Comparison of long-term outcome between clinically high risk lobular versus ductal breast cancer: a propensity score matched study

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Summary

Background Abemaciclib is currently approved for the adjuvant treatment of high-risk, lymph node (LN)-positive, hormone receptor (HR)-positive breast cancer (BC). In a real-world setting the clinicopathologic features of patients potentially eligible for adjuvant abemaciclib remain to be defined. There are conflicting data regarding the biological behavior and long-term outcomes across invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). In our study we retrospectively assessed the real-world data and long-term outcome of selected high-risk features ILC compared to IDC, according to the MonarchE trial inclusion criteria.

Methods We identified 15,071 patients who got surgery at the European Institute of Oncology for a first primary, non-metastatic, HR-positive, HER2-negative BC from 2000 to 2008. 11,981 (79.5%) patients had an IDC and 1524 (10.1%) an ILC. The remaining 1566 patients (10.4%) had either combined ductal and lobular breast cancer or another histological breast cancer subtype. According to the eligibility criteria of the MonarchE study, we identified two high-risk groups, based on high number of positive lymph nodes, large tumor size, or a high cellular proliferation as measured by tumor grade or biomarkers. Patients were matched by propensity score.

Findings A total of 2872 (21.3%) patients were selected as clinically high-risk, including 361/1524 ILC (23.7%) and 2511/11,981 IDC (21%). 322 high-risk ILC were matched with similar high-risk IDC. The median follow-up was 13.2 years for survival. In the matched set, invasive disease-free survival (IDFS) (log-rank P = 0.09) and overall survival (OS) (log-rank P = 0.48) were not statistically significantly different between the two histological groups. For IDC patients, the 5-year and 10-year IDFS rates (95% CI) were 77.7% (72.9–82.2) and 57.3% (51.7–63.1) respectively, compared to the 5-year and 10-year IDFS rates of ILC patients that were 75.5% (70.6–80.2) and 50.7% (45.0–56.6). The 5-year and 10-year distant relapse free survival (DRFS) rates were 80% (75.3–84.2) and 65.3% (59.8–70.7) in IDC cohort, compared to the 5-year and the 10-year DRFS rates of 78.7% (74.0–83.1) and 61.5% (55.9–67.1) in the ILC cohort. Such data match the recent outcomes efficacy results of the MonarchE control arm. More patients in the ILC (n = 17) than in the IDC group (n = 10) developed axillary recurrence. At multivariable analysis, stratified for specific clinical features, age <35 years, pT2-3, axillary involvement with more than 10 positive axillary nodes were found to be predictors of unfavorable IDFS and OS in the overall matched high-risk population.

Interpretation Findings from this matched cohort study reported similar IDFS and DRFS rates for high risk HR positive early BC when compared to the control arm overall IDFS and DRFS rates reported from the MonarchE trial. Our study demonstrated rates of concordant long-term outcome status beyond histologic subtype. These data support

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an escalation strategy for these two different histological entities when diagnosed with high-risk features. In our dataset approximately 21% rate of high-risk HR positive early BC patients are potentially eligible for adjuvant abemaciclib treatment.

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Keywords: Invasive lobular breast cancer; Invasive ductal breast cancer; Abemaciclib; MonarchE trial; Recurrence

Research in context

Evidence before this study

Abemaciclib is currently approved for the adjuvant treatment of high recurrence risk, lymph node-positive, hormone receptor (HR)-positive breast cancer (BC). There are conflicting data regarding the biological behavior and long-term outcomes across invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). We searched PubMed for English-language research articles published before 2 November 2023 using "invasive ductal breast cancer", "invasive lobular breast cancer", "comparison", "abemaciclib", "MonarchE", "outcome" as search terms. Long-term data validated the persistent and strong benefit of adjuvant abemaciclib for clinically high-risk, HR-positive, HER2 negative BC in term of invasive disease-free survival (IDFS) and distant-recurrence free survival (DRFS). However, the real-world proportion and clinicopathologic features of patients potentially eligible for adjuvant abemaciclib is currently object of research. Furthermore, comparison about management and outcome between IDC and ILC patients report inconclusive and heterogeneous findings. All these considerations could affect a proper clinical management of such women. To our knowledge, a real-world data on long-term outcome of clinically high-risk IDC patients compared to analogue ILC patients might reinforce available evidence of abemaciclib benefit and explore the role of histotype in influencing prognosis of such patients.

Added value of this study

This matched cohort study reported similar IDFS and DRFS rates for clinically high risk HR positive early BC, when compared to the control arm overall IDFS and DRFS rates, documented from the MonarchE trial. Long-term outcome rates did not differ based on histologic subtypes, supporting the use of abemaciclib for such patients with both IDC and ILC. Our real-world findings revealed the prognostic value of distinctive high-risk clinical and pathological features compared to intrinsic histological type.

Implications of all the available evidence

Treatment of HR positive Her2 negative ILC patients with high prognostic risk should not differ from that of IDC patients, selected with the same MonarchE criteria.

Introduction

Invasive lobular carcinoma (ILC) is the second most common histological special subtype of breast cancer (BC), accounting for 5%–15% of all breast cancers.[1,2]

It is characterized by a peculiar morphological pattern and clinical research is increasingly recognizing that it has distinct clinical, pathologic, molecular, and biological characteristics compared with invasive ductal cancer (IDC).[1–7]

The association with its encoding gene *CDH1* inactivation, translating in the lack of intercellular adhesion tumor and in a cancer morphology in which cells invade tissues in a chain-like single-file manner, due to the loss of E-cadherin expression, is distinctive of ILC.[8,9] This unique growth pattern is therefore characterized by greater difficulties in imaging detection, determining a higher stage of disease at diagnosis, which are correlated with more frequent multifocality, and consequent superior rates of mastectomies.[10] ILC is also predominantly hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2) negative, presenting low grade and proliferative index.[10,11]

Although these tumor characteristics are generally associated with a favorable prognosis, ILC has a higher risk of late distant recurrence and may exhibit aggressive metastatic behavior associated with worse long-term outcomes than IDC at the same stage[12–17] (Supplementary Table S1).

Indeed, ILC represents a clinical challenge compared to IDC, and research is dedicating its efforts to study the biological heterogeneity of the ILC in order to identify personalized paradigms of long-term treatment and management of the disease.[10,18–21]

Current clinical practice guidelines anyway recommend similar treatment approaches for both histological subtypes.[22]

A current and lively research area is investigating the management of patients affected by hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2) negative BC generally treated with endocrine

therapy yet presenting a likelihood of recurrence due to peculiar clinical and pathological features. Several recent clinical trials were designed to treat patients at high risk of recurrence, studying the combination of new adjuvant treatments to current standard-of-care adjuvant endocrine for patients with HR positive, HER2 negative BC.[23–29]

Novel treatment strategies included CDK4 and CDK6 inhibitors,[23] a mainstay of treatment for HR positive HER-2 negative, node-positive early high-risk BC. *High risk* was defined "by a compilation of clinical and pathologic factors including nodal status, tumor size, grade, and a marker of cellular proliferation (Ki-67)".[23] Indeed, findings of the monarchE trial[30] have recently provided systemic therapy recommendations for such BC patients. Recent published long-term monarchE trial data has globally confirmed the advantage of adjuvant abemaciclib added to endocrine therapy in HR positive HER2 negative high-risk BC patients, represented by the increase in absolute invasive disease-free survival and distant relapse-free survival benefit at 4 years.[30]

To date, the frequency of patients with BC potentially eligible for abemaciclib treatment is not clear, as well as the data on the prognosis of ILCs compared to IDCs are conflicting (Supplementary Table S1): hence, the main purpose of this study is to quantify the characteristics and long-term outcomes of a real-world high-risk population according to monarchE trial criteria, comparing ILC to IDC cohorts.

Methods

Study design and patients

We retrospectively analyzed a cohort of patients who received treatments for invasive BC at the European Institute of Oncology (IEO) between January 1, 2000, and December 31, 2008.

HER2 was not routinely assessed before 2000, therefore we limited the study to 15,071 patients operated at the IEO for a first primary, non-metastatic, HR-positive, HER2-negative BC during such period.

We identified two ER positive HER2 negative groups defined in this specific context clinically "*high-risk*", since considered to have high-risk disease based on the criteria used in the MonarchE trial (Fig. 1, Table 1).[30]

Indeed, the trial used distinct criteria to define high-risk and indicate the use of abemaciclib, including large (>T2) or high-grade (Grade 3) tumors with at least one positive axillary lymph-node, as well as at least four positive nodes (N2 node status), irrespective of the grade or the tumour size.[31]

Group 1: Patients with ≥4 positive axillary lymphnodes (ALN) or with 1–3 positive ALN and either poorly differentiated tumor (histologic grade G3) or large tumor (≥5 cm).

Group 2: Patients with 1–3 positive ALN and Ki-67 ≥ 20% and G1-2 tumor and tumor size <5 cm.

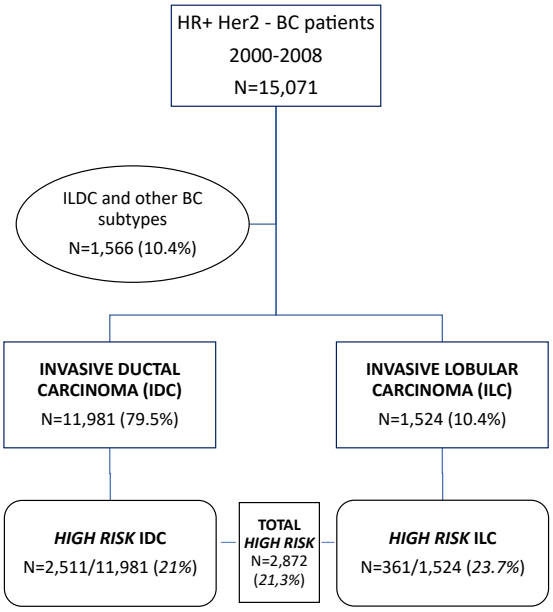

***Fig. 1:* Flow-chart of patients included in the study**. HR+: hormonal receptor positive; Her2-: human epidermal growth factor receptor-2 negative; ILDC: combined invasive ductal and lobular breast cancer.

Women who either received neoadjuvant treatment or presented with metastatic breast disease at the time of admission or within 3 months after surgery, with triple negative and HER-2 positive BC were excluded. Information about any pathogenic germline mutation is missing in the overall cohort.

Ethics statement

All patients gave informed consent. The study was approved in accordance with the 1964 Helsinki Declaration and its later amendments and it has been approved and authorized by the Institutional Review Board (code authorization number: UID 3556). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[32]

Clinical data and outcomes

We limited our analysis to patients with invasive HR-positive and HER2-negative BC. Factors considered in the analysis included lobular and ductal histotype, age at diagnosis, typology of surgery, T and N pathologic classification (updated to the seventh edition of the AJCC staging manual), concomitant in situ disease, multifocal or multicentric tumor, tumor grade, progesterone receptor (PgR) status, Ki-67 proliferative index, peritumoral vascular invasion (PVI), molecular subtype, systemic therapy, chemotherapy and radiotherapy (Table 2). Histopathological diagnosis was rendered according to World Health Organization (WHO) criteria.[33]

	Total	Ductal	Lobular	
Total	13,505 (100)	11,981 (100)	1524 (100)	
Low-risk	10,633 (78.7)	9470 (79.0)	1163 (76.3)	
High risk group 1	2221 (16.5)	1920 (16.0)	301 (19.8)	
High risk group 2	651 (4.8)	591 (4.9)	60 (3.9)	P = 0.0004
Selected for the study				
High risk	2872 (21.3)	2511 (21.0)	361 (23.7)	

Table 1: **Distribution of risk categories by histology.**

Doubtful cases were discussed collegially and, when deemed necessary, immunohistology was used.

The study endpoints included the incidence of:

- Invasive disease-free survival (IDFS) defined as time from surgery to the first occurrence of local or regional recurrence, contralateral recurrence, second primary non-breast invasive cancer, distant recurrence, or death attributable to any cause according to the STEEP criteria,
- Distant relapse free survival (DRFS) defined as time from surgery to the first occurrence of distant recurrence or death attributable to any cause,
- Ipsilateral breast tumor recurrence (IBTR) defined as the reappearance of carcinoma either at the site of the surgical intervention or as any new carcinoma appearing in the other quadrants of the same breast;
- Axillary lymph node recurrence (ALNR),
- Distant metastasis (DM),
- Contralateral BC (CBC).
- Overall survival (OS) defined from the date of surgery to death from any cause or last contact.

Breast cancer specific survival (BCSS), defined from the date of BC surgery to death attributable to BC or last follow-up, was not calculated for missing data on deaths.

Further endpoints included also the univariate and multivariable analyses of clinical features significantly involved in unfavorable outcome, which were calculated on the combined high-risk matched population.

Statistical analysis

Differences in the distribution of patients, tumors, or treatments characteristics between lobular and ductal cancer were assessed using the chi-square test for categorical variables and the Mantel Haenszel test for trend for ordinal variables. To account for differences in clinic-pathological characteristics between lobular and ductal breast cancer patients (Table 2 and Supplementary Table S2), lobular cancer patients were matched using propensity scores for monarchE criteria (high-risk group1, high-risk group2), type of surgery (breast conserving surgery, mastectomy), age group (<35, 35–49, ≥50 years), pT (pT1, pT2, pT3, pT4), pN (1–3, 4–9, ≥10 positive nodes), ER (<80%, ≥80%), tumor grade (G1, G2, G3), PVI (absent, present), Ki-67 (continuous), using Greedy Matching Techniques.[34] An equal number of patients with lobular and ductal breast cancer were selected for the matched analysis. After matching, variables were balanced with standardized difference <0.2.

The cumulative incidence of BC-related events (IBTR, ALNR, DM, CBC) was estimated using the method of Kalbfeisch and Prentice, accounting for competing events (including any first BC-related event, second non-breast cancer, and death as first event). Gray's test was used to assess differences in the cumulative incidence of specific events between the two groups. Survival plots were drawn using Kaplan–Meier methods, and the log-rank test was used to assess differences in survival between the two groups. The cumulative incidence of events and OS were assessed at 5 and 10 years of follow-up. Hazard ratios (HRs) for the development of events or death in the lobular versus the ductal cancer group were determined using univariate Cox proportional hazards regression models. Univariate and multivariable Cox proportional hazards regression stratified for age, high-risk group, Surgery, pT, pN, ER, Grade, PVI and Ki67, was also used to identify factors associated with the development of events or death in the combined matched set. The proportional hazard assumption was tested by introducing a constructed time-dependent variable and tested for its statistical significance. The assumption was met for all presented results. Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). Statistical significance was defined as 2-sided $P < 0.05$.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript and in the decision to submit the paper for publication.

FM, GCo, PM, PV and GCu have directly accessed and verified data to analyse for the study publication. All Authors agreed to submit the paper for publication.

Results

Study population

The original cohort comprised 15,071 eligible patients with BC of whom 11,981 (79.5%) patients had an invasive ductal BC (IDC), 1524 (10.1%) an invasive lobular BC (ILC). The remaining 1566 (10.4%) patients had either combined ductal and lobular breast cancer or other histological breast cancer subtype. A total of 2872 (21.3%) high-risk patients (2511 IDC and 361 ILC) were selected for the study (Fig. 1, Table 1), of which 2221 (16.5%) included in the high-risk group 1, and 651 (4.8%) in the high-risk group 2 (Tables 1 and 2). High-risk cohort includes 361/1524 ILC (23.7%) and 2511/11,981 IDC (21%). ILC presented a more increased propensity for larger T stage and extensive axillary metastases, with

	Before propensity-score matching		SMD	After propensity-score matching		SMD
	Ductal	Lobular		Ductal	Lobular	
	N (%)	N (%)		N (%)	N (%)	
Year of surgery			0.193			0.354
2000	218 (8.7)	23 (6.4)		27 (8.4)	18 (5.6)	
2001	235 (9.4)	49 (13.6)		23 (7.1)	47 (14.6)	
2002	275 (11.0)	36 (10.0)		40 (12.4)	33 (10.2)	
2003	288 (11.5)	41 (11.4)		33 (10.2)	38 (11.8)	
2004	314 (12.5)	40 (11.1)		44 (13.7)	34 (10.6)	
2005	293 (11.7)	35 (9.7)		45 (14.0)	33 (10.2)	
2006	307 (12.2)	52 (14.4)		32 (9.9)	49 (15.2)	
2007	300 (11.9)	38 (10.5)		42 (13.0)	31 (9.6)	
2008	281 (11.2)	47 (13.0)		36 (11.2)	39 (12.1)	
Age			0.343			0.195
Median [range]	49 [19–84]	52 [28–82]		52 [35–81]	52 [28–82]	
<35	166 (6.6)	4 (1.1)		0 (0.0)	4 (1.2)	
35–49	1142 (45.5)	145 (40.2)		134 (41.6)	130 (40.4)	
50–69	993 (39.5)	184 (51.0)		153 (47.5)	163 (50.6)	
70+	210 (8.4)	28 (7.8)		35 (10.9)	25 (7.8)	
High risk group[b]			0.173			0.016
Group 1	1920 (76.5)	301 (83.4)		260 (80.7)	262 (81.4)	
Group 2	591 (23.5)	60 (16.6)		62 (19.3)	60 (18.6)	
Surgery			0.291			0.031
Mastectomy	955 (38.0)	189 (52.4)		158 (49.1)	153 (47.5)	
BCS	1556 (62.0)	172 (47.6)		164 (50.9)	169 (52.5)	
pT			0.530			0.048
pT1	1066 (42.5)	105 (29.1)		100 (31.1)	105 (32.6)	
pT2	1143 (45.5)	148 (41.0)		142 (44.1)	142 (44.1)	
pT3	247 (9.8)	105 (29.1)		76 (23.6)	72 (22.4)	
pT4	38 (1.5)	3 (0.8)		4 (1.2)	3 (0.9)	
pTx	17 (0.7)	0 (0.0)				
pT (is)			0.066			0.117
Absent	2097 (83.5)	310 (85.9)		261 (81.1)	275 (85.4)	
Present	414 (16.5)	51 (14.1)		61 (18.9)	47 (14.6)	
pT (m)			0.142			0.145
Absent	1885 (75.1)	248 (68.7)		242 (75.2)	221 (68.6)	
Present	626 (24.9)	113 (31.3)		80 (24.8)	101 (31.4)	
Positive nodes			0.373			0.029
1–3	1222 (48.7)	133 (36.8)		122 (37.9)	126 (39.1)	
4–9	771 (30.7)	94 (26.0)		90 (28.0)	90 (28.0)	
10+	518 (20.6)	134 (37.1)		110 (34.2)	106 (32.9)	
Tumor grade			0.453			0.084
G1	76 (3.0)	22 (6.1)		17 (5.3)	18 (5.6)	
G2	1107 (44.1)	213 (59.0)		188 (58.4)	182 (56.5)	
G3	976 (38.9)	70 (19.4)		59 (18.3)	69 (21.4)	
Unknown	352 (14.0)	56 (15.5)		58 (18.0)	53 (16.5)	
ER status			0.170			0.015
1–80%	439 (17.5)	88 (24.4)		76 (23.6)	74 (23.0)	
≥80%	2072 (82.5)	273 (75.6)		246 (76.4)	248 (77.0)	
PgR status			0.050			0.090
Negative	361 (14.4)	56 (15.5)		60 (18.6)	51 (15.8)	
1–80%	1306 (52.0)	179 (49.6)		160 (49.7)	158 (49.1)	
≥80%	844 (33.6)	126 (34.9)		102 (31.7)	113 (35.1)	

(Table 2 continues on next page)

	Before propensity-score matching		SMD	After propensity-score matching		SMD
	Ductal	Lobular		Ductal	Lobular	
	N (%)	N (%)		N (%)	N (%)	
(Continued from previous page)						
Ki-67			0.665			0.077
<14	330 (13.1)	129 (35.7)		94 (29.2)	105 (32.6)	
14–20	272 (10.8)	66 (18.3)		53 (16.5)	53 (16.5)	
20–50	1902 (75.7)	166 (46.0)		175 (54.3)	164 (50.9)	
Unknown	7 (0.3)	0 (0.0)		0 (0.0)	0 (0.0)	
PVI			1.204			0.068
Absent	1049 (41.8)	327 (90.6)		281 (87.3)	288 (89.4)	
Present	1462 (58.2)	34 (9.4)		41 (12.7)	34 (10.6)	
Radiotherapy			0.265			0.109
None	473 (18.8)	108 (29.9)		80 (24.8)	95 (29.5)	
PBI[a]	402 (16.0)	45 (12.5)		49 (15.2)	43 (13.4)	
WBI	1587 (63.2)	203 (56.2)		189 (58.7)	180 (55.9)	
Unknown	49 (2.0)	5 (1.4)		4 (1.2)	4 (1.2)	
Systemic therapy			0.235			0.116
None	20 (0.8)	2 (0.6)		2 (0.6)	2 (0.6)	
HT only	926 (36.9)	166 (46.0)		144 (44.7)	150 (46.6)	
CT only	26 (1.0)	7 (1.9)		1 (0.3)	4 (1.2)	
Both HT + CT	1522 (60.6)	186 (51.5)		175 (54.3)	166 (51.6)	
Unknown	17 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Chemotherapy			0.181			0.105
None	952 (37.9)	168 (46.5)		146 (45.3)	152 (47.2)	
AC	991 (39.5)	118 (32.7)		120 (37.3)	106 (32.9)	
CMF	123 (4.9)	17 (4.7)		11 (3.4)	15 (4.7)	
AC + CMF	95 (3.8)	11 (3.0)		8 (2.5)	9 (2.8)	
Other	350 (13.9)	47 (13.0)		37 (11.5)	40 (12.4)	

SMD: Standardized Mean Difference; BC: breast cancer; BCS: breast-conserving surgery; MT: mastectomy; ER: estrogen receptor; PgR: progesteron receptor; PVI: peritumoral vascular invasion; is: in situ; m: multifocality; CT: chemotherapy; HT: hormone therapy; PBI: partial breast irradiation; WBI, whole-breast Irradiation. [a]ELIOT on the nipple area complex in patients who received nipple-sparing mastectomy or ELIOT on the tumor bed in patients treated with breast conserving surgery. [b]Group 1: Patients with ≥4 positive axillary lymphnodes (ALN) or with 1–3 positive ALN and either poorly differentiated tumor (histologic grade G3) or large tumor (≥5 cm); Group 2: Patients with 1–3 positive ALN and Ki-67 ≥ 20% and G1-2 tumor and tumor size <5 cm. [c]Matched for high-risk group†<, type of surgery, age-group, pT, pN, ER, tumor grade, PVI and Ki67.

Table 2: **Characteristics of high-risk patients with lobular and ductal BC, before and after propensity score matching[c].**

more than 10 positive lymph-nodes (37.1% in ILC vs 20.6 in IDC, p < 0.001) (Table 2). In both groups a low rate of patients received chemotherapy.

After propensity score matching 322 high-risk ILC were matched with similar high-risk IDC (Fig. 1, Table 2). No statistically significant differences were found between the two histotypes in terms of clinical and pathological characteristics. The frequency of aromatases inhibitors and tamoxifen use was reported in Supplementary Table S3.

Among the patients in the matched series, 80.7% of the high-risk IDC cohort resulted in the group 1, and 19.3% in the group 2. In the high-risk ILC cohort 81.4% patients resulted in the group 1 and 18.6% in the group 2 (Table 2).

Outcomes

The median observation follow-up of selected matched patients is 8.2 years for events (time to first event) and 13.2 years for survival (time to last follow-up/death).

In the matched set, there was no statistical difference in events at 10 years between the two histotypes: non-significant statistical difference was found in the 10-year cumulative incidence of IBTR (6.3%, 95% CI 3.9–9.6 for IDC vs 6.2%, 95% CI 3.8–9.4 for ILC) and DM (30.5%, 95% CI, 25.3–35.9 for IDC vs 31%, 95% CI 25.7–36.4) (Fig. 2, Table 3).

More patients in the ILC cohort (n = 17) than in the IDC cohort (n = 10) developed axillary recurrence, but the difference was not statistically significant (Gray's test P = 0.20). The 10-year cumulative incidence of ALNR was 3.8% in ILC (95% CI, 2.0–6.5) vs 2.4% (95% CI, 1.0–4.6) in IDC. Contralateral BC as well was found in 12 patients with ILC compared to 8 with IDC, but the difference was not statistically significant (Gray's test P = 0.27). The 10-year cumulative incidence of CBC was 3.3% (95% CI, 1.6–5.9) in the ILC group vs 1.4% (95% CI, 0.5–3.3) in the IDC group.

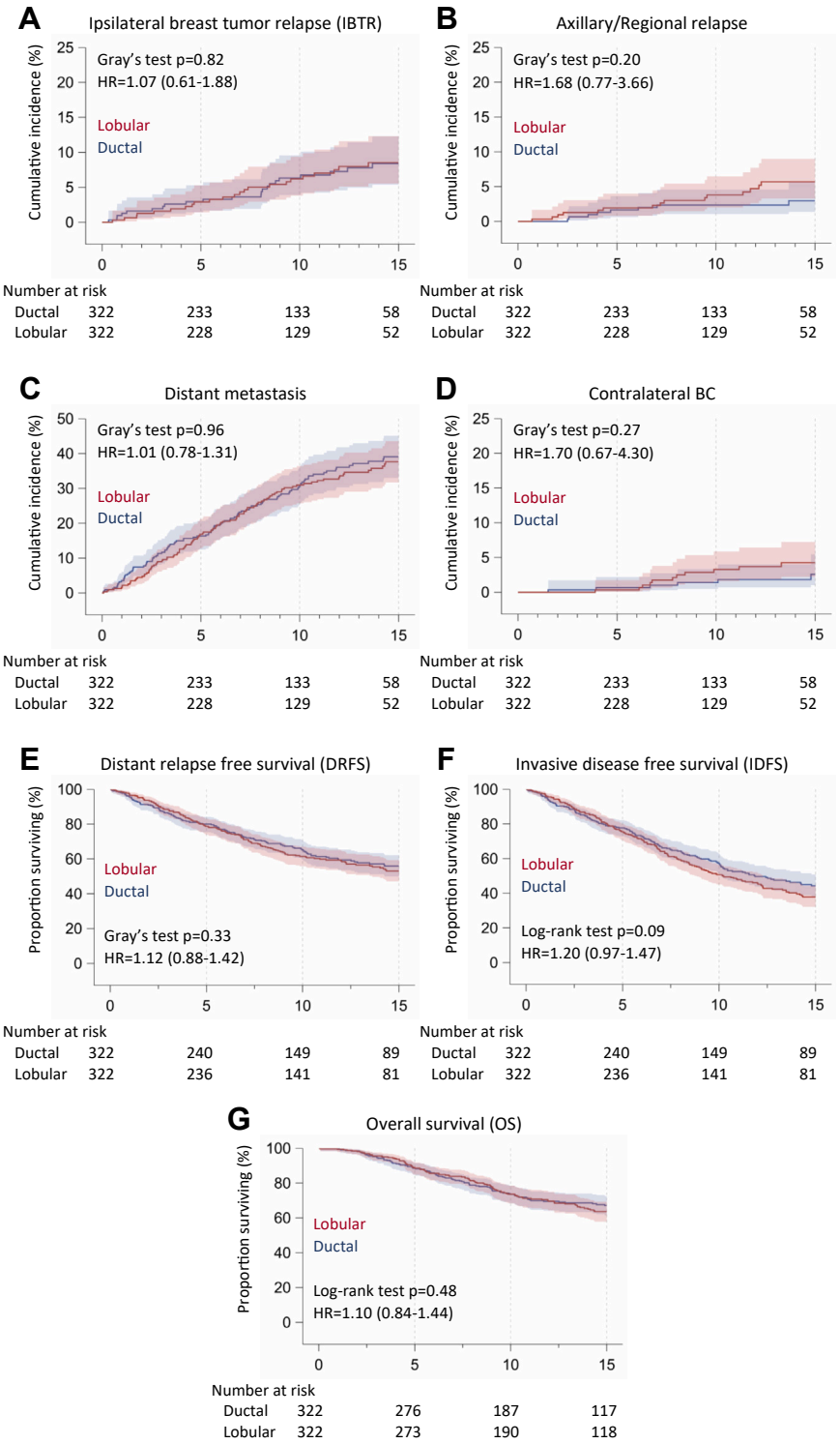

Fig. 2: Cumulative incidence of ipsilateral breast tumor relapse (A), axillary/regional relapse (B), distant metastasis (C), contralateral breast cancer (D), distant relapse free survival (E), invasive disease free survival (F) and overall survival (G) in the matched set. HR: hazard ratio.

	Ductal			Lobular			P-value
	Events	5-year percent rate (95% CI)	10-year percent rate (95% CI)	Events	5-year percent rate (95% CI)	10-year percent rate (95% CI)	
Ipsilateral breast tumor recurrence	24	2.9 (1.4–5.3)	6.3 (3.9–9.6)	25	2.9 (1.4–5.2)	6.2 (3.8–9.4)	0.82
Group 1†	17	3.2 (1.5–5.9)	5.5 (3.1–8.9)	19	3.2 (1.5–5.9)	6.3 (3.7–9.9)	0.80
Group 2†	7	1.8 (0.1–8.6)	9.9 (3.6–20.1)	6	1.7 (0.1–8.0)	5.7 (1.4–14.3)	0.93
Lymph node recurrence	10	1.7 (0.6–3.6)	2.4 (1.0–4.6)	17	1.9 (0.8–4.9)	3.8 (2.0–6.5)	0.20
Group 1†	8	1.6 (0.5–3.8)	2.1 (0.8–6.7)	15	2.4 (1.0–4.9)	3.7 (1.8–6.7)	0.16
Group 2†	2	1.8 (0.1–8.6)	3.7 (0.7–11.3)	2	0.0 (0.0–0.0)	4.2 (7.5–12.9)	0.97
Distant metastasis	114	16.3 (12.4–20.7)	30.5 (25.3–35.9)	116	16.8 (12.9–21.2)	31.0 (25.7–36.4)	0.96
Group 1†	96	18.3 (14.5–24.3)	32.7 (26.7–38.7)	105	19.2 (14.5–24.3)	35.1 (29.1–41.2)	0.63
Group 2†	18	7.3 (2.3–16.2)	21.1 (11.1–33.1)	11	6.8 (2.2–15.3)	12.6 (5.5–22.9)	0.24
Contralateral breast cancer	8	0.7 (0.1–2.2)	1.4 (0.5–3.3)	12	0.3 (0.0–1.7)	3.3 (1.6–5.9)	0.27
Group 1†	6	0.8 (0.2–2.7)	1.2 (0.3–3.3)	10	0.4 (0.0–2.1)	3.1 (1.4–5.9)	0.34
Group 2†	2	0.0 (0.0–0.0)	2.1 (0.2–9.7)	2	0.0 (0.0–0.0)	4.1 (0.7–12.6)	0.57
	Events deaths	**5-year survival rate (95% CI)**	**10-year survival rate (95% CI)**	**Events deaths**	**5-year survival rate (95% CI)**	**10-year survival rate (95% CI)**	**P-value**
Distant relapse free survival	133	80.0 (75.3–84.2)	65.3 (59.8–70.7)	146	78.7 (74.0–83.1)	61.5 (55.9–67.1)	0.33
Group 1†	111	77.9 (72.6–82.8)	63.3 (57.2–69.4)	133	76.2 (70.7–81.2)	56.4 (50.2–62.9)	0.11
Group 2†	22	89.3 (79.6–95.7)	74.0 (61.6–84.9)	13	89.7 (80.3–95.9)	84.0 (73.1–92.2)	0.14
Invasive disease free survival	170	77.7 (72.9–82.2)	57.3 (51.7–63.1)	191	75.5 (70.6–80.2)	50.7 (45.0–56.6)	0.09
Group 1†	138	75.5 (70.1–80.6)	56.5 (50.3–63.0)	165	72.6 (66.9–78.0)	47.2 (41.0–53.8)	0.04
Group 2†	32	87.5 (77.4–94.6)	60.8 (47.8–74.1)	26	88.0 (78.3–94.8)	66.3 (53.3–78.8)	0.57
Overall survival	102	88.5 (84.7–91.8)	73.5 (68.4–78.4)	113	88.6 (84.8–91.8)	73.6 (68.4–78.5)	0.48
Group 1†	87	87.0 (82.3–90.6)	72.2 (66.0–77.4)	102	87.5 (82.8–91.0)	71.4 (65.2–76.7)	0.30
Group 2†	15	94.9 (85.1–98.3)	79.2 (66.3–87.6)	11	93.2 (82.9–97.4)	83.3 (70.3–91.0)	0.39

P-value based on Gray's test in presence of competing risk and Log-rank test in absence of competing risk. †Group 1: Patients with ≥4 positive axillary lymphnodes (ALN) or with 1–3 positive ALN and either poorly differentiated tumor (histologic grade G3) or large tumor (≥5 cm); Group 2: Patients with 1–3 positive ALN and Ki-67 ≥ 20% and G1-2 tumor and tumor size <5 cm.

Table 3: **Five-year and 10-year event rates and survival rates in the matched set.**

IDFS (log-rank P = 0.09) and OS (log-rank P = 0.48) were not statistically significantly different between the two histotypes. The 5-year and 10-year IDFS rates (95% CI) were respectively 77.7% (72.9–82.2) and 57.3% (51.7–63.1) for IDC compared to 75.5% (70.6–80.2) and 50.7% (45.0–56.6) for ILC. The 5-year and 10-year DRFS rates were respectively 80.0% (75.3–84.2) and 65.3% (59.8–70.7) for IDC, compared to 78.7% (74.0–83.1) and 61.5% (55.9–67.1) for ILC (Table 3, Fig. 2E and F). The 10-year OS rate was 73.5% (95% CI, 68.4–78.4) for IDC and 73.6% (95% CI, 68.4–78.5) for ILC (Table 3, Fig. 2G). No significant statistical differences in OS and all events were also found comparing the two groups of risk for each histotype (Fig. 2).

In the combined high risk matched population, locally advanced BC (pT4) resulted as an adverse prognostic factor for ALNR [HR 7.19 (95% CI, 1.54–33.6)], DRFS [HR 3.26 (95% CI, 1.34–7.89)] and OS [HR 2.82 (95% CI, 1.05–7.57)] at univariate analysis (Supplementary Table S4), as well as negative progesterone receptor status for DM [HR 1.54 (95% CI, 1.04–2.29)] and OS [HR 1.71 (95% CI, 1.14–2.57)] (Supplementary Table S4).

At multivariable analysis in the combined cohort, adjusted for specific clinical and pathological features (age, high risk group, surgery, pT, pN, ER, grade, PVI, and Ki67), age <35 years, pT2-3, axillary involvement with more than 10 positive axillary nodes were found to be predictors of unfavorable IDFS, DRFS and OS in the combined matched population (Supplementary Table S5).

Discussion

Our real-world data on high-risk ER-positive HER2-negative BC patients selected according to clinicopathological criteria from the monarchE study, comparing lobular and ductal histotype-matched cohorts, showed a rate of approximately 21% high-risk, potentially eligible patients for adjuvant treatment with abemaciclib.

To date, recently published data suggested that patients with these characteristics according to the MonarchE criteria have a high risk of recurrence, including metastatic disease, which is approximately three times greater than that of a patient without these traits.[19]

Therefore, the use of available standard adjuvant therapies and new adjuvant therapeutic options to prevent early recurrences and reduce the risk of metastases in BC patients with a high probability of recurrence

assumes a peculiar value in the current scientific landscape.

The approval of abemaciclib for the adjuvant treatment of clinically high-risk, node-positive and ER-positive HER2 negative BC has redefined treatment algorithms for this disease,[23] thanks to long-term data validating the persistent and strong benefit of adjuvant abemaciclib, due to recent updated data on 4-year DFS.[30] The study randomized 5637 patients, defined at high risk according to specific clinical criteria: high-risk was defined as ≥4 pathologically positive axillary nodes or 1–3 positive nodes and at least one of the following characteristics: tumor size ≥5 cm, histologic grade 3 disease, or Ki-67 ≥ 20%, even if Ki-67 index was not required for enrolment, given abemaciclib benefit was reported consistent regardless of Ki-67 index.[23]

Abemaciclib became the first CDK4 and 6 inhibitors globally approved for use in the adjuvant setting.[30] However, the real-world proportion and clinicopathologic characteristics of patients potentially eligible for adjuvant abemaciclib is currently object of research.

Several key clinical hallmarks distinguish ILC from IDC, such as less-evident mammographic detection and unusual metastatic sites, such as abdomen and pelvis.[35] Thus, beyond its molecular/morphological pattern and association with *CDH1* inactivation, ILC does not show pathognomonic clinical features. Indeed, the comparison between ILC and IDC could provide clinical insight and useful tools that could be useful for the management of ILC, as currently ILC has managed similarly to IDC.[36]

While it is generally accepted that ILC has a better prognosis than IDC, is endocrine-responsive, is treated above all with endocrine therapy and responds poorly to chemotherapy,[37] the novel research do not unequivocally support these findings[38]: indeed, chemotherapy is an area of debate,[10] given the low efficacy demonstrated in ILC, as well as the utility of multigene prognostic tests, which is being investigated.[20,21,39,40] In addition, despite ILC constitutes a specific morpho-molecular entity of BC, it presents many variants: multiple clinical phenotypes which depict a special histologic spectrum of cancers.[1]

Furthermore, the scientific controversy surrounding the prognosis of ILC still persists [36,37]. Several retrospective studies on large cohorts have been conducted in recent years, comparing the long-term outcome of ILC to that of IDC, with undoubtedly heterogeneous and contrasting results (Supplementary Table S1). Some reported a similar prognosis between ILC and IDC,[41–44] conversely others demonstrated that ILC had better OS than IDC.[45,46] Recently, Zhao and colleagues reported a better OS for ILC compared with IDC in the total SEER population studied of 171,881 BC patients, more marked in those with HR positive HER2 negative BC, also after matching.[46]

However, further studies with adequate follow-up have shown that ILC has worse long-term outcomes than IDC, due to late recurrences,[17,35,47,48] indeed late distant recurrence is a challenge for the treatment of ILC.

To better differentiate the clinicopathological features and outcomes between ILC and IDC, Oesterreich et al. conducted a retrospective cohort study of 3617 ILC and 30,045 IDC patients diagnosed between 1990 and 2017 at three large USA cancer centers. They reported patient outcomes after a median follow-up of 66 months: although DFS was similar between ILC and IDC patients, among the subset of estrogen receptor (ER)-positive HER2-negative patients, DFS and OS were significantly worse for ILC patients, underlining that ER-positive ILC is a statistically significant unfavorable prognostic factor and recurrences occurred in ILC patients after 10 years of follow-up.[3] This observation may reflect the greater propensity of ILC for tumor dormancy.[49] Of note, compared with IDC patients, ILC patients were diagnosed at later stages (stage III-IV) with more lymph-node involvement (N2–N3).[3] This has been also observed in other previous studies, such as in the analysis of a large SEER database[13] and could be likely justify by the late ILC detection, given the diagnostic limitations of imaging in ILC management.

Compared to such available data (Supplementary Table S1), findings from our matched cohort demonstrated rates of concordant long-term outcome status by histologic subtype, suggesting an equivalent clinical management and therapeutic strategy for these two different histological entities with such high-risk features.

Indeed, IDFS, DRFS and OS were not statistically significantly different between high-risk ILC and high-risk IDC, as well as comparing group 1 to group 2 (Fig. 2E–G).

As recently published,[30] the primary endpoint of MonarchE trial was IDFS and DRFS, which correspond to IDFS and DRFS analyzed in our study.

In the matched set, the 3-year IDFS rate of ILC group was 86.9% (82.9–90.4), compared to the 3-year IDFS of 85.2% (81.0–88.9) for IDC. The 3-year DRFS rate of ILC group was as well 88.5% (84.7–91.7), compared to the 3-year DRFS of 86.5% (82.4–90.0) of IDC group. These data did not reveal a IDFS and DRFS difference between the two high-risk matched histotypes. Nevertheless, these findings were in line with recent updated results from MonarchE trial[30]: indeed, the reported overall 3-year invasive IDFS of the endocrine therapy (ET) alone group was 84.4% (83.0–85.8) (95% CI) compared to 89.2% (87.9–90.3) (95% CI) of the abemaciclib plus endocrine therapy group. Moreover, recent updated MonarchE data presented at the ESMO congress reported a 5-year DRFS rate of 78.5% (76.6, 80.3) (95% CI) in the ET alone group, quite similar to the 5-year DRFS rate of our high-risk population (80.0% (75.3–84.2) (95%

CI) for IDC patients and 78.7% (75.3–84.2) (95% CI) for ILC patients).

Thus, our real-world data on IDFS and DRFS are reflected in those just reported for the endocrine alone group of the MonarchE study.

However, ALNR was more prevalent in the ILC group [HR, 1.68 (95% CI, 0.77–3.66); P = 0.20] (Fig. 2B and Table 3), with a difference in risk after 10 years of follow-up (Fig. 2 B), suggesting the likely major benefit of abemaciclib treatment in the high-risk ILC group. Indeed, recent findings from a retrospective, observational French cohort study revealed ILC as a significant predictive factor of N2 status, reporting a twofold higher risk of N2 pathological stage for patients with ILC compared to those with IDC (OR: 2.32, 95% CI 1.01–5.06, P = 0.047), with an implicit greater benefit from abemaciclib.[31] Benefit of CDK4/6 inhibitors in de novo metastatic or lobular histology has been also recently explored in 5 phase 3 randomized trials, reporting that the addition of CDK4/6 inhibitors to endocrine-based therapy would confer a similar benefit in the relative risk of disease progression or death for these specific subsets of patients compared to the general population, underling anyway the need of further dedicated researches.[50]

Surgical management of the axilla in this context could open the debate, currently quite lively in the scientific community, especially among breast surgeons, on the value of axillary dissection (ALND) in case of limited axillary burden of the sentinel lymph node (SLN) in case of early BC. If in ILC the risk of worse long-term prognosis is associated with extensive lymph node involvement and higher propensity for axillary recurrence, is the omission of ALND an adequate surgical approach in selected groups of patients, in accordance with current evidence and international recommendations?[51–54]

The dilemma is whether omission of ALND could lead to undertreatment of such ER positive HER2 negative cN0 patients, potentially at increased risk for recurrences and therefore who would benefit from abemaciclib treatment. As recently pointed out,[55,56] the decision process should always include a multidisciplinary and personalized approach, bearing in mind that the MonarchE trial was conceived as a non-surgical trial and that breast surgeon should adhere to the growing trend towards axillary surgical de-escalation,[55,57–60] as well as to evidence from prospective randomized surgical studies on surgical axillary management, such as IBCSG 23-01, ACOSOG Z0011, SINODAR ONE and AMAROS.[51–54]

Moreover, in the multivariate analysis of the combined matched cohort, negative progesterone receptor (PgR) status results as a predictor of unfavorable outcome, both OS [HR = 1.82 (95% CI, 1.01–3.28)] and DM [HR = 1.93 (95% CI, 1.11–3.36)]. Negative PgR status was determined in 14% of IDC and 15.5% of ILC cohorts, almost superimposable rate with that reported by Osterreich et al., who observed a PR negativity in ER-positive/HER2-negative ILC of 16% vs 12% in ER-positive/HER2-negative IDC.[3] Loss of PgR expression may be a result of pre-transcriptional alterations involving in the down-regulation of PgR, with distinct consequences on the biology of cancer cells. It is relatively more common than the ER negative/PgR positive type, constituting approximately 12–24% of all BC cases.[61] PgR loss may cause resistance to endocrine therapy and a more aggressive outcome,[62] as well as a possible higher likelihood of occult nodal malignancy.[63] The possible resistance to endocrine therapy of these peculiar phenotypes represents a predisposing factor for disease recurrence after surgical treatment, as well as for disease progression in the metastatic setting.[64] The worsening of OS in our overall clinically high-risk population by univariate analysis could further suggest the protective value of abemaciclib supplementation to adjuvant endocrine therapy in such patients at elevated risk for late recurrence.

Limitations of our manuscript are the retrospective nature of the study and missing data on death which have limited information on BCSS. Besides, the treatment of BC has progressively changed during the course of the study. A further limitation is the use of propensity score matching which cannot control for unmeasured confounders. Another limitation is related to the absence of information regarding the germline BRCA mutational status. To minimize any possible risk of bias, we considered a large population of patients with BC by use of a matched approach, with a long-term follow-up of more than 8 years.

In conclusion, our real-word data reported superimposable IDFS and DRFS rates compared to the overall IDFS and DRFS rates presented by the recent outcomes efficacy results of the MonarchE trial.

They reinforced the concept that the treatment of HR positive Her2 negative ILC patients with specific clinical and pathological parameters of high prognostic risk, would require a multidisciplinary and individualized management strategy and should not differ from that of IDC patients, selected with the same MonarchE criteria. Indeed, our results demonstrated long-term concordance rates by histological subtype, underlining the value of peculiar high-risk clinical and pathological features, compared to the histological type itself, which would not appear to significantly influence the prognostic course of such patients.

These data reported an approximately 21% rate of clinically high-risk patients and would suggest that the globally approved adjuvant treatment with abemaciclib on both high-risk BC groups might have a more positive benefit-risk in ILC.

Contributors

All Authors contributed equally in data curation, formal analysis, investigation, methodology, validation, visualisation, writing, review & editing. FM: data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision,

validation, visualisation, writing, review & editing. GCo: data curation, formal analysis, investigation, methodology, funding acquisition, project administration, resources, software, supervision, validation, visualisation, writing, review & editing. PM: data curation, statistical analysis, interpretation, revision of the manuscript. PV: funding acquisition, project administration, resources, supervision, validation, visualisation, writing, review & editing. GCu: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualisation, writing, review & editing.

All authors were involved in the discussion and revised the manuscript. All authors approved the final version for publication.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author and permission from European Institute of Oncology.

Declaration of interests

Prof. Giuseppe Curigliano: Grants or contracts from any entity: **Merck**; Consulting fees: **BMS, Roche, Pfizer, Novartis, Lilly, Astra Zeneca, Daichii Sankyo, Merck, Seagen, Ellipsis, Gilead, Menarini**; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: **Lilly, Pfizer, Relay, Gilead, Novartis**; Support for attending meetings and/or travel: **Daichii Sankyo**.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102552.

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