ASCO Genitourinary Cancers Symposium

Real-world effectiveness of PARP inhibitors (PARPi) in metastatic-castration resistant prostate cancer (mCRPC) by genomic homologous recombination repair alterations and homologous recombination deficiency signature (*HRDsig*)

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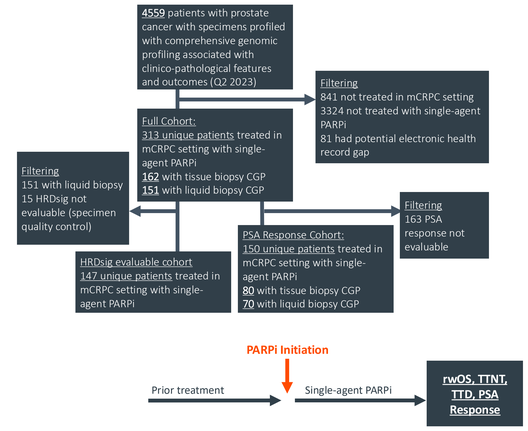
BACKGROUND

- Multiple randomized controlled trials have demonstrated efficacy of poly ADP-ribose polymerase (PARP) inhibitors in patients with metastatic castration resistant prostate cancer (mCRPC) harboring deleterious *BRCA1* or *BRCA2* alterations (*BRCA*alt).
- Alterations in other DNA homologous recombination repair (HRR) gene pathways are common and the efficacy of PARPi in these populations is less clear.
- **Objective**: We sought to evaluate the real-world effectiveness of PARPi in commonly defined HRR groups and explore clinical validity of HRDsig to additionally predict outcomes on PARPi.

MATERIALS AND METHODS

- This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine Prostate Cancer clinico-genomic database (FH-FMI CGDB), originating from approximately 280 US cancer clinics (~800 sites of care).
- Retrospective longitudinal clinical data were derived from electronic health record (EHR) data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI comprehensive genomic profiling (CGP) tests in the FH-FMI CGDB by de-identified, deterministic matching.
- Genomic alterations were identified via comprehensive genomic profiling (CGP) of >300 cancer-related genes on FMI's next-generation sequencing (NGS) test: FoundationOne® CDx or FoundationOneLiquid® CDx.
- Patients with mCRPC and tumor genomic profiling (tissue or liquid) who underwent single agent PARPi treatment were included, grouped by biomarkers with deleterious alterations detected: *BRCA1/2*, *ATM*, other HRR (ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1, CHEK2, CDK12, FANCA, FANCL, MRE11, RAD51B, RAD51C, RAD51D, RAD54L, PALB2), or no HRR.
- Patients with tumor tissue profiling were grouped by novel homologous recombination signature (*HRDsig)* status
- Kaplan Meier estimates and multivariable Cox PH models assessed time to next therapy (**TTNT**), time to treatment discontinuation (**TTD**), and real-world overall survival (**rwOS**).

COHORT OVERVIEW



RESULTS

Table 1: Clinicopathologic Patient Characteristics

	LBx (N=151)	TBx (N=162)	Total (N=313)	p value
Age				0.003
Median (Q1, Q3)	75.0 (68.5, 80.0)	71.0 (65.0, 77.0)	73.0 (66.0, 79.0)	
ECOG				0.329
1	53 (35.1%)	65 (40.1%)	118 (37.7%)	
2	28 (18.5%)	20 (12.3%)	48 (15.3%)	
3+	40 (26.5%)	50 (30.9%)	90 (28.8%)	
Unknown	30 (19.9%)	27 (16.7%)	57 (18.2%)	
Treatment Setting				0.498
1st line mCRPC	8 (5.3%)	13 (8.0%)	21 (6.7%)	
2nd line mCRPC	36 (23.8%)	46 (28.4%)	82 (26.2%)	
3rd line mCRPC	39 (25.8%)	34 (21.0%)	73 (23.3%)	
4th+ line mCRPC	68 (45.0%)	69 (42.6%)	137 (43.8%)	
HRR Category				< 0.001
No HRR alteration	12 (7.9%)	20 (12.3%)	32 (10.2%)	
ATM alt	52 (34.4%)	27 (16.7%)	79 (25.2%)	
BRCA1/2 alt	50 (33.1%)	80 (49.4%)	130 (41.5%)	
Other HRD alt	37 (24.5%)	35 (21.6%)	72 (23.0%)	
Pre-Tx PSA				0.934
Median (Q1, Q3)	86.2 (18.8, 367.9)	81.7 (17.6, 310.5)	83.8 (17.9, 322.6)	
N-Miss	67	72	139	
Pre-Tx Albumin				0.527
Below LLN	20 (14.8%)	24 (17.6%)	44 (16.2%)	
Normal	115 (85.2%)	112 (82.4%)	227 (83.8%)	
N-Miss	16	26	42	
Pre-Tx Alkaline Phosphatase				0.977
Above ULN	47 (34.8%)	44 (34.6%)	91 (34.7%)	
Normal	88 (65.2%)	83 (65.4%)	171 (65.3%)	
N-Miss	16	35	51	
Pre-Tx Hemoglobin				0.458
Below LLN	106 (79.7%)	114 (83.2%)	220 (81.5%)	
Normal	27 (20.3%)	23 (16.8%)	50 (18.5%)	
N-Miss	18	25	43	
Practice Type				0.308
Academic	33 (21.9%)	28 (17.3%)	61 (19.5%)	
Community	118 (78.1%)	134 (82.7%)	252 (80.5%)	
Prior NHT				0.11
No	7 (4.6%)	15 (9.3%)	22 (7.0%)	
Yes	144 (95.4%)	147 (90.7%)	291 (93.0%)	
Prior Taxane				0.114
No	74 (49.0%)	65 (40.1%)	139 (44.4%)	
Yes	77 (51.0%)	97 (59.9%)	174 (55.6%)	
Prior Platinum				0.146
No	136 (90.1%)	153 (94.4%)	289 (92.3%)	
Yes	15 (9.9%)	9 (5.6%)	24 (7.7%)	
Pre-Tx Opioid Use				0.669
No Evidence	105 (69.5%)	109 (67.3%)	214 (68.4%)	
Yes	46 (30.5%)	53 (32.7%)	99 (31.6%)	
Treatment Recieved				0.686
Olaparib	143 (94.7%)	155 (95.7%)	298 (95.2%)	
Rucaparib	8 (5.3%)	7 (4.3%)	15 (4.8%)	
PSA Response				0.592
Evaluable	70 (46.4%)	80 (49.4%)	150 (47.9%)	
Unevaluable	81 (53.6%)	82 (50.6%)	163 (52.1%)	

Figure 1: Outcomes on PARPi by Biomarker Group. Swimmer's plots of TTNT per patient receiving single-agent PARPi and receiving genomic profiling via tissue biopsy.

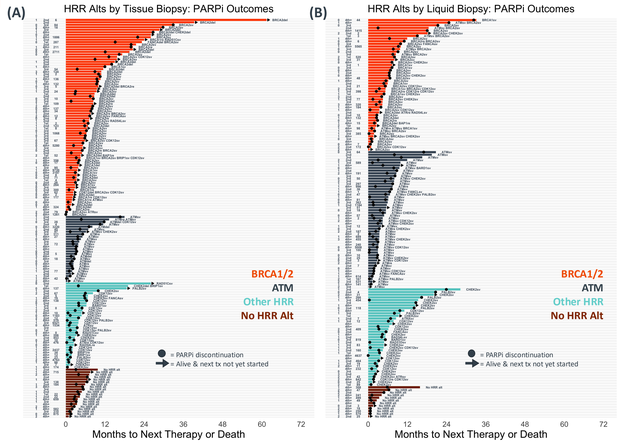


Figure 2: *BRCA*alt is associated with improved (A) TTNT (B) TTD (C) and rwOS in multivariable models. Multivariable Cox PH models are shown, adjusting for baseline prognostic factors in the tissue biopsy (TBx) and liquid biopsy (LBx) cohorts.

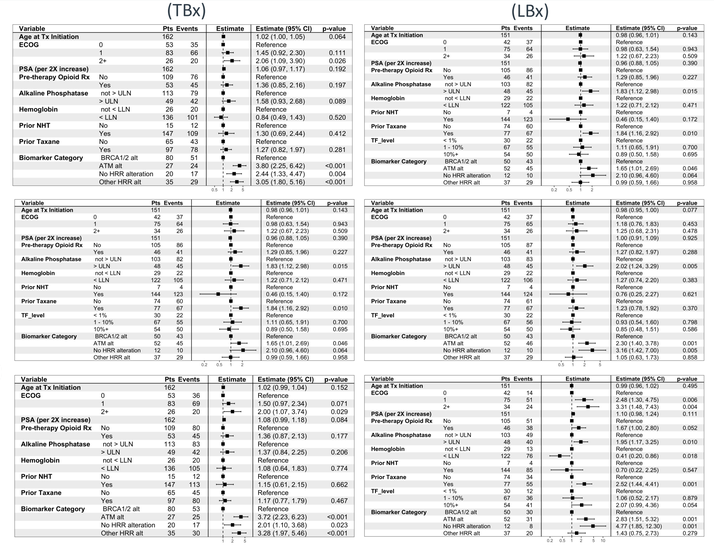


Figure 3: *BRCA*alt is associated with improved on therapy PSA response. The change in PSA from baseline to on-therapy is shown

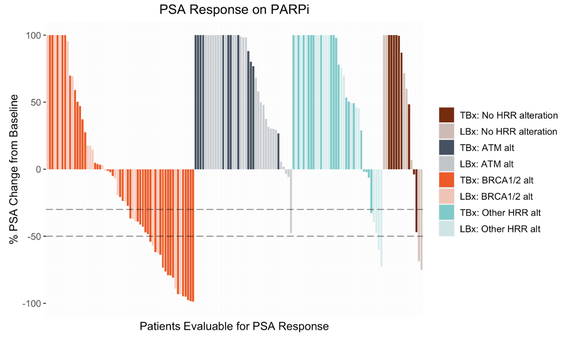
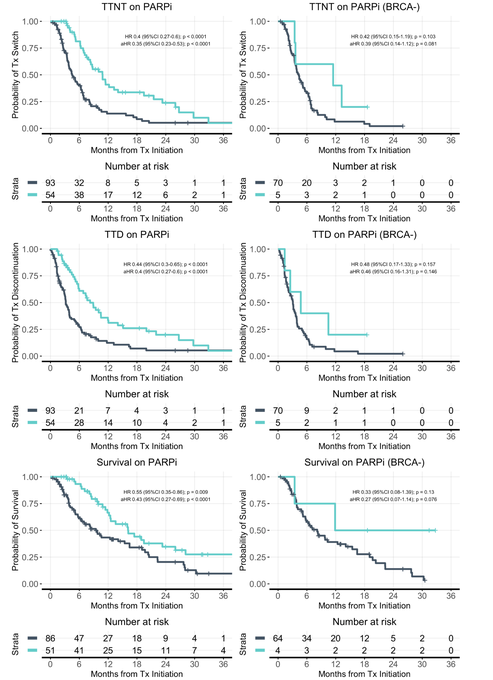


Figure 4: Novel *HRDsig* is associated with improved PARPi outcomes and identifies a subset of BRCA- patients who may benefit from PARPi. (A) TTNT, (B) TTD, and (C) rwOS stratified by either the entire patient cohort or BRCA- patients only.



CONCLUSIONS

- Our data show no significant outcomes difference between non-*BRCA*alt groups (defined as ATM, other HRR, and no HRR) in the tissue CGP cohort with respect to proxies of drug effectiveness
- *BRCA* alterations identified on liquid CGP were not associated with improved PARPi outcomes compared to patients with other HRR mutations.
- HRDsig may be able to identify a non-*BRCA*alt subgroup with enhanced benefit. Associations of *BRCA*alt(-)/HRDsig(+) and PARPi performance deserve further attention in additional cohorts.