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TBCRC 013: Prognostic Impact of 21-Gene Recurrence Score (RS) in Patients Presenting with Stage IV Breast Cancer

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Abstract

Purpose—The objective of this study was to determine whether the 21-gene Recurrence Score (RS) provides clinically meaningful information in patients with *de novo* stage IV breast cancer enrolled in Translational Breast Cancer Research Consortium (TBCRC) 013.

Patients and Methods—TBCRC 013 was a multi-center prospective registry evaluating the role of surgery of the primary tumor in patients with *de novo* stage IV breast cancer. From 07/2009–04/2012, 127 patients from 14 sites were enrolled; 109 patients (86%) had pre-treatment primary tumor samples suitable for 21-gene RS analysis. Clinical variables, time to first progression (TTP), and 2-year overall survival (OS) were correlated with 21-gene RS using log-rank, Kaplan-Meier, and Cox regression.

Results—Median patient age was 52 years (21–79); the majority were hormone receptor positive/HER2 negative (72 [66%]) or hormone receptor positive/HER2 positive (20 [18%]). At a median follow-up of 29 months, median TTP was 20 months (95% CI 16–26) and median survival was 49 months (95% CI 40–NR). RS were generated for 101 (93%) primary tumor samples; 22 (23%) low risk (<18), 29 (28%) intermediate risk (18–30); and 50 (49%) high risk (≥31). For all patients, RS was associated with TTP (p=0.01) and 2-year OS (p=0.04). In multivariate Cox models among estrogen receptor positive/HER2 negative patients (n=69), RS was independently

prognostic for TTP (hazard ratio 1.40, 95% CI 1.05–1.86, p=0.02) and 2-year OS (hazard ratio 1.83, 95% CI 1.14–2.95, p=0.013).

Conclusion—The 21-gene RS is independently prognostic for both TTP and 2-year OS in ER positive/HER2 negative *de novo* stage IV breast cancer. Prospective validation is needed to determine the potential role for this assay in clinical management of this patient subset.

Keywords

de novo stage IV breast cancer; recurrence score

INTRODUCTION

The 21-gene Recurrence Score® (RS) is a useful clinical tool for assessing risk of distant recurrence and magnitude of chemotherapy benefit in patients with early-stage estrogen receptor (ER) positive breast cancer treated with tamoxifen.[1–3] The application of the 21-gene RS to clinical practice in ER positive/node-negative patients has been demonstrated to change treatment recommendations, and the RS has been incorporated in both the American Society of Clinical Oncology and National Comprehensive Cancer Network published treatment guidelines for early-stage ER positive breast cancer.[4,5]

In metastatic breast cancer, there is limited level 1 evidence to guide clinical decision making, and, as such, treatment recommendations are largely based on traditional factors, such as ER, progesterone receptor (PR), HER2, and number and sites of metastases. Recently, international consensus guidelines for treatment of advanced breast cancer have been developed[6,7], yet durability of response to first-line therapy varies and there are no validated clinical tools for assessing risk of progression of disease or likelihood of achieving a durable response once therapy is initiated. In addition, although survival among patients with metastatic breast cancer has improved, largely due to advances in targeted therapy, there continues to be a wide range in reported outcomes[8–12], and there are many unanswered questions related to management strategies, optimal drug sequencing, and the potential for individualized treatment based on predictive markers.

Translational Breast Cancer Research Consortium (TBCRC) 013 was a multi-center prospective registry study with the primary goal of evaluating the role of surgery of the primary tumor in patients presenting with stage IV breast cancer. Patients also provided primary tumor tissue for embedded correlative science aims. The objective of the current analysis was to determine whether the 21-gene RS performed on the primary tumor provides clinically meaningful information in patients with *de novo* stage IV breast cancer enrolled in TBCRC 013. Further analysis of the role of surgery in this trial is ongoing.

METHODS

TBCRC 013 was a multi-center prospective registry study evaluating the role of surgery of the primary tumor in patients presenting with *de novo* stage IV breast cancer. Eligibility included patients with *de novo* stage IV breast cancer with an intact primary tumor (cohort A) or those diagnosed with metastatic disease within 3 months of primary breast surgery

(cohort B). All patients provided consent for access to formalin-fixed paraffin-embedded (FFPE) tissue from the primary tumor and a metastatic lesion for correlative studies. We aimed to enroll 100 patients with intact tumors and adequate primary tumor tissue for the RS analysis.

From July 2009 to April 2012, 127 eligible patients from 14 institutions were enrolled in two cohorts: Cohort A, intact primary tumor (n = 112); and Cohort B, metastases within 3 months of primary surgery (n = 15). Of these, 109 patients (86%) had pre-treatment primary tumor diagnostic biopsy samples suitable for 21-gene RS analysis and comprised the RS analysis cohort reported here.

As this was a registry study, patients were treated according to institutional practice patterns, without study-specific intervention. Presenting clinical and pathologic features were determined at the institutional level; including tumor grade, ER, PR, and HER2 status.. Treatment regimens and outcomes were reported.

Baseline characteristics were compared using Fisher's exact test for categorical factors and the Wilcoxon test for continuous ones. Clinical variables, time to first progression (TTP), and 2-year overall survival (OS) were correlated with the 21-gene RS using log-rank tests, Kaplan-Meier estimates, and Cox regression with medians and 95% confidence intervals (CI). Analyses were performed including all patients (any ER or HER2 status) as well as for the ER positive (immunohistochemistry [IHC]) and the ER positive and HER2 negative subsets (IHC, fluorescence in situ hybridization [FISH]). Exploratory analyses were performed among patients with ER positive/HER2 negative breast cancer stratified by choice of first-line treatment (endocrine therapy versus chemotherapy).

RESULTS

Among the 109 patients in the 21-gene RS analysis cohort, median patient age was 52 years (range, 21–79 years), and the median primary tumor size was 3.1 cm (range, 0.7–15.0 cm). The study cohort was comprised of patients with predominantly ER positive (84%), HER2 negative (72%) invasive ductal cancer (86%), and fifty (46%) patients presented with bone-only metastases (Table 1). The only significant difference between patients enrolled in cohort A (94 patients) and cohort B (15 patients), was the higher frequency of clinical N1 disease in patients in Cohort A (85% versus 26%, p = 0.001). There were no significant differences between the 21-gene RS population (n = 109) and the overall TBCRC 013 registry population (n = 127), and there were no differences in outcome associated with elective surgery at the time of this analysis (*data not shown*). At a median follow-up of 29 months, median TTP was 20 months (95% confidence interval [CI], 16–26 months) and median survival was 49 months (95% CI, 40–not reached months; Fig 1).

Recurrence score results were successfully generated from pre-treatment diagnostic biopsies of the primary tumor for 101 patients (93%). The median and mean recurrence scores for the population were 30.7 (range, 0–100) and 36, respectively; the interquartile range was 19.5–49.5. The histogram of RS values is depicted in Supplementary Fig 1, and characteristics of the patients whose samples failed to generate a RS are in Supplementary Table 1. Risk group

distribution was defined as: Low (RS < 18); Intermediate (RS 18–30); and High (RS≥31). Twenty-two (20%) patients had a low-risk RS, all of whom were ER positive/HER2 negative by IHC (Table 1). Among 29 patients with Intermediate Risk RS, 26 were ER positive/HER2 negative and 3 were ER positive/HER2 positive (IHC/FISH). The remaining 50 (46%) patients had high-risk RS. The high-risk group included 21 patients with ER positive/HER2 negative tumors, 13 patients with ER positive/HER2 positive tumors, 10 patients with ER negative/HER2 positive tumors, and 6 patients with triple-negative disease (Supplementary Fig 2). The only clinical variable found to be correlated with risk group was locally reported tumor grade (Table 2).

When stratified by RS result, patients with low- and intermediate-risk scores had improved TTP and 2-year OS compared to patients with high-risk scores. This was true when all patients were included in the analysis, yet the difference was most pronounced among the ER positive/HER2 negative subset, where median TTP has not been reached among those with low risk scores and 2-year OS was 100% for both the low and intermediate risk groups (Fig 2, Table 3). In univariate analysis, tumor grade was not significantly associated with OS (p=0.22) or TTP (p=0.05). In multivariate Cox models, including age and RS result as a continuous variable, adjusting for tumor size and site of first metastatic disease (bone only versus other), the 21-gene RS was independently prognostic for TTP and 2-year OS in ER positive/HER2 negative patients with stage IV disease (Table 4).

In an exploratory analysis to determine if the 21-gene RS may be useful in predicting response to therapy in this cohort, we examined the 69 patients in the ER positive/HER2 negative group by first-line treatment received (Supplementary Table 2). As this was a registry study, patients were selected for treatment at the discretion of their treating physician; 49 (71%) patients received first-line endocrine therapy and 20 (29%) received first-line chemotherapy. Despite the correlation between tumor grade and risk group, there was no association between tumor grade and the decision to proceed with first-line chemotherapy (Supplementary Table 2). Patients who received first-line chemotherapy were younger (median age, 50 years versus 54 years), had larger primary tumors, and had more visceral and multi-organ disease, yet these differences were not statistically significant. Eighty-five percent of the patients who received first-line chemotherapy had intermediate- (n = 10) or high-risk (n = 7) recurrence scores, suggesting that physicians are appropriately selecting many patients for more aggressive treatment; however, 61% of the patients who received first-line endocrine therapy also had intermediate- or high-risk RS highlighting the opportunity for clinical decision making tools to impact treatment decisions in this setting (Supplementary Table 2).

In this exploratory analysis, both TTP and 2-year OS were shorter among ER positive/HER2 negative patients with high-risk RS who received first-line endocrine therapy, whereas there was no difference by RS in TTP or 2-year OS among ER positive/HER2 negative patients with high-risk scores who received first-line chemotherapy (Supplementary Fig 3, Supplementary Fig 4, Supplementary Table 3). Although exploratory, these findings suggest that a high-risk RS may be a surrogate for relative endocrine resistance in *de novo* stage IV disease, leading to the hypothesis that the RS may be a tool to select patients with ER positive/HER2 negative *de novo* stage IV breast cancer who may benefit from first-line

chemotherapy. In this patient cohort, use of the RS ≥ 31 to select first-line chemotherapy or first-line endocrine therapy would have resulted in a treatment change for 17 (25%) of patients. We note, however, that these findings require prospective validation before being incorporated into clinical practice.

DISCUSSION

In metastatic breast cancer, the goals of care are to optimize both length and quality of life. Several advances have been made, particularly for HER2 positive and luminal-like subtypes, and survival has improved; however, median OS is still reported as 2–3 years.[8–12] The use of treatment guidelines, primarily in early-stage breast cancer, has been associated with significant improvements in survival[13], yet for metastatic breast cancer there is limited level 1 evidence, and only recently have international consensus guidelines been developed.[6,7] In ER positive/HER2 negative breast cancer, endocrine therapy is the preferred option, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance, or there is disease needing a fast response.[7] Here we have demonstrated that the 21-gene RS when performed on the primary tumor in patients with ER positive/HER2 negative breast cancer is independently prognostic for both time to disease progression and 2-year OS in *de novo* stage IV breast cancer, leading to the hypothesis that this molecular profile may be useful in the clinical management of this patient subset.

We have also demonstrated that the natural history of *de novo* ER positive stage IV breast cancer differs from metastatic disease that recurs after adjuvant therapy. At a median follow-up of 29 months, the TTP for the whole cohort was 20 months (95% CI, 16–26 months) and median survival was 49 months (95% CI, 40–not reached months). Among the 85 patients with ER positive disease, the median TTP ranged from 32 months for patients with a low risk score to 15 months for patients with a high risk score. This difference was even more pronounced in the ER positive/HER2 negative cohort where the median TTP for patients with a low risk score had not been reached at a median follow-up of 29 months. This information could potentially be used in discussing treatment options and expectations in this patient cohort; specifically, with respect to the expected duration of response to first-line therapy and subsequent need for treatment modifications.

Guidelines state that treatment choice in metastatic breast cancer should take into account hormone receptor and HER2 status, tumor burden (number and site of metastases), patient age, performance status, co-morbidities, menopausal status, and the need for rapid disease/symptom control. As we performed the 21-gene RS on all-comers, not surprisingly, the majority of patients with HER2 positive tumors and all patients with triple-negative tumors had high-risk RS results. It is important to note we are not advocating for this approach, as treatment algorithms in patients with hormone receptor negative disease and HER2 positive disease differ substantially from those for hormone receptor positive disease; however, this analysis does provide proof of principle that RS results differ substantially by breast cancer subtype. In this dataset, the median RS result ranged from a low of 23 (0–59) to a high of 62 (33–73) for patients with hormone receptor positive/HER2 negative disease and triple-negative disease, respectively (Supplementary Fig 2). Not surprisingly, median RS was also correlated with tumor grade, ranging from 12 (7–33) among patients with grade I tumors to

33 (4–50) among patients with grade III tumors, yet there was no relationship between RS risk group and other clinical factors typically considered when making treatment recommendations (Table 2).

When we limited our analysis to only those patients with ER positive/HER2 negative disease, the distribution of low, intermediate, and high risk scores was 32%, 38%, and 30%, respectively; similar to the distribution of scores seen in early-stage disease, and, again, we see the correlation between tumor grade and risk group (Supplementary Table 4). However, on exploration of first-line treatment choices, made independently by physicians and patients, there was no significant association with tumor grade and the decision to proceed with first-line chemotherapy or endocrine therapy; highlighting the potential for the 21-gene RS to provide clinically meaningful information for this cohort of patients—although we acknowledge that this requires further prospective study and validation..

Patients with ER positive/HER2 negative disease who received first-line chemotherapy tended to be younger, and were more likely to have larger primary tumors and to have visceral disease and/or more than one site of metastatic disease when compared to patients who received first-line endocrine therapy (Supplementary Table 2). Although these comparisons did not achieve statistical significance, they are consistent with the expected biases toward more aggressive treatment in younger women with greater disease burdens. Further exploratory analysis of TTP and survival in this cohort when examined by first-line treatment demonstrated that both outcomes were inferior among ER positive/HER2 negative patients with high-risk RS results who received first-line endocrine therapy, whereas there was no difference by RS in TTP or 2-year OS among ER positive/HER2 negative patients who received first-line chemotherapy (Supplementary Fig 3, Supplementary Fig 4, Supplementary Table 3). Although exploratory, these findings suggest that a high-risk RS may be a surrogate for relative endocrine resistance in *de novo* stage IV disease. When selected by clinical criteria, 15% of patients who received first-line chemotherapy had low-risk RS, suggesting that endocrine therapy may have been more appropriate, and, perhaps more importantly, 61% of patients who received first-line endocrine therapy had intermediate- or high-risk scores, suggesting that these patients may have disease that is less responsive to endocrine therapy; a hypothesis that requires testing in a prospective clinical trial.

In summary, the TBCRC 013 registry population provides new insights into the natural history of *de novo* stage IV breast cancer. Importantly, the majority of women presenting with *de novo* stage IV breast cancer have ER positive/HER2 negative disease and experience durable responses to first-line physician directed therapy. Yet within this population, which represented over one-third of patients enrolled in PALOMA-3[14], the potential to individualize treatment based on predictive markers remains an unmet clinical need. In the ER positive/HER2 negative cohort, 30% of patients had a high risk RS, somewhat higher than seen in the setting of node-negative disease. If a high-risk recurrence score was considered an indication for chemotherapy and a low-risk score considered a contraindication to chemotherapy, first-line treatment decisions would have differed for 25% of the population with the potential to impact both OS and quality of life. Given the growing body of evidence demonstrating the ability of the 21-gene RS result to predict prognosis and

benefit from chemotherapy in both early-stage node-positive and node-negative disease[1–3,15,16], these findings further suggest that biology is the major determinant of outcome and warrant further prospective investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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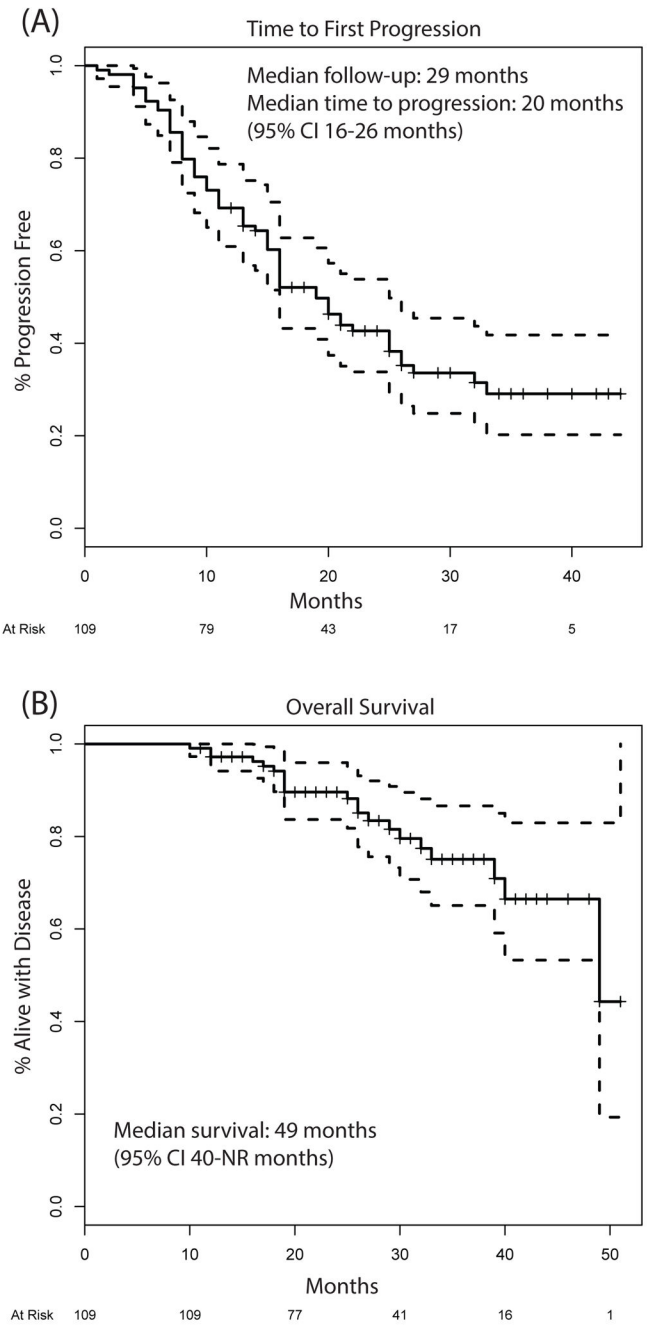

Fig 1.

(A) Time to first progression and (B) overall survival for entire 21-gene Recurrence Score cohort (n = 109).

Abbreviations: TTP, time to first progression, CI, confidence interval; NR, not reached.

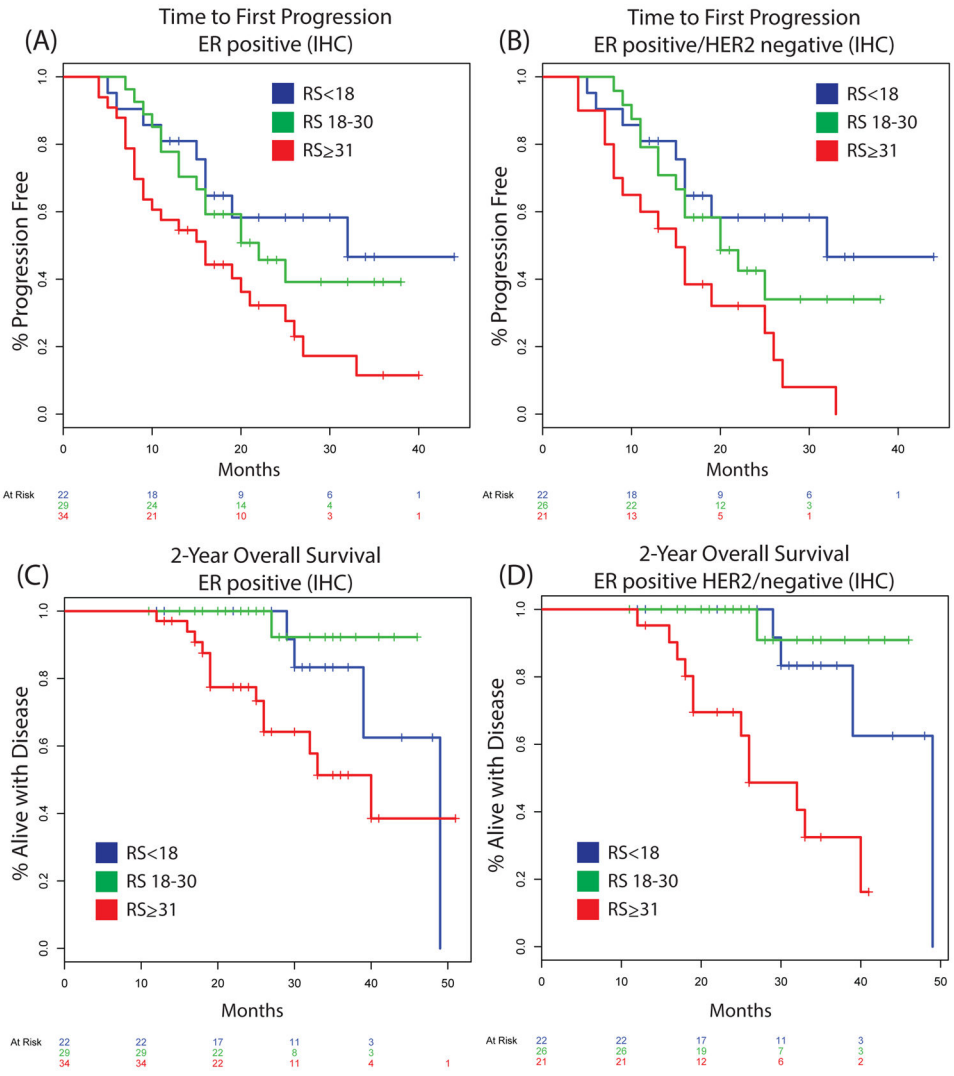

Fig 2.

(A, B) Median time to first progression and (C, D) 2-year overall survival by risk group among estrogen receptor positive (n=85) and ER positive/HER2 negative (n=69) patients presenting with *de novo* stage IV disease. Abbreviations: ER, estrogen receptor; IHC, immunohistochemistry; RS, recurrence score.

Table 1

Clinical Characteristics of the 21-Gene Recurrence Score Population (n = 109)

Age at diagnosis, median (range)	52 years (21–79)
Primary tumor size, median (range)	3.1 cm (0.7–15.0)
Clinical node status	
N1/2	77 (71%)
N0	18 (16%)
Unknown	14 (13%)
ECOG status	
0	58 (53%)
1	46 (42%)
> 1	5 (5%)
Tumor Subtype	
HR positive/HER2 negative	72 (66%)
HR positive/HER2 positive	20 (18%)
HR negative/HER2 positive	10 (9%)
Triple negative	7 (6%)
Site of metastasis at first diagnosis	
Bone only	50 (46%)
Visceral only	26 (24%)
Both (bone and visceral)	25 (23%)
Other *	8 (7%)
Number of metastasis sites at first diagnosis	
Single organ	65 (60%)
> 1 organ	44 (40%)
First systemic treatment	
Chemotherapy	26 (24%)
Endocrine therapy	52 (48%)
Chemotherapy and endocrine therapy	3 (3%)
Chemotherapy plus trastuzumab	20 (18%)
Endocrine therapy plus trastuzumab	6 (6%)
Recurrence score distribution	
Low (< 18)	22 (20%)
Intermediate (18–30)	29 (27%)
High (≥31)	50 (46%)
Not available	8 (7%)

* Includes skin, pleura, contralateral axillary lymph nodes, mediastinal lymph nodes, paratracheal lymph nodes, endobronchial lymph nodes, Hilar lymph nodes, and prepectoral lymph nodes

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor.

Table 2

Clinical Characteristics by Recurrence Score

	Recurrence Score Risk Group			
	Low risk (RS < 18) n = 22	**Intermediate risk (RS 18–30) n = 29**	**High risk (RS ≥ 31) n = 50**	**p-value**
Age, years (range)	58 (38–73)	52 (29–79)	50 (21–77)	0.16
Tumor size, cm (range)	2.6 (0.8–9.0)	3.0 (0.7–15.0)	3.5 (1.0–15.0)	0.17
Tumor grade **				
I	5 (23%)	1 (4%)	1 (2%)	< 0.001
II	15 (68%)	12 (52%)	8 (18%)	
III	2 (9%)	10 (44%)	37 (80%)	
ECOG status				0.33
0	21 (96%)	28 (97%)	47 (94%)	
> 0	1 (4%)	1 (3%)	3 (6%)	
Cohort				0.27
A	20 (91%)	22 (76%)	44 (88%)	
B	2 (9%)	7 (24%)	6 (12%)	
Site of first metastasis				0.15
Bone	14 (64%)	16 (55%)	18 (36%)	
Visceral	2 (9%)	4 (14%)	18 (36%)	
Both	1 (5%)	2 (7%)	3 (6%)	
Other *	5 (23%)	7 (24%)	11 (22%)	
Number of metastases				0.35
1	6 (27%)	11(38%)	23 (46%)	
> 1	16 (73%)	18 (62%)	27 (54%)	

* Includes mediastinal LNs, paratracheal LNs, endobronchial LNs, hilar LNs, prepectoral LNs, skin, and pleura

** Tumor grade reported locally, missing data for 6 patients in the Intermediate Risk Group and 4 patients in the High-Risk Group

Abbreviations: RS, recurrence score; ECOG, Eastern Cooperative Oncology Group.

Table 3

Median Time to Progression and 2-Year Overall Survival by Risk Group Among Patients Presenting with *de novo* Stage IV Disease

	Low risk (RS < 18)	Intermediate risk (RS 18–30)	High risk (RS ≥ 31)	Log rank, p
	Median TTP, months			
All patients (n = 101)	NR (16–NR)	22 (16–NR)	16 (9–25)	0.010
ER positive (n = 85)	32 (16–NR)	22 (16–NR)	15 (9–25)	0.007
ER positive/HER2 negative (n = 69)	NR (16–NR)	20 (16–NR)	15 (8–27)	0.003
	2-Year overall survival, %			
All patients (n = 101)	100 (78–100)	100 (78–100)	80 (69–93)	0.035
ER positive (n = 85)	100 (78–100)	100 (78–100)	77 (64–94)	0.008
ER positive/HER2 negative (n = 69)	100 (78–100)	100 (75–100)	69 (51–93)	< 0.001

Abbreviations: RS, recurrence score; NR, not reached; ER, estrogen receptor.

Table 4

Multivariate Cox Models for Time to First Progression and 2-Year Overall Survival Among ER Positive/HER2 Negative Patients Presenting with *de novo* Stage IV Disease.

	Time to First Progression		
	Hazard Ratio	**95% CI**	**p-value**
Recurrence score, 50pt	5.36	1.28–22.51	0.022
Recurrence score, 10pt	1.40	1.05–1.86	0.022
Age at diagnosis, years	0.99	0.96–1.02	0.660
Tumor size, cm	1.07	0.94–1.22	0.311
Site first metastases	0.57	0.28–1.16	0.123
	2-Year Overall Survival		
	Hazard Ratio	**95% CI**	**P value**
Recurrence score, 50pt	20.58	1.89–224.2	0.013
Recurrence score, 10pt	1.83	1.14–2.95	0.013
Age at diagnosis, years	1.01	0.97–1.06	0.655
Tumor size (cm)	1.00	0.79–1.25	0.972
Site first metastases	0.83	0.28–2.48	0.737

Adjusted Cox Models, RS and age as continuous variables, site 1st metastases: bone only versus other.

Abbreviations: ER, estrogen receptor; CI, confidence interval.