

ABSTRACT

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. Here, we report changes in biomarkers based on analyses up to 4 months. Clinical endpoints will be analyzed at completion of the 12-month visit.

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), S-PINP, S-CTX-I, S-ICTP and PSA were analyzed (radium-223 versus saline) following the 4-month visit.

Results: 33 patients received radium-223 and 31 pts received saline. Active treatment resulted in a statistically significant decrease in bone-ALP from baseline compared to placebo. The mean (\pm SD) change from baseline to 4 weeks after last injection for radium-223 (33 patients) was $-58\% \pm 37$ versus $+47\% \pm 107$ in the placebo group (29 patients), $P < 0.001$. A similar pattern was seen for S-PINP. Statistically significant changes in the bone resorption parameters S-CTX-I and S-ICTP between the active drug and placebo were also observed. In the radium-223 group, 15 of 31 patients showed PSA response ($\geq 50\%$ decrease from baseline), compared to only 5 of 28 patients in the placebo group. Minimal bone marrow toxicity for all patients participating in the study was shown.

Conclusions: Radium-223 treatment demonstrated a strong effect on the microenvironment of bone metastases as indicated by a statistically significant change compared to placebo on bone-ALP, other markers of bone turn-over, as well as a favorable PSA response. Minimal bone marrow toxicity after repeated doses is encouraging and warrants further clinical development of radium-223 as a targeted agent for the treatment of bone metastases.

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

Bone-Seeking Radium-223 Adjuvant to External Beam Radiotherapy Demonstrates Significant Decline in Bone-Alkaline Phosphatase and PSA in Patients with Hormone Refractory Prostate Cancer (HRPC)

S. Nilsson*, L. Franzén, C. Tyrrell, R. Blom, J. Tennvall, B. Lennernäs, J. Yachnin*, D. C. Johannessen, M. Sokal, U. Petersson, C. Parker, K Pigott, Ø.S. Bruland

*Karolinska Hospital and Institute, Stockholm, Sweden; Länssjukhuset Sundsvall-Härnösand, Sundsvall, Sweden; Plymouth General Hospital, Plymouth, United Kingdom; University Hospital Linköping, Linköping, Sweden; University Hospital Lund, Lund, Sweden; Sahlgrenska University Hospital, Gothenburg, Sweden; Haukeland University Hospital, Bergen, Norway; Nottingham City Hospital, Nottingham, United Kingdom; Centrallasarettet i Västerås, Västerås, Sweden; Royal Marsden Hospital, Sutton, UK; Royal Free Hospital, London, UK; The Norwegian Radium Hospital and Algeta ASA, Oslo, Norway



Algeta ASA, PO Box 54 Kjelsås, NO-0411 Oslo, Norway.
Telephone: +47 23 00 79 90. Telefax: +47 23 00 79 91.
www.algeta.com

2006 Prostate Cancer Symposium
Co-sponsored by ASCO/ASTRO/PCF/SUO
San Francisco, CA, February 24 - 26, 2006

Bone-Seeking Radium-223 Adjuvant to External Beam Radiotherapy Demonstrates Significant Decline in Bone-Alkaline Phosphatase and PSA in Patients with Hormone Refractory Prostate Cancer (HRPC)

S. Nilsson*, L. Franzén, C. Tyrrell, R. Blom, J. Tennvall, B. Lennernäs, J. Yachnin*, D. C. Johannessen, M. Sokal, U. Petersson, C. Parker, K Pigott, Ø. S. Bruland

*Karolinska Hospital and Institute, Stockholm, Sweden; Länssjukhuset Sundsvall-Härnösand, Sundsvall, Sweden; Plymouth General Hospital, Plymouth, United Kingdom; University Hospital Linköping, Linköping, Sweden; University Hospital Lund, Lund, Sweden; Sahlgrenska University Hospital, Gothenburg, Sweden; Haukeland University Hospital, Bergen, Norway; Nottingham City Hospital, Nottingham, United Kingdom; Centrallasarettet i Västerås, Västerås, Sweden; Royal Marsden Hospital, Sutton, UK; Royal Free Hospital, London, UK; The Norwegian Radium Hospital and Algeta ASA, Oslo, Norway

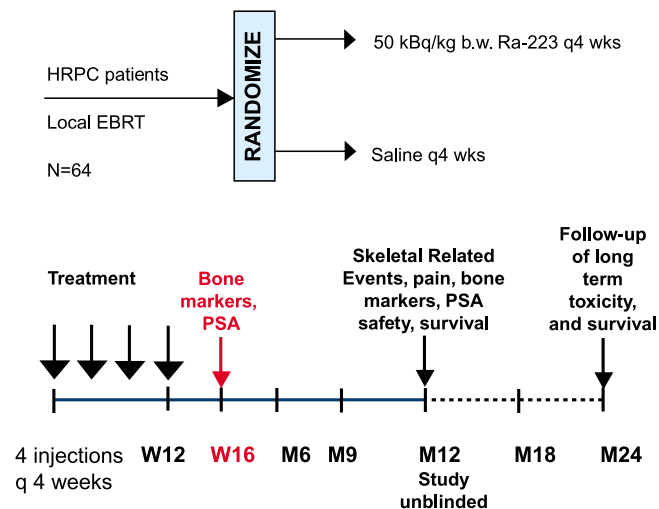
Background

The alpha emitter radium-223 (Alpharadin®, $t_{1/2} = 11.4$ days) is a bone-seeking radionuclide currently being developed as a novel treatment of bone metastases (1). Radium-223 has shown minimal toxicity in a phase I study (2). The present placebo controlled trial was initiated to study therapeutic efficacy, previously demonstrated in a tumour model in nude rats (3), in patients with HRPC and painful skeletal metastases using biomarkers and clinical endpoints as outcome measures.

Here, we report changes in biomarkers based on analyses up to 16 weeks. Clinical endpoints will be analyzed at completion of the 12-month follow up.

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), S-PINP, S-CTX-I, S-ICTP and PSA were analyzed (radium-223 versus saline) following the 16 weeks visit. All patients who received at least one administration of study drug were included in the analysis. Statistical methods: For numeric data two-sided Wilcoxon rank sum tests, stratified for centre, were used. For qualitative data the Fisher's Exact Test was used.

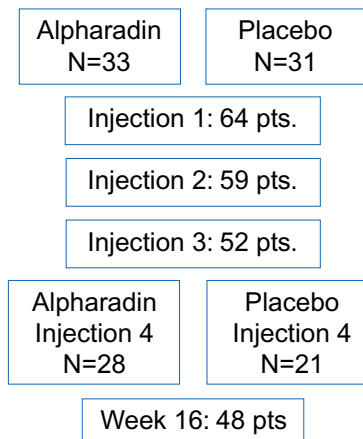


Week 16: The treatment phase is completed. Study made unblinded for bone markers and PSA on a study drug group level (radium-223 vs saline). All individual data are blinded up to the Month 12 (July 06) follow-up visit.

Main Eligibility Criteria

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

Patient Disposition



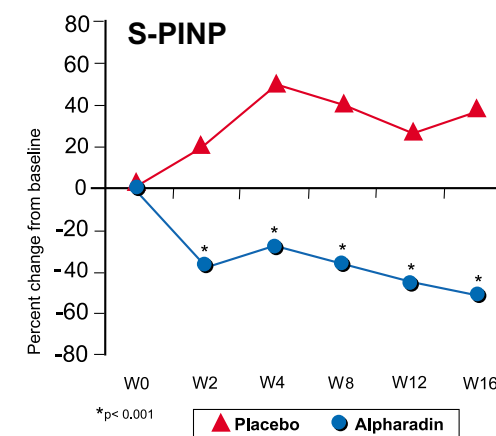
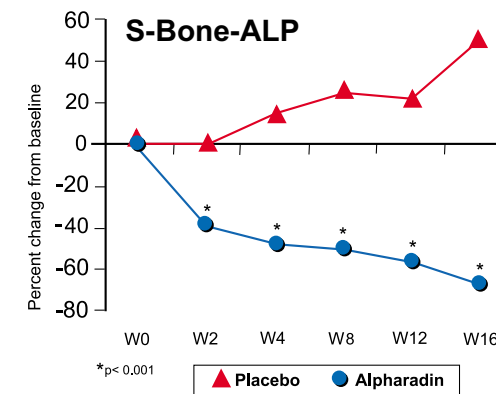
Hematological Toxicity

CTC toxicity grade 3 - Observed in three patients

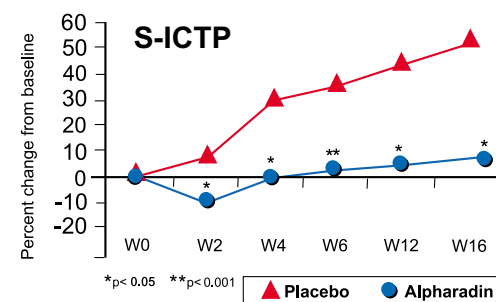
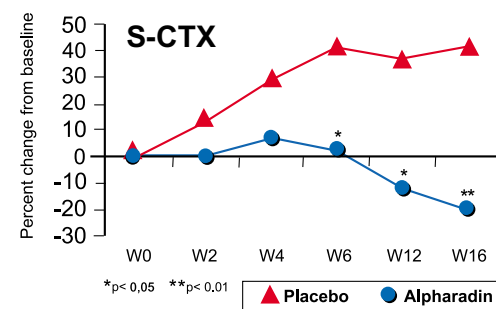
- Neutrophils ($0.5 - <1.0 \times 10^9/L$): One patient at weeks 6, 12 and 16
- WBC ($1.0 - <2.0 \times 10^9/L$): One patient at week 16
- Platelets ($10 - <50 \times 10^9/L$): One patient at week 8

CTC toxicity grade 4 - Not observed

Bone Formation Markers



Bone Resorption Markers



PSA

PSA RESPONSE

Confirmed PSA Responder: The PSA level from baseline is decreased at last 50% for two successive measurements at last 4 weeks apart

PSA Responder: The PSA level from baseline is decreased at least 50%.

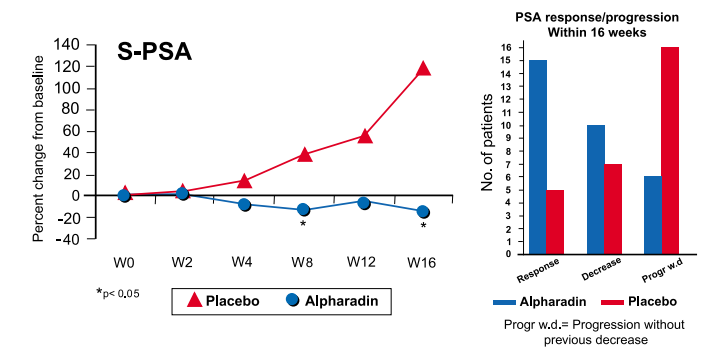
	Alpharadin® (N=31)	Placebo (N=28)	P-value
Confirmed PSA Responder	10 (32%)	5 (18%)	0.2432
PSA Responder	15 (48%)	5 (18%)	0.0263

PSA PROGRESSION

Confirmed PSA Progressor: Patient with no decrease (<10% from baseline), and the PSA level from baseline has increased at last 25% for two successive measurements at least 4 weeks apart.

PSA Progressor: Patients with no decrease (<10% from baseline), and the PSA level from baseline has increased at least 25%

	Alpharadin® (N=31)	Placebo (N=28)	P-value
Confirmed PSA Progressor	5 (16%)	10 (36%)	0.1339
PSA Progressor	6 (19%)	16 (57%)	0.0035



Conclusions

Alpharadin demonstrated:

- Minimal bone marrow toxicity after repeated administration
- Strong effect on bone micro-environment shown with bone-ALP and other markers of bone turnover
- Favourable PSA response

The results are encouraging and warrant further clinical development of radium-223 as a targeted agent for the treatment of bone metastases.

References

- Henriksen G et al., J Nucl Med 2003;44 (2): 252-259
- Nilsson S et al., Clin Cancer Res 2005;11 (12): 4451-4459
- Henriksen G et al., Cancer Res 2002;62: 3120-3125