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Prognostic Impact of g*BRCA* Mutation Status on Outcomes with CDK4/6 Inhibitor Therapy in HR+/HER2- Metastatic Breast Cancer: A Real-World Cohort Study

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INTRODUCTION

- CDK4/6 inhibitors (CDK4/6i) are considered the standard of care for patients with hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC).
- We evaluated the association of g*BRCA* status with treatment patterns and clinical outcomes in a large real-world cohort of patients receiving CDK4/6 inhibitor–based therapy.

METHODS

- This retrospective study included 3,000 HR+/HER2– mBC patients treated with CDK4/6 inhibitors from January 2015 to December 2024.
- Patients were divided into three groups: gBRCA-mutated (n=86), gBRCA wild-type (n=913), and no germline testing (n=2001).
- Primary endpoints were progression-free survival (PFS) from the start of CDK4/6 therapy and overall survival (OS) from the time of first metastasis. Kaplan-Meier and Cox models were used to analyze survival outcomes by gBRCA status, with backward model selection for multivariable Cox analysis.

RESULTS

- Of the 3,000 patients treated with CDK4/6 inhibitors, 86 (3%) had a gBRCA mutation, 913 (30%) were gBRCA-negative, and 2,001 (67%) had no germline testing (Table 1).
- gBRCA-mutated patients were younger at diagnosis (median age 44 vs. 52 years) and more likely to have received platinum agents (24% vs. 9%) and PARP inhibitors (59% vs. 2%).
- After CDK4/6 progression, 48% of gBRCA-mutated patients received subsequent targeted therapy.
- No significant differences in ER/PR expression, HER2 IHC, or progression sites were found between groups.

RESULTS

Table 1: Summary of Patient Characteristics

	g*BRCA* status				
	g*BRCA* +	g*BRCA* -	No germline testing	Total	P-value
	(N=86)	(N=913)	(N=2001)	(N=3000)	
PFS duration since start of CDK4/6i					<.001[1]
Events/N	73/86	642/913	1323/2001	2038/3000	
Median (95% CI)	9.65 (7.40-13.92)	17.82 (15.93-20.66)	15.54 (14.12-16.60)	15.87 (15.01-16.73)	
Overall survival since start of CDK4/6i					<.001[1]
Events/N	45/86	376/913	792/2001	1213/3000	
Median (95% CI)	47.2 (38.0-65.5)	75.0 (68.3-82.8)	68.1 (61.5-73.6)	68.86 (66.48-73.85)	
Age at Diagnosis					<.001[2]
Mean (SD)	44.6 (11.47)	46.0 (11.40)	52.1 (11.76)	50.0 (12.00)	
Median (Range)	44.0 (27.0, 81.0)	45.0 (21.0, 92.0)	52.0 (19.0, 90.0)	49.0 (19.0, 92.0)	
PARPi, n (%)					<.001[3]
Not Received	35 (41%)	890 (97%)	1962 (98%)	2887 (96%)	
Received after CDK4/6i	45 (52%)	21 (2%)	36 (2%)	102 (3%)	
Received before CDK4/6i	6 (7%)	2 (0%)	3 (0%)	11 (0%)	
Platinum, n (%)					<.001[3]
Not containing regimen	65 (76%)	834 (91%)	1856 (93%)	2755 (92%)	
Containing regimen	21 (24%)	79 (9%)	145 (7%)	245 (8%)	
Type of subsequent agent after CDK4/6i, n (%)					<.001[3]
Targeted	33 (48%)	251 (39%)	482 (38%)	766 (39%)	
Chemo	28 (41%)	260 (40%)	547 (43%)	835 (42%)	
Endocrine	4 (6%)	69 (11%)	169 (13%)	242 (12%)	
Investigation	4 (6%)	64 (10%)	62 (5%)	130 (7%)	
Missing	17	269	741	1027	
Menopausal status at Dx, n (%)					<.001[3]
Postmenopausal	37 (44%)	409 (46%)	1370 (69%)	1816 (61%)	
Premenopausal	48 (56%)	484 (54%)	607 (31%)	1139 (38%)	
Missing	1	15	23	39	

[1]Logrank p-value; [2]Kruskal-Wallis p-value; [3]Chi-Square p-value;

RESULTS

Table 2: Multivariable Analysis for PFS 1st line CDK4/6i based on Based on Backward Model Selection

Variables	level	Hazard ratio (95% CI)	P- Value	Overall P-Value
PARPi	Not received vs received before CDK4/6i	0.70 (0.21, 2.31)	0.556	0.299
	Received after CDK4/6i vs before CDK4/6i	0.53 (0.16, 1.76)	0.300	
Platinum containing regimen	containing vs. without containing regimen	1.85 (1.39, 2.48)	< 0.001	< 0.001
BRCA status	Pos vs. neg	1.91 (1.24, 2.92)	0.003	0.003
Subsequent agent after CDK4/6i	Targeted vs. investigation	1.22 (0.89, 1.68)	0.224	< 0.001
	Chemo vs. investigation	1.80 (1.29, 2.50)	< 0.001	
	Endocrine vs. investigation	1.02 (0.68, 1.52)	0.934	

Table 3: Multivariable Analysis for OS 1st line CDK4/6i based on Based on Backward Model Selection

Variables	level	Hazard ratio (95% CI)	P- Value	Overall P-Value
Neoadjuvant agent	Have vs without	2.08 (1.60, 2.71)	< 0.001	< 0.001
PARPi	Not received vs received before CDK4/6i	1.06 (0.33, 3.36)	0.922	0.143
	Received after CDK4/6i vs before CDK4/6i	0.57 (0.18, 1.80)	0.340	
Vascular invasion	Pos vs neg	0.72 (0.55, 0.94)	0.014	0.014
BRCA status	Pos vs. neg	2.78 (1.53, 5.05)	< 0.001	< 0.001
Adjuvant hormone therapy duration	<12 vs. ≥ 12 months	1.28 (0.75, 2.18)	0.359	0.359

- Both **progression-free survival (PFS)** and **overall survival (OS)** significantly differed according to g*BRCA* status (p<0.001 for both).
- In multivariable analysis for 1st line CDK4/6i PFS **(Table 2) :** g*BRCA* mutation and prior platinum exposure were independently associated with shorter progression-free survival, while subsequent chemotherapy after CDK4/6 inhibitors was also linked to poorer outcomes, and PARP inhibitor use showed no significant effect.
- In multivariable analysis for 1st line CDK4/6i OS **(Table 3)** : g*BRCA* mutation and prior neoadjuvant chemotherapy independently predicted worse overall survival, while vascular invasion was associated with improved survival, and PARP inhibitor use or endocrine therapy duration showed no significant effect.

Figure 1: Kaplan-Meier Estimates of PFS by g*BRCA* Subgroups

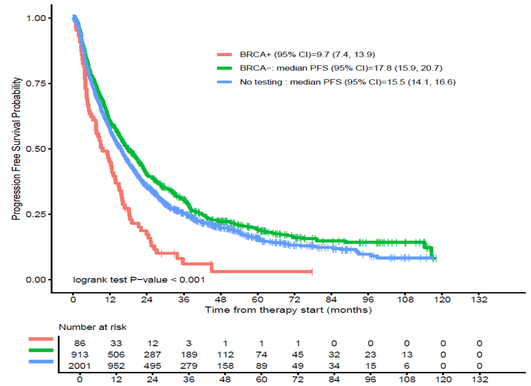
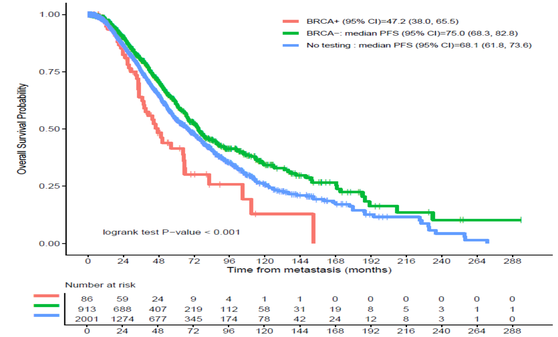


Figure 2: Kaplan-Meier Estimates of OS by g*BRCA* Subgroups



CONCLUSIONS

- In this large real-world cohort, g*BRCA* mutations were associated with significantly worse OS and PFS among patients with HR+/HER2– mBC treated with CDK4/6 inhibitors.
- These findings suggest that g*BRCA* mutation status may have prognostic implications even in luminal disease and should be considered in treatment sequencing decisions.
- Prospective validation and exploration of optimal therapeutic combinations, including early use of PARP inhibitors or ADCs in this population, are warranted.

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