Real-world effectiveness of palbociclib + endocrine therapy in tumor histological subgroups of patients with HR+/HER2- Advanced Breast Cancer: Interim Results of the PERFORM study

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DISCUSSION

In our study, pts with ILC tended to be older and presented more frequently with de novo metastatic disease compared to those with NST histology. In line with previous reports, histology-specific metastatic patterns were observed, showing fewer distant metastases in the lung, liver, and pleura, and more frequent metastases in the bones, peritoneum and ovaries for pts with ILC histology compared to pts with NST.[10] Treatment patterns and outcomes, including CBR, DCR and 12-months PFS rates were comparable between pts with ILC and those with NST breast cancer. These data align with other real-world data analyses that describe clinicopathological differences of metastatic ILC from invasive metastatic ductal carcinoma, without significant prognostic impact of the histologic subgroup.[12] Overall, these findings (re)confirm the feasibility and effectiveness of 1L palbociclib plus ET therapy in a real-world setting, regardless of histological subtype.

CONCLUSION

The addition of a CDK4/6 inhibitor to ET benefits pts with HR+/HER2- ABC, regardless of the underlying histological subtype.[13] In line with other RWE[14], our data suggest that pts with ILC and NST tumors demonstrate nearly comparable outcomes in the 1L setting with CDK4/6 inhibition plus ET.

As a large, international, prospective, longitudinal observational study, PERFORM provides valuable RWE on patient characteristics and effectiveness of 1L treatment with palbociclib + ET according to histologic subtypes. The design of PERFORM extends existing evidence, especially for pts with ILC tumors, and includes analyses on effectiveness of subsequent lines of therapy, potentially in the context of additional biomarkers, health-related quality of life over the course of disease, OS, and other clinically meaningful outcomes.

BACKGROUND

Endocrine therapy (ET) + CDK4/6 inhibitors is the standard-of-care first-line (1L) treatment for patients (pts) with HR+/HER2- advanced breast cancer (ABC), based on the results of the pivotal trials.[1–5] The most common histological subtype is the breast carcinoma of no special type (NST), which is characterized by the absence of distinct morphological features that would allow other classification and which accounts for 70–80%.[6] Invasive lobular carcinoma (ILC) is the second most common histological subtype accounting for approx. 15% of all breast cancers.[7]

ILC is a distinct entity, which is characterized by specific genetic features leading to altered regulation of oncogenic pathways, a unique biology and specific disease characteristics.[6] One key feature of ILC is the loss of E-Cadherin which is predominantly caused by inactivating mutations in the encoding *CDH1* gene. This leads to altered cell-to-cell adhesion and thus the non-cohesive, targetoid histological pattern.[6–8] ILC is predominantly ER+, PgR+, HER2-, tends to occur at older age with a higher prevalence of multifocality and differs in the pattern of metastatic spread.[9] Metastases to the bones, peritoneum, ovaries, leptomeninges and digestive tract are found more frequently in patients with ILC compared to NST, whereas metastases to the lung or liver are found with lower frequency.[9] While ILC generally presents a more favorable prognosis in early-stage breast cancer, it is associated with poorer outcomes in the advanced disease setting.[10] In addition, ILC is less readily detected by conventional screening modalities, which often results in diagnosis at a more advanced stage, characterized by increased tumor size and greater lymph node involvement.[9,10]

Despite its unique biology and associated clinical features, there are no tailored treatment options and limited recommendations provided by current guidelines for pts with ILC. This histological subtype is still rarely addressed in specific randomized clinical trials. Therefore, real-world evidence (RWE) can provide valuable insights to enhance clinical understanding. This analysis aims to expand upon the existing knowledge of ILC and NST by utilizing data from the prospective non-interventional study (NIS) PERFORM.

METHODS

The prospective NIS PERFORM (NCT04767594) enrolled pts with HR+/HER2- ABC treated with 1L palbociclib + ET in Germany and Austria. The information on histological subtype was collected at the time of initial diagnosis. Response evaluations are performed according to local routine, using imaging and clinical assessments.

Progression-free survival (PFS) was estimated using the Kaplan-Meier method and is defined as start of 1L treatment to first progression or death, whichever comes first. Pts without tumor progression or death at the time of analysis were censored at their date of last contact or at the start date of a 2L therapy, whichever came first. Observation time was calculated using the date of informed consent as start date and the last documented visit date as end date. Overall response rate (ORR) is defined as proportion of pts with best overall response of complete response (CR) or partial response (PR) in 1L treatment. Pts without tumor assessment in 1L were regarded as non-responders.

Based on preliminary results of Interim Analysis 4 (IA4), performed four years after inclusion of the first patient, we describe patient characteristics and effectiveness according to different histological subtypes, focusing on describing pts with the histologic subtype ILC and NST in terms of patient and disease characteristics, treatment patterns and outcomes. Documentation, including data cleaning, is still ongoing for this study and enrollment was still ongoing at time of data-base cut.

RESULTS

Between 10/2020 and 09/2024, 1412 pts were enrolled at 188 study sites across Germany and Austria, 1321 pts were followed ≥6 months, and 1171 pts were evaluable for analysis (i.e., with at least on dose of palbociclib and not violating any in- or exclusion criteria).[11]

Out of 1171 pts, the majority presented with a histology of NST (717 [61.2%]). As expected, the second most common subtype was ILC (254 pts; 21.7%). 199 pts (17.0%) presented with other histologies including 18 (1.5%) mucinous, 7 (0.6%) tubular, 4 (0.3%) cribriform histologic subtypes **(Table 1)**. Median age at start of 1L treatment was 70.4 years (range 43.4–92.9) in the ILC and 68.7 years (range 33.1–96.1) in the NST subgroup **(Table 1)**. Other baseline characteristics, including sex, menopausal status, and ECOG performance status, were similarly distributed between subgroups **(Table 1)**. The rate of de novo ABC trended higher in pts with ILC (47.2%) compared to NST (39.3%). In comparison to pts with NST histology, those with ILC had lower frequencies of distant metastases in the lung (8.3% and 23.6%), liver (11.0% and 17.0%), and pleura (4.7% and 13.0%). However, metastases in the bone (70.9% and 59.7%), peritoneum (13.0% and 1.1%), and ovaries (2.0% and 0.1%) were more common in pts with ILC. An overview of demographic data and clinical characteristics is given in **Table 2**. Median observation time for pts with ILC and NST was 21.0 and 23.2 months, respectively and 59.4% of pts discontinued 1L treatment in both groups at data base cut **(Table 3 and 4)**. Progressive disease was the main reason for end of treatment (39.0% in ILC and 37.7% in NST). Treatment modifications occurred in 73.6% of pts with ILC histology and in 72.4% of pts with NST **(Table 3)**. ORR was 26.8% for ILC and 37.4% for NST, and clinical benefit rate (CBR) was 67.6% and 65.0%, respectively **(Table 4)**. Median PFS was 21.6 and 25.7 months for pts with ILC and NST, respectively **(Figure 1)**. At 12 months, PFS rates were 68.5% for ILC and 71.3% for NST, respectively **(Table 4)**.

LIMITATIONS

Limitations are the descriptive, exploratory, hypothesis-generating character of the analysis. This was a descriptive analysis of pts with ILC and NST patients for context within the PERFORM study. Additionally, extended follow-up is needed.

Figure 1. Progression-free survival of 1L treatment by histology.

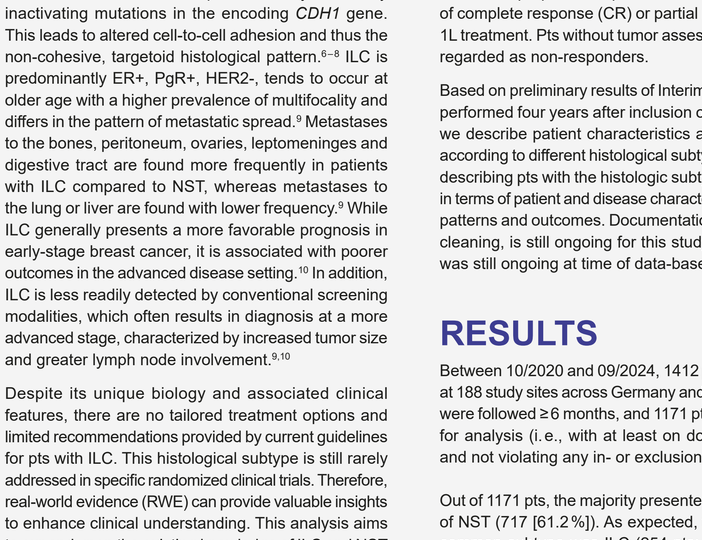

Table 1. Tumor histology at initial diagnosis

	Total (n = 1171)
Histology of primary tumor [n (%)]	
Invasive breast carcinoma of no special type (NST)	717 (61.2)
Invasive lobular carcinoma (ILC)	254 (21.7)
Other carcinoma	170 (14.5)
Mucinous carcinoma	18 (1.5)
Tubular carcinoma	7 (0.6)
Cribriform carcinoma	4 (0.3)
Missing	1 (0.1)
Ductal carcinoma in situ (DCIS) component [n (%)]	
Yes	227 (19.4)
No	696 (59.4)
Unknown	248 (21.2)

Table 2. Patient and tumor characteristics

	ILC (n = 254)	NST (n = 717)
Age at start of 1L treatment [years]		
Mean (± StD)	68.8 (± 11.26)	68.8 (± 11.26)
Median (25% / 75% quantiles)	70.4 (60.4–77.9)	70.4 (60.4–77.9)
Min-Max	43.4–92.9	43.4–92.9
Sex [n (%)]		
Female	253 (99.6)	710 (99.0)
Male	1 (0.4)	7 (1.0)
Menopausal status [n (%)]		
Pre-/Perimenopausal	18 (7.1)	59 (8.2)
Postmenopausal	235 (92.5)	651 (90.8)
Not derivable	1 (0.4)	7 (1.0)
ECOG Performance Status [n (%)]		
0	108 (42.5)	314 (43.8)
1	108 (42.5)	298 (41.6)
≥ 2	31 (12.2%)	85 (11.9)
Missing	7 (2.8)	20 (2.8)
***De novo* advanced disease [n (%)]**		
Yes	120 (47.2)	282 (39.3)
No	134 (52.8)	435 (60.7)
Disease site present at inclusion [n (%)]		
Visceral*	108 (42.5)	343 (47.8)
Non-visceral only (excl. bone only)	25 (9.8)	75 (10.5)
Bone only	102 (40.2)	244 (34.0)
No metastases present at inclusion**	19 (7.5)	55 (7.7)
Affected organ site present at inclusion [n (%)]		
Bone	180 (70.9)	428 (59.7)
Lung	21 (8.3)	169 (23.6)
Liver	28 (11.0)	122 (17.0)
Pleura	12 (4.7)	93 (13.0)
Lymph nodes (regional)	17 (6.7)	65 (9.1)
Lymph nodes (distal)	14 (5.5)	61 (8.5)
Skin	11 (4.3)	20 (2.8)
Brain	4 (1.6)	12 (1.7)
Soft tissue	4 (1.6)	11 (1.5)
Peritoneum	33 (13.0)	8 (1.1)
Breast contralateral	0 (0.0)	4 (0.6)
Breast ipsilateral	0 (0.0)	3 (0.4)
Colon	3 (1.2)	2 (0.3)
Spinal cord	3 (1.2)	2 (0.3)
Uterus	2 (0.8)	2 (0.3)
Adrenal gland	1 (0.4)	1 (0.1)
Ovary	5 (2.0)	1 (0.1)
Spleen	1 (0.4)	1 (0.1)
Bladder	2 (0.8)	0 (0.0)
Kidney	2 (0.8)	0 (0.0)
Rectum	1 (0.4)	0 (0.0)
Other	21 (8.3)	25 (3.5)
Missing	19 (7.5)	55 (7.7)

* Patients with visceral disease site present at inclusion are those with at least one tumor lesion at inclusion that was not located in the bone, lymph nodes (distal or regional), skin, or soft tissue. Patients with non-visceral disease site present at inclusion are those with at least one tumor lesion at inclusion that was located in the lymph nodes (distal or regional), skin, or soft tissue.

** Subgroup without metastases present at inclusion includes patients with locally advanced breast cancer and patients with removed metastases (surgery, radiation) after initial diagnosis.

Table 3. Palbociclib treatment status and pattern

	ILC (n = 254)	NST (n = 717)
Palbociclib treatment status [n (%)]		
Treatment ongoing	103 (40.6)	291 (40.6)
Treatment discontinued	151 (59.4)	426 (59.4)
Reason for end of 1L treatment [n (%)]		
(Serious) Adverse Event	27 (10.6)	65 (9.1)
Progressive disease	99 (39.0)	270 (37.7)
Other	25 (9.8)	91 (12.7)
At least one modification of palbociclib therapy [n (%)]		
Yes	187 (73.6)	519 (72.4)
No	67 (26.4)	198 (27.6)

Table 4. Effectiveness of 1L treatment

	ILC (n = 254)	NST (n = 717)
Best response [n (%)]		
CR	16 (6.3)	46 (6.4)
PR	52 (20.5)	222 (31.0)
SD ≥ 24 weeks	97 (38.2)	217 (30.3)
SD < 24 weeks	28 (11.0)	62 (8.6)
Non-CR/Non-PD	3 (1.2)	2 (0.3)
Non-PD (acc. to PI)	0 (0.0)	3 (0.4)
PD	23 (9.1)	72 (10.0)
Missing	35 (13.8)	93 (13.0)
ORR (%)	**26.8**	**37.4**
CBR (%)	**67.6**	**65.0**
DCR (%)	**76.0**	**76.3**
PFS in 1L		
Events [n (%)]	133 (52.4)	326 (45.5)
Median [months (95% CI)]	21.6 (17.7, 26.5)	25.7 (22.6, 32.0)
12-month rate [% (95% CI)]	68.5 (62.1, 74.0)	71.3 (67.7, 74.6)
24-month rate [% (95% CI)]	47.7 (40.7, 54.4)	51.3 (47.1, 55.4)

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Conflicts of Interest:
Rupert Bartsch: Honoraria, Consulting or Advisory Role, Responsible Investigator Study Site, Travel/Accomodation Expenses | Matthias Korell: Responsible Investigator Study Site | Georg Pfeiler: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses | Thomas Gabrysiak: Responsible Investigator Study Site | Volker Petersen: Responsible Investigator Study Site | Mustafa Deryal: Responsible Investigator Study Site | Thomas Fietz: Consulting or Advisory Role, Responsible Investigator Study Site | Julia Caroline Radosa: Honoraria, Consulting or Advisory Role, Expert Testimony, Responsible Investigator Study Site, Travel/Accomodation Expenses | Thomas Decker: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site | Björn Schöttker: Responsible Investigator Study Site | Jan Knoblich: Responsible Investigator Study Site | Uwe Rhein: Responsible Investigator Study Site | Natalja Deuerling: Responsible Investigator Study Site | Martin Glasstetter: Full/Part-time employment | Dunja Klein: Full/Part-time employment | Johanna Dzieran: Full/Part-time employment, Stocks/Shares | Thomas Schiffer: Full/Part-time employment, Stocks/Shares | Katharina Lunglmeier: Full/Part-time employment, Stocks/Shares | André Breitbach: Full/Part-time employment, Stocks/Shares | Michael Patrick Lux: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses

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Abbreviations:
1L: First-line / first line | ABC: Advanced Breast Cancer | Acc. to PI: According to Principal Investigator | BRCA2: Breast Cancer gene 2 | CBR: Clinical Benefit Rate | CDH1: Cadherin-1 | CDK4/6i: Cyclin-Dependent-Kinase 4/6 inhibitor | CDKi: Cyclin-Dependent-Kinase inhibitor | CI: Confidence Interval | CR: Complete Response | DCR: Disease Control Rate | ECOG: Eastern Cooperative Oncology Group Performance Status | ET: Endocrine Therapy | ER: Estrogen Receptor | HER2: Human-Epidermal-Growth-Factor-Receptor 2 | HR: Hormone Receptor | IA: Interim Analysis | ILC: Invasive Lobular Carcinoma | n: Number | NA: Not Applicable | NST: No Specific Type | ORR: Overall Response Rate | PD: Progressive Disease | PFS: Progression-Free Survival | PI3K: Phosphatidylinositol-3-Kinase | PgR: Progesterone Receptor | PR: Partial Response | PTEN: Phosphatase and Tensin Homolog | Q: Quartile | SD: Stable Disease | RWE: Real-World Evidence