Radionuclide Therapy of Prostate Cancer

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USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

USC University of Southern California

SNMMI Society of Nuclear Medicine and Molecular Imaging
Celebrating 60 Years
Outline

• Alpha particle therapy
• Biology of bone metastases (prostate cancer)
• ALSYMPCA Clinical Trial
• Nuts & bolts of Ra-223 dichloride (Xofigo®) therapy
• NCI-SNMMI TRT Workshops
Alpha Particle Therapy

- >100 alpha-emitting radioisotopes but most decay too fast
- Positively charged helium nuclei
- Short range 50-80 μm (vs. several mm’s for beta particle)
- High linear transfer energy (LET) 100 keV/μm (vs. beta particle 0.2 keV/μm) at approximate range of ds DNA diameter (2 nm)
- Relative Biologic Effect (RBE) 3-7 fold > X-Ray reference radiation for cell sterilization
- **Targeted beta Rx:** “crossfire” or “bystander” effect of antigen-neg. tumor cells due to longer range (several mm) but at cost of nl. tissue toxicity - better for large tumors
- **Targeted alpha Rx:** more specific tumor cell killing with less damage to surrounding nl. tissue (min. residual dz or uMets)

Helium

1 Å = 100,000 fm
Radiation Effects on DNA


- **Low-LET** $\beta$-radiation produces single-strand DNA breaks$^1$
- **Single-strand breaks** are easily repaired$^1$

- **High-LET** $\alpha$-particles produce **double-strand** DNA breaks$^1$
- Difficult-to-repair double-strand breaks are **lethal$^2$**
Radiolysis of Intracellular Water

## Alpha Emitting Radioisotopes


<table>
<thead>
<tr>
<th>Isotope</th>
<th>Particle(s) emitted</th>
<th>Half-life</th>
<th>Energy of α-particle (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁹¹⁷At</td>
<td>1 α</td>
<td>7.2 h</td>
<td>6</td>
</tr>
<tr>
<td>²²⁵Ac</td>
<td>4 α, 2 β</td>
<td>10 d</td>
<td>6–8</td>
</tr>
<tr>
<td>²¹⁲Bi</td>
<td>1 α, 1 β</td>
<td>60.6 min</td>
<td>6</td>
</tr>
<tr>
<td>²¹³Bi</td>
<td>1 α, 2 β</td>
<td>46 min</td>
<td>6</td>
</tr>
<tr>
<td>²²³Ra</td>
<td>4 α, 2 β</td>
<td>11.4 d</td>
<td>6–7</td>
</tr>
<tr>
<td>²¹²Pb</td>
<td>1 α, 2 β</td>
<td>10.6 h</td>
<td>7.8</td>
</tr>
<tr>
<td>¹⁴⁹Tb</td>
<td>1 α</td>
<td>4.2 h</td>
<td>4</td>
</tr>
</tbody>
</table>

*At: Astatine; Ac: Actinium; Bi: Bismuth, Ra: Radium; Pb: lead; Tb: Terbium*
Prostate Cancer Evolving Treatment Landscape

Typical clinical presentation of patients through different phases of prostate cancer. Time is not proportional.

The line represents the burden of disease at different disease phases.

Adapted from Higano CS. In: Figg WD et al. Drug Management of Prostate Cancer. 2010:321.
Sites of prostate metastases at autopsy

n=556 / 1589 (35.0%) patients with CaP

- Bone: 90.1%
- Lung: 45.7%
- Liver: 25%
- Pleura: 21%
- Adrenal gland: 12.8%
- Meninges: 5.9%
- Kidney: 3.4%
- Other: 3.1%

Bubendorf et al, Hum Pathol 2000; 31: 578
Prostate Cancer Bone Metastasis

• > 90% of patients with metastatic CRPC have radiologic evidence of bone metastases¹
• Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or external beam radiotherapy²
• Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost³
• Current bone-targeted therapies have not been shown to improve survival (except recently by ALSYMPCA)

Prostate Cancer Bone Metastases
Skeletal Related Events

- Without treatment, SREs occur about every 8 months
- Median time to first SRE is about 11 months after bone metastases diagnosis
- At >24 months, almost 50% experience SRE
- The longer a patient lives, the more likely chance of SREs
- SREs cause impaired QoL and decreased survival
The Curies: Discovery of Radium

• The Curies informed the l’Académie des Sciences, on December 26, 1898, that they had come upon an additional very active substance that behaved chemically almost like pure barium. They suggested the name of radium for the new element.

• 25 known isotopes, 4 found in nature; $^{226}\text{Ra}$ most common; $^{223}\text{Ra}$ generated naturally through decay of Uranium (U) or Thorium (Th).

1903 Madame Curie presented her doctoral thesis and shared the Nobel Prize with her husband, Pierre Curie (and Henri Becquerel).
IS RADIUM A CURE FOR CANCER?*

By Dr. Louis Wickham,
Director of the Radium Institute, Paris.

It is difficult, without any exaggeration, not to recognize that radium-therapy, as I have often repeated, has won its place in the therapeutic armamentarium, that the fine French discovery of Curie and of Madame Curie has borne definite and certain fruit in the medical field.

- “Alpha particles in medicine may be newly explored 115 years after their discovery” – Vapiwala N, Glatstein E. NEJM 2013.
- US Labor law change after lawsuit filed against US Radium Corp. by dying “Radium Girls” dial painters in mid 1920’s; Nasal Radium irradiation administered to children to prevent middle ear problems or enlarged tonsils 1940’s-early 1970’s.
Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium Mimetic

Radium-223

- Calcium mimetic (bone-seeking) with Hydroxyapatite \( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \) as target
- Provided from uranium mill tailings or in generator form from \(^{227}\text{Ac} \) (\( t_{1/2} = 21.8 \) y) parent
  - \(^{227}\text{Ac} \Rightarrow ^{227}\text{Th} \Rightarrow ^{223}\text{Ra} \)
- \( T_{1/2} = 11.43 \) days
- Emitted energy distribution
  - \( 93.5\% \) as \( \alpha \) particle, \( 5.78 \) MeV (avg.)
  - \(<3.6\%\) as \( \beta \) particle
  - \(<1.1\%\) as \( \gamma \) radiation
  - \( 28\text{MeV} \) combined energy for complete decay including \( 0.9 \) MeV as \( \gamma \) radiation
As calcium-mimetic, Radium-223 dichloride self-targets to osteoblastic zones near bone metastases.

$^{223}$Ra Dichloride Biodistribution
Carrasquillo JA et al. *EJNMMI* 2013

- High Energy General Purpose collimator with 20% energy windows centered on 82, 154, 269, 351, 402 Kev
Estimated equivalent dose after iv injection of 50 kBq/kg of $^{223}\text{Ra}$

<table>
<thead>
<tr>
<th>Target organs</th>
<th>Dose equivalents (Sv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>$5.70 \times 10^{-2}$</td>
</tr>
<tr>
<td>Brain</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Breast</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Heart wall</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Kidneys</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Liver</td>
<td>$6.35 \times 10^{-1}$</td>
</tr>
<tr>
<td>Muscle</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Ovaries</td>
<td>$5.65 \times 10^{-2}$</td>
</tr>
<tr>
<td>Pancreas</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Testes</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Thyroid</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Bone surface</td>
<td>$13.05$</td>
</tr>
<tr>
<td>Stomach</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Small intestine</td>
<td>$5.65 \times 10^{-2}$</td>
</tr>
<tr>
<td>Upper large intestine</td>
<td>$1.68 \times 10^{-1}$</td>
</tr>
<tr>
<td>Lower large intestine</td>
<td>$3.67 \times 10^{-1}$</td>
</tr>
<tr>
<td>Skin</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Spleen</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Thymus</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Uterus</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
<tr>
<td>Expiratory tract</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Lung</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Colon</td>
<td>$2.54 \times 10^{-1}$</td>
</tr>
<tr>
<td>Thoracic lymph node</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Esophagus</td>
<td>$5.55 \times 10^{-2}$</td>
</tr>
<tr>
<td>Gonads</td>
<td>$5.65 \times 10^{-2}$</td>
</tr>
<tr>
<td>Remainder</td>
<td>$5.60 \times 10^{-2}$</td>
</tr>
</tbody>
</table>
223Ra-dichloride

- indication, bone scan, labs, signed consent (MD present)
- well hydrated, good running i.v.
- check blood work
  - ANC $\geq 1.5 \times 10^9$/L
  - platelet count $\geq 100 \times 10^9$/L
  - hemoglobin $\geq 10$ g/dL.
  - Prior to subsequent administrations, ANC $\geq 1 \times 10^9$/L. platelet count $\geq 50 \times 10^9$/L
  - 223Ra should be discontinued if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
- double gloves; packaging surveyed after vial removal
- Dispose in clinical waste stream after decay-in-storage (10 CFR 35.92)
1 min i.v. injection in an arm vein *(95 uCi for 70kg)*
underpad chux on floor, chair, and table without arms
double bagged red biohazard bag
IV pole with 500 ml saline and tubing primed
connect the 3-way stopcock to the patient i.v.
MD will push dose from vial
Pull i.v. and place contaminated materials in a latex glove and tape-shut
put in red biohazard bag; measure for residual using standard meter
Survey technologist’s and MD’s hands and feet
prior to release, check HR and BP, then call MD to clear the patient
223Ra-dichloride
patient instructions

- Minimal exposure to others below regulatory limit (0.007 mrem/h <<0.5)
- drink plenty of fluids
- use medical gloves when wiping up blood, urine, stool or vomit and when touching or washing dirty clothes; (~75% of activity excreted within 1 week, mainly feces)
- urinate as frequently as possible, while sitting; Flush toilet twice; If any urine splattered, wipe with toilet paper and flush down toilet
- If diarrhea or urinary incontinence, use disposable underwear or diaper pants during first week after each injection
- If cut yourself or vomit, wipe up with toilet paper and flush in toilet
- Underwear worn during the first week after each injection should be washed separately; same applies to bed linen and any clothing soiled with urine, stool or blood (otherwise no need for separation; no salivary/sweat excretion)
- Avoid prolonged contact with pregnant women and small children during first week after each injection; avoid fathering child until 6m post Rx
Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA)

C. Parker,1 S. Nilsson,2 D. Heinrich,3 J.M. O’ Sullivan,4 S. Fossà,5 A. Chodacki,6 P. Wiechno,7 J. Logue,8 M. Seke,9 A. Widmark,10 D.C. Johannessen,11 P. Hoskin,12 D. Bottomley,13 R. Coleman,14 N. Vogelzang,15 C.G. O’ Bryan-Tear,16 J. Garcia-Vargas,17 M. Shan,17 and O. Sartor18

1The Royal Marsden NHS Foundation Trust, Sutton, UK; 2Karolinska University Hospital, Stockholm, Sweden; 3Akershus University Hospital, Lørenskog, Norway; 4Centre for Cancer Research and Cell Biology, Queen’s University, Belfast, Northern Ireland; 5Radiumhospitalet, Oslo, Norway; 6Hospital Kochova, Chomutov, Czech Republic; 7Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; 8Christie Hospital, Manchester, UK; 9Centrallåsarettet Växjö, Växjö, Sweden; 10Umeå University, Umeå, Sweden; 11Ullevål University Hospital, Oslo, Norway; 12Mount Vernon Hospital Cancer Centre, Middlesex, UK; 13St. James Hospital, Leeds, UK; 14Weston Park Hospital, Sheffield, UK; 15Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; 16Algeta ASA, Oslo Norway; 17Bayer Healthcare Pharmaceuticals, Montville, NJ, USA; 18Tulane Cancer Center, New Orleans, LA, USA
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

**PATIENTS**
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

**STRATIFICATION**
- Total ALP: < 220 U/L vs ≥ 220 U/L
- Bisphosphonate use: Yes vs No
- Prior docetaxel: Yes vs No

**TREATMENT**
- 6 injections at 4-week intervals
- Radium-223 (50 kBq/kg) + Best standard of care
- Placebo (saline) + Best standard of care

**RANDOMISED**
- N = 921

Planned follow-up 3 years

Clinicaltrials.gov identifier: NCT00699751
ALSYMPCA Study Endpoints

• **Primary Endpoint**
  – Overall survival (OS)

• **Secondary Endpoints**
  – Time to first SRE
  – Time to total ALP progression
  – Total ALP response
  – Total ALP normalization
  – Time to PSA progression
  – Safety
  – Quality of life
## ALSYMPCA
### Patient Demographics (n = 921)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>n = 614</td>
<td>n = 307</td>
</tr>
<tr>
<td>Age, y Mean</td>
<td>70.2</td>
<td>70.8</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>575 (94)</td>
<td>290 (95)</td>
</tr>
<tr>
<td>Baseline ECOG score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>536 (87)</td>
<td>265 (86)</td>
</tr>
<tr>
<td>2</td>
<td>76 (12)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Extent of disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 metastases</td>
<td>100 (16)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>6–20 metastases</td>
<td>262 (43)</td>
<td>147 (48)</td>
</tr>
<tr>
<td>&gt; 20 metastases/superscan</td>
<td>249 (41)</td>
<td>121 (40)</td>
</tr>
<tr>
<td>WHO ladder, cancer pain index ≥ 2, n (%)</td>
<td>345 (56)</td>
<td>168 (55)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Radium-223 (n = 614)</td>
<td>Placebo (n = 307)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.2 (8.5-15.7)</td>
<td>12.1 (8.5-16.4)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>40 (24-53)</td>
<td>40 (23-50)</td>
</tr>
<tr>
<td>Total ALP, µg/L</td>
<td>211 (32-6431)</td>
<td>223 (29-4805)</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>315 (76-2171)</td>
<td>336 (132-3856)</td>
</tr>
<tr>
<td>PSA, µg/L</td>
<td>146 (3.8-6026)</td>
<td>173 (1.5-14500)</td>
</tr>
<tr>
<td>Current bisphosphonates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>250 (40.7)</td>
<td>124 (40.4)</td>
</tr>
<tr>
<td>Prior docetaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>352 (57.3)</td>
<td>174 (56.7)</td>
</tr>
</tbody>
</table>
### ALSYMPCA: Overall Survival

**3.6 month OS benefit**

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 dichloride (n = 614)</th>
<th>Placebo (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>14.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.58–0.83</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Radium-223**

- Month 0: 614
- Month 3: 578
- Month 6: 504
- Month 9: 369
- Month 12: 274
- Month 15: 178
- Month 18: 105
- Month 21: 60
- Month 24: 41
- Month 27: 18
- Month 30: 7
- Month 33: 1
- Month 36: 0
- Month 39: 0

**Placebo**

- Month 0: 307
- Month 3: 288
- Month 6: 228
- Month 9: 157
- Month 12: 103
- Month 15: 67
- Month 18: 39
- Month 21: 24
- Month 24: 14
- Month 27: 7
- Month 30: 4
- Month 33: 2
- Month 36: 1
- Month 39: 0

**ALSYMPCA : Overall Survival Stratified by Prior Docetaxel Use**

**No prior docetaxel use:**
- **4.6 months OS benefit**

- **42.7% of Radium-223 dichloride arm**
- **43.3% of placebo arm had no prior docetaxel**

**Prior docetaxel use:**
- **3.1 months OS benefit**

ALSYPPCA: Time to First SRE

5.8 month benefit

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 dichloride (n = 614)</th>
<th>Placebo (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to SRE (months)</td>
<td>15.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.52–0.83</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>

**ALSYMPCA: Time to First SRE Components**

<table>
<thead>
<tr>
<th>SRE Component</th>
<th>Radium-223 dichloride (n = 614)</th>
<th>Placebo (n = 307)</th>
<th>Time to Event (Radium-223 dichloride vs. Placebo)</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>External-beam radiotherapy</td>
<td>186 (30.3)</td>
<td>105 (34.2)</td>
<td></td>
<td>0.00117</td>
<td>0.67 (0.52-0.85)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>25 (4.1)</td>
<td>21 (6.8)</td>
<td></td>
<td>0.025</td>
<td>0.51 (0.28-0.93)</td>
</tr>
<tr>
<td>Pathologic bone fracture</td>
<td>32 (5.2)</td>
<td>20 (6.5)</td>
<td></td>
<td>0.09</td>
<td>0.62 (0.35-1.09)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>12 (2)</td>
<td>7 (2.3)</td>
<td></td>
<td>0.479</td>
<td>0.71 (0.28-1.8)</td>
</tr>
</tbody>
</table>

# ALSYMPCA: Survival Benefit Across Patient Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td>921</td>
<td></td>
<td>0.695</td>
<td>0.581–0.832</td>
</tr>
<tr>
<td>Total ALP #</td>
<td>&lt; 220 U/L</td>
<td>517</td>
<td></td>
<td>0.825</td>
<td>0.635–1.072</td>
</tr>
<tr>
<td></td>
<td>&gt;= 220 U/L</td>
<td>404</td>
<td></td>
<td>0.619</td>
<td>0.486–0.788</td>
</tr>
<tr>
<td>Current Use of Bisphosphonates #</td>
<td>Yes</td>
<td>374</td>
<td></td>
<td>0.699</td>
<td>0.525–0.931</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>547</td>
<td></td>
<td>0.736</td>
<td>0.587–0.923</td>
</tr>
<tr>
<td>Prior Use of Docetaxel #</td>
<td>Yes</td>
<td>526</td>
<td></td>
<td>0.710</td>
<td>0.565–0.891</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>395</td>
<td></td>
<td>0.745</td>
<td>0.562–0.987</td>
</tr>
<tr>
<td>Baseline ECOG Status</td>
<td>0 or 1</td>
<td>801</td>
<td></td>
<td>0.675</td>
<td>0.555–0.821</td>
</tr>
<tr>
<td></td>
<td>2 or Higher</td>
<td>118</td>
<td></td>
<td>0.820</td>
<td>0.498–1.351</td>
</tr>
</tbody>
</table>

## ALSYMPCA: Adverse Events

**no clinically meaningful differences in frequency of Grade 3/4 AEs**

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 dichloride</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 600; %)</td>
<td>(n = 301, %)</td>
</tr>
<tr>
<td></td>
<td>Radium-223 dichloride</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 600, %)</td>
<td>(n = 301, %)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31.2)</td>
<td>77 (13)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>13 (2)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>69 (11.5)</td>
<td>39 (6.5)</td>
</tr>
<tr>
<td><strong>Non-hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>125 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>9 (1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (35.5)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18.5)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

In CRPC patients with symptomatic bone metastases, Radium-223 dichloride vs. placebo:
- significantly prolonged OS compared with BSC alone by 3.6 months (HR=0.7; P=0.001) → 30.5% reduction in risk of death
- significantly prolonged median time to first SRE compared with BSC alone by 5.8 months (HR=0.66, P<0.001)
- had relatively similar frequency of grade 3/4 AEs (bone pain, anemia) of 57% compared to 63% from BSC alone
- Common adverse events
  - Non-hematologic: bone pain, nausea, diarrhea, vomiting
  - Hematologic: anemia, thrombocytopenia (no 2nd CA yet)
- Clinical trials of retreatment with Ra-223 or in combination with either docetaxel, enzalutamide, or abiraterone

Ra-223 provides a new standard of care for the treatment of CRPC with bone metastases; incorporated into updated NCCN Guidelines v3.2013

**ALSYMPCA: Summary**

• 25 patients with met CRPC receive total of 91 doses
  – 6 patients received all 6 scheduled doses
  – 2 completed 5 doses, 6 received 4 doses, 2 completed 3 doses, 6 patients had 2 doses, 3 patients received one dose
• 9 patients discontinued after receiving at least one dose due to progressive disease
• 5 required blood transfusions (prior to Ra to increase Hgb to 10)
• 5 developed GI symptom; 4 worsening bone pain; 1 developed dermatitis
• Downward trends in serum Alk Phos and PSA in 11 and 5 pts, respectively
• About 25% of cohort completed entire 6-dose regimen; advancing soft tissue disease primary reason for cessation; adverse events mild and manageable; decline in serum bALP more common than decline in PSA
Remaining Issues

• Timing, sequencing, combination and abbreviated therapies
  – Any benefit from incomplete course (< 6 treatments)
  – If used earlier, what will be effect on subsequent therapies (dosing, efficacy, risks)
  – Can higher doses and cycles be used? (NCT02023697)
  – maximize synergistic clinical efficacy with other therapies
    • 13 D vs 33 D+Ra223 (favorable impact on bALP > PSA declines; NCT01106352) - Morris MJ et al. ASCO 2015 Abstract 5012
  – minimize cross resistance, side effects (adverse events)
  – strive for cost-effective care

• Use in other cancers

• Need for clinical trials and adaptation to individual patients
Targeted Radionuclide Therapy - Prostate Cancer

- 89Sr-chloride and 153Sm-EDTMP (bone pain palliation) - D’angelo QJNMMI 2012
- 223Ra dichloride - Parker, NEJM 2013
- 177Lu-labeled anti-PSMA monoclonal antibody 3/F11 (177Lu-DOTA-3/F11) - Behe, In Vivo 2011
- 90Y-labeled anti-PSMA J591 antibody - Vallabhajosula, Clin Cancer Res 2005
- 213Bi-labeled anti-PSMA J591 antibody - Li, PCPD 2002
- Anti-PSMA liposomes loaded with 225Ac - Bandekar, JNM 2014
- 177Lu-labeled GRPr antagonist - Dumont, JNM 2013
- 177Lu-labeled RGD-BBN heterodimer - Jiang, Nucl Med Commun 2013
- 188Re-MAG2-RGD-BBN - Cui, Nucl Med Biol 2013

PSMA=Prostate Specific Membrane Antigen, GRPr=gastrin-releasing peptide receptor, RGD=Arg-Gly-Asp, BBN=bombesin
The NIH-SNMMI Summit on Targeted Radionuclide Therapy, Bethesda, MD – March 2013, October 2014


Targeted Radionuclide Therapy: Proceedings of a Joint Workshop Hosted by the National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging

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Overarching Targeted Radionuclide Therapy Goal

- "Give the right target-radionuclide combination as part of the right "multi-step" treatment strategy to the right patient by the right "provider team" at the right time to achieve the right outcome at the right price"
Acknowledgement

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