PS2-02-07: Impact of *BRCA* Homozygous Copy Loss on Clinical Outcomes of Patients (pts) with Metastatic Breast Cancer (MBC) Receiving PARP Inhibitors (PARPi)

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BACKGROUND

- PARPi are used in the treatment of patients with MBC and *BRCA1/2* genomic alterations (GA), by targeting underlying homologous recombination deficiency (HRD).
- This study explored clinical and genomic factors associated with PARPi sensitivity in a real-world MBC cohort.

METHODS

- This retrospective study included 290 pts with MBC who underwent genomic testing via FoundationOne®/ FoundationOne®CDx (F1CDx®) tissue comprehensive genomic profiling (CGP) prior to treatment (Tx) with a PARPi.
- Data was obtained from the U.S.-wide de-identified Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic Database (FH-FMI CGDB) between 01/2011-12/2024. Clinical data from the FH Research Database(1) are linked to genomic data, derived from FMI's CGP tests (F1CDx®) in the FH-FMI CGDB by deterministic matching, providing a deidentified dataset (2-3).
- HRD genomic alterations (GA) were defined as mutations, homozygous copy loss, or structural rearrangements in any of the following genes: *BRCA1/2, ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1/2, CDK12, FANCA, FANCL, MRE11, RAD51B/C/D, RAD54L* or *PALB2*.
- HRD signature (HRDsig) status was calculated using genome-wide copy number features, with scores from 0 to 1 and a predefined cutoff of 0.7 to call HRDsig(+).
- *BRCA1/2* germline status was inferred using a validated somatic-germline-zygosity algorithm.
- Time to next treatment or death (TTNT) on PARPi was analyzed using Cox models adjusted for clinical variables.

11,985 pts with tissue biopsy

Cohort selection

FILTERING:

- ✓ 479 pts associated with older tissue biopsies
- ✓ 2,147 pts non-metastatic BC
- ✓ 8,966 pts did not receive PARPi
- ✓ 26 pts with missing hormone receptor status
- ✓ 42 pts with missing treatment information
- ✓ 9 pre-Tx samples with delayed entry

290 pts receiving PARPi

PATIENTS CHARACTERISTICS

Table 1. Baseline characteristics of patients

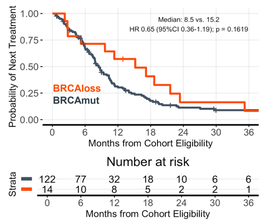
Characteristics*	HR+ (N=186)	HR- (N=104)	Total (N=290)	p value
Age at line start				0.441
Median (Q1, Q3)	57.0 (49.2, 66.0)	57.5 (42.8, 65.2)	57.0 (47.0, 66.0)	
Gender				0.287
Female	178 (95.7%)	>99 (>95.1%)	280 (96.6%)	
Male	8 (4.3%)	<=5 (<=4.9%)	10 (3.4%)	
HER2 status				0.001
IHC 0	57 (30.6%)	55 (52.9%)	112 (38.6%)	
IHC 1+	72 (38.7%)	26 (25.0%)	98 (33.8%)	
IHC 2+	43 (23.1%)	12 (11.5%)	55 (19.0%)	
HER3+ or ISH+	12 (6.5%)	9 (8.7%)	21 (7.2%)	
Unknown	2 (1.1%)	2 (1.9%)	4 (1.4%)	
Metastatic sites at diagnosis				< 0.001
Bone only	17 (9.1%)	8 (7.7%)	25 (8.6%)	
CNS	26 (14.0%)	34 (32.7%)	60 (20.7%)	
Visceral (with no CNS disease)	143 (76.9%)	62 (59.6%)	205 (70.7%)	
PARPi received				0.005
Niraparib	1 (0.5%)	3 (2.9%)	4 (1.4%)	
Olaparib	171 (91.9%)	81 (77.9%)	252 (86.9%)	
Rucaparib	2 (1.1%)	1 (1.0%)	3 (1.0%)	
Talazoparib	12 (6.5%)	19 (18.3%)	31 (10.7%)	
PARPi regimen				0.051
PARPi + CDK4/6 Inhibitor	7 (3.8%)	1 (1.0%)	8 (2.8%)	
PARPi + Chemotherapy	18 (9.7%)	7 (6.7%)	25 (8.6%)	
PARPi + Clinical study drug	1 (0.5%)	1 (1.0%)	2 (0.7%)	
PARPi + Endocrine Therapy	21 (11.3%)	3 (2.9%)	24 (8.3%)	
PARPi + Immunotherapy or Chemoimmunotherapy	6 (3.2%)	7 (6.7%)	13 (4.5%)	
PARPi + Other Targeted Therapies	5 (2.7%)	1 (1.0%)	6 (2.1%)	
PARPi Monotherapy	128 (68.8%)	84 (80.8%)	212 (73.1%)	
Line of therapy received PARPi				< 0.001
1	18 (9.7%)	23 (22.1%)	41 (14.1%)	
2	42 (22.6%)	36 (34.6%)	78 (26.9%)	
3	37 (19.9%)	19 (18.3%)	56 (19.3%)	
>=4	89 (47.8%)	26 (25.0%)	115 (39.7%)	
Number of lines of previous endocrine-therapy				< 0.001
0	71 (38.2%)	8 (7.7%)	79 (27.2%)	
1	46 (24.7%)	5 (4.8%)	51 (17.6%)	
2	35 (18.8%)	2 (1.9%)	37 (12.8%)	
>=3	34 (18.3%)	89 (85.6%)	123 (42.4%)	
Number of lines of prior platinum in metastatic setting				0.005
0	26 (14.0%)	28 (26.9%)	54 (18.6%)	
1	1 (0.5%)	4 (3.8%)	5 (1.7%)	
2	1 (0.5%)	0 (0.0%)	1 (0.3%)	
>=3	158 (84.9%)	72 (69.2%)	230 (79.3%)	
Prior CDK4/6 in metastatic setting				< 0.001
No	54 (29.0%)	93 (89.4%)	147 (50.7%)	
Yes	132 (71.0%)	11 (10.6%)	143 (49.3%)	
Prior ADC in metastatic setting				0.212
No	174 (93.5%)	93 (89.4%)	267 (92.1%)	
Yes	12 (6.5%)	11 (10.6%)	23 (7.9%)	
Specimen collection				0.066
After Met Dx	159 (85.5%)	80 (76.9%)	239 (82.4%)	
Before Met Dx	27 (14.5%)	24 (23.1%)	51 (17.6%)	

HR+: Hormone receptor–positive; HR–: Hormone receptor–negative; IHC: Immunohistochemistry; HER2: Human epidermal growth factor receptor 2; ISH: In situ hybridization; Met: Metastases; Dx: Diagnosis; ADC: antibody-drug conjugate

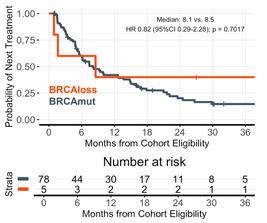
RESULTS

Figure 1. TTNT for *BRCA1/2*loss vs. *BRCA1/2*mut for patients receiving PARPi

A. HR(+): TTNT *BRCA1/2*loss



B. HR(-): TTNT *BRCA1/2*loss



C.HR(+): TTNT *BRCA1/2*loss multivariable model

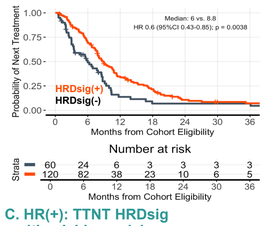
Variable		N Events	Estimate	Estimate (95% CI)	p-value
BRCAloss	BRCA1/2 mut or ns	122	103	Reference	
	BRCA1/2 loss	14	13	1.40 (0.19, 4.62)	0.612
Age		136	106	1.00 (0.99, 1.02)	0.612
Line of Tx	1	18	10	Reference	
	2	39	28	1.79 (0.77, 4.19)	0.175
	3	28	25	2.17 (0.88, 5.37)	0.095
	4+	99	93	2.29 (0.94, 5.59)	0.069
ECOG PS	0	52	42	Reference	
	1	61	44	1.12 (0.70, 1.78)	0.636
	2+	14	14	1.86 (0.94, 3.66)	0.074
	Unknown	59	46	1.30 (0.72, 2.35)	0.383
Metastatic sites	Bone only	17	9	Reference	
	CNS	19	15	1.68 (0.59, 4.79)	0.332
	Visceral (with no CNS disease)	106	84	1.73 (0.72, 4.16)	0.220
Prior ADC	No	129	111	Reference	
	Yes	7	5	1.49 (0.55, 4.05)	0.439
Prior CDK4/6	No	41	33	Reference	
	Yes	95	83	1.73 (0.62, 5.28)	0.258
Prior Platinum	No	116	98	Reference	
	Yes	20	18	1.59 (0.72, 3.72)	0.367
PARPi regimen	PARPi +/- ET	114	97	Reference	
	PARPi combo	22	19	0.90 (0.53, 1.50)	0.695
Site of biopsy	Primary	31	25	Reference	
	Metastatic/Unknown	103	91	0.99 (0.60, 1.63)	0.962

D. HR(-): TTNT *BRCA1/2*loss multivariable model

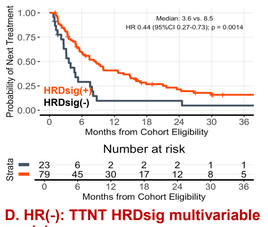
Variable		N Events	Estimate	Estimate (95% CI)	p-value
BRCAloss	BRCA1/2 mut or ns	78	61	Reference	
	BRCA1/2 loss	5	4	0.55 (0.17, 1.72)	0.300
Age		83	67	0.98 (0.96, 1.01)	0.163
Line of Tx	1	18	16	Reference	
	2	21	23	0.62 (0.36, 1.75)	0.601
	3	15	11	0.62 (0.24, 1.62)	0.332
	4+	16	15	1.05 (0.39, 2.83)	0.921
ECOG PS	0	34	26	Reference	
	1	32	25	0.69 (0.33, 1.45)	0.330
	2+	11	9	1.93 (0.73, 5.05)	0.183
	Unknown	6	5	1.60 (0.45, 5.66)	0.462
Metastatic sites	Bone only	8	5	Reference	
	CNS	28	21	1.66 (0.60, 5.67)	0.260
	Visceral (with no CNS disease)	48	39	2.12 (0.75, 5.97)	0.109
Prior ADC	No	77	59	Reference	
	Yes	6	6	2.95 (0.85, 10.20)	0.088
Prior CDK4/6	No	73	56	Reference	
	Yes	10	9	0.93 (0.35, 2.46)	0.887
Prior Platinum	No	62	48	Reference	
	Yes	21	17	1.70 (0.72, 3.60)	0.148
PARPi regimen	PARPi +/- ET	73	57	Reference	
	PARPi combo	10	8	0.93 (0.41, 2.10)	0.863
Site of biopsy	Primary	30	23	Reference	
	Metastatic/Unknown	53	44	1.14 (0.65, 2.02)	0.649

Figure 2. TTNT for HRDsig(+) vs. HRDsig(-) for patients receiving PARPi

A. HR(+): TTNT HRDsig



B. HR(-): TTNT HRDsig



C. HR(+): TTNT HRDsig multivariable model

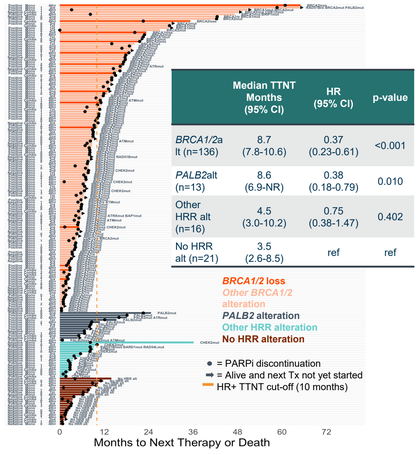
Variable		N Events	Estimate	Estimate (95% CI)	p-value
HRDsig	Negative	92	52	Reference	
	Positive	150	107	0.52 (0.36, 0.76)	<0.001
Age		186		1.00 (0.98, 1.01)	0.612
Line of Tx	1	16	12	Reference	
	2	40	33	0.88 (0.40, 1.92)	0.748
	3	30	32	1.03 (0.44, 2.37)	0.951
	4+	87	80	0.98 (0.42, 2.26)	0.960
ECOG PS	0	66	56	Reference	
	1	78	61	0.84 (0.54, 1.33)	0.542
	2+	16	13	1.44 (0.66, 2.86)	0.061
	Unknown	30	25	1.04 (0.62, 1.74)	0.885
Metastatic sites	Bone only	17	12	Reference	
	CNS	23	19	1.83 (0.66, 5.90)	0.266
	Visceral (with no CNS disease)	146	126	1.32 (0.66, 2.64)	0.433
Prior ADC	No	168	147	Reference	
	Yes	12	10	2.53 (1.23, 5.19)	0.011
Prior CDK4/6	No	50	47	Reference	
	Yes	130	110	0.69 (0.39, 2.36)	0.183
Prior Platinum	No	153	132	Reference	
	Yes	27	25	1.22 (0.73, 2.06)	0.449
PARPi regimen	PARPi +/- ET	146	127	Reference	
	PARPi combo	34	30	1.02 (0.66, 1.57)	0.938
Site of biopsy	Primary	47	36	Reference	
	Metastatic/Unknown	133	121	1.02 (0.66, 1.58)	0.914

D. HR(-): TTNT HRDsig multivariable model

Variable		N Events	Estimate	Estimate (95% CI)	p-value
HRDsig	Negative	73	21	Reference	
	Positive	110	62	1.90 (0.22, 0.86)	0.017
Age		103		0.98 (0.96, 1.00)	0.033
Line of Tx	1	18	18	Reference	
	2	35	27	0.84 (0.42, 1.69)	0.632
	3	18	14	0.71 (0.33, 1.54)	0.386
	4+	26	24	0.94 (0.40, 2.22)	0.893
ECOG PS	0	37	29	Reference	
	1	41	33	0.99 (0.54, 1.81)	0.964
	2+	15	13	2.94 (1.25, 6.92)	0.014
	Unknown	3	2	0.96 (0.20, 2.46)	0.890
Metastatic sites	Bone only	7	5	Reference	
	CNS	34	27	1.43 (0.48, 4.25)	0.522
	Visceral (with no CNS disease)	61	51	1.69 (0.61, 4.63)	0.311
Prior ADC	No	91	73	Reference	
	Yes	11	10	1.56 (0.57, 4.31)	0.387
Prior CDK4/6	No	91	75	Reference	
	Yes	11	8	0.90 (0.39, 2.28)	0.902
Prior Platinum	No	70	57	Reference	
	Yes	32	26	1.31 (0.78, 2.44)	0.264
PARPi regimen	PARPi +/- ET	69	49	Reference	
	PARPi combo	16	14	1.15 (0.61, 2.16)	0.672
Site of biopsy	Primary	39	29	Reference	
	Metastatic/Unknown	63	54	1.01 (0.62, 1.64)	0.979

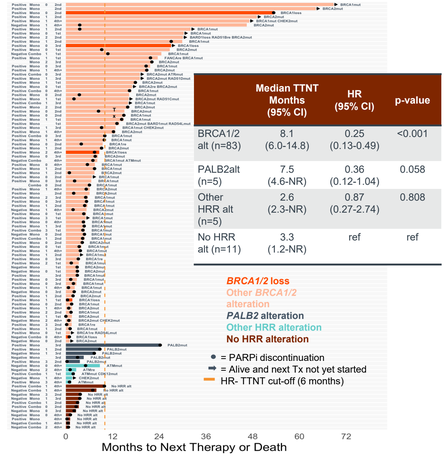
Figure 3. Swimmer plots show TTNT (each bar represents PARPi line of therapy duration) and TTD (dots represent treatment discontinuation).

A. HR+ (n=186): Time to PARPi discontinuation and TTNT or death



	Median TTNT Months (95% CI)	HR (95% CI)	p-value
*BRCA1/2*alt (n=136)	8.7 (7.8-10.6)	0.37 (0.23-0.61)	<0.001
*PALB2*alt (n=13)	8.6 (6.9-NR)	0.38 (0.18-0.79)	0.010
Other HRR alt (n=16)	4.5 (3.0-10.2)	0.75 (0.38-1.47)	0.402
No HRR alt (n=21)	3.5 (2.6-8.5)	ref	ref

B. HR- (n=104): Time to PARPi discontinuation and TTNT or death



	Median TTNT Months (95% CI)	HR (95% CI)	p-value
BRCA1/2 alt (n=83)	8.1 (6.0-14.8)	0.25 (0.13-0.49)	<0.001
PALB2alt (n=5)	7.5 (4.6-NR)	0.36 (0.12-1.04)	0.058
Other HRR alt (n=5)	2.6 (2.3-NR)	0.87 (0.27-2.74)	0.808
No HRR alt (n=11)	3.3 (1.2-NR)	ref	ref

CONCLUSIONS

- In HR+ MBC, the clinical benefit of PARPi is clearly driven by ***BRCA1/2* and *PALB2 genomic alterations***, with the most pronounced outcomes observed in patients harboring ***BRCA* homozygous copy loss.**
- The potential value of **HRD signature testing in *BRCA/PALB2* wild-type cohorts requires rigorous evaluation**.
- These findings **underscore the critical role of comprehensive genomic profiling** and the necessity of detecting and reporting **homozygous copy loss alterations** to directly inform PARPi treatment decisions.

REFERENCES

1. https://flatiron.com/database-characterization 2. Singal G, et al. JAMA. 2019;321(14):1391-1399. 3. Milbury CA, et al. PLoS One. 2022;17(3):e0264138.

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