BRCA copy number loss and/or deletions detected by cell-free DNA in patients with metastatic breast cancer: incidence and association with clinical/genomic features

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BACKGROUND

- ***BRCA*** **mutations may impact outcomes in metastatic breast cancer (MBC).**
- **While germline and somatic *BRCA* mutations have been studied, the incidence and impact of cell-free DNA (cfDNA) *BRCA* copy number loss and/or deletions (CNL/D) are not known.**
- **We evaluated cfDNA *BRCA* CNL/D, and the association with clinical/genomic features in MBC.**

METHODS

- **Patients with MBC with cfDNA (Guardant360 next-generation sequencing) results from 12/2021 (when Guardant360 began reporting *BRCA CNL/D*) to 1/2024 were identified.**
- **Patients were identified from 3 academic centers in the Precision Medicine Action for Cancer Consortium**
- **A retrospective analysis was conducted to identify clinical/genomic features associated with cfDNA *BRCA1 and/or 2* CNL/D.**
- **Median therapy durations and overall survival (OS) after detection of cfDNA *BRCA* CNL/D were estimated with the Kaplan-Meier method.**

RESULTS

- **Among 1,198 patients with MBC who underwent cfDNA testing, 65 (5.4%) had cfDNA *BRCA* CNL/D.**
- **Table 1. Demographics of patients with cfDNA *BRCA* CNL/D.**

Characteristic	Value
Age (median) at MBC diagnosis	60 years
Subtype	
HR+/HER2-	47/65 (72%)
TNBC	15/65 (23%)
HER2+	3/65 (4.6%)
# prior therapies for MBC before cfDNA testing (median)	
Hormone therapy (HR+/HER2-)	1
Chemotherapy (all subtypes)	0

- **Table 2. Types of cfDNA *BRCA* CNL/D.**

Type of *BRCA* copy number loss and/or deletions	# of patients (total N=65 but some patients had ≥1 type of *BRCA* copy number loss and/or deletions)
BRCA **single copy number loss**	20 (31%)
BRCA **single copy deletion**	17 (26%)
BRCA **biallelic loss (single copy deletion & co-occurring loss of function variant)**	9 (14%)
BRCA **biallelic loss (homozygous deletion)**	4 (6%)
BRCA **exon deletion**	4 (6%)
BRCA **copy number loss not otherwise specified**	15 (23%)

RESULTS (CONTINUED)

- **Table 3. Genomic features of cfDNA *BRCA* CNL/D.**

Characteristic	# of patients
Type of cfDNA *BRCA* CNL/D	
BRCA1	16/65 (25%)
BRCA2	37/65 (57%)
BRCA 1 and BRCA2	12/65 (18%)
Co-existing pathogenic cfDNA *BRCA* mutation	13/65 (20%)
Co-existing cfDNA *TP53* mutation	40/65 (62%)
cfDNA high tumor mutation burden (TMB) ≥ 10 mut/Mb	43/65 (66%)
Concomitant tumor tissue *BRCA1/2* mutation	10/32 (31%)
Concomitant germline *BRCA1/2* mutation	5/45 (11%)

- **Table 4.Outcomes of patients with cfDNA *BRCA* CNL/D.**

Characteristic	Value
Median duration on 1st therapy post cfDNA *BRCA* CNL/D detection	94 days (95% CI: 54-134 days)
Median duration of platinum chemotherapy in 5 patients post cfDNA *BRCA* CNL/D detection	168 days (Range: 32-582 days)
Median duration of PARP inhibitor in 4 patients post cfDNA *BRCA* CNL/D detection	105 days (Range: 26-231 days)
Median overall survival post cfDNA *BRCA* CNL/D	490 days (95% CI: 232-748 days)

CONCLUSIONS

- **CfDNA *BRCA* CNL/D are detectable in a subset of patients with MBC, with most presenting in the absence of a germline *BRCA1/2* mutation.**
- **CfDNA *BRCA* CNL/D co-occurred frequently with *TP53* mutations and elevated TMB, suggesting the possibility that cfDNA *BRCA* CNL/D may arise from increased mutagenesis in MBC.**
- **Further research is needed to define the impact of platinum and PARP inhibitor therapy in this population.**

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