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Parikh, S, Murray, L orcid.org/0000-0003-0658-6455, Kenning, L et al. (10 more authors) (2018) Real-world Outcomes and Factors Predicting Survival and Completion of Radium 223 in Metastatic Castrate-resistant Prostate Cancer. Clinical Oncology, 30 (9). pp. 548-555. ISSN 0936-6555

https://doi.org/10.1016/j.clon.2018.06.004

Real world outcomes and factors predicting survival and completion of Ra-223 in metastatic castrate resistant prostate cancer

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Running Title: Real world outcomes with Ra-223

Keywords: metastatic castrate resistant prostate cancer, Neutrophil-to-lymphocyte ratio,
Overall survival, Radium-223
Total number of pages:
Total number of tables and figures:

This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

Abstract:

Background and Purpose

To analyse outcomes in metastatic castrate resistant prostate cancer (mCRPC) patients treated with Radium 223 (Ra-223) across the Yorkshire and Humber Cancer Network.

Material and Methods

A regional, multi-centre, retrospective cohort study of 189 men undergoing Ra-223 for mCRPC between March 2014 and April 2017 was undertaken. Factors predicting overall survival (OS) and completion of planned treatment were assessed.

Results

The median OS for the entire cohort was 10.5 months. Those completing 5-6 cycles of Ra-223 had higher OS of 18.6 months. On multivariable analysis, four factors remained independent significant predictors of OS: age (p=0.005 HR1.07 (1.02-1.12)), number of cycles of Ra-223; 5-6 vs. 1-4 (p=<0.001 HR 0.10 (0.005-0.20)), baseline alkaline phosphatase (ALP) (p=0.044 HR 1.06 (1.002-1.12)), and Neutrophil-to-Lymphocyte Ratio (NLR)

(p=0.033 HR 1.19 (1.01-1.40)). Baseline performance status 0 vs. 2 (p=0.026, OR 0.080 (0.001-0.74) and higher baseline haemoglobin (p=0.028 OR 1.04 (1.004-1.074)) were independent predictors of completion of 5-6 cycles of Ra-223.

Conclusions

Younger age, completion of 5-6 cycles of Ra-223, lower ALP and NLR are predictors of OS. This is the first study to report NLR as an independent predictor of OS in a Ra-223 cohort. Good performance status and higher baseline haemoglobin predict completion of 5-6 cycles of Ra- 223.

Introduction

Prostate cancer is the most common cancer diagnosed in European men, causing 72,000 deaths per year across Europe [1]. Several new systemic therapies have been shown to prolong survival in metastatic Castrate Resistant Prostate Cancer (CRPC) and have been approved for use, including enzalutamide, abiraterone, cabazitaxel and Ra-223.

Radium-223 (Ra-223) is a novel bone seeking alpha-particle emitter with a half-life of 11.4 days. Ra-223 mimics calcium, forming complexes with hydroxyapatite and targeting regions of high bone turnover such as osteoblastic metastases which are commonly seen in advanced prostate cancer. The high linear energy transfer of alpha particles induces double strand DNA breaks, while the 2-10 cell width range limits toxicity to surrounding tissue and marrow [2]. Ra-223 is administered as an intravenous injection every 4 weeks for a period of 6 months.

The ALSYMPCA trial [3], randomised 921 men with predominantly bone mCRPC to 6 cycles of Ra-223 or placebo, and demonstrated an overall survival benefit of 3.6 months in those treated with Ra-223. Patients were required to have symptomatic bone-metastatic disease, with no known visceral metastatic disease and no lymph node metastases larger than 3cm. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and a life expectancy of greater than 6 months were also required. NICE subsequently issued technology appraisal guidance and Ra-223 is now widely available [4].

The Yorkshire and Humber Clinical Network covers a large geographical area of over 5000 square miles and delivers oncology services to a population of 5.4 million located in diverse communities ranging from dense, deprived urban areas to remote and rural communities [5]. There are three cancer centres based in Hull, Leeds and Sheffield and specialised radiation cancer services such as Ra-223 are delivered from these bases. The purpose of this regional, multi-centre, retrospective audit is to analyse real world outcomes in mCRPC patients treated with Ra-223 from the establishment of the service in 2014.

Materials and Methods:

Patients

All patients with mCRPC who received at least 1 dose of Ra-223 since the introduction of this service in 2014 at the 3 treating centres in Yorkshire and Humber were included. Only patients who either completed all planned Ra-223 cycles or had discontinued Ra-223 were included, those mid-treatment

at the time of analysis were excluded. The cohort was divided into two groups: patients who completed 1-4 cycles of Ra-223 (70 patients; Group 1-4), and those who completed 5-6 cycles of Ra-223 (119 patients; Group 5-6).

Data collection

Retrospective data collection was completed from electronic and paper medical records. Patients routinely had full blood counts, renal and liver function tests, and prostate specific antigen (PSA) checked before each cycle. Baseline bloods were documented. As a proportion of blood tests were performed in primary care or peripheral hospitals, however, not all results were retrievable for study purposes. Alkaline phosphate (ALP) response was defined as a decrease of 50% from baseline alkaline phosphatase levels during treatment months. Similarly, a PSA response was defined as a 50% decrease from baseline. Baseline ECOG performance status was noted.

Co-morbidities were classified according to the Adult Comorbidity Evaluation (ACE-27) score [6]. Pain scores were not clearly documented in patient notes and hence excluded from the analysis.

Major adverse events including need for transfusions and skeletal-related events (SRE) during treatment months were documented. Skeletal related events were defined as metastatic spinal cord compression, symptomatic pathological fracture, palliative radiotherapy to relieve symptoms or surgery to bone.

Statistics

The primary outcome measure was median overall survival. Kaplan Meier survival curves from commencement of Ra-223 to time of death were plotted. Reverse Kaplan Meier was used to calculate median follow up. Cox Regression was used to identify factors predicting overall survival. The following factors were included in the univariate survival analysis: age, ACE comorbidity score, 1-4 vs. 5-6 cycles of Ra-223, Gleason score, ECOG performance status, baseline bloods including haemoglobin, PSA , ALP, albumin and neutrophil-to-lymphocyte ratio (NLR), previous use of docetaxel, number of previous lines of therapy, ALP and PSA response. Logistic Regression was used to identify which baseline characteristics predicted comple-

tion of 5-6 cycles of Ra-223 compared to 1-4 cycles. All above factors except for ALP and PSA response were used in univariate logistic regression. Factors with p-value of <0.1 on univariate analysis were carried into the multivariate analyses, which were performed using a backwards selection method.

Results:

189 patients with mCRPC underwent treatment with Ra-223 across the region between March 2014 and April 2017. Median age was 72 years (range 51 -86 years). 115/189 (61%) patients died during the study period with 74/189 (39%) remaining alive at the time of analysis. 94% of patients in Group 1-4, but only 41% of patients in Group 5-6 died during the study period. 8/189 patients died within 1 month of last Ra-223 treatment. Median follow up was 16.8 months.

The median overall survival for the entire cohort was 10.5 months (95% CI, 8.7 - 12.3 months).
On comparison according to number of cycles completed, Group1-4 had a median survival of 4.5 months (95% CI, 3.3 - 5.7 months) and Group 5-6 had a median survival of 18.6 months (95% CI, 16.9 - 20.1 months; p= <0.001, Figure 1a)

The clinical characteristics of the entire patient group and the analysis of potential factors associated with overall survival are demonstrated in Table 1 and Table 2 respectively. Baseline blood results were available for 90% of patients, with the exception of neutrophil-lymphocyte ratio which was available in 77% of patients and albumin level which was available in only 49% of patients. 68% of patients had calculated ACE-27 scores (data available from only 2 centres). On univariate analysis the following factors were associated with poorer overall survival: increasing age, completion of only 1-4 cycles, poorer initial PS, lower baseline Hb, higher initial PSA, higher baseline ALP, higher NLR and poorer PSA response during treatment. On multivariable analysis, only four of these factors remained independent significant predictors of overall survival: age (p=0.005 HR1.07 (1.02-1.12)), number of cycles of Ra-223; 5-6 vs. 1-4 (p=<0.001 HR 0.10 (0.005-0.20)), baseline alkaline phosphatase (p=0.044 HR 1.06 (1.002-1.12)), and NLR (p=0.033 HR 1.19 (1.01-1.40)).

Table 3 demonstrates analysis of the patient factors associated with completion of 5-6 cycles of Ra-223. Initial performance status and baseline blood results were found to be significantly associated with successful completion of 5-6 treatment on univariate logistic regression. On multivariable analysis, only performance status 2 vs. 0 (p=0.026, OR 0.080 (0.001-0.74)) and higher baseline Hb (p=0.028 OR 1.04 (1.004-1.074)) remained independently significant.

The reasons for stopping Ra-223 before the 6th cycle were documented in 2 of the 3 centres (N=69). Death or disease progression were the most common reasons (75% patients) for early cessation of Ra-223 (Table 4).

Adverse event data was available for 134 patients: 18% of patients in both Groups 1-4 and 5-6 (10/56 and 14/78 patients) suffered SREs while on Ra-223.

Discussion:

The landmark ALSYMPCA trial demonstrated that Ra-223 prolongs median overall survival and has a favourable impact on pain and quality of life [3]. In real-world practice, however, outcomes are often found to be variable due to treatments being offered to patients who are more complex or would not have met the entry criteria for clinical trials. The overall median survival of 10.5 months for Ra-223 patients observed here is inferior to that reported for both the Ra-223 and the placebo groups (14.9 vs. 11.3) in the ALSYMPCA trial. Other real world retrospective studies have reported median overall survival ranging from 8.3 months to 12.9 months [7-9], in-keeping with that observed in this cohort.

In this cohort, nearly 47% (88/189) of patients were exposed to 2 or 3 lines of prior survival enhancing therapy, namely combinations of enzalutamide, abiraterone, cabazitaxel or doxetaxel. Neither enzalutamide nor abiraterone was licensed for use during the ALSYMPCA trial and thus the ALSYMP-

CA trial observations may not be applicable to more heavily pre-treated mCRPC patients. Furthermore, 37% of patients in this current study completed only 1-4 cycles of Ra-223-223 compared to 27% of patients in Ra-223 arm of the ALSYMPCA trial. [10]

Previous retrospective studies have identified prognostic factors associated with survival after Ra-223 (Table 5). Most studies have focused on two outcome measures, namely, overall survival or completion of 5-6 cycles of Ra-223. All studies were retrospective and used logistic regression or step-wise cox regression proportional hazards in order to predict variables that might be associated with favourable outcomes. Heterogeneity in results is clear from Table 5.

Nevertheless, there is agreement across studies that the number of cycles of Ra-223 is a predictor of overall survival, but as this can only be determined retrospectively, it does not guide initial patient selection. In our cohort, median overall survival in Group 1-4 was 4.5 months and Group 5-6 was 18.6 months (Figure 1a). In a similar retrospective study, Stolten et al reported median overall survival of 16 months for those who completed 6 cycles of Ra-223 vs. 4 months for those who completed fewer than 6 cycles [11].Furthermore, median overall survival for patients who received 1-4 Ra-223 cycles vs. 5-6 cycles was 6.2 vs. 17.9 months in ALSYMPCA trial and 6.3 vs. >16 months in the international Expanded Access Program (iEAP) [10]. Interestingly, the overall survival median for 1-4 vs. 5-6 placebo injections in ALSYMPCA trial was 6.1 vs. 15.8 months. Therefore, median survival for patients who received 1-4 injections of either Ra-223 or placebo in these studies was similar (6.1 months for placebo in ALSYMPCA vs. 6.2 months for Ra-223 in ALSYMPCA vs. 6.3 months for 1-4 in iEAP Ra-223), implying potentially little benefit if 4 or fewer cycles are delivered. The poor baseline status of patients in the 1-4 Group may account for their poor overall survival and suggests that any benefit in overall survival is dependent on patients being well enough to complete all 6 cycles of Ra-223 -223. While this can be difficult to predict, we propose that Ra-223 should be initiated in only those patients in whom it is felt likely that they will be able to complete the planned course, namely those with ECOG PS 0-1 and higher baseline haemoglobin.

With regards to use of systemic drugs, Etchebehere et al have reported overall survival benefit in those patients who completed 6 cycles of Ra-223 despite disease progression mid-treatment compared to those who switched to chemotherapy [9]. Also of note, iEAP has shown trends towards survival benefit with concomitant abiraterone and Ra-223-223 [10, 12].

In general, PSA response does not reflect response to Ra-223 treatment. Alkaline phosphatase is a marker of bone turnover and has been used as a surrogate marker for disease response. A higher baseline Alkaline Phosphatase was shown to be an independent poor prognostic indicator in our study (albeit with a small hazard ratio), similar to that reported by Wong et al [7].
Baseline haemoglobin and ECOG performance status scores were identified as factors predicting completion of 5-6 cycles of Ra-223 from both the iEAP and this current study. [10] Interestingly, predicting completion of cycles was independent of prior docetaxel use or number of line of prior chemotherapy.

The limitations of this study include lack of complete information on co-morbidity and no patient reported outcomes such as pain scores and general quality of life. The incorporation of patient reported outcomes into everyday clinical practice is challenging but would provide valuable information to guide treatment decisions.

To our knowledge, this is also the first study analysing and reporting the baseline neutrophil-to-lymphocyte ratio as an independent survival predictor in mCRPC patients receiving Ra-223 (Figure 1b). NLR has been hypothesised to be an indirect measurement of tumour inflammation. A higher NLR has been extensively reported as an adverse prognostic biomarker, including results from a meta-analysis of >40,000 patients with a variety of cancers [13]. High baseline NLR is associated with a poor overall survival in mCRPC patients treated with low dose corticosteroids, abiraterone, enzalutamide and cabazitaxel [14 -17]. However, until now, this has yet to be reported in the Ra-223 cohort. It is of importance to note that in our study, data from 2 centres suggests that at least 42% (56/133) patients were prescribed concurrent low dose corticosteroids with Ra-223. However, due to limitations of retrospective data collection, the steroid-status of each patient pre-Ra-223 and during therapy could not be conclusively determined. Corticosteroids are known to increase the NLR and a possible confounding effect cannot be discounted. However, Lorente et al [17] have reported an independent associa-

tion between baseline NLR and survival in mCRPC patients treated with second-line chemotherapy, irrespective of baseline corticosteroid use. Though the role of corticosteroids in mCRPC remains controversial, their use for palliation of symptoms is well established. Larger studies are required to confirm the robustness of NLR as a prognostic marker in the mCRPC and Radium-223 cohort, and independent of baseline steroid use, thus reflecting real world practice.

In conclusion, the lack of head to head trials between abiraterone, enzalutamide and Ra-223 makes it difficult to identify the ideal drug for a given clinical scenario. Furthermore, although Ra-223 is generally well-tolerated, data suggests current surrogate biomarkers of disease response such as ALP response do not predict overall survival. Rather younger age, completion of 5-6 of cycles of Ra-223, lower baseline ALP, and lower baseline neutrophil-to-lymphocyte ratio were independent predictors of increased overall survival. Importantly, suggested survival benefit from Ra-223 seems limited to the sub-group of patients actually able to complete 5-6 cycles of Ra-223, and factors predicting treatment completion are higher baseline haemoglobin and better performance status. We would also like to stress the importance of auditing real world practice. In our study the median survival of Group 1-4 (70/189 or 37% of patients) was 4.5 months, which is shorter than the time taken to complete 5-6 cycles of Ra-223 that is expected to improve survival. This reflects the clinical difficulties in identifying appropriate therapy for contemporarily treated mCRPC patients. Research focus on the optimal combination, timing and sequence of available therapies for mCRPC, and further studies on prognostic factors, must remain a priority. Developing a prognostic tool to predict completion of Ra-223 cycles by risk-stratification of patients according to baseline status would be helpful.

Conflict of Interest Statement:

S Parikh, L Kenning, G Wright, O Din, S Dixit received speaker's honoraria from Bayer Pharmaceuticals.
O Din received travel grants and grant funding for extra staff from Bayer Pharmaceuticals

References:

1. EU science hub. European Commission's Science and Knowledge Service. https://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe

2. Harrison MR, Wong TZ, Armstrong AJ, George DJ. Ra-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. Cancer Manag Res. 2013; 5:1-14.

3. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossået SD et al. Alpha Emitter Ra-223 and survival in metastatic prostate cancer. N Engl J Med. 2013; 369(3):213-23.

4. National Institute of Health and Care Excellence. Ra-223 dichloride for treating hormone relapsed prostate cancer with bone metastases. Technology Appraisal Guidance [TA412]. Published 28 September 2016. www.nice.org.uk/guidance/TA412/chapter/1-Recommendations

5. Yorkshire and Humber NHS Clinical Senate. www.yhsenate.nhs.uk

6. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital based cancer registry. JAMA 2004; 291: 2441-47.

7. Wong W, Anderson E, Mohammadi H, Daniels TB, Schild SE, Keole SR, et al. Factors Associated With Survival Following Ra-223 Treatment for Metastatic Castration-resistant Prostate Cancer. Clin Genitourinary Cancer. 2017;15(6):e969-e975

8. Hague C, Logue JP. Clinical experience with Ra-223in the treatment of patients with advanced castrate-resistant prostate cancer and symptomatic bone metastases. Ther Adv Urol. 2016, 8(3):175-180.

9. Etchebehere EC, Milton DR, Araujo JC, Swanston NM, Macapinlac HA, Rohren EM. Factors affecting Ra223 therapy: clinical experience after 532 cycles from a single institution. Eur J Nucl Med Mol Imaging. 2016;43(1):8-20.

10. Saad F, Keizman D, O'Sullivan JM. Analysis of overall survival by number of Ra-223 injections received in an international expanded access program (iEAP). J Clin Oncol. 2016; 34 suppl 15,S5082.

11. Stolten MD, Steinberger AE, Cotogno PM, Ledet EM, Lewis BE, Sartor O. Parameters associated with 6 cycles of Ra-223 dichloride therapy in Metastatic Castrate Resistant Prostate Cancer.Int J Radiat Oncol Biol Phys. 2015; 93(3):E196

12. J. O'Sullivan, S. Gillessen, A. Heidenreich. Effects of concomitant use of abiraterone and/or enzalutamide with Ra-223 on safety and overall survival in metastatic castration-resistant prostate cancer (mCRPC) patients treated in an international early access program (EAP). Eur J Cancer. 2015, 51(3):S497-498

13. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña AJ, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis.
Natl Cancer Inst. 2014; 106(6): 124

14. Conteduca V, Crabb SJ, Jones RJ, Caffo O, Elliott T, Scarpiet E, et al. Persistent Neutrophil to Lymphocyte Ratio >3 during Treatment with Enzalutamide and Clinical Outcome in Patients with Castration-Resistant Prostate Cancer. PLoS One. 2016;11(7):e0158952.

15. Boegemann M, Schlack K, Thomes S. The Role of the Neutrophil to Lymphocyte Ratio for Survival Outcomes in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Abiraterone. Int J Mol Sci 2017;18(2),380.

16. Mehra N, Sharp A, Lorente D, Dolling D, Sumanasuriya S, Johnson B, et al. Neutrophil to Lymphocyte Ratio in Castration-Resistant Prostate Cancer Patients Treated With Daily Oral Corticosteroids. Clin Genitourin Cancer. 2017;15(6):678-684.

17. D. Lorente, J. Mateo, A. J. Templeton, Z. Zafeiriou, D. Bianchini, R. Ferraldeschi, et al. Baseline neutrophil–lymphocyte ratio (NLR) is associated with survival and response to treatment with second-line chemotherapy for advanced prostate cancer independent of baseline steroid use. Ann Oncol. 2015; 26: 750–755

Table 1. Patient Characteristics

Patient factors	**n=no. of patients Total n = 189**	**Median value**	**Range**
Treatment Centres			
Leeds vs Hull vs Sheffield	n=105 vs 55 vs 23		
Age (years)	n= 189	72	51 - 87
Number of Cycle of Ra-223			
Group 5-6 vs 1-4	n=119 vs 70		
Gleason Score at diagnosis			
Gleason 6-7 vs 8-10	n= 34 vs 92	-	
Performance Status (reference category 0)			
ECOG 0 vs 1 vs 2	n = 29 vs 110 vs 50		
ACE Comorbidity Score			
ACE score 0-1 vs 2-3	n = 97 vs 32		
Previous docetaxel			
Yes vs No	n =102 vs 87		
Baseline Haemoglobin (Hb) (g/L)	n = 174	121	63 - 155
Prostate Specific Antigen (PSA) (ng/ml)	n = 171	90	0.4 - 7739
Alkaline Phosphatase (ALP) (IU/L)	n = 171	230	36 - 2360

Table 1. Patient Characteristics

Albumin (g/L)	n = 93	40	23 - 47
Neutrophil/Lymphocyte Ratio (NLR)	n = 146	3.42	0.25 - 13.79
Alkaline Phosphatase (ALP) response (reference group 0)			
0- 0 to 49% decrease in ALP	n = 69		
1- ≥ 50% decrease in ALP	n = 82		
2- Rise in ALP	n = 31		
Prostate Specific Antigen response (reference group 0)			
0 - 0 to <49% decrease in PSA	n = 33		
1 - ≥ 50% decrease in PSA	n = 21		
2 - (Rise in PSA)	n = 127		

Table 2: Factors predicting survival

Patient factors	**Univariate p value**	**Univariate Hazard Ratio (95% CI)**	**Multi-variable p value**	**Multivariable Hazard Ratio (95% CI)**
Age	0.015	1.03 (1.006 - 1.06)	**0.005**	**1.07 (1.02 - 1.12)**
Cycles of Ra223: Group 5-6 vs 1-4	<0.001	11.62 (7.31 - 18.46)	**<0.001**	**0.10 (0.05 - 0.20)**
Gleason 6-7 vs 8-10	0.049	1.87 (1.003 - 3.49)		
Performance Status (reference category 0)				
ECOG 0	<0.001			
ECOG 1		2.27 (1.16 - 4.42)		
ECOG 2		6.34 (3.14 - 12.82)		
ACE Comorbidity score 0-1 vs 2-3	0.828			
Previous docetaxel: Yes vs No	0.963			
Baseline Haemoglobin (g/L) per 10 unit rise	<0.001	0.77 (0.68-0.88)		
Prostate Specific Antigen (PSA) (ng/ml) per 100 unit rise.	0.005	1.03 (1.010-1.057)		
Alkaline Phosphatase (IU/L) per 100 unit rise	<0.001	3.54 (2.27-5.54)	**0.044**	**1.06 (1.002-1.12)**
Albumin (g/L) per unit rise	0.25			

Table 2: Factors predicting survival

Neutrophil to Lymphocyte Ratio	<0.001	1.17 (1.08 - 1.27)	**0.033**	**1.19 (1.01 - 1.40)**
Alkaline Phosphatase (ALP) response (reference group 0)				
0- 0 to 49% decrease in ALP	0.275			
1- ≥ 50% decrease. in ALP				
2- Rise in ALP				
Prostate Specific Antigen response (reference group 0)				
0 - 0 to <49% decrease in PSA	0.008			
1 - ≥ 50% decrease in PSA		0.38 (0.142 - 1.019)		
2 - (Rise in PSA)		1.14 (0.87 - 2.38)		

Table 3 : Multivariate analysis of initial patient factors predicting successful completion of 5-6 cycles of Ra-223.

	GROUP 1-4 **1-4 Cycles of Ra223** **(N = 70)**	**GROUP 5-6** **5-6 Cycles of Ra223** **(N = 119)**	**p value**	**Odds ratio** **(95% CI)**	**Multi-** **variable** **p value**	**Multivariable** **Odds Ratio (95%** **CI)**
ECOG PS 0	N = 4	N = 25	<0.001		0.078	
ECOG PS 1	N = 36	N = 74		0.33 (0.11 - 1.02)	0.067	0.013 (0.02 - 1.15)
ECOG PS 2	N = 30	N = 20		0.11 (0.03 - 0.35)	**0.026**	**0.080** **(0.01-0.74)**
Median baseline Hb (IQR)	111 (103-126) N = 62	123 (115.5-131) N = 112	<0.001	1.05 (1.02 - 1.07)	**0.028**	**1.04** **(1.004 - 1.074)**
Median baseline ALP (IQR)	346 (200 - 681) N = 60	172.5 (97 - 343) N = 111	0.011	0.999 (0.10-1.00)		
Median baseline albumin (IQR)	39 (34.5 - 42.5) N = 35	40 (37 - 43) N = 58	0.09	1.08 (0.98 - 1.18)		

Table 4 : Reasons for stopping Ra-223 before 6th cycle. Note data available from 2 of 3 centres only.

	1-4 Cycles of Ra223 N = 56	**5 Cycles of Ra223 N=13**
Death	2 (4%)	1 (8%)
General Deterioration/Disease Progression	41 (73%)	8 (62%)
Sepsis	5 (9%)	1 (8%)
Pain	4 (7%)	1 (8%)
Myelotoxicity	2 (4%)	2 (15%)
PSA exponential rise	1 (2%)	0 (0%)

Table 5: Comparison of current study with other published retrospective cohort studies and randomised trials.

	Overall Survival			**Completion of 5-6 cycles of Ra-223 vs 1-4 cycles**			**6vs<6 cycles Ra223**
	Wong et al n=64	Etchebe-here et al n=110	Current study n=189	Saad et al n=696 iEAP	Saad et al n= 599 ALSYMPCA	Current study n=189	Stolten et al n=55
FACTORS			**Significance in Multivariable analysis**				
Age	N/A	N/A	**YES HR 1.07**	NS	NS	NS	NS
Time from PC diag-nosis Ra223	N/A	N/A	N/A	NS	NS	N/A	**YES**
No Prior Chemother-apy	**YES HR 0.25**	NS	NS	NS	NS	NS	NS
< 5 bone mets	**YES HR <0.001**	N/A	N/A	N/A	N/A	N/A	N/A
No. of Cycles of Ra 223	N/A	**YES HR 0.56**	**YES HR 0.10**	Outcome measure	Outcome measure	Outcome measure	Outcome meas-ure

Abiraterone during/after Ra223	N/A	**YES** **HR 0.32**	N/A	N/A	N/A	N/A	N/A
No prior Abiraterone failure	N/A	N/A	N/A	N/A	N/A	N/A	**YES**
ECOG 0-1 vs 2	NS	NS	NS	**YES** **OR 0.71**	NS	**YES** **OR 0.80**	N/A
Less Baseline Pain	N/A	NS	N/A	**YES** **OR 0.64**	NS	N/A	N/A
Baseline Haemoglobin	NS	NS	NS	**YES** **OD 0.71** **(cut at 10g/dl)**	NS	**YES** **OR 1.04**	N/A
Baseline ALP (IU/L)	**YES** **HR 0.22** **(cut at 115)**	NS	**YES** **HR 1.06**	NS	NS	NS	NS
Baseline PSA (ug/L)	NS		NS	**YES** **OR 0.63** **(cut at 141)**	**YES** **OR 0.68** **(log PSA)**	NS	NS
Baseline Albumin	N/A	N/A	NS	NS	**YES** **OR 0.94**	NS	NS

Baseline LDH	N/A	N/A	N/A	NS	**YES** **OR 0.08** **(log LDH)**	N/A	**YES**
Baseline NLR	N/A	N/A	**YES** **HR 1.19**	N/A	N/A	NS	N/A
ALP response	**YES** **(30% ↓)** **HR 0.26**	N/A	NS	N/A	N/A	NS	N/A

N/A - Factors not reported in study. NS - not significant. PC - prostate cancer. NLR - neutrophil-to-lymphocyte ratio. ALP- Alkaline phosphatase. PSA - prostate specific antigen. LDH- lactate dehydrogenase