PALLAS
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Long-Term Prognostic and Predictive Value of Lobular Histology in the PALLAS Trial (ABCSG-42/AFT-05/PrE0109/BIG-14-13)

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Background

- Invasive lobular carcinoma (ILC) accounts for up to 15% of breast cancer (BC) cases and has distinct clinical and biological features compared to invasive carcinoma of no special type (IBC-NST).[1]
- The PENELOPE-B trial suggested a greater benefit from adjuvant palbociclib in patients with ILC compared to those with IBC-NST.[2]
- We assessed the prognostic and predictive value of histology (ILC vs IBC-NST) in patients treated with endocrine therapy (ET) ± palbociclib in PALLAS.

Methods

Study design

- **PALLAS** (NCT02513394) is a **phase III clinical trial** in which patients with stage II–III, hormone receptor–positive (HR+) and human epidermal growth factor receptor 2 negative (HER2–) breast cancer were randomized to receive **adjuvant ET plus 2 years of palbociclib or ET alone**.[3]
- Data cutoff for this analysis: May 6, 2025 (**median follow-up: 6.9 years**).

Study population

- Patients with **invasive breast carcinoma of no special type (IBC-NST)** or **pure invasive lobular carcinoma (ILC)** per local pathology assessment were included.

Baseline characteristics:

- Comparison between ILC and IBC-NST using chi-square or Wilcoxon tests.
- Univariable and multivariable logistic regression were used to evaluate associations between histology and clinical variables (age, T and N stage, grade, progesterone receptor [PR], prior chemotherapy, surgery type, and country).

Endpoints: invasive disease-free survival (**IDFS; primary**), distant recurrence-free survival (**DRFS**), locoregional recurrence-free survival (**LRRFS**), and overall survival (**OS**).[4]

Statistical analyses:

- Time-to-event endpoints were analyzed using Kaplan–Meier and Cox proportional hazards models. Proportional hazards assumption were tested using weighted Schoenfeld residuals; if violated, **time-dependent Cox models applied for early (<3 y) vs late (>3 y) periods**.
- Multivariable Cox models were adjusted for **age, T-stage, N-stage, grade, and PR** expression.
- Predictive value was assessed via **histology-by-treatment interaction** terms (palbociclib + ET vs ET alone).

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Baseline Characteristics

- Among 5,748 patients in the ITT population, **4,982 (87%)** were included in this analysis (**3,838 with IBC-NST [67%] and 1,144 with ILC [20%]**).
- Compared with IBC-NST, **ILC was associated with older age, higher T stage, fewer grade 3 tumors, higher mastectomy rates, less (neo)adjuvant chemotherapy**, and **less tamoxifen as initial ET** (Table 1).
- **ILC prevalence varied by country**: lower in Asia (Japan 10.5%, Korea 0%, Taiwan 2.8%) and higher in Europe (23.1%) and North America (24.0%).

Table 1. Baseline Characteristics

	IBC-NST (n = 3838)	ILC (n = 1144)	p-value
Age, median (IQR)	51 (44–60)	54 (48–63)	<0.001
Postmenopausal	1954 (50.9)	695 (60.8)	<0.001
Region			0.015
Europe	1730 (45.1)	519 (45.4)	
North America	1652 (43.0)	523 (45.7)	
Other	456 (11.9)	102 (8.9)	
BMI, median (IQR)	26.8 (23.3–31.3)	26.6 (23.5–30.9)	0.63
T-stage			<0.001
T0/T1/Tis/TX	776 (20.2)	123 (10.8)	
T2	2279 (59.4)	544 (47.6)	
T3/T4	783 (20.4)	477 (41.7)	
N-stage			<0.001
N0	448 (11.7)	204 (17.8)	
N1	1981 (51.6)	491 (42.9)	
N2	988 (25.7)	216 (18.9)	
N3	420 (10.9)	233 (20.4)	
Grade			<0.001
G1	387 (10.1)	145 (12.7)	
G2	2003 (52.2)	789 (69.0)	
G3	1286 (33.5)	145 (12.7)	
Prior chemotherapy	3308 (86.2)	826 (72.2)	<0.001
Prior radiation therapy	3428 (89.3)	1003 (87.7)	0.14
Surgery: mastectomy	2242 (58.4)	852 (74.5)	<0.001
PR positive	3359 (87.5)	1017 (88.9)	0.21
Initial endocrine therapy			<0.001
Aromatase inhibitor	2500 (65.1)	813 (71.1)	
Tamoxifen	1326 (34.5)	330 (28.8)	

P-values are from univariable comparisons. Values are n (%) unless otherwise specified.
IQR = interquartile range; BMI = body mass index; PR = progesterone receptor.

Results

Prognostic Value of Histology

- In the overall population**, 7-year IDFS was 79.3% for IBC-NST and 75.8% for ILC**.
- While the IDFS difference was significant in univariable analysis (HR 1.17, 95% CI 1.01–1.35), it was not in multivariable analysis (HR 1.06, 0.91–1.24) (Table 2, Figure 1).
- The proportional hazards assumption was violated, and time-dependent modeling demonstrated that **worse outcomes for ILC on IDFS, DRFS, and OS emerged predominantly beyond 3 years** (Table 3).

Figure 1. IDFS (A) and DRFS (B) by Histologic Subtype (ILC vs. IBC-NST)

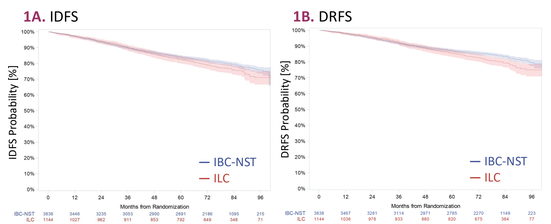


Table 2. Prognostic value of histology (ILC vs IBC-NST)

	Events (ILC / IBC-NST)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
IDFS	240 / 690	1.17 (1.01–1.35)	1.06 (0.91–1.24)
LRRFS	41 / 161	0.85 (0.61–1.20)	0.83 (0.58–1.19)
DRFS	203 / 555	1.22 (1.04–1.44)	1.09 (0.92–1.30)
OS	125 / 353	1.18 (0.96–1.44)	1.01 (0.81–1.26)

Table 3. Time-dependent prognostic value (ILC vs IBC-NST)

	Adjusted HR (95% CI), 0–3 years	Adjusted HR (95% CI), >3 years
IDFS	0.87 (0.69–1.09)	1.27 (1.04–1.57)
LRRFS	0.76 (0.44–1.30)	0.89 (0.56–1.42)
DRFS	0.80 (0.62–1.04)	1.41 (1.13–1.75)
OS	0.70 (0.47–1.06)	1.17 (0.91–1.50)

ILC: invasive lobular carcinoma, IBC-NST: invasive breast carcinoma of no special type

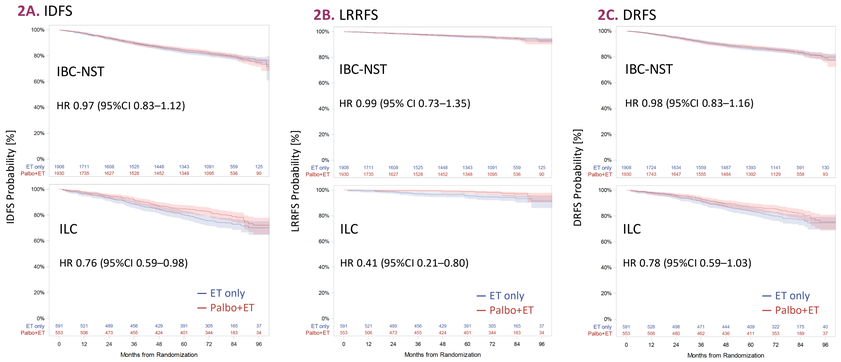
Predictive Value of Histology

- When evaluating the predictive value, **palbociclib appeared to confer greater benefit in ILC** for all endpoints (HRs ranging from 0.41 to 0.86) *but* not in IBC-NST (HRs ranging from 0.97 to 1.01), although the histology-by-treatment interaction was significant only for LRRFS (Table 4, Figure 2).

Table 4. Predictive value of histology (Palbociclib+ET vs ET only)

		Unadjusted HR (95% CI)	Interaction P-value
IDFS	IBC-NST	0.97 (0.83–1.12)	0.11
	ILC	0.76 (0.59–0.98)	
LRRFS	IBC-NST	0.99 (0.73–1.35)	0.02
	ILC	0.41 (0.21–0.80)	
DRFS	IBC-NST	0.98 (0.83–1.16)	0.17
	ILC	0.78 (0.59–1.03)	
OS	IBC-NST	1.01 (0.82–1.24)	0.44
	ILC	0.86 (0.61–1.22)	

Figure 2. Treatment Effect by Histology (Palbo + ET vs ET Only)



Conclusions

- In this large, randomized dataset of patients with early-stage HR+/HER2– breast cancer with long-term follow-up, **ILC demonstrated distinct clinicopathologic features and regional variation in its relative prevalence.**
- While ILC was not an independent prognostic factor over the entire follow-up, time-dependent modeling revealed **worse long-term outcomes which only emerged after 3 years.**
- **Palbociclib** appeared to be associated **with more favorable outcomes in ILC than in IBC-NST across endpoints**.
- These findings suggest a potential benefit of palbociclib in ILC that warrants further investigation in other adjuvant trials evaluating CDK4/6 inhibitors.

References: 1. Van Baelen et al. Ann Oncol. 2025, 2. Loibl et al. Ann Oncol. 2025, 3. Mayer et al. Ann Oncol. 2025, 4. Gnant et al. J Clin Oncol. 2021.

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