A Randomized, Placebo-Controlled, Phase 2 Study of Radium-223 in the Treatment of Metastatic Hormone Refractory Prostate Cancer (HRPC). Twelve Months Follow-Up Data

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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 skeletal metastases (1,2). 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. Twelve months data are presented as well as 18 months survival data.

METHODS AND TRIAL DESIGN

Main eligibility criteria:

- Confirmed hormone refractory prostate cancer with painful skeletal metastases
- Referred for palliative external beam radiotherapy for skeletal pain
- No known metastases to organs other than skeleton

Methods: After receiving palliative external beam radiotherapy HRPC-patients were randomized to 4 i.v. injections of radium-223 (50 kBq/kg b.w.) or saline, repeated at four-week intervals. The study was unblinded following the 12-month visit.

Skeletal-related events (SREs) were defined as any of: (i) A 25% increase in pain severity index (PSI) compared to baseline for two consecutive measurements. (ii) Increase in analgesic consumption. Analgesia was classified according to the WHO ladder for cancer pain; A change to a higher level or increase in strong opioids of 50% or more was regarded as a SRE. (iii) Neurological symptoms secondary to skeletal manifestations of prostate cancer; (iv) New pathologic bone fractures (vertebral and non-vertebral); (v) Tumour related orthopaedic surgical intervention; (vi) Subsequent external beam radiation to relieve skeletal pain; or (vii) Use of radioisotopes to relieve new skeletal related symptoms; (viii) Use of corticosteroids for skeletal pain, at doses aimed for pain palliation; (ix) Use of chemotherapy, bisphosphonates; or hormones, for the treatment of skeletal disease progression.

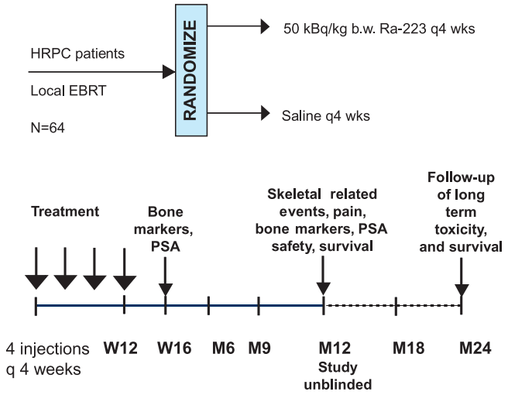


Figure 1. Study design.

PATIENT CHARACTERISTICS

Patient Characteristic	Alpharadin (n=33)	Placebo (n=31)	P – value Wilcoxon
Age (years)	73, 72.8 (57-88)	72, 71.7 (60-84)	0.510
Hb (G/L)	12.6, 12,48 (10.0-15.3)	12.9, 12.60 (9.9-14.9)	0.559
PSA (ng/mL)	167, 511 (10-6000)	233, 480 (1-4002)	0.915
Bone-ALP (ng/mL)	56.7, 121.2 (12.7-1145)	67.7, 131.9 (11.2-705.9)	0.356
Total ALP (U/L)	228, 436.5 (80-3047)	279, 501.0 (51-2280)	0.337
Albumin (G/L)	40, 38.9 (28-46)	38, 38.6 (30-47)	0.604
LDH (U/L)	348, 351.1 (154-750)	344.5, 426.4 (144-1284)	0.483
ECOG PS 0 1 2	9 (27%) 18 (55%) 6 (18%)	6 (19%) 20 (65%) 5 (16%)	0.734
Extent of Disease < 6 mets 6-20 mets > 20 mets Superscan	 12 (36%) 10 (30%) 10 (30%) 1 (3%)	 7 (23%) 13 (42%) 10 (32%) 1 (3%)	0.686
Pain Severity Index	3.5, 3.879 (1.0-7.75)	4, 3.782 (0.75-7.75)	0.994

Table 1. Baseline patient characteristics (ITT population). Median, Mean (range)

SAFETY

	Alpharadin (n=33)	Placebo (n=31)
Diarrhoea	9	10
Constipation	12	2
Vomiting	8	6
Nausea	9	10
Fatigue	8	7
Bone pain	10	16
Myalgia	5	4
Tumor flare	6	7
Anaemia	5	7

Table 2. Adverse events reported by more than 15% of the study population during the treatment period regardless of relationship to study medication (Number of patients).

	Alpharadin (n=33)		Placebo (n=30)	
Toxicity Grade	3	4	3	4
Platelets			1	
Neutrophils	1			
WBC	1			
Hb	1			1

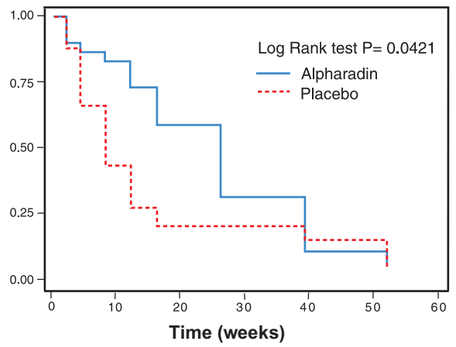
Table 3. Worst NCI CTC toxicity grade (version 2.0). All events were transient and reversible during continued treatment.

SERUM MARKERS

Patient Characteristic	Alpharadin	Placebo	P – value Wilcoxon
PSA	-23.8% (-99, 546)	+44.9% (-91, 563)	0.0026
Bone-ALP	-66.6% (-92.2, 124.9)	+9.3% (-77.4, 384.1)	<0.001
Total ALP	-46.2% (-89.3, 102.5)	+30.7% (-75.4, 212.9)	<0.001
PINP	-63.2% (-93.7, 151.0)	+38.3% (-72.5, 602.8)	<0.001
CTX-I	-31.4% (-74.3, 143.3)	+31.7% (-57.5, 395.8)	0.0023
ICTP	+14.6% (-54.6, 158.9)	+43.2% (-56.3, 242.1)	0.011

Table 4. Median (range) relative change in serum biomarkers from baseline to 4 weeks after the last study injection. ITT population.

TIME TO PSA PROGRESSION



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

Figure 2. Median time to PSA progression was increased from 8 weeks to 26 weeks by Alpharadin treatment.

SRE AND SURVIVAL

Parameter	Median timer to event		Cox proportional hazard	
	Alpharadin	Placebo	Hazard ration	p - value
SRE - ITT	14 weeks	11 weeks	1.753	0.0659
SRE - PP	16 weeks	11 weeks	1.815	0.0585
Survival - ITT	65.3 weeks	46.4 weeks	2.117	0.0200
Surivival - PP	71.0 weeks	46.4 weeks	2.286	0.0158

Table 5. Median time to first skeletal related event (SRE) or survival. ITT (intent-to-treat) includes all treated patients while PP (per-protocol) excludes 5 patients that did not receive 2 injections with study drug and one patient where the study group allocation was accidentally revealed. Adjusted for covariates.

TIME TO FIRST SRE (ITT population)

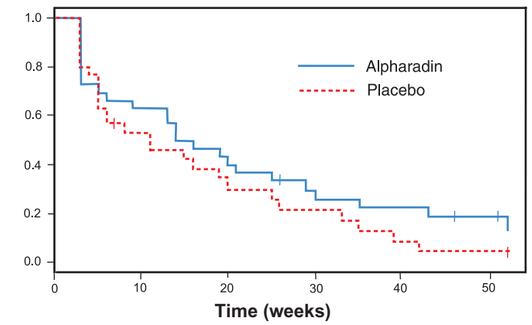


Figure 3. Time to first SRE. ITT population.

OVERALL SURVIVAL (ITT population)

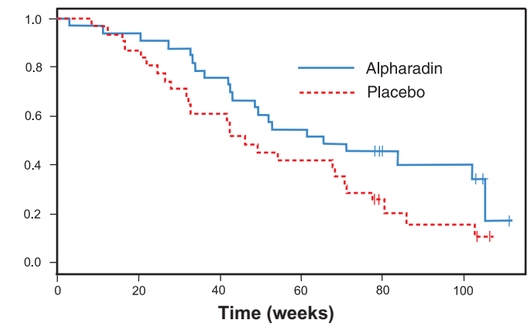


Figure 4. Overall survival. 18 months follow-up. If time of death was missing, observation was censored at 18 months. If later observation existed, this was used.

CONCLUSIONS

All efficacy parameters were consistently in favour of radium-223 treatment. A benign hemotoxicity profile was seen. Four injections of radium-223 was well tolerated during the 12 weeks treatment period, and an extended treatment period may further delay disease progression. In this small study, a possible survival benefit for radium-223 at 18 months follow up was seen. Larger clinical studies are warranted.

REFERENCES

1) Nilsson S et al., Clin Cancer Res.; 11 (12): 4451-4459, 2005
2) Bruland ØS et al., Clin Cancer Res.; 12 (20 Suppl): 6250s-6255s, 2006