Some key issues to understand this promising new treatment strategy:

1. Epidemiology
2. Tumorbiology
3. Radiobiology
4. Target distribution
5. Phase 3 + Video
Skeletal Metastases
Magnitude of the problem

Frequency of bone metastases in patients with advanced disease from various types of malignancies
Skeletal Metastases - Expected Survival

Virtually all patients presenting with skeletal metastases will succumb to their underlying malignant disease.

Fig. 1. Typical overall survival curve of patients treated with palliative radiotherapy for painful bone metastases. Based on data from the Danish bone trial [12].

Skeletal Metastases
Spectrum of the Problem

- Pain
- Pathological fracture
- Spinal cord & cauda equina compression
- Cranial nerve entrapment
- Hypercalcemia
- Bone marrow suppression
- Impaired mobility & QoL

E. Munch - ”The Scream” 1893
Shortcomings in the current oncological treatment of Skeletal Metastases

- Lack of effective cytotoxic agents to combat disseminated, overt cancer
- External radiotherapy is an effective local palliative treatment modality
- However, with low therapeutic index
  - Impair/destroy “in field red bone-marrow”
  - Re-treatment often problematic
- Multiple metastatic lesions
Metastatic Prostate Cancer

Bone mets dominate – less visceral metastases

Skeletal mets govern the prognosis –

….. cause of death!

Disease related pancytopenia

Pronounced Blastic-/Sclerotic phenotype

E. Munch – ”Death as The Helmsman”
Widespread Disease in the Axial Skeleton

• Bone scintigraphy in a 60 year old patient with multiple skeletal metastases from prostate cancer

External radiotherapy may relieve pain at localized sites – but will destroy the bone-marrow at irradiated sites

Image shows the biodistribution of bone-seeking radiopharmaceuticals with a very potent targeting of osteoblastic/sclerotic metastatic sites
Reviews the use of external palliative radiotherapy, the bone-seeking radiopharmaceutical approved to relieve pain and the benefits of the alpha-emitting Radium-223.
Targeted Radionuclide Therapy

- % injected amount of radioactivity reaching the target
- Biodistribution
  - Routes of excretion
  - Other organs/tissues than cancer being targeted?!
- Kinetics of targeted radioisotope at the targeted sites
- Microdistribution of radionuclide within a targeted lesion
- Radiobiological effects of the radioisotope
- Fate of the decay-products – radioactive daughters
- Dosimetry - Microdosimetry
Bone-seeking Radiopharmaceuticals
Biodistribution - "a class-effect"

Diagnostic (photons):
• $^{99m}\text{Tc} \text{ MDP}$
  – Very high ratios in osteosclerotic/-blastic lesions:
    • Metastases/normal bone 4-10
    • Metastases/soft tissues up to 300

Palliation (electrons) Single injection – bone marrow toxicity dose limiting:
• $^{89}\text{Sr}$ - Metastron$^R$ (Amersham)
• $^{153}\text{Sm} \text{ EDTMP}$ - Quadramet$^R$ (Cytogen/Shering)
• $^{186/188}\text{Re} \text{ HEDP}$ (Mallinkrodt)

Therapeutic (alpha particles) Multiple treatments – few adverse events:
• $^{223}\text{Ra}$ - Alpharadin$^R$ (Algeta)
Bone surface

Bone marrow

Gamma radiation

Range of alpha particle

Radium-223

Strontium-89 “Metastron”
Why use $^{223}$Ra?

- Intravenously targeted to skeletal metastases
- Radium is a natural bone seeker – like Strontium
  - no need for carrier molecule
- Very strong cytotoxicity in targeted areas/cells due to high LET
- A cost efficient alpha particle emitter

- Small molecule (cationic form) - compared to monoclonal antibodies
Why use alpha emitters?

<table>
<thead>
<tr>
<th></th>
<th><strong>Alpha</strong> $\alpha$</th>
<th><strong>Beta</strong> $\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range in tissue</td>
<td>40 – 90 $\mu$m</td>
<td>500– 6000 $\mu$m</td>
</tr>
<tr>
<td>Linear Energy Transfer</td>
<td>60 – 230 keV/ $\mu$m</td>
<td>0.015 - 0.4 keV/ $\mu$m</td>
</tr>
<tr>
<td>DNA hits to kill a cell</td>
<td>1 - 5</td>
<td>100 – 1000</td>
</tr>
<tr>
<td>Relative particle mass</td>
<td>7000</td>
<td>1</td>
</tr>
</tbody>
</table>
• High Linear Energy Transfer
• RBE x 3-5 compared to std.xrt
• Unaffected by O₂ - tension
• Effective killing of chemo- and radio-resistant cells
• Cytotoxic also for cells in G₀ - (Dormant metastases)

Dose-rate independant
Skeletal Structure – Spongiuous Bone

Radium-223 deposition (A)
Skeletal Metastasis (B)

This illustrates the situation in mixed/lytic lesions.
Much more favourable target distribution in prostate cancer!
A mesh of new bone matrix entwined in between cords of tumor cells

Target = OH apatite
Primitive bone matrix produced and present throughout the entire metastasis

CT-image A coronal section

Sclerotic skeletal mets from HRPC

Dept. of Radiology
The Norwegian Radium Hospital
Target distribution
Osteoblastic/Sclerotic vrs. Lytic Bone Metastasis

Figure 7.5: Sclerotic metastases. MRI aspects on T1-weighted image (A) and T2-weighted image (B) shows deeply hyposignal, responding to hyperdensity on CT images (C,D)
Prostate cancer patient from BC 1 – 05 study

“Superscan”
Micro-autoradiography in dogs
Alpha-tracks visible

- Normal bone vs. Osteoblastic metastasis
Overview of clinical development programme

**Phase I**

- **ATI-BC-1 a&b (n=31)**
  - Safety and tolerability, preliminary efficacy and PK
  - Single and multiple doses: Up to 250 kBq/kg
  - Prostate and breast cancer
  - Complete

- **BC1-05 (n=6)**
  - Biodistribution, PK, dosimetry.
  - Asymptomatic or symptomatic HRPC
  - Recruitment & Report complete. Manuscript(s) in preparation.

- **BC1-08 (n=18)**
  - Biodistribution, PK, dosimetry. US trial at MSKCC
  - HRPC with skeletal metastases.
  - Single doses: 50, 100, 200 kBq/kg
  - Recruiting

**Phase II**

- **BC1-02 (n=64)**
  - Efficacy and safety
  - HRPC patients with painful skeletal metastasis referred for palliative EBR
  - Multiple doses: 4 x 50 kBq/kg or placebo at 4 weeks interval
  - Recruitment complete
  - Two year data published

- **BC1-04 (n=117)**
  - Efficacy and safety
  - Asymptomatic or symptomatic HRPC
  - Multiple doses: 3 x 25, 50, or 80 kBq/kg at 6 weeks interval
  - Recruitment & Report complete
  - Manuscript(s) in preparation

**Phase III**

- **BC1-03 (n=100)**
  - Efficacy and safety
  - HRPC with painful skeletal metastasis
  - Single doses: 5, 25, 50 or 100 kBq/kg
  - Recruitment & Report complete
  - Manuscript(s) in preparation

- **BC1-06 (n=750)**
  - Confirmatory efficacy and safety.
  - HRPC with symptomatic skeletal metastases, not planned use of cytostatics within 6 months.
  - Multiple doses: 6 x 50 kBq/kg or placebo at 4 weeks interval.
  - Recruitment ongoing
Alpharadin-film

Click on the name above to activate the video
Acknowledge: PhD Roy H. Larsen co-founder of ATI and Professor Sten Nilsson, Karolinska Hospital

Collaborating Clinical Sites
Thanks for your time & attention
Decay cascade of $^{223}$Ra

- $^{223}$Ra: 11.4 d
- $^{219}$Rn: 4.0 s
- $^{215}$Po: 1.8 ms
- $^{211}$Po: 0.5 s
- $^{211}$Bi: 2.2 m
- $^{211}$Pb: 36.1 m
- $^{207}$Pb: stable
- $^{207}$Tl: 4.8 m

- $\alpha$-emitter (94% of emitted energy)
- Total Energy / decay: Approx. 28 MeV
Phase I (Nilsson et al. 2005 Clin Cancer Res)

- 25 patients with advanced breast or prostate cancer completed study – No SAE
- 5 dose levels: 37, 74, 130, 170 and 200 kBq/kg
- Pain palliation observed in more than 50% of the patients, also observed at the first dose level
- 4 pts. became without the need for opioids
- DLT & MTD not reached
- Reduction in serum alkaline phosphatase
- No significant hematological toxicities
Phase II trial BC1-02 Prostate Cancer Design (64 pts.)

HRPC patients → LOCAL EBRT → RANDOMIZE

50 kBq/kg b.w. Ra-223 q4 wks
Saline q4 wks

Treatment

Bone markers, PSA

Skeletal Related Events, pain, bone markers, PSA safety, survival

Follow-up of long term toxicity, and survival

4 injections q 4 weeks
W12 W16 M6 M9 M12 M18 M24

Study unblinded
Primary Study Objectives

The primary objective was to study the biological effectiveness of radium-223 therapy, measured as:

Decline in bone specific alkaline phosphatase levels

Time to occurrence of Skeletal Related Events
Secondary Study Objectives

- Changes of a panel of biochemical markers of bone turnover and PSA
- Overall survival
- Haematology toxicity & Adverse events
- Blood chemistry
- Palliative effect & Quality of life
- Long term radiation toxicity
Alpharadin BC1-02 study – Bone-ALP

Relative change (%) from baseline

- Pronounced and rapid reduction of bone-ALP levels by Alpharadin already after one injection. Reduction sustained for at least 6 months
- Alpharadin treatment beyond 3 months may increase the duration of the bone-ALP reduction
- Patients with the highest bone-ALP values had a tendency of dropping out of the study over time, especially in the placebo group
# Primary Efficacy End-point

Relative change (%) in Bone-ALP levels from baseline to 4 weeks after last administration of study drug:

<table>
<thead>
<tr>
<th></th>
<th>Alpharadin®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean Std</td>
<td>N  Mean Std</td>
</tr>
<tr>
<td>Change</td>
<td>33  −58%  37</td>
<td>29  +47%  107</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

A significant difference (p<0.001) between Alpharadin and placebo was found.  
**This result meets the primary end-point of the study.**
## Alpharadin – Positive effect on biomarkers

Relative change from baseline to 4 weeks after last injection

<table>
<thead>
<tr>
<th>Marker</th>
<th>Alpharadin (Median)</th>
<th>Placebo (Median)</th>
<th>P-value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (Prostate-Specific Antigen)</td>
<td>-24%</td>
<td>+45%</td>
<td>0.0026</td>
</tr>
<tr>
<td>Bone-ALP (ALkaline Phosphatase – a bone formation marker)</td>
<td>-67%</td>
<td>+9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total ALP (ALkaline Phosphatase – a bone formation marker)</td>
<td>-46%</td>
<td>+31%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PINP (bone formation marker)</td>
<td>-63%</td>
<td>+38%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CTX-I (bone resorption marker)</td>
<td>-31%</td>
<td>+32%</td>
<td>0.0023</td>
</tr>
<tr>
<td>ICTP (bone resorption marker)</td>
<td>+15%</td>
<td>+43%</td>
<td>0.011</td>
</tr>
</tbody>
</table>

All reductions had a duration of more than 6 months but less than 9 months after start of treatment with the exception of PSA that had a duration of more than 4 months but less than 6 months.
Alpharadin BC1-02 study – PSA

Prostate Specific Antigen (PSA) – relative change (%) from baseline

- Pronounced reduction of PSA by Alpharadin
- PSA values return to baseline after 6 months
- Alpharadin treatment beyond 3 months may increase the duration of the PSA reduction
- Patients with the highest PSA values had a tendency of dropping out of the study over time, especially in the placebo group
## BC1-02 PSA response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alpharadin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change from baseline (Range)</td>
<td>- 24% (-99 to +546)</td>
<td>+45% (-91 to +564)</td>
<td>0.003</td>
</tr>
<tr>
<td>Patients with confirmed PSA response* (fraction)</td>
<td>35% (11/31)</td>
<td>18% (5/28)</td>
<td>0.153</td>
</tr>
<tr>
<td>Median time to PSA progression* (95% CI)</td>
<td>26 weeks (16-39)</td>
<td>8 weeks (4-12)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

**Definitions**

* Confirmed PSA response
  50% reduction from baseline, confirmed by 2nd measurement ≥ 4 weeks later

* PSA progression
  increase of ≥ 25% from nadir or baseline in patients without 50% PSA response
  Increase of ≥ 50% from nadir in patients with 50% PSA response
## SRE and Survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median time to event</th>
<th>Cox proportional hazard</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alpharadin</td>
<td>Placebo</td>
<td>Hazard ration</td>
</tr>
<tr>
<td>SRE-ITT</td>
<td>14 weeks</td>
<td>11 weeks</td>
<td>1.753</td>
</tr>
<tr>
<td>SRE-PP</td>
<td>16 weeks</td>
<td>11 weeks</td>
<td>1.815</td>
</tr>
<tr>
<td>Survival-ITT</td>
<td>65.3 weeks</td>
<td>46.4 weeks</td>
<td>2.117</td>
</tr>
<tr>
<td>Survival-PP</td>
<td>71.0 weeks</td>
<td>46.4 weeks</td>
<td>2.286</td>
</tr>
</tbody>
</table>

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 at least 2 injections with study drug and one patient where the study group allocation was accidentally revealed. Adjusted for covariates.

Alpharadin – Positive survival data (BC1-02)

Alpharadin improved overall survival from median 46.4 weeks to 65.3 weeks (41% improvement) - Intent to treat data

1) Corresponding result for the Per-Protocol (PP) population (receiving 2 or more injections) is 46.4 weeks for the placebo group and 71.0 weeks for the Alpharadin group (53% improvement).

15/33 patients (45%) patients in the Alpharadin group vs. 8/31 patients (26%) in the placebo group were alive at 18 months follow-up

Patients receiving Alpharadin had a 53% reduced risk of death compared to placebo at each individual time point
Overall survival 24 months follow up (ITT population)

Median time to survival 46.4 weeks in the placebo group and 65.3 weeks in the Alpharadin group. Hazard ratio 2.103, p = 0.017. 30% of the patients were alive in the Alpharadin group versus 13% in the placebo group.
Conclusions

• Radium-223 (T1/2 = 11.4 d) in chloride form is an innovative agent for treating skeletal metastases from prostate (and breast cancer?)

• Effectiveness due to
  – rapid uptake on bone surfaces (50-60%)
  – strong localization at sites of active bone formation (ob/os metastases)
  – long retention time & high LET irradiation

• Safety due to
  – low uptake in soft tissues
  – bowel clearance rather than urinary excretion
Phase III – ”ALSYMPCA”
activated 2008 – 90 patients enrolled

HRPC – patients post- or unfit for tax. 750 pts (+ 100 centres)
6 monthly injections 50kBq/kg - 2/1 randomization active vrs. placebo

Primary Objective:
• To compare overall survival in patients with HRPC with skeletal metastases receiving Alpharadin™ or placebo.

Secondary Objectives:
• SRE’s – time to first & multi-event analyses
• Changes and time to progression in the biochemical markers such as PSA and bone-ALP
• Characterisation of the acute and chronic safety of Alpharadin
Historical Platform

Radium-224 in Ankylosing Spond.

- +++ 1000 patients were treated years 1950-85
- Reintroduced & approved in Germany by Altmann Therapie, GmbH – $^{224}\text{SpondylAT}^R$

Radium-224 has a physical half life of 3.66 days

A significant fraction of the daughter isotopes escape from bone

This is due to Radon-220 with a physical half life of 55.6.sec
Late effects & Carcinogenicity
A long-term follow up already exists

- Nekolla et al., (Radiation Res., 2000) Young patients given multiple high doses of Radium-224 had a significantly higher incidence of cancers of the bone, breast, connective tissue, thyroid, liver, kidney and bladder - but a reduction in lung cancer (control group).

- Tumor risk was strongly reduced in adults vs. juveniles.

Wick et al., (Radiation Res., 1999) – 10 weekly injections of about 1 MBq Radium-224

A control group of matched patients with ankylosing spondylitis

Similar life expectancy and overall tumor incidence was found for the two groups.
Woman with breast cancer & skeletal metastases:

Increased osteoblastic/sclerotic phenotype following 6 months of Ibandonate therapy

Prior bisphosphonate therapy may induce a more “avid phenotype” of the bone mets. – Making a better case for Alpharadin therapy?!?!
Figure 6.3. (A) Posterior planar $^{99m}$Tc MDP bone scan in a patient with breast cancer. (B) Transaxial, coronal and sagittal (top to bottom) tomographic (SPECT) images of the lumbar spine from the same study. Focal abnormalities are seen in the mid-cervical, mid-thoracic and upper lumbar spine. On transaxial SPECT images, the upper lumbar spine abnormality can be seen to extend posteriorly from the vertebral body into the posterior elements, a pattern that is likely to represent a metastatic deposit rather than coincidental degenerative disease.