PERFORM

INTERIM RESULTS OF THE NON-INTERVENTIONAL STUDY PERFORM EVALUATING PALBOCICLIB IN COMBINATION WITH ENDOCRINE THERAPY FOR HR+/HER2- ADVANCED BREAST CANCER

RISK SCORE ASSESSMENT IN CLINICAL ROUTINE INCLUDING GENE EXPRESSION TESTING

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BACKGROUND

Endocrine-therapy (ET) combined with CDK4/6 inhibitors is the standard of care as 1st-line therapy for HR+/HER2- advanced or metastatic breast cancer (ABC) patients based upon results of the pivotal phase III trials. Real-world data on treatment patterns, activity and tolerability in patients underrepresented in clinical trials, and quality of life (QoL) across several treatment lines in the ABC setting still can add valuable information. Additionally, patterns of biomarker analyses and genetic testing in clinical routine during course of disease are of interest for this patient population. In the adjuvant setting of HR+/HER2- breast cancer, gene expression tests can predict benefit from adjuvant chemotherapy but there is limited data on their use in routine clinical practice. Detection of *BRCA1/2* germline mutations is not only relevant for estimating the risk of developing breast cancer but can also predict response to a targeted therapy with a PARPi or can be used as guidance für subsequent treatment strategies. In the metastatic setting it is known, that in HR+/HER2- ABC *gBRCA1/2* mutation testing rates are low (comparing to TNBC), especially in elderly patients with unknown family history of breast/ovarian cancer[1], although about 5%[1] of all unselected patients with ABC have a pathogenic *gBRCA1/2* mutation. As these patients are eligible for targeted therapy with PARPi, real-world data on *gBRCA* testing in routine clinical practice could support future testing strategies.[1]

METHODS

Overall, 1,900 patients receiving 1st-line palbociclib/ET will be enrolled in the prospective non-interventional study PERFORM in 320 sites across Germany and Austria. Primary endpoint is progression-free survival. Secondary endpoints include treatment patterns, effectiveness (including also second- and third-line effectiveness), treatment expectation/satisfaction, potential impact of socioeconomic status and QoL as well as patterns of biomarker analyses and genetic testing. At baseline, a risk score assessment of family history of *gBRCA1/2* mutation according to DKG e.V. as well as genetic tests and their outcome are documented, if done in clinical routine. Two years after first-patient-in, the second interim analysis was conducted, focusing on patient/disease characteristics and genetic testing.

CONCLUSION

The second interim analysis of the PERFORM study provides first insights into clinical routine of genetic testing prior to inclusion in 1st-line patients with HR+/HER2- ABC treated with palbociclib and ET. Gene expression analysis at initial diagnosis has rarely been documented in this patient population. This might be explained by lack of indication for testing due to early tumor stages at initial diagnosis and test availability at initial diagnosis (median time between initial EBC diagnosis and relapse of ~8 years). Although recommended by current national and international guidelines, predisposition to *gBRCA*-related cancers was rarely documented for patients at start of 1st-line palbociclib treatment. This could be due to insufficient documentation, as the eCRF at baseline explicitly asks for the DKG e.V. risk score which may not be available in all patient documents. Furthermore, targeted treatment for *gBRCA* mutation is limited to later HR+/HER2- ABC treatment lines. Therefore, further analyses will show if testing rates will increase during the course of disease.

RESULTS

Patient characteristics

704 of 938 patients enrolled between 10/2020 and 09/2022 were followed for ≥6 months, and 624 patients were evaluable. Median age was 68 years (range 33-89), 92% (n=574) were postmenopausal **(Table 1)** and 30% of all patients were ≥75 years at inclusion. In total, 241 (39%) of patients presented with *de novo* ABC and 383 (61%) had relapsed after primary treatment of early-stage disease. For these patients, median time from primary diagnosis to inclusion was 8.26 years (range 0.3-41) **(Table 2)**. No new receptor status was determined in 25.6% (n=98) of patients at inclusion.

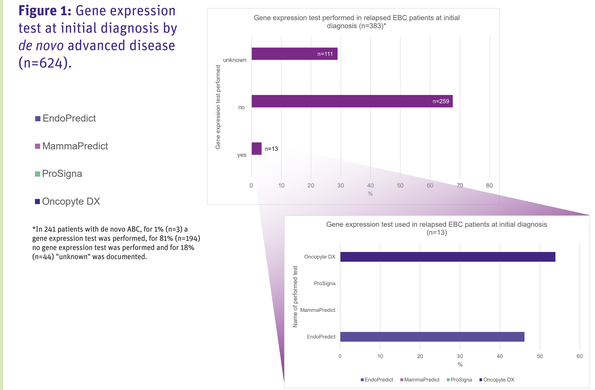
BRCA risk assessment and testing

A risk assessment regarding *gBRCA1/2* was documented for 14.1% (n=88) of patients before start of 1st-line treatment. For 2.6% (n=16) a family history of *gBRCA1/2* related cancers was reported and a genetic panel test was performed in 6.6% (n=41) **(Table 3)**.

Gene expression tests

Gene expression tests at initial diagnosis of EBC to predict benefit of adjuvant chemotherapy were documented in 3.4% (n=13/383) of the patients with relapse. In 1.3% (n=3/241) a gene expression test was documented for *de novo* ABC patients. If tested in the adjuvant setting (n=13) the tests used were Oncotype DX in 53.8% (n=7) and EndoPredict in 46.2% (n=6), respectively **(Figure 1)**. 57.1% (n=4/7) of those patients tested with the Oncotype DX showed a low recurrence score and high risk of recurrence for most of those patients tested with EndoPredict (83%) (n=5/6) **(Table 4)**.

Figure 1: Gene expression test at initial diagnosis by *de novo* advanced disease (n=624).



*In 241 patients with de novo ABC, for 1% (n=3) a gene expression test was performed, for 81% (n=194) no gene expression test was performed and for 18% (n=44) "unknown" was documented.

Table 1: Patient characteristics at start of 1st-line treatment (n=624).

Characteristics	n (%)
Age at start of first-line treatment [years]	
Median (Q1–Q3)	68 (59 – 77)
Min–Max	33 – 89
Missing	0
Age group	
<65 years	259 (41.5)
65-74 years	180 (28.8)
75-79 years	99 (15.9)
≥80 years	86 (13.8)
Sex	
Female	620 (99.4)
Male	4 (0.6)
Menopausal status	
Pre-/Perimenopausal	46 (7.4)
Postmenopausal	574 (92.0)
Not derivable	4 (0.6)
ECOG Performance Status	
0	280 (44.9)
1	261 (41.8)
2	58 (9.3)
3	13 (2.1)
4	0 (0.0)
No assessment done	12 (1.9)

Table 3: Family history of *gBRCA1/2*-related cancer (n=624).

	n (%)
Risk score (DKG e.V) ascertained	
Yes	88 (14.1)
No	534 (85.6)
Missing	2 (0.3)
Risk score	
n	87
Mean (± SD)	1.87 (± 1.508)
Median (25%/75% quantiles)	1.00 (1.00 - 2.00)
Min-Max	0.0 - 7.0
Family History of gBRCA1/2-related Cancer(s)	
Yes	16 (2.6)
No	316 (50.6)
Unknown	290 (46.5)
Missing	2 (0.3)
Has a HRD panel test been performed?	
Yes	41 (6.6)
No	362 (58.0)
Unknown	219 (35.1)
Missing	2 (0.3)

HRD: Homologous recombinant deficiency.

Table 2: Disease characteristics at inclusion by *de novo* advanced disease.

	Total (n=624, n(%))	Yes (n=241, n (%))	No (n=383, n (%))
Tumor stage at ABC diagnosis			
Locoregionally advanced	33 (5.3)	15 (6.2)	18 (4.7)
Metastatic	361 (57.9)	57 (23.7)	304 (79.4)
Locoregionally advanced and metastatic	228 (36.5)	169 (70.1)	59 (15.4)
Missing	2 (0.3)	0 (0.0)	2 (0.5)
Time since initial diagnosis [years]			
N	624	241	383
Mean (±SD)	6.24 (±7.70)	0.28 (±1.66)	10.0 (±7.64)
Median (Q1/Q3)	3.2 (0.12/10.45)	0.10 (0.06/0.15)	8.26 (3.99/14.24)
Min–Max	0.0-41.2	0.0-23.7	0.3-41.2
Number of metastatic sites present at inclusion			
0	52 (8.3)[1]	18 (7.5)[1]	34 (8.9)[1]
1	376 (60.3)	145 (60.2)	231 (60.3)
2	122 (19.6)	50 (20.7)	72 (18.8)
3	54 (8.7)	17 (7.1)	37 (9.7)
≥4	20 (3.2)	11 (4.6)	9 (2.3)
Tumor distribution pattern at inclusion			
Unifocal	190 (30.4)	153 (63.5)	37 (9.7)
Multifocal	52 (8.3)	39 (16.2)	13 (3.4)
Multicenter	27 (4.3)	20 (8.3)	7 (1.8)
Other	48 (7.7)	29 (12.0)	19 (5.0)
No local relapse	306 (49.0)	0 (0.0)	306 (79.9)
Missing	1 (0.2)	0 (0.0)	1 (0.3)
Disease site present at inclusion			
Visceral	287 (46.0%)	106 (44.0%)	181 (47.3%)
Non-visceral only (excl. bone only)	73 (11.7%)	26 (10.8%)	47 (12.3%)
Bone only	212 (34.0%)	91 (37.8%)	121 (31.6%)
No metastases present at inclusion	52 (8.3%)	18 (7.5%)	34 (8.9%)
HER2 amplification/overexpression status			
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	525 (84.1)	241 (100.0)	284 (74.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
No new receptor status at inclusion	98 (15.7)	0 (0.0)	98 (25.6)
Missing	1 (0.2)	0 (0.0)	1 (0.3)
Estrogen receptor (ER) status			
Positive	521 (83.5)	240 (99.6)	281 (73.4)
Negative	3 (0.5)	0 (0.0)	3 (0.8)
Unknown	1 (0.2)	1 (0.4)	0 (0.0)
No new receptor status at inclusion	98 (15.7)	0 (0.0)	98 (25.6)
Missing	1 (0.2)	0 (0.0)	1 (0.3)
Progesterone receptor (PgR) status			
Positive	453 (72.6)	240 (99.6)	213 (55.6)
Negative	68 (10.9)	0 (0.0)	68 (17.8)
Unknown	4 (0.6)	1 (0.4)	3 (0.8)
No new receptor status at inclusion	98 (15.7)	0 (0.0)	98 (25.6)
Missing	1 (0.2)	0 (0.0)	1 (0.3)
Hormone receptor (HR) status			
Positive	525 (84.1)	241 (100.0)	284 (74.2)
Negative	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
No new receptor status at inclusion	98 (15.7)	0 (0.0)	98 (25.6)
Missing	1 (0.2)	0 (0.0)	1 (0.3)

[1] For some patients, metastases may not be present anymore at inclusion due to e.g. surgery.

Abbreviations:

ABC: Advanced Breast Cancer | CDK4/6: Cyclin-dependent-kinase 4/6 | gBRCA1/2: Germline Breast cancer gene 1/2 | DKG e.V.: Deutsche Krebsgesellschaft eingetragener Verein | eCRF: Electronic Case Report Form | EBC: Early Breast Cancer | ECOG: Eastern Cooperative Oncology Group | ER: Estrogen receptor | ET: Endocrine therapy | HER2: Human-epidermal-growth-factor-receptor 2 | HR: Hormone receptor | HRD: Homologous recombinant deficiency | mut: Mutation | PARPi: Poly(ADP-ribose)-Polymerase Inhibitor | PgR: Progesterone receptor | Q: Quartile | QoL: Quality of life | SD: Standard deviation

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Conflicts of Interest:

Julia Radosa: Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accomodation/Expenses

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