European Journal of Cancer 217 (2025) 115222

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Survival outcomes for patients with invasive lobular cancer by MammaPrint: Results from the MINDACT phase III trial☆

O. Metzger Filho [a,1], F. Cardoso [b,*,1], C. Poncet [c], C. Desmedt [d], S. Linn [e], J. Wesseling [e], F. Hilbers [e], S. Delaloge [f], J.-Y. Pierga [g], E. Brain [h], S. Vrijaldenhoven [i], P.A. Neijenhuis [j], E.J.Th Rutgers [e], M. Piccart [k], L.J. van 't Veer [l,2], G. Viale [m,2]

[a] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[b] Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal
[c] The European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium
[d] Laboratory for Translational Breast Cancer Research, Department of Oncology, KU Leuven, Leuven, Belgium
[e] Divisions of Diagnostic Oncology, Medical Oncology and Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands
[f] Institut Gustave Roussy, Villejuif, France
[g] Institut Curie, Paris & Saint-Cloud, Université de Paris, France
[h] Institut Curie, Hôpital Rene Huguenin, Saint-Cloud, France
[i] Noordwest Ziekenhuisgroep, Alkmaar, Netherlands
[j] Alrijne Ziekenhuis, Leiderdorp, Netherlands
[k] Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[l] Department Laboratory Medicine, University California San Francisco, CA, USA
[m] European Institute of Oncology IRCSS, Milan, Italy

ARTICLE INFO

Keywords:
Invasive lobular carcinoma
Invasive ductal carcinoma
MINDACT
70-gene signature MammaPrint

ABSTRACT

Background: Evaluation of the prognostic performance and clinical utility of the MammaPrint 70-gene signature in early-stage invasive lobular carcinoma (ILC) for whom such analyses in a randomized trial is awaited.
Patients and methods: Exploratory subgroup analysis of MINDACT trial patients with centrally assessed histology (n = 5929) with invasive breast cancer of no-special-type (NST), or pure ILC. In the trial patients were categorized based on the 70-gene signature for genomic risk and modified Adjuvant!Online for clinical risk. Survival outcomes at 8.7 years median follow-up by 70-gene signature were compared between NST and ILC for Distant Metastasis-Free Survival (DMFS), Disease-Free Survival (DFS) and Overall Survival (OS).
Results: 5313 patients were ILC (n = 487) or NST (n = 4826). ILC was further classified into classic ILC (n = 255) or ILC variants (n = 232). The 70-gene signature classified 16.2 % of ILC and 39.1 % of NST as genomic high-risk (gH). Survival outcomes for ILC vs. NST revealed similar estimates according to genomic risk overall and across subsets. The 70-gene signature classified 10.2 % of classic ILC and 22.8 % of ILC variants as gH. 5-yr DFS estimates for ILC variants 88.4 % (95 %CI: 83.1–92.1) was inferior to classic ILC 93.0 % (95 %CI: 88.7–95.7).
Conclusions: Sixteen percent of ILC were classified high genomic risk by the 70-gene signature, with unfavorable survival outcomes. Survival estimates were similar for patients with ILC and NST classified as either low- or high-genomic risk, suggesting that the 70-gene signature also has prognostic value in ILC and may be a clinically useful tool for adjuvant treatment decision-making in ILC.

☆ Trial registrationEuropean Organization for Research and Treatment of Cancer-1041; Breast International Group- 3–04; ClinicalTrials.gov, NTC00433589; and the European Clinical Trials database, EudraCT2005–002625–31

* Correspondence to: Senior Consultant Medical Oncology, President ABC Global Alliance, Champalimaud Foundation, Av. De Brasília s/n, Lisbon 1400-038, Portugal.
E-mail address: fcardoso@abcglobalalliance.org (F. Cardoso).

[1] First authors (equal contribution)
[2] Last authors (equal contribution)

https://doi.org/10.1016/j.ejca.2025.115222
Received 2 November 2024; Received in revised form 5 January 2025; Accepted 6 January 2025
Available online 22 January 2025

1. Introduction

Invasive lobular carcinoma (ILC) accounts for 10–15 % of all breast cancers and represents the second most common histological subtype of breast cancer [1]. ILC differs from invasive carcinoma of no special type (NST, formerly called invasive ductal breast cancer) in the transcriptional profile, genomic landscape, patterns of disease relapse, and responsiveness to systemic therapies [2–10]. ILC is classically described as estrogen receptor-positive with low to intermediate histological grade, and a discohesive growth pattern attributed to loss of function of e-cadherin [11]. Approximately half of ILC tumors are so-called "classic ILC" and variants such as pleomorphic and solid ILC; these variants have been associated with worse outcomes as compared with classic ILC [11, 12].

In the early-stage setting, most patients diagnosed with ILC are treated with adjuvant endocrine therapy, while decisions related to the use of chemotherapy remain controversial. Data from retrospective series point to inferior response rates to preoperative chemotherapy [9,13] in ILC compared with NST [14–16]. These data have contributed to the perceived notion of ILC tumors being less responsive to chemotherapy, although this theory remains to be confirmed NST [10]. If so, one could speculate that patients who have ILC with high-risk features have a worse prognosis than patients who have NST with such high-risk features. Hence, comparing outcomes of patients diagnosed with ILC and NST matched by genomic risk subsets should be pursued as an initial step to shed light on this controversy.

MINDACT demonstrated that patients diagnosed with high risk defined by clinical features, but low genomic risk by the 70-gene signature, had an excellent distant metastasis-free survival (DMFS) outcome when treated with adjuvant endocrine therapy and no adjuvant chemotherapy. In this study, we evaluated the prognostic performance and clinical utility of 70-gene signature among patients diagnosed with ILC confirmed at central pathology review and enrolled in the phase III MINDACT clinical trial [17,18].

2. Patients and methods

2.1. Patients

This analysis includes patients enrolled 2007 through 2011 in the MINDACT phase III study and diagnosed with either ILC or NST (Fig. 1). The median follow-up of patients is 8.7 years (IQR 7.8 – 9.7) with 5-year follow-up information available for over 90 % of the study population [18]. Histological subtypes were defined based on the central pathology assessment performed on the primary tumor. The MINDACT study population included patients aged 18–70 years, with histologically confirmed primary invasive breast cancer (stage T1, T2 or operable T3) with up to three positive lymph nodes, no distant metastases, and a World Health Organization (WHO) performance status of 0–1. The 70-gene signature (i.e., MammaPrint) was used to determine the genomic risk, and a modified version of Adjuvant! Online (modified from version 8.0 including human epidermal growth factor receptor 2 (HER2) status) was used to determine the clinical risk. Patients with low clinical and low genomic risk results did not receive chemotherapy, and patients with high clinical and high genomic risk did receive chemotherapy (mostly anthracycline-based or taxane-based, or a combination). Patients with discordant risk results (i.e., patients with high clinical risk but low genomic risk, and those with low clinical risk but high genomic risk) were randomly assigned (1:1) to receive chemotherapy or not based on either the clinical risk or the genomic risk. Randomization was done centrally and used a minimization technique that was stratified by institution, risk group and clinical–pathological characteristics. Treatment allocation was not masked. The study primary endpoint was to test whether the DMFS rate at 5 years in patients with high clinical risk and low genomic risk not receiving chemotherapy had a lower boundary of the 95 % confidence interval (CI) above the predefined non-inferiority boundary of 92 %. The primary test population included patients with high clinical risk and low genomic risk who adhered to the treatment allocation of no chemotherapy and had no change in risk post-enrollment. In this exploratory analysis, we sought to evaluate the prognostic performance and potential clinical utility of the 70-gene signature for patients diagnosed with ILC. All participants provided written informed consent. Ethics committees and relevant health authorities approved the protocol, which was carried out in accordance with the Declaration of Helsinki.

2.2. Pathology assessment

Central pathology evaluation of histological subtype was performed on hematoxylin and eosin-stained slides at the European Institute of Oncology, Milan, Italy. This analysis was restricted to tumors identified as NST and ILC (i.e., classic type and ILC variants) only by local

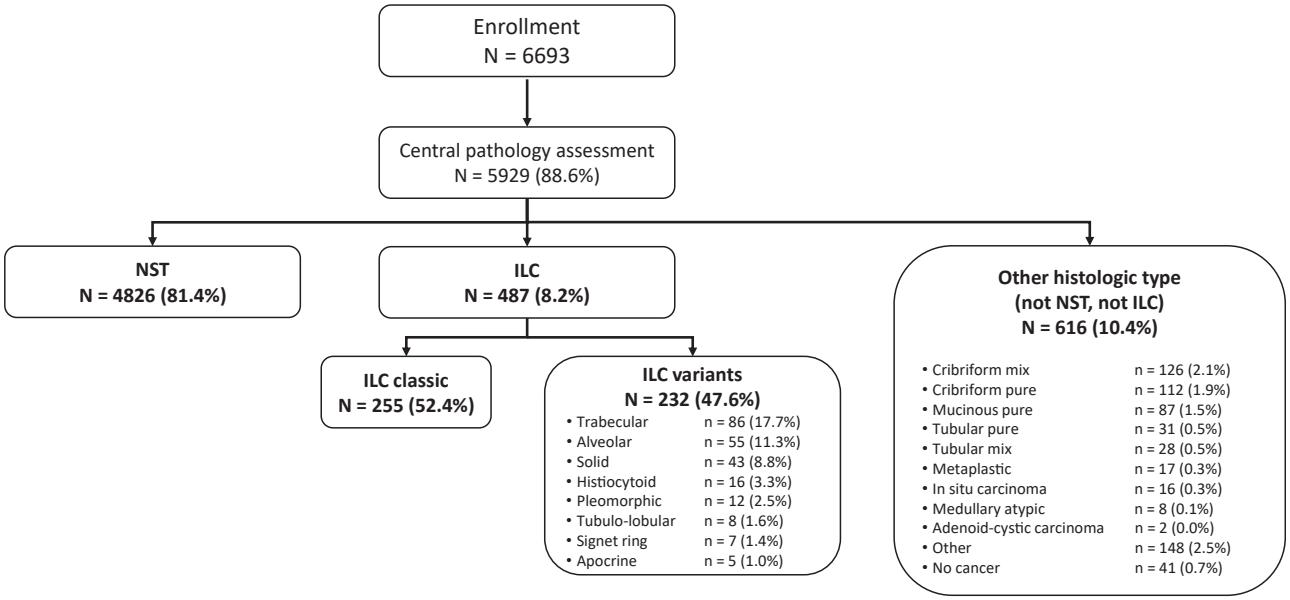

Fig. 1. Patient disposition.

pathology. Data from patients with mixed histology were not included in the analysis. MINDACT eligibility criteria initially included a minimum 50 % tumor cell cellularity based on central pathology assessment to determine eligibility. The tumor cell eligibility criterion was subsequently changed to 30 % in a protocol amendment April 2008. Most patients diagnosed with ILC were enrolled once the cut off was reduced to 30 %.

2.3. Endpoints and statistical methods

The agreement between local and central assessment of histologic subtype was assessed using unweighted Kappa coefficients across the three categories: NST, ILC, and not NST nor ILC.

The current analysis uses protocol-specified endpoints. DMFS, the study primary endpoint, was defined as time from randomization to the earliest time of distant metastasis or death. Contralateral breast cancers and secondary cancers were not considered DMFS events. Disease-free survival (DFS) was defined as the time from randomization to the earliest time of a loco-regional recurrence (i.e., invasive or in situ), distant metastasis, invasive contralateral breast cancer, second primary malignancy, or death from any cause. Lobular carcinoma in situ was not considered an event for DFS. Overall survival (OS) was defined as time from randomization to death from any cause. Time to event endpoints for DMFS, DFS and OS were displayed using Kaplan-Meier curves across histological subtypes. The association between histological subtypes and clinical outcomes was explored using multivariate cox regression adjusted for clinicopathologic factors (i.e., age [≤50 years vs. > 50 years], tumor size [≤1 cm, >1–2 cm, >2 cm], nodal status [negative vs. positive], HER2 status [negative vs. positive], histologic grade [1, 2, 3]), 70-gene risk signature (low vs. high), and chemotherapy use (yes vs. no) and endocrine therapy use with regards to HR status (HR negative, HR positive with endocrine therapy, HR positive without endocrine therapy).

3. Results

Among 6693 patients enrolled into MINDACT, 5929 (88.6 %) patients had a central pathology assessment available (Fig. 1). Local and central pathology assessment of histological subtypes identified the same histology in 4877 patients (concordance: 82.3 % (95 % CI: 81.3;83.3), corresponding to an unweighted Kappa coefficient of 0.43 (95 % CI: 0.40;0.46). The discordance between local and central pathology assessment was mainly driven by histologic subtypes other than ILC and NST, accounting for rarer subtypes of breast cancer. When restricting to patients diagnosed with ILC and NST, the Kappa coefficient increased to 0.71 (95 %CI: 0.67;0.74), Table 1. Still, only 395 out the 614 patients (64.3 %) diagnosed locally as ILC were confirmed as ILC by central pathology review, while only 64 out of the 4900 patients diagnosed locally with NST were confirmed as ILC, suggesting an overestimation of pathological ILC diagnosis by local pathology.

The current study population includes 487 patients diagnosed with ILC and 4826 patients diagnosed with NST defined by central pathology assessment. The subset of ILC was subclassified into classic ILC (n = 255) and ILC variants (n = 232). The subset of ILC variants was composed of rarer variants of ILC including trabecular, alveolar, solid, pleomorphic, histiocytoid, apocrine, signet ring and tubulo-lobular.

Clinical and pathological characteristics according to histological subtypes are shown in Table 2. When compared to NST, ILC tumors were larger (> 2 cm, 41.1 % vs. 27.1 %), more often treated with mastectomy (32 % vs. 16 %), more often ER-positive (98.8 % vs. 87.7 %), and less often HER2-positive (3.5 % vs. 10.6 %). Nodal status was balanced between groups (18.5 % and 21.5 % being node-positive in the ILC and NST group, respectively). Patients diagnosed with NST were more often premenopausal at the time of diagnosis (36.3 % vs. 29 %) and more commonly treated with adjuvant chemotherapy (45.1 % vs. 30.6 %) The clinical risk classification was balanced between ILC and NST subsets

Table 1
Cross tabulation of histologic subtypes by local and central pathology evaluation.

	NST (N = 4826)	ILC (N = 487)	Other (not NST, not ILCr) (N = 616)	Total (N = 5929)
	N (%)	*N (%)*	*N (%)*	*N (%)*
Histologic type by local assessment				
NST	4371 (90.6)	64 (13.1)	465 (75.5)	4900 (82.6)
ILC	219 (4.5)	395 (81.1)	40 (6.5)	654 (11.0)
Other (not NST, not ILC)	232 (4.8)	28 (5.7)	111 (18.0)	371 (6.3)
Missing	4 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Overall concordance (95 %CI)	4877/5929 82.3 % (95 %CI: 81.3;83.3)			
Unweighted Kappa coefficient (95 %CI)	0.43 (95 %CI: 0.40;0.46)			
Unweighted Kappa coefficient (95 %CI) (excluding Other histologic types), see shaded cells considered	0.71 (95 %CI: 0.67;0.74)			

Abbreviations: NST, invasive breast cancer of no special type; **ILC,** Invasive Lobular Carcinoma; **CI,** confidence interval.

with 48.3 % and 51.5 % classified as clinical high-risk (cH), respectively. The 70-gene signature classified 16.2 % and 83.8 % of ILC tumors as high- and low- genomic risk respectively. The distribution of genomic risk varied by ILC subsets, with 10.2 % of classic ILC and 22.9 % of ILC variants classified as high-genomic risk (gH). In the subset of NST, the 70-gene signature classified 39.1 % and 60.9 % of NST tumors as gH and low-genomic risk (gL), respectively. Among patients diagnosed with ILC, clinical and genomic risk assessments were concordant in 45.8 % for clinical low-risk (cL)/genomic low-risk (gL) and 10.3 % for cH/gH). The estimates were discordant in 6 % for cL/gH and in 38 % for cH/gL.

The estimated outcomes for patients diagnosed with ILC and NST were similar at median follow-up of 8.7 years (Interquartile Range (IQR) 7.8–9.7) (Supplementary Fig. 1). When adjusted for clinico-pathologic variables and treatment, patients diagnosed with ILC and NST had similar survival outcomes for DMFS (HR = 0.87; 95 % CI: 0.63–1.21, p = 0.63), DFS (HR = 0.91; 95 % CI: 0.72–1.15, p = 0.73) and OS (HR = 1.07; 95 % CI: 0.74–1.56, p = 0.4) (Supplementary Table 1).

The prognostic information obtained with the 70-gene signature classification appeared to be similar for patients diagnosed with ILC and for patients with NST (Fig. 2). Five-year DMFS estimates were 96.6 % (94.2 % - 98 %) and 96.4 % (95.6 % - 97 %) for ILC and NST g-low, and 88.1 % (78.4 % - 93.6 %) and 92.1 % (90.8 % - 93.3 %) for ILC and NST g-high, respectively. At 5 years, the prognostic performance of 70-gene signature in identifying gL risk subsets with favorable DMFS outcomes was similar for ILC and NST subsets (*p* for interaction =.54), (Fig. 2**)**. The estimates for DFS (Fig. 2) and OS (Fig. 2c) were also similar for ILC an NST when matched by genomic subsets.

4. Discussion

The present study revealed the prognostic performance of the 70-gene signature for patients diagnosed with ILC. The 70-gene signature classified 16 % of ILC and 39 % of NST tumors as gH. Risk stratification varied within the subsets of ILC, with 10.2 % of classic ILC and 23 % of ILC variants classified as high genomic risk. Survival outcomes, including DFMS, DFS and OS were similar for ILC and NST patients by the 70-gene signature risk subsets. Notably, in this MINDACT study

Table 2
Comparison of baseline characteristics from patients with ILC and NST included in this analysis.

	NST (N = 4826) *N (%)*	ILC (N = 487) *N (%)*
Age		
Median	54.8	57.0
Range	23.4–71.0	33.0–70.8
Q1-Q3	47.3–62.0	50.0–63.2
< = 50 years old	1647 (34.1)	121 (24.8)
> 50 years old	3179 (65.9)	366 (75.2)
Menopausal status		
Premenopausal	1794 (37.2)	144 (29.6)
Postmenopausal	2859 (59.2)	323 (66.3)
Missing	173 (3.6)	20 (4.1)
WHO performance status		
0	4627 (95.9)	470 (96.5)
1	198 (4.1)	16 (3.3)
2	1 (0.0)	1 (0.2)
Lymph node status		
Node negative	3789 (78.5)	397 (81.5)
1 positive LN	695 (14.4)	66 (13.6)
2 positive LN	223 (4.6)	14 (2.9)
3 positive LN	115 (2.4)	10 (2.1)
> 3 positive LN	4 (0.1)	0 (0.0)
Type of breast cancer surgery performed		
Breast conserving surgery	4030 (83.5)	331 (68.0)
Mastectomy	796 (16.5)	156 (32.0)
Lymph node resection procedure		
Full axillary dissection	1589 (32.9)	172 (35.3)
Sentinel lymph node sampling	3237 (67.1)	315 (64.7)
Pathological tumor size		
< = 1 cm	655 (13.6)	46 (9.4)
1–2 cm	2863 (59.3)	241 (49.5)
2–5 cm	1278 (26.5)	172 (35.3)
. > 5 cm	30 (0.6)	28 (5.7)
ER (central pathology) cut at 1 %		
-	594 (12.3)	6 (1.2)
+	4230 (87.7)	481 (98.8)
Missing	2 (0.0)	0 (0.0)
PgR (central pathology) cut at 1 %		
-	971 (20.1)	46 (9.4)
+	3849 (79.8)	438 (89.9)
Missing	6 (0.1)	3 (0.6)
HR status (pathology)		
Negative (Both ER and PgR -)	579 (12.0)	6 (1.2)
Positive (ER and/or PgR +)	4245 (88.0)	481 (98.8)
Missing	2 (0.0)	0 (0.0)
HER2 status (central pathology)		
-	4287 (88.8)	469 (96.3)
+	510 (10.6)	17 (3.5)
Missing	29 (0.6)	1 (0.2)
Ki67 (central pathology) cut at 14 % and 20 %		
. < 14 %	1425 (29.5)	264 (54.2)
14 % - < 20 %	1181 (24.5)	140 (28.7)
20 % - 100 %	2206 (45.7)	80 (16.4)
Missing	14 (0.3)	3 (0.6)
Histological grade (central pathology)		
1	973 (20.2)	82 (16.8)
2	2609 (54.1)	379 (77.8)
3	1234 (25.6)	26 (5.3)
Missing	10 (0.2)	0 (0.0)
Risk (clinical/genomic)		
cL/gL	1890 (39.2)	223 (45.8)
cL/gH	454 (9.4)	30 (6.2)
cH/gL	1048 (21.7)	185 (38.0)
cH/gH	1434 (29.7)	49 (10.1)
Clinical risk		
Low risk	2344 (48.5)	253 (52.0)
High risk	2482 (51.4)	234 (48.0)
Genomic risk		
Low risk	2938 (60.9)	408 (83.8)
High risk	1888 (39.1)	79 (16.2)
Radiotherapy received		
No	580 (12.0)	90 (18.5)
Yes	4205 (87.1)	392 (80.5)
Missing	41 (0.8)	5 (1.0)
Local treatment (surgery +- RT)		
Breast conserving only	34 (0.7)	2 (0.4)
Breast conserving + RT	3968 (82.2)	326 (66.9)
Mastectomy only	546 (11.3)	88 (18.1)
Mastectomy + RT	237 (4.9)	66 (13.6)
Breast conserving (RT unknown)	28 (0.6)	3 (0.6)
Mastectomy (RT unknown)	13 (0.3)	2 (0.4)
Adjuvant chemotherapy received		
No	2635 (54.6)	337 (69.2)
Yes	2176 (45.1)	149 (30.6)
Missing	15 (0.3)	1 (0.2)
Adjuvant endocrine therapy received		
No	1000 (20.7)	51 (10.5)
Yes	3777 (78.3)	429 (88.1)
Missing	49 (1.0)	7 (1.4)

Abbreviations: NST, invasive breast cancer of no special type; **ILC,** Invasive Lobular Carcinoma; **LN,** lymph nodes; **ER,** estrogen receptor; **PgR,** progesterone receptor; RT, radiotherapy.

population a higher proportion of ILC patients as compared to the NST patients, is 70-gene signature low risk.

Our study is one of the first reports coming from a prospective phase III study demonstrating the prognostic utility of a genomic signature for patients diagnosed with early-stage ILC. It however has some limitations inherent to its exploratory nature, small numbers within the subsets of ILC, and the inability to answer the benefits of chemotherapy by genomic subsets.

One of the strengths of this study was the central pathology review of histological subtypes. This highlighted the possible overdiagnosis of ILC by local pathologists, as only 60.4 % of the patients diagnosed with ILC locally had the lobular diagnosis confirmed by central pathology. These results are in line with those reported by Christgen and colleagues [19] in the West German Study Group PlanB trial. We emphasize the need to harmonize and standardize ILC diagnosis [20].

Since the central pathology review also included the determination of the ILC subtype, we could investigate risk stratification according to the 70-gene signature for classic ILC and ILC variants. In the subset of classic ILC, the 70-gene signature classified 10.2 % of tumors as high-risk. This is particularly important as classic ILC tumor is enriched for features indicating favorable biology (e.g., low to intermediate histologic grade) posing challenges to risk stratification using clinicopathologic features. Moreover, the classification of 23 % of ILC variants as high genomic risk is equally important [11,21]. Our observations are in line with those from Christgen and colleagues [19] regarding the Oncotype DX recurrence score in the West German Study Group PlanB trial. Similarly, the genomic risk stratification for ILC and ILC variants was also evaluated in a retrospective series using the Genomic Grade Index (GGI) assay. The GGI assay classified 16 % of classic ILC and 27 % of pleomorphic ILC tumors as high genomic risk with inferior survival outcomes [22]. Less common variants of ILC such as pleomorphic ILC and solid ILC are associated with poor prognostic features and inferior survival outcomes when compared to classic ILC [4,11,12,22]. Altogether, these observations point to the importance of reporting on the ILC subtype in pathology reports.

The prognostic utility of the 70-gene signature for patients diagnosed with ILC was previously evaluated in a retrospective series with a total of 217 ILC tumors with inferior outcomes in the subset classified as 70-gene signature high-risk [23,24].

In the current study, patients diagnosed with ILC and NST had similar survival estimates when matched by the 70-gene genomic risk. The survival outcomes were similar when focusing on DMFS, the primary endpoint of MINDACT, but the same was observed for DFS and OS.

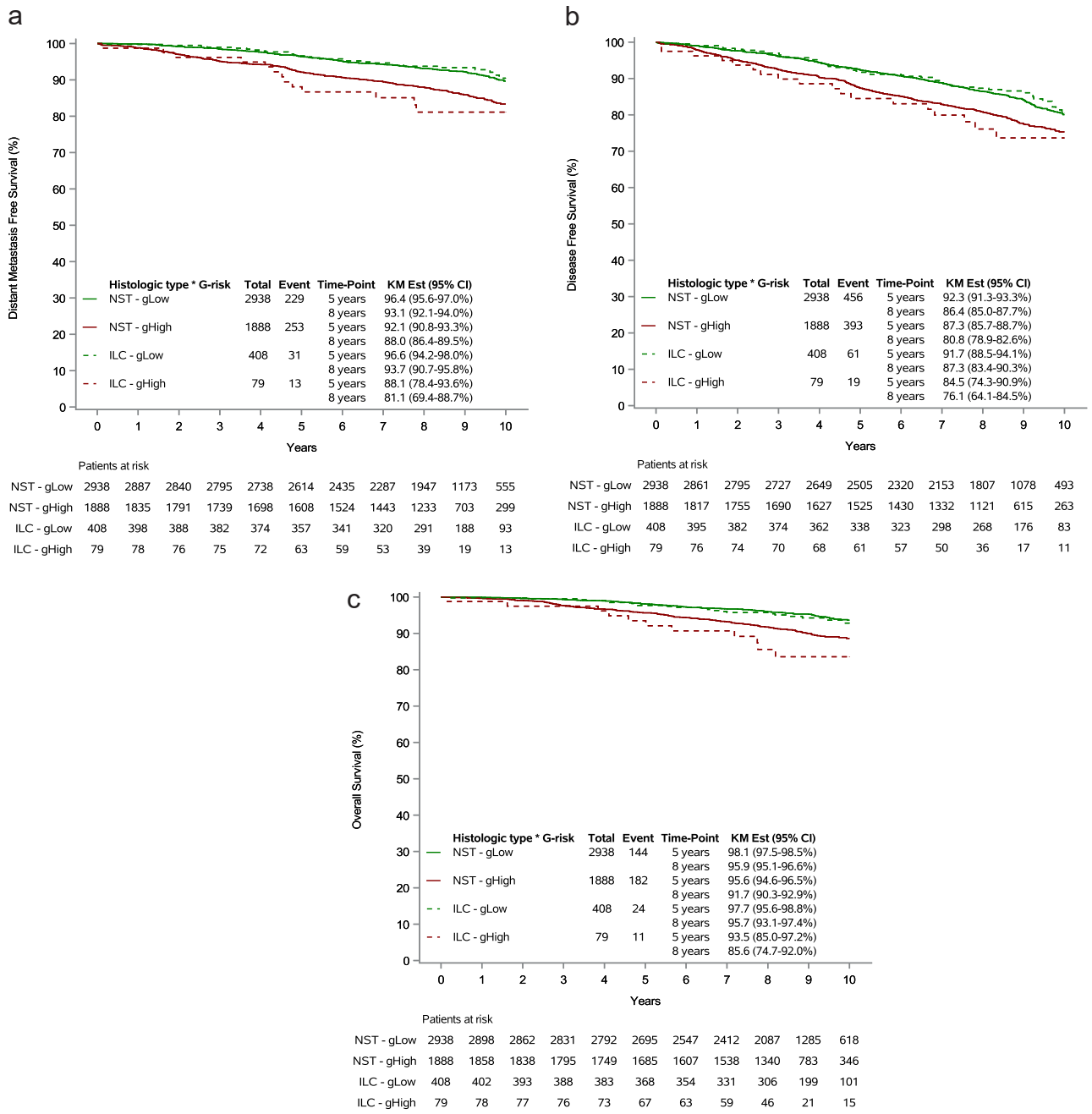

Fig. 2. DMFS, DFS and OS by histologic type and genomic risk. a. DMFS by histologic type and genomic risk. b. DFS by histologic type and genomic risk. c. OS by histologic type and genomic risk. **Abbreviations: DMFS,** Distant Metastasis-Free Survival; **DFS,** Disease-Free Survival; **OS,** Overall Survival.

Of relevance, clinical risk stratification at baseline was well balanced for ILC and NST subsets facilitating the interpretation of our survival analyses (Table 2). It also shows that 18.5 % of ILC patients had 1–3 node-positive disease of whom the majority has one positive node (similar to 21.5 % NST), and that 41.1 % of ILC had a tumor size over 2 cm (as expected a higher proportion than 27 % as seen in NST), implying that the 70-gene signature also holds prognostic value for these patients with somewhat higher stage ILC.

Our analyses were conducted using the updated results from MINDACT with 5-year follow-up information available for over 90 % of the study population. The mature follow-up information in the initial 5 years provides us with critical insights for a careful discussion about risk stratification and treatment decisions. The median follow-up of 8.7 years (IQR 7.8 – 9.7) allowed us to investigate risk of relapse beyond 5 years (i.e., late relapse), an important factor when evaluating survival outcomes in the subset of ILC, considering the propensity for late relapse, although our evaluation beyond 10 years is currently sparse [25]. While we were not able to investigate chemotherapy treatment benefit by genomic subsets due to small numbers in each subgroup, there are important observations to be made. As previously demonstrated, the clinical utility of the 70-gene signature is depicted by its ability to identify favorable long-term DMFS among patients diagnosed with high-clinical risk, but low genomic risk [18]. In our study, and despite the limited numbers, the 70-gene signature appeared to have a similar prognostic performance for patients diagnosed with ILC, which could imply that those with a 70-gene low-risk signature could consider to forego chemotherapy regardless of clinical risk. While it is tempting to imply that patients diagnosed with ILC and high genomic risk should benefit from chemotherapy, our results do not support such conclusion due to limited statistical power to compare outcomes in patients with ILC treated or not

with adjuvant chemotherapy. It is important to note that a prospective, randomized clinical trial to evaluate the benefits of adjuvant chemotherapy for patients diagnosed with ILC may not be feasible. Patients and providers may be unlikely to support a study where patients diagnosed with ILC and high genomic risk would be randomized to adjuvant chemotherapy vs. not. Hence, 70-gene signature testing for ILC tumors may inform clinical practice, by providing clinicians and patients with prognostic information that could facilitate treatment decisions.

Retrospective population-based series with large number of participants such as the Netherlands Cancer Registry (n = 3685 patients) [26], the California Cancer Registry (n = 4095 patients) [27], and the SEER database [28] reported on the lack of benefit with adjuvant chemotherapy for patients diagnosed with ILC. These were followed more recently by a systemic literature review and meta-analysis (n = 38,387 patients) on adjuvant chemotherapy in ILC [29], and an Oxford meta-analysis (n = 37298 patients) for dose-dense chemotherapy regimens [30], where neither found significant benefit of adjuvant chemotherapy. Looking into specific groups of ILC, a survival advantage of adjuvant chemotherapy was identified in high-risk, ER-positive, HER2-negative ILC (defined as having either macroscopic lymph node involvement, or a tumor size >20 mm and lymphovascular invasion), but not in low-risk ILC [31,32]. The benefit of chemotherapy in these studies, as well as other specific subsets of ILC was comprehensively summarized in a review paper by van Baelen et al, concluding that there is a subset of patients with high-risk ILC who could benefit from chemotherapy [33].

Several smaller studies to date have evaluated prognostic test, mostly Oncotype and MammaPrint, for their prognostic and predictive ability [33]. In a retrospective series from SEER including patients diagnosed with ILC and available Oncotype DX Recurrence Score (RS), the authors reported on a significant association between RS and OS, but failed to demonstrate benefits with adjuvant chemotherapy within the subset of patients with high RS tumors [34]. The small number of ILC tumors classified as high-risk and the favorable long-term prognosis within this subset limit the interpretation of the results.

The prognostic utility of RS was evaluated in a retrospective analysis of the West German Study Group PlanB trial [19]. The study included 353 (14 %) patients diagnosed with ILC and 2332 (86 %) with non-ILC assessed by central pathology review of histological subtypes. RS classified 20 %, 72 % and 8 % of the ILC tumor as low-, intermediate and high-RS, respectively. In a multivariate analysis, the subset of ILC tumors classified as high-RS, had a non-significant trend towards inferior 5-year DFS. Moreover, additional retrospective series reported on significant associations between genomic risk assessment and outcomes for patients diagnosed with ILC, including PAM50 [35], Endopredict [36] and Breast Cancer Index [37].

The incidence of discordant clinical and genomic risk in patients with invasive lobular or ductal carcinoma of the breast and its impact on prognosis and chemotherapy benefit was studied for MammaPrint in a National Cancer Database Study (n = 1497 patients) [38]. This registry study did not reveal a chemotherapy benefit for ILC patients with genomic high-risk features, though numbers are low and patients were not randomized for such treatment.

It is important to note that, so far, no data exist suggesting that ILC classified as high genomic risk, through any of the available genomic signatures, has a better response to chemotherapy. Likewise, no data support the decision to withhold chemotherapy in ILC based exclusively on genomic risk results. No available genomic test has demonstrated clinical utility for chemotherapy-decision making for ILC, specifically for ILC, but as reported here, patients diagnosed with ILC were included in the seminal phase III studies.

5. Conclusion

Our findings indicate the prognostic value of the 70-gene signature among patients diagnosed with early stage ILC. There are three important messages to inform practice from this study. First, the 70-gene signature classified 16 % of ILC tumors as high-genomic risk, reflecting worse survival outcomes. Second, patients diagnosed with ILC, and NST had similar long-term survival outcomes when matched by the 70-gene signature genomic risk. Third, our data do not indicate nor rule out a potential benefit for adjuvant chemotherapy for the subset of patients diagnosed with ILC and genomic risk high.

In summary, the prognostic information obtained with the 70-gene signature may be useful for prognostication and adjuvant therapy treatment decisions for patients diagnosed with ILC.

Funding

The current study was funded by the Breast Cancer Research Foundation (BCRF). The funders did not play a role in designing the study or in the research.

Author Contributions

OMF, FC, CD, SL, JW, BV served as members of the MINDACT lobular cancer working group. BV was the lead pathologist and LJV was the lead scientist of the trial. MP, FC and ER were the study coordinators of the EORTC 10041/ BIG 3-04 trial, and SD, JYP, EB, SA, PAN, ER, and MP represented top recruiting centers for the trial. OMF, FC, CD, SL, JW, BV, CP, FH and LJV designed this study. CP prepared the statistical analyses, figures and tables. All authors contributed to data interpretation, manuscript writing, have given final approval for publication and are accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **FC** reports consulting roles for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, and Touchime. **LJV** reports stock ownership and part-time employment with Agendia N.V. **GV** reports institutional and research support from Roche/Genentech, Ventana Medical Systems, and Dako/Agilent Technologies; and honoraria or consulting fees from Ventana, Dako/Agilent, Roche, MSD Oncology, AstraZeneca, Daiichi-Sankyo, Pfizer, and Eli Lilly. **OMF** reports Honoraria from Merck, AstraZeneca, Consulting or Advisory Role for Grupo Oncoclinicas, Research Funding from Pfizer (Inst), Roche/Genentech (Inst), Travel, Accommodations, Expenses from Grupo Oncoclinicas. **MP** reports invited speaker for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche- Genentech; consultant for Roche-Genentech; advisory board for Frame Therapeutics, Gilead, Menarini, NBE Therapeutics, Odonate, Roche- Genentech, SeaGen, Seattle Genetics; member of boards of directors, scientific board for Oncolytics; research grants to her Institution from AstraZeneca, Lilly, Gilead; funding to her Institution from Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon. All remaining authors have declared no conflicts of interest.

Acknowledgements

We are grateful to all patients and families who participated in this study.

The MINDACT trial was supported by grants from the European Commission Sixth Framework Programme (FP6-LSHC-CT-2004–503426, to the TRANSBIG Network of Excellence), the Breast Cancer Research Foundation, Novartis, F Hoffmann-La Roche, Sanofi-Aventis, Eli Lilly, Veridex, the European Breast Cancer Council–Breast Cancer Working Group (grant for the MINDACT biobank), the

Jacqueline Seroussi Memorial Foundation for Cancer Research (2006 JSMF Award), Prix Mois du Cancer du Sein (2004 award), Susan G Komen for the Cure (SG05–0922–02), Fondation Belge contre le Cancer (SCIE 2005–27), Dutch Cancer Society, the Netherlands Genomics Initiative–Cancer Genomics Center (2008–2012), Association le Cancer du Sein, Parlons-en!, the Brussels Breast Cancer Walk-Run and the American Women's Club of Brussels, NIF Trust, German Cancer Aid, the Grant Simpson Trust and Cancer Research UK, Ligue Nationale contre le Cancer, and the EORTC Cancer Research Fund. Whole-genome analysis was provided by Agendia without cost. We are grateful to the European Commission Sixth Framework Programme (FP6-LSHC-CT-2004–503426), the European Community Seventh Framework Programme (HEALTH-F2–2009–223175 to the Collaborative Oncological Gene-environment Study), BIG, F Hoffmann-La Roche, Novartis, Sanofi-Aventis, for supporting this independent EORTC study. Special thanks to: all national coordinating centres and BIG groups participating in MINDACT (BOOG, EORTC-BCG, GOIRC, NCRI-BCSG, SOLTI, UNICANCER-UCBG, WSG); steering committee members: William Audeh, Jan Bogaerts, Etienne Brain, Fatima Cardoso, Isabelle Daissormont, Suzette Delaloge, Mauro DeLorenzi, Aleksandra Dudek-Peric, Debora Fumagalli, Florentine Hilbers, Susan Knox, Sherko Kümmel, Michał Ławniczak, Helene Manduzio, Erika Matos, Sonia Pernas Simon, Martine Piccart, Coralie Poncet, Jolanda Remmelzwaal, Isabel Rubio, Emiel Rutgers, Christos Sotiriou, Alastair Thompson, Renata Todeschini, Laura van 't Veer, Giuseppe Viale, Khalil Zaman, Gabriele Zoppoli; EORTC and BIG teams: Livia Meirsman, Leen Slaets and Carolyn Straehle; all the many academic institutions and collaborators participating in TRANSBIG as well as the scientific or logistical support from Guus Hart, Femke de Snoo, Lisette Stork-Sloots, and Marc Buyse. In addition, we recognise the important contributions on protocol development, study conduct, and data management of BIG and EORTC Teams and Fellows, as well as all clinical principal investigators at the participating hospitals.

Previous presentation

This research was partially presented at the 12th European Breast Cancer Conference, October 2–3, 2020 (virtual).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115222.

Data availability

The MINDACT dataset with patient characteristics and clinical outcomes is available through the European Organisation for Research and Treatment of Cancer EORTC (www.eortc.org/data-sharing/). Following a successful data request procedure, the EORTC can share all or a selection of the clinical–pathological or full-transcriptome data for translational research.

References

[1] Li CI, Anderson BO, Daling JR, et al. Trends in incidence rates of invasive lobular and ductal breast carcinoma. JAMA 2003;289(11):1421–4.
[2] Arpino G., Bardou V., Clark G. et al. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. 6. 2004:R149 - R156.
[3] Desmedt C, Zoppoli G, Gundem G, et al. Genomic characterization of primary invasive lobular breast cancer. J Clin Oncol 2016.
[4] Weigelt B., Geyer F.C., Natrajan R. et al. The molecular underpinning of lobular histological growth pattern: a genome-wide transcriptomic analysis of invasive lobular carcinomas and grade- and molecular subtype-matched invasive ductal carcinomas of no special type. J Pathol; 220 (1): 45-57.
[5] McCart Reed AE, Lal S, Kutasovic JR, et al. LobSig is a multigene predictor of outcome in invasive lobular carcinoma. NPJ Breast Cancer 2019;5:18.
[6] Bertucci F, Orsetti B, Negre V, et al. Lobular and ductal carcinomas of the breast have distinct genomic and expression profiles. Oncogene 2008;27(40):5359–72.
[7] Ciriello G, Gatza ML, Beck AH, et al. Comprehensive molecular portraits of invasive lobular breast cancer. Cell 2015;163(2):506–19.
[8] Michaut M, Chin SF, Majewski I, et al. Integration of genomic, transcriptomic and proteomic data identifies two biologically distinct subtypes of invasive lobular breast cancer. Sci Rep 2016;6:18517.
[9] Katz A, Saad ED, Porter P, et al. Primary systemic chemotherapy of invasive lobular carcinoma of the breast. Lancet Oncol 2007;8(1):55–62.
[10] Van Baelen K, Geukens T, Maetens M, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol 2022;33(8):769–85.
[11] Iorfida M, Maiorano E, Orvieto E, et al. Invasive lobular breast cancer: subtypes and outcome. Breast Cancer Res Treat 2012;133(2):713–23.
[12] Middleton LP, Palacios DM, Bryant BR, et al. Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol 2000;24(12):1650–6.
[13] Lips EH, Mukhtar RA, Yau C, et al. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. Breast Cancer Res Treat 2012;136(1):35–43.
[14] Cocquyt VF, Blondeel PN, Depypere HT, et al. Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. Eur J Surg Oncol 2003;29(4):361–7.
[15] Tubiana-Hulin M, Stevens D, Lasry S, et al. Response to neoadjuvant chemotherapy in lobular and ductal breast carcinomas: a retrospective study on 860 patients from one institution. Ann Oncol 2006;17(8):1228–33.
[16] Delpech Y, Coutant C, Hsu L, et al. Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas. Br J Cancer 2013;108(2):285–91.
[17] Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375(8):717–29.
[18] Piccart M, Van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 2021;22(4):476–88.
[19] Christgen M, Gluz O, Harbeck N, et al. Differential impact of prognostic parameters in hormone receptor-positive lobular breast cancer. Cancer 2020;126(22):4847–58.
[20] De Schepper M, Vincent-Salomon A, Christgen M, et al. Results of a worldwide survey on the currently used histopathological diagnostic criteria for invasive lobular breast cancer. Mod Pathol 2022;35(12):1812–20.
[21] Tadros AB, Wen HY, Morrow M. Breast cancers of special histologic subtypes are biologically diverse. Ann Surg Oncol 2018;25(11):3158–64.
[22] Metzger-Filho O, Michiels S, Bertucci F, et al. Genomic grade adds prognostic value in invasive lobular carcinoma. Ann Oncol 2013;24(2):377–84.
[23] Beumer IJ, Persoon M, Witteveen A, et al. Prognostic value of MammaPrint((R)) in invasive lobular breast cancer. Biomark Insights 2016;11:139–46.
[24] Jenkins JA, Marmor S, Hui JYC, et al. The 70-gene signature test as a prognostic and predictive biomarker in patients with invasive lobular breast cancer. Breast Cancer Res Treat 2022;191(2):401–7.
[25] Pestalozzi BC, Zahrieh D, Mallon E, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol 2008;26(18):3006–14.
[26] Truin W, Voogd AC, Vreugdenhil G, et al. Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer. Ann Oncol 2012;23(11):2859–65.
[27] Marmor S, Hui JYC, Huang JL, et al. Relative effectiveness of adjuvant chemotherapy for invasive lobular compared with invasive ductal carcinoma of the breast. Cancer 2017;123(16):3015–21.
[28] Hu G, Hu G, Zhang C, et al. Adjuvant chemotherapy could not bring survival benefit to HR-positive, HER2-negative, pT1b-c/N0-1/M0 invasive lobular carcinoma of the breast: a propensity score matching study based on SEER database. BMC Cancer 2020;20(1):136.
[29] Trapani D, Gandini S, Corti C, et al. Benefit of adjuvant chemotherapy in patients with lobular breast cancer: a systematic review of the literature and metanalysis. Cancer Treat Rev 2021;97:102205.
[30] Early Breast Cancer Trialists' Collaborative G. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet 2019;393(10179):1440–52.
[31] de Nonneville A, Jauffret C, Goncalves A, et al. Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit. Breast Cancer Res Treat 2019;175(2):379–87.
[32] Tamirisa N, Williamson HV, Thomas SM, et al. The impact of chemotherapy sequence on survival in node-positive invasive lobular carcinoma. J Surg Oncol 2019;120(2):132–41.
[33] Van Baelen K, Geukens T, Maetens M, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol 2022;33(8):769–85.
[34] Kizy S, Huang JL, Marmor S, et al. Impact of the 21-gene recurrence score on outcome in patients with invasive lobular carcinoma of the breast. Breast Cancer Res Treat 2017;165(3):757–63.
[35] Laenkholm AV, Jensen MB, Eriksen JO, et al. Population-based study of prosigna-PAM50 and outcome among postmenopausal women with estrogen receptor-positive and HER2-negative operable invasive lobular or ductal breast cancer. Clin Breast Cancer 2020;20(4):e423–32.

[36] Sestak I, Filipits M, Buus R, et al. Prognostic value of endopredict in women with hormone receptor-positive, HER2-negative invasive lobular breast cancer. Clin Cancer Res 2020;26(17):4682–7.
[37] Nunes R, Sella T, Treuner K, et al. Prognostic utility of breast cancer index to stratify distant recurrence risk in invasive lobular carcinoma. Clin Cancer Res 2021;27(20):5688–96.
[38] Abel MK, Shui AM, Melisko M, et al. The incidence of discordant clinical and genomic risk in patients with invasive lobular or ductal carcinoma of the breast: a National Cancer Database Study. NPJ Breast Cancer 2021;7(1):156.