JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment

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Published online ahead of print at www.jco.org on February 29, 2016.

Supported by Genomic Health, Sanofi Aventis, and Amgen.

Presented in part at the 2011 San Antonio Breast Cancer Symposium, San Antonio, TX, December 6-10, 2011; the 2012 Annual American Society of Oncology Meeting, Chicago, IL, June 1-5, 2012; and the 2014 San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01049425.

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0732-183X/16/3499-1/$20.00

DOI: 10.1200/JCO.2015.63.5383

ABSTRACT

Purpose
The 21-gene Recurrence Score (RS) assay is a validated prognostic/predictive tool in early hormone receptor–positive breast cancer (BC); however, only a few prospective outcome results have been available so far. In the phase III PlanB trial, RS was prospectively used to define a subset of patients who received only endocrine therapy. We present 3-year outcome data and concordance analysis (among biomarkers/RS).

Patients and Methods
Central tumor bank was established prospectively from PlanB (intermediate and high-risk, locally human epidermal growth factor receptor 2–negative BC). After an early amendment, HR-positive, pN0-1 patients with RS ≤ 11 were recommended to omit chemotherapy.

Results
From 2009 to 2011, PlanB enrolled 3,198 patients with a median age of 56 years; 41.1% had node-positive and 32.5% grade 3 disease. In 348 patients (15.3%), chemotherapy was omitted based on RS ≤ 11. After 35 months median follow-up, 3-year disease-free survival in patients with RS ≤ 11 and endocrine therapy alone was 98% versus 92% and 98% in RS > 25 and RS 12 to 25 in chemotherapy-treated patients, respectively. Nodal status, central and local grade, the Ki-67 protein encoded by the *MKI67* gene, estrogen receptor, progesterone receptor, tumor size, and RS were univariate prognostic factors for disease-free survival; only nodal status, both central and local grade, and RS were independent multivariate factors. Histologic grade was discordant between central and local laboratories in 44%. RS was positively but moderately correlated with the Ki-67 protein encoded by the *MKI67* gene and grade and negatively correlated with progesterone receptor and estrogen receptor.

Conclusion
In this prospective trial, patients with enhanced clinical risk and omitted chemotherapy on the basis of RS ≤ 11 had excellent 3-year survival. The substantial discordance observed between traditional prognostic markers and RS emphasizes the need for standardized assessment and supports the potential integration of standardized, well-validated genomic assays such as RS with clinicopathologic prognostic factors for chemotherapy indication in early hormone receptor–positive BC.

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Adjuvant chemotherapy recommendations in estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative early breast cancer have traditionally been based on tumor size, nodal status, histologic grade, and immunohistochemistry (IHC) assessment of ER, progesterone receptor (PR), and to some extent the protein encoded by the *MKI67* gene (Ki-67). Advances in technology have enabled extensive genomic assessment of patients with breast cancer revealing substantial heterogeneity, with multiple subgroups within patients with ER-positive HER2-negative breast cancer.[1,2]

Genomic signatures such as the 21-gene Recurrence Score (RS) Assay (Onco*type* DX; Genomic Health Inc, Redwood City, CA) and others have been developed in the last decade for standardized relapse risk assessment in hormone receptor (HR)–positive HER2-negative breast cancer (for review see Gluz et al[3]), but the RS assay is by far the most extensively validated test with multiple prospectively designed studies of archival specimens from clinical studies with long-term follow-up. There are studies demonstrating low recurrence rates in patients with N0 to N1 breast cancer and low RS results in patients treated with endocrine therapy alone.[4-7] Other studies have shown that patients with high RS results gained substantial benefit from adjuvant chemoendocrine therapy versus endocrine therapy alone, whereas patients with low RS results have had minimal if any benefit from chemotherapy.[8,9] The benefit of adjuvant chemotherapy for patients with intermediate RS remains unclear and is currently being investigated in prospective clinical trials.

The 21-gene assay is widely recommended for guiding adjuvant treatment decisions in patients with HR-positive breast cancer for whom the benefit of chemotherapy is unclear.[10,11] The St Gallen Consensus Panel also recently stated that patients with luminal B subtype (eg, defined by the protein encoded by the *MKI67* gene [Ki-67]/PR) should be considered for chemotherapy for selected patients, including those with high RS ($>$ 25) or grade 3 tumors,[11] Notably, the current St Gallen Consensus recommends use of the marker but states that for Ki-67 there seems to be no optimal cut point.[12]

Nonetheless, there is still controversy surrounding the prognostic impact of adding genomic signatures to centrally measured IHC markers and the use of genomic assays for guiding adjuvant treatment decisions, particularly in Europe, as there are no data from prospective studies where patients have been treated according to the RS results.[5,13]

Improved decision making requires understanding of how to include genomic risk assessment with current prognostic parameters such as nodal status, grade, tumor size, and IHC markers (ie, ER, PR, and Ki-67). However, the latter marker is controversial given the lack of data on optimal Ki-67 measurement method and cutoff[12,14] as well as the substantial interobserver variability in receptor assessment[15-17] and Ki-67 staining.[18,19] In this context, it is relevant to understand to what extent there are substantial differences between central and local assessment.

The goals of the present analysis within the translational research program of the PlanB trial were to prospectively assess risk of recurrence at 3 years in patients with RS $\leq$ 11, to compare histologic grade review (performed locally *v* centrally), to evaluate the association between grade/single IHC–assessed markers (ER, PR, and Ki-67) and RS results focusing on HR-positive breast cancer, and to investigate the prognostic usefulness of these markers and RS, particularly in patients treated by endocrine therapy alone.

PATIENTS AND METHODS

Patient Population

This report presents analyses from the translational research program of the prospective, randomized, multicenter PlanB trial. The trial included female patients (18 to 75 years old) with node-positive or high-risk (T2, grade 2 and 3, high uPA/PAI-1, or age $<$ 35 years old) node-negative HER2-negative early breast cancer after adequate surgical treatment (complete resection of tumors, sentinel-node biopsy in N0, or axillary dissection in node-positive patients) with no evidence of distant metastasis, Eastern Cooperative Oncology Group performance status $<$ 1 or Karnofsky Index $>$ 80%, and signed informed consent.

PlanB was initiated in 2009 as a chemotherapy trial for comparing anthracycline-containing (four cycles of epirubicin/cyclophosphamide followed by four cycles of docetaxel every 3 weeks) and anthracycline-free (six cycles of docetaxel/cyclophosphamide every 3 weeks) chemotherapy. The trial was based on an observation from a retrospective meta-analysis demonstrating more pronounced benefit from anthracyclines in HER2-positive disease.[20] In August 2009, after inclusion of 274 patients, the PlanB trial was amended to recommend omission of chemotherapy (ie, treatment with endocrine therapy alone) in patients with HR-positive disease with RS $\leq$ 11. This cutoff was chosen by the study group on the basis of retrospective evidence from Paik et al,[4] who estimated 10% distant relapse risk as the upper limit of the 95% CI at RS of 11.

Study Design

The trial was approved by German ethics boards and conducted in accordance with the Declaration of Helsinki.

The objective of the translational research program was to compare independent prospective central pathology review and assessment of IHC markers with RS and local pathology within the PlanB trial. Tumors that were ER-positive or PR-positive by local pathology assessment are referred to as locally HR-positive tumors.

All patients were followed up at 3-month intervals for the first 3 years according to national guidelines; follow-up is planned every 6 months for the subsequent 6 years. Data were obtained from electronic case record forms and were verified by regular monitoring visits to the study sites. Primary surgically removed tumor tissue was sent to the central pathology laboratory of Genomic Health (Redwood City, CA) for RS analysis. Slide review, IHC, and fluorescence in situ hybridization analysis were performed in an independent central laboratory (Institute of Pathology, Hannover Medical School, Hannover, Germany). One experienced breast pathologist (M.C.) assessed histology and central grade using hematoxylin and eosin–stained slides, and a second pathologist (H.H.K.) reviewed them; both were blinded to the clinical data and to Ki-67 expression. Tissue microarrays (diameter, 1.4 mm) were constructed during the first slide review by choosing one morphologically representative region from each tumor sample. Slides were stained for ER (rabbit [SP1]; Neomarkers, Fremont, CA), PR (mouse monoclonal PgR636; DAKO, Glostrup, Denmark), and Ki-67 (clone 30-9 rabbit monoclonal; Ventana, Tucson, AZ) using standard protocols. Tumors were classified as ER or PR positive if immunostaining was present in $\geq$ 1% of tumor nuclei. Ki-67 was evaluated by one experienced breast pathologist, specialized in proliferation measurement (H.H.K.) in at least 100 tumor cells within the highest-density area; the measurement was performed semiquantitatively (in 5% increments) and quantitatively (in 1% increments).

Statistical Analysis

All survival analyses reported here refer to the primary end point of 3-year disease-free survival (DFS), where an event was defined as any invasive cancer event or death (with or without recurrence). The recommendation for omitting chemotherapy in patients with RS $\leq$ 11 was based on the assumption that the 5-year DFS rate should be $\geq$ 90%. The 3-year DFS data can be used to monitor this assumption for ongoing trials such as the West German Study Group–Adjuvant Dynamic Marker-Adjusted Personalized Therapy HR-positive HER2-negative trial. Assuming exponential survival, if

3-year survival is > 92%, one can rule out a 5-year DFS worse than 90% at 95% confidence with approximately 330 patients omitting chemotherapy.

Reported survival percentages (eg, 3-year survival) were based on the Kaplan-Meier estimator. Univariate and multivariate Cox proportional hazard models for DFS were performed. For Cox analysis, RS, tumor size, and Ki-67 were coded as continuous variables, using fractional ranks; grade was coded as G3 versus G2 or G1; and lymph node status was coded as pN1-3 versus pN0 and pN2-3 versus pN1-2. Survival was analyzed in the subgroup of patients treated by endocrine therapy alone (omitting chemotherapy) on the basis of RS ≤ 11 and in other subgroups defined according to the objectives of the trial.

Summary statistics including concordance were computed for local versus central marker assessment. In the case of 2 × 2 or 3 × 3 contingency tables of relative frequencies, sums of diagonal entries were computed. These correspond to exact agreement of classification. Certain marker subgroups (eg, central PR ≤ 20% *v* > 20%) were defined according to cutoffs[13] and used individually or in combination to characterize associations with RS results, by summary statistics. Associations of markers with RS results were also characterized by Spearman correlations (r_s). All statistical analyses were performed using SPSS v.23 (IBM Corp, Armonk, NY).

RESULTS

Baseline Characteristics and Therapy

From April 2009 to December 2011, 3,198 patients were recruited from 93 German centers (for CONSORT diagram, see Fig 1); of these, 2,449 were randomly assigned to receive the evaluated chemotherapy regimens. Median age was 56 years; 85.9% were locally HR-positive. RS results were available for 2,568 locally HR-positive patients; of these, 18.1% were classified as low RS (≤ 11), 60.4% intermediate RS (12 to 25), and 21.6% high RS (> 25). Table 1 presents patient baseline characteristics for the 2,642 locally HR-positive patients with available tissue within tumor bank. In 348 patients (n = 344 within tumor bank; 31.4% node positive, 20% G3), chemotherapy was omitted on the basis of RS ≤ 11, corresponding to 15.3% of pN0 to 1 patients after amendment; six additional patients refused further study participation. Most of the locally HR-positive patients with RS were also included in the tumor bank population (2,553 of 2,568; Fig 1).

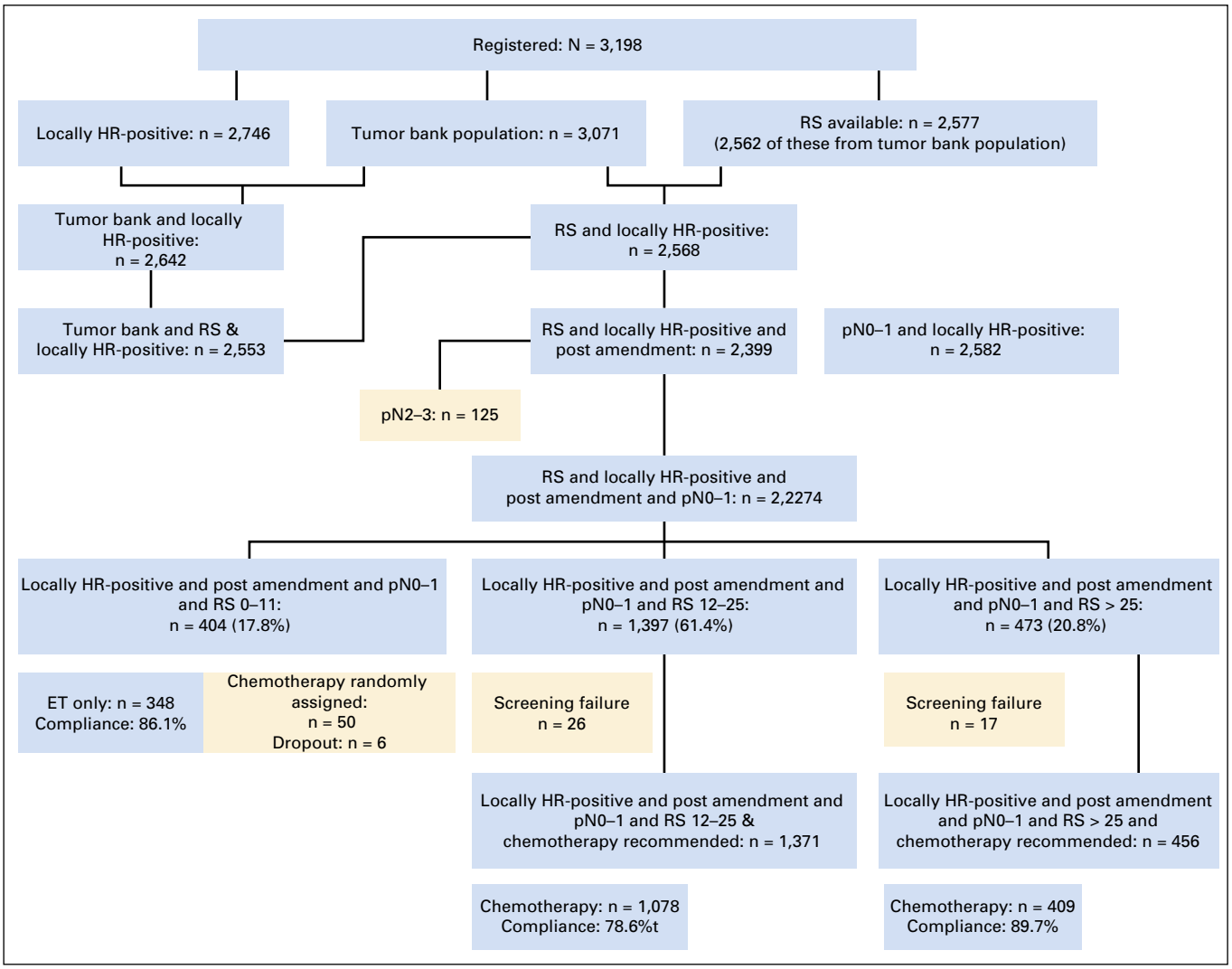

Fig 1. PlanB CONSORT diagram. ET, endocrine therapy; HR, hormone receptor; RS, Recurrence Score.

Table 1. Patient Baseline Characteristics (Locally HR-Positive, Tumor Bank Patients)

Characteristic	N = 2,642
Age, median, years	56
Tumor size, median, mm	19
Nodal status, No. (%)	
pN0	1,554 (58.8)
pN1	930 (35.2)
pN2	122 (4.6)
pN3	36 (1.4)
Ki-67 status, median, %	
Quantitative	14
Semiquantitative	15
Central ER status, No. (%)	
Positive	2,390 (90.5)
Negative	82 (3.1)
Unknown	170 (6.4)
Central PR status, No. (%)	
Positive	1,969 (74.5)
Negative	483 (18.3)
Unknown	190 (7.2)
Central HR status, No. (%)	
Positive	2,421 (91.6)
Negative	64 (2.4)
Unknown	157 (5.9)
Local grade, No. (%)	
G1	165 (6.2)
G2	1,629 (61.7)
G3	526 (19.9)
Unknown	322 (12.2)
Central grade, No. (%)	
G1	134 (5.1)
G2	1,636 (61.9)
G3	825 (31.2)
Unknown	47 (1.8)
Therapy, No. (%)	
Endocrine	344 (13.0)
Arm A	988 (37.4)
Arm B	982 (37.2)
Out of study	328 (12.4)
Recurrence Score result, No. (%)	
≤ 11	459 (17.4)
12-25	1,544 (58.4)
> 25	550 (20.8)
Unknown	89 (3.4)

Abbreviations: ER, estrogen receptor; HR, hormone receptor; Ki-67, protein encoded by the *MKI67* gene; PR, progesterone receptor.

Grade Assessment: Concordance Between Local and Central Pathology

Concordance between local and central grade was 68.0% for all tumors: 66.3% for locally HR-positive tumors (Table 2) and 88% for locally HR-negative tumors. A moderate correlation was observed between central (or local grade) and the RS result as a continuous variable ($r = 0.32$ for both) for locally HR-positive tumors.

Association Between IHC-Based Markers and the RS Result

Association of IHC-based markers with RS results was analyzed in locally HR-positive, tumor bank patients. The majority (63.5%) of patients with high RS (> 25) had central G3, but only approximately half (49.9%) had local G3 status. Moreover, 57.0% of central G3 patients and 50.1% of local G3 patients had RS ≤ 25. If both pathologic assessments were concordant (G1/2 or G3), the association with RS was higher (Fig 2A). Even among the few (14%) locally HR-positive tumor bank patients who were both locally and centrally G3, 39.1% still had RS ≤ 25, although only 5.8% had low RS (≤ 11; Fig 2A).

RS had a weak to moderate positive Spearman correlation with Ki-67 (quantitative and semiquantitative) and with central and local grade; it had a moderate negative correlation with IHC-determined PR and a weak negative correlation with IHC-determined ER (Appendix Fig A1, online only).

In view of these bivariate correlations, we assessed the RS distribution by Ki-67 (semiquantitative) levels (Fig 2B) and by combination of Ki-67 (semiquantitative) and PR levels (Appendix Fig A2). Fewer than 5% of patients with Ki-67 < 20% and PR > 20% had RS > 25. All patients in the small group with Ki-67 ≥ 40% and PR ≤ 20% had RS > 25 (Appendix Fig A2).

Prognostic Effects of Clinicopathologic Parameters and the RS Result

Of 135 events reported for the whole trial, 73 events were reported in the HR-positive population (54 distant relapses, 11 secondary neoplasms [mostly contralateral BC] and local relapses, eight deaths without relapse).

Three-year DFS was substantially poorer in those with RS > 25 than in others: 3-year DFS was 91.9% (95% CI, 89.0% to 94.8%) in patients with high RS versus 97.8% (95% CI, 96.8% to 98.8%) in patients with intermediate RS and 97.4% in patients with RS ≤ 11 (95% CI, 95.6% to 99.1%; $P < .001$; Fig 3A).

If analysis was focused on patients with pN0 to 1 BC treated with no chemotherapy within the RS ≤ 11 group and treated by chemotherapy with RS ≥ 12, it resulted in 3-year DFS of 94.9% within the RS > 25 group (95% CI, 91.4% to 98.4%) versus 97.5% (95% CI, 95.9% to 99.0%) within RS 12 to 25 group and 98.4% (95% CI, 97.0% to 99.8%) within the RS ≤ 11 group ($P = .05$ for RS > 25 *v* others; Fig 3B).

Table 2. Contingency Table of Central and Local Grade Assessment in Locally Hormone Receptor–Positive Tumor Bank Patients (N = 2,287)

Histologic Grade by Central Laboratory	Histologic Grade by Local Laboratory		
	Grade 1 (n = 164)	Grade 2 (n = 1,602)	Grade 3 (n = 521)
1 (n = 120)	46 (38.3)	70 (58.3)	4 (3.3)
2 (n = 1,422)	106 (7.5)	1,135 (79.8)	181 (12.7)
3 (n = 745)	12 (1.6)	397 (53.3)	336 (45.1)

NOTE. Data are presented as No. (% within central grade).

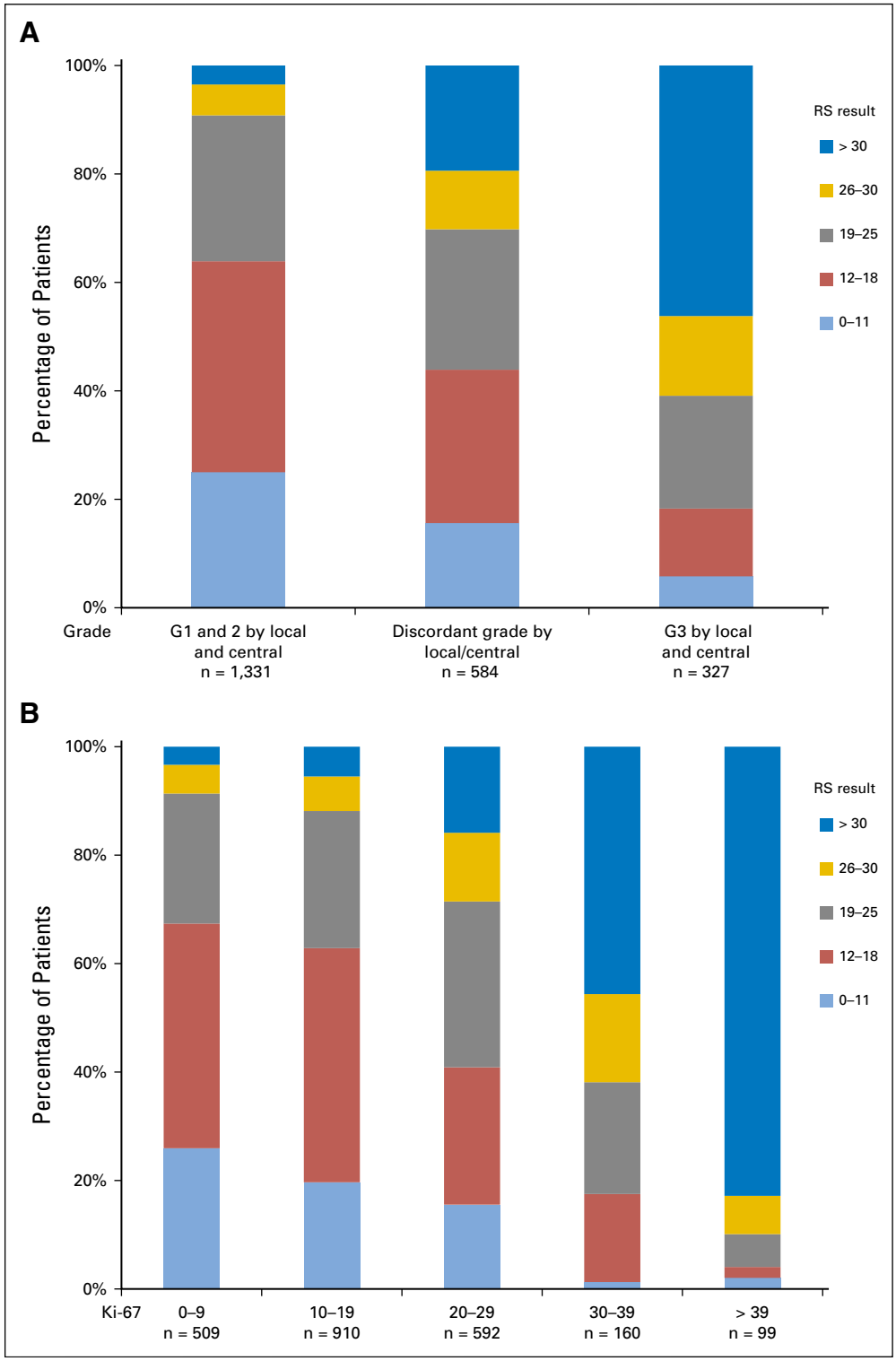

Fig 2. Recurrence Score (RS) distribution by grade (A) and by centrally assessed protein encoded by the *MKI67* gene (Ki-67, semiquantitative) expression (B) in locally hormone receptor–positive tumor bank patients with measured RS. G, grade.

For central grade subgroups, we observed 3-year DFS of 98.4% (95% CI, 99.8% to 96.9%), 98.6% (95% CI, 99.5% to 97.6%), and 95.7% (95% CI, 99.4% to 92.0%) for RS 0 to 11, 12 to 25, and > 25 subgroups within central G1 to 2 tumors (not significant for RS > 25 *v* others) and 93.2% (95% CI, 99.9% to 86.4%), 95.2% (95% CI, 98.0% to 92.4%) and 89.9% (95% CI, 93.8% to 85.9%) within central G3 tumors ($P = .025$ for RS > 25 *v* others), respectively.

Nodal status, central and local grade, continuous Ki-67, ER and PR, tumor size, and RS were univariate prognostic factors for DFS in all locally HR-positive tumor bank patients. Entering these factors into multivariate analysis (Table 3), RS (fractionally

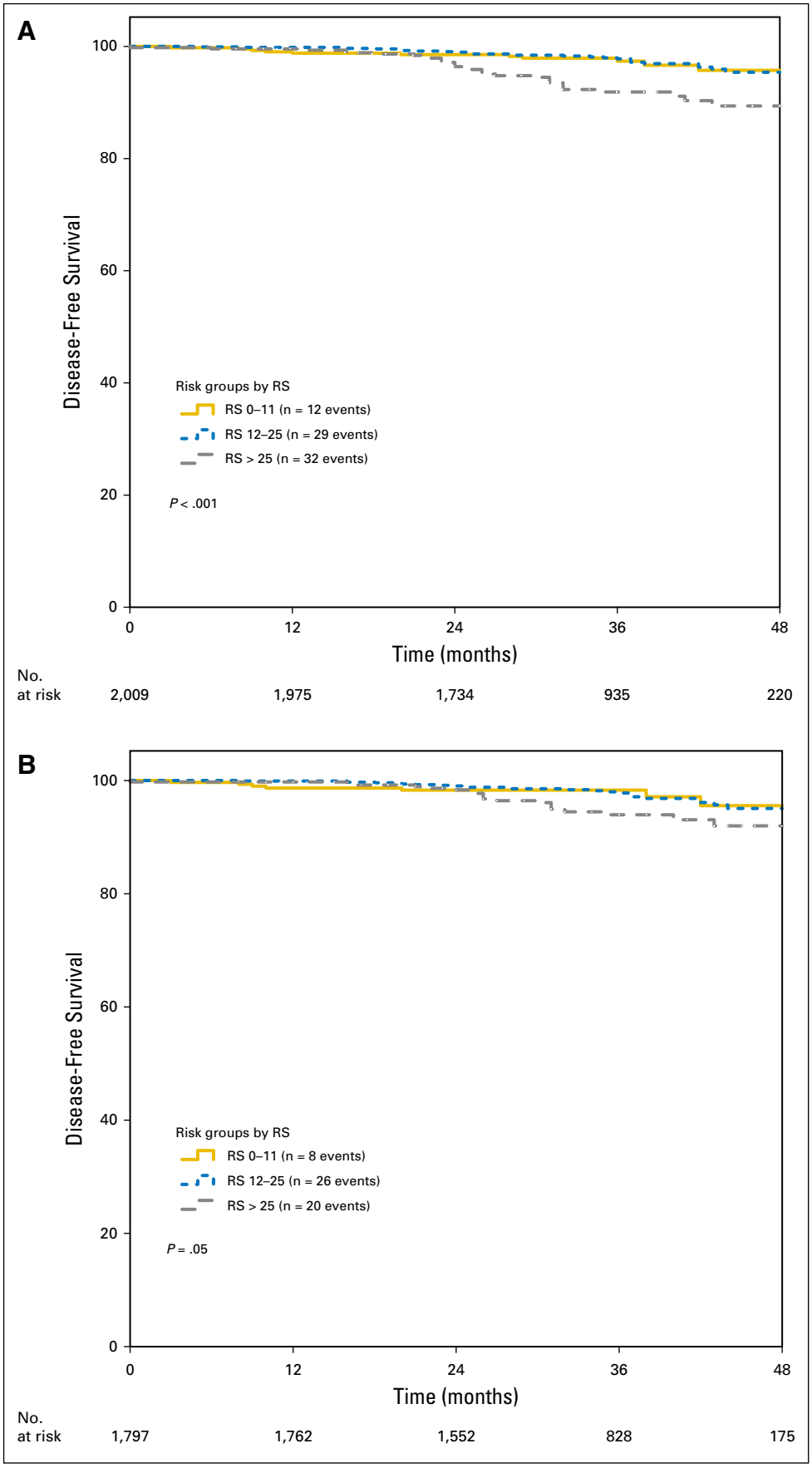

Fig 3. (A) Disease-free survival by Recurrence Score (RS) groups in locally assessed hormone receptor–positive patients with measured RS. (B) Disease-free survival by RS groups in locally assessed hormone receptor–positive pN0 to 1 patients with measured RS treated with no chemotherapy within the RS < 12 group and RS ≥ 12 treated by chemotherapy. In the pN1 patients: 3-year disease-free survival: 89.4% versus 97.2% and 97.9% in RS > 25 versus RS 12 to 25 versus RS ≤ 11 group, respectively. In the pN0 patients, 3-year disease-free survival rates of 97% versus 98.5% and 98.6% in RS > 25, RS 12 to 25, and RS ≤ 11 subgroups were observed.

ranked), both central G3 and local G3 (*v* G1 or G2), and nodal status (pN1 to 3 *v* pN0 and pN2 to 3 *v* pN1 to 2) were significant multivariate prognostic factors for DFS in this population. When these univariate and multivariate analyses were performed on the subpopulation of patients with RS ≥ 12, all of whom received chemotherapy, the results were similar (Table 3).

DISCUSSION

The most important finding in our study is the high 3-year DFS (98%) in patients with low RS (≤ 11) and no chemotherapy, despite being high risk by traditional parameters. Even with an only 3-year follow-up, such a high rate of DFS almost excludes possible benefit from adjuvant chemotherapy. We also found high 3-year DFS (98%) in chemotherapy-treated patients with intermediate RS (12 to 25) and poorer 3-year DFS (92%) in chemotherapy-treated patients with RS > 25. These are the first prospective data to our knowledge to report clinical outcome both in patients with node-negative and with node-positive BC where the RS results had been used in decision making in a large phase III trial. These findings confirm the recently published prospective TAILORx (Trial Assigning IndividuaLized Options for Treatment) results in node-negative patients[21] and retrospective analyses of prospective clinical trials.[4,5]

Despite its widespread use and inclusion in treatment guidelines, it is important to understand the role of the RS result in the context of traditional parameters assessed by local or centralized, high-quality, controlled pathology review and of established IHC markers. RS was an independent prognostic marker, together with both central and local grade nodal status (but not continuously measured Ki-67, ER, or PR). This finding is consistent with previously reported data from prospective retrospective studies, although grade has not consistently been significant in multivariable analysis including RS.[5] Our results support consideration of these parameters, together with RS, for prognostic assessment. The lack of significance of Ki-67 in the multivariable model including RS is consistent with results of the PACS01 study.[22]

We have shown by central and local pathology review that significant disagreement in grade assessment (discordance of 44% in locally HR-positive tumors) is present, despite the observed prognostic impact of both central and local grade regarding early relapse. Discordance rates seen here are in line with the 28% to 33% reported by other studies[17,23] and with our previously reported data.[24] Notably, Kennecke et al[25] reported 40% grade discordance in node-negative breast cancer. As adjuvant chemotherapy is strongly recommended in patients with G3 tumors, there is an urgent need for additional work on how to further standardize grade assessment in HR-positive breast cancer. We observed a significant but moderate correlation between RS and local and central grade ($r = 0.32$ for both). Central pathologic grade review led to improved association between RS and grade in those patients with concordant local and central grade; however, even in patients with both centrally and locally G3 tumors, 39% had RS ≤ 25. Most of the patients in this group had highly positive ER and/or PR tumors (median ER, 100%; median PR, 90%) with intermediate proliferation (median Ki-67, 20%). Notably, although both grade and RS results have been shown to provide independent prognostic information in some multivariate models[17] and to be predictive for efficacy of neoadjuvant chemotherapy,[26] only RS has been shown, by interaction analysis, to be predictive for the benefit gained from chemoendocrine therapy.[8,9] Subgroup analysis of the prognostic impact of RS subgroups within central grade categories shows a higher prognostic impact of RS in poorly differentiated tumors. Yet, these results should be interpreted with caution and viewed as merely hypothesis generating because of the short follow-up and low event numbers within the small subgroups.

Table 3. Univariate and Multivariate DFS Models in the Locally Assessed HR-Positive, Tumor Bank Population With Measured RS (n = 2,553) and in the Subpopulation With RS ≥ 12 (n = 2,003)

		All RS Results (Mixed Population; Endocrine Therapy– and Chemotherapy-Treated Patients)				RS ≥ 12 (Homogeneous Population; All Chemotherapy Treated)			
Factor	Coding	Univariate Hazard Ratio (95% CI)	*P*	Multivariate Hazard Ratio (95% CI)	*P*	Univariate Hazard Ratio (95% CI)	*P*	Multivariate Hazard Ratio (95% CI)	*P*
Recurrence Score	Fractionally ranked* (75th-25th percentile)	2.31 (1.52 to 3.52)	< .001	1.68 (1.04 to 2.74)	.035	4.10 (2.21 to 7.61)	< .001	2.43 (1.21 to 4.88)	.013
Nodal status									
	pN1-3 *v* pN0	2.30 (1.42 to 3.73)	.001	2.45 (1.39 to 4.29)	.001	2.69 (1.56 to 4.62)	< .001	2.98 (1.59 to 5.58)	.001
	pN2-3 *v* pN0-1	3.41 (1.93 to 6.03)	< .001			4.39 (2.45 to 7.87)	< .001	2.53 (1.33 to 4.82)	.006
	pN3 *v* pN0-2	6.03 (2.43 to 14.97)	< .001	2.33 (1.25 to 4.37)	.005	7.19 (2.87 to 17.97)	< .001		
Tumor stage	pT2-4 *v* pT1	1.62 (1.02 to 2.58)	.04	ns		ns			
Local grade	G3 *v* G1 and 2	2.46 (1.55 to 3.91)	< .001	1.75 (1.01 to 3.02)	.05	2.64 (1.60 to 4.36)	< .001	1.9 (1.06 to 3.42)	.032
Central grade	G3 *v* G1 and 2	3.06 (1.92 to 4.90)	< .001	2.27 (1.28 to 4.02)	.005	3.06 (1.81 to 5.16)	< .001	1.97 (1.05 to 3.71)	.035
Ki-67 semiquantitative	Fractionally ranked (75th-25th percentile)	2.53 (1.56 to 4.10)	< .001	ns		2.60 (1.54 to 4.38)	< .001	ns	
ER, %	Fractionally ranked (75th-25th percentile)	0.62 (0.39 to 0.98)	.04	ns		ns			
PR, %	Fractionally ranked (75th-25th percentile)	0.61 (0.40 to 0.93)	.02	ns		0.58 (0.36 to 0.93)	.024	ns	
Treatment	Endocrine *v* chemotherapy	ns				na			

Abbreviations: ER, estrogen receptor; G, grade; HR, hormone receptor; Ki-67, protein encoded by the *MKI67* gene; na, not applicable; ns, not significant; PR, progesterone receptor; RS, Recurrence Score.
*The continuous variables recurrence score, semiquantitative Ki-67, ER labeling index, and PR labeling index were coded as fractional ranks (from 0 to 1), with the hazard ratio calculated relative to an increment of 0.5 in fractional rank (eg, the hazard ratio for 75th percentile [fractional rank 0.75] *v* 25th percentile [fractional rank 0.25]).

A prospective comparison between IHC subclassification and reverse transcriptase polymerase chain reaction–based genomic signature revealed that an absolute majority (> 95%) of patients with luminal A–like tumors by IHC (defined by low Ki-67 and high PR expression) had RS ≤ 25, with uncertain benefit from chemotherapy. Conversely, patients with high Ki-67 and low PR expression all had RS > 25. The most pronounced impact of RS on clinical decision making presumably resides in the large group of patients with intermediate Ki-67 (15% to 35%) and particularly in patients with discordant pathologic assessments of grade, Ki-67, and PR. Notably, although Ki-67 has been shown to be a strong prognostic[27] and predictive marker for efficacy of neoadjuvant chemotherapy, or for addition of taxanes to anthracyclines,[28] it has no predictive utility for chemoendocrine versus endocrine therapy alone (unlike RS[9]), as demonstrated in individual trials[29] and a meta-analysis.[30] The clinical challenge related to Ki-67 use is complicated by the lack of standardization of Ki-67 measurements,[14] which is currently being addressed in prospective trials.[18] In this trial, we used two approaches (semiquantitative and quantitative) to measure Ki-67, both of which were positively correlated with the RS results.

Limitations of this study are the availability of only central Ki-67 assessment (by a large academic laboratory), the nonobligatory clinical implementation of the RS result (obtained before randomization), and the lack of RS in the small group of patients recruited before the amendment. Our early survival results need to be confirmed by longer follow-up in PlanB and by other trials before drawing definitive conclusions on interactions among the various prognostic markers. The hazard rate for patients with high risk by RS may increase beginning around 20 to 24 months after completion of adjuvant chemotherapy, as is not unexpected in HR-positive/HER2-negative BC. Modeling of this effect within a time-varying survival model would be reasonable within a longer follow-up analysis of PlanB. Our study did not test if there was a chemotherapy benefit compared with endocrine therapy alone in patients with RS ≥ 12. Nonetheless, it provides important data supporting the use of nodal status and high-quality pathology for analysis of residual relapse risk in patients, despite receiving adjuvant chemotherapy.

In conclusion, this is, to our knowledge, the first-to-report prospective chemotherapy trial where patients were treated according to the RS result; patients with zero to three involved lymph nodes, at high risk by traditional parameters, but with RS ≤ 11 had excellent 3-year survival despite receiving no adjuvant chemotherapy. Furthermore, the observed association between RS groups and survival confirms retrospective evidence from other prospective retrospective studies. We also found substantial discordance in grade assessment between local and central pathology, both associated with prognosis. This suggests that better standardization is required but also emphasizes that RS may help to make treatment decisions more homogenous and reliable, independent of where patients are treated. Our clinical outcome findings, as well as recently published prospective results of the low-risk arm of the TAILORx trial,[21] suggest that chemotherapy in patients with low RS (≤ 11) does not confer clinical benefit, whereas it is yet unknown if the addition of chemotherapy to endocrine therapy will offer benefit to patients with intermediate RS (RS,12 to 25). Several prospective trials are currently investigating the benefit of chemotherapy in patients with intermediate RS, either by randomization (TAILORx/RxPonder [Rx for Positive-Node, Endocrine-Responsive Breast Cancer]) or by dynamic testing of early therapy response (West German Study Group–Adjuvant Dynamic Marker-Adjusted Personalized Therapy[31]).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Financial support: Steven Shak
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment

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Research Funding: Roche (Inst), Genomic Health (Inst), TEVA Pharmaceuticals Industries (Inst), Celgene (Inst), Bayer HealthCare Pharmaceuticals (Inst), NanoString Technologies (Inst), Agendia NV (Inst), Amgen (Inst), AOK Rheinland/Hamburg (Inst)

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Research Funding: Genentech (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst)

Acknowledgment

We thank all patients who participated in the trial and all PlanB investigators. We thank all PlanB pathologists for providing tumor blocks to the central tumor bank. We also thank C. Buehne, I. Renner, and Palleos for study management; the PlanB central pathology at Medizinische Hochschule Hannover; A. Bareket Samish for her editorial assistance; and the study sponsors, Genomic Heath, Amgen, and Sanofi Aventis.

Appendix

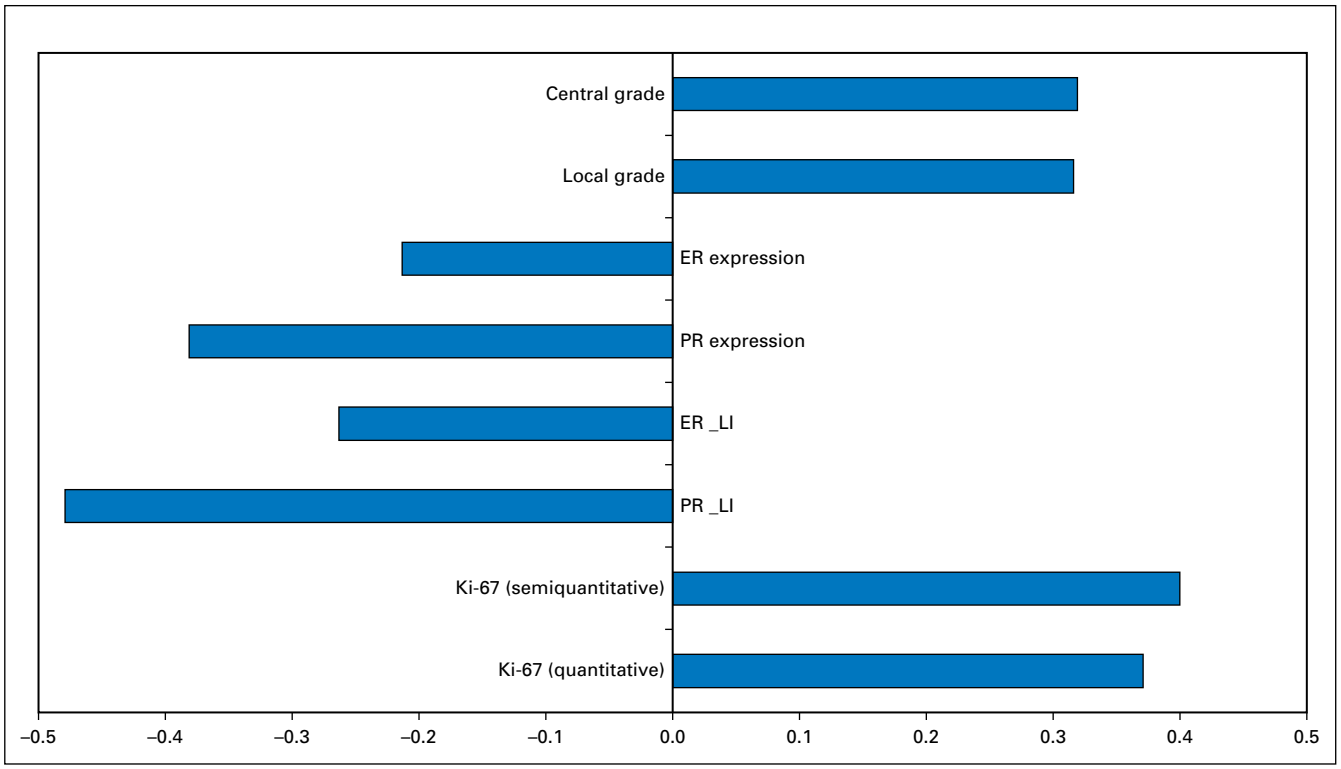

Fig A1. Spearman correlation of single markers (local and central grade, estrogen receptor [ER], progesterone receptor [PR], and protein encoded by the *MKI67* gene [Ki-67]) and recurrence score results. LI, labeling index.

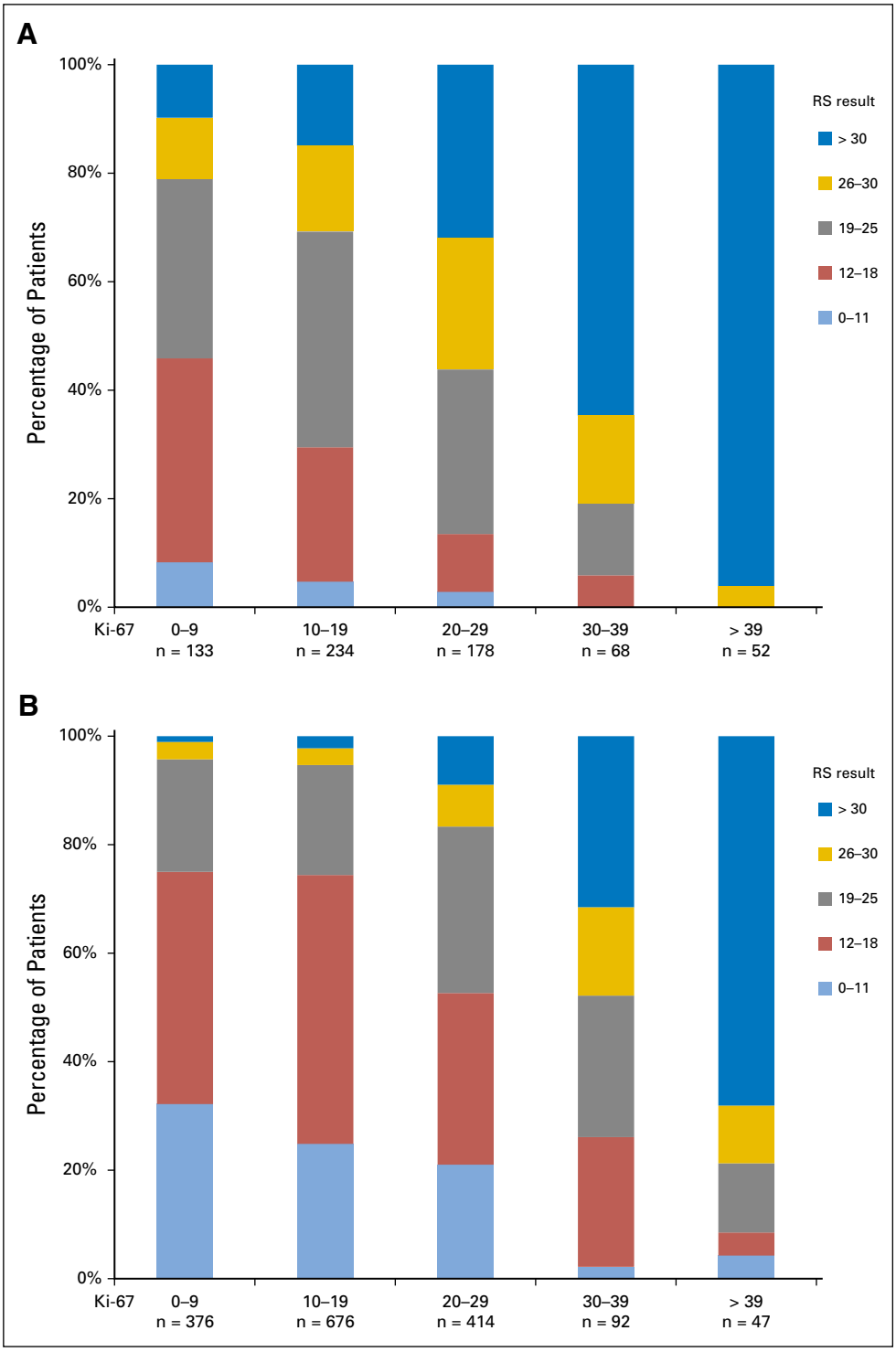

Fig A2. Recurrence score (RS) distribution by centrally assessed protein encoded by the *MKI67* gene (Ki-67; semiquantitative) expression (A) in the subpopulation of patients with progesterone receptor ≤ 20%, and (B) in the subpopulation of patients with progesterone receptor > 20%.