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(PD52-12) Analysis of the prognostic significance of circulating tumor DNA (ctDNA) in metastatic castrate resistant prostate cancer (mCRPC)

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Background

- The genomic landscape of mCRPC has been of considerable interest in the recent years due to the need to develop more targeted agents in this space.
- Commonly mutated pathways in mCRPC include androgen signaling, homologous recombination repair, and PI3K/AKT signaling[1].
- Tissue NGS can often be difficult to obtain due to bone predominant disease and significant genomic heterogeneity between the primary prostate tumor and metastatic sites in mCRPC [3,4].
- Given this, “liquid biopsy” by circulating tumor DNA (ctDNA) next generation sequencing platforms have been of increasing interest.

1. Armenia J, Wankowicz SAM, Liu D, et al. *Nat Genet*. 2018;50(5):645–651.
2. Abida W, Cyrta J, Heller G, et al. *Proc Natl Acad Sci U S A*. 2019;116(23):11428–11436.
3. Annala, Matti, et al. *Cancer Discovery* 8.4 (2018): 444-57.
4. Vandekerkhove, Gillian, et al. *European Urology* 75.4 (2019): 667-75.

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mCRPC=Metastatic castration resistant prostate cancer; NGS=Next generation sequencing.

Methods

Retrospective analysis of metastatic castrate resistant prostate cancer patients treated at UC San Diego who underwent ctDNA analysis via CLIA based testing from 2014 to 2019.

- The **primary endpoint** was to **characterize the genomic landscape of ctDNA alterations in patients with mCRPC.**
- Secondary endpoints included assessment of overall survival as measured from *time of ctDNA collection* to death or last follow up in stratified univariate and multivariate analysis.
- Overall survival was stratified by the following:
  - Presence of tumor suppressor alterations *(TP53, RB1, PTEN).*
  - Presence of androgen receptor alterations (point mutation or amplification)
  - ctDNA maximum allelic fraction: *defined as the highest mutational allelic fraction detected on ctDNA analysis.*
  - Number of detected genomic alterations.

Results: Baseline Clinical Characteristics

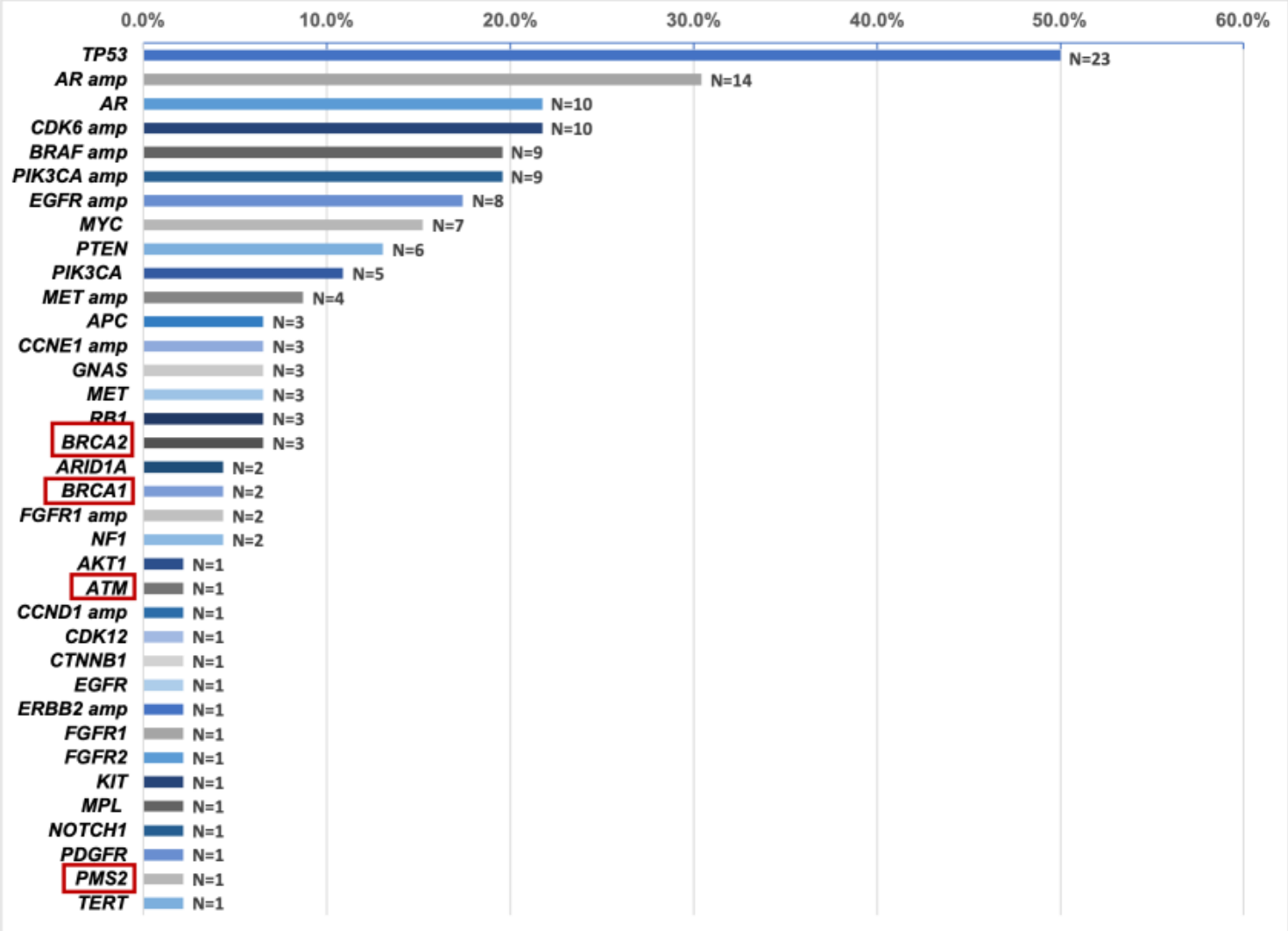
Baseline Characteristics	N (%), N=46
Age (median, years)	64 (44-80)
Race	
Caucasian (Non-Hispanic)	38 (82.6%)
Hispanic	3 (8.3%)
Asian	3 (8.3%)
Black	2 (4.3%)
Gleason Score at Diagnosis	
6	4 (9.5%)
7	13 (31.0%)
≥8	25 (59.5%)
Disease status at diagnosis	
Localized	32 (69.5%)
De Novo Metastatic	14 (30.4%)
Management of localized disease (n=32)	
Prostatectomy	14 (43.8%)
Definitive Radiation Therapy	11 (34.4%)
Neither	7 (21.9%)
Median time from diagnosis to metastasis (months)	58 months (12-268)
Median time from diagnosis to CRPC (months)	38.5 months (3-282)
Disease status prior to the development of M1 CRPC	
Castrate sensitive, metastatic	42 (91.3%)
Castrate resistant, non-metastatic	4 (8.7%)

Results: Genomic Characteristics

Time of ctDNA collection	N (%), N=46 total
Age (median, years)	71 (46-89)
Median time from CRPC diagnosis to ctDNA, (range)	13 months (0-45)
Disease Status at time of ctDNA analysis	
Castrate resistant	46 (100%)
M1 disease	45 (97.8%)
M0 disease	1 (2.2%)
Median number of prior therapies in the castrate resistant setting	1 (0-5)
Sites of metastatic disease	
Bone	46 (100%)
Lymph Node	18 (39.1%)
Lung	3 (6.5%)
Liver	2 (4.3%)
ctDNA platforms	
Guardant	32 (69.6%)
Foundation Medicine	9 (19.6%)
Tempus	5 (10.9%)
Patients with ≥1 detected alteration	43 (94%)
Median number of genomic alterations on ctDNA	2 (0-8)
Median maximum allelic fraction (range)	5.1% (0-87%)
Patients w/ tissue NGS, (% of total cohort)	25 (54.3%)
Sources of tissue NGS (n=25)	
Prostate	19 (76%)
Bone	3 (12%)
Lymph Node	2 (8%)
Lung	1 (4%)
Median time between NGS and ctDNA, (range)	18 months (0- 128)

Results: Genomic Alterations

- The most common genomic alterations detected were ***TP53* point mutation, *AR* amplification, and *AR* point mutation**
- Actionable mutations in *BRCA1, BRCA2, ATM*, and *PMS2* were detected at low frequencies in the cohort (n=7, 15%)



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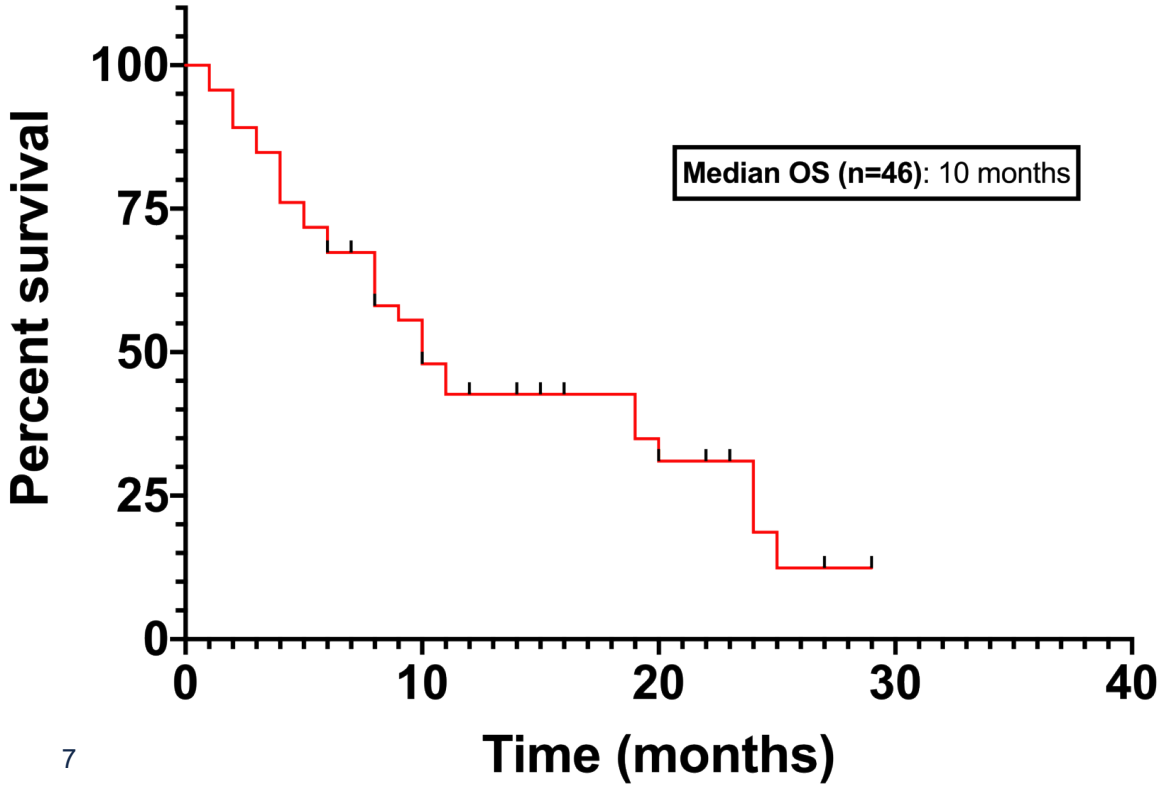
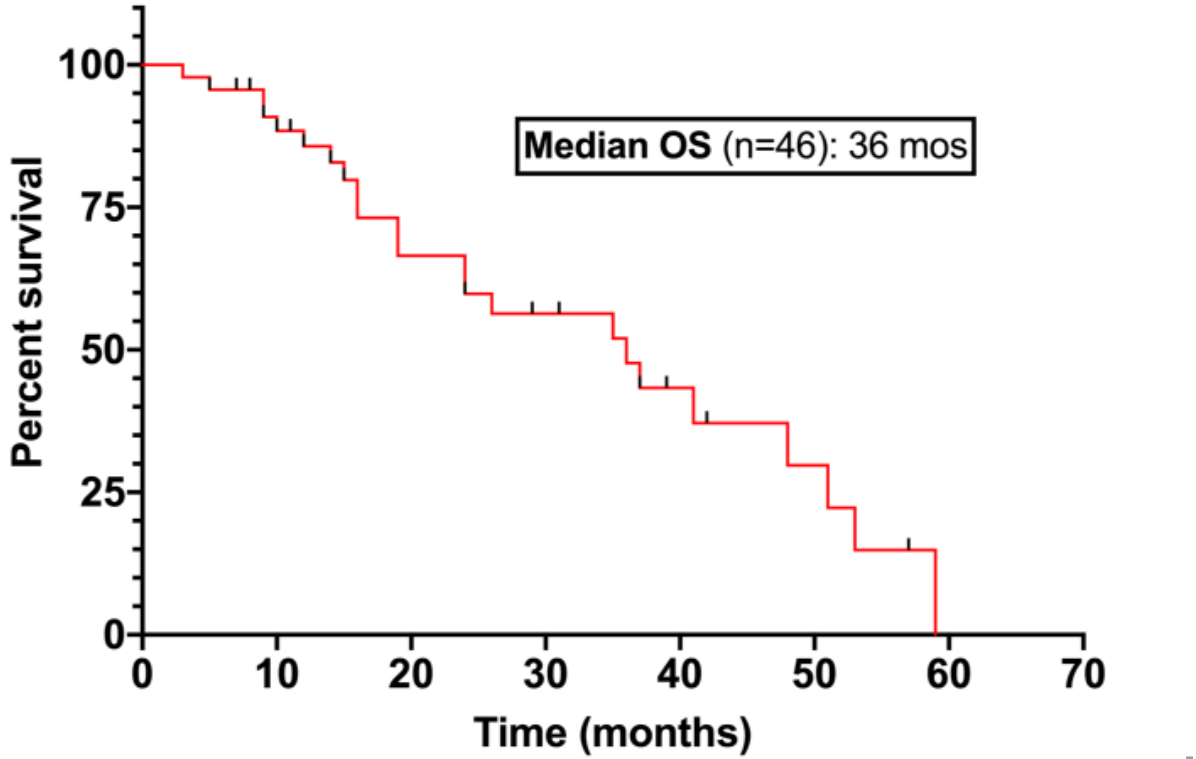
Results: Overall Survival of Cohort

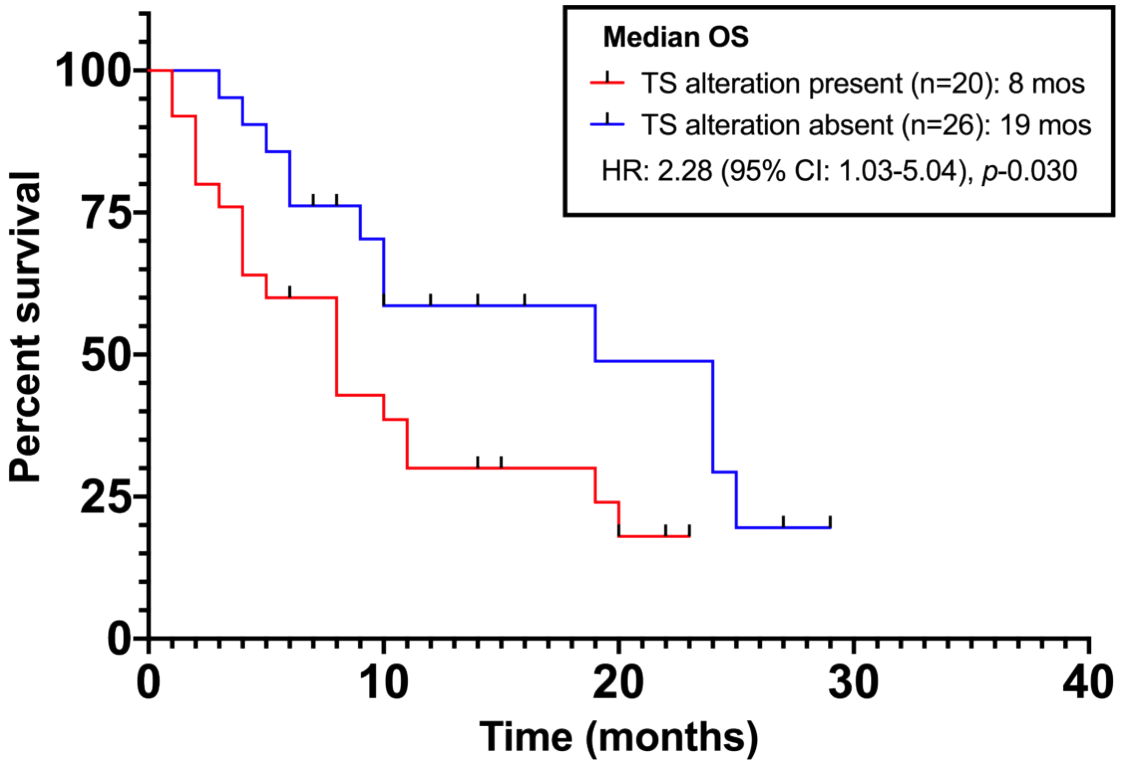
- Median OS of the mCRPC cohort was 10 months, measured from time of ctDNA collection to death or last follow-up.
- When measured from diagnosis of mCRPC to death or last follow-up, median OS was 36 months.

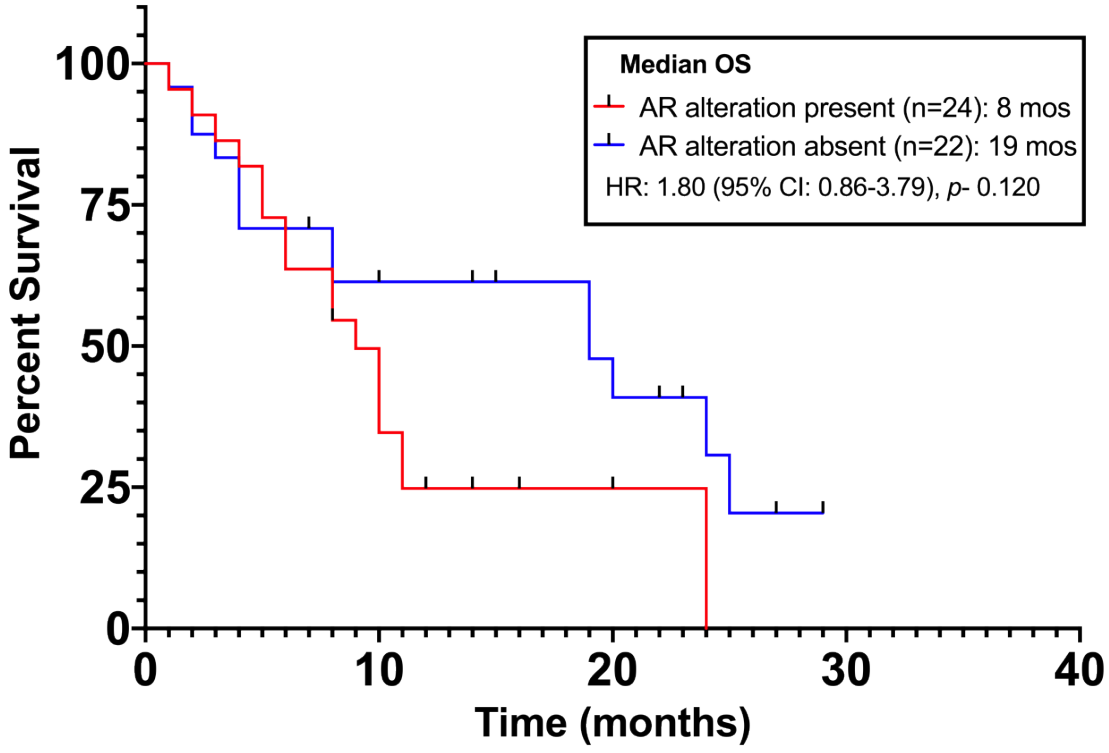




Results: Stratified Overall Survival by Genomic Alteration

- The presence of a tumor suppressor mutation in ***p53***, ***RB1***, or ***PTEN*** correlated with worsened survival.
- The presence of **AR amplification** or **AR point mutation** did not correlate with worsened OS

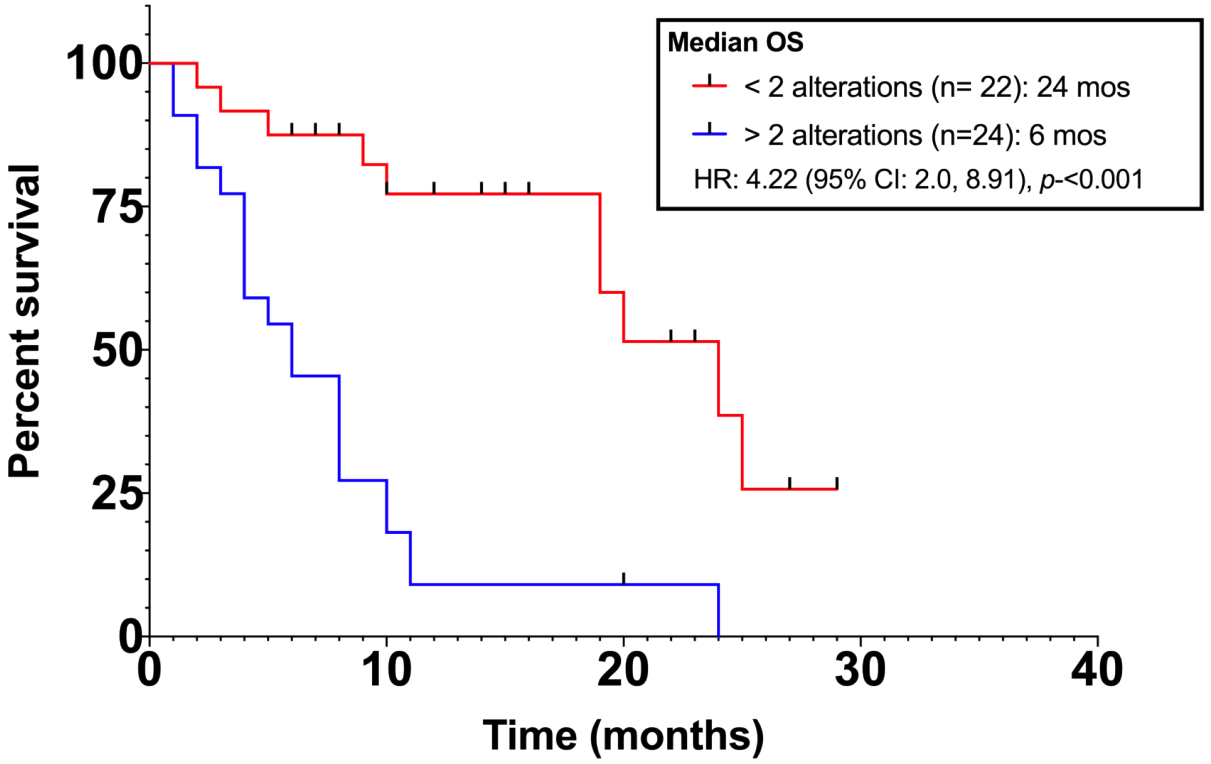


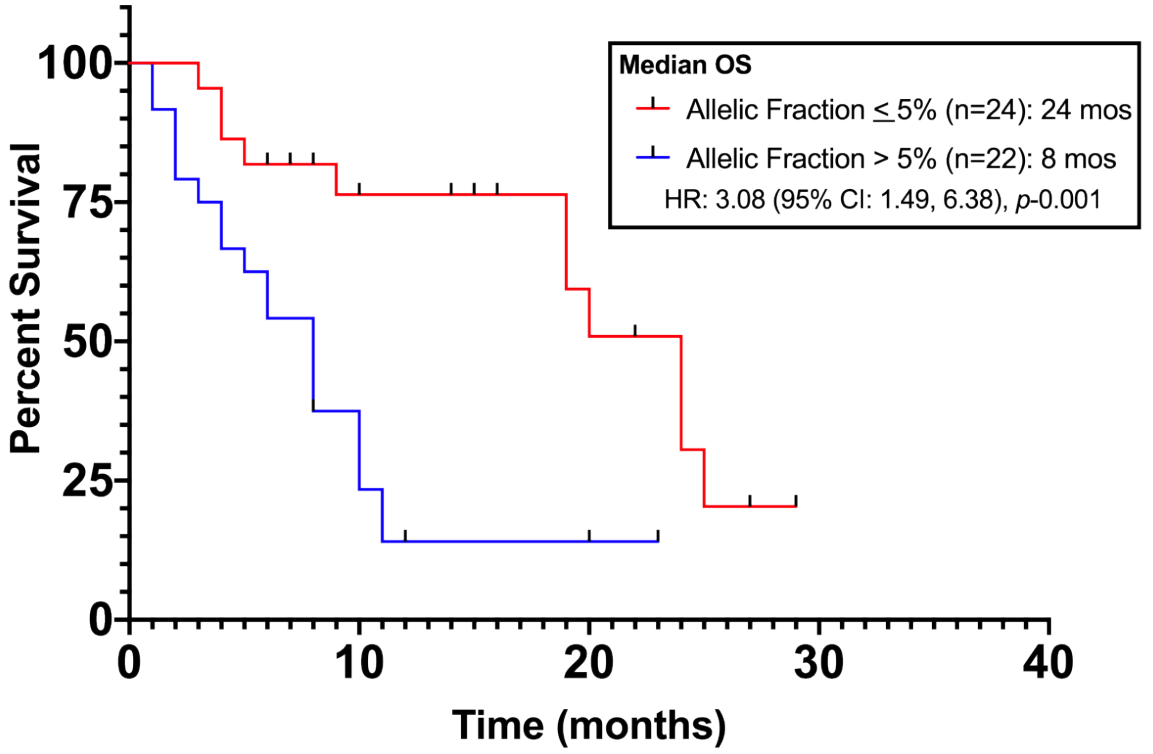


AR=Androgen Receptor; TS= tumor suppressor

Results: Stratified OS by allelic fraction and alteration number

- The presence of >2 genomic alterations or maximum allelic fraction of >5% on ctDNA analysis was associated with significantly worsened OS.





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Results: Multivariate Regression

- Number of detected alterations remained a strongly significant predictor of mortality in multivariate analysis.

		Univariate analysis		Multivariate Analysis**	
Characteristics		**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age		1.01 (0.96-1.06)	0.65	-	-
Lines of systemic therapy for mCRPC at ctDNA analysis					
	1st line 2nd line or greater	**Reference** **2.13 (1.03-4.38)**	**0.041***	Reference 1.77 (0.80-3.92)	0.16
Log(PSA) at time ctDNA analysis		0.967 (0.64-1.46)	0.87	-	-
Presence of visceral metastases		1.17 (0.44-3.08)	0.756	-	-
Genomic Alterations					
	TS alteration present vs not	**2.28 (1.03- 5.04)**	**0.030***	0.96 (0.37-2.49)	0.93
	AR alteration present vs not	1.80 (0.86-3.79)	0.12	0.542 (0.19-1.54)	0.25
Number of mutations					
	≤ 2 mutations detected > 2 mutations detected	**Reference** **4.81 (2.16-10.7)**	**<0.001***	**Reference** **5.24 (1.54-17.9)**	**0.008***
ECOG at time of ctDNA analysis					
	ECOG 0-1 ECOG 2-4	**Reference** **3.085 (1.43- 6.48)**	**0.004***	Reference 1.61 (0.67-4.50)	0.368
Opioid Use at time of ctDNA analysis		1.67 (0.815-3.43)	0.16	0.99 (0.63-1.55)	0.956
Lab Parameters at time of ctDNA analysis					
	Alkaline Phosphatase	1.0 (0.99-1.002)	0.26	-	-
	Albumin	**0.34 (0.17-0.66)**	**0.001***	0.70 (0.33-1.50)	0.35
	Hemoglobin	**0.717 (0.60-0.87)**	**<0.001***	0.86 (0.59-1.23)	0.42

****Variables with a *p*-value of < 0.2 in univariate analysis were included in multivariate analysis.**

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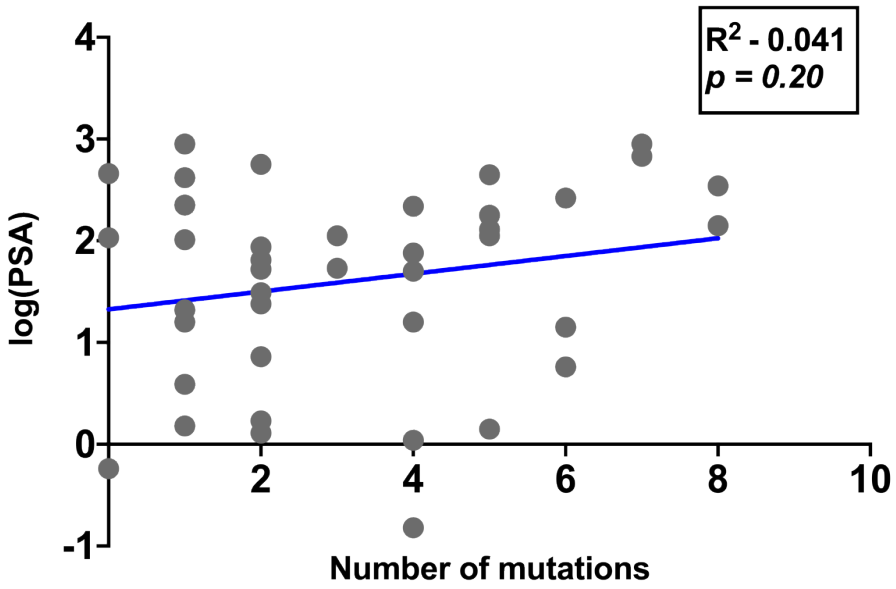
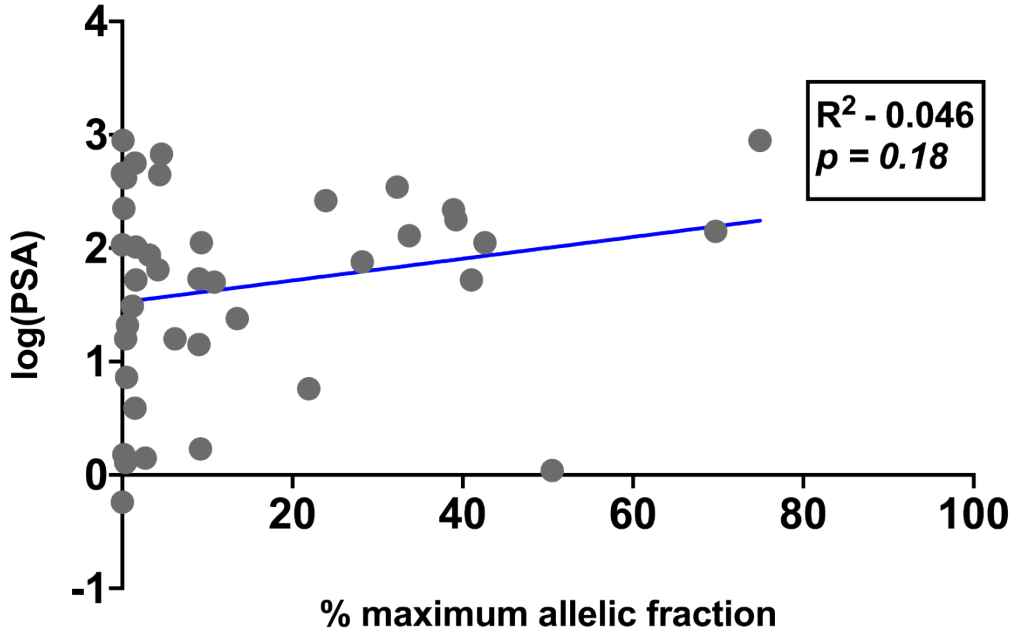
AR=Androgen Receptor; TS= tumor suppressor

Results: Correlation with PSA

- There was no statistically significant association between number of detected alterations or maximum allelic fraction and PSA at the time of ctDNA analysis





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Conclusions

- ctDNA analysis is a useful sequencing platform in mCRPC given the difficulty in obtaining tissue NGS.
- ctDNA alterations were detected in the majority of patients in this mCRPC population.
- ctDNA offers not only therapeutic information for targeted therapy, but prognostic information based on higher mutational burden and allelic fraction which were associated with negative prognosis.
- The number of alterations and maximum allelic fraction do not appear to correlate strongly with PSA, and ctDNA may serve as an additional noninvasive biomarker for mCRPC patients.
- Further prospective validation of these data are needed.

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QUESTIONS?

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