

Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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A B S T R A C T

Purpose

To evaluate the relative effectiveness of letrozole compared with tamoxifen for patients with invasive ductal or lobular carcinoma.

Patients and Methods

Patients diagnosed with early-stage invasive ductal carcinoma (IDC) or classic invasive lobular carcinoma (ILC) who were randomly assigned onto the Breast International Group (BIG) 1-98 trial and who had centrally reviewed pathology data were included (N = 2,923). HER2-negative IDC and ILC were additionally classified as hormone receptor–positive with high (luminal B [LB]–like) or low (luminal A [LA]–like) proliferative activity by Ki-67 labeling index. Survival analyses were performed with weighted Cox models that used inverse probability of censoring weighted modeling.

Results

The median follow-up time was 8.1 years. In multivariable models for disease-free survival (DFS), significant interactions between treatment and histology (ILC or IDC; $P = .006$) and treatment and subgroup (LB like or LA like; $P = .01$) were observed. In the ILC subset, there was a 66% reduction in the hazard of a DFS event with letrozole for LB (hazard ratio [HR], 0.34; 95% CI, 0.21 to 0.55) and a 50% reduction for LA subtypes (HR, 0.50; 95% CI, 0.32 to 0.78). In the IDC subset, there was a significant 35% reduction in the hazard of a DFS event with letrozole for the LB subtype (HR, 0.65; 95% CI, 0.53 to 0.79), but no difference between treatments was noted for IDC and the LA subtype (HR, 0.95; 95% CI, 0.76 to 1.20).

Conclusion

The magnitude of benefit of adjuvant letrozole is greater for patients diagnosed with lobular carcinoma versus ductal carcinoma.

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INTRODUCTION

Invasive lobular carcinoma (ILC) is the second-most common breast cancer subtype and accounts for approximately 10% of all breast cancers.¹ ILC differs from invasive ductal carcinoma (IDC), the most common breast cancer subtype, with respect to epidemiology, clinicopathologic characteristics, and responsiveness to systemic therapies.^{1,2} Morphologically, ILC is commonly characterized as noncohesive infiltrating cells classified as hormone receptor–positive, with a low to intermediate histologic grade. In addition, morphologic variants of ILC (eg, pleomorphic, alveolar ILC) have been described to define ILC tumors that lack the characteristic diffuse, nonlinear growth pattern of classic ILC.^{3,4}

Retrospective studies have consistently demonstrated that primary ILC is less responsive than IDC to chemotherapy.⁵⁻¹³ Limited information is available to compare the efficacy of hormonal therapy in ILC and IDC,^{14,15} and it is unclear whether the benefit of different therapies (ie, tamoxifen or aromatase inhibitors [AIs]) differs by histologic subtype (ie, ILC *v* IDC).

The Breast International Group (BIG) 1-98 study is a four-arm study comparing 5 years of monotherapy with tamoxifen, 5 years with letrozole, or the two treatments administered sequentially in postmenopausal women who have hormone receptor–positive early-stage breast cancer.^{16,17} In the present analysis, we investigated the magnitude of benefit of endocrine treatment (tamoxifen or letrozole) in patients diagnosed with classic ILC or

IDC who were enrolled in the monotherapy arms of the study. It is important to note that the classification of breast cancer has evolved from a pure morphologic classification (ie, ILC, IDC) to include hormone receptors and human epidermal growth factor receptor 2 (HER2), and the classification now encompasses a group of heterogeneous, genomically defined breast cancer subtypes.^{18,19} BIG 1-98 enrolled participants diagnosed with hormone receptor–positive breast cancer and, as such, accounts for a population that could be genomically defined as having luminal breast cancer. Luminal breast cancers encompass at least two subgroups with distinct survival outcomes: luminal A (LA) is represented as estrogen receptor (ER)–positive tumors that have low proliferative activity; luminal B (LB) also is represented by ER-positive tumors, but have high proliferative activity and worse outcomes than LA types. In the present analysis, the differential effectiveness of tamoxifen versus letrozole in ILC versus IDC is performed while taking into the consideration the distribution of high- and low-proliferative ER subtypes in both subgroups.

PATIENTS AND METHODS

This analysis is limited to patients assigned to monotherapy with either tamoxifen or letrozole at a median of 8.1 years of follow-up time. There were 4,922 patients enrolled in the monotherapy arms of BIG 1-98. This analysis includes patients who had centrally reviewed histology data (n = 4,080) and whose tumors were classified as IDC or classic ILC (n = 2,923; Fig 1). HER2-positive tumors were not included in the present analysis. The BIG 1-98 patient population was postmenopausal women with early invasive breast cancer whose tumors were assessed by local pathologists as hormone receptor positive (ie, ER and/or progesterone receptor [PgR] positive). Between March 1998 and March 2000, patients were randomly assigned to receive adjuvant endocrine therapy in one of the monotherapy arms comprising either letrozole 2.5 mg/d or tamoxifen 20 mg/d for 5 years; from April 1999 to May 2003, patients were randomly assigned to all four arms, including the sequence of 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen.

All participants provided written informed consent. Ethics committees and relevant health authorities approved the protocol.

Pathology Assessment

Central pathology evaluation of histologic subtype was performed at the University of Glasgow, United Kingdom. Data reported were the dominant and secondary histologic subtype, histologic grade, and peritumoral vascular invasion. This analysis is restricted to dominant IDC and dominant ILC (classic type) only. Data from patients who had dominant ductal and secondary ILC and vice versa (ie, mixed histology) were not included in the analysis.

Central pathology evaluation, including ER status, PgR status, HER2 status, and the Ki-67 labeling index (LI), was performed in the International Breast Cancer Study Group Central Pathology Laboratory, European Institute of Oncology, Milan, Italy. Expressions of ER, PgR, HER2, and the Ki-67 LI in the primary tumors were determined by immunohistochemistry (IHC).²⁰⁻²² ER-negative and PgR-negative negative statuses were each defined as fewer than 1% immunoreactive cells, in accordance with recent guidelines.²³ Whole tumor sections were incubated with the specific primary mouse monoclonal antibodies to ER (clone 1D5; 1:100 dilution) or PgR (clone 1A6; 1:800 dilution; DAKO, Glostrup, Denmark). HER2 status was assessed by IHC and fluorescence in situ hybridization.²⁴ Tumors were considered HER2 positive if they were amplified by fluorescence in situ hybridization or if IHC was 3+ positive.²⁴ The Ki-67 LI was assessed using the mouse monoclonal antibody MIB-1 (1:200 dilution; DAKO); the percentage of cells that showed definite nuclear immunoreactivity with MIB-1 among 2,000 invasive neoplastic cells in randomly selected high-power fields (×400) at the periphery of the tumor was recorded.

Subtype Definitions

Tumors were classified as LA-like or LB-like subtypes according to IHC surrogates. LA-like subtypes were ER and/or PgR positive and HER2 negative and had a Ki-67 LI less than 14%; LB-like subtypes were ER and/or PgR were positive and HER2 negative but had a Ki-67 LI ≥ 14%. The Ki-67 LI cutoff point of 14% was selected as the one most likely to represent LA and LB breast cancer molecular subtypes.^{18,25-27}

End Points and Statistical Methods

The protocol-specified primary end point was disease-free survival (DFS), which was defined as the time from random assignment to the earliest

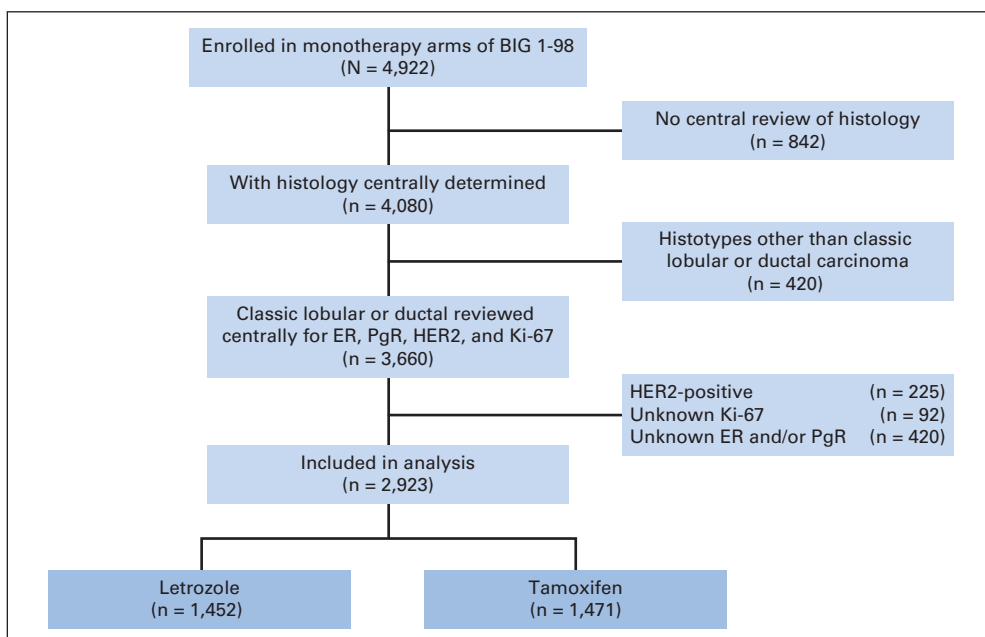


Fig 1. CONSORT diagram showing the analytic cohort of 2,923 patients with tumors classified as ductal (n = 2,599) and lobular (n = 324) enrolled in the monotherapy arm of the BIG 1-98 clinical trial that compared 5 years of letrozole with 5 years of tamoxifen. ER, estrogen receptor; HER2, human epidermal growth factor receptor; PgR, progesterone receptor.

time of an invasive locoregional recurrence, distant metastasis, invasive contralateral breast cancer, second primary malignancy, or death as a result of any cause. Overall survival (OS) was defined as the time from random assignment to death as a result of any cause. Estimates of 5-year and 8-year time-to-event percentages (for DFS and OS) were based on the Kaplan-Meier method and were compared across treatment groups with stratified log-rank tests. Analyses of outcomes employed both the intention-to-treat and inverse probability of censoring weighting (IPCW) approaches.

IPCW was used to account for selective cross over to letrozole of patients in the tamoxifen arm after the positive initial findings of BIG 1-98 were reported in 2005.²⁸ The IPCW method^{17,29,30} weights the follow-up information provided by patients who remain on tamoxifen so that, in the analysis,

their follow-up assessment accounts not only for themselves but also for patients with similar characteristics whose follow-up assessments were artificially censored at the time of selective cross over to letrozole. The weights used are those estimated on the basis of the full data set analysis, with a median of 8.1 years of follow-up time.

Cox models are stratified by prior chemotherapy use and the random assignment option (two-arm or four-arm assignment). Independent variables in the Cox models for interaction were ILC/IDC, treatment assignment, and their interaction. Multivariable models added patient age, tumor size, nodal status, tumor grade, local therapy received (mastectomy or less than mastectomy \pm radiotherapy), and LA- or LB-like type to the covariates in the basic interaction models listed above. Statistical

Table 1. Demographic, Disease, and Treatment Characteristics According to Histologic Subtype

Characteristic	Histologic Subtype (N = 2,923)				Fisher's Exact P
	Ductal (n = 2,599)		Lobular (n = 324)		
	No.	%	No.	%	
Chemotherapy strata					.01
No chemotherapy	2,059	79.2	237	73.1	
Received chemotherapy	540	20.8	87	26.9	
Random assignment strata					.001
4-arm	1,880	72.3	262	80.9	
2-arm	719	27.7	62	19.1	
Subtype					< .001
Lum A	1,436	55.3	237	73.1	
Lum B	1,163	44.7	87	26.9	
Age, years					.19
≤ 55	584	22.5	86	26.5	
56-70	1,638	63.0	199	61.4	
≥ 71	377	14.5	39	12.0	
Obese (BMI ≥ 30 kg/m ²)					.93
No	1,929	74.2	243	75.0	
Yes	561	21.6	67	20.7	
Unknown	109	4.2	14	4.3	
Nodal status					.29
Nx/N0	1,473	56.7	178	54.9	
N1-N3	709	27.3	83	25.6	
≥ N4	417	16.0	63	19.4	
Tumor size, cm					< .001
< 2	1,685	64.8	158	48.8	
≥ 2	905	34.8	162	50.0	
Missing	9	0.3	4	1.2	
Tumor grade (centrally assessed)					< .001
1	553	21.3	13	4.0	
2	1,443	55.5	309	95.4	
3	589	22.7	2	0.6	
Missing	14	0.5	—	—	
Peritumoral invasion (centrally assessed)					< .001
No	2,304	88.6	317	97.8	
Yes	285	11.0	7	2.2	
Missing	10	0.4	—	—	
Treatment assigned					.32
Letrozole	1,300	50.0	152	46.9	
Tamoxifen	1,299	50.0	172	53.1	
Local therapy					< .001
LTM/RT	1,426	54.9	145	44.8	
LTM/no RT	85	3.3	4	1.2	
Mastectomy/RT	423	16.3	86	26.5	
Mastectomy/no RT	663	25.5	88	27.2	
Other	2	0.1	1	0.3	

Abbreviations: BMI, body mass index; LTM: less than mastectomy; Lum A, luminal A; Lum B, luminal B; RT, radiotherapy.

significance was defined as $P \leq .05$; there were no adjustments for multiple comparisons.

RESULTS

A total of 2,923 patients who had early-stage breast cancer were analyzed in this study at a median follow-up time of 8.1 years, including 2,599 patients with IDC and 324 patients with ILC. Clinical and pathologic characteristics according to histologic subtypes are shown in Table 1. The percentages of LA and LB subtypes according to histology were 73.1% and 26.9%, respectively, for ILC, and 55.3% and 44.7%, respectively, for IDC. ILC tumors had larger tumor sizes than IDC tumors (ILC v IDC size ≥ 2 cm, 50% v 34.8%); nodal involvement was comparable between IDC and ILC. Rates of obesity, which may affect the risk of recurrence,³¹ were well balanced between women who had IDC and ILC. Treatment compliance, defined as completion of 5 years of treatment, was similar in the ILC and IDC subsets (67% and 71% of patients, respectively). Chemotherapy was administered before study initiation to 26.9% and 20.8% of patients with ILC and IDC, respectively. Additional information about clinical and pathologic characteristics according to histologic subtype and treatment is shown in Appendix Table A1 (online only).

IPCW estimates for DFS and OS are shown in Figures 2A and 2B. The 8-year DFS estimate was 66% for tamoxifen compared with 82% for letrozole in the ILC subset (hazard ratio [HR], 0.48; 95% CI, 0.31 to 0.74) and was 75% for tamoxifen and 82% for letrozole in the IDC subset (HR, 0.80; 95% CI, 0.68 to 0.94). In this comparison, the effect of treatment on DFS depended on the histology of the tumor (interaction $P = .03$; Fig 2A). The 8-year OS estimate was 74% for tamoxifen compared with 89% for letrozole in the ILC subset (HR, 0.40; 95% CI, 0.23 to 0.69) and 84% for tamoxifen and 88% for letrozole in the IDC subset (HR, 0.73; 95% CI, 0.60 to 0.89). The effect of treatment on OS also depended on the histology of the tumor (interaction $P = .045$; Fig 2B). IPCW estimates for DFS according to breast cancer subtype

in the LA-like and LB-like subsets are shown in Figure 3. ILC tumors classified as LA like had inferior outcomes when treated with tamoxifen, whereas ILC tumors classified as LB like and IDC tumors classified as either LA like or LB like had similar outcomes when treated with letrozole, as shown in the overlapping curves in Figure 3. Additional analyses were performed by using intention-to-treat analyses and showed similar estimates as observed with IPCW (Appendix Fig A1, online only).

In multivariable models for DFS adjusted for classic clinicopathologic features, significant interactions between treatment and histology (ILC or IDC; interaction $P = .006$) and treatment and subtype (LB like or LA like; interaction $P = .01$) were observed (Fig 4). Women who had IDC and the LB-like subtype experienced a significant 35% reduction in the hazard of a DFS event with letrozole (HR, 0.65; 95% CI, 0.53 to 0.79); however, no difference between treatments was noted in women who had IDC and the LA-like subtype (HR, 0.95; 95% CI, 0.76 to 1.20). In the ILC subset, there was a 66% reduction in the hazard of a DFS event for LB-like subtypes (HR, 0.34; 95% CI, 0.21 to 0.55) and a 50% reduction in the hazard of a DFS event with letrozole for LA-like subtypes (HR, 0.50; 95% CI, 0.32 to 0.78).

In the multivariable analysis for OS, a significant interaction between treatment and histology (interaction $P = .035$) was observed, which suggests that the effect of letrozole compared with tamoxifen is significantly greater for ILC compared with IDC. Women with IDC experienced a statistically significant 28% reduction in the hazard of death with letrozole (HR, 0.72; 95% CI, 0.59 to 0.88). In women with ILC, there was a 62% reduction in the hazard of death with letrozole (HR, 0.38; 95% CI 0.22 to 0.67)

DISCUSSION

This study demonstrates that the magnitude of benefit of adjuvant letrozole varies by histologic subtype. Significant reductions in the risk

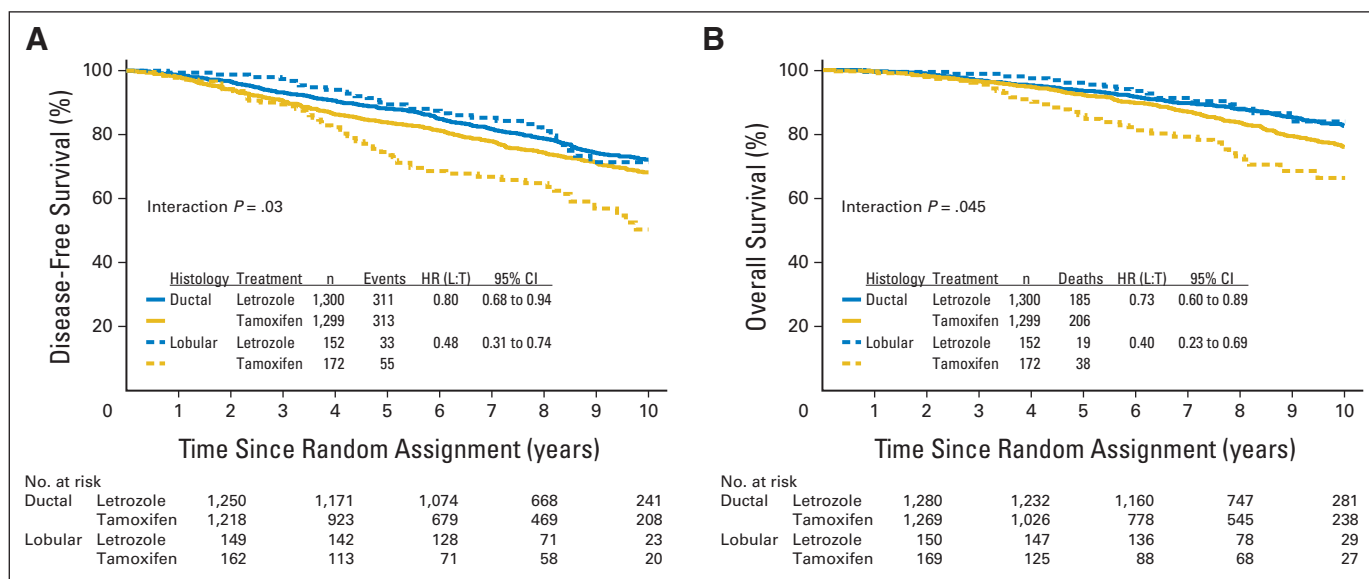


Fig 2. Inverse probability of censoring weighted Kaplan-Meier estimates of (A) disease-free survival and (B) overall survival according to histology (ductal, lobular) and treatment (letrozole, tamoxifen) among the 2,923 patients in the analytic cohort. HR, hazard ratio; L, letrozole; T, tamoxifen.

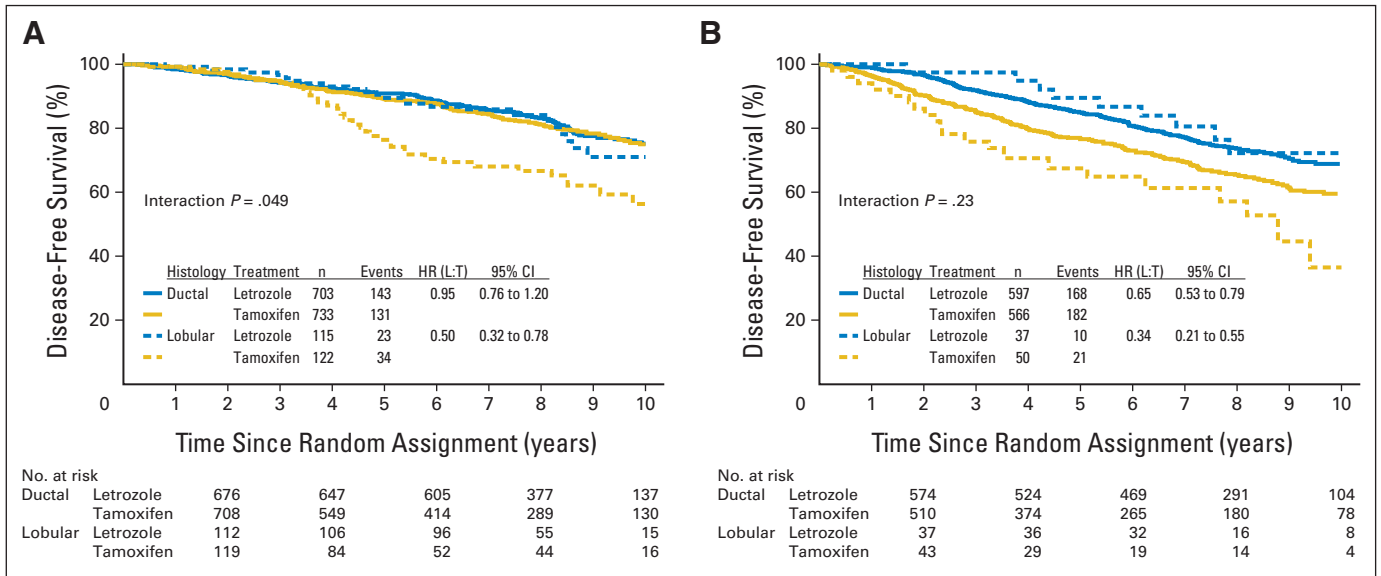


Fig 3. Inverse probability of censoring weighted Kaplan-Meier estimates of disease-free survival according to treatment and histology within subgroups defined as (A) luminal A-like and (B) luminal B-like. HR, hazard ratio; L, letrozole; T, tamoxifen.

of DFS events with letrozole monotherapy versus tamoxifen monotherapy were noted in women diagnosed with ILC regardless of whether the tumor was LA like or LB like. By contrast, in the IDC subset, there was a significant reduction in the risk of DFS events with letrozole for the LB-like subtype but no difference between letrozole and tamoxifen with the LA-like subtype.

A major strength of this study is that the population comes from a large, phase III clinical trial with a median patient follow-up time of more than 8 years.³² Central pathology review for histologic breast cancer subtypes allowed us to reliably identify patients diagnosed with classic ILC and investigate for the first time the effectiveness of adjuvant tamoxifen and letrozole in this subset. In addition, determination of biomarkers (ER, PgR, HER2, and Ki-67) was performed in a central laboratory with extensive breast cancer pathology experience.

The use of an IHC-based surrogate to divide the ER-positive tumors into low- and high-proliferative subsets (ie, LA like or LB like) is a limitation. Currently, the use of Ki-67 in clinical practice is limited by uncertain technical reproducibility and subjective interpreta-

tion.^{25,26} Moreover, the use of a reduced set of biomarkers is not expected to replace genomic classifiers. Despite the limitations, a good approximation of genomically defined breast cancer subtypes can be achieved by IHC-based surrogates when biomarkers are assessed with existing recommendations.^{26,33} In agreement with a retrospective analysis, in which genomic data from more than 180 ILC tumors classified the majority (75%) of ILC tumors as the LA type,^{4,34} the present analysis classified 73% of ILC tumors as LA like and 27% as LB like. In contrast, the IDC subset had a smaller representation (55%) of LA-like tumors and a higher representation (45%) of LB-like tumors.

Data from a retrospective analysis that included 2,000 women with breast cancers classified into subtypes according to the same IHC-based surrogate and observed for greater than 12 years, demonstrated a worse prognosis for LB-like tumors than LA-like tumors.³⁵ It also showed a consistently higher hazard of early (< 5 years after diagnosis) and late (> 5 years) recurrence with LB-like tumors versus LA-like tumors. The present analysis takes into consideration the

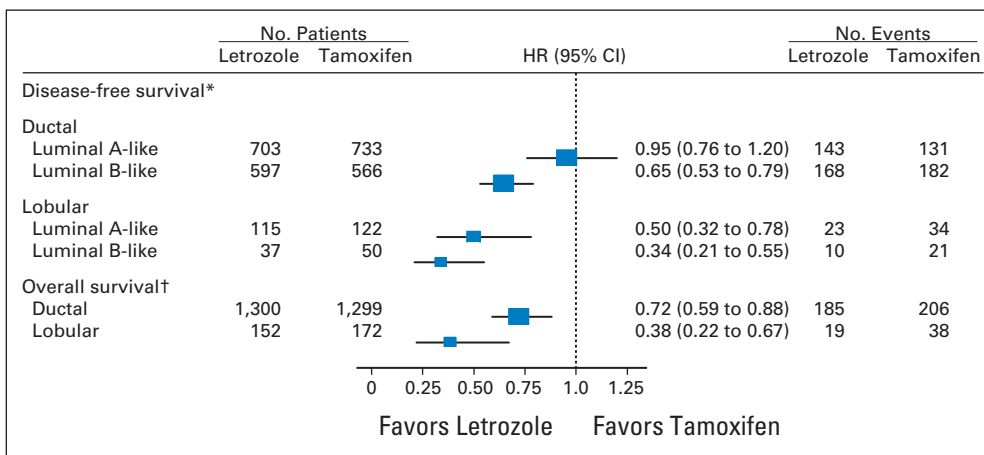


Fig 4. Disease-free survival and overall survival hazard ratio (HR) estimates and 95% CIs comparing the efficacy of letrozole versus tamoxifen for histologic subgroups. The results were based on multivariable models that included classic clinicopathologic variables as predictors: age, tumor size, nodal status, histologic grade, histology (ductal/lobular), local therapy, subtype (luminal A or B), and treatment. The box size is inversely proportional to the SE of the HR; the extended horizontal lines indicate the 95% CIs. (*) Treatment by histology (ductal/lobular), $P = .006$; treatment by subtype (LA/LB), $P = .01$. (†) Treatment by histology (ductal/lobular), $P = .035$.

different distribution of LA-like and LB-like tumors in ILC and IDC subsets and allows for a more precise investigation of the benefit of AIs versus tamoxifen in both subsets.

There are other definitions of IHC-based surrogate classifications. One adds PgR expression to the existing definition of the LA-like subtype and requires that tumors have PgR \geq 20%.³⁶ Our results were consistent when the analysis was performed with this modified IHC-based surrogate (data not shown), and our conclusions were not dependent on one surrogate definition.

The retrospective nature of this analysis and the reduced number of ILC occurrences are limiting factors. It is unclear at this stage whether inferior outcomes for patients diagnosed with ILC and treated with tamoxifen would be confirmed in additional studies. In a randomized study comparing 2 years of tamoxifen with observation, the advantage of tamoxifen was more pronounced in the subset of patients with IDC than in those with ILC, but the number of patients with ILC was small ($n = 43$).¹⁴ In a retrospective subset analyses of patients enrolled on the Exemestane Adjuvant Multinational (TEAM) phase III study, similar outcomes were observed for patients with ILC and IDC who were treated with single-agent exemestane or tamoxifen followed by exemestane.³⁷ The lack of a tamoxifen monotherapy arm and a shorter follow-up time are limiting factors to the interpretation of these results. More recently, results from the Austrian Breast and Colorectal Cancer Study Group (ABCSCG) VIII trial showed improved OS for patients with ILC who were treated with tamoxifen followed by anastrozole versus those treated with tamoxifen monotherapy.³⁸ Additional results from BIG 1-98 failed to demonstrate similar results for the comparison of tamoxifen followed by letrozole versus tamoxifen monotherapy.³⁹ Comparisons of sequential arms (eg, tamoxifen followed by an AI) versus tamoxifen monotherapy should be interpreted with caution, and additional analysis with larger number of patients (ie, patients with ILC) is warranted before definitive conclusions are made.

The IPCW methodology, which attempts to remove a bias caused by treatment cross over, has strengths and limitations that have been noted in the published literature.³⁰ Quantifying bias in IPCW estimates can be difficult but will be limited as long as data are available about factors that affect patient decisions to cross over and are prognostic for future outcomes. The BIG 1-98 study is well suited for the use of IPCW methods, because patients before recurrence were relatively healthy and because prognostic factors were recorded as part of study follow-up times and were available for estimation of the IPCW weights.

Preclinical and translational efforts have suggested the mechanisms of resistance to tamoxifen in the subset of ILC. This includes the expression of different forms of ERs, including estrogen-related receptor γ ,⁴⁰ persistence of ER β expression,⁴¹ and fibroblast growth factor receptor signaling.⁴² In addition to the above-mentioned mechanisms, higher levels of ER and PgR ex-

pression in ILC than IDC could hypothetically contribute to a greater benefit of an AI in ILC, but data that link ER/PgR levels and AI efficacy are inconsistent across studies.^{22,43,44}

In clinical practice, the choice of an AI versus tamoxifen usually includes the assessment of the baseline risk of disease recurrence as determined by tumor burden, tumor biology, comorbidities, toxicity profile of tamoxifen and the AI, and patient preference.^{32,45,46} Although the current results suggest the addition of histologic subtype (ie, ILC and IDC), in the choice of an AI versus tamoxifen, it is important to note that these findings are derived from a retrospective analysis and should be interpreted with caution.

Among patients diagnosed with IDC, the effect of letrozole seems confined to the LB cohort. This result is in agreement with previous analyses conducted with the BIG 1-98 data that show a greater magnitude of benefit for letrozole versus tamoxifen monotherapy among patients with high Ki-67.²⁰ Despite our limited ability to classify tumors into LA- or LB-like subtypes in clinical practice, the results of the present study could be useful in special circumstances. As an example, switching from AI to tamoxifen among those experiencing severe adverse effects might represent a good option, specifically for patients diagnosed with IDC tumors that have features indicative of low-proliferative activity.

In conclusion, although the current data suggest a greater benefit of adjuvant letrozole than tamoxifen for patients diagnosed with ILC, subsequent validation in larger data sets is necessary before implementing a routine clinical recommendation of AI for patients diagnosed with ILC.

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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REFERENCES

- Rakha EA, Ellis IO: Lobular breast carcinoma and its variants. *Semin Diagn Pathol* 27:49-61, 2010
- Li CI, Anderson BO, Daling JR, et al: Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA* 289:1421-1424, 2003
- Iorfida M, Maiorano E, Orvieto E, et al: Invasive lobular breast cancer: Subtypes and outcome. *Breast Cancer Res Treat* 133:713-723, 2012
- Metzger Filho O, Michiels S, Bertucci F, et al: Genomic grade adds prognostic value in invasive lobular carcinoma. *Ann Oncol* 24:377-384, 2013
- 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* 17:1228-1233, 2006
- Mathieu MC, Rouzier R, Llombart-Cussac A, et al: The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile. *Eur J Cancer* 40:342-351, 2004
- Newman LA, Buzdar AU, Singletary SE, et al: A prospective trial of preoperative chemotherapy in resectable breast cancer: Predictors of breast-conservation therapy feasibility. *Ann Surg Oncol* 9:228-234, 2002
- Lips EH, Mukhtar RA, Yau C, et al: Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Cancer Res Treat* 136:35-43, 2012

9. Delpech Y, Coutant C, Hsu L, et al: Clinical benefit from neoadjuvant chemotherapy in estrogen receptor-positive invasive ductal and lobular carcinomas. *Br J Cancer* 108:285-291, 2013
10. Cristofanilli M, Gonzalez-Angulo A, Sneige N, et al: Invasive lobular carcinoma classic type: Response to primary chemotherapy and survival outcomes. *J Clin Oncol* 23:41-48, 2005
11. 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* 29:361-367, 2003
12. Wenzel C, Bartsch R, Hussian D, et al: Invasive ductal carcinoma and invasive lobular carcinoma of breast differ in response following neoadjuvant therapy with epidoxorubicin and docetaxel + G-CSF. *Breast Cancer Res Treat* 104:109-114, 2007
13. Bollet MA, Savignoni A, Pierga JY, et al: High rates of breast conservation for large ductal and lobular invasive carcinomas combining multimodality strategies. *Br J Cancer* 98:734-741, 2008
14. Jirstrom K, Ryden L, Anagnostaki L, et al: Pathology parameters and adjuvant tamoxifen response in a randomized premenopausal breast cancer trial. *J Clin Pathol* 58:1135-1142, 2005
15. Rakha EA, El-Sayed ME, Powe DG, et al: Invasive lobular carcinoma of the breast: Response to hormonal therapy and outcomes. *Eur J Cancer* 44:73-83, 2008
16. Giobbie-Hurder A, Price KN, Gelber RD, et al: Design, conduct, and analyses of Breast International Group (BIG) 1-98: A randomized, double-blind, phase-III study comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive, early breast cancer. *Clin Trials* 6:272-287, 2009
17. Regan MM, Price KN, Giobbie-Hurder A, et al: Interpreting Breast International Group (BIG) 1-98: A randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. *Breast Cancer Res* 13:209, 2011
18. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumors. *Nature* 406:747-752, 2000
19. Sotiriou C, Pusztai L: Gene-expression signatures in breast cancer. *N Engl J Med* 360:790-800, 2009
20. Viale G, Giobbie-Hurder A, Regan MM, et al: Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: Results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. *J Clin Oncol* 26:5569-5575, 2008
21. Viale G, Regan MM, Mastropasqua MG, et al: Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. *J Natl Cancer Inst* 100:207-212, 2008
22. Ewertz M, Gray KP, Regan MM, et al: Obesity and risk of recurrence or death after adjuvant endocrine therapy with letrozole or tamoxifen in the Breast International Group 1-98 trial. *J Clin Oncol* 30:3967-3975, 2012
23. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 28:2784-2795, 2010
24. Rasmussen BB, Regan MM, Lykkesfeldt AE, et al: Adjuvant letrozole versus tamoxifen according to centrally assessed *ERBB2* status for postmenopausal women with endocrine-responsive early breast cancer: Supplementary results from the BIG 1-98 randomized trial. *Lancet Oncol* 9:23-28, 2008
25. Cheang MC, Chia SK, Voduc D, et al: Ki67 index, HER2 status, and prognosis of Patients with luminal B breast cancer. *J Natl Cancer Inst* 101:736-750, 2009
26. Goldhirsch A, Wood WC, Coates AS, et al: Strategies for subtypes: Dealing with the diversity of breast cancer—Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer, 2011. *Ann Oncol* 22:1736-1747, 2011
27. Goldhirsch A, Winer EP, Coates AS, et al: Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer, 2013. *Ann Oncol* 24:2206-2223, 2013
28. Thurlimann B, Keshaviah A, Coates AS, et al: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 353:2747-2757, 2005
29. Colleoni M, Giobbie-Hurder A, Regan MM, et al: Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. *J Clin Oncol* 29:1117-1124, 2011
30. Finkelstein DM, Schoenfeld DA: Correcting for discretionary treatment crossover in an analysis of survival in the Breast International Group BIG 1-98 trial by using the inverse probability of censoring weighted method. *J Clin Oncol* 29:1093-1095, 2011
31. Ligibel JA, Winer EP: Aromatase inhibition in obese women: How much is enough? *J Clin Oncol* 30:2940-2942, 2012
32. Regan MM, Neven P, Giobbie-Hurder A, et al: Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: The BIG 1-98 randomized clinical trial at 8.1 years median follow-up. *Lancet Oncol* 12:1101-1108, 2011
33. Dowsett M, Nielsen TO, A'Hern R, et al: Assessment of Ki67 in breast cancer: Recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst* 103:1656-1664, 2011
34. Metzger Filho O, Singhal SK, Michiels S, et al: Invasive lobular carcinoma: A luminal breast cancer histotype enriched for epithelial-to-mesenchymal transition features. *Cancer Res* 71:24s, 2011 (abstr P2-18-01)
35. Metzger Filho O, Sun Z, Viale G, et al: Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: Results from International Breast Cancer Study Group trials VIII and IX. *J Clin Oncol* 31:3083-3090, 2013
36. Prat A, Cheang MC, Martin M, et al: Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. *J Clin Oncol* 31:203-209, 2013
37. van de Water W, Fontein DB, van Nes JG, et al: Influence of semi-quantitative estrogen receptor expression on adjuvant endocrine therapy efficacy in ductal and lobular breast cancer: A TEAM study analysis. *Eur J Cancer* 49:297-304, 2013
38. Knauer M, Gruber C, Dietze O, et al: Survival advantage of anastrozol compared to tamoxifen for lobular breast cancer in the ABCSG-8 study. *Cancer Res* 75, 2015 (suppl 9; abstr S2-06)
39. Metzger Filho O, Giobbie-Hurder A, Mallon EA, et al: Relative effectiveness of letrozole alone or in sequence with tamoxifen for patients diagnosed with invasive lobular carcinoma. *J Clin Oncol* 31:14s, 2013 (abstr 529)
40. Riggins RB, Lan JP, Zhu Y, et al: ERGgamma mediates tamoxifen resistance in novel models of invasive lobular breast cancer. *Cancer Res* 68:8908-8917, 2008
41. Huang B, Omoto Y, Iwase H, et al: Differential expression of estrogen receptor alpha, beta1, and beta2 in lobular and ductal breast cancer. *Proc Natl Acad Sci USA* 111:1933-1938, 2014
42. Sikora MJ, Cooper KL, Bahreini A, et al: Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. *Cancer Res* 74:1463-1474, 2014
43. Viale G, Regan MM, Dell'Orto P, et al: Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. *Ann Oncol* 22:2201-2207, 2011
44. Jakesz R, Jonat W, Gnani M, et al: Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 366:455-462, 2005
45. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004. *J Clin Oncol* 23:619-629, 2005
46. Goldhirsch A, Ingle JN, Gelber RD, et al: Thresholds for therapies: Highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 20:1319-1329, 2009

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GLOSSARY TERMS

Aromatase inhibitor (AI): Inhibitors used in treating breast cancer in postmenopausal women. Aromatase inhibitors inhibit the conversion of androgens to estrogens by the enzyme aromatase, thus depriving the tumor of estrogenic signals. Because of decreased production of estrogen, estrogen receptors, which are important in the progression of breast cancer, cannot be activated.

Estrogen receptor (ER): Ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ER α and ER β). ER α is one of the most important proteins controlling breast cancer function. ER β is present in much lower levels in breast cancer, and its function is uncertain. ER status guides therapeutic decisions in breast cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial**

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Table A1. Baseline Demographic, Disease, and Treatment Characteristics by Histology and Treatment

Characteristic	Treatment by Histologic Subtype							
	Ductal				Lobular			
	Letrozole (n = 1,300)		Tamoxifen (n = 1,299)		Letrozole (n = 152)		Tamoxifen (n = 172)	
	No.	%	No.	%	No.	%	No.	%
Chemotherapy strata								
No chemotherapy	1,040	80.0	1,019	78.4	111	73.0	126	73.3
Received chemotherapy	260	20.0	280	21.6	41	27.0	46	26.7
Random assignment strata								
4-arm	941	72.4	939	72.3	123	80.9	139	80.8
2-arm	359	27.6	360	27.7	29	19.1	33	19.2
Subtype								
Lum A	703	54.1	733	56.4	115	75.7	122	70.9
Lum B	597	45.9	566	43.6	37	24.3	50	29.1
Age, years								
≤ 55	288	22.2	296	22.8	41	27.0	45	26.2
56-70	818	62.9	820	63.1	90	59.2	109	63.4
≥ 71	194	14.9	183	14.1	21	13.8	18	10.5
Obese (BMI ≥ 30 kg/m ²)								
No	974	74.9	955	73.5	109	71.7	134	77.9
Yes	275	21.2	286	22.0	34	22.4	33	19.2
Unknown	51	3.9	58	4.5	9	5.9	5	2.9
Nodal status								
Nx/N0	740	56.9	733	56.4	83	54.6	95	55.2
N1-N3	357	27.5	352	27.1	39	25.7	44	25.6
≥ N4	203	15.6	214	16.5	30	19.7	33	19.2
Tumor size, cm								
< 2	855	65.8	830	63.9	73	48.0	85	49.4
≥ 2	441	33.9	464	35.7	78	51.3	84	48.8
Missing	4	0.3	5	0.4	1	0.7	3	1.7
Tumor grade (centrally assessed)								
1	268	20.6	285	21.9	8	5.3	5	2.9
2	729	56.1	714	55.0	144	94.7	165	95.9
3	296	22.8	293	22.6	—	—	2	1.2
Missing	7	0.5	7	0.5	—	—	—	—
Peritumoral invasion (centrally assessed)								
No	1,155	88.8	1,149	88.5	149	98.0	168	97.7
Yes	142	10.9	143	11.0	3	2.0	4	2.3
Missing	3	0.2	7	0.5	—	—	—	—
Local therapy								
LTM/RT	718	55.2	708	54.5	69	45.4	76	44.2
LTM/no RT	41	3.2	44	3.4	2	1.3	2	1.2
Mastectomy/RT	206	15.8	217	16.7	39	25.7	47	27.3
Mastectomy/no RT	334	25.7	329	25.3	41	27.0	47	27.3
Other	1	0.1	1	0.1	1	0.7	—	—

Abbreviations: BMI, body mass index; LTM: less than mastectomy; Lum A, luminal A; Lum B, luminal B; RT, radiotherapy.

Effectiveness of Endocrine Therapies for Invasive Lobular Carcinoma

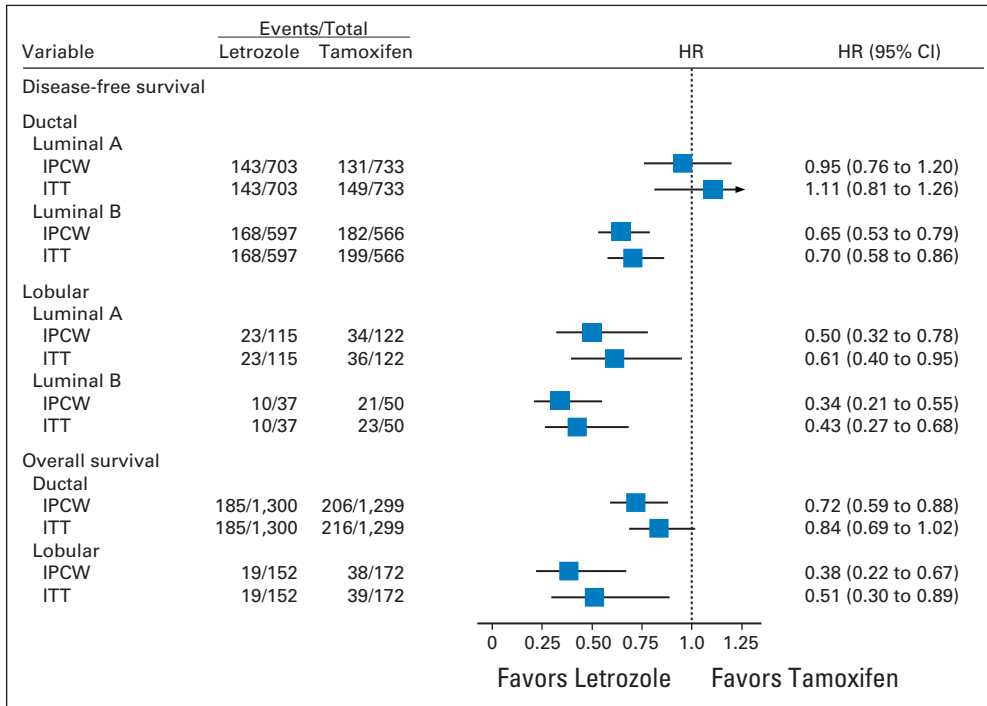


Fig A1. Inverse probability of censoring weighted (IPCW) and intention-to-treat (ITT) hazard ratio (HR) estimates of the relative effect of letrozole versus tamoxifen for disease-free survival and overall survival.