Clinical Experience and Radiation Safety of the First-in-Class Alpha-Pharmaceutical, Alpharadin™ (radium-223), in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases

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BACKGROUND

- The main cause of disability or death in patients with castration-resistant prostate cancer (CRPC) is the presence of bone metastases[1]
- Alpharadin, an alpha-particle–emitting radionuclide, is capable of targeting bone metastases and localizing its radiotherapeutic effects over a short distance, and has the potential to provide a survival benefit[2]
- Alpharadin is a first-in-class alpha-pharmaceutical with a potent and highly targeted antitumor effect on bone metastases,[2] and a highly tolerable side effect profile[3]

ALPHA-PARTICLE EMITTERS

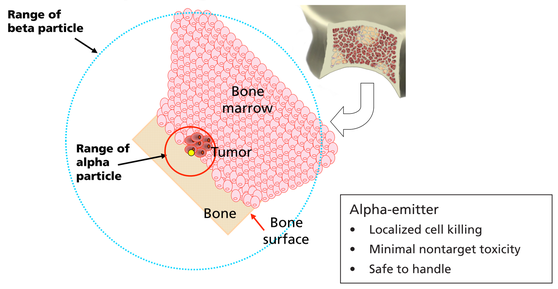
Advantages of alpha-particle emitters

- Unlike beta-emitting radiopharmaceuticals, alpha-emitters have an ultra-short penetration of 2-10 cell diameters, generating a highly localized and intense radiation zone[2] (Table 1)
- High-energy alpha-particle radiation has a high probability of inducing double-stranded DNA breaks,[4] resulting in a potent, highly localized cytotoxic effect in target areas containing metastatic cancer cells (Figure 1)
- The short path length of alpha-particles also ensures that toxicity to adjacent healthy tissue and particularly the bone marrow is kept to a minimum[2]

Table 1. Characteristics of alpha- and beta-emitters

	Alpha	Beta
Initial energy, MeV	3-8	0.01-2.5
Range in tissue, µm	40-90	50-5000
LET, keV/µm	60-230	0.015-0.4
Charge	+2	-1
Ion pairs per µm	2000-7000	5-20

Figure 1. Comparison of path length between alpha- and beta-emitters



Properties of Alpharadin (radium-223 chloride)

- Alpharadin is a calcium mimetic, alpha-emitting pharmaceutical based on radium-223 chloride (^{223}Ra)
- Alpharadin decays via a series of short-lived alpha-, beta-, and gamma-emitting daughters
- The percentages of total emitted decay energy particles are 93.5% alpha, 3.2% beta, and < 2% gamma x-ray
- Standard dose calibrators can be used to assay Alpharadin
- Alpharadin is a ready-to-use product

RADIATION SAFETY IN THE CLINICAL ENVIRONMENT

Handling and administration during clinical trials

- The radiologic half-life of Alpharadin (11.4 days) allowed sufficient time for its preparation, distribution (including long-distance shipment), and administration to patients
- No specialized equipment was required during administration
- The ultra-short penetration of alpha-particles, and the fact that alpha-radiation is readily blocked, allowed for ease of Alpharadin handling and standard radiation protection measures during shipping and administration (Figure 2, Table 2)

Figure 2. Administration of Alpharadin injection

- Patients were treated on an outpatient basis
- Minimal restrictions were placed on contact with other persons after treatment
- Due to the small component of gamma-radiation associated with the decay of Alpharadin, standard equipment for contamination monitoring was used

Table 2. Estimates of radiation exposure doses to fingers during handling of vials and syringes in the BC1-02 study*

	Activity of sample, MBq	Dose rate from handling, µSv/h	Time used for handling, min	Max dose to hands, µSv	4 injections per patient, µSv
Vial of Alpharadin as received	10	1000	1	17	67
Syringe for a 70-kg patient	3.5	350	3	18	70

*These should be considered maximum estimates, as they assume direct contact with the vial throughout the handling procedure. For comparison, the dose limit to fingers is 500,000 µSv per year (500 mSv).

Contamination monitoring

- While alpha-probes can be used in the detection of Alpharadin, many clinical sites used standard beta/gamma-probes for contamination monitoring of the working areas
- Advantages of using beta/gamma-emission for monitoring included
  - Monitoring distance is less critical (Table 3)
  - High counting efficiency for beta/gamma-emissions
  - More consistent wipe tests
  - Familiarity with equipment

Table 3. Dose rate measured using standard Alpharadin vial, normalized per MBq of Alpharadin (unshielded glass vial) (Automess 6150 AD5 S/N 102260, Automess GmbH, Ladenburg, DE)

Distance from vial	Dose rate, µSv/h/MBq
At surface	< 100
At 10 cm	< 5
At 1 meter	< 0.1

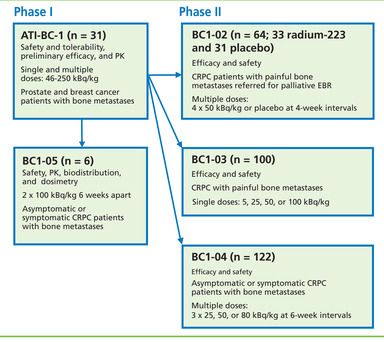
Radioactive waste during clinical trials

- Alpharadin became nonactive after 10 half-lives (ie, around 4 mo)
- Waste was then discarded as normal clinical waste
- Total activity of clinical waste was low
- Waste volumes were small, since Alpharadin is supplied ready to use

CLINICAL EXPERIENCE: SIGNIFICANT FINDINGS

- 292 patients with bone metastases and mainly CRPC have received Alpharadin in 2 open-label phase I trials (37 patients); 2 double-blind, dose-response phase II trials (222 patients); and 1 double-blind, placebo-controlled phase II trial (33 patients received Alpharadin and 31 received placebo) (Figure 3)
- Injected single doses varied from 5 to 250 kBq/kg b.w.[5] Repeated dosing regimens varied in number and schedule

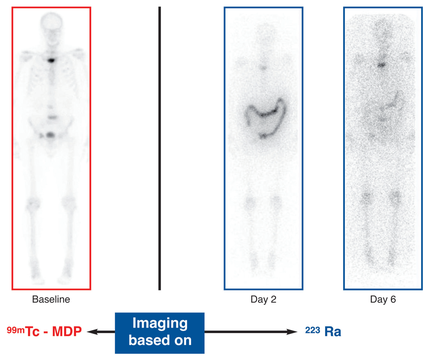
Figure 3. Phase I and II studies



Biodistribution: localization of Alpharadin after administration

- In the BC1-05 phase I study, patients (n = 6) received 2 Alpharadin injections of 100 kBq/kg, each 6 weeks apart[6]
- Alpharadin was quickly eliminated from blood, taken up in bone, and excreted via small intestine. The major route of elimination was through the gut via feces
- Thus, the kidneys, urinary bladder, and urethra were exposed to a minimal amount of radiation
- The distribution pattern as seen on whole-body scintillation gamma-camera imaging is shown in Figure 4[6]

Figure 4. Biodistribution after Alpharadin injections



Safety: hematologic adverse effects

- Of the 292 patients receiving Alpharadin across all phase I and II studies, less than 1% experienced National Cancer Institute Common Terminology Criteria (NCI CTC) grade 4 hematologic adverse events during the study period (Table 4)
- 4.8% of patients experienced NCI CTC grade 3 anemia, and fewer than 3% experienced grade 3 toxicity for platelets, neutrophils, or white blood cells (WBC) (Table 4)

Table 4. Hematologic adverse events across all studies (n = 292)

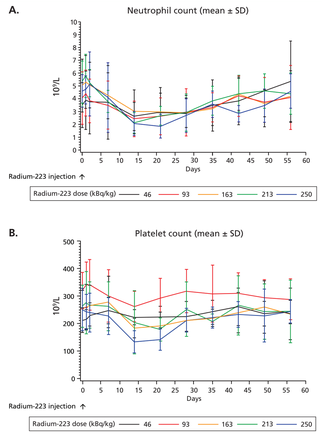
Worst grade for hematologic toxic effects by patient during treatment, all patients receiving radium-223 in any study and any dose (n = 292)

	Radium-223 (n = 33)			
NCI CTC Grade	1	2	3	4
Platelets	59 (20%)	6 (2%)	6 (2%)	3 (1%)
Neutrophils	57 (20%)	32 (11%)	5 (1.7%)	2 (0.7%)
WBC	53 (18%)	41 (14%)	8 (2.7%)	0
Hemoglobin	149 (51%)	72 (25%)	14 (4.8%)	3 (1%)

Hematologic profile following a single injection of Alpharadin

- In the ATI-BC-1 phase I study, 5 patients in each dose group received doses of 46, 93, 163, 213, and 250 kBq/kg b.w. as a single injection (Figure 5A)
- Mild, transient neutropenia was generally observed; 2 patients experienced NCI CTC grade 3 reductions in neutrophils (1 each at Alpharadin doses of 163 and 250 kBq/kg b.w.)
- A mild decrease in platelet counts was observed, although most values at nadir were within normal range (Figure 5B)
- No change in hemoglobin was observed (graph not shown)

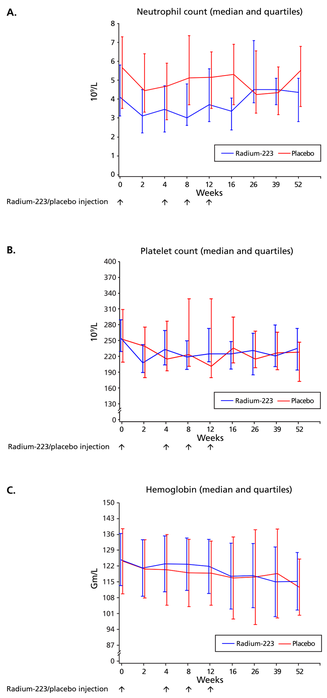
Figure 5. Neutrophil and platelet counts observed in phase I study (ATI-BC-1)



Hematologic profile following repeated injections of Alpharadin

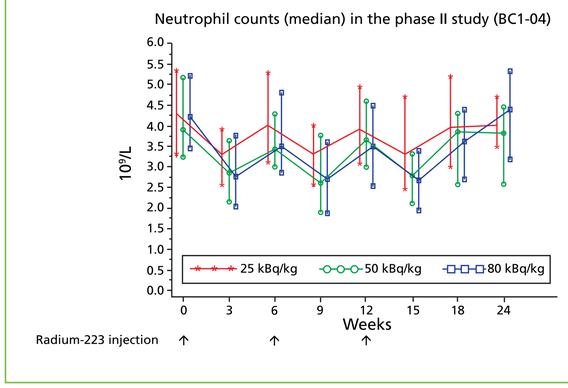
- In the placebo-controlled phase II study (BC1-02), median neutrophil counts were 3.1, 3.0, 3.7, and 3.4 x 10^9/L on weeks 2, 8, 12, and 16 (lowest neutrophil count overall was 0.9 x 10^9/L) (Figure 6A)
- A slight decrease in median platelet counts was observed during Alpharadin treatment. Platelet counts following treatment were similar to those in the placebo group (Figure 6B)
- No apparent changes in hemoglobin levels were seen in the patients receiving Alpharadin compared with placebo-treated patients (Figure 6C)

Figure 6. Hematologic profile of repeated doses of radium-223 observed in the placebo-controlled phase II study (BC1-02)*



- In the phase II BC1-04 study, 3 injections of Alpharadin (25, 50, or 80 kBq/kg) were given 6 weeks apart (n = 122). Median neutrophil counts returned to baseline after completion of treatment (Figure 7)

Figure 7. Mild, transient neutropenia observed in the phase II BC1-04 study



Efficacy: multiple-injection phase II placebo-controlled study (BC1-02)

- In the phase II placebo-controlled study (BC1-02), 4 injections of Alpharadin (50 kBq/kg) were given 4 weeks apart (n = 33, Alpharadin; n = 31, placebo), at weeks 0, 4, 8, and 12
- Alpharadin increased median survival by 4.5 months versus placebo when added to standard of care (65 vs 46 wk, respectively; HR 2.10 [1.14-3.88]; *P* = .017)[7]
- Serum bone ALP was significantly decreased, and time to PSA progression was significantly prolonged[7]

CONCLUSIONS

Safety

- In a combined analysis of phase I and II clinical trials of almost 300 patients with bone metastases and mainly CRPC, Alpharadin demonstrated a highly tolerable safety profile characterized by low-grade adverse events and a low propensity for hematologic events
- In these studies, neutrophil counts returned to baseline after completion of treatment; this was observed for different doses and with different injection intervals
- The hematologic profile of Alpharadin suggests that it may be combined with myelosuppressive chemotherapy and may be safely dosed beyond 4 injections

Efficacy

- Safety findings were accompanied by improvements in overall survival, disease-related biomarkers, and pain
- In the placebo-controlled phase II study (BC1-02), Alpharadin demonstrated an overall survival advantage compared with placebo in patients with bone metastases and CRPC
- Based on the safety and efficacy profile of Alpharadin observed in clinical trials, a dose of 50 kBq/kg was chosen for the randomized phase III survival study ALSYMPCA, currently ongoing worldwide[8]
- A phase I dose-escalation study of Alpharadin in combination with docetaxel is also ongoing (BC1-10)[9]

Radiation protection experience from clinical trials

- Alpharadin is a ready-to-use product. In clinical trials, Alpharadin was administered on an outpatient basis using standard radiation protection measures
- The small volume of radioactive waste produced during Alpharadin handling was stored for 4 months, then discarded as normal clinical waste

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