

ROLE OF SERUM BIOMARKERS OF BONE METABOLISM IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) PATIENTS (PTS) TREATED WITH RADIUM-223 (RA223) – PRORADIUM STUDY FINAL RESULTS

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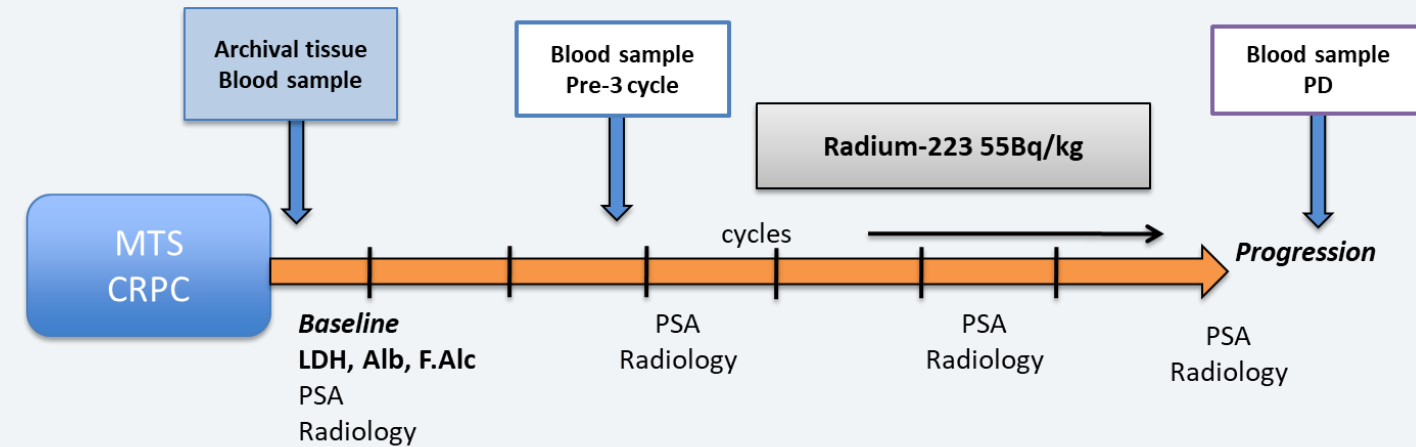
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BACKGROUND

- Radium-223 is a life-prolonging alpha-emitter bone targeted therapy for metastatic Castration-Resistant Prostate Cancer (mCRPC) patients with bone metastases¹. However, evidence on biomarkers that may help us in patient selection are lacking.
- Total alkaline phosphatase (tALP) appeared to be a potential marker of Radium-223 effect in early studies². Other bone-related markers, as bone-specific ALP (BALP), have demonstrated its prognostic value in mCRPC patients with bone metastases^{3,4}.
- Our Hypothesis: Bone-related markers may affect the clinical outcome of mCRPC patients treated with Radium-223**

MATERIAL AND METHODS

- PRORADIUM** (ClinicalTrials.gov ID:NCT022925702) is a prospective, multicentre, observational cohort study in mCRPC patients treated with Radium-223. 35 spanish centres have participated in this collaborative biomarkers platform.



- OBJECTIVES**
- 1. The primary aim was to assess the impact of baseline serum biomarkers of bone formation (BALP and C-terminal of type 1 collagen propeptide [CICP]) and bone resorption (N-telopeptide [NTx] and pyridinoline [PYD]) on overall survival (OS).

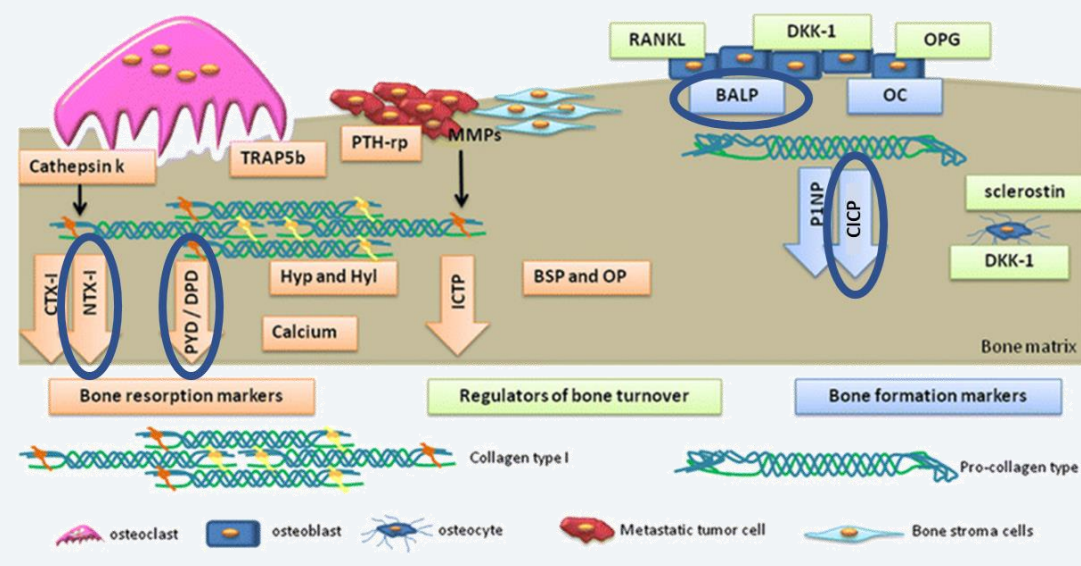


Figure 1. Bone remodelling biomarkers. Adapted from Ferreira et al⁵

2. Secondary aims include the correlation of progression-free survival (PFS), time to PSA progression (TTPP) and skeletal events free-survival (SRE-FS) with serum bone markers.

RESULTS

- 169 patients were included. Serum biomarkers were successfully analyzed in 153 patients.
- Median age was 74 years, 85.2% had ECOG 0-1, 57.5% completed 5-6 cycles.
- Higher baseline levels of serum biomarkers have been correlated with prognostic factors as presented in Table 1. CICP and BALP were associated to a high number of metastases in bone-scan (p=0.001 and p=0.002) and baseline pain (p=0.003, p=0.028, respectively). CICP, BALP and NTx were significantly associated with high PSA baseline level, ECOG 2 and elevated baseline ALP/LDH.

	All patients N=169	CICP (ug/L) p-value	BALP (ug/L) p-value	PYD (ng/mL) p-value	NTx (nM) p-value
Age at starting Ra223 Median (range)	74.4 (45.7-90.6)	0.094	0.001	0.125	0.265
Histology grade - Gleason ≤7 - Gleason ≥8	65 (38.9%) 102 (61.1%)	0.146	0.030	0.431	0.481
M1 at diagnosis - No - Yes	88 (52.1%) 81 (47.9%)	0.660	0.855	0.432	0.624
PSA (ng/dL) Median (range)	64,6 (0.03-1670)	<0.001	<0.001	0.315	0.001
Bone metastases - ≤ 5 bone metastases - > 5 bone metastases	36 (21.3%) 133 (78.7%)	0.001	0.002	0.828	0.058
Performance Status - ECOG 0-1 - ECOG ≥2	144 (85.2%) 25 (14.8%)	0.015	0.017	0.028	<0.001
Baseline Pain - No - Yes	43 (25.4%) 126 (74.6%)	0.028	0.003	0.097	0.949
ALP - Normal - Elevated (>ULN)	78 (46.4%) 90 (53.6%)	<0.001	<0.001	0.125	<0.001
LDH - Normal - Elevated (>ULN)	73 (47.7%) 80 (52.3%)	0.015	0.002	0.211	0.011
Hemoglobin - ≥ 10 gr/dL - < 10 gr/dL	159 (94.1%) 10 (5.9%)	0.042	0.154	0.010	0.083
Albumin - ≥ 3 g/dL - < 3 g/dL	143 (97.3%) 4 (2.7%)	0.040	0.187	0.211	0.024
Prior treatment for mCRPC - ≤ 2 lines - > 2 lines	68 (40.2%) 101 (59.8%)	0.255	0.735	0.896	0.066

Table 1: Baseline characteristics and correlation with median levels of bone formation/resorption biomarkers.

- After a median follow-up of 31.1 months, 147 deaths were observed, with a median overall survival (OS) of 12.1 months (95%CI: 9.5-14.7).
- Continuous value of BALP and CICP correlated with a shorter TTPP (BALP: Q1 5.4m/Q4 3.3m, p=0.013; CICP: Q1 5.5m/Q4 3.6m, p=0.011) and rPFS (BALP: Q1 10.2m/Q4 5.4m, p=0.009; CICP: Q1 9.3m/Q4 6.9m, p=0.037), respectively.
- The elevation of 3-4 bone biomarkers over the median was significantly associated with worse OS (15.2 vs 9.9 m, HR 1.63, p=0.007, Fig 3). There were not associations found with SRE-FS.

Figure 3. Prognostic model including ≥ 3 bone-related biomarkers

	n	Median OS (months)	95%CI	
			Inf	Sup
0-2	92	15.2	11.2	19.2
3-4 above median	61	9.9	8.3	11.5
Global	153	12.2	9.6	14.8

- 0-2 biomarkers over the median
- 3-4 biomarkers over the median

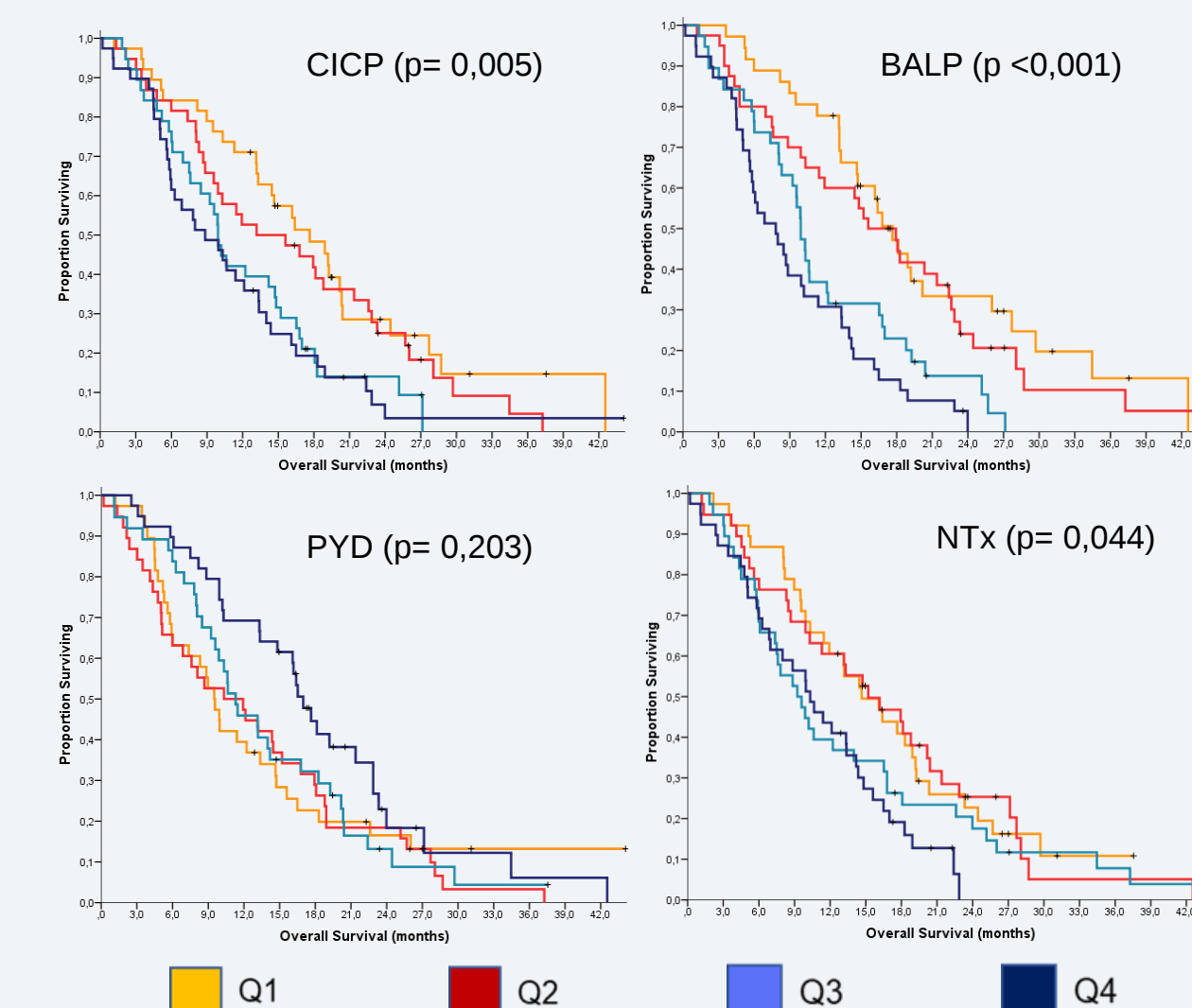
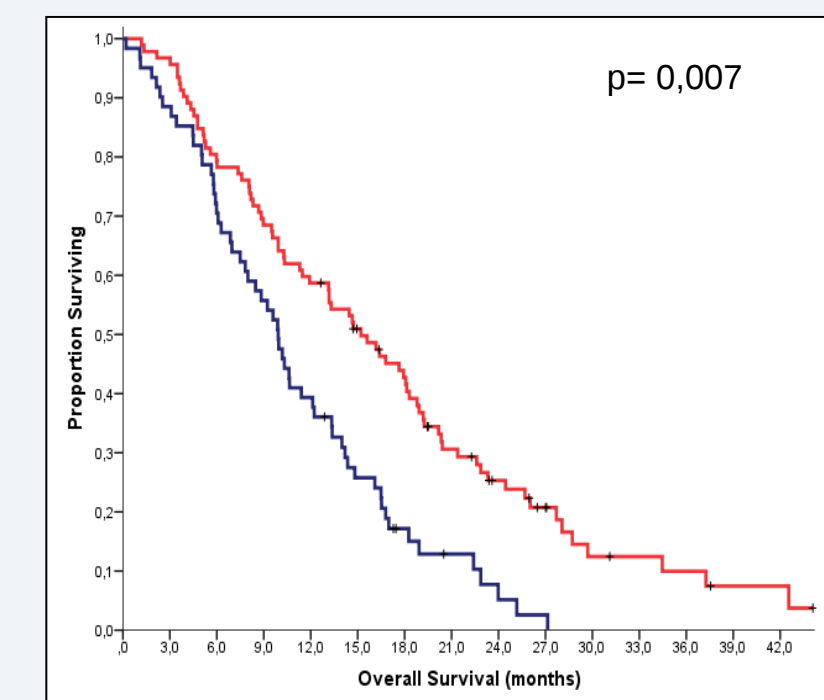


Figure 2. Baseline bone-related biomarkers by quartiles and OS



CONCLUSIONS

- Our results suggest that baseline serum markers of bone formation may serve as prognostic biomarkers in mCRPC patients treated with Radium-223.
- Validation analysis will be needed to confirm these results

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References

- Parker C et al. N Eng J Med, 2013; 2 Sartor O. Ann of Oncol, 2017; 3 Fizazi K, Eur Urol, 2015;
- Lara PN, J Natl Cancer Inst, 2014; 5 Ferreira et al. Bonekey Rep 2015