Abstract 5061

Associations Between Androgen-Directed Treatments and *AR* Mutational Landscapes in the Circulating Tumor DNA of a Real-World Metastatic Prostate Cancer Cohort

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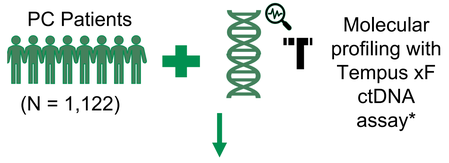
INTRODUCTION

- *AR* pathogenic/likely pathogenic mutations (mutAR) evolve under the selective pressure of testosterone suppression and *AR* targeted agents.
- Therapeutic targeting of CRPC patients with a mutAR is of interest.
- We evaluate mutAR in the circulating tumor DNA (ctDNA) of patients previously treated with abiraterone (Abi), enzalutamide (Enza) and both (Abi + Enza) in a large Tempus real-world mCRPC cohort.

METHODS



*If patients had multiple NGS samples, the most recent sample was used. The assay is a targeted liquid biopsy panel that detects single-nucleotide variants and insertions and/or deletions in 105 genes, copy number variants in six genes, and chromosomal rearrangements in seven genes. AR Amplifications were not included in this analyses.

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SUMMARY

- Pathogenic/likely pathogenic *AR* mutations were detected in **14.7% of patients treated with Abi, 15.0% treated with Enza, and 26.8% of patients treated with both Abi and Enza (p<0.001).**
- In mutAR, Thr878A single hit mutations occurred in **5.0% of patients treated with Abi, 0.5% of patients treated with Enza, and 5.7% of patients treated with both Abi and Enza (q=0.002).**
- In patients treated with Abi, somatic co-mutations in ***JAK1*, *CTNNB1*, *SPOP*, and *PTEN*** occurred more frequently in mutAR than wtAR **(q=0.004, 0.010, 0.020, and 0.045, respectively).**

RESULTS

Table 1. Cohort demographics and clinical characteristics

	Post Abi, N = 483	Post Enza, N = 374	Post Abi + Enza, N = 265	p-value[1]
Age at Diagnosis				0.070
Median (IQR)	65 (59, 71)	65 (61, 71)	64 (58, 70)	
Range	38, 88	40, 87	37, 86	
Unknown	0	0	1	
Race				0.014
White	198 (41%)	190 (51%)	129 (49%)	
Black or African American	59 (12%)	53 (14%)	32 (12%)	
Asian	15 (3.1%)	6 (1.6%)	4 (1.5%)	
Other	13 (2.7%)	6 (1.6%)	12 (4.5%)	
Unknown	198 (41%)	119 (32%)	88 (33%)	
Ethnicity				0.004
Not Hispanic/Latino	144 (30%)	118 (32%)	70 (26%)	
Hispanic/Latino	45 (9.3%)	12 (3.2%)	15 (5.7%)	
Unknown	294 (61%)	244 (65%)	180 (68%)	
Metastasis event prior to sample collection	435 (90%)	325 (87%)	236 (89%)	<0.001
Unknown	13 (2.7%)	17 (4.5%)	23 (8.7%)	
Diagnosis to Sample Collection Time				<0.001
>2 to 5 years	195 (40%)	114 (30%)	76 (29%)	
>1 to 2 years	93 (19%)	37 (9.9%)	7 (2.6%)	
>6 to 12 months	23 (4.8%)	11 (2.9%)	0 (0%)	
Unknown	172 (36%)	212 (57%)	182 (69%)	

Table 2: Frequency of mutARs by treatment group

	Post Abi N = 483	Post Enza N = 374	Post Abi + Enza N = 265	p-value[1]	q-value[2]
ARmut	**71 (15%)**	**56 (15%)**	**71 (27%)**	**<0.001**	**<0.001**
Leu702His	13 (2.7%)	18 (4.8%)	18 (6.8%)	0.028	0.056
Thr878Ala	**24 (5.0%)**	**2 (0.5%)**	**15 (5.7%)**	**<0.001**	**0.002**
His875Tyr	5 (1.0%)	7 (1.9%)	6 (2.3%)	0.4	0.4
Leu702His + Thr878Ala	6 (1.2%)	2 (0.5%)	7 (2.6%)	0.084	0.13
Leu702His + His875Tyr	2 (0.4%)	5 (1.3%)	7 (2.6%)	0.026	0.056
Thr878Ala + His875Tyr	3 (0.6%)	1 (0.3%)	1 (0.4%)	0.9	0.9
^ Other single hits or combinations (see Table 5)	18 (3.7%)	21 (5.6%)	17 (6.4%)	0.2	0.3

Figure 1. Ten most frequently co-mutated genes (mutAR + mutX) by treatment group.

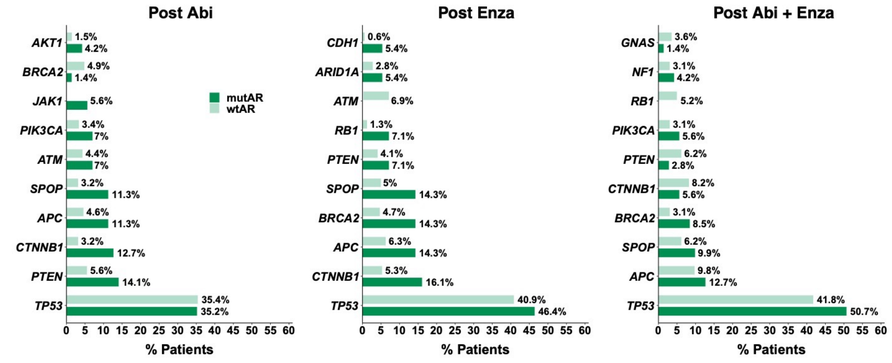

Table 3: Genes somatically co-mutated at different rates in mutAR vs wtAR post-Abi#

	mutAR N = 71	wtAR[3] N = 412	p-value[1]	q-value[2]
JAK1	4 (5.6%)	0 (0%)	<0.001	**0.004**
CTNNB1	9 (13%)	13 (3.2%)	0.002	**0.010**
SPOP	8 (11%)	13 (3.2%)	0.006	**0.020**
PTEN	10 (14%)	23 (5.6%)	0.018	**0.045**
APC	8 (11%)	19 (4.6%)	0.044	0.087

Table 4: Genes possibly somatically co-mutated at different rates in mutAR vs wtAR post-Enza#

	mutAR N = 56	wtAR[3] N = 318	p-value[1]	q-value[2]
CTNNB1	9 (16%)	17 (5.3%)	0.008	0.070
BRCA2	8 (14%)	15 (4.7%)	0.012	0.070
SPOP	8 (14%)	16 (5.0%)	0.016	0.070
RB1	4 (7.1%)	4 (1.3%)	0.020	0.070
CDH1	3 (5.4%)	2 (0.6%)	0.026	0.072
APC	8 (14%)	20 (6.3%)	0.050	0.10

Table 5. Additional mutARs in the population studied

	Post Abi N = 483	Post Enza, N = 374	Post Abi + Enza N = 265
Trp742Cys	2 (0.4%)	3 (0.8%)	1 (0.4%)
Leu702His + Thr878Ala + His875Tyr	2 (0.4%)	0 (0%)	2 (0.8%)
Phe877Leu	0 (0%)	4 (1.1%)	0 (0%)
Thr878Ser	2 (0.4%)	0 (0%)	1 (0.4%)
Leu702His + p.Phe877Leu	0 (0%)	2 (0.5%)	0 (0%)
Thr878Ala + His875Tyr + Val716Met	2 (0.4%)	0 (0%)	0 (0%)
Thr878Ala + Trp742Cys	1 (0.2%)	0 (0%)	1 (0.4%)
Thr878Ala + Val716Met	2 (0.4%)	0 (0%)	0 (0%)
Trp742Leu + Trp742Cys	0 (0%)	1 (0.3%)	1 (0.4%)
Other	7 (1.4%)	11 (2.9%)	11 (4.2%)

[1]Pearson's Chi-squared test; Fishers Exact test

[2]False discovery rate correction for multiple testing

[3]wtAR is defined as no pathogenic/likely pathogenic somatic mutation in the AR gene

^Other single hits or multi-hit combinations" are defined as an AR amino acid effect or combination of amino acid effects that are not Leu702His, Thr878Ala, His875Tyr, or combinations explicitly described.

#Genes displayed are those with Chi² p-values <= 0.05 occurring in 3% of greater of mutAR or wtAR.