Real-World Clinical Outcomes and Genomic Profiles of Patients with Metastatic Castration Resistant ProstateCancer (mCRPC) Harboring Both Androgen Receptor ligand binding domain (AR-lbd) Missense Mutations and AR Copy Number Amplifications.

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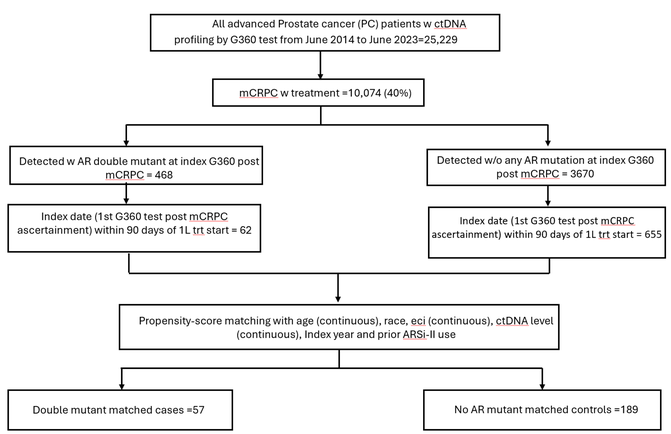
Introduction

- Missense mutations in androgen receptor ligand binding domain (AR-LBD-mut) and AR copy number amplifications (AR-CN-amp) are potential mechanisms of resistance to second-generation antiandrogen (ARSi-II) therapies (abiraterone, enzalutamide, apalutamide and darolutamide) among mCRPC patients.
- There is limited real world evidence (RWE) on these double-mutant mCRPC patients.
- Thus, we analyzed the genomic profile and clinical outcomes of such patients and compared them to the patients with no detectable AR mutations, in first line (1L) RWE setting.

Methods

- **Data Source:** Patients were identified from the claims-based clinical-genomic database GuardantINFORM, which links cell-free circulating tumor DNA (cfDNA) results to de-identified claims data, with study time period from June 2014 to June 2023.
- **Inclusion and exclusion criteria:**
  - Adult mCRPC patients in the US who received cell-free circulating tumor (ctDNA) testing via Guardant360 (G360) test.
  - The AR-aberration–positive cohort (case) consists of patients with both AR-mut in the LBD domain (665-919[1]; oncogenic variants) and AR-CN-amp.
  - The absence of any aberration in the AR region was defined as AR–negative (control).
  - Patients with index date (first G360 test post mCRPC ascertainment) within 90 days of 1L treatment start were included.
  - We compared the mutation profile and 1L RW time to treatment discontinuation (rwTTD) among the matched cohorts
- **Matching:**
  - Propensity score matching was used using variables: age, race, Elixhauser Comorbidity Index (ECI), ctDNA level, index year and prior ARSi-II use.
  - 1:k matching was done for up to 4 controls per case.

Figure 1. Consort Diagram



Results

62 cases and 655 controls were included in the analysis (**Figure 1**). Propensity score matching resulted in 57 cases matched with 189 controls. Unmatched patient demographic and clinical characteristics is summarized **Table 1.** 1L treatment (Top 3) among the matched cases were docetaxel+leuprolide (14%), enzalutamide (12%) and leuprolide+ra-223 (9%) while among the controls it was leuprolide (14%), enzalutamide (7%) and docetaxel+leuprolide (7%). Matched cases showed shorter median rwTTD compared to the control cohort [4.4 months (95% CI 3.1-5.7) vs 5.6 months (95% CI 4.6-7.4), p= 0.017] as shown in **Figure 2**. The oncoprints are shown in **Figure 3** which shows that the matched cases are enriched with FGFR1, CCNE1 and CDK6 as co-occurring mutations.

Table 1. Patient demographic and clinical characteristics

Parameters		Before Matching		After Matching (Weighted)	
		Case (N=62)	Control (N=655)	Case (N=57)	Control (N=57)
Age	Mean (SD)	69.2 (8.1)	70.6 (9.2)	69.2 (8.9)	69.1 (8.2)
ctDNA level*	Mean (SD)	23 (23.3)	8.6 (16.6)	19.2 (18.4)	17.4 (20.5)
TMB Score	Mean (SD)	31.6 (56.5)	9.5 (6.5)	9.4 (2.4)	9.4 (4.7)
	Unknown (N %)	50 (81%)	476 (73%)	48 (84%)	147 (78%)
Race*	White (N %)	29 (47%)	438 (67%)	29 (50%)	29 (50%)
	African American (N %)	9 (15%)	76 (12%)	6 (11%)	6 (11%)
	Others (N %)	7 (11%)	25 (4%)	6 (11%)	6 (11%)
	Unknown (N %)	17 (27%)	116 (17%)	16 (28%)	16 (28%)
Ethnicity	Hispanic (N %)	2 (3%)	38 (6%)	2 (3%)	4 (7%)
	Non-Hispanic (N %)	28 (45%)	315 (48%)	26 (46%)	25 (43%)
	Unknown (N %)	32 (52%)	302 (46%)	29 (51%)	28 (50%)
Location	Northeast (N %)	7 (11%)	88 (13%)	6 (11%)	8 (14%)
	Midwest (N %)	16 (26%)	160 (24%)	15 (26%)	11 (19%)
	South (N %)	24 (39%)	256 (39%)	23 (40%)	26 (45%)
	West (N %)	15 (24%)	120 (18%)	13 (23%)	10 (18%)
	Unknown (N %)	0 (0%)	31 (5%)	0 (0%)	2 (4%)
ECI Score (weighted)	Mean (SD)	18.6 (8.8)	18.9 (7.6)	18.7 (9)	18 (7.8)
ARSI-II use prior 1L	N (%)	17 (27%)	156 (24%)	14 (25%)	17 (29%)

* where p<0.05 among unmatched cases and controls

Figure 2. Weighted rwTTD curve for matched cases and controls

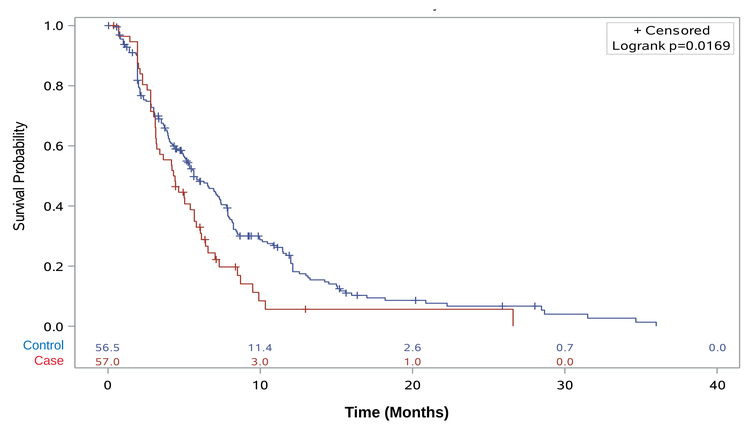
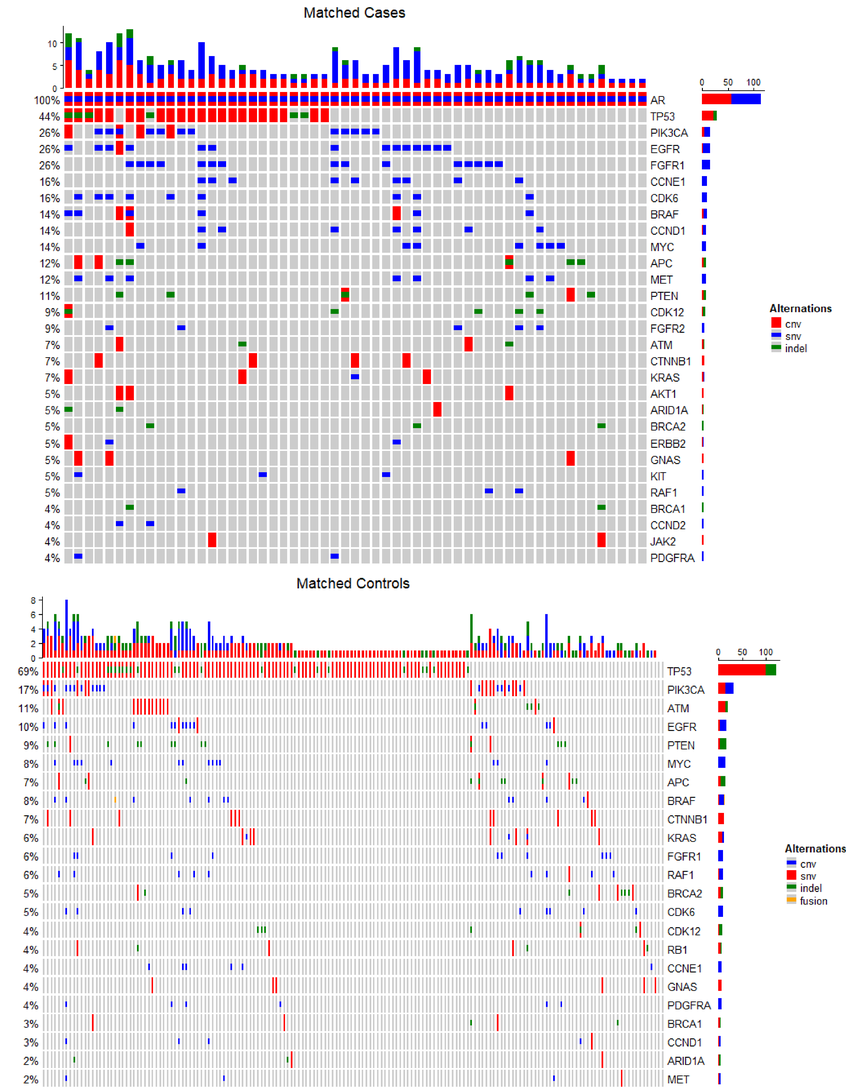


Figure 3. Oncoprints of the cases and controls



Conclusions

- In this RW analysis, these double mutant mCRPC patients exhibit worse clinical outcome as compared to the control cohort.
- Double mutant patients also show different genomic profile relative to patients without these mutations.
- Further investigation is needed to elucidate the significance of the AR-aberrations and improve prognosis for these patients.

References

1. Tan MH, Li J, Xu HE, Melcher K, Yong EL. Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacol Sin. 2015 Jan;36(1):3-23. doi: 10.1038/aps.2014.18. Epub 2014 Jun 9. PMID: 24909511; PMCID: PMC4571323.

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