Double-Blind, Placebo-Controlled Trial of Radium-223 Adjuvant to External Beam Radiotherapy Demonstrates Significant Decline in Bone-Alkaline Phosphatase and PSA in Patients with Hormone Refractory Prostate Cancer (HRPC)

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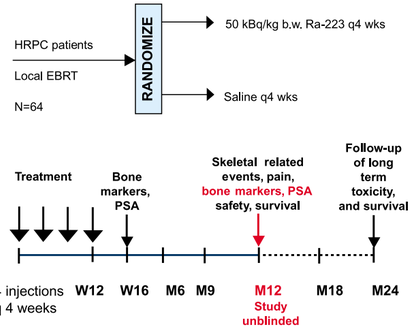
Background

The alpha emitter radium-223 (Alpharadin™; $t_{1/2}$ = 11.4 days) is a bone-seeking radionuclide currently explored as a novel treatment of bone metastases. Radium-223 has shown minimal toxicity in a phase I study (1). The present trial was initiated to study therapeutic efficacy in HRPC-patients with painful skeletal metastases using biomarkers and clinical endpoints as outcome measures. Safety and changes in biomarkers are reported based on analyses at 12 months after start of treatment.

Methods and Trial Design

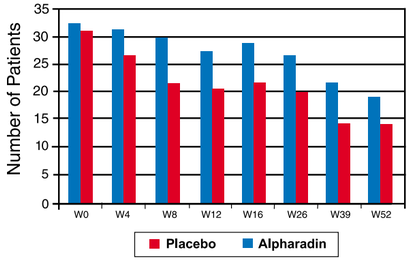
Methods: After receiving palliative external beam radiotherapy HRPC-patients were randomised to 4 i.v. injections of radium-223 (50 kBq/kg b.w.) or saline, repeated at four-week intervals. Bone-isoenzyme ALP (primary endpoint) and PSA were analyzed (radium-223 versus saline) following the 12-month visit when the data was unblinded.



Main Eligibility Criteria

- **Confirmed hormone refractory prostate cancer with painful skeletal metastases.**
- **Referred to palliative external radiotherapy for skeletal metastases.**
- **No other currently active malignancy or known metastases to other organ than skeleton.**

Patient Disposition (ITT)



- **Fewer placebo treated patients received 4 injections.**
- **Five patients received less than 2 injections (1 Alpharadin, 4 Placebo).**

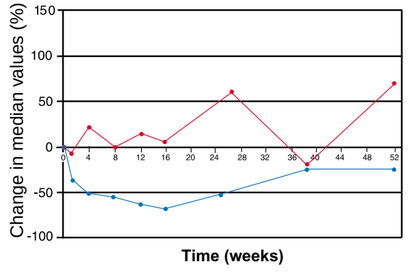
Hematological Toxicity

		Alpharadin**		Placebo**	
	Toxicity Grade*	3	4	3	4
0 – 16 w	Platelets			1	
	WBC	1			
	Neutrophils	1			
	Hb	1			1
16 - 52 w	Platelets	2			
	WBC				
	Neutrophils			1	
	Hb			2	

* NCI CTC v. 2.0
** Number of events

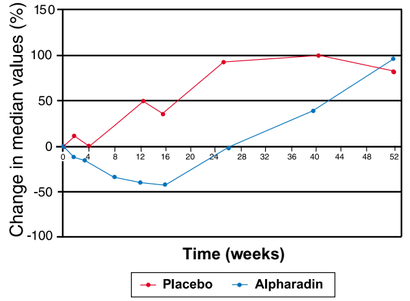
- **No grade 4 hematological events in Alpharadin treated patients.**
- **No grade 2-4 trombocytopenia in Alpharadin treated patients during treatment period.**
- **All events were transient.**
- **Transient neutropenia resolved during continued treatment.**

Bone Alkaline Phosphatase



- **Pronounced and rapid reduction of Bone-ALP levels by Alpharadin already after one injection.**
- **Reduction sustained to at least 6 months.**
- **Patients with the highest Bone-ALP values had a tendency of dropping out of the study over time, especially in the placebo group.**

Prostate Specific Antigen (PSA)



- **Pronounced reduction of PSA by Alpharadin.**
- **PSA values return to baseline at 6 months.**

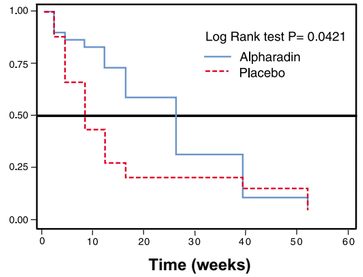
PSA Response Rate

	Alpharadin N=31	Placebo N=28	P-value*
10% decrease or better	26 (84%)	14 (50%)	0.007
30% response	21 (68%)	7 (25%)	0.001
30% confirmed response**	16 (52%)	7 (25%)	0.036
50% response	15 (48%)	6 (21%)	0.032
Confirmed 50% response**	11 (35%)	5 (18%)	0.149

* Cochran-Mantel Haenzel 2-sided
** Responses were confirmed with a second assessment 4 weeks later or more.

- **Please note that patients may have received several other treatments affecting PSA.**

Time to PSA Progression (ITT)



*Defined as increase from nadir with at least 25% for men with no PSA response and 50% for all others. Bubley et al., 1999.

- **Median time to PSA progression was increased from 8 weeks to 26 weeks by Alpharadin treatment.**

Conclusions

Radium-223 treatment demonstrated strong and consistent effects in this double-blind placebo-controlled trial in 64 patients. Statistically significant effects were shown on a range of markers of bone turn-over as well as a favorable PSA response. The beneficial effects had duration of approximately 3 months after end of treatment. The favorable side effect profile may allow longer duration of treatment.

References

1) Nilsson S, et al. Clin Cancer Res 2005;11(12): 4451-4459.