

A double-blind, randomised dose-response phase II, multicentre study of radium-223 (Alpharadin®) for the palliation of painful bone metastases in castration-refractory prostate cancer patients

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BACKGROUND

Alpharadin® (radium-223) is a novel alpha pharmaceutical in development for treatment of bone metastases. This new generation bone seeker emits alpha particles with high linear energy transfer (LET) alpha radiation with extremely short range, thus sparing bone marrow. These characteristics generate highly localized radiation zones which may inhibit tumour progression and induce pain relief. The aim of the study was to investigate if there is a pain relieving effect and a dose-response relationship after a single dose of Alpharadin.

METHODS AND STUDY DESIGN

100 castration-refractory prostate cancer patients with painful bone metastases were randomised in a double-blind dose-ranging study. The primary efficacy endpoint was Pain Index based on a combination of the change in diary pain rating (VAS scale) and the change in analgesic consumption during a 16 weeks period. Pain and physical function were also measured using BPI (Brief Pain Inventory). Bone-ALP and safety were assessed.

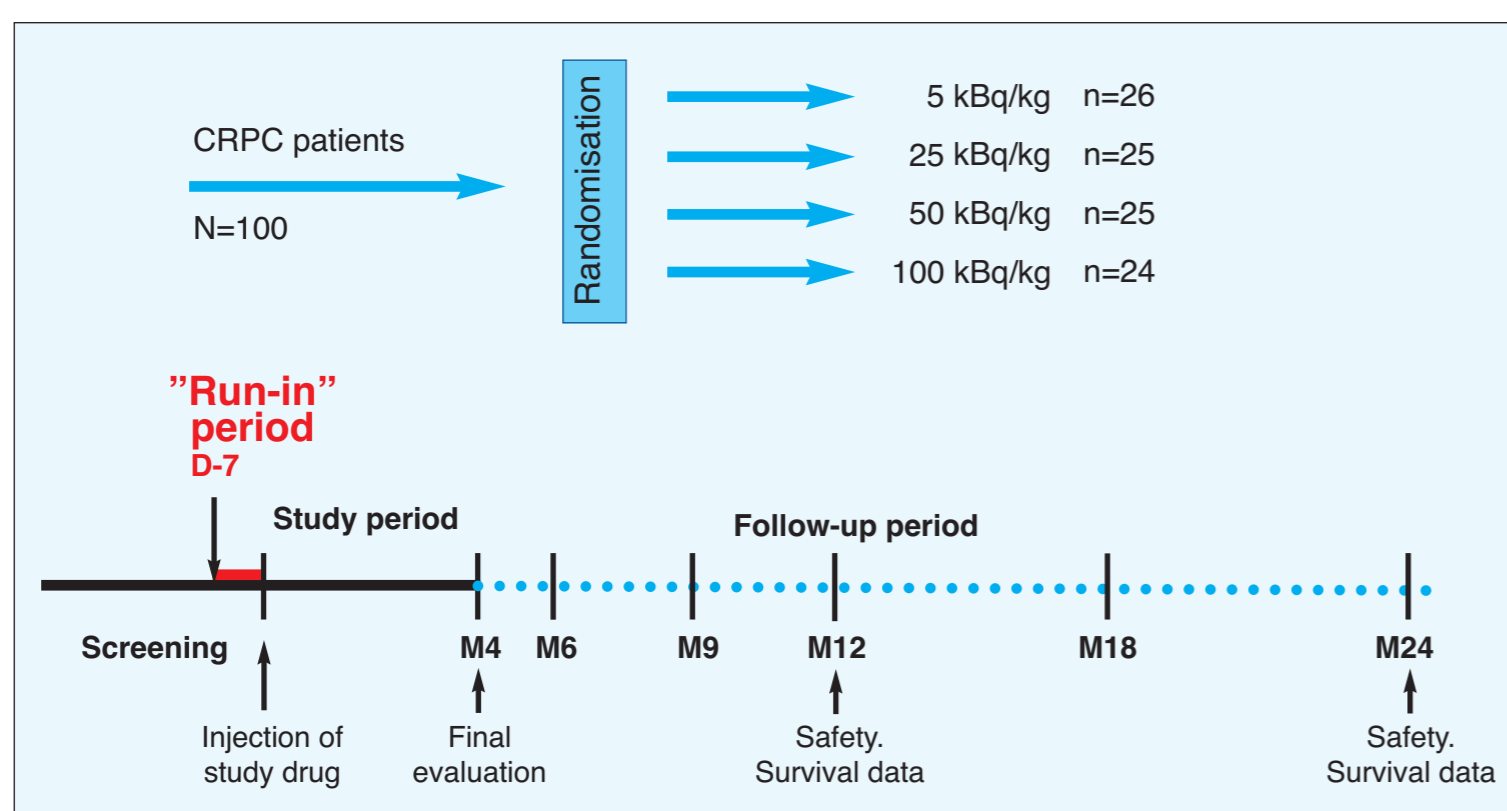


Figure 1. Study design

PATIENT CHARACTERISTICS

| Patient characteristics | 5 kBq/kg b.w. (N=26) | 25 kBq/kg b.w. (N=25) | 50 kBq/kg b.w. (N=25) | 100 kBq/kg b.w. (N=24) |
|-------------------------------|----------------------|-----------------------|-----------------------|------------------------|
| Age (years)* | 70 (7) | 69 (9) | 67 (7) | 69 (7) |
| Weight (kg)* | 85 (11) | 81 (12) | 77 (12) | 82 (13) |
| Extent of disease | (n=22) | (n=24) | (n=24) | (n=23) |
| 1 (<6) | 2 9% | 5 21% | 4 17% | 1 4% |
| 2 (6 to 20) | 9 41% | 9 38% | 5 21% | 8 35% |
| 3 (>20) | 9 41% | 9 38% | 11 46% | 10 44% |
| 4 (superscan) | 2 9% | 1 4% | 4 17% | 4 17% |
| Daily Diary Pain VAS (mm)** | 42 (13), 40 | 48 (17), 46 | 41 (13), 37 | 43 (14), 45 |
| Haemoglobin (g/L)** | 120 (13), 119 | 119 (16), 122 | 127 (18), 131 | 121 (19), 124 |
| Albumin (g/L)** | 39 (5), 39 | 37 (5), 37 | 39 (3), 39 | 41 (13), 38 |
| Lactate dehydrogenase (U/L)** | 451 (273), 376 | 378 (342), 285 | 330 (170), 267 | 507 (463), 326 |
| PSA (µg/L)** | 707 (1245), 228 | 356 (624), 139 | 358 (724), 157 | 420 (553), 130 |
| Bone-ALP (ng/mL)** | 163 (195), 89 | 167 (309), 72 | 166 (187), 98 | 247 (455), 124 |

Table 1. Baseline patient characteristics (ITT analysis set)

* Mean (SD)
** Mean (SD), median

In addition, all patients were Caucasian and had an Eastern Co-operative Oncology Group (ECOG) performance score ≤ 2 .

SAFETY

There were minor decreases in platelet counts, white blood cell counts and neutrophils in the two highest dose groups (50 and 100 kBq/kg b.w.). These tended to occur in the first 2 weeks after the injection, but subsequently returned to baseline.

Adverse events were mainly gastrointestinal in nature. None of the AEs were unexpected. The most frequently reported AEs across all dose groups were nausea (43%), fatigue (26%), vomiting (24%), diarrhoea (22%), constipation (20%), decreased haemoglobin (15%), urinary tract infection (14%), peripheral oedema (12%) and anaemia (11%). There was no apparent increasing incidence with increasing dose level for any of these AEs.

PAIN INDEX

The pain index was a composite score based on change in bone pain on visual analog scale (VAS) and change in analgesic consumption from baseline, as recorded in the patient diary.

Pain index:

1 = complete pain response; 2 = marked pain response; 3 = moderate pain response; 4 = minimal pain response; 5 = no pain response (stable); 6 = pain progression.

| Visit | 5 kBq/kg b.w. | 25 kBq/kg b.w. | 50 kBq/kg b.w. | 100 kBq/kg b.w. | Jonckheere-Terpsta test for trends |
|----------|----------------|----------------|----------------|-----------------|------------------------------------|
| Week 2* | 4.8 (1.4), 5.0 | 4.1 (1.8), 5.0 | 3.9 (1.4), 4.0 | 3.9 (1.6), 5.0 | p=0.035 |
| Week 4* | 4.0 (1.8), 3.5 | 3.9 (1.9), 4.0 | 3.6 (1.6), 4.0 | 3.3 (1.8), 3.0 | p=0.123 |
| Week 8* | 4.2 (1.8), 5.0 | 3.6 (2.0), 3.0 | 3.8 (1.9), 4.0 | 3.1 (1.7), 2.0 | p=0.103 |
| Week 12* | 3.9 (2.2), 4.0 | 3.6 (2.3), 3.5 | 4.6 (1.8), 5.0 | 3.8 (1.8), 3.0 | p=0.717 |
| Week 16* | 4.3 (2.1), 5.5 | 3.1 (2.0), 2.0 | 4.2 (2.0), 5.0 | 3.4 (2.1), 2.0 | p=0.598 |

Table 2. Summary of pain index scores (1 to 6; Representing change from baseline) and statistical analysis (PP analysis set)

* Mean (SD), median

PAIN RESPONDERS

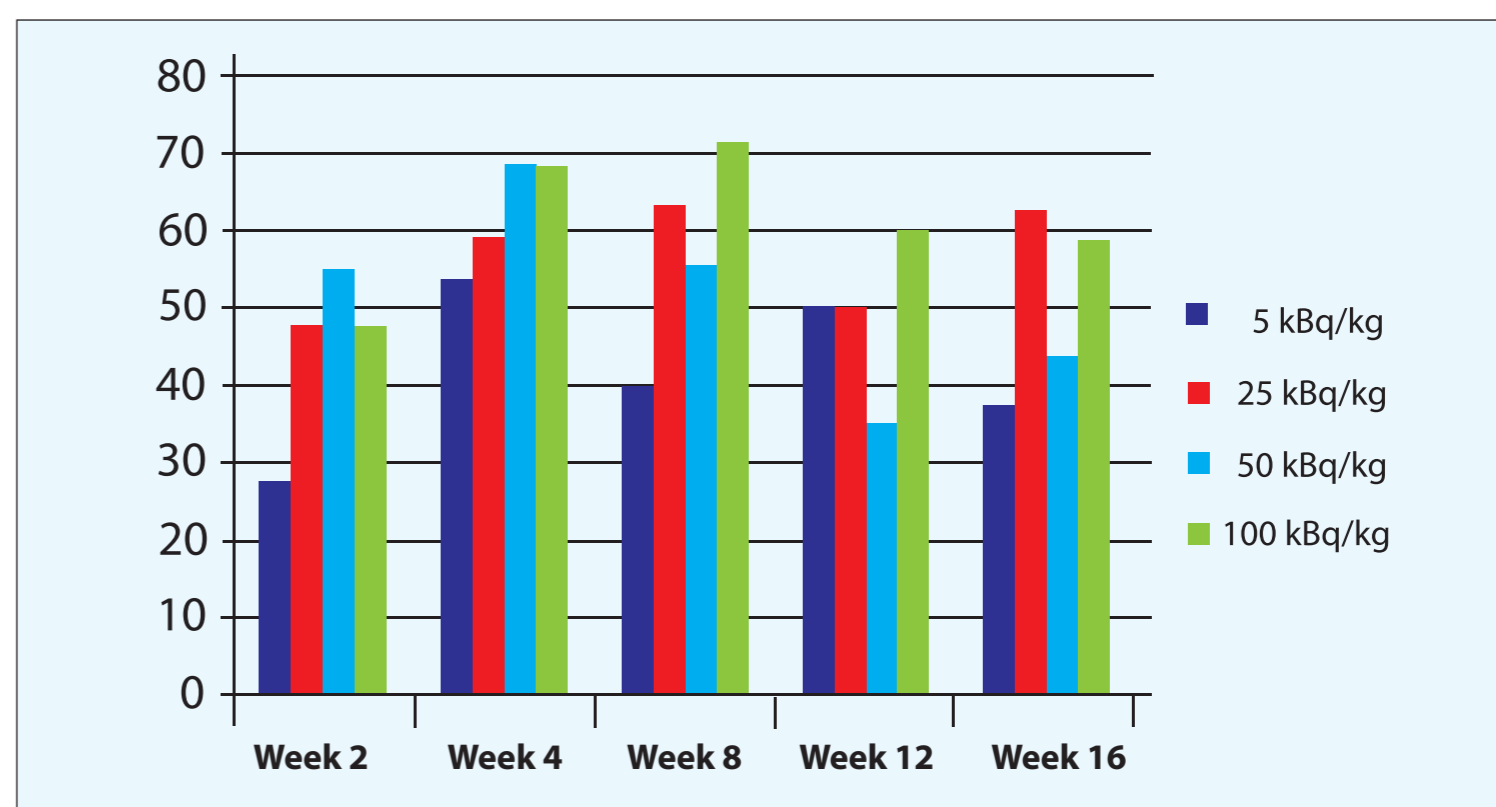


Figure 2. Percentage of responders (PP analysis set)

Pain responders in Figure 2 include only pain index categories 1 – 4

At 8 weeks after injection there were 40, 63, 56 and 71% responders (including only pain index categories 1 – 4) in the four dose levels: 5, 25, 50 or 100 kBq/kg b.w., respectively. Within each dose group, for the responders, a significant pain relieving effect was observed in the patients' diary VAS score.

Median decrease were -15, -30, -26 and -22 mm and the p values were 0.01, 0.001, 0.0005 and <0.0001 respectively.

INCREASED ANALGESIC CONSUMPTION

| Visit | Number (%) of patients | |
|---------|------------------------|------------------------|
| | 5 and 25 kBq/kg b.w. | 50 and 100 kBq/kg b.w. |
| Week 2 | 13 (27%) | 1 (2%) |
| Week 4 | 16 (33%) | 4 (10%) |
| Week 8 | 12 (31%) | 7 (18%) |
| Week 12 | 13 (34%) | 12 (32%) |
| Week 16 | 10 (31%) | 11 (33%) |

Table 3. Summary of patients with an increase in analgesic medication from baseline (PP analysis set).

The numbers show a more pronounced increase in analgesic consumption in the two lowest dose groups compared to the two highest dose groups.

BONE MARKERS

The dose-related reduction of bone-ALP indicates a strong effect on the metastatic bone disease that develops as a result of the interaction between tumour cells and bone cells.

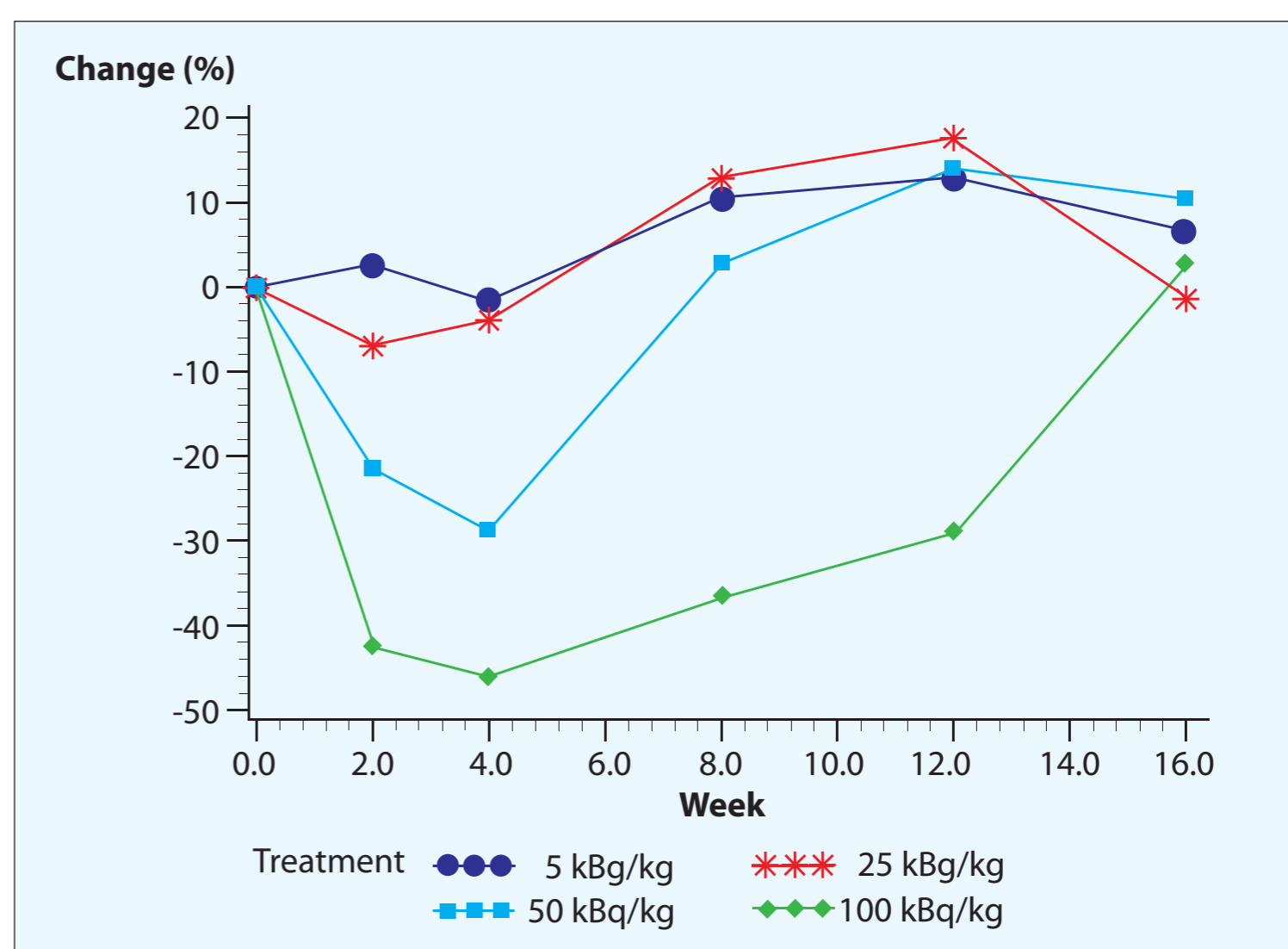


Figure 3. Median percentage change in bone-ALP (ng/mL) from baseline (ITT analysis set)

CONCLUSION

A single dose of Alpharadin (radium-223) exhibits a pain palliative effect in patients with painful bone metastases in castration-refractory prostate cancer patients. The most prominent effects were documented for the highest dose level, not only on pain relief but also on reduced bone-ALP.

At 2 weeks post injection the primary endpoint (pain index) showed a significant dose-response relationship following a single injection of Alpharadin (5, 25, 50 and 100 kBq/kg b.w.), with trends towards a dose response at 4 and 8 weeks.

Up to 70% of patients experienced a pain response at week 4 in the two highest dose groups (50 and 100 kBq/kg b.w.), and this was maintained in the highest dose group at Week 8.

Alpharadin was well tolerated and confirmed the benign side effect profile seen in other studies.