The prognostic role of longitudinal assessment of plasma androgen receptor (*AR*) copy number (CN) in metastatic castration resistant prostate cancer (mCRPC): analysis from a prospective biomarkers trial.

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Background

Baseline plasma *AR* CN seems a promising biomarker for mCRPC outcome and treatment response; however, the role of its longitudinal testing is unproven yet.
We aimed to evaluate the prognostic role of longitudinal assessment of *AR* CN, evaluated prior to each treatment line for mCRPC.

Methods

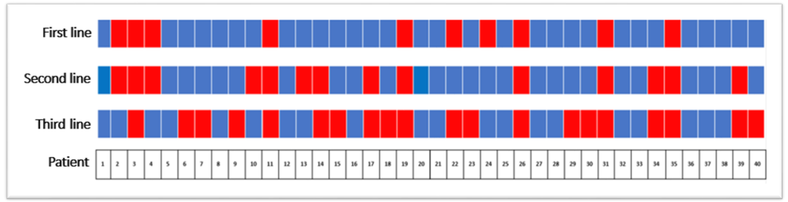
A subgroup analysis of a prospective biomarker trial (IRST-B073) was performed retrieving all mCRPC patients who received docetaxel, cabazitaxel and an AR signaling inhibitor (ARSI: abiraterone or enzalutamide).
Treatment sequence was chosen according to clinical practice. Plasma AR CN status was assessed with digital PCR prior to each treatment line.
AR CN status was classified as normal or gain, using a cut-off value=2. For each patient, at every assessment, we recorded also PSA and LDH values, presence of bone or visceral metastases.
Each variable was correlated with clinical outcomes (PFS, OS). Data are expressed as median, hazard ratio (HR) and [95% CI].

Table 1. Patients' characteristics prior to each treatment line.

	Line of Treatment		
	First	Second	Third
	N (%)	N (%)	N (%)
Type of treatment			
ARSI	17 (42.5)	11 (27.5)	12 (30.0)
Docetaxel	23 (42.5)	17 (42.5)	0
Cabazitaxel	0	12 (30.0)	28 (70.0)
Presence of bone metastases			
No	5 (12.5)	3 (7.5)	2 (5.0)
Yes	35 (87.5)	37 (92.5)	38 (95.0)
Presence of visceral metastases			
No	34 (85.0)	34 (85.0)	31 (77.5)
Yes	6 (15.0)	6 (15.0)	9 (22.5)
AR CN status			
Normal	30 (75.0)	25 (62.5)	20 (50.0)
Gain	10 (25.0)	15 (37.5)	20 (50.0)
PSA, ng/ml: median value (range, IQR)	21 (1.8-531, 10.5-115)	25 (0.5-580; 8.5-136)	39 (0.4-593; 18-115.5)

Results

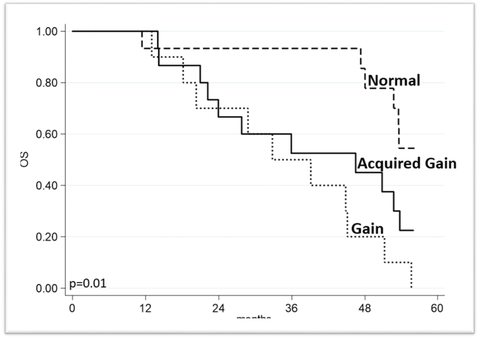
Study population. Forty patients were included; median follow up was 89 months (range: 11-111).
As first line, 23 patients received docetaxel and 17 ARSI; overall PFS was 6.8 and OS 50.8 months. As second line, 17 received docetaxel, 12 cabazitaxel and 11 ARSI; overall PFS was 6.6 and OS 28.4 months. As third line, 28 received cabazitaxel and 12 ARSI; overall PFS was 5.2 and OS 16.6 months. Patients' characteristics are reported in Table 1.
For every patient, *AR* CN status prior to each treatment line is represented below.



Legend. AR CN status: normal – blue; gain – red.

In detail, *AR* CN status was normal in all samples in 15 (38%) patients (*AR* CN normal group), changed from normal to gain in 15 (38%) (acquired *AR* CN gain group), and was gain in all samples in 10 (24%) (*AR* CN gain group).

According to these three groups, median OS was 69 months in *AR* CN normal group (reference), 47 months in acquired *AR* CN gain group (HR 2.4 [1.0-5.8]), and 37 months in *AR* CN gain group (HR 4.9 [1.8-12.9]) (p=0.01).



At multivariate analysis, at each assessment OS was independently correlated with AR CN status and with median PSA, as shown in Table 2.

Table 2. Multivariate analysis of overall survival in the three treatment lines.

	Overall Survival	
	HR (95% CI)	p
First treatment		
***AR* CN status** (gain vs normal)	**4.1 (1.6-10.5)**	**0.003**
PSA (≥21 vs <21)	**4.4 (1.8-10.9)**	**0.001**
Second treatment		
***AR* CN status** (gain vs normal)	**2.4 (1.1-5.3)**	**0.037**
PSA (≥25 vs <25)	**3.4 (1.6-7.2)**	**0.002**
Third treatment		
***AR* CN status** (gain vs normal)	**2.1 (1.0-4.3)**	**0.049**
PSA (≥39 vs <39)	**2.5 (1.2-5.6)**	**0.020**

Conclusions

- In this analysis, we prospectively confirm the prognostic role of plasma *AR* CN status in mCRPC patients.
- Plasma *AR* CN correlates with OS not only at baseline (prior to first line), but also in the assessments prior to following lines.
- Plasma *AR* CN status correlates with OS not only in ARSI-treated patients, but also in those receiving taxanes.
- *AR* CN status may change from normal to gain across treatments in a significant amount of cases, identifying a group of patients with intermediate outcomes.
- Longitudinal assessment of *AR* CN status could represent a promising approach to capture the intrinsic and dynamic heterogeneity of mCRPC emerging during different treatment lines.

Disclosure

The first and presenting author has no conflicts of interest to declare.

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