THERANOSTICS: Regulatory Considerations for Product Development
Welcome and Workshop Objectives

Adebayo Laniyonu, Ph.D.
and
Bonnie Clarke
Overview of the day:
8:45 – break
10:30 – break
12:00-12:45 – lunch
3:00 – adjourn
1. Describe available regulatory pathways for investigational drug studies
2. Discuss quality considerations for radionuclide and pharmacophore
3. Describe strategies for efficient nonclinical and CMC product development for theranostics pair.
4. Discuss differences in early development, co-development, and post-approval development strategies

5. Discuss the development of radiopharmaceuticals as theranostic pairs

6. Offer statistical and clinical trials considerations for theranostic products
Bottomline “Take Away” objective

The Organizers of this Workshop recognize the importance of Theranostics Product Development and will work collaboratively with stakeholders to optimize regulatory approaches.
Theranostics, precision medicine tools for oncology

Libero Marzella
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER/FDA
Theranostics overview

• definition
• various contexts of use: focus on oncology
• radiopharmaceuticals as theranostic product pairs
• facilitating development of diagnostic imaging products
Theranostics

definitions, objectives
various precision medicine tools for individualized patient treatment

targeted therapies that combine diagnosis, treatment planning, drug delivery, response assessment

aim to improve patient outcomes
Theranostics, biomarkers as precision medicine tools

Biomarkers: the omics revolution

- **scope:** omics spans the expression of genetic information from genes to transcripts, proteins, and metabolites
- **promise:** enhance understanding of mechanisms of disease and heterogeneity of disease expression; facilitate development of targeted therapies
Theranostics, biomarkers as precision medicine tools

• in 2017, 50% of early-stage and 30% of late stage molecular entities in development included the use of biomarker tests [4].
• one third of recent drug approvals have had DNA-based biomarkers included in their original FDA submissions [5]

As cited by: Yearb Med Inform 2018:211-22
http://dx.doi.org/10.1055/s-0038-1667085
Theranostics, *in vitro* diagnostics as precision medicine tools

*in vitro* diagnostics: wide range of products

- tissue biopsy, liquid biopsy (exosomes), serum assays
  - regulated as devices by PMA, *de novo*, or 510(k)
  - developed and labeled for use singly or together with therapeutic as “companion” diagnostic devices
  - companion diagnostics are cross-labeled i.e. a specific diagnostic device is for use only with a specific therapeutic product

- see links below for guidance on co-development and listing of co-developed products

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
Theranostics, diagnostic imaging drugs as precision medicine tools

• *in vivo* imaging diagnostics
  – optical imaging using near infrared fluorescent drugs for intraoperative uses e.g. indocyanine green
  – SPECT, PET imaging using various radiopharmaceuticals e.g. somatostatin receptor imaging using In 111 pentetreotide, Ga 68 octatreotate,
  – other imaging modalities using pharmacophores consisting of targeting and signaling moieties
Theranostic “pairs” CD-20 oncotargets

• I\(^{131}\) tositumomab dosimetric and therapeutic dosing (withdrawn from marketing for commercial reasons)

• Y\(^{90}\) ibritumomab tiuxetan therapeutic; In\(^{111}\) radiolabeled product used for dosimetry in clinical trials
Theranostic radiopharmaceutical “pairs”

- Ga 68 dotatate (dx), Lu 177 dotatate (rx) somatostatin receptor oncotargets; sequential FDA approval
- I 131 iobenguane norepinephrine transporter oncotarget; FDA approval first as diagnostic then as therapeutic; I 131 example of radionuclide with usable dual emission ($\gamma,\beta$)
- Literature reports of studies of other theranostic pairs targeting various tumors
Theranostics, diagnostic imaging drug development approaches

• co-development of diagnostic as theranostic pair for enrichment/selection of study patients, prognostic value, early assessment of treatment response, individualized by-cycle therapeutic dosing

• “validated” biomarkers or approved diagnostics for use in early development for exploratory assessments or as surrogates of efficacy

• post-approval development of diagnostic drugs for new use with approved therapeutics to enhance safety or efficacy

• post-approval development of therapeutic as new drug (repurposed as pharmacophore combined with a signaling moiety) to assess expression of pharmacologic target
Co-development plan: “validation” of diagnostic

• pharmacologic target
• preclinical proof of concept
• precision and accuracy
  – reproducibility
    • test-retest
    • reference standard: histopathology, phantom
  – clinical performance
    • biodistribution, dosimetry
    • signal to noise quantitation
    • diagnostic sensitivity, specificity
Theranostics, summary

• novel radiopharmaceutical theranostic pairs under active development in oncology
• pathways for maximizing efficiency of development of the “pair”
• diagnostic performance of the “nostic”
  – other claims to be considered
Theranostics: Regulatory Considerations in USA, SNMMI 2019:
Targets, Delivery, Radionuclides, Applications, Perspectives and Opportunities

Richard L. Wahl, M.D.
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, MO
Disclosures

Consultant: Clarity Pharmaceuticals

Research Support: BMS, White Rabbit AI

Travel support: Siemens, RSNA

FDA: Dosing described with Y-90 Zevalin exceeds the package insert recommended dosage and I-131 tositumomab is no longer available.

The terms of these arrangements are being managed by Washington University School of Medicine in accordance with its conflict of interest policies.
Overview of Lecture

• Targets, Delivery, Radionuclides and Therapeutic Applications
• Non-Malignant Diseases
• Radioisotopes
• Economic Model of Theranostics in the USA
• Empirical vs Precision Dosing
• Disruptive Elements of this form of Therapy
• What happened to I-131 Tositumomab?
• What about Toxicity/Myelodysplastic Syndrome?
• How will we build this field? Training? Workforce? Commercial pathways? Opportunities and gaps
Therapeutic Nuclear Medicine Agents Approved in the USA

- I-131 (NaI). Thyroid Cancer, Graves Disease
- I-131 Tositumomab/tositumomab (Bexxar*)
- Y-90 Ibritumomab Tiuxetan (Zevalin)
- Sm153 EDTMP, Sr89
- Ra223 (Xofigo)
- Lu177 dotatate (Lutathera)
- I-131 MIBG (Azedra)
Targets

• Cancer
  – Bulky cancer, minimal residual disease
  – Solid tumors vs hematogenous
  – Many tumor associated markers, CD X, integrins, same pathways as PET agents

• Non Malignant Diseases
  Arthritis, e.g. RA, colloids
  Infections?  ???
Therapeutic Radioisotopes

• Beta emitters—what energy? I-131, Lu177, Cu67, Y-90
  – Pure beta, or beta plus gamma-or positron?
• Alpha emitters: Bi213, Ac225, Pb212, At211
• Auger emitters I123, In111
• One isotope or more than one?
• Sequential, combined, with or w/o external beam or other Rx? rationale?
Routes of Delivery

• Intravenous and systemic
• Intraarterial (e.g. hepatic artery) other arterial trees
• Intracavitary: Intraperitoneal, Intrapleural,
  – Interstitial (e.g. brain tumors), intratumoral,
  – Topical?
Basic Considerations

- Is there a companion diagnostic (e.g. SSTR2 targeting)
- Is the same agent used for imaging and Rx? I-131
- Is there a need for an imaging dose at all?
- Is the therapeutic margin large or small?
- Is there heterogeneity in the drug delivery in vivo or in systemic clearance
- Can the therapy be given more than once?
What patient groups?

• Similar or heterogeneous?
• Extensive prior therapy or de novo disease?
• Toxicities may differ
• Is disease extensive and in critical locations?
• What is functional and immune status of patient
• Does the patient have characteristics suggesting they would be more radiosensitive or at risk of toxicity?
I-131 anti CD-20 RIT: The First “Precision Theranostic”?

- Specific Targeting to an identifiable protein targeted identified in a specific patient (CD-20)
- Patient Specific Precision Radiation Dose calculated using a tracer dose of radiation
- Of course, I-131 for thyroid cancer has done this as well, esp. when given with the “Leeper” dosimetry scheme for high dose cancer therapy
Iodine I 131 Tositumomab Characteristics and Mechanism Of Action

- **Tositumomab**
  - Murine IgG2a anti-CD20 MAb
  - B-cell specific
  - Induction of apoptosis
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cellular cytotoxicity (ADCC)

- **Iodine-131 radioisotope**
  - Cytotoxic beta emission
  - Physical half-life of 8 days
  - Short path length
  - Gamma emission allows dosimetry
Effect of Clearance Rate on Radiation Exposure (mCi)

Individuals with a rapid clearance rate require a higher dose of radiation (in mCi)

Rapid Clearance

<table>
<thead>
<tr>
<th>Days</th>
<th>Treatment dose, mCi</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>100</td>
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<tr>
<td>2</td>
<td>50</td>
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<td>3</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
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</table>

Slow Clearance

<table>
<thead>
<tr>
<th>Days</th>
<th>Treatment dose, mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
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<tr>
<td>2</td>
<td>50</td>
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<tr>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>

75 cGy
**Bexxar Treatment Regimen**

**Day 0**

**Dosimetric Dose**
- 450 mg unlabeled tositumomab,
- 35 mg tositumomab radiolabeled I 131 (5 mCi)

- Unlabeled dose infused over 1 hour
- Radiolabeled tracer dose infused over 20 minutes

**Day 7–14**

**Therapeutic Dose**
- 450 mg unlabeled tositumomab,
- 35 mg tositumomab radiolabeled I 131 to deliver specific cGy TBD (variable mCi)

- Unlabeled dose infused over 1 hour
- Radiolabeled therapeutic dose infused over 20 minutes

**Total Body Counts x 3**
- Day 0
- Day 2, 3, or 4
- Day 6 or 7

**Thyroid protective agent: Day -1 continuing through 14 days post-therapeutic dose**
Tositumomab
Dosimetric Package
Therapeutic Package
Purpose of Administering Unlabeled Tositumomab Prior to Iodine I 131 Tositumomab

- To occupy non-tumor CD20 sites on:
  - Circulating B cells
  - Splenic B cells
- To provide a longer residence time of the radioconjugated antibody
- To potentially improve tumor uptake of radioactive antibody
Effect of Unlabeled Antibody Pre-Dose on Distribution

1hr post Tositumomab injection
R  ANT  L
No pre-dose

1hr post Tositumomab injection
R  ANT  L
Pre-dose

Data on File. Corixa Corporation.
Dosimetry for BEXXAR

- Dosimetry studies confirmed a 4-fold variation in the clearance rate (or effective half-life) of Iodine 131 Tositumomab
  - Factors affecting clearance of the antibody include tumor size, splenomegaly, and the amount of bone marrow involvement
- Due to variations in the clearance rate, the administered amount of radioactivity (in mCi) is adjusted individually to ensure that all patients receive the prescribed TBD of 75 cGy
- Using dosimetry with Iodine-131-labeled antibodies enables physicians to directly measure the clearance rate in order to prospectively individualize the therapeutic dose

Range of mCi Required to Deliver Targeted Total Body Radiation Dose

* Patients were prescribed either 65cGy or 75 cGy depending on their platelet count. Data were standardized to 75 cGy.

* Patients were prescribed either 65cGy or 75 cGy depending on their platelet count. Data were standardized to 75 cGy.

Data on File, GlaxoSmithKline.
**Determination of Maximum Tolerated Total Body Dose (TBD) of BEXXAR**

75 cGy was established as Maximum Tolerated TBD

<table>
<thead>
<tr>
<th>Dose Level (cGy)</th>
<th>Patients With DLT⁺/Number Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0/3</td>
</tr>
<tr>
<td>35</td>
<td>0/4</td>
</tr>
<tr>
<td>45</td>
<td>0/3</td>
</tr>
<tr>
<td>55</td>
<td>0/3</td>
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<tr>
<td>65</td>
<td>0/3</td>
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<tr>
<td>75⁺</td>
<td>1/6</td>
</tr>
<tr>
<td>85</td>
<td>2/3</td>
</tr>
</tbody>
</table>

⁺DLT (Dose-Limiting Toxicity) = Grade 3 hematologic toxicity >2 weeks duration, Grade 4 hematologic toxicity >1 week duration, or Grade 3/4 non-hematologic toxicity.

† 75 cGy = MTD.

Data on File. Corixa Corporation.
### Response in Patients With NHL Previously Treated With Rituximab (N=40)

<table>
<thead>
<tr>
<th></th>
<th>Response Rate (%) (95% CI*)</th>
<th>Median Duration of Response (Mos) (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>68% (51%- 81%)</td>
<td>16 (1+ - 35+)</td>
</tr>
<tr>
<td>Complete Response†</td>
<td>33% (19%- 49%)</td>
<td>NR‡ (4- 35+)</td>
</tr>
<tr>
<td>Median duration of follow-up</td>
<td></td>
<td>26 months</td>
</tr>
</tbody>
</table>

* CI = Confidence Interval.
† Complete response rate = Pathologic and clinical complete responses.
‡ NR = Not reached.
**INDICATIONS AND USAGE**

**Relapsed or Refractory CD20-Positive, Non-Hodgkin’s Lymphoma**

The BEXXAR therapeutic regimen (tositumomab and iodine 131 tositumomab) is indicated for the treatment of patients with CD20-positive relapsed or refractory, low grade, follicular, or transformed non-Hodgkin’s lymphoma who have progressed during or after rituximab therapy, including patients with rituximab-refractory non-Hodgkin’s lymphoma.

Determination of the effectiveness of the BEXXAR therapeutic regimen is based on overall response rates in patients whose disease is refractory to chemotherapy and rituximab. The effects of the BEXXAR therapeutic regimen on survival are not known.

**Important Limitations of Use**

- The BEXXAR therapeutic regimen is only indicated for a single course of treatment.
- The safety and efficacy of additional courses of the BEXXAR therapeutic regimen have not been established.
- The BEXXAR therapeutic regimen is not indicated for first-line treatment of patients with CD20-positive non-Hodgkin’s lymphoma.
FDA Approvals

• Bexxar submitted 1999, approved 2003
• Zevalin approve 2002
• Rituximab approved 1997
Phase III Randomized Intergroup Trial of CHOP Plus Rituximab Compared With CHOP Chemotherapy Plus $^{131}$Iodine-Tositumomab for Previously Untreated Follicular Non-Hodgkin Lymphoma: SWOG S0016

CONSORT diagram illustrating patient flow on Southwest Oncology Group protocol S0016.

Press O W et al. JCO 2013;31:314-320
Fig 3. Comparison of (A) progression-free survival (PFS) and (B) overall survival (OS) of patients with advanced-stage follicular lymphoma who received either six cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) or six cycles of CHOP-RIT (cyclophosphamide, doxorubicin, vincristine, and prednisone followed by consolidation with iodine-131–tositumomab radioimmunotherapy).

Published in: Mazyar Shadman; Hongli Li; Lisa Rimsza; John P. Leonard; Mark S. Kaminski; Rita M. Braziel; Catherine M. Spier; Ajay K. Gopal; David G. Maloney; Bruce D. Cheson; Shaker Dakhil; Michael LeBlanc; Sonali M. Smith; Richard I. Fisher; Jonathan W. Friedberg; Oliver W. Press; JCO 2018, 36, 697-703.
DOI: 10.1200/JCO.2017.74.5083
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Fig 4. Cumulative incidences of death resulting from (A) secondary malignancies and (B) acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Estimates of 10-year cumulative incidence were (A) 3.2% and 7.1% ($P = .16$) and (B) 0.9% and 4.0% ($P = .02$) in the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP-RIT (cyclophosphamide, doxorubicin, vincristine, and prednisone followed by consolidation with iodine-131–tositumomab radioimmunotherapy) groups, respectively.
US Healthcare System

- Fragmented
- Medicare (national) for those > 65 yo
- Medicaid (state) for the very poor, disabled, children/young
- Private insurance for the 18-65 yo
- “No” insurance for 10% of the population
- Pricing models differ: Dx agents paid much less than Rx drugs, Rx high $
- Medicare has been “slow” to pay
- “low/no” pay for physics/dosimetry
- “low” pay for treating physicians
Willie, why do you rob banks?

“That’s Where the Money is…”

― Willie Sutton
“Too Expensive”

- $25,000/dose (one dose is all that is required)
Medicare Cuts Payout on 2 Cancer Drugs

By ALEX BERENSON  DEC. 7, 2007

New Medicare rules for a small but promising class of cancer drugs may cause thousands of lymphoma patients to lose access to the treatment, which in some cases is the only therapy available to them.
Medicare pays 10K less than cost of drug/dose

Under the new rules, after Jan. 1, Medicare will reimburse hospitals about $16,000 for each treatment with the drugs, which a patient needs to receive only once. GlaxoSmithKline, which markets Bexxar, says it is priced at almost $30,000 a treatment, and Biogen Idec, which sells Zevalin, says it costs nearly as much. While high, such prices are not unusual for new cancer therapies, which can cost $50,000 or more for a year of treatment.

“I’m not usually a vengeful or resentful person,” she said. “But I am feeling a bit resentful about having this taken away — if I can’t have access to a drug that would extend my life.”
Market Forces Cited in Lymphoma Drugs’ Disuse

Linda Stephens, left, has been cancer-free for seven years; Dan Wheeler, three years; Betsy de Parry five years. Before treatment, all three had late-stage non-Hodgkin’s lymphoma.

By ALEX BERENSON
Published: July 14, 2007
GSK to discontinue manufacture and sale of the BEXXAR® therapeutic regimen (tositumomab and iodine I 131 tositumomab)

13 August 2013

The decision to discontinue BEXXAR involved a thoughtful and careful evaluation of patient needs and the clinical use of the therapy, which was approved for use in the U.S. in 2003 and in Canada in 2005. The use of BEXXAR has been extremely limited and is projected to continue to decline. Additionally, there are other treatment options available for patients with relapsed non-Hodgkin's lymphoma.
Problems: Economic

- Patients “lost” by oncologists referring patients to nuclear medicine
- Lost patient represents lost revenue to oncologist in US health care FFS environment
- CMS in the US was paying less than the cost of the drug for the treatment
- CMS lumped the “dosimetric dose” as a generic imaging agent and did not pay adequately for the Rx
- Therapy was initially not reimbursed like other cancer therapies, but like Dx agent.
- One vendor of RIT was selling a non radioactive competitor molecule.
Problems: Logistical

- Logistical:
  - Patient specific dosimetry viewed as difficult
  - \( I-131 \) therapy means “inpatient” in some locales
  - Not all sites could do the therapy
  - Shelf life of \( I131 \) Mab brief, raising cost of goods
  - Could not be performed by the “oncologist”
  - Approval of Bexxar took 4 years at FDA
  - Company sold and re-sold
  - Oncologists can’t “give” Bexxar or Zevalin
Problems: Scientific

- Murine Antibody. Only approved for single administration
- Gamma emitter delivers dose off target
- Risk of myelodysplastic syndromes
- Other non radioactive therapies have emerged of similar ? Efficacy
- Front line single Rx approach was never approved by FDA nor was a pivotal trial conducted
ALSYPMA Overall Survival

HR = 0.695 95% CI, 0.581, 0.832
P = 0.00007

Placebo: n = 307
Median OS: 11.3 m

223Ra: n = 614
Median OS: 14.9 m
Progression-free Survival and Overall Survival.

Investments in Radiotherapeutic Agents

- Oncologic Drugs (proprietary) are richly reimbursed in the USA at present
- 4 doses of “Lutathera” cost nearly $200,000 USD for drug alone
- Xofigo (RaCl2): $70,000 USD
I-131 MIBG

(a)

(b)
AZEDRA® (iobenguane I 131) is a prescription medicine used to treat adult and pediatric patients 12 years and older with cancers known as pheochromocytoma and paraganglioma that are positive for the norepinephrine transporter (as determined by an iobenguane scan), and who require systemic anticancer therapy.
“To D or not to D”
That is the Question

• D=Dosimetry

• Should all TRT require dosimetry?
• If so, When, how?
• Or is a biological read out sufficient?
Drug Therapy for Cancer

- One Dose fits all—more or less
- Dose adjusted based on body mass
- Infrequently, drug levels are measured if there is variability in effect
- Biological readout is commonly used for chemotherapy: platelet counts, WBC, mucositis: Subsequent doses are adjusted downward or delayed
To D or not to D?

• Dosimetry
• Dose (mass)
• It Depends
Initial Deployments of RIT

- 1st generation therapies
- Murine monoclonal antibodies
- HAMA a real possibility
- Maximum dose to given, only “one” shot
- Reagents cross reacted with normal tissues
- Considerable variability across patients in biological clearance of reagents
- Dosimetry can adjust for this
Good vs Perfect vs None

- Will the search for perfection result in delays in deployment of PRIMED?
- Dosimetry is at best an estimate
- Doesn’t address intratumoral heterogeneity in simplest form
- Doesn’t consider patient specific tumor radiosensitivity or inherent radiosensitivity of normal tissues
- What is the need, and does it help?
How to do Precision RPT?

- Prospective dosimetry based on a radiotracer—PET or SPECT or ? Probe?
- Post Rx dosimetry to adjust a subsequent treatment dose—SPECT?
- Dose patient repeatedly with a starting average dose, then adjust dose up or down based on toxicity or lack thereof
Radiopeptide Rx

- Repeated small doses without dosimetry/
- Dosimetry to modulate renal dose
- Both approaches work
Radioimmunotherapy With Y-90 Zevalin

- **Ibritumomab**
  - Murine monoclonal antibody parent of Rituximab
- **Tiuxetan**
  - Conjugated to antibody, forming strong urea-type bond
  - Stable retention of Y-90
The Zevalin Therapeutic Regimen

**Imaging dose**

Rituximab 250 mg/m²

Followed by In-111 Zevalin 5.0 mCi

---

**Therapeutic dose**

Rituximab 250 mg/m²

Followed by Y-90 Zevalin (0.4 or 0.3 mCi/kg*; max dose 32.0 mCi)

---

Day 1 2 3 4 5 6 7 8 9

Scans

2–24 hours 48–72 hours 90–120 hours (optional)

---

*0.4 mCi/kg in patients with a platelet count ≥150,000 cells/mm³ or 0.3 mCi/kg with a platelet count 100,000 to 149,000 cells/mm³. Maximum dose is 32.0 mCi.
2–24 hours

48–72 hours

90–120 hours (optional)
Zevalin and Rituximab Randomized Phase III Trial: Response Rates*

FIT Primary End Point: Median PFS in All Patients*

Zevalin: median 37 mo  
\( n = 208 \)

Control: median 13.5 mo  
\( n = 206 \)

*Median observation period was 3.5 years.
Why Myeloablative Radioimmunotherapy?

- While many patients with NHL respond to RIT with anti CD-20 Monoclonal Antibodies, many do not
- Some histologies such as high grade, especially transformed lymphomas and mantle cell appear to have lower response rates to RIT than follicular NHLs
- Dose of radioactivity in standard RIT is limited by myelotoxicity
- Stem Cell transplants are increasingly used to intensify chemotherapy
- Press, Eary and colleagues have used bone marrow transplants to intensify the doses of I-131 tositumomab RIT. Cardiopulmonary dose limiting.
Feasibility Study of Precision, Prospective, SPECT-CT/Planar Organ Dosimetry Based, Outpatient Myeloablative Radioimmunotherapy with Autologous Stem Cell Transplantation (ASCT): Dose-Escalation using the In/ Yttrium 90 (90Y) Ibritumomab Tiuxetan (Zevalin) Theranostic in Patients With Relapsed or Refractory B-Cell Non-Hodgkin’s Lymphoma (NHL)

Richard L. Wahl¹,²,⁴, Eric Frey², Heather A. Jacene²,⁵, Brad S. Kahl³,⁶, Steven Piantadosi¹,⁷, Jesus A. Bianco³,² Richard J. Hammes³, Lynn S. Billing¹, Kathryn Rogers¹, Miah Jung¹, Bin He¹,⁸, George Sgouros², Ian W. Flinn¹,⁶, Lode J. Swinnen
Organ Dosimetry SPECT/CT--Dose Escalation Study of $^{90}$Y-Z with ASCT: Study Schema

- Cyclophosphamide (2.5 g/m²)
  - Single dose

- Filgrastim (10 µg/kg)

- Stem cell collection

- Days
  - 1
  - 15
  - ~27

- Imaging dose
  - $^{111}$In ibritumomab tiuxetan (5 mCi)

- Therapeutic dose
  - $^{90}$Y ibritumomab tiuxetan (personalized by cohort*)

*Dose cohorts of $^{90}$Y ibritumomab tiuxetan +
- 0.4 mCi/kg
- 14–18 Gy to the liver not to exceed heart/kidney dose
- 24 Gy to the liver
- 28 Gy to the liver
- 30.5 Gy to the liver

- Std chemo for SCT?
Planar/SPECT Hybrid Method

- SPECT Proj.
- CT

24 hr Reconstruction

Planar Activity Estimation

SPECT

Compute Activity in Organ VOIs

24 Hr Organ Activities

Residence Time

Rescaled T.A.C.

CTSPECT Proj.

Anterior

Posterior

1 5 24 72 144 (Hour)
Administered Dose of Y-90

Cohort 1: 0.4 mCi/kg (n = 3) (.4 mCi/kg)

Cohort 2: 14–18 Gy (n = 5) (.99-1.2 mCi/kg)

Cohort 3: 24 Gy (n = 6) (1.03-1.9 mCi/kg)

Cohort 4: 28 Gy (n = 3) (1.37-1.88 mCi/kg)

Cohort 5: 30.5 Gy (n=1) (1.40 mCi/kg)
Conclusions:

- Significant dose escalation of 90Y ibritumomab tiuxetan is possible with ASCT, resulting in an effective outpatient treatment regimen for patients with low-grade and aggressive lymphoma and a poor prognosis.
- Delays in engraftment have not been observed at the current cohort-specific doses.
- Despite the fact that the liver is the organ that receives the highest radiation absorbed doses, no significant hepatotoxicity has been observed at estimated radiation absorbed doses of 28 Gy.
- Dose escalation continues and the maximum tolerated dose has yet to be determined.
- Additional trials and longer follow-up are needed to determine the benefits of high-dose RIT plus ASCT.
Radioimmunotherapy in Non-Hodgkin Lymphoma: Opinions of U.S. Medical Oncologists and Hematologists

Niklaus G. Schaeffer¹, Jiemin Ma², Peng Huang³, Judy Buchanan¹, and Richard L. Wahl¹

¹Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; ²Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; and ³Division of Oncology Biostatistics, Johns Hopkins University, Baltimore, Maryland
### TABLE 1. Concerns About Treatment of NHL Patients with $^{90}$Y-Ibritumomab Tiuxetan or $^{131}$I-Tositumomab

<table>
<thead>
<tr>
<th>Concern</th>
<th>Mean value*</th>
<th>P (proportional odds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no treatment site of $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan convenient for my patients</td>
<td>1.608</td>
<td>2.418</td>
</tr>
<tr>
<td>It is or would be economically adverse for my practice to use $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan</td>
<td>1.775</td>
<td>2.209</td>
</tr>
<tr>
<td>The nuclear physicians are not too interested in treating patients with $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan</td>
<td>2.05</td>
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<td>Referring patients for $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan is too complicated</td>
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<tr>
<td>There are possible unexpected late side effects (MDS)</td>
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<td>3.269</td>
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<tr>
<td>There are too many effective nonradioactive treatment alternatives for the NHL</td>
<td>3.013</td>
<td>2.993</td>
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</table>

*1 = no concern; 5 = major concern, with P value indicating significant difference.

---

**J Nucl Med 2010; 51:987–994**
<table>
<thead>
<tr>
<th>Concern</th>
<th>Mean value</th>
<th>P (proportional odds)</th>
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<td>There is no treatment site of $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan convenient for my patients</td>
<td>1.608</td>
<td>&lt;0.01</td>
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<td>It is or would be economically adverse for my practice to use $^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan</td>
<td>1.775</td>
<td>&lt;0.01</td>
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<tr>
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<td>$^{131}$I-tositumomab or $^{90}$Y-ibritumomab tiuxetan is too expensive</td>
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<tr>
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<td>0.14</td>
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*1 = no concern; 5 = major concern, with P value indicating significant difference.
Why did Bexxar Fail?
Why is Zevalin limping along?

• “When you look at the whole story, there’s no single reason for failure. There were regulatory delays, manufacturing snafus, strong competition, reimbursement challenges, and issues around physician referral patterns”
Lymphoma Future?

- Fully Humanized Anti CD-20 antibodies
- Alpha Emitters
- Cost Effective Therapies for the elderly
Next Generation anti CD-20

Evaluation of Next-Generation Anti-CD20 Antibodies Labeled with Zirconium 89 in Human Lymphoma Xenografts

Jason T. Yoon1, Mark S. Longtine2, Bernadette V. Marquez-Nostra3 and Richard L. Wahl2

J Nuc Med Jan 18, 2018, epub
Astatine-211 conjugated to an anti-CD20 monoclonal antibody eradicates disseminated B-cell lymphoma in a mouse model


Blood
Volume 125(13):2111-2119
March 26, 2015
Radiopharmaceutical Therapies

- Overall limitation is delivery of radiopharmaceutical to the tumor limiting efficacy.
- Some agents have therapeutic margins large enough to be effective without sophisticated imaging and dosimetry.
- If therapeutic margins are low, stem cell support can be required.
- Second organ toxicity can occur in patients with transplant and appear to be more common if no dosimetry is done.
Proper Training for Radiopharmaceutical Therapy

- Radiology
- Nuclear Medicine
- Radiation Oncology
- Medical Oncology
- Medical Physics
- Pharmacists
- Business?
Opportunities

• Exploration of targets in cancer
• Exploration of targets in non-malignant diseases—e.g. arthritis
• Radioisotope supply and chelation methods
• Regional delivery approaches
• PET and SPECT based dosimetry vs Biological read out
• Understanding of toxicities and patient factors leading to response/toxicity
• Optimal Clinical Trial designs?
Radiopharmaceutical Therapies

- As single agents, considerable efficacy
- Combinations with other treatments may be essential to result in curative approaches
- Collaboration and integration of RPT with more standard oncologic Rx is necessary
- A cadre of trained therapeutically oriented nuclear medicine specialists is required
- Incentives to use RPT should be aligned with health care system
- Dosimetry based Rx is likely to become more standard over coming years.
• Acknowledgements:

• Mark Kaminski
• Ken Zasadny
• Heather Jacene
• Eric Frey
• George Sgouros
• Lode Swinnen
• Ian Flinn
Quality Considerations for Theranostic Radiopharmaceuticals-Radionuclides and Pharmacophore Ligands

John K. Amartey, Ph.D.
FDA/CDER
Office of Pharmaceutical Quality
Office of New Drug Products
Outline

• FDA theranostic approvals: - Ga-68 DOTATATE and Lu-177 DOTATATE
• Pharmacophore ligands of interest - quality attributes
• Production of radionuclides of interest for nuclear theranostic application
Introduction

• Nuclear *theranostic* integrates *diagnostic* and *therapeutic* functions within the same molecular structure except for the radionuclide.

• In oncology it is based upon radiolabeling of cancer type-specific biomarker, which allows precise molecular imaging.

• Generally, biodistribution of the diagnostic and therapeutic radiopharmaceuticals are similar, but the effective half-lives may differ.
Ga-68 DOTATATE

• An approved kit for the preparation of Ga-68-DOTATATE (approved by FDA in 2016)

• Ga-68-DOTATATE is a diagnostic radiopharmaceutical targeting neuroendocrine tumors

• Commercial generators have been qualified for use with the kit - radiolabeling to be performed at the local radiopharmacies
Lu-177 DOTATATE

• Lu-177-DOTATATE was approved in 2018 for treatment of neuroendocrine tumors
  – Manufactured and supplied as a finished dosage form

• Ga-68 DOTATATE has been used for selection and assessment of patients for Lu-177 DOTATATE treatment and other therapies
  – Increased use of Ga-68 for other common tumor types has created stress for supply chain
  – FDA continues to work with stakeholders and governmental agencies to mitigate any radioisotope shortages (Ge-68 and Ga-68)
Ga-68 and Lu-177 DOTATATE

• The pharmacophore ligand is the same (DOTATATE) in these two products
  – DOTATATE is a somatostatin (SST) analog linked to DOTA, a metal chelator (strongly chelates Ga-68 and Lu-177 respectively)
  – Selective to the SST Receptor-2
  – These receptors are highly expressed in neuroendocrine and other tumors, but at low levels in some normal tissues

(DOTA = 1,4,7,10-Tetraazacyclododecane-N,N’,N’’,N’’’-tetraacetic acid)
Some Quality Attributes of the Pharmacophore Ligands

- Synthesis and structure elucidation data (spectroscopic, etc.)
- Chemical purity
- Enantiomeric purity
- Biologically compatible counterion (e.g. acetate)
- Residual solvents
- Water content
- Elemental impurity control (Cu, Fe, Zn, etc.)
- Stability information
- Microbiological control
Production of Ge-68*

• Parent radionuclide for the manufacture of Ge-68/Ga-68 generators
  – Proton irradiation of target in a cyclotron
    • Pure gallium as the target material
      – Purity should be controlled
    • An alloy (such as of gallium and nickel)
      – Composition should be specified and controlled
  – High quality target material required
  – There are limited number of suppliers of the radionuclide

Generator Produced Ga-68

• The Ge-68 (parent) radionuclide for generator derived Ga-68 (daughter)

• Ge-68 ($t_{1/2}$ 270.8 days); Ga-68 ($t_{1/2}$ 68 minutes)
  – Ge-68 is absorbed on a solid support and decay to Ga-68
  – Ga-68 is eluted from the generator with HCl solution
  – Ge-68 breakthrough limit $\leq 0.001\%$ (Ph. Eur.)
Generator Produced Ga-68

• cGMP generators (for NDA submissions)
  – Generator(s) is qualified with the proposed kit
  – Type II DMF or complete CMC may be provided in the NDA

• Non-cGMP generators may be used for IND studies
  – DMF or certificate of analysis (COA) is adequate
Cyclotron Produced Ga-68*

- Cyclotron production of Ga-68 is by proton irradiation of:
  - A liquid target material (e.g. Zn-68 solution)
  - A solid target material (e.g. Zn-68 foil or plated Zn)
- Target materials and target preparation should be standardized and well controlled
- The Ga-68 solution should be qualified with approved kit(s) or established (well characterized) ligand(s)

(*Pandey et al. 2014; Zeiler et al. 2019)
Cyclotron Produced Ga-68 contd..

• Some advantages
  – GBq quantities of radioactivity may be attained with the technology
  – Readily available Ga-68 for radiolabeling
  – No Ge-68 breakthrough impurity present
Cyclotron Ga-68 Regulatory Considerations

– Relevant radionuclidic impurities should be justified for safety and controlled

– Equivalency of the generator and cyclotron produced Ga-68 chloride solution should be established
  • Successfully and consistently label approved kit(s) with acceptable specifications for the drug product

– There is a Ph. Eur. monograph for generator produced Ga-68 (and a draft monograph for the cyclotron product)

– New Ga-68 sources to an approved product are added through prior approval supplement
Production of Lu-177

• Lu-177; $T_{1/2} = 6.67$ days; $\beta^-$-and $\gamma$-emitter
• There are two established methods for production of the radionuclide in a reactor
  — Direct method: thermal neutron bombardment of enriched Lu-176 to generate Lu-177 (carrier added)
    • Control of Lu-177m radionuclidic impurity
  — Indirect method: thermal neutron bombardment of enriched Yb-176 to produce Yb-177 which in turn decays to Lu-177 (no carrier)
  — Reference supporting DMFs in the application if available with letter of authorization

Summary

• Ga-68 and Lu-177 are two examples of radionuclides of theranostic importance
  – Alternative production of Ga-68 is needed to improve availability
  – The need to develop other theranostic radionuclides (positron, beta-gamma and alpha emitters)

• Development of pharmacophores for other diseases is desired (e.g. PSMA ligands for prostate cancer)
  – These pharmacophores should have acceptable quality attributes to be effective for their intended use
    (Guidance for Industry ICH Q3A and Q3B(R2))

• Nuclear theranostic pairs have similar chemical structures, except for the radionuclide, and have similar biodistribution and effective half-lives may differ.
Characterization of Metal Complexes

Chris Galliford, Ph.D.
FDA/CDER
Office of Pharmaceutical Quality
Office of New Drug Products
Characterization of Metal Complexes

- The purpose of this short presentation is to illustrate some optimal practices for developing CMC information that will support IND applications and hopefully future NDA submissions for new radiometal-based imaging and/or theranostic agents.

- To support an IND application, the identity of the radiometal chelate should be adequately characterized. Where possible, the identity of the complex should be supported by analytical data obtained from its corresponding non-radioactive analog.

- For example, if radio-HPLC is used in the release specifications for a chelated metal drug; a high purity, fully characterized metal complex should serve as the reference standard. For example:

  \[
  \text{radiopharmaceutical} \quad \begin{array}{c}
  \text{M}^{\text{hot}} \\
  \end{array} \\
  \begin{array}{c}
  \text{cold complex (non-radioactive)} \\
  \text{for characterization studies}
  \end{array}
  \]

- The importance of adequate characterization will be illustrated in the following case studies.
Case Study 1: *Diastereoisomers in the carbon backbone of the drug substance*

A substituted pyclen-based metal chelate with multiple stereogenic centers in the substituted side chain:

- The manufacturing process begins with racemic starting material, so diastereoisomers are already present prior to chelation of the metal.
- In the early stages of drug development, chelation generated a mixture of isomers as the drug product. An analytical HPLC method was used to determine *the ratio of isomers in the mixture*.
- Using this method, each batch could then be manufactured with a release specification for the range of isomers in the mixture, thus ensuring batch to batch reproducibility and manufacturing consistency.
Case Study 1: *Diastereoisomers in the carbon backbone of the drug substance*

- As the candidate drug advanced through clinical development, analytical and later preparative HPLC methods were developed to separate the isomers.
- These methods were developed using the cold complex (i.e. the analytical reference standard) which led to a single chelate being selected as the drug candidate.
- The initial mixture contains four main isomers (A to D).
- Formation of some chelates appears to be favored.
- Therefore, the release specifications include a range for the ratio of isomers A:B:C:D.
68Ga generators are an increasingly popular method to develop new radiopharmaceuticals. However, after chelating gallium, it is possible that isomers will then exist around the structure. For example, in the case of HBED chelates, there are three distinct isomers. Each individual isomer is a discrete chemical entity and may have different kinetic and thermodynamic stabilities.

The isomers may also undergo chelation at different rates and may also interconvert after their formation, introducing a risk to the reproducibility of the drug product from batch to batch.

Therefore, we strongly recommend characterizing the mixture of isomers so that a ratio of isomers can be measured and verified from batch to batch and also between all manufacturing sites for a given study drug.
Case Study 3: *Drugs with multiple sites for chelation*

A ligand-targeted theranostic agent that contains a site for chelating an imaging agent (in this case $^{68}$Ga) and a second site for chelating a radiometal intended for radiotherapy:

- From a CMC perspective, the site of chelation is slightly ambiguous, and therefore, a fully characterized reference standard of the Ga-chelate would be needed to support the identity of the $^{68}$Ga-HBED-chelated drug as drawn.

- In this case, there is also a risk of radiometal translocation from one chelating group to the other that should be addressed and controlled in the QC strategy at the end of synthesis and also during stability.
Case Study 4: *Drugs with multiple sites for chelation*

Peptide with multiple non-equivalent NOTA sites for chelation:

- Despite being a peptide, the drug substance is not a protein as it is less than 40 amino acid residues in length.

- As well as an ambiguous site of chelation, radiosynthesis is highly likely to result in a mixture of different mono, di and tri-chelated drug substances. As in the previous example, there is also a risk of radiometal translocation. These quality issues need to be controlled.

- In this case, the sponsor worked diligently to provide the ratio of different chelates, using both HPLC and uHPLC to further separate the mixture.

- *From a CMC perspective, any potential variability in the drug product is adequately controlled.*
Summary

- The structure of a radiometal chelate should be adequately supported by a fully characterized non-radioactive reference standard.

- During early development, if the drug exists as a mixture of isomers, the ratio of isomers should be identified and controlled so that the same drug is administered to patients from batch to batch. It is generally not necessary to submit identity information for each isomer at this stage.

- As drug development proceeds, analytical method development should also evolve, particularly through the use of cold chemistry.

- Advanced chromatographic techniques such as HPLC and uHPLC can be used to separate and characterize mixtures of closely related structures. We encourage the use of these techniques to gain as much information about the different complexes as possible.

- In general, with a robust analytical method in hand, an appropriate r-TLC method may still be used to release a drug product, provided it has been adequately validated by an appropriate HPLC-based method.

- The goal of the analytical method is not only to release individual batches of drug, but also to ensure a reproducible drug product mixture so that the same drug is administered to patients from batch to batch.
Radionuclide Availability and Novel Radionuclides

Are we there yet?

Cathy S. Cutler Ph.D.

Medical Isotope Research and Production Program

Collider Accelerator Dept.
Outline

• What’s out there
• Current status of Technetium-99m
• Status of Ge-68 availability
• Process on making alpha emitters availability
Blue available
Research/planning be produced
Yellow commercially available

11C PET
18F PET
44Sc PET / 47Sc β− therapy
45Ti PET
52,54Mn PET
55Co PET
64Cu PET / 67Cu β− therapy
68Ga PET / 67Ga Auger therapy
86Y PET / 90Y β− therapy
89Zr PET
90Nb PET
99mTc SPECT / 94mTc PET
103mRh Auger therapy
111In SPECT
119Sb Auger / 118Sb PET / 117Sb SPECT
124I PET / 125I Auger therapy
149Tb Alpha therapy / 161Tb β− therapy
165Er Auger therapy
177Lu β− therapy
203Pb / 212Pb Alpha therapy
213Bi Alpha therapy
223,224Ra Alpha therapy
225Ac Alpha therapy
227,228Th Alpha therapy
Providing for US Medical Needs

- Tc-99m remains the most frequently used radioisotope in more than 40 million diagnostic studies performed annually.
- US uses over 50% of the world’s Tc-99m supply and had no US supply.
- US Government has nonproliferation concerns regarding use of HEU.
- Shortages of Mo-99 in 2009 and 2010 due to the unexpected shut down of two major production facilities highlighted the need for new, non-HEU based Mo-99 production in the US.
Reactor/Generator Supply Model

Issues:
- Economics/subsidies
- Politics/misuse
- Social/environmental
- Single point of failure
- Capacity

Centralized Production ➔ Processing ➔ Generator Manufacturer ➔ Radiopharmacy ➔ Clinic
Global Molybdenum-99 (Mo-99) Supply Matrix

- The majority of the world’s supply of Mo-99 comes from six multi-purpose research reactors.
- These 6 reactors around the world produce >98% of the Mo-99.
- There are four primary processors using these reactors to produce Mo-99.

All photos used with permission of individual reactor operators.
Current U.S. Mo-99 Supply Matrix;
(NRU ended production Oct 2016 & Standby operations 2018)

Note: 1) designates LEU-produced Mo-99
2) designates HEU-produced Mo-99
3) designates non-HEU/LEU produced Mo-99
Curium has Increased Their Mo-99 Production Capacity

- Curium previously processed Mo-99 targets four days a week on two production lines.
- In 2017 began producing six days per week.
- That increased their Mo-99 production to nearly 5,000 Ci per week.
- They are utilizing higher flux positions in the HFR and have access to more irradiation capacity at the MARIA reactor.

Pictures courtesy Curium
ANSTO is Increasing their Mo-99 Production Capacity

• ANSTO has built a Mo-99 processing and waste handling facility outside of Sydney.

• The new facility will increase their capacity from 1,000 Ci to 3,500 Ci per week.

• They just recently received approval of new capacity realizing their goal of mid-2019.

• They have increased production capacity to 1,500 Ci per week.

Pictures courtesy of ANSTO (Australian Nuclear Science and Technology Organization)
NNSA has partnered with US commercial entities since 2009, to accelerate the development of non-HEU technologies to produce US based Mo-99.

DOE/NNSA has provided matching funding opportunities up to $25 M each for development of Mo-99 domestic production methods, not relying on HEU, to 5 projects: BWXT, GE-Hitachi, SHINE, NorthStar and more recently GA-Nordion. Of these only SHINE and NorthStar remain.

Of those projects only two remain:

- NorthStar Medical Radioisotopes, received FDA approval in 2018 (which has two projects ongoing)
- SHINE Medical Technologies

DOE just closed another RFP in which they will award several alternate Mo-99 producers a portion of $60M.
• Issued first Funding Opportunity Announcement (FOA) in 2010 to accelerate commercial projects

• Issued a second FOA in July 2018 for new cooperative agreements
  – Four U.S. companies selected for further negotiations that may lead to new cooperative agreement awards
    - NorthStar Medical Radioisotopes, Beloit WI
    - Shine Medical Technologies, Janesville, WI
    - Northwest Medical Isotopes, Corvallis, OR
    - Niowave, Inc., Lansing, MI

• Each new cooperative agreement award will:
  • Require 50/50 industry cost-sharing
  • Have a period of performance of 3 years
• National Laboratory Support

- Since 2012, NNSA has provided over $100 million in non-proprietary technical support at the national laboratories to 10 companies to accelerate development of a diverse set of Mo-99 production technologies

- Currently, NNSA is providing non-proprietary laboratory support to assist in development of Mo-99 production technologies at:
  - NorthStar Medical Radioisotopes
  - SHINE Medical Technologies
  - Northwest Medical Isotopes
  - Niowave
  - BWX Technologies
  - Coqui Radiopharmaceuticals
  - Global Medical Isotopes Systems
  - Magneto-Intertial Fusion Technologies
  - Eden Radioisotopes
  - Flibe Energy
Global Mo-99 Production Capacities 2016*

* Source: OECD High Level Working Group on Medical Isotopes
Summary—Mo-99

• The increased CURIUM and ANSTO Mo-99 production capacity increases will be a big help to global supply.

• Projects for the conversion to LEU-based targets are progressing well and appear as though they will be completed by the end of 2018 or early 2019.
• NorthStar generator has been approved by FDA and they are supplying to multiple users

• The prospect of additional Mo-99 supply from new market entrant, Shine is till moving forward along

• Multiple players are still moving forward with plans to supply

• The FRM2 and JHR reactors may provide the industry with additional target irradiation capacity

• The current supply outlook for Mo-99 remains good
68Ge/68Ga Generator
Secular Equilibrium

$^{68}$Ge ($T_{1/2} = 280$ d) $\xrightarrow{EC}^{68}$Ga ($T_{1/2} = 68$ min) $\xrightarrow{\beta^+/EC}^{68}$Zn (stable)

- Expiration time: 1.5 year
- Cost: ~$40,000 research grade; ~$60,000 GMP grade (EZ)
- Column: titanium dioxide
- Eluate: 0.1 M HCl
- Radiopharmaceuticals:
  - $^{68}$Ga-NETSPOT®
  - DOTATOC, PSMA

- Generators produced by
  - Eckert Ziegler (EZ); Berlin, Germany;
  - Isotope Technologies Garching (ITG) Germany
  - IDB Holland/iThemba
  - IRE/Galli Eo
68Ge/68Ga Generator
Secular Equilibrium

\[ ^{68}\text{Ge} \quad (T_{1/2} = 280 \text{ d}) \xrightarrow{\text{EC}} \quad ^{68}\text{Ga} \quad (T_{1/2} = 68 \text{ min}) \xrightarrow{\beta^+/\text{EC}} \quad ^{68}\text{Zn} \quad \text{(stable)} \]

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  - Isotope Technologies Garching (ITG) Germany
  - IDB Holland/iThemba
  - IRE/Galli Eo
Ge-68 Production

• Brookhaven National Lab, Brookhaven, NY
• Curium, St. Louis
• Los Alamos National Lab, in-process of Ge-68 production
• Lantheus

• Ga-68 generator shortage was not due to Ge-68 availability

Jehanne Gillo, Director of Department of Energy (DOE) Isotope Program. Dr. Gillo stated on April 2, 2018 that availability of Ge-68 was not the cause of the shortage
Generator Shortage

- SNMMI—letter to FDA
- Due to the 400 elution limit placed on the generator
  - Shortages across the US, *(now increased to 550 elutions)*.
  - Reduced availability on certain times or days to expand the use, and not be completely unavailable
- NETSPOT originally only qualified the Eckert Zigler Generator
- IRE-Galli Eo has now been approved by FDA for use in compounding NETSPOT
Cyclotron Produced Ga-68 contd..

– GBq quantities of radioactivity may be attained with the technology
– Readily available Ga-68 for radiolabeling
– No Ge-68 breakthrough impurity present
Cyclotron Ga-68 Regulatory Considerations

- Successfully and consistently label approved kit(s) with acceptable specifications for the drug product
Production of Lu-177

- Direct method: thermal neutron bombardment of enriched Lu-176 to generate Lu-177 (carrier added)
  - Control of Lu-177m radionuclidic impurity
- Indirect method: thermal neutron bombardment of enriched Yb-176 to produce Yb-177 which in turn decays to Lu-177 (no carrier)
- Reference supporting DMFs in the application if available with letter of authorization
# Radionuclide Properties

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<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{225}\text{Ac}$</td>
<td>10 days</td>
</tr>
<tr>
<td>$^{211}\text{At}$</td>
<td>7.2 hr</td>
</tr>
<tr>
<td>$^{212}\text{Bi}$</td>
<td>60 min</td>
</tr>
<tr>
<td>$^{213}\text{Bi}$</td>
<td>46 min</td>
</tr>
<tr>
<td>$^{212}\text{Pb}$</td>
<td>10.6 hr</td>
</tr>
<tr>
<td>$^{223}\text{Ra}$</td>
<td>11.43 days</td>
</tr>
<tr>
<td>$^{227}\text{Th}$</td>
<td>18.7 days</td>
</tr>
</tbody>
</table>
Actinium-225/Bismuth-213

- Decay of U-233
  - Limited quantity, processing uncertain
  - Current source for DOE-produced Ac-225
- Reactor production
  - Bulk Ra-226 targets can produce useful quantities
  - DOE developing production
- Accelerator production
  - Proton bombardment of Th-230 or Th-232
  - Low yield
  - DOE-funded research measured yields
- Ac-225 from Th-229 cows relatively inexpensive
- High energy (100+ MeV) proton bombardment of Th-232
  - High yield
  - Limited number of accelerators
  - Ongoing development
- Proton bombardment of Ra-226
  - High yield
  - Only requires medium energy cyclotron (peak cross section ~15 MeV)
  - Processing/recycling Ra-226 targets radiologically challenging/expensive
  - Evaluating establishment of production
- Photon bombardment of Ra-226
  - High yield
  - Processing/recycling Ra-226 targets radiologically challenging/expensive
  - Evaluating establishment of production
• Decay of U-232
  • Source for DOE Ra-224 generators
  • Limited quantities available
• Decay of Th-232
  • Source for AREVA Med generators
  • Possibly large quantities from Th reactor fuel fab
• Reactor production
  • Irradiate Ra-226 (see next slide)
  • Large quantities produced
  • DOE developing production
Thorium-227/Radium-223

- Provided as Th-227, Ra-223 or an Ac-227/Th-227/Ra-223 generator
- Ac-227 production
  - Recovery from old sources (e.g., AcBe neutron sources)
    - Current source for DOE-produced Th-227 and Ra-223
    - Reactor production (prior slide)
    - Irradiate Ra-226
    - Large quantities produced
    - DOE developed production
Astatine-211

- Provided as At-211 or from a Rn-211/At-211 generator
- Production of At-211 (7.2 h)
  - $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$
  - Requires moderate energy (peak cross section ~26 MeV) alpha particle beam
  - Need high current beam to provide clinical quantities
- Production of Rn-211 (14.6 h) (in development)
  - Proton spallation of U or Th
  - Requires high energy proton beam
  - Low yield
  - Limited number of accelerators
Summary

– Alternative production of Ga-68 is needed to improve availability
– The need to develop other theranostic radionuclides (positron, beta-gamma and alpha emitters)
– DMF submission in 2020 for both generator and accelerator material
Therapeutic Radiopharmaceuticals in oncology: nonclinical studies to support FIH trials and use of theranostics

Haleh Saber, PhD
Deputy Director
Division of Hematology Oncology Toxicology (DHOT)
OHOP/ CDER

June 2019
Abbreviations

- BW: body weight
- D: absorbed dose
- CNS: central nervous system
- CV: cardiovascular
- FIH: first-in-human
- %ID: percent of injected dose (percent of injected activity)
- mAb: monoclonal antibody
- NC: nonclinical
- OHOP: Office of Hematology and Oncology Products
- RBE: relative biological effectiveness
- T1/2: half-life
  - Te: effective half-life; Tb: biological half-life; Tp: physical half-life
- Tx: treatment
Nonclinical studies in support of FIH studies
  – Toxicology and animal biodistribution studies
    • Described in the draft FDA Guidance

Use of theranostics
Examples of abbreviated nonclinical program, when clinical data are available
Additional information: FIH dose selection and nonclinical studies in support of product approval
Nonclinical (NC) studies in support of FIH studies

• Pharmacology/ proof-of-concept

• Safety pharmacology (CNS, CV, respiratory)
  – Stand-alone studies usually not needed
  – Assessment through:
    • Biodistribution study (information re: radiation)
      – Distribution of radioactivity into CNS? Potential for anatomic and functional neurological deficits: radiation-induced vascular abnormalities, demyelination, and necrosis in the brain
    • General toxicology (information re: ligand)
Nonclinical (NC) studies in support of FIH studies (cont’d)

• Toxicology studies, to assess:
  – *Ligand related effects
    • General toxicology study in a relevant species
    • One species usually sufficient
    • Frequency of administration: follow ICH S9 (www.ich.org)

* Targeting or chelating agent

• Animal biodistribution, to aid in:
  – Selection of FIH radioactive dose (i.e. for human dosimetry)
  – Assessing toxicities from radiation, based on distribution of radiation and the knowledge of organ-specific radiation toxicities. Toxicity endpoints (e.g. non-sacrificial) may be added.
NC studies in support of FIH studies (cont’d): Animal biodistribution

Needed to support human dosimetry. Usually:

- Single dose administration
- One species
- Activity over time in organs of animals: total # of decays
  - Can be used to estimate time-integrated activity in human organs → needed for estimated absorbed doses in human organs

D values in human organs used to set the FIH dose for human dosimetry
(consider RBEs for equivalent doses when comparing to organ threshold from external beams)

Use human dosimetry data to select the therapeutic dose of the radiopharmaceutical
Animal biodistribution and dosimetry: Use of theranostic pairs \textit{(assume no clinical data)}

- Animal biodistribution done with a therapeutic radiopharmaceutical that is not suitable for human dosimetry?

\[
D = \text{total transitions} \times \text{energy per transition} \times \text{fraction absorbed from source/mass}
\]

\textit{111-In-Peptide against target x}

\textit{90-Y-Peptide against target x}
Theranostic pairs (cont’d)

• Ideally the pair will have comparable PK data in animals and humans, e.g: distribution and T1/2
• Consider the effective T1/2 (Te)
• Assume:
  – The isotope for therapy (animal study): Tp= 30 days
  – The isotope for imaging (human dosimetry): Tp= 7 days
  – The ligand is a peptide: Tb= 1 day
  – Te will be approximately 1 day for both

\[
\frac{1}{T_e} = \frac{1}{T_p} + \frac{1}{T_b}
\]
Abbreviated nonclinical program

• Animal biodistribution studies
  – Estimates at best
  – May underpredict effects in humans
    • Biological targeting moiety may be immunogenic in animals
      – higher clearance \rightarrow reduced \# of transitions

From the draft guidance

“The recommendations in this guidance generally apply to new products with no previous clinical experience...When there is experience with the radionuclide or the ligand components of the radiopharmaceutical being developed, the nonclinical program can be abbreviated as needed, and the FIH dose can be based on clinical data, as appropriate.”
Abbreviated nonclinical program:

*examples*

- Estimation of absorbed doses in human organs
- Human dosimetry
- Human therapeutic phase

131-I- CD20 mAb
90-Y- CD20 mAb
111-In- CD20 mAb

131-I- CD20 mAb’
111-In- CD20 mAb”
Abbreviated nonclinical program (cont’d)

• The ligand used in an investigational radiopharmaceutical is an approved antibody. The Applicant has the right of reference to data in the BLA (e.g. their own data). The antibody will be radiolabeled for targeted delivery of a radionuclide.
  – No short-term or long-term toxicology study of the ligand is needed.

• The sponsor has conducted single dose toxicology studies with the ligand for a diagnostic product. They have decided to pursue treatment of cancer and propose every 6-week administration x 3.
  – No tox study of the ligand needed to initiate the clinical study
Abbreviated nonclinical program (cont’d)

- Pharmacology studies in support of a diagnostic product may be applicable to the therapeutic radiopharmaceuticals
  - e.g. same ligand, same target
  - Fill in the gap: Binding of ligand to target previously demonstrated for the diagnostic product development. Anti-tumor activity to be demonstrated for Tx
preIND meetings

• Engage OHOP if the diagnostic product may be used in a Tx setting
  – At times minor differences, e.g. in the isotope used.
    • Can do one set of studies to satisfy both indications
ADDITIONAL INFORMATION:
- First-in-human dose selection
- Additional nonclinical studies during product development and for approval
First-in-human dose

Consider both

- Radiation administered dose: see slide 6
- Mass dose (cold pharmaceutical): follow ICH S9
Long-term toxicity assessment

• Toxicity from the ligand:
  – Decide whether it is needed based on:
    • The dose per administration, half-life, number and frequency of dosing in patients, and other relevant data
      – Small doses of ligand (mcg ranges)?
      – Ligand with a short half-life (e.g. 1 h) and low frequency of administration (e.g. every 6 weeks)? *FIH-enabling toxicology study of the ligand may be sufficient*
        May justify not conducting a chronic study with the ligand
  – When needed
    • A study in a single species is usually sufficient
    • May follow the recommendations in ICH S9
    • May be combined with the late radiation toxicity study
Long-term toxicity assessment (cont’d)

• Assessment of late-radiation toxicity:
  – Warranted when patients have a long life expectancy that could be affected by late radiation adverse effects
  – Could be based on an integrated summary that takes into consideration the distribution of radiation (from animal biodistribution and human dosimetry studies) and publications describing late radiation effects.
  – When a study is being conducted: see FDA guidance "Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals."
Other toxicology studies

• Genotoxicity, reproductive toxicology, and carcinogenicity studies?
  – Not needed. Alpha, beta, and gamma decays are expected to cause DNA damage → inherently genotoxic and carcinogenic and can damage male and female germ cells and developing embryo/fetus
  – Product label should indicate these risks
Non-Clinical Dosimetry and PK: Alpha-Particle emitters

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Johns Hopkins University, School of Medicine
Baltimore MD
Disclosures

Consultant: Bayer
Scientific Advisory Board: Orano Med
Founder: Radiopharmaceutical Imaging and Dosimetry (Rapid), LLC
Dosimetry/Imaging Role

Radioactive chemotherapy

Pharmacodynamic study
- Utilization/metabolism
- Early stage in development

of no use after drug development
- Treat empirically
- Clinical trials to find optimum

Systemic Radiation Delivery

Essential to implementing patient therapy

Only if validated and found to impact treatment outcome
Biomarkers

- Select patients most likely to respond
- Avoid toxicity
- Tumor biopsy
- Serum sampling
- Genetic and epigenetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials
Dosimetry

- Select patients most likely to respond
- Avoid toxicity
- Quantitative Imaging
- Blood Sampling
- Genetic and epigenetic marker analysis

- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized

- Incorporated in the design of clinical trials
Pre-clinical Studies for RPT

Could be used to:

• Identify unexpected high uptake
• Assess target/normal tissues uptake or TIA ratios assuming pre-clin model that expresses target to which RPT agent binds.
• Project rough normal organ dosimetry in a reference human geometry to help guide clin trial design →Starting Admin Act level
• If needed, collect μ-scale biod/PK in sub-regions of critical organs: kidneys, GI, RM

Should not be used to:

• Project human tumor dosimetry/efficacy
• Establish human MTD
Pre-Clin studies for αRPT

Could be used to:

- If needed, use modeling to extend PK info to tissues not easily sampled or to evaluate impact of tumor burden differences.
- For extreme (or worst) case analysis to guide pre-clin studies and human trial design.
- RBE = 5

Could be used to:

- Identify unexpected high uptake
- Assess target/normal tissues uptake or TIA ratios assuming pre-clin model that expresses target to which RPT agent binds.
- Project rough normal organ dosimetry in a reference human geometry to help guide clin trial design →Starting Admin Act level
- If needed, collect μ-scale biod/PK in sub-regions of critical organs: kidneys, GI, RM

Should not be used to:

- Project human tumor dosimetry/efficacy
- Establish human MTD
Model to Model

Relative concentration (RC):

\[ RC(x) \equiv \frac{[O(x)]}{[WB]} \bigg|_{M1} = \frac{[O(x)]}{[WB]} \bigg|_{M2} \]

- \( RC(x) = 1 \)  \( T^2 \) uniformly distributed in body
- \( RC(x) > 1 \)  \( T^2 \) concentrates in \( x \)
- \( RC(x) < 1 \)  \( T^2 \) is excluded from \( x \)

Assume same kinetics
Where we’ve been

[Graph showing trends in publications by year and type of emitters]
Why RPT is promising

X-Beam

Radiation delivery

Cell death

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Kitiwat Khamwan

Ivan Guan
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Sagar Ranka

Eric Frey
Richard Wahl
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Barjor Gimi
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DOE
Christy S. John, Ph.D.
Office of Clinical Pharmacology/Office of Translational Sciences

June 22, 2019
Outline

• Types of Imaging Agents

• Diagnostic Imaging Radiopharmaceuticals
  – Dose Finding
  – DDI

• Radiotherapeutic Agents
  – Dose Finding
  – DDI
  – Specific Population,
  – QTc

• Conclusion
Overview of Regulated Imaging Drugs

Radiopharmaceuticals

- Microdose (mass dose < 100 ug or <30 nmol for MoAb)

Magnetic Resonance Imaging (MRI)

- Macrodose (mg/gm)

Computed Tomography (CT)

- Macrodose (mg/gm)

Ultrasound (US)

- Bubble/Gases

Optical Imaging

- Macrodose (mg)

Diagnosis (Dx) vs. Therapy (Rx)

- DMIP
- OHOP
Diagnostic Imaging Radiopharmaceuticals

- Single dose administration

- Require high sensitivity and specificity against a standard of truth or positive predictive value

- Dose should be effective in diagnosing a pathology and be safe
Diagnostic Imaging Radiopharmaceuticals

• Single dose pharmacokinetics study
  – Biodistribution
  – Metabolism
  – Elimination/Excretion

• Dosimetry study
  – Identify target organs
  – Assess absorbed radiation doses

• Drug-drug interaction study
Diagnostic Radiopharmaceuticals - Dose Optimization

- Optimal dose selection
  - PD as a surrogate, e.g. SUV, T/B, T/NT

- Image timing window

- Identify optimal dose and imaging window based on PK and PD to be used for pivotal registration trials
Pediatric Dosing: Ga-68-DOTATE

Pediatric dosing is usually weight based (mCi/kg)

- Adult Dose – 200 MBq (5.4 mCi)
- Pediatric dose – 2 MBq/kg (0.054 mCi/kg)
Dosimetry Study

• Identify target organs

• Assess absorbed radiation doses

• Determine effective dose

• For pediatric indication, provide estimated radiation absorbed doses to children of various age groups
Drug-Drug Interaction

Why should a drug interaction be conducted for a single dose diagnostic agent?
Effect of Concomitant Drugs on Imaging- Ioflupane

• DaTscan (Ioflupane I 123 Injection) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS).

• DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy).
Section 7: DRUG INTERACTIONS

- The ioflupane within DaTscan binds to the dopamine transporter. Drugs that bind to the dopamine transporter with high affinity may interfere with the image obtained following DaTscan administration. These potentially interfering drugs consist of: amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, and sertraline. Selective serotonin reuptake inhibitors (paroxetine and citalopram) may increase or decrease ioflupane binding to the dopamine transporter.

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022454Orig1s004lbl.pdf

Sponsor should evaluate the effect of concomitant drugs that work through common mechanistic pathways
Diagnostic Radiopharmaceuticals: Other Studies

- Inhibition or Induction of CYP enzymes – not needed
- Multidose dose safety study – not needed
- QTc prolongation study – not needed
- Patients with organ impairment – not needed
How to determine an optimal “hot” dose and dosing frequency?
An Example- Sponsor Proposed Method

• Starting dose (mCi) selection was based on classical drug dose escalation in non clinical study

• Administered increasing amount of radioactivity to animals

• Determined NOAEL

• Translated to HED, have 10X safety margin- selected dose in mCi for human study
Nonclinical Dosimetry

Non-clinical dosimetry studies extrapolated to humans can be used as a first approximation for radiation absorbed doses for human organs to select a starting human dose.
Radiotherapeutic Agents: Dose Ranging Study

- Conduct FIH PK, biodistribution, dosimetry, and tolerability of single dose in a cohort of 6-8 patients with a diagnostic dose
- Determine radiation absorbed doses to various critical organs
- Conduct multiple doses in target population at different schedules
  - 5 doses of 50 kBq/kg at 2 weeks interval
  - 2 doses of 125 kBq/kg can be given at 5 weeks interval
- Determine dose limiting toxicities (DLTs) and maximum tolerated dose (MTD)
Dose for Radiotherapeutic Agents

• Limits of radiation absorbed doses for systemic therapy are not known.

• Radiation dose limits are adjusted based on tolerated absorbed radiation doses in human organs (e.g., using threshold from external radiation therapy as a starting point (18 Gy for kidney or 2 Gy for bone marrow, etc.), not to exceed prespecified limits.

• Cumulative radiation administered dose should be used to determine the FIH therapy dose when dose fractionation is proposed.
Dose Escalation

• Evaluate clinical response in dose escalation trials (eg. 25, 50, 80 kBq/kg) for four-six doses at interval of X weeks (depends of T_{1/2} of agent) in target population

• Dose expansion cohort can be studied to confirm that the dose selected is appropriate

• Based on totality of data PD, PK, radiation dosimetry, and radiation exposure to critical organs (bone marrow or kidney etc.), safety and efficacy, a dose is selected for registration trial(s)
Radiotherapeutic Agents: Monoclonal Antibodies Conjugated to Radionuclides

- Determine the PK and dose linearity with different doses of “cold MoAb”
  - PK can be linear or non-linear- TMDD

- Determine the affect of “cold antibody mass” on the biodistribution of “hot” conjugate

- Find the optimal “hot” dose for therapy as described earlier
Therapeutic Agent: Drug Interaction Potential

• Perform in-vitro evaluation of drug metabolism by cytochrome P450 enzymes.

• Determine if your drug is substrate of CYP P450 enzymes and drug transporters

• Perform in vivo studies, if necessary

Safety and efficacy of the drug could be altered based on drug interaction impacting drug disposition
Evaluation of QTc Prolongation

QTc prolongation potential for macro-dose therapeutic radiopharmaceuticals, optical imaging and MR contrast agent should be evaluated

- in vitro (HERG channel test)
- clinical study warranted if a positive signal at clinically relevant concentrations is observed
Dosing Recommendations: Specific Populations

• If drug is eliminated by predominantly renal route or hepatic route, do renal function or liver function affect the therapy efficacy and safety results?

• PK study is recommended in patients with mild, moderate and severe renal impairment or patients with hepatic impairment

• FDA Guidances are available for design of PK studies in patients with impaired renal function or impaired hepatic function

• Is a dose adjustment needed in patients with renal or hepatic impairment?
Conclusions

• Wide range of imaging drugs

• Clinical Pharmacology studies vary depending on –
  – Diagnostic intent
  – Therapeutic intent

• Dose optimization is critical
Last But NOT Least

• Early interaction with FDA is encouraged

• More often interaction, open communication is encouraged

• Communication is not only recommended but required!
Acknowledgment

– L. Marzella, M.D, Ph.D.
– A. Rahman, Ph.D.
– H. Saber, Ph.D.
Issues in Radiation Dosimetry: Absorbed-Dose Implications for Safety and Individual Treatment-Planning

Stanley H. Stern, Ph.D.
FDA/CDER Office of New Drugs
Division of Medical Imaging Products

SNMMI Annual Meeting – Categorical Seminar on Theranostics: Regulatory Considerations for Product Development
June 22, 2019, Anaheim, California
Contextual Aspects

- Patients with recurrent, refractory, or metastatic disease?

- To select patients for Tx? According to what criteria?
- To project estimates of tumor dose and off-target dose to normal organs and tissues?
- Fidelity? Dx match to Tx bio-distribute, uptake, retain, excrete?
• Issue: First-in-human (FIH) trials

- “… Sufficient data from animal or human studies…” to calculate “radiation-absorbed dose to the whole body and critical organs....”
- Phase 1 trials “...must include studies...” to “obtain sufficient data for dosimetry calculations”
Extrapolation to human organs via mass-scaling:

\[
\frac{\text{Organ mass}_{\text{Human}}}{\text{Body mass}_{\text{Human}}} \times \frac{\text{Organ mass}_{\text{Animal}}}{\text{Body mass}_{\text{Animal}}}
\]

Ratios are distributed log-normally:

- Median (geom. mean) = 0.43
- Variance (geom.) = 16
“Experimental validation of calculated absorbed doses have indicated agreement within 20–60%...” [of respective reference-organ dose values].

“Calculations have shown...that estimates of absorbed dose to different organs will not generally deviate from actual absorbed doses in patients by more than a factor of three...” [related to variations in biodistribution].

- Patient-to-patient
- Therapy cycle-to-cycle
- Study-to-study
<table>
<thead>
<tr>
<th>Organ</th>
<th>~1%-rate: mortality or organ failure associated with disease</th>
<th>Time to death or organ failure</th>
<th>Threshold (Gy) for ~1%-rate mortality or organ failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Cardiovascular mortality</td>
<td>&gt;10 – 15 y</td>
<td>~ 0.5*</td>
</tr>
<tr>
<td>Brain (carotid artery)</td>
<td>Cerebrovascular mortality</td>
<td>&gt;10 y</td>
<td>~ 0.5*</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renal failure</td>
<td>1 – 15 y</td>
<td>18</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pneumonitis mortality</td>
<td>1 – 7 mo</td>
<td>15 – 18</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly, ascites: possible organ failure</td>
<td>0.5 – 3 mo</td>
<td>30 – 32</td>
</tr>
<tr>
<td>Red marrow</td>
<td>H-ARS mortality</td>
<td>1 – 2 mo</td>
<td>12</td>
</tr>
<tr>
<td>Small intestine</td>
<td>GI-ARS mortality</td>
<td>6 – 9 d</td>
<td>40</td>
</tr>
</tbody>
</table>

*Per ICRP Pub 118, “It is emphasized that great uncertainty is attached” to the thresholds associated with cardio- and cerebrovascular disease.
- Pts ≤ 50 kg, inject 3.7 MBq/kg; > 50 kg, inject 185 – 222 MBq
- A/P whole-body imaging @ 1 h, 1 – 2 d, 2 – 5 d
- For each pt, estimate normal-organ absorbed dose per injection activity via MIRD methodology, if possible with pt organ masses (e.g., from imaging)
- Tx plan for each pt: Reduce cumulative (in 2 cycles) Tx activity to be administered so as not to exceed toxicity threshold-dose to a critical organ
Summary and Conclusion

- Estimation of organ doses extrapolated from animal data
- Human absorbed-dose variability
- Dose thresholds for radiation toxicity associated with the administration of radiopharmaceuticals
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209607s000lbl.pdf

(FDA Reference ID: 4298552).
Efficacy Endpoints for Diagnostics

Betsy Ballard, MD
Division of Medical Imaging Products
Office of Drug Evaluation IV CDER/FDA
Imaging Drug Indications

- Structural delineation

- Disease or pathology detection or assessment

- Functional, physiological, or biochemical assessment

- Diagnostic or therapeutic patient management
Imaging Indications Relevant to Theranostics

• Drug should “detect and locate a specific disease or pathological state in at least one defined clinical setting”
  – Example: Drug detects prostate cancer metastasis in patients with biochemical evidence of disease recurrence

• Drug performance should be evaluated directly in the setting and population of intended clinical use
Endpoint Assessments

• Analytical characterization of diagnostic
  – Individual patient dosimetry, radiation absorbed dose to normal organ and tumor, and biodistribution
  – Determine diagnostic dose, imaging window, image interpretation, safety

• Performance characterization of a diagnostic agent
  – Sensitivity and specificity
  – Positive predictive value
  – False positive/false negative rates
Endpoint Assessments

• Should exceed a pre-determined clinically meaningful threshold

• Show superiority or non-inferiority to an approved comparator

• Blinded, independent central read of images with 2 of 3 readers in agreement

• *Note that evidence for the efficacy of the diagnostic agent might be derived from clinical outcomes of therapeutic studies*
Reference Standards

• Histopathology

• Composite reference standards
  – Combination of histopathology, follow-up from conventional imaging, or clinical follow-up
Clinical Usefulness/Benefit

- Usefulness of the results must:
  - Be inherent
  - Demonstrated in a clinical trial

- A strong drug performance may not have value if there is little or no clinical utility
Parallel development of diagnostic and therapeutic investigational agents

- Analytical characterization of diagnostic, for example
  - In vitro characterization of receptor occupancy
  - Proof of concept in animal studies
    - Receptor binding, biodistribution
    - Estimated human dosimetry
  - Accuracy estimates
Parallel development of diagnostic and therapeutic investigational agents

• Data from a diagnostic agent development may be used to inform the therapeutic development
  – Biodistribution and dosimetry
  – Estimates initial first in human dosing
  – Set dose limits to off target organs
Parallel development of diagnostic and therapeutic investigational agents

- Clinical outcome data from therapeutic studies that could be leveraged for the diagnostic development
  - Patient selection
  - Response to therapy
  - Predictive (enrichment strategy for response or toxicity)
Recent CDER Experience

• Developed as an independent diagnostic agent
  – $^{68}$Ga Dotatate (Netspot): localization of SSTR + NETs
  – post-market off-label use for patient selection, clinical management, and response to treatment (Hope et al, 2017)
  – $^{64}$Cu-Dotatate

• Developed as an independent therapeutic agent
  – $^{177}$Lu Dotatate (Lutathera): treatment of SSTR + GEPNETs
  – No dosimetry requirement for marketing
In Conclusion

Diagnostic and therapeutic agents can be developed efficiently in parallel with cooperation between the sponsor, DMIP, and disease specific OHOP team with early and frequent collaboration.

Data from the development programs can be leveraged to choose endpoints, determine indication statements, and inform labeling.
Guidance Documents

FDA webpage

Guidances:
Clinical Trial Imaging Endpoint Process Standards Guidance for Industry
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications
Guidance for Industry Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies
Guidance for Industry, Investigators, and Reviewers Exploratory IND Studies

PET FDA page
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm
multiple documents available on this page (scroll to bottom of page)

Guidances
Guidance Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs
Design Basics for Therapeutic Clinical Trials

Ashley Ward, MD
Office of Hematology and Oncology Products
Agenda

- FDA approval standards
- Endpoints for oncology clinical trials
- Other important trial design issues
  - Type I error
  - Adjusting for multiplicity
  - Sample size considerations
  - Reducing bias
  - Assessing contribution of effect
FDA Approval Standards

• Requires **substantial evidence of efficacy and safety**

• **Regular approval**
  – Based on direct measure of clinical benefit, or effect on established surrogate of clinical benefit
  – Interpreted to mean how patient “feels, functions or survives”

• **Accelerated approval** (for serious and life-threatening conditions)
  – Based on surrogate or intermediate clinical endpoint *reasonably likely* to predict benefit
  – Requires meaningful improvement over available therapy
  – May require post-approval clinical trial(s) to verify benefit
Potential Endpoints in Oncology Trials

- Overall survival
- Symptom endpoints
- Disease-free or event-free survival
- Progression-free survival
- Objective response rate
- Complete response rate

For more information, see “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry” at:
https://www.fda.gov/media/71195/download
# Direct Measures of Clinical Benefit

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Overall Survival** | Randomized trial | • Easily and precisely measured  
• Based on objective and qualitative measurement | • May be affected by crossover or the availability of effective salvage regimens  
• Needs longer follow-up  
• Includes non-cancer deaths |
| **Symptom Endpoints** | Randomized trial | • Generally assessed earlier and with smaller sample size than overall survival | • Blinding is important for assessing the endpoint  
• Potentially subject to assessment bias  
• Lack of validated instruments  
• Definitions vary among studies  
• Balanced timing of assessments among treatment arms critical |
# Established* Surrogates of Clinical Benefit
(*in some indications)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Disease-Free or Event-Free Survival | • Randomized trial  
• Blinded independent central review               | • Generally assessed earlier and with smaller sample size than overall survival  
• Generally based on objective and qualitative measurement               | • Potentially subject to assessment bias  
• Definitions vary among studies  
• Balanced timing of assessments among treatment arms is critical  
• Includes non-cancer deaths |
| Progression-Free Survival     | • Randomized trial  
• Blinded independent central review               | • Generally assessed earlier and with smaller sample size than overall survival | • Potentially subject to assessment bias  
• Definitions vary among studies  
• Frequent radiological or other assessments  
• Balanced timing of assessments among treatment arms is critical  
• May not always correlate with survival |
Surrogate Endpoints Reasonably Likely to Predict Clinical Benefit*
(*in some indications)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Objective Response Rate, or Complete</td>
<td>• Randomized or single arm trial</td>
<td>• Generally assessed earlier and with smaller sample size than overall survival</td>
<td>• Definitions vary among studies</td>
</tr>
<tr>
<td>Response Rate**</td>
<td>• Blinded independent central review</td>
<td>• Effect on tumor attributable to drug(s), not natural history</td>
<td>• Frequent radiological or other assessments</td>
</tr>
</tbody>
</table>
<pre><code>                                                                                           | • Generally based on objective and qualitative assessment                  | • May not always correlate with survival |
</code></pre>
**Type I Error**

- Null hypothesis: no difference between two drugs
- Alternative hypothesis: there is a difference between two drugs
- Type I error = the probability that one accepts the alternative hypothesis when the null is true (i.e. that you decide a drug is more effective than the comparator, when in reality, it is not)
**Multiplicity**

- In general, FDA requires a Type I error of 5% in pivotal trials
  - If truth is that there is no difference between two drugs, and we repeated experiment many times, 5% of the time, we would conclude there is a difference

- Type I error can become inflated if a test is performed many times without adjustment ("multiplicity")

- Example: You run an experiment to determine if the probability of getting a heads on a coin flip is exactly 50%
  - Plan to flip the coin 100 times and use Type I error of 5%
  - But you get impatient and decide to run the test every 10 flips
  - With each 10 flips, the test has a type I error of 5%
  - Over 100 flips, you will have a total type I error of 40% (40% of the time, you would decide that the probability of heads was different than 50% for a fair coin)
Adjusting for Multiplicity

• In the coin flipping example, the tests performed every 10 flips are called interim analyses.

• In clinical trials, multiplicity occurs under the following scenarios:
  – More than one primary endpoint
  – Interim analyses
  – Testing secondary endpoints

• The protocol must therefore specify a plan to adjust for multiplicity.
Sample Size Considerations

• Targeted treatment effect: How big of an effect on OS are you looking for?
  – As the targeted treatment effect increases, required sample size decrease
  – i.e., takes fewer patients to show a bigger difference

• Power: the probability of detecting the targeted treatment effect, assuming it is “true”
  – As the power increases, required sample size increases
  – i.e., takes more patients to be more certain you won’t commit Type II error (false negative)

• Other considerations:
  – Number of endpoints
  – Length of study
  – Anticipated accrual rate and event rate
  – Number of interim analyses
  – Feasibility
Reducing Bias in Clinical Trials

• Randomization
• Blinding
• Pre-specification
  – Analyses
  – Populations within the trial on which the analyses are to be conducted
  – Rules for discontinuing therapy
• Independent review of response
• Financial disclosures
Contribution of Effect

- Hypothetical trial design:
  - Chemotherapy + Drug X
- Does not isolate effect of Drug X
  - Is chemotherapy necessary? Would Drug X alone be effective?
- Ideal design would have three arms:
  - Chemotherapy, Drug X, and Chemotherapy + Drug X
- In such a trial, we would want to see that the combination is better than both monotherapies
  - In some cases, sponsor can make an argument based on previous clinical or non-clinical data that Drug X alone would not be effective
  - In such a case, it may be considered unethical to randomize patients to a Drug X monotherapy arm
Acknowledgements

Many thanks to:

- Denise Casey, MD
- ‘Lola Fashoyin-Aje, MD, MPH
- Jonathan Vallejo, PhD

For allowing me to borrow and adapt the slides they created for the Accelerating Anticancer Agent Development and Validation (AAADV) workshop core curriculum earlier this year.
Theranostics: Clinical Development
Safety Considerations

Denise Casey, MD
Office of Hematology and Oncology Products
Radiopharmaceuticals: Safety Considerations

• Acute toxicity
  – Hematologic
  – Renal
  – Hormonal (neuroendocrine tumors)

• Longterm toxicity
  – Hematologic
  – Renal
  – Secondary malignancies

• Risk mitigation
  – Safety monitoring and supportive care
  – Labelling and Post-marketing requirements
Recent Radiotherapeutic Approvals

Lutetium Lu-177 dotatate (LUTATHERA®)

- for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Iobenguane I-131 (AZEDRA®)

- for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.
General Considerations

- Long-term toxicity should be considered in the benefit:risk assessment for radiolabeled products, especially when intended to treat indolent growing tumors.

- Dosimetry can mitigate risk but might not predict individual susceptibility to toxicity related to genetic and other factors not considered in dosimetry modeling.

- A guiding principle for dose-finding studies is to determine the minimal effective rather than maximum tolerated dose.
Bone Marrow Toxicity
Acute/Subacute Hematologic Toxicity

- Bone marrow is radiosensitive and a dose-limiting organ
- Maximum absorbed dose of 2 Gy to BM
  - Potential binding of products to bone marrow stem cells
  - Cross-dose from source organs and tumors
  - Variation in bone marrow absorbed dose between patients
- Acute/subacute myelosuppression is generally tolerable
- Risk factors associated with grade 3 or 4 toxicity:
  - Age > 70 yrs
  - Prior chemotherapy
  - Creatinine clearance
  - Bone metastases
I-131 Iobenguane: Hematologic Toxicity

• Safety data from 88 patients with recurrent or unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma
  – Grade 3-4 thrombocytopenia: 50%
  – Grade 3-4 neutropenia: 59%; Grade 4=16%
  – Grade 3-4 anemia: 24%
  – Febrile neutropenia: 5%

• Blood count nadirs occurred 4 – 8 weeks following infusion
  – Median time to nadir: platelets - 4.3 wks, neutrophils - 5.4 wks, Hb: 6.7 wks

• Median time to recovery was 2 wks for platelets and neutrophils

• 24% of patients received red cell transfusions; 16% received platelets

• Approximately 9% required G-CSF and 3% received erythropoietin
Lutetium Lu-177 dotatate: Hematologic Toxicity

- NETTER-1: 223 patients with progressive, midgut carcinoid tumors randomized to Lu-177 dotatate (n=111) or LA octreotide (n=112)
- Myelosuppression was common

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)</th>
<th>Long-Acting Octreotide (60 mg) (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>Anemia</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>
Longterm hematologic toxicity: Myelodysplasia and Leukemia

- Risk factors for chronic toxicity
  - Duration from first to last cycle of PRRT
  - Prior chemotherapy and/or RT
  - Platelet toxicity during PRRT
  - Tumor invasion of marrow

- Lutetium Lu-177 dotatate
  - NETTER-1 (n=111): 3% pts developed MDS
  - ERASMUS (n=811): 2% pts developed MDS
    <1% pts developed acute leukemia

- Iobenguane I-131
  - 6/88 (7%) developed MDS or acute leukemia at 9 months to 7 years
  - All patients received prior chemo or radiotherapy
Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with $^{177}$Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors (Bergsma et al, Journal of Nuclear Medicine 2018)

- 4% (11/274) patients developed PHD
- RR of 2.7 based on registry data
- Median latency period of 41 mo
- No correlation with gender, age, bone mets, prior chemotx, prior EBRT, renal fx, heme toxicity during PRRT
Renal Toxicity
Radiopharmaceuticals: Renal Toxicity

- Kidney uptake of radiopeptides can cause nephrotoxicity after PRRT.
  - Radiopeptides reabsorbed in the proximal tubule.
  - Renal retention causes a high radiation dose to kidneys.
Radiolabeled SSAs: Renal Toxicity

- Acute kidney damage occurs 2 weeks to 6 months after PRRT
- Chronic kidney damage less common
  - damage to glomeruli, tubular atrophy and interstitial fibrosis
- Risk factors: baseline anemia, HTN, diabetes
- Risk of radiation nephropathy dependent on the radionuclide
  - $^{90}$Y-octreotide has higher energy emission and longer penetration range than $^{177}$Lu-octreotide
- Amino acid co-infusion-competitive inhibition at PT
- Lutetium Lu-177 dotatate (NETTER-1)
  - Gr 3-4 creatinine elevation was 1%
  - No meaningful difference between arms for creatinine or creatinine clearance at median follow up of 19 mos.
Neuroendocrine Tumors: Acute Hormonal Crises

• NETs have characteristic symptoms based on excessive and uncontrolled release of metabolically active substances

• Carcinoid crisis = medical emergency
  – Manipulation of a carcinoid tumor or pheochromocytoma - anesthesia, procedures, chemotx
  – Flushing, hypotension, extreme changes in BP, diarrhea, bronchoconstriction, arrhythmias

• “Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3] octreotate” (de Keizer, 2008)
  – 6/479 pts (1%) with GEPNET or pheochromocytoma experienced hormonal crises during cycle 1
Radiopharmaceuticals: Risk Mitigation

- Choice of radionuclide
- Eligibility criteria
- Individual dosimetry
- Safety monitoring during infusions
- Amino Acid coinfusion
- Supportive care
  - Antiemetics
  - Stem cell infusion protocols
- Sufficient safety follow-up
Risk Mitigation: Post Marketing Requirements

• Objectives
  – To conduct further safety studies of patient populations at highest risk
  – To provide evidence-based dose modifications and monitoring recommendations

• PMRs for Iobenguane I-131 and Lutetium Lu-177 dotatate
  – Requirement to submit cumulative safety analyses after 5 and 10 years of follow-up to characterize the risks of MDS, leukemia and other secondary malignancies
  – Lu-177 dotatate has a PMR to investigate longterm renal toxicity
Summary

• Radiopharmaceuticals have an important role in the targeted treatment of various cancers.

• The benefit-risk assessments for approved radiopharmaceuticals have been positive, and the safety profiles often compare favorably to cytotoxic chemotherapy.

• There are clinical practices to safely administer radiopharmaceuticals and mitigate risk for acute and chronic radiation-associated toxicity.

• Longterm follow up of patients is essential.
Therapeutic Approval Experience

Ashley Ward, MD
Office of Hematology and Oncology Products
Agenda

Discuss the following radiopharmaceutical therapeutic approvals:

• Ibritumomab tiuxetan (February 2002)
• Radium Ra 223 dichloride (May 2013)
• Iobenguane I 131 (July 2018)
• Lutetium Lu 177 dotatate (January 2018)
Indium In-111 ibritumomab tiuxetan and Yttrium Y-90 ibritumomab tiuxetan

Indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell lymphoma, including patients with Rituximab-refractory follicular NHL

Mechanism of action:
- Monoclonal antibody directed against CD20 linked to the chelator tiuxetan, which provides a high affinity chelation site for In-111 and Y-90
- Beta-particle emitter
- Also may have some antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity
Registrational Study Design (106-04)

N=143 patients with:
- Relapsed or refractory low-grade follicular B-cell NHL, or transformed NHL
- Measurable disease

Stratified by:
- Histology

Randomized 1:1

Y-90 Ibritumomab + Rituximab
Rituximab 250 mg/m² and 5.0 mCi In-111 Ibritumomab

Then, 7 days later:
Rituximab 250 mg/m² and 0.4 mCi/kg Y-90 Ibritumomab

Rituximab
375 mg/m² IV once weekly x 4

Primary endpoint: ORR by blinded independent review

Supportive study 106-06: Open-label, single-arm, multi-center study in 57 patients with advanced follicular B-cell NHL who were refractory to rituximab
- Received same regimen as patients on Study 106-04
Results: Improved ORR and CR Compared to Rituximab Alone

<table>
<thead>
<tr>
<th></th>
<th>Study 106-04</th>
<th>Study 106-06</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibritumomab</td>
<td>Rituximab</td>
</tr>
<tr>
<td>(n = 64)</td>
<td>(n = 66)</td>
<td>(n = 54)</td>
</tr>
<tr>
<td>Overall response</td>
<td>83%</td>
<td>55%</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of</td>
<td>14.3 months</td>
<td>11.5 months</td>
</tr>
<tr>
<td>response (95% CI)</td>
<td>[1.8 – 47.6+]</td>
<td>[1.2 – 49.7+]</td>
</tr>
<tr>
<td>Median time to</td>
<td>12.1 months</td>
<td>10.1 months</td>
</tr>
<tr>
<td>progression (95% CI)</td>
<td>[2.1 – 49.0+]</td>
<td>[0.7 – 51.3+]</td>
</tr>
</tbody>
</table>
Notable Development Issues

• Multiple other studies conducted prior to beginning the registrational trial to work out the dose and regimen in patients with and without thrombocytopenia at baseline

• Different entities used for dosimetry and therapy because at the time, gamma emission was required for imaging

• Dosimetry: testes and GI tract are highest exposed organs

• Oncology Drugs Advisory Committee discussion focused on level of evidence; regular approval for rituximab-refractory population and accelerated approval for broader relapsed/refractory population

• Immunogenicity (chimeric mAb)

• Uncertain long-term safety
  – potential for secondary malignancies (MDS/AML)
  – addressed through post-marketing requirements
Radium Ra-223 dichloride

*Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease*

Mechanism of action:
- Alpha-particle emitter
- Mimics calcium, forms complexes with hydroxyapatite at areas of increased bone turnover (e.g., bone metastases)
- Causes double-strand DNA breaks in adjacent cells
- Short alpha-particle range limits damage to surrounding normal tissue
Registrational Study Design

N=922 patients with:
- Symptomatic\(^1\) CRPC
- ≥ 2 bone metastases
- No visceral metastases

Stratified by:
- Total ALP (< 220 U/L / ≥ 200 U/L)
- Use of bisphosphonates (y/n)
- Prior use of docetaxel (y/n)

Randomized 2:1

Radium-223 dichloride (50 kBq/kg)
+ best standard of care\(^2\)
6 IV administrations, 4 weeks apart

Placebo
+ best standard of care\(^2\)
6 IV administrations, 4 weeks apart

3 year F/U
Primary endpoint: overall survival
No scheduled radiographic assessments

---

\(^1\) Defined as regular use of analgesics for cancer-related bone pain or treatment with EBRT for bone pain within 12 weeks before randomization

\(^2\) Best standard of care included: local EBRT, corticosteroids, antiandrogens, estrogens, estramustine, and ketoconazole
Results: Improved Overall Survival Compared to Placebo

Survival results supported by delay in time to first symptomatic skeletal event on Ra-223 arm (mostly XRT to bone mets)

Results of updated analysis presented. Results of interim analysis were statistically significant, with $p = 0.00185$
Notable Development Issues

- Six meetings with the FDA prior to IND submission to reach agreements on nonclinical toxicology studies, starting dose, and dosimetry design
- Dosimetry: bone, red marrow, and intestine are highest exposed organs
- Previous approvals of radiopharmaceuticals for bone metastases indicated for pain reduction (no effect on cancer itself); this one improved overall survival
- Uncertain long-term safety
  - bone marrow suppression
  - potential for secondary malignancies
  - addressed through post-marketing requirements
- Dose not optimized
  - Lowest quartile weight patients had inferior efficacy
  - Dose-dependent improvements in some efficacy endpoints observed without apparent increase in toxicity
  - Post-marketing requirement to conduct a dose-optimization study
Indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy

Mechanism of action:
- Radioactive molecule similar in structure to norepinephrine and subject to same uptake and accumulation pathways
- Beta- and gamma-particle emitter
- Radioactive decay causes cell death and tumor necrosis
Registrational Study Design (IB12B)

N=74 patients with:
- Iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma
- Requires therapy and ineligible for curative therapy
- Age ≥ 12 years

Iobenguane I-131
Dosimetric dose of 5-6 mCi for patients weighing > 50 kg and 0.1 mCi/kg for patients weighing ≤ 50 kg

Then
Up to two therapeutic doses, 3 months apart, of 500 mCi for patients weighing > 62.5 kg and 8 mCi/kg for patients weighing ≤ 62.5 kg

Primary endpoint:
Proportion of patients with ≥ 50% reduction of all antihypertensive medications lasting at least 6 months
ORR also assessed
## Results: Reduction of antihypertensive medications and overall tumor response

<table>
<thead>
<tr>
<th></th>
<th>At least the first therapeutic dose</th>
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<tbody>
<tr>
<td><strong>N=68</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reduction of all antihypertensive medications by at least 50% maintained for at least 6 months, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>17</td>
</tr>
<tr>
<td>Proportion of patients (95% CI$^a$)</td>
<td>25% (16%, 37%)</td>
</tr>
</tbody>
</table>

**Best confirmed overall tumor response per RECIST**

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<tbody>
<tr>
<td><strong>N=15</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Overall response rate (95% CI$^b$)</strong></td>
<td>22% (14%, 33%)</td>
</tr>
<tr>
<td>% Responders with Duration of Response $\geq$ 6 months</td>
<td>53%</td>
</tr>
</tbody>
</table>

$^a$ Calculated using the Agresti-Coull method.

$^b$ Exact Confidence Interval
Notable Development Issues

• Primary endpoint was new/unique in oncology
  – Reduction in antihypertensive medication of at least 50% for at least 6 months
  – Considered specifically for the proposed indication
  – Hypertension caused by underlying tumor and key contributor to morbidity associated with the tumor
  – Hypertension appears to correlate with tumor activity

• ORR by established response criteria (RECIST) provided evidence that 131I-iobenguane demonstrated anti-tumor activity, and not merely antihypertensive activity

• Agreement on endpoints made after extensive discussion between sponsor and the FDA; captured in a Special Protocol Assessment

• 12/68 (18%) of patients on registrational trial required dose reduction based on radiation dose estimates that exceeded theoretical limits → dosimetry dose included in final dosing guidelines
Lutetium Lu-177 dotatate

Indicated for the treatment of patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults

Mechanism of action:
- Radiolabeled somatostatin analog
- Beta-particle emitter
- Induces cellular damage by formation of free radicals in somatostatin-receptor positive cells and in neighboring cells
Registrational Study Design (NETTER-1)

N=229 patients with:
- progressive, well-differentiated, advanced or metastatic midgut carcinoid tumors
- Confirmed presence of somatostatin receptors on all lesions (OctreoScan uptake ≥ normal liver)
- No prior treatment with peptide receptor radionuclide therapy
- No prior external radiation therapy to > 25% marrow

Stratified by:
- OctreoScan tumor uptake score
- Length of time on most recent constant dose of octreotide

Randomized 1:1

Lutetium Lu-177 dotatate
200 mCi IV every 8 weeks for up to 4 doses
With
Octreotide 30 mg IM after each lutetium dose and then every 4 weeks

Octreotide
60 mg IM every 4 weeks

Primary endpoint: PFS by blinded independent review

Supportive study ERASMUS: Open-label, single-arm, expanded access protocol in n=360 patients with foregut, midgut, and hindgut gastroenteropancreatic tumors (GEP-NETs)
Results: Improved Progression-Free Survival Compared to Octreotide Alone

<table>
<thead>
<tr>
<th></th>
<th>Lutetium and Octreotide (30mg) (n = 116)</th>
<th>Octreotide (60mg) (n= 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS (months) (95% CI)</td>
<td>NR (NE, NE)</td>
<td>8.5 (5.8, 9.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.21 (0.13, 0.32)</td>
<td></td>
</tr>
<tr>
<td>mOS (months) (95% CI)</td>
<td>NR (31.0, NE)</td>
<td>27.4 (22.2, NE)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.52 (0.32, 0.84)</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>13% (7%, 19%)</td>
<td>4% (0.1%, 7%)</td>
</tr>
</tbody>
</table>
Notable Development Issues

• PFS benefit observed at early interim analysis. Sponsor continued the study as planned as per FDA and EMA recommendation due to the potential for bias in early (interim) PFS assessment with low fraction of events.

• Final indication broader than that studied on the registrational trial, based on supportive data from the broader GEP-NET population on ERASMUS.

• Selection of the therapeutic dosing regimen for Lutetium Lu-177 dotatate was based on dosimetry data from a dose escalation study (ERASMUS) which resulted in a cumulative radiation dose that remained near but below the defined radiation toxicity threshold to the kidney (23 Gy) and bone marrow (2 Gy).
  – No dosimetry dose required in final product labeling.
Take Home Points

• Early and frequent interaction with the FDA (both the Office of Hematology and Oncology Products and the Division of Medical Imaging Products) is recommended.

• Focus on data required for patient selection (diagnostic purposes) and data required for the assessment of safety and efficacy.
  – Sufficient data to support patient selection for clinical trial ≠ sufficient data for establishment of a diagnostic agent ... may depend on patient population

• Rare diseases may require careful thought about appropriate endpoints.

• Discuss with the FDA whether individual dosimetry is necessary outside of the clinical trial setting.
Theranostics Efficacy Study Design Considerations: An Alternative Framework

Sue-Jane Wang, Ph.D.
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
Acknowledgments

• Louis Marzella, MD, PhD
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• Division of Medical Imaging Drug Products, CDER, FDA
  – Clinical Teams
  – Statistical Team
  – CMC Team
  – Radiation Oncologists
• Oncology Colleagues
  – Clinical
  – Statistical
Outline

• Theranostics
• Current Practice With Potential Improvements
• Tangible Imaging Drug Indication(s)
• Interim Remarks

Disclosures and Disclaimer

• No financial relationships to disclose
• Views expressed are those of the authors and should not be construed to represent U.S. Food and Drug Administration
Diagram shows example of single-entity theranostic system that combines initial staging with imaging (green sunburst as active moiety) followed by therapy with therapeutic version of imaging (red lightning bolt).
Current Practice with Potential Improvements

• From “Sequential” to “In Parallel with Leveraging” paradigm to drug approvals

  as a “Diagnostic - Therapeutic Pair”

• Interests in leveraging therapeutic trials by aiming to
  – Reduce combined development time for therapeutics and diagnostics
  – Improve design efficiency by addressing study objectives for therapeutics and diagnostics each
  – Make additional indications feasible for marketed diagnostic imaging drugs
  – Establish test reproducibility: imaging (sub)study may be needed
Regulatory Experience Thus Far - Sequential

• Thera: Lutetium Lu 177 Dotatate (approval 2018)
  – **Indication**: treatment of somatostatin receptor-positive (SSTR+) gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults

• Nostic: Indium In-111 Pentetreotide kit (approval 1994)
  – Diagnosis success 86.4% (=267/309) evaluable; in a small subgroup of 39 subjects who had tissue confirmation, sensitivity, specificity were 85.7% and 50% for “Nostic”; 68% and 12% for CT/MRI
  – **Indication**: scintigraphic localization of primary and metastatic NET bearing somatostatin receptors

• Relevant clinical trials performed led to Lutetium Lu 177 Dotatate approval*
  – NETTER-1 (main study): 2-arm active controlled, primary: PFS, n=229
  – NETTER-1 (substudy): 1-arm, non-randomized cohort treated with “Thera” only (n=22) to evaluate dosimetry

* From FDA multi-disciplinary review and evaluation
Figure 1. Kaplan-Meier Curves for Progression-Free Survival in NETTER-1

<table>
<thead>
<tr>
<th>Time in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

- **Lutathera**
- **Octreotide**

### Cox un-stratified HR (95% CI)

<table>
<thead>
<tr>
<th>Cox un-stratified HR (95% CI)</th>
<th>0.18 (0.11, 0.29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value, unstratified log-rank test</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

### Cox Stratified HR (95% CI)

<table>
<thead>
<tr>
<th>Cox Stratified HR (95% CI)</th>
<th>0.18 (0.11, 0.29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value, stratified log-rank</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Lutetium Lu 177 Dotatate Drug label and FDA multi-disciplinary review and evaluation
Degree of Tracer Uptake on Radiopharmaceutical vs SSTR+ Disease Detection by Imaging Modality

Table 1. Number & Percent of patients imaged by Krenning score and imaging modality for each reader

<table>
<thead>
<tr>
<th>Krenning Score</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planar</td>
<td>SPECT</td>
<td>PET</td>
</tr>
<tr>
<td>0-1</td>
<td>n= 117</td>
<td>93</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>% 78%</td>
<td>62%</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>n= 5</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>n= 17</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>n= 11</td>
<td>18</td>
<td>83</td>
</tr>
<tr>
<td>2-3-4</td>
<td>n= 33</td>
<td>57</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>% 22%</td>
<td>38%</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Krenning score**: a semi-quantitative method of assessing the degree of tracer uptake on radiopharmaceutical imaging drug (2: relative uptake score slightly <= to liver; 3: > liver; 4: > spleen with 0-1: none or much < liver)

**Detection rate of SSTR+ disease**: 24%, 38%, 71% (Planar, SPECT, PET)

*Hope T, Calais J, Zhang L, Dieckmann W, Millo C. (Journal of Nuclear Medicine, 2019)
Table 3. Number and Percent of positive scans using one radiopharmaceutical imaging drug with planar and SPECT in patients with SSTR-positive disease by another radiopharmaceutical imaging drug, broken down by tumor burden score

<table>
<thead>
<tr>
<th>Tumor burden score</th>
<th>Planar</th>
<th>SPECT</th>
<th>Planar</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>R1</td>
</tr>
<tr>
<td>#</td>
<td>14</td>
<td>10</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>%</td>
<td>17%</td>
<td>13%</td>
<td>17%</td>
<td>29%</td>
</tr>
<tr>
<td>≥ 3</td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>R1</td>
</tr>
<tr>
<td>#</td>
<td>14</td>
<td>21</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>58%</td>
<td>72%</td>
<td>86%</td>
<td>71%</td>
</tr>
</tbody>
</table>

**Tumor burden score**: 1 (1-3 lesions < 2cm); 2 (>3 lesions all < 2cm); 3 (multiple lesions [2-5cm]); 4 (<5 lesions & >= 1 lesion > 5cm); 5 (>5 lesions & >= 1 lesion>5cm)

*Hope T, Calais J, Zhang L, Dieckmann W, Millo C. (Journal of Nuclear Medicine, 2019)
Had Therapeutics-Diagnostics Been Pursued In Parallel With Leveraging

- Early studies to establish analytical characterization of imaging agent, test-retest, repeatability of imaging measurement, reproducibility of test result
- In vitro data to characterize drug target engagement for the diagnostic and the therapeutic drug
- Dosimetry study: bio-distribution, early safety
- Studies to select imaging dose
- Preliminary clinical finding of therapeutic trials showing proof of concept
Had They Been Pursued In Parallel With Leveraging (Con’t)

• Dual Goals: use of investigational imaging agent to select patients (e.g., SSTR+) into therapeutic trials during development of imaging drug and therapeutics
  
  o Study inclusion of patient selection with positive scan
  o Pre-specification of important imaging factor(s) if relevant
  o Baseline tumor burden
  o Post treatment tumor response, disease progression
  o A pre-specified landmark time point for restaging or multiple time points for clinical follow up
  o Evaluation of agreement between conventional imaging and investigational imaging taken
Utilities with Leveraging

Leveraging therapeutic trial that is under planning may include

• Add a pre-specified analysis (or analyses) using available data to support diagnostic imaging drug efficacy evaluation

• Add a design element aiming for an imaging claim
  – e.g., prognostic imaging

• An add-on protocol may address clinical utility of imaging drug performance and analytical characterization
  – The add-on protocol should use available clinical trial data to support desired indication or additional claims that relates to use of diagnostic imaging drug in the context of radiopharmaceutical therapy

• Potential approval of diagnostic imaging drug may not be directly linked to the effectiveness of therapeutics
Tangible Imaging Indication(s)

- Diagnostic, prognostic
- Baseline imaging scan for patient selection
- Post treatment initiation imaging scan(s)
  - Indirect verification of proper patient selection, e.g., homogeneous clinical outcome finding
  - Treatment response monitoring
  - Diagnosis of disease recurrence
- Clinical management based on outcomes, e.g., PFS, OS
- Complementary imaging diagnostic in the pairing of theranostics possible
Interim Remarks

• In-Parallel-With-Leveraging paradigm for diagnostic-therapeutic pair drug approvals present the potential of favorable design efficiency with reduced combined development time compared to sequential paradigm

• Analytical characterization of imaging agent performance needed

• Leveraging clinical trials conducted for therapeutic claims for potentially (additional) imaging indication(s)

• If ‘nostic’ is an unapproved drug, a new NDA is needed for marketing it with the ‘thera’ as a theranostics pair
Molecular imaging for theranostics

Pathogenesis

Diagnosis

Treatment plan

One stone kills two or three birds

Ko et al. 2014/Clinical Endoscopy
Said Daibes, PhD

Medical Radiation Safety Team
U.S. Nuclear Regulatory Commission

June 22, 2019
• Contains the requirements and provisions for the medical use of byproduct material and for issuance of specific licenses authorizing the medical use of this material.
• Requirements and provisions provide for the radiation safety of workers, the general public, patients, and human research subjects.
• Application or letter of intent is submitted
• Radiation Safety Assessment performed
    • Radionuclide and Progeny Emissions
    • Radiation Detection and Protection
    • Monitoring and Measurements
• Authorized User Training and Experience needs
• Patient Administration
  – Patient Preparation
• Release Considerations
• Dose Delivery and Handling
• Waste Disposal
Radiopharmaceuticals

- Subpart D-Unsealed Byproduct Material-Written Directive Not Required
  - (35.100-35.290, Imaging and Localization Studies)
- Subpart E-Unsealed Byproduct Material-Written Directive Required
  - (35.300-35.396, Treatment)
- Subpart K-Other Medical Uses of Byproduct Material or Radiation From Byproduct Material
  - (35.1000, Emergent Technologies)
Point of Contact

Said Daibes, PhD
Medical Health Physicist
US-Nuclear Regulatory Commission
NMSS/MSTR/MSEB
Tel: 3014156863

Email: said.daibes@nrc.gov
Acronyms

• CFR – Code of Federal Regulations
NCI Resources for Clinical Trials

Lalitha K. Shankar, MD, PhD,
Chief, Clinical Trials Branch
Cancer Imaging Program
Clinical Trial Networks in the Division of Cancer Treatment and Diagnosis

- Experimental Therapeutics Clinical Trials Network (ETCTN)
- NCI National Clinical Trials Network (NCTN)
- Pediatric Brain Tumor Consortium (PBTC)
- Adult Brain Tumor Consortium (ABTC)
- Pediatric Early Phase Clinical Trials Network (PEP CTN)
For efficient assessment of promising imaging agents and modalities and their role in the development of therapeutic strategies and cancer management:

- Development of a national distribution system for investigational imaging agents
- Biomarker, imaging, and quality of life studies funding program (BIQSFP)
- Imaging and Radiation Therapy Core (IROC) for the NCTN
- Clinical Imaging and Disease Specific Steering Committees
- PAs and PARs
PAR-18-011: Early Phase Clinical Trials in Imaging and Image-Guided Interventions

(R01 Clinical Trials Required)

Program Contact: Lori A. Henderson, Ph.D.
Clinical Trials Branch, Cancer Imaging Program
hendersonlori@mail.nih.gov
PAR-18-011: Purpose & Research Objectives

- Fund research projects that propose Phase I or early Phase II clinical trials of imaging agents and methodologies, or feasibility studies of imaging devices, image-guided surgery or therapies, image-guided radiation therapy and/or systemic radionuclides to improve cancer management

- Applicable to a broad range of clinical imaging evaluations associated with or without therapeutic endpoints

- Strategies to assess feasibility can include a novel area of investigation, new experimental systems, and/or existing technologies in a new area

AREAS OF GENERAL INTERESTS

- Assessment of PET, SPECT, MR, US and optical imaging devices and methods (advances in multi-modality instrumentation and clinical imaging protocols)

- Novel imaging agents and nanocomponent formulations (biodistribution, pharmacokinetics, tracer kinetic modeling, etc.), nanocomponent devices and formulations

- Evaluation of imaging biomarkers to distinguish aggressive from indolent tumors/disease, selecting appropriate risk adaptive therapies, or risk stratification
Must propose one or more NIH-defined clinical trial

Does not fund preclinical studies as part of the research plan

R01 Project Period: Maximum 3 years

R01 Project Budget: Less than $500,000 in direct costs for the total project period. No more than $250,000 in direct costs may be requested in any single year.

Expires: February 15, 2020

Non-Standard Application Submission due dates apply

Letter of Intent requested 30 days in advance
PAR-18-560: Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis

(R01 Clinical Trial Required)

Program Contact: Lori A. Henderson, Ph.D.
Clinical Trials Branch, Cancer Imaging Program
hendersonlori@mail.nih.gov
PAR-18-560: Purpose & Research Objectives

- Fund research projects that implement early phase (Phase 0, I, and II) investigator-initiated clinical trials focused on cancer-targeted diagnostic and therapeutic interventions of direct relevance to NCI’s mission & programs.

- Applicable to a broad range of clinical trial evaluations designed to improve the diagnosis and treatment of cancer.

- Strategies to assess feasibility can include a novel area of investigation, new experimental systems, and/or existing technologies in a new area.

- Replaces the NIH R01 Parent Research Grant FOA - Clinical Trial Required

AREAS OF GENERAL INTERESTS

- Clinical evaluation of new or improved anticancer drugs and biologics, including immunotherapies, new or improved imaging technologies (agents, devices, image-guided therapies) and surgical interventions, novel approaches to radiation therapy, and incorporation of complementary medicine approaches to treatment.
PAR-18-560: REQUIREMENTS

- Should address the priorities of one or more of the following NCI program areas:
  - Cancer Therapeutic Evaluation Program
  - Cancer Diagnosis Program
  - Office of Complementary & Alternative Medicine
  - Cancer Imaging Program
  - Radiation Research Program
  - Office of HIV and AIDS Malignancies

For Details: Visit cancer.gov

- Must propose one or more NIH-defined clinical trial(s)
- Can combine preclinical and clinical research in a single study
- R01 Project Period and Budget: Maximum 5 years with less than $500,000 in direct costs per year
- Expires: January 8, 2021
- Standard Application Submission due dates apply
- Letter of Intent Requested 30 days in advance
SBIR and STTR
SBIR & STTR

- The Small Business Innovation Research (SBIR) [PA-14-071](https://www.federalregister.gov/a/PA-14-071); 2.9% set aside
- Small Business Technology Transfer (STTR) [PA-14-072](https://www.federalregister.gov/a/PA-14-072); 0.4% set aside
- ~$700M annually at NIH; $115 at NCI
  - Contact: Deepa Narayanan ([deepa.narayanan@nih.gov](mailto:deepa.narayanan@nih.gov))
SBIR & STTR: Three-Phase Program

Phase I
- Proof-of-Concept study
- $150,000 over 6 months (SBIR) or 1 year (STTR)
- Fast Track Application
- Combined Phase I & II
- Research & Development
- Commercialization plan required
- $1 million over 2 years

Phase II
- Direct to Phase II
- Skip Phase I

Phase III
- Commercialization stage
- Use of non-SBIR/STTR funds
- COMMERCIALIZATION

• Hard caps on award sizes: $225,000 for Phase I; $1.5 million for Phase II
• Certain awards may exceed these caps if covered by topic-specific waivers
• Actual funding may vary by topic
NCI Experimental Therapeutics Program (NExT)
NOT A GRANT PROGRAM

- Provides access to NCI resources and expertise – NCI performs the project
- Simple application process
- External expert review
- Internal expert review
- Full team support
- Applicant involved in project
NExT Development Resources

- Multi- and interdisciplinary clinical/translational teams
- Early access to leading-edge translational technologies
- PK/PD modeling and assay development
- Toxicology/Safety Pharmacology
- Formulation & GMP Scale-Up
- Imaging for biodistribution
- Development & validation of pharmacodynamics assays
- Development & validation of clinical assays
- Proof-of-concept or first in human studies
Next Resources Currently Support

- Investigational drugs and biologics
- Investigational imaging agents
- Academic, biotech and pharma projects
- Phase 0, 1 and 2 clinical trials
- HTS, Hit-to-Lead and Lead optimization

**NOT basic research**
Access to NExT

Who: Researchers in academia, government and industry, nationally and internationally.

http://next.cancer.gov/
Theranostics: Regulatory Considerations for Product Development – Panel Discussion on Industry perspectives
Targeted molecules can be used for Diagnostics and Therapeutics using different labelling isotopes.

**Ga-68** labeled

Ga-68 PET
- Diagnosis
- Treatment Selection
- Follow-up

**Same Targeting Molecule**

GAMMA rays detected by PET/CT

**Lu-177** labeled

Lu-177 RLT
- Targeted treatment

BETA radiation treats tumors from within

Therapy and complementary diagnostic
"IF YOU CAN SEE IT YOU CAN TREAT IT"
Advantages of Nuclear Medicine – theranostic approach to therapy

- General features/advantages of the theranostic approach
- Added values during drug development
Results of the NETTER-1 study

177Lu-DOTATATE was safe and more effective than Octreotide 60 mg:

- **PFS** (Not Reached vs 8.5 months, p<0.0001)
- **ORR** (13% vs 4%, p=0.0008)
- **OS** (Not Reached vs. 27.4 months, interim analysis; p=0.0043)

A Marketing Authorization was granted for this product in Europe and in USA, in September 2017 and January 2018 respectively.
## Nuclear Medicine: Opportunities and Limitations

### Table 3. Results and Side Effects of Chemotherapy in Patients With Neuroendocrine Tumors Compared With the Present Study

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor Types</th>
<th>No. of Patients</th>
<th>PR and CR (%)</th>
<th>Median Response Duration (months)</th>
<th>Hematologic Toxicity</th>
<th>Nausea and Vomiting (%)</th>
<th>Other Major Side Effects</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Carc</td>
<td>33</td>
<td>21*</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>—</td>
<td>Moertel</td>
</tr>
<tr>
<td>FU</td>
<td>Carc</td>
<td>19</td>
<td>26*</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>—</td>
<td>Moertel</td>
</tr>
<tr>
<td>STZ + FU</td>
<td>Carc</td>
<td>43</td>
<td>33*</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>—</td>
<td>Moertel</td>
</tr>
<tr>
<td>STZ</td>
<td>NEP</td>
<td>42</td>
<td>36*</td>
<td>17</td>
<td>0</td>
<td>83</td>
<td>Renal toxicity, 29%; liver failure, 2%</td>
<td>Moertel et al</td>
</tr>
<tr>
<td>STZ + FU</td>
<td>NEP</td>
<td>42</td>
<td>63*</td>
<td>17</td>
<td>0</td>
<td>85</td>
<td>Renal toxicity, 31%</td>
<td>Moertel et al</td>
</tr>
<tr>
<td>STZ + FU</td>
<td>NEP</td>
<td>33</td>
<td>46*</td>
<td>7</td>
<td>5</td>
<td>81</td>
<td>Diarrhea, 33%; renal insufficiency, 7%</td>
<td>Moertel et al</td>
</tr>
<tr>
<td>STZ + doxorubicin</td>
<td>NEP</td>
<td>36</td>
<td>69*</td>
<td>20</td>
<td>5</td>
<td>80</td>
<td>Diarrhea, 5%; renal insufficiency, 4%; heart failure, 9%</td>
<td>Moertel et al</td>
</tr>
<tr>
<td>STZ + doxorubicin</td>
<td>NEP</td>
<td>16</td>
<td>6**</td>
<td>&gt; 18</td>
<td>18</td>
<td>19</td>
<td>Diarrhea, 19%; cardiac toxicity, 19%</td>
<td>Cheng and Saltz</td>
</tr>
<tr>
<td>DTIC</td>
<td>Carc</td>
<td>16</td>
<td>13</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>—</td>
<td>Van Hazel et al</td>
</tr>
<tr>
<td>DTIC</td>
<td>Carc</td>
<td>56</td>
<td>16</td>
<td>3</td>
<td>9</td>
<td>88</td>
<td>Diarrhea, 23%</td>
<td>Bukowski et al</td>
</tr>
<tr>
<td>DTIC</td>
<td>Carc/NEP</td>
<td>7</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>—</td>
<td>Ritze et al</td>
</tr>
<tr>
<td>FU + IF-A</td>
<td>Carc/NEP</td>
<td>24</td>
<td>21</td>
<td>13</td>
<td>42</td>
<td>NA</td>
<td>Diarrhea, 8%</td>
<td>Andreyev et al</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Carc</td>
<td>36</td>
<td>9</td>
<td>14</td>
<td>32</td>
<td>26</td>
<td>—</td>
<td>Neij et al</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Carc/NEP</td>
<td>24</td>
<td>4</td>
<td>3</td>
<td>61</td>
<td>63</td>
<td>Diarrhea, 54%; neurologic toxicity, 61%</td>
<td>Ansell et al</td>
</tr>
<tr>
<td>177 Lu-octreotide</td>
<td>Carc/NEP</td>
<td>131</td>
<td>28</td>
<td>&gt; 36</td>
<td>&lt; 2</td>
<td>31</td>
<td>Renal insufficiency, 1%; liver failure, 1%</td>
<td>Present study</td>
</tr>
</tbody>
</table>

Kwekkeboom 2005, Clin Oncol 23:2754-2762
The treatment was well tolerated, with no clinically significant renal toxicity and mild-transient hematological toxicity.

- No correlation was observed between the mild observed renal/bone marrow toxicity and organ absorbed dose.

- The high variability of dosimetry data and lack of correlation between kidney and bone marrow absorbed dose and toxicity confirm that clinical, hematological and biochemical assessments are the most reliable tools to monitor potential toxic effects.
Time-activity curves in tumor masses indicate that $^{177}$Lu-DOTATATE generally has prolonged intense uptake in tumor lesions.

Cumulative absorbed doses are high, and particularly elevated in the majority of lesions.

Causes for inter/intra-patient variability include SSR expression level, specific shape, vascularization.

Data confirm high persistence in tumor lesions.
As for the more classical PK/PD approach, dosimetry is an important tool at initial stages of development, to support the identification of a well-tolerated and efficacious cumulative dose and therapeutic scheme to be used in Phase III studies.

The definition of optimal dose regimens are guided by efficacy and safety considerations. They are specific for a given clinical indication and patient population and aim at maximizing the benefit for oncological patients.

The selected dose will maximize the probability of efficacy in the overall patient population, while keeping control of the toxicity parameters. On the contrary, a personalized dosimetry-based approach would have several limitations:
- Risk of undertreating the patient
- Low patient compliance
- High costs for Health Care systems
- Access to treatment limited to fewer centers
- Production and logistic challenges for personalized doses
Targeted molecules can be used for Diagnostic and Therapeutics using different labelling isotopes => you see what you treat

The Theragnostic approach allows a more effective patient selection, maximizing the likelihood of therapeutic efficacy

The Theragnostic approach allows for dosimetric calculations => an important tool at initial stages of development, to support the identification of the therapeutic scheme to be used in Phase III studies

The Theragnostic approach is a Unique asset of Nuclear Medicine that will lead to a significant expansion of our discipline.
The Image as a Biomarker – the Potential of Theranostics and Imaging Companion Diagnostics in Oncology

Sandy McEwan
Professor Emeritus, Department of Oncology, University of Alberta
Vice-President Radiopharmaceuticals, Ipsen
Disclosures

• Vice-President Radiopharmaceuticals, Ipsen
Systemic Radiation Therapy
(Radioligand Therapy)

The systemic administration of a targeted radionuclide utilizing short range beta (alpha) particles or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer:

PRRT defines the targeting moiety as a peptide, targeting a defined receptor
Theranostics: Companion diagnostic imaging agent defines treatment potential for SRT

Companion Diagnostic may be IHC or an image

Rx
TARGETED THERAPEUTIC

Dx
COMPANION DIAGNOSTIC IMAGE

THERANOSTICS
Merging drug therapy and diagnostics to advance personalized medicine

Therapeutic strategy uses same targeting strategy as Dx but delivers therapeutic radiation

Modified from:
http://agpharma.com/products/products.html
Characteristics of these Therapies

• Companion diagnostic/theranostic
  • In vitro: Iodine symporter, SSTR-2 receptors
  • In vivo Dx: *Iodine, $^{68}$Ga-Octreotate
  • In vivo Rx: $^{131}$Iodine, $^{177}$Lu-Octreotate

• Validation/Heterogeneity
  • Distribution of target within primary tumour/metastases
    • Validation of target
  • Distribution of target across metastases
Imaging in Patients with Cancer

**Current Paradigm**
- Identify the presence or absence of tumor
  - Primary diagnosis and staging
  - Treatment effect
  - Monitoring
  - Recurrence
  - Follow-up and restaging
- Assessing toxicity
- Screening

**Future Paradigm**
- **precision medicine**
- Current indications
- Tumor biology characterization
- *Leads to treatment stratification*
  - Staging
  - Companion diagnostic
  - Theranostic
- Assaying response
- Predicting progression
- Predicting /assaying toxicity
- RT planning
Measuring response in a post RECIST world: from black and white to shades of grey

“Cancer Therapies

• .... expected to have lower toxicities

• .... studies in murine models often demonstrated growth inhibition rather than tumor regression

• .... were expected to require a longer duration of administration

• Could there be instances where a drug could be effective without meeting the RECIST criteria?”

• “We argue that these response criteria do not adequately evaluate the activity of the newest generation of anticancer agents.”
Assessment of Response - RECIST
Tumors as Complex Tissues

Hanahan D and Weinberg RA. *Cell* 2011; 144:646 - 674
Characteristics of Imaging Biomarkers in Diagnostic and Therapeutic Practice

• Typically radiopharmaceuticals
• Assay of biological and functional tumor characteristics
  • Molecular medicine
• Targeted
  • To tumor
  • To biological process or target
  • To metabolic, biochemical, genomic, proteomic pathway
• Quantitative
  • Relative, absolute or temporal
• Diagnostic and predictive
  • Stratifies for treatment
  • Demonstrates early metabolic changes in response to therapy
  • Predicts treatment response
Surgical CR After 6 Cycles

PET “CR”
After 6 Cycles

Jan 2013

Jan 2015
Images as Companion Diagnostics

- Historically have been standard of care (e.g., thyroid cancer)
- Can differentiate tumor heterogeneity in vivo
- Predictors of response to (Iodine-131, bone seeking RPs, Lutathera)
- Can reduce accruals needed for statistical confidence
- Companion diagnostic image can be used independently of theranostic pathways
- Support development of practice guidelines
- Support development of care pathways

Need to develop “R”RECIST criteria for systemically administered radiopharmaceuticals (comparable to “I”RECIST)
Hypoxia Imaging: Tirapazamine Trial

Companion diagnostic image can be used independently of theranostic pathways

FDG Pre Rx  FDG Post Rx

FMISO Pre Rx

KM Survival Standard of Care
–v – SOC + Tirapazamine
• Companion diagnostic tests have the potential to simplify the drug-discovery process, make clinical trials more efficient and informative, and be used to individualize the therapy of cancer patients (Bioanalysis 2011;3(4):383-389).
There are a number of challenges associated with the development of such tests, including balancing decisions about how a biomarker test can both accelerate drug development and inform optimal use of the drug, coordinating the design and versions of diagnostic tests with the drug development process, and the regulatory challenges in developing effective mechanisms to synchronize reviews of therapeutics with diagnostic devices used to personalize treatment.

Quote attributed to Reena Philip, PhD, Director, Division of Molecular Genetics and Pathology, Office of In Vitro Diagnostic Devices and Radiological Health, Center for Devices and Radiological Health, FDA.
Recruitment

Imaging Biomarker Study

IB +ve

IB -ve

I B -ve

I B +ve

Cohort not Imaged

Control

Intervention

Control

Intervention

Control

Intervention

DATA

BLINDED
Complexity and Complexification – The Field
Radiopharmaceuticals and the Regulator

• Important differences to standard pharmaceutical development
  • Just in time manufacturing
    • Complex supply chain
  • Local manufacturing from kit –v- central manufacturing (Dx or Rx)
  • Health regulator requirements in manufacturing
  • Nuclear regulator requirements in manufacturing
  • Nuclear regulator requirements in treatment suite

• The role of the image
  • Pre clinical
  • Clinical

• Market size

• CRO inexperience in the field
Complexity and Complexification - Diagnostic Radiopharmaceuticals and the Regulator

• Choice of radionuclide
  • PET
  • SPECT
• RP’s as companion diagnostics
  • Same molecule
  • Different molecule same target
  • Companion diagnostic for systemic therapy
• Typically microdosing
  • Should inform benefit/risk ratio and prospectively identify patient population
• Biodistribution to validate preclinical data and safety
• Validate presence of target
  • What is the standard of truth
• Sensitivity, specificity, PPV, NPV
  • But what is role in purely theranostic setting
Complexity and Complexification - Therapeutic Radiopharmaceuticals and the Regulator

- Important differences to standard pharmaceutical development
- How to define the target population
  - By cancer type
  - Presence or absence of receptor
- Combination therapies
- Phase 1 must be informed by the image
  - Patient selection and safety criteria
    - Complexities associated with the radioactive patient
  - Validate biodistribution with diagnostic
  - Dose escalation atypical for standard pharmaceutical phase 1
- Phase 2/3 defined by the image and defined population
- Manufacturing issues
  - Clinical – v- commercial production
  - Local – v- central manufacturing
- Dosimetry – v – biology
  - LDHR hypothesis
- Exotic radioisotopes – $\alpha$ emitters
Images/Theranostic Pairs as Companion Diagnostics – The Needs

• Clearly articulated and defined regulatory pathway
• Clearly articulated and defined clinical trial designs
  • Appropriate integration of the image into the design
• Validation requirements for the image as a biomarker/theranostic pair
• How to test SRT/drug combinations
• Understanding of the biology of systemically administered radiation therapy and integrating this into the development pathway
  • Has relevance to our understanding the role of response criteria
  • Has relevance to our understanding the role of dosimetry
• Requires integration of efforts by regulator, specialty societies, academia and industry
• Companion pathway may include conventional drugs or systemic radiotherapeutics
Practical Considerations and Learnings in Alpha-based Radiotherapeutics

Patricia E. Cole, PhD, MD
Lead Clinical Imaging Strategist
Strategic Business Unit Oncology
Bayer US
Whippany, NJ 07981
SNMMI Disclosure

• Patricia E. Cole is an employee of Bayer US
Targeted Thorium Conjugates (TTCs)

• 3 Key Components

A platform amenable to a diverse range of targeting moieties
Antibodies, Peptides, Small Molecules
Targeted Thorium Conjugates: What Can Be Imaged?

• WANT:
  • Information on quantitative uptake with precision and accuracy
  • Activity distribution over time

• UTILIZE:
  • Gamma emissions from Th-227 decay

• CHALLENGES:
  • Low gamma activity (several emissions at 235, 255 eV; abundance is 20%)
  • Very poor signal to background
  • Overlapping energies in Th-227 and Ra-223
    • Th-227 (215-255eV) and RA-223 (255-285eV)

Example of Patient Gamma Camera Images

Activity administered: 2.8 MBq Th-227 and 0.17 MBq Ra-223 (from ingrowth)

Fused: $^{227}\text{Th}$, $^{223}\text{Ra}$ and edge-enhanced scout

Images from energy windows
3 hours post-injection

Dosimetry of Alpha Particle Therapeutics

• Quantification of uptake even in large normal tissue organs is difficult.

• For $\alpha$-particles, also need to consider dose within the organ:
  - Dose is not uniform because of short range of $\alpha$-particles (50-100 microns).
  - In contrast, high energy $\beta$-particles and photons penetrate entire organ.

• Issues:
  - Counts are poor for $\alpha$ decay.
  - Gamma images are low resolution with poor signal to background.
  - **Difficult to quantify.**
  - Cannot even image until administered dose is $\sim 2.5$ MBq.
    - For most studies, this corresponds to the 2nd to 3rd dose escalation step.
Meaning of Absorbed Dose Estimates

• Biological effect of an absorbed dose
  • Depends on the relative biological effectiveness (RBE)
    • RBE = 1 for photons and beta emitters
    • RBE for alpha emitters for deterministic events (e.g., safety, efficacy): ~ 3-7

• Significant variability in estimating absorbed dose for alpha emitters
Implications for Clinical Decision-making

• Use of alpha emitter dosimetry to make clinical decisions is currently not feasible
  • Quantification of uptake in organs has significant variability
    • Even more variability for smaller structures (tumor lesions)
  • Absorbed dose estimates have variability due to uncertainty in RBE value

Conclusion
Compounded variabilities in uptake quantification and absorbed dose estimates currently require reliance on clinical/laboratory/safety outcomes to determine dose/schedule
Thank You