Radiopharmaceutical Therapy in Radiation Oncology

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MARKEY CANCER CENTER / RADIATION MEDICINE

NOTHING TO DISCLOSE

06 November 2021
LEARNING OBJECTIVES

(1) RECOGNIZE TWO RADIOPHARMACEUTICAL AGENTS IN CLINICAL PRACTICE

(2) RECOMMEND PATIENTS MOST APPROPRIATE FOR RADIOPHARMACEUTICAL THERAPY

(3) APPRAISE SIDE EFFECTS OF RADIOPHARMACEUTICAL THERAPY
(1) RECOGNIZE TWO RADIOPHARMACEUTICAL AGENTS IN CLINICAL PRACTICE
(2) RECOMMEND PATIENTS MOST APPROPRIATE FOR RADIOPHARMACEUTICAL THERAPY
(3) APPRAISE SIDE EFFECTS OF RADIOPHARMACEUTICAL THERAPY

**Radiopharmaceutical CE Questions**

(1) DEFINE A ‘NEAT’ RADIOPHARMACEUTICAL.
(2) WHAT SHIELDING IS NEEDED FOR AN ALPHA-DECAYING AGENT?
(3) WHAT IS THE TYPICAL RANGE OF A BETA PARTICLE?
SURVIVORSHIP
RADIOThERAPY
MARKEY CANCER CENTER

RADIOTHERAPY

DEFINITIVE TELERAPY

PALLIATIVE TELERAPY

BRACHYTHERAPY

RADIOPHARMACEUTICALS

66% 23% 9% 2%
Radiotherapy – Next 15 Years

- Brachytherapy: 9%
- Palliative Teletherapy: 14%
- Definitive Teletherapy: 17%
- Radiopharmaceuticals: 60%
Radiopharmaceuticals

NCI considers radiopharmaceuticals as drugs that are:

1. Infused
2. Inhaled
3. Ingested
4. Injected

Radiopharmaceuticals target cancer cells and kill them.
NCI CONSIDERS RADIOPHARMACEUTICALS AS DRUGS BECAUSE THEY HAVE ANTI-CANCER DRUG-LIKE PROPERTIES SUCH AS:

HAVING PREDICTABLE ORGAN TOXICITIES
HAVING QUANTIFIABLE PHARMACOKINETICS
HAVING PRESCRIPTIONS FIXED BY BODY WEIGHT
EMITTING RADIATION THAT OVERWHELMs A CANCER CELL'S DNA DAMAGE RESPONSE TO KILL CANCER CELLS

ctep.cancer.gov/investigatorResources
pancreas cells

radiation

homing conjugated radiopharmaceutical

pancreas interstitium
DECAY

**Alpha-Particle**

- **Parent**: Helium
- **Daughter**: Helium

**Beta-Particle**

- **Parent**: Electron
- **Daughter**: Electron

**Conversion Electron**

- **Parent**: Electron
- **Daughter**: Electron
**DECAY**

**ALPHA-PARTICLE**

- Th
- Ac
- Ra
- Rn
- Po
- Pb
- Tl

**BETA-PARTICLE**

- Lu-177

\[ E_{\text{max}} = 497.8 \text{ keV} \]

\[
\begin{array}{c}
\text{HF-177} \\
0.3213 \\
0.2497 \\
0.1129 \\
\end{array}
\]

**CONVERSION ELECTRON**

- Sn-117m
- CE-L1
- CE-K2
- CE-K1
- Sn-117
**Alpha-Particle**

Distance in Water ($\mu$M) vs. LET (Kev/$\mu$M)

Average = 40 $\mu$M

**Beta-Particle**

Distance in Water ($\mu$M) vs. LET (Kev/$\mu$M)

Average = 300 $\mu$M

**Conversion Electron**

Distance in Water ($\mu$M) vs. LET (Kev/$\mu$M)

Average = 270 $\mu$M
NCI SELECTS RADIOPHARMACEUTICALS FOR CLINICAL TRIALS AFTER CONSIDERING THEIR PARTICLE RANGE & POTENTIAL TOXICITY:

1. Helium nucleus (α particle)
   - 10 cancer cell diameters

2. Electron (β particle)
   - 27 cancer cell diameters

3. Conversion electron (Auger electron)
   - 21 cancer cell diameters

cell.cancer.gov/investigatorResources
<table>
<thead>
<tr>
<th></th>
<th>Paper</th>
<th>Aluminum</th>
<th>Lead</th>
<th>Concrete</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-Particle</strong></td>
<td><img src="image1.png" alt="Paper" /> <img src="image2.png" alt="Aluminum" /> <img src="image3.png" alt="Lead" /> <img src="image4.png" alt="Concrete" /></td>
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<tr>
<td><strong>Beta-Particle</strong></td>
<td><img src="image1.png" alt="Paper" /> <img src="image2.png" alt="Aluminum" /> <img src="image3.png" alt="Lead" /> <img src="image4.png" alt="Concrete" /></td>
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<tr>
<td><strong>Conversion Electron</strong></td>
<td><img src="image1.png" alt="Paper" /> <img src="image2.png" alt="Aluminum" /> <img src="image3.png" alt="Lead" /> <img src="image4.png" alt="Concrete" /></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**Pharmacokinetics**

**Alpha-Particle**

- In blood after injection: @ 15 min = 22% of activity

**Beta-Particle**

- In blood after injection: @ 15 min = 18% of activity

**Conversion Electron**

- In blood after injection: @ 15 min = 14% of activity

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**Graphs:**

- **Alpha-Particle** graph shows a rapid decrease in the fraction of injected activity over time after injection.
- **Beta-Particle** graph shows a slower decrease compared to Alpha-Particle.
- **Conversion Electron** graph shows the least decrease compared to Alpha-Particle and Beta-Particle.
**PHARMACOKINETICS**

**ALPHA-PARTICLE DECAY**
- Radium-223
- $\alpha - \beta$
- @15 MIN

**BETA-PARTICLE DECAY**
- Lutetium-177
- $\beta - \gamma$
- @15 MIN

**CONVERSION ELECTRON DECAY**
- Tin-117M
- $\beta - \gamma$
- @15 MIN
IMAGING & DOSIMETRY

**Alpha-Particle**
- Radium-223

**Beta-Particle**
- Lutetium-177

**Conversion Electron**
- Tin-117M
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Acceptable value before first treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (HGB)</td>
<td>&gt;8 g/dL</td>
</tr>
<tr>
<td>White blood cell count (WBC)</td>
<td>&gt;2K/mm³</td>
</tr>
<tr>
<td>Platelet count (PLT)</td>
<td>&gt;70K/mm³</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (eGFR)</td>
<td>&gt;50 mL/min</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>≤3 × ULN</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&gt;3.0 g/dL</td>
</tr>
</tbody>
</table>

ULN = upper limits of normal.
FIGURE 2. Example room preparation for therapy. A dedicated bathroom should be used and wrapped in order to prevent urine contamination.
### TABLE 2

Content Requirements for the Amino Acid Solution

<table>
<thead>
<tr>
<th>Item</th>
<th>Specification</th>
</tr>
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<tbody>
<tr>
<td>Lysine HCl content</td>
<td>Between 18 and 24 g</td>
</tr>
<tr>
<td>Arginine HCl content</td>
<td>Between 18 and 24 g</td>
</tr>
<tr>
<td>Volume</td>
<td>1.5 to 2.2 L for commercial</td>
</tr>
<tr>
<td></td>
<td>(1.0 L for compounded)</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>&lt;1,050 mOsmol</td>
</tr>
</tbody>
</table>
FIGURE 3. Administration techniques. (A) Gravity method. (B) Pump method with vial. (C) Pump method with syringe. Please see Supplemental Table 2 for further details on the administration techniques.
<table>
<thead>
<tr>
<th>Duration</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>Sleep in separate bed, avoid intimate contact. For infants/children or pregnant partner, the time period should be extended.</td>
</tr>
<tr>
<td>Urination</td>
<td>Flush toilet twice with the lid closed after each use (all patients should be advised to sit down when urinating to minimize/avoid splashing), and to use separate towels and washcloths.</td>
</tr>
<tr>
<td>General recommendations</td>
<td>Use a general distance guideline of no closer than 3 feet for not more than 1 h per day. Try to maintain a distance of 6 feet from others. Minimize public transportation and use of public facilities. Return to work in 3 d, depending on patient tolerance.</td>
</tr>
</tbody>
</table>

**TABLE 4**
Radiation Safety Recommendations After $^{177}$Lu-DOTATATE Treatment

---

<table>
<thead>
<tr>
<th>Time after treatment</th>
<th>Clinical evaluation</th>
<th>Laboratory tests</th>
<th>Markers</th>
<th>Diagnostic imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4 wk</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>X</td>
<td>X</td>
<td>Per team</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>X</td>
<td>X</td>
<td>Per team</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>X</td>
<td>X</td>
<td>Per team</td>
<td></td>
</tr>
<tr>
<td>Long term</td>
<td>Per team</td>
<td>Per team</td>
<td>Per team</td>
<td>Per team</td>
</tr>
</tbody>
</table>

*Increase monitoring based on clinical presentation, symptoms, concern for progressive disease, or posttreatment sequelae.

*Complete blood count with differential, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, and serum creatinine/GFR

*Monitoring of markers should be based on clinical indication/presentation.

*Imaging is recommended once between one and three months after therapy.
PATIENTS MOST APPROPRIATE FOR RADIOPHARMACEUTICALS
(1) MORE THAN ONE METASTATIC LESION
(2) TUMOR EXPRESSES TARGETING MOLECULE
(3) AT LEAST ONE PRIOR LINE OF THERAPY
(4) WILLINGNESS TO UNDERGO THERAPY
Phase II trial of Radium-223 and M3814 (peposertib)-Avelumab in metastatic castrate-resistant prostate cancer (mCRPC) patients

Evidence:

- **MC38 murine colon carcinoma**
  - vehicle
  - M3814 150 mg/kg po qd
  - Avelumab 400µg/mouse iv d3,6,9
  - M3814 + Avelumab d3,6,9

Participants:

- **RPh II: mCRPC**
  - PSA > 1 ng/dL
  - 2 or more bone lesions
  - > 1 line therapy directed at metastases
    - hormone-based
    - taxane-based
    - Steroid/bisphosphonate or denosumab
  - < 5 visceral metastases
    - ≤ 2 cm organ
    - ≤ 2.5 cm nodal

Treatment:

- M3814 200-400 mg PO BIDf q4weeks x6
- Avelumab 10 mg m-2 IV q2weeks x12
- Radium-223 55 kBq / kg IV q4weeks x6

Safety Lead-Ins:

- 223Ra+M3814, then 223Rad+M3814+Ave

Correlatives:

- Radiation dosimetry (RAPID contract)
- tALK, bALK osteocalcin, PSA (commercial)
- WES & RNA-seq (MoCha)
- T-cell clonality / TCR repertoire (Adaptive BioTech contract)

N = 25 per arm
Phase II trial of Radium-223 in combination with paclitaxel in patients with metastatic breast cancer

Evidence:

paclitaxel + α-emitting radionuclide $^{213}$Bi-hu3S193

Survival curve in mice receiving saline (▪), 9.2 μg hu3S193 (▪), 300 μg paclitaxel (×), 15 μCi $^{213}$Bi-hu3S193 and 300 μg paclitaxel (♦), 30 μCi $^{213}$Bi-hu3S193 and 300 μg paclitaxel (♦), or 60 μCi $^{213}$Bi-hu3S193 and 300 μg paclitaxel (♦).

Participants:

RPh II: Breast Cancer (>1L)
- ER+ HER2-
- ER- PR- HER2-
- 2 or more bone lesions
- No steroid/bisphosphonate or denosumab
- < 5 visceral metastases
  - ≤ 2 cm organ
  - ≤ 2.5 cm nodal

Correlatives:

Radiation dosimetry (RAPID contract)

TALK, bALK osteocalcin (commercial)

WES & RNA-seq (MoCha)

Treatment:

Paclitaxel 90 mg m$^{-2}$ IV x3 weeks on / x1 week off, q4weeks x 6
Radium-223 55 kBq / kg IV q4weeks, x6

Participants:

RPh II: Breast Cancer (>1L)
- ER+ HER2-
- ER- PR- HER2-
- 2 or more bone lesions
- No steroid/bisphosphonate or denosumab
- < 5 visceral metastases
  - ≤ 2 cm organ
  - ≤ 2.5 cm nodal

N = 34 per arm
A phase I study of oral triapine and ¹⁷⁷Lu dotatate in somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients

**Participants:**
- **Treatment:**
  - ¹⁷⁷Lu 200 mCi IV q60 days for up to four (4) cycles
  - Triapine DL1 100, 150, 200 mg PO QD D1-14 q60 on each ¹⁷⁷Lu cycle

**Evidence:**
- Serum 3-AP (micromolar)
- 100 mg IV (N=14)
- 50 mg PO (N=8)
- 100 mg PO (N=3)
- 150 mg PO (N=4)
- 200 mg PO (N=2)

**Objectives:**
- Phase I:
  - Safety, MTD, RP2D
  - Pharmacokinetics
  - Gallium/lutetium scans
  - NETest (commercial RNA)
  - WES/RNA-seq

**Correlatives:**
- ⁶⁸Gallium (integral) and ¹⁷⁷Lutetium imaging & dosimetry
- WES & RNA-seq (integrated) (MoCha)
- NETest (exploratory) (Wren Laboratories)

**Analysis:** Ph1: BOIN 25% target toxicity, 14-patient expansion for safety
A phase Ib study of M3814 (pemoperitib) and $^{177}$Lu dotatate in somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor patients

Participants:
- **Phase I:** GEP-NET pts (>1L somatostatin)
  - Females/Males >18 years
  - Lesion(s) demonstrates $^{68}$Ga uptake on scintigraphy (<6 mo)
  - ECOG 0, 1, 2
  - No prior radiopharmaceutical
  - Creatinine < 1.7 mg/dl, platelets > 75,000/mm$^3$, ANC > 2000 /mm$^3$, bilirubin < 3 ULN

Evidence:
- $^{68}$Ga dotatate

Correlatives:
- $^{68}$Ga or $^{64}$Cu (integral) and $^{177}$Lutetium IROC imaging & dosimetry
- WES & RNA-seq & ctDNA (exploratory) (NCLN)
- M3814 PK (integrated) (UPitt)

Objectives:
- Phase I:
  - Safety 60-day, MTD, RP2D
  - Ga or Cu/Lu scans
  - M3814 PK
  - WES/RNA-seq
  - ctDNA
  - DoR, PFS, ORR

Treatment:
- $^{177}$Lu 200 mCi IV q60 days for up to four (4) cycles
- M3814 50, 100, 150, 200 mg PO QD D1-21 q28 on each $^{177}$Lu cycle

Correlatives:
- $^{68}$Ga dotatate
- $^{177}$Lu dotatate
- $^{68}$Ga dotatate
A single-arm phase II study of bone-targeted $^{117m}$Sn-DTPA in symptomatic castration-resistant prostate cancer patients with skeletal metastases

**Evidence:**

**Participants:**
- Ph II: mCRPC pts (≥ 1-line hormones)
- mCRPC w/ 2 bone lesions (1 painful)
- Lesion demonstrates $^{99m}$Tc uptake on bone scintigraphy
- ECOG 0, 1, 2
- No new systemic chemotherapy or radiotherapy w/in 4 weeks
- No hemiobody irradiation
- Creatinine < 1.5 mg/dl, hemoglobin > 10 g/dL, platelets > 100,000/mm³, ANC > 1500/mm³
- ADT & bone health agents allowed, per institutional standard

**Objectives:**
- **Primary Objective:** ORR at 12 weeks by RECIST 1.1
- **Secondary Objectives:**
  - $^{117m}$Sn-DTPA dosimetry
  - PSA & bALKphos time to progression
  - Pain score / analgesic requirement
  - PRO-CTCAE; EORTC QLQ-C30; safety
  - SSE / PFS / OS

**Correlatives:**
- WES / RNA-seq (NCLN)
- CD4/CD8+ T-cells (UKY)
- Polo-like kinase 1 (PLK1) IHC as predictor of response (UKY)

**Hypothesis:**

$^{117m}$Sn-DTPA, an effective bone-seeking radionuclide with relative sparing of the bone marrow toxicity, can be safely used as a therapeutic agent for pain palliation in the treatment of patients with symptomatic castration-resistant prostate cancer metastatic to at least two bone sites detected by $^{99m}$Tc bone scintigraphy.
SIDE EFFECTS OF RADIOPHARMACEUTICALS
A) neat radiopharmaceutical (without targeting ligand)
\[^{223}\text{Radium} – \text{NExT cycle 27}\]

B) neat radiopharmaceutical (without targeting ligand)
\[^{117m}\text{Sn} – \text{NExT cycle 31}\]
**ALSYMPCA: STUDY DESIGN**

**PATIENTS (N=921)**
- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxel

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

**Radium-223 (50 kBq/kg* IV) 6 injections at 4-week intervals + best standard of care**

**Placebo (saline) 6 injections at 4-week intervals + best standard of care**

**KEY INCLUSION CRITERIA**
- Histologically confirmed, progressive CRPC with ≥2 bone metastases (on skeletal scintigraphy) and no known visceral metastases
- Patients had either received docetaxel, were not fit enough or willing to receive docetaxel, or did not have docetaxel available

**EXCLUSION CRITERIA**
- Treatment with chemotherapy within the previous 4 weeks or failure to recover from AEs due to chemotherapy
- Prior hemibody external radiation therapy
- Systemic radiation therapy with radioisotopes within the previous 24 weeks
- Malignant lymphadenopathy >3 cm in short-axis diameter
- History or presence of visceral metastases

**ALSYMPCA was halted early after the positive efficacy results reported out from a planned interim analysis occurring when 809 patients had 314 deaths. An updated analysis of efficacy and safety was done when all 921 enrollees had 528 deaths.**

Radium-223 resulted in a 30% reduction in risk of death (HR=0.70) for patients compared with placebo.

**MEDIAN OS (months)**
- Radium-223: 14.9
- Placebo: 11.3

**HR (95% CI):** 0.70 (0.58–0.83)

**P:** <0.001

Confirmed decline was defined as any decrease from baseline at week 12, confirmed ≥3 weeks later. Includes all patients with tALP and LDH determinations at baseline and week 12.

**tALP**

- **MEDIAN OS (mo)**
  - Radium-223 patients with confirmed tALP decline (n=400) 17.8 mo
  - Radium-223 patients without confirmed tALP decline (n=97) 10.4 mo
  - HR=0.45, 95% CI (0.34-0.61)
  - *P*<0.0001

**LDH**

- **MEDIAN OS (mo)**
  - Radium-223 patients with confirmed LDH decline at wk12 (n=196) 19.5 mo
  - Radium-223 patients without confirmed LDH decline at wk12 (n=97) 14.5 mo
  - HR=0.55, 95% CI (0.42-0.73)
  - *P*<0.0001

### Clinical Trial Experience

#### NUMBER OF PATIENTS WITH AEs OCCURRING IN ≥5% OF PATIENTS IN EITHER TREATMENT GROUP

<table>
<thead>
<tr>
<th>EVENT</th>
<th>RADIUM-223 (n=600)</th>
<th></th>
<th></th>
<th>PLACEBO (n=301)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ALL GRADES, n (%)</td>
<td>GRADE 3, n (%)</td>
<td>GRADE 4, n (%)</td>
<td>GRADE 5, a, n (%)</td>
<td>ALL GRADES, n (%)</td>
<td>GRADE 3, n (%)</td>
</tr>
<tr>
<td><strong>Hematologic AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>65 (11)</td>
<td>11 (2)</td>
<td>0</td>
<td>92 (31)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>20 (3)</td>
<td>18 (3)</td>
<td>1 (&lt;1)</td>
<td>17 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>9 (2)</td>
<td>4 (1)</td>
<td>0</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Nonhematologic AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
<td>64 (21)</td>
<td>4 (1)</td>
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<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>9 (2)</td>
<td>0</td>
<td>0</td>
<td>45 (15)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>10 (2)</td>
<td>0</td>
<td>0</td>
<td>104 (35)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (19)</td>
<td>10 (2)</td>
<td>0</td>
<td>0</td>
<td>41 (14)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>35 (6)</td>
<td>5 (1)</td>
<td>0</td>
<td>0</td>
<td>18 (6)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>154 (26)</td>
<td>21 (4)</td>
<td>3 (1)</td>
<td>0</td>
<td>77 (26)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>27 (5)</td>
<td>9 (2)</td>
<td>2 (&lt;1)</td>
<td>5 (1)</td>
<td>21 (7)</td>
<td>8 (3)</td>
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<tr>
<td>Peripheral edema</td>
<td>76 (13)</td>
<td>10 (2)</td>
<td>0</td>
<td>0</td>
<td>30 (10)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>38 (6)</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
<td>19 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18 (3)</td>
<td>9 (2)</td>
<td>0</td>
<td>4 (1)</td>
<td>16 (5)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

**AE, adverse event.**

a. Only 1 grade 5 hematologic AE was considered possibly related to study drug: thrombocytopenia in 1 patient in the radium-223 group.

### NUMBER OF PATIENTS WITH AEs OCCURRING IN ≥5% OF PATIENTS IN EITHER TREATMENT GROUP

<table>
<thead>
<tr>
<th>EVENT</th>
<th>RADIUM-223 (n=800)</th>
<th>PLACEBO (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL GRADES, n (%)</td>
<td>GRADE 3, n (%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>47 (8)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>69 (12)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>102 (17)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35 (6)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>120 (20)</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>22 (4)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Malignant neoplasm progression</td>
<td>77 (13)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>25 (4)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (5)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>30 (5)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>25 (4)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>49 (8)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>

**AE, adverse event.**

a. Only 1 grade 5 hematologic AE was considered possibly related to study drug: thrombocytopenia in 1 patient in the radium-223 group.

Let (keV/µm)
distance in water (µm)

\[ x = 40 \mu m \]
\[ x = 350 \mu m \]
\[ x = 270 \mu m \]

DNA ionization

---or---

--or--

pancreas cell

Cancer Therapy Evaluation Program radiopharmaceutical clinical development vision
ctep.cancer.gov

alpha-particle

\([^{223}\text{Radium} - \text{NExT cycle 27}]\)

beta-particle

\([^{177}\text{Lutetium} - \text{NExT cycle 32}]\)

conversion electron

\([^{117}\text{Tin} - \text{NExT cycle 31}]\)
NETTER-1: STUDY DESIGN

PATIENTS (N=342)
- Midgut neuroendocrine tumors, inoperable
- Progress on octreotide LAR (20-30 mg q3-4 weeks) for at least 12 weeks before entry
- Somatostatin receptor positive disease by scintigraphy

STRATIFICATION
- Somatostatin receptor: 2, 3, or 4
- Octreotide use: ≤ 6 mo vs > 6 mo

Lutetium-177 (7.4 GBq [200 mCi] IV)
4 infusions at 8-week intervals
+ best standard of care
+ octreotide 30 mg at 4-week intervals

Octreotide 60 mg
at 4-week intervals
+ best standard of care

• 41 centers in US or EU
• Planned follow-up was 5 years

NETTER-1 was halted early after the positive efficacy results reported out from a planned interim analysis occurring when 124 patients had 74 events of disease progression or deaths. An updated survival analysis was done after 158 deaths.

KEY INCLUSION CRITERIA
- Histologically confirmed, progressive midgut neuroendocrine tumors with somatostatin-positive disease (on somatostatin scintigraphy)
- Patients had received octreotide, over the course of a maximum period of 3 years

EXCLUSION CRITERIA
- Serum creatinine > 1.7 mg/dL
- Prior octreotide with more than 30 mg within 12 weeks of random allocation
- Systemic radiation therapy with radioisotopes at any time
- Any surgery, liver-directed transarterial therapy or chemotherapy within 12 weeks of random allocation

Lutetium-177 + octreotide resulted in a 60% reduction in risk of death (HR=0.40) for patients compared with placebo + octreotide.

### Table 4. Adverse Events (Safety Population). *

<table>
<thead>
<tr>
<th>Event</th>
<th>¹⁷⁷Lu-Dotatate Group (N=111)</th>
<th>Control Group (N=110)</th>
<th>P Value †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
<td>Any Grade</td>
</tr>
<tr>
<td><strong>Any adverse event</strong></td>
<td>105 (95)</td>
<td>46 (41)</td>
<td>92 (84)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>65 (59)</td>
<td>4 (4)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52 (47)</td>
<td>8 (7)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29 (26)</td>
<td>3 (3)</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (29)</td>
<td>3 (3)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Distension</td>
<td>14 (13)</td>
<td>0</td>
<td>15 (14)</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>44 (40)</td>
<td>2 (2)</td>
<td>28 (25)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>16 (14)</td>
<td>0</td>
<td>8 (7)</td>
</tr>
<tr>
<td><strong>Blood disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 (25)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (14)</td>
<td>0</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>20 (18)</td>
<td>10 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (10)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (5)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Grade 3 or Higher Sequelae

Percent of Cohort (%)

- Anemia
  - Alpha-Particle: 11%
  - Beta-Particle: 1%

- Neutropenia
  - Alpha-Particle: 2%
  - Beta-Particle: 2%

- Thrombocytopenia
  - Alpha-Particle: 3%
  - Beta-Particle: 2%
GRADE 3 OR HIGHER SEQUELAE

PERCENT OF COHORT (%)

<table>
<thead>
<tr>
<th></th>
<th>Alpha-Particle</th>
<th>Beta-Particle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
SUMMARY

(1) RECOGNIZE TWO RADIOPHARMACEUTICAL AGENTS IN CLINICAL PRACTICE
(2) RECOMMEND PATIENTS MOST APPROPRIATE FOR RADIOPHARMACEUTICAL THERAPY
(3) APPRAISE SIDE EFFECTS OF RADIOPHARMACEUTICAL THERAPY
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(1) RECOGNIZE TWO RADIOPHARMACEUTICAL AGENTS IN CLINICAL PRACTICE
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RADIOPHARMACEUTICAL CE QUESTIONS

(1) DEFINE A ‘NEAT’ RADIOPHARMACEUTICAL.
(2) WHAT SHIELDING IS NEEDED FOR ALPHA-DECAYING AGENT?
(3) WHAT IS THE TYPICAL RANGE OF A BETA PARTICLE?