR) and BCFI (time to local recurrence, regional recurrence, or DR or contralateral breast cancer) starting 2.5 years after randomization.

All end points followed the STEEP (Standardized Definitions for Efficacy End Points) criteria.[37] The distribution of EET-related AEs among the 70-gene assay–classified risk groups was also evaluated.

Molecular Testing

MammaPrint, a microarray gene expression analysis, was performed at Agendia Inc.[38-41] Samples contained 30% tumor cells or greater, and extracted RNA from formalin-fixed paraffin-embedded tissue was converted to cDNA, amplified, labeled, and hybridized onto Agendia's diagnostic arrays (custom-designed, Agilent Technologies). The test indexes were generated while blinded to clinical outcome, defining 3 risk categories: high risk (index: −1.000 to 0), low risk (index: 0.001 to 0.355), and ultralow risk (index: 0.356 to 1.000).

Statistical Analysis

Clinical and tumor characteristics were compared with the overall IDEAL cohort using χ^2 tests for goodness of fit and compared within each therapy group to check for biases. Proportions were compared using χ^2, Fisher exact test for small groups, unpaired, 2-tailed *t* test for continuous normally distributed data, and Mann-Whitney test for comparison of medians. Kaplan-Meier analysis

and log-rank test were used to assess differences in DR, RFI, and BCFI between treatment groups for each gene expression assay risk category. Competing risk analyses were not performed since the same results are obtained across different end points and more complex end points include the former end point. In earlier translational analyses of the IDEAL cohort, no competing risk analyses were performed for the same reason, enabling a direct comparison with previous analyses. Hazard ratios and 95% CIs were computed with stratified Cox proportional hazards regression model to estimate relative benefits within each gene expression assay risk group. Likelihood ratio tests based on stratified Cox proportional hazards were used to evaluate treatment-by-risk group interaction.

All reported *P* values are 2-sided, and $P < .05$ indicated statistical significance. The frequency of AEs and treatment compliance data collected during active treatment in the IDEAL trial[9,42] were evaluated across the gene expression assay risk groups (eTable in Supplement 2). Statistical analyses were performed from April 2022 to September 2024 using SPSS, version 27.0 (SPSS Inc), or R, version 4.1.1 (R Project for Statistical Computing).

Results

Patient Characteristics

Tumor specimens were available for 869 of 1821 eligible patients of the original IDEAL trial. Gene expression assay results were generated for 545 patients. Patients with a recurrence within 2.5 years after randomization were excluded, resulting in a translational cohort of 515 women (mean [SD] age at randomization, 59.9 [9.5] years), of whom 265 were in the 2.5-year treatment arm and 250 in the 5-year treatment arm (eFigure in Supplement 2).

There were no statistical differences in clinical and treatment characteristics between the translational and original cohorts (**Table 1**). In this study, the mean (SD) tumor size was 24.9 (14.2) mm, and most tumors were invasive ductal carcinoma and grade 2 or 3 (**Table 2**). Of 479 patients with known Clinical Treatment Score post-5 years (CTS5),[43] 87 patients (16.9%) had low risk of recurrence (53 with 70-gene assay–classified ultralow and low risk, and 34 with high risk), 180 (35.0%) had intermediate risk of recurrence (87 with 70-gene assay–classified ultralow and low risk, and 93 with high risk), and 212 (41.2%) had high risk of recurrence (98 with 70-gene assay–classified ultralow and low risk, and 114 with high risk). Of the 515 patients, 356 (69.1%) received adjuvant chemotherapy and 353 (58.5%) received radiotherapy. Treatment arms were balanced with comparable clinical and pathology characteristics (Table 2).

As in the original IDEAL cohort, there was no significant benefit from 5 years vs 2.5 years of EET in the unstratified translational cohort for all end points (**Table 3**). The 10-year postrandomization DR probability was 87.8% (95% CI, 83.7%-91.9%) in the 2.5-year group vs 92.4% (95% CI, 89.1%-95.7%) in the 5-year group (hazard ratio, 0.61; 95% CI, 0.34-1.09; $P = .10$). The 10-year RFI rates were 86.2% (95% CI, 81.9%-90.5%) and 89.2% (95% CI, 85.3%-93.1%) in the 2.5- and 5-year groups, respectively (hazard ratio, 0.75; 95% CI, 0.45-1.25; $P = .27$), and the 10-year BCFI rates were comparable for each group (Table 3).

The 70-gene assay classified 259 patients (50.3%) as high risk (134 in the 2.5-year and 125 in the 5-year groups), 223 (43.3%) as low risk (112 in the 2.5-year and 111 in the 5-year groups), and 33 (6.4%) as ultralow risk (19 in the 2.5-year and 14 in the 5-year groups). Among patients with 70-gene assay–classified high risk, 34 (13.1%) had CTS5 low risk, 93 (35.9%) intermediate risk, and 114 (44.0%) high clinical risk. Among patients with 70-gene assay–classified low risk, 43 (19.3%) had CTS5 low, 74 (33.2%) intermediate, and 90 (40.3%) high clinical risk.

EET Benefit

Patients with 70-gene assay–classified low risk exhibited the largest benefit from extended letrozole treatment at 10 years. The DR-free rate was 85.2% (95% CI, 78.5%-91.9%) in the 2.5-year group vs 95.3% (95% CI, 91.2%-99.4%) in the 5-year group, and relative risk was lower (hazard ratio, 0.32; 95% CI, 0.12-0.87; $P = .03$) (**Figure**, A and Table 3). Treatment interaction comparing 70-gene assay–

classified low risk to high risk was not significant. In contrast, patients with 70-gene assay–classified high risk showed no significant benefit from 5 years vs 2.5 years of EET, with 10-year DR-free rates of 90.0% (95% CI, 84.9%-95.1%) and 90.9% (95% CI, 85.8%-96.0%), respectively (hazard ratio, 0.88; 95% CI, 0.40-1.97; *P* = .76) (Figure, B and Table 3).

Among patients with 70-gene assay–classified low-risk tumors, the 10-year RFI rate was 81.5% (95% CI, 74.2%-88.8%) for the 2.5-year group vs 93.2% (95% CI, 88.3%-98.1%) for the 5-year group, and relative risk was lower (hazard ratio, 0.35; 95% CI, 0.15-0.82; *P* = .02) (Figure, C and Table 3). The association of letrozole with RFI rate was significantly different in 70-gene assay–classified low risk vs high risk (*P* for interaction = .02). Conversely, patients with high risk showed no significant EET benefit, with 10-year RFI rates of 90.1% (95% CI, 85.0%-95.2%) in the 2.5-year arm vs 86.5% (95% CI, 80.2%-92.8%) in the 5-year arm (hazard ratio, 1.28; 95% CI, 0.62-2.67; *P* = .51) (Figure, D and Table 3). The EET benefit and relative risk reduction for BCFI was observed but not significant in the low-risk group (10-year BCFI rates: 80.6% [95% CI, 73.2%-88.0%] in the 2.5-year arm vs 90.3% [95% CI, 84.6%-96.0%] in the 5-year arm; hazard ratio, 0.48; 95% CI, 0.23-1.02; *P* = .06) (Table 3). Patients with high risk showed no EET benefit for BCFI (hazard ratio, 1.10; 95% CI, 0.57-2.14; *P* = .78) (Table 3). There was no significant treatment interaction for BCFI between low-risk and high-risk groups. Although few patients had an ultralow-risk tumor, they did not derive any EET benefit for all end points (Table 3).

Safety and Treatment Compliance Among 70-Gene Assay–Classified Risk Groups

Of the 515 patients, 332 (64.5%) reported AEs, 168 in the 2.5-year group and 164 in the 5-year EET group (eTable in Supplement 2). A total of 876 AEs (412 in 2.5-year group, and 464 in 5-year group)

Table 1. Clinical and Treatment Characteristics of Patients in the Original IDEAL Trial and Translational Cohorts

Characteristic	Patients, No. (%)		*P* value
	Translational cohort (n = 515)	IDEAL trial cohort (n = 1821)	
Tumor type			
Ductal	415 (80.6)	1415 (77.7)	.35
Lobular	75 (14.6)	296 (16.3)	
Other	25 (4.8)	110 (6.0)	
Grade			
1	72 (14.0)	286 (15.7)	.07
2	216 (41.9)	774 (42.5)	
3	194 (37.7)	566 (31.1)	
Unknown	33 (6.4)	195 (10.7)	
Tumor size, mean (SD), mm	24.9 (14.2)	24.6 (14.5)	.66
Nodal stage			
pN0	148 (28.7)	476 (26.1)	.42
pN1	262 (50.9)	994 (54.6)	
pN2	82 (15.9)	257 (14.1)	
pN3	22 (4.3)	85 (4.7)	
Missing data	1 (0.2)	9 (0.5)	
ERBB2			
Negative	117 (22.7)	392 (21.5)	.85
Positive	124 (24.1)	445 (24.5)	
Unknown	274 (53.2)	984 (54.0)	
EET treatment			
2.5-y Letrozole	265 (51.5)	908 (49.8)	.52
5-y Letrozole	250 (48.5)	913 (50.2)	
Chemotherapy			
Yes	356 (69.1)	1243 (68.3)	.71
No	159 (30.9)	578 (31.7)	

Abbreviations: EET, extended endocrine therapy; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole.

were reported among the 332 patients, of which most were grade 1 or 2 (90.3% in the overall IDEAL trial).[9]

The most frequently reported AEs in both groups were musculoskeletal and connective tissue (202 [23.1%]), gastrointestinal (91 [10.4%]), and vascular disorders (91 [10.4%]). As expected, AE

Table 2. Patient Characteristics of Translational Cohort in Each Treatment Arm

Characteristics	Patients in translational cohort, No. (%)			P value
	2.5-y EET letrozole (n = 265)	5-y EET letrozole (n = 250)	Total (n = 515)	
Age at randomization, mean (SD), y	60.0 (9.0)	59.7 (10.0)	59.9 (9.5)	.52
Tumor size, mean (SD), mm	25.9 (15.8)	24.0 (12.2)	24.9 (14.2)	.27
Tumor type				
Ductal	210 (79.2)	205 (82.0)	415 (80.6)	.59
Lobular	39 (14.7)	36 (14.4)	75 (14.6)	
Other	16 (6.1)	9 (3.6)	25 (4.8)	
Grade				
1	38 (14.3)	34 (13.6)	72 (14.0)	.71
2	112 (42.3)	104 (41.6)	216 (41.9)	
3	98 (37.0)	96 (38.4)	194 (37.7)	
Unknown	17 (6.5)	16 (6.4)	33 (6.4)	
Nodal stage				
pN0	82 (30.9)	66 (26.4)	148 (28.7)	.32
pN1	130 (49.1)	132 (52.8)	262 (50.9)	
pN2	45 (17.0)	37 (14.8)	82 (15.9)	
pN3	8 (3.0)	14 (5.6)	22 (4.3)	
Missing data	0	1 (0.4)	1 (0.2)	
ER				
Negative	5 (1.9)	10 (4.0)	15 (2.9)	.19
Positive	260 (98.1)	240 (96.0)	500 (97.1)	
PR				
Negative	43 (16.2)	51 (20.4)	94 (18.3)	.47
Positive	209 (78.9)	188 (75.2)	397 (77.1)	
Unknown	13 (4.9)	11 (4.4)	24 (4.7)	
ERBB2				
Negative	62 (23.4)	55 (22.0)	117 (22.7)	.83
Positive	61 (23.0)	63 (25.2)	124 (24.1)	
Unknown	142 (53.6)	132 (52.8)	274 (53.2)	
CTS5 risk				
Low	44 (16.6)	43 (17.2)	87 (16.9)	.89
Intermediate	91 (34.3)	89 (35.6)	180 (35.0)	
High	113 (42.6)	99 (39.6)	212 (41.2)	
Unknown	17 (6.4)	19 (7.6)	36 (7.0)	
Chemotherapy				
No	80 (30.2)	79 (31.6)	159 (30.9)	.73
Yes	185 (69.8)	171 (68.4)	356 (69.1)	
Radiotherapy				.65
No	81 (30.6)	81 (32.4)	162 (31.5)	
Yes	184 (69.4)	169 (67.6)	353 (58.5)	
Previous endocrine therapy duration, mean (SD), y	5.01 (0.36)	5.06 (0.20)	5.04 (0.29)	.66
Letrozole status within 2.5 y				
Never started	3 (1.1)	0	3 (0.6)	.41
Discontinued within 2.5 y	58 (21.9)	57 (22.8)	115 (22.3)	
Receiving therapy	203 (76.6)	192 (76.8)	395 (76.7)	
Missing data	1 (0.4)	1 (0.4)	2 (0.4)	

Abbreviations: CTS5, Clinical Treatment Score post-5 years; EET, extended endocrine therapy; ER, estrogen receptor; PR, progesterone receptor.

frequency was comparable across 70-gene assay risk groups within each treatment arm. The mean number of AEs per person was 2.45 in those with high-risk, 2.54 with low-risk, and 1.78 with ultralow-risk tumors treated with 2.5 year of EET compared with 2.67 patients with high-risk tumors, 2.95

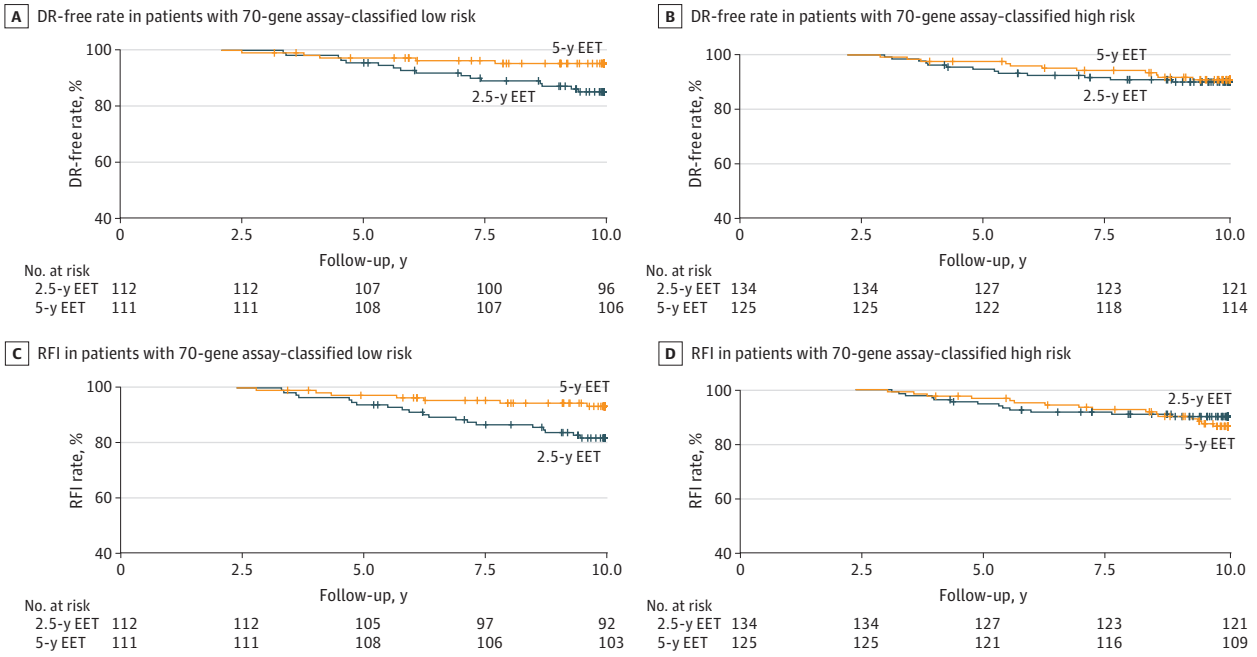
Table 3. Ten-Year Outcome of 5 Years vs 2.5 Years of Extended Endocrine Therapy (EET) Stratified by 70-Gene Assay–Classified Risk

70-Gene assay–classification and end point	2.5-y EET		5-y EET		Absolute benefit, % difference	HR (95% CI)	*P* value	*P* value for interaction[a]
	No. of events	10-y Outcome (95% CI), %	No. of events	10-y Outcome (95% CI), %				
Unstratified risk (n = 515)								
DR free	31	87.8 (83.7-91.9)	19	92.4 (89.1-95.7)	4.6	0.61 (0.34-1.09)	.10	NA
RFI	35	86.2 (81.9-90.5)	27	89.2 (85.3-93.1)	3.0	0.75 (0.45-1.25)	.27	NA
BCFI	42	83.9 (79.4-88.4)	32	87.2 (82.9-91.5)	3.3	0.77 (0.48-1.23)	.27	NA
High risk (n = 259)								
DR free	13	90.0 (84.9-95.1)	11	90.9 (85.8-96.0)	0.9	0.88 (0.40-1.97)	.76	[Reference]
RFI	13	90.1 (85.0-95.2)	16	86.5 (80.2-92.8)	−3.6	1.28 (0.62-2.67)	.51	[Reference]
BCFI	18	87.0 (81.1-92.9)	18	84.8 (78.3-91.3)	−2.2	1.10 (0.57-2.14)	.78	[Reference]
Low risk (n = 223)								
DR free	16	85.2 (78.5-91.9)	5	95.3 (91.2-99.4)	10.1	0.32 (0.12-0.87)	.03	.12
RFI	20	81.5 (74.2-88.8)	8	93.2 (88.3-98.1)	11.7	0.35 (0.15-0.82)	.02	.02
BCFI	21	80.6 (73.2-88.0)	11	90.3 (84.6-96.0)	9.7	0.48 (0.23-1.02)	.06	.10
Ultralow risk (n = 33)								
DR free	2	87.7 (71.6-100)	3	84.6 (65.0-100)	−3.1	1.52 (0.21-10.78)	.68	NA
RFI	2	87.7 (71.6-100)	3	84.6 (65.0-100)	−3.1	1.52 (0.21-10.78)	.68	NA
BCFI	3	82.3 (63.9-100)	3	84.6 (65.0-100)	2.3	1.01 (0.17-6.06)	.99	NA

Abbreviations: BCFI, breast cancer–free interval; DR, distant recurrence; HR, hazard ratio; NA, not applicable; RFI, recurrence-free interval.

[a] *P* value for interaction: low risk vs high risk (reference).

Figure. Projection of Extended Endocrine Therapy (EET) Benefit by a 70-Gene Assay Based on Freedom From Distant Recurrence (DR) and Recurrence-Free Interval (RFI)



Kaplan-Meier method was used to analyze freedom from DR and RFI comparing 2.5 years with 5 years of extended letrozole treatment. Log-rank test was used to determine significant differences.

with low-risk tumors, and 3.38 with ultralow-risk tumors treated with 5 year of EET; because of the low AE frequency per person, SDs could not be reported (eTable in Supplement 2).

Of patients who reported AEs, 94 (28.3%) discontinued therapy early likely due to treatment-emergent AEs[9,26] (43 in 2.5-year group, and 51 in 5-year group) (eTable in Supplement 2). Within the 2.5-year EET group, 22 patients (24.7%) with high-risk tumors, 20 (28.6%) with low-risk tumors, and 1 (11.1%) with ultralow-risk tumors stopped treatment early. Similarly, in the 5-year EET group, 26 patients (31.3%) with high-risk tumors, 22 (30.1%) with low-risk tumors, and 3 (37.5%) with ultralow-risk tumors discontinued treatment early.

Discussion

Clinical trials investigating optimal EET duration to reduce the long-term recurrence risk for HR-positive breast cancer have reported modest benefits, prompting the need to optimize patient selection. This secondary analysis validated the ability of the 70-gene assay to identify patients who benefit from EET or do not benefit, helping them avoid EET-associated AEs and the adverse implications for quality of life. This translational work represents the second independent study to validate the assay's utility in projecting EET benefit to a total of 10 years, consistent with NSABP B-42 findings.[35]

Patients with 70-gene assay–classified low-risk tumors (43%) derived significant 2- to 4-fold improvement in outcome with 5 vs 2.5 years of EET compared with a nonsignificant EET benefit for the unstratified cohort. Low-risk tumors revealed significant absolute benefit of 10.1% for DR (DR-free rates, 85.2% in the 2.5-year group vs 95.3% in the 5-year group), 11.7% for RFI (RFI rates, 81.5% in the 2.5-year group vs 93.2% in the 5-year group), and 9.7% for BCFI (BCFI rates, 80.6% in the 2.5-year group vs 90.3% in the 5-year group). Similarly, in NSABP B-42 there was a significant absolute benefit for patients with 70-gene assay–classified low risk for the same primary end point DR of 4.0%, and the same secondary end point BCFI of 7.9%, whereas the unstratified cohort showed no significant EET benefit.[35]

Previous studies reported a significant decrease in second primary breast malignant neoplasms with EET, suggesting that benefit is derived from preventing secondary breast cancer rather than relapse.[9,44-47] However, in this study, the DR and RFI end points did not include second primary breast cancers as an event, which supports that the EET benefit is attributed to recurrence risk reduction.

The EET benefit in patients with genomically low-risk tumors is important in considering data from the STO-5 trial, which compared 2 years of endocrine therapy with placebo and demonstrated that patients with low risk are at greater risk for later DR rather than early recurrence.[34] In STO-5, distant recurrence–free interval hazard rates steadily increased in untreated patients with low-risk tumors, and substantial tamoxifen benefit was found at 20 years of follow-up.[34] The biological mechanisms underlying late recurrences in this tumor subgroup are not fully understood but may be due to changes in the tumor microenvironment that, over time, activate dormant tumor cells and increase metastatic potential.[48] It is these late recurrences that appear to be preventable by EET.

In contrast, patients with 70-gene assay–classified high-risk tumors did not seem to benefit from EET. These patients exhibited an early risk of relapse, in which most recurrences occurred during the first 5 years after diagnosis. In the STO-5 trial, distant recurrence–free interval hazard rates significantly decreased after 5 years in genomically high-risk tumors, corresponding to most endocrine therapy benefit within the first 5 years.[34] In this study, patients with high risk did not seem to benefit from EET likely due to reduced risk of late recurrence and thereby an intrinsic decreased sensitivity to hormone therapy.

Patients with ultralow-risk tumors did not have improved outcomes with EET. Although the patient sample size in this subgroup was small, this finding is consistent with that of the NSABP B-42 trial, wherein no EET benefit was observed among 252 patients with 70-gene assay–classified ultralow-risk tumors. Several clinical trials have shown that patients with these tumors have a low risk

of DR and excellent long-term prognosis (>97% 10-year distant metastasis–free interval and >98% 10-year Breast Cancer Severity Score).[19-23] The STO-3 and MINDACT trials demonstrated no significant difference in long-term outcomes between patients with ultralow-risk tumors who received endocrine therapy vs those without any systemic treatment.[19-21] For patients with ultralow-risk tumors, it seems EET is not the treatment for reducing the risk of recurrences.

The Breast Cancer Index, which predicts high vs low likelihood of EET benefit based on its 2-gene H/I ratio, was evaluated in the IDEAL trial. Patients with tumors with a high Breast Cancer Index derived significant EET benefit for RFI and DFI (identical end point to BCFI here), whereas those with tumors with a low Breast Cancer Index did not benefit.[31] Similar results were observed in the NCIC CTG MA-17[32] and aTTom trials,[33] leading to the Breast Cancer Index's inclusion in the NCCN Guidelines.[10] In the recently published NSABP B-42 translational analysis, high vs low Breast Cancer Index did not show statistically significant difference in extended letrozole therapy benefit for the primary end point of RFI.[49] However, in time-dependent analysis for DR, patients with high Breast Cancer Index showed significant EET benefit after 4 years. In the NSABP B-42 trial, patients with 70-gene assay–classified low-risk tumors showed significant extended letrozole therapy benefit for DR and BCFI.[49] In the IDEAL and NSABP B-42 trials, both the 70-gene expression risk-of-recurrence assay and Breast Cancer Index have the ability to identify a subset of patients of approximately 45% who benefit from EET.

Current EET recommendations rely on clinically high-risk features, but studies suggest that these factors are insufficient for predicting late recurrence or EET benefit as observed in the original IDEAL trial.[9] In some studies, nodal status has been shown to predict EET benefit or it was found to be dependent on treatment sequence.[50] Clinical factors, including grade and Ki-67 expression, were reported to be only moderately prognostic of DR after the first 5 years after diagnosis.[2] In the TEAM and IDEAL trials, CTS5 high-risk tumors had lower observed late DR than predicted,[51] suggesting an overestimation of late recurrence risk in patients with clinically high risk. In the current analyses, over 53% of patients with CTS5 high risk were estimated not to benefit from EET based on a 70-gene assay–classified high-risk result. Conversely, about half of patients with low or intermediate clinical risk were 70-gene assay–classified low risk and projected to benefit from EET. These results indicate that the assay may better optimize patient selection for EET compared with clinical characteristics. A majority (80%) of patients in this study either had lymph node–negative breast cancer or 1 to 3 positive lymph nodes. The assay's projection of EET benefit should be limited to this patient population.

Prolonged endocrine therapy in this study group was associated with considerable rates of treatment discontinuation (28.3% with AE data), similar to the overall IDEAL trial (28.0% with AE data).[9,42,52] Patients with a 70-gene assay–classified high- or ultralow-risk result, representing more than half of the patient cohort, did not benefit from extended treatment and thus may have experienced an AE-associated impaired quality of life. These data support physicians in making individualized risk-benefit–based decisions, identifying patients who do not benefit from EET and may avoid treatment-emergent AEs as well as patients for whom treatment compliance is critical because they have the highest risk of late recurrence and derive most benefit from EET.

Strengths and Limitations

A strength of this study is the analyses used updated 10.2 years of follow-up and included AE data. In addition, the distribution of patient clinical and tumor characteristics was similar between the translational and the original IDEAL trial cohort (Table 1) and between the treatment arms (Table 2).

Limitations of this study are, first, its retrospective design and inclusion of a subset of patients due to limited tissue sample availability, which prevented analyses to be adjusted for covariates. Additionally, there was limited racial diversity in the study population, which was likely primarily White individuals compared with the population in the NSABP B-42 trial, which was more diverse in race and ethnicity.[7,24] Second, nonsignificant treatment by risk interactions were observed for DR and BCFI, possibly due to low event rates observed in the translational cohort. The significant

interaction for BCFI in the NSABP B-42 trial may be due to more secondary primary breast cancers than observed in the IDEAL trial. Moreover, the sample size for the ultralow-risk group was small; therefore, results in this group should be interpreted with caution. Extended letrozole treatment duration differed between the IDEAL (5- vs 2.5-year) and NSABP B-42 (5-year vs placebo) trials. Third, both translational analyses of the IDEAL and NSABP B-42 trials are limited to postmenopausal patients; future studies should evaluate this 70-gene assay as a potential biomarker for EET benefit in premenopausal patients.

Conclusions

In this secondary analysis of the IDEAL randomized clinical trial, identification of postmenopausal patients with HR-positive EBC who benefited from extended letrozole treatment was associated with the molecular biology of the tumors, measured as 70-gene assay–classified low risk. The finding suggest that late recurrences in 70-gene assay–classified low-risk tumors may be preventable with EET. Patients with genomically high-risk or ultralow-risk tumors could potentially avoid endocrine overtreatment and associated adverse events. Overall, these data suggest a novel clinical utility for the 70-gene expression risk-of-recurrence assay, extending its value beyond guiding neoadjuvant and adjuvant chemotherapy decisions to informing the optimal duration of adjuvant endocrine therapy.

ARTICLE INFORMATION

Accepted for Publication: September 16, 2024.

Published: November 27, 2024. doi:10.1001/jamanetworkopen.2024.47530

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Conflict of Interest Disclosures: Prof van 't Veer is a part-time employee of and holds stock in Agendia Inc. Dr Kleijn reported being a former employee of Agendia Inc. Mrs Dreezen reported receiving consulting fees from Agendia. Drs Menicucci and Audeh reported being employees of Agendia Inc. No other disclosures were reported.

Funding/Support: This work was supported by the Leiden University Medical Center.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Data from this study were presented at the 2022 San Antonio Breast Cancer Symposium, December 9, 2022, San Antonio, Texas, and at the 18th St Gallen International Breast Cancer Conference; March 15, 2023; Vienna, Austria.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank all of the patients who participated in the trial. We also thank the IDEAL Investigators and coordinators across the 73 participating hospitals.

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SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eFigure. CONSORT Diagram of IDEAL Shows 869 Eligible IDEAL Patients With Available Biospecimens

eTable. Distribution of Adverse Events and Treatment Non-Compliance Stratified by Treatment Arm and MammaPrint Risk

SUPPLEMENT 3.

Data Sharing Statement