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United States Nuclear Regulatory Commission
Protecting People and the Environment

Overview: 2019-2020 ACMUI Activities

Darlene Metter, M.D.
ACMUI Chair/Diagnostic Radiologist
November 18, 2020


Today's Agenda

- A. Robert Schleipman, Ph.D. (ACMUI Vice-Chair)
  - ACMUI's Comments on the Staff's Evaluation of Training and Experience for Radiopharmaceuticals Requiring a Written Directive

- Ms. Melissa Martin (ACMUI Nuclear Medicine Physicist)
  - ACMUI's Comments on Extravasations

Today's Agenda cont'd

- Mr. Michael Sheetz (ACMUI Radiation Safety Officer)
  - ACMUI's Comments on Patient Intervention and Other Actions Exclusive of Medical Events

- Hossein Jadvar, M.D., Ph.D. (ACMUI Nuclear Medicine Physician)
  - Trending Radiopharmaceuticals

Overview of the ACMUI

- ACMUI Role
- Membership
- 2019-2020 Topics
- Current Subcommittees
- Future

Role of the ACMUI

- Advise the U.S. Nuclear Regulatory Commission (NRC) staff on policy & technical issues that arise in the regulation of the medical use of radioactive material in diagnosis & therapy.
- Comment on changes to NRC regulations & guidance.
- Evaluate certain non-routine uses of radioactive material.

Role of the ACMUI (cont'd)

- Provide technical assistance in licensing, inspection & enforcement cases.
- Bring key issues to the attention of the Commission for appropriate action.

ACMUI Membership (12 members)

- Healthcare Administrator (Dr. Arthur Schleipman)
- Nuclear Medicine Physician (Dr. Hossein Jadvar)
- 2 Radiation Oncologists (Drs. Ronald Ennis & Harvey Wolkov)
- Nuclear Cardiologist (Dr. Vasken Dilsizian)
- Diagnostic Radiologist (Dr. Darlene Metter)
- Nuclear Pharmacist (Mr. Richard Green)

ACMUI Membership (12 members)

- 2 Medical Physicists
  Nuclear Medicine (Ms. Melissa Martin)
  Radiation Therapy (Mr. Zoubir Ouhib)
- Radiation Safety Officer (Mr. Michael Sheetz)
- Patients' Rights Advocate (Mr. Gary Bloom*)
- FDA Representative (Dr. Michael O'Hara)
- Agreement State Representative (Ms. Megan Shober)

*Recently resigned from the ACMUI

ACMUI Topics Addressed in 2019-2020

- Training & Experience Requirements for All Modalities
- Training & Experience Requirements for Administration of Radiopharmaceuticals Requiring a Written Directive
- Y-90 Microspheres Brachytherapy Licensing Guidance
- Germanium-68/Gallium-68 Pharmacy Grade Generator Licensing Guidance

2019-2020 ACMUI Topics

- Xcision GammaPod Licensing Guidance
- Evaluation of Infiltrations/Extravasations
- Regulatory Guide 8.39, “Release of Patients Administered Radioactive Material” Revision 1 (Phase I)
- Analysis of 2018 Medical Events (ME) & Appropriateness of ME Reporting
- Status of Emerging Technologies Licensed under 10 CFR 35.1000

2019-2020 ACMUI Topics

- US Pharmacopeia General Chapter <825>
- Trends in Radiopharmaceuticals
- Recommendations for NRC COVID-19 Regulatory Relief Options
- ACMUI Interventional Radiologist
- ACMUI Bylaws
- ACMUI Institutional Memory
- ACMUI External Communications

Staff Presentations to ACMUI (2019-2020)

- Summary of Changes to 10 CFR Part 35
- Medical Events Updates
- Medical Event Abnormal Occurrence Criteria
- NRC Staff's Evaluation of T&E Requirements
- Past ACMUI Recommendations & NRC Response
- NRC Regulatory Process & Other Tools
- ACMUI Reporting Structure, Membership Composition & Balance
- NMED Overview

Current ACMUI Subcommittees

- T&E for All Modalities
- Infiltrations/Extravasations
- Medical Events
- Bylaws
- Institutional Memory
- Patient Intervention
- Interventional Radiologist
- COVID-19 Impact on Medical Community
- Abnormal Occurrence

Future

- ACMUI will continue to
  - Provide advice and technical assistance
  - Comment on NRC regulations and guidance
  - Evaluate uses of radioactive material
  - Bring key issues to the attention of the Commission

Acronyms

- ACMUI - Advisory Committee on Medical Uses of Isotopes
- CFR - Code of Federal Regulations
- FDA - U.S. Food & Drug Administration
- INFOSEC - Information Security
- ME - Medical Event
- NMED - Nuclear Material Events Database
- NRC - U.S. Nuclear Regulatory Commission
- T&E - training and experience
- Y-90 - yttrium-90

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ACMUI's Comments on the Evaluation of Training and Experience Requirements for the Administration of Radiopharmaceuticals Requiring a Written Directive

A. Robert Schleipman, PhD
ACMUI Vice Chair/Healthcare Administrator
November 18, 2020

ACMUI Training and Experience Subcommittee

Subcommittee membership

Gary Bloom
Ronald Ennis, M.D.
Darlene Metter, M.D.
A. Robert Schleipman, PhD (Chair)
Michael Sheetz
Megan Shober

NRC staff resource: Maryann Ayoade

Background

In SRM-M170817, the Commission directed the staff to evaluate:

1) whether it makes sense to establish tailored T&E requirements for different categories of radiopharmaceuticals
2) how those categories should be determined (such as by risks posed by groups of radionuclides or by delivery method)
3) what the appropriate T&E requirements would be for each category
4) whether those requirements should be based on hours of T&E or focused more on competency.

Background

The staff's draft Commission paper built on extensive public stakeholder feedback, consultation, and coordination with the Organization of Agreement States (OAS) and the Advisory Committee on the Medical Uses of Isotopes (ACMUI), as well as review of corresponding international regulations, review of related medical events, and consideration of how the current T&E requirements conform to a risk-informed approach and align with the NRC's Medical Policy Statement.

The ACMUI Subcommittee issued a review on 6 October 2019.

ACMUI Training and Experience Subcommittee

The Subcommittee noted several introductory points:

a. As to ongoing concerns for a current or burgeoning shortage of authorized users (AUs) affecting patient access, the draft paper concludes that the NRC staff could not determine whether the number and location of licensees are sufficient to satisfy patient demand, and importantly, "…***the NRC cannot regulate T&E with a primary goal of increasing patient access to radiopharmaceuticals or improving geographic distribution of AUs.***"

b. NRC staff also discussed that emerging radiopharmaceutical therapies are growing in volume, are increasingly patient-focused, and that administration protocols of these emerging radiopharmaceuticals will inherently be more complex.

ACMUI Training and Experience Subcommittee

Two major regulatory approaches presented for Commission consideration:

1) A performance-based approach that removes the current prescriptive T&E requirements and NRC review and approval of AUs (with three sub-options)

2) Maintaining and/or enhancing the NRC's existing regulatory framework for T&E (with four sub-options)

Option 1a.

Option 1a. "Specialty Board Credentialing," where physicians must be certified by any medical specialty board to use radiopharmaceuticals.

-In our view, such a certification must provide the same high level of knowledge of radiation safety and care as the current deemed-status Boards. As delineated in 10 CFR 35.390, this requires extensive T&E of appropriate topics which currently requires 700 hours devoted to these topics.

-This would require other boards to provide and develop the expertise among their membership to develop the curriculum and create training programs for their new trainees, and those already in practice within their specialty.

Option 1a. cont'd

Option 1a. "Specialty Board Credentialing," where physicians must be certified by any medical specialty board to use radiopharmaceuticals.

-If Option 1a were to allow specialty boards to significantly dilute educational and training requirements to determine AU status as each board sees fit, we have significant reservations, as we believe this would compromise patient and public safety.

-Does not state whether or not an alternate pathway would continue to exist.

Option 1b.

Option 1b. "Licensee Credentialing," where licensees must develop their own procedures to determine whether their physicians are adequately trained to use radiopharmaceuticals.

-Current T&E requirements are based on NRC regulations in 35.390. Without this national standard, thousands of AUs may be approved with varying levels of local or site-specific determined "expertise," resulting in a wide disparity in "expert practice."

-If the AU relocates to a different hospital or medical facility, the site-specific licensee credentialing may not be equivalent, and hence, would need to be initiated as a new application with potentially disparate T&E requirements.

Option 1b. cont'd

Option 1b. "Licensee Credentialing," where licensees must develop their own procedures to determine whether their physicians are adequately trained to use radiopharmaceuticals.

-There will be no standard platform of AU credentialing, and local or site-specific responsibility for determining licensee credentialing might be administratively conducted without a physician in that specific specialty, or perhaps be delegated to a non-physician.

-With thousands of individual site-specific licensees, the regulatory and inspection oversight would be immense and cost prohibitive.

-Also uncertain how this would be operationalized in small clinics and stand-alone practices with minimal administrative infrastructures.

Option 1c.

Option 1c. "NRC-Recognized Specialty Board Credentialing," where physicians must be certified by a medical specialty board recognized by the NRC.

-Any newly proposed medical specialty board certification…must ensure completion of an appropriate number of hours of didactic education and hands-on training and experience to assure public health and safety.

-NRC recognition is [currently] conferred on a medical specialty board as a formal acknowledgment of meeting, and continuing to meet NRC requirements for AU status for its certified diplomates, and is at least partially based on those boards' requirements for comprehensive training, content, and experiential components in radiobiology, dosimetry, and radiation protection practices.

-The alternate T&E pathway for AU status (10 CFR 35.390(b)(1)) will no longer exist under Option 1c. As currently used, the alternate pathway offers flexibility and timely certification of new authorized users.

Option 2a.

Option 2a: "Status Quo," would make no changes to the NRC's T&E requirements."

-The practice of radionuclide therapy under the current requirements has maintained public health and safety as evidenced by the very few reported medical events in the National Medical Events Database (NMED) relative to the overall annual number of radionuclide therapies in the U.S.

-This was further supported by the public stakeholder input from the nuclear medicine and radiation oncology communities, as well as the ACMUI.

-As practitioners in the medical radiation specialties, we do not feel the current regulatory T&E standards are in conflict with the Medical Policy Statement.

Option 2b.

Option 2b. "Tailored Requirements," would tailor and reduce T&E to create additional AU pathways for administration of specific categories of radiopharmaceuticals

-One of the key elements of Option 2b is to reduce training requirements in cases where the licensed material is received as a unit dose. The Subcommittee believes that handling a radiopharmaceutical in unit-dose form alone does not decrease the required level of safety to warrant a reduction in training.

-This option would likely be exceptionally burdensome for the NRC as a careful review of applicable T&E elements will need to be entertained time and again as new agents are developed.

- This variegated system would present regulatory challenges for the regulator, AU, and RSO in determining whether a particular AU was authorized for a particular agent.

Option 2c.

Option 2c. "Emerging Radiopharmaceuticals," would conduct individual reviews of each new radiopharmaceutical to determine drug-specific tailored T&E and other related requirements.

-This would be time-intensive and potentially delay introduction or access to new therapies.

- Could create the potential for inconsistent requirements, since 35.1000 guidance has a compatibility level D, which allows for significant variation in the Agreement State regulation.

- It would also be burdensome to re-authorize every AU for each new emerging radiopharmaceuticals.

Option 2c. cont'd

Option 2c. "Emerging Radiopharmaceuticals," would conduct individual reviews of each new radiopharmaceutical to determine drug-specific tailored T&E and other related requirements.

- Determining the required training for these tailored approaches to each emerging radiopharmaceutical would be time-intensive and require multiple regulatory steps, which might be counter-productive for facile adoption of future novel radiopharmaceuticals.

- If the NRC classifies a radiopharmaceutical in 10 CFR 35.300, the existing training requirements under 35.300 are adequate.

Option 2d.

Option 2d. "Team-Based Requirements," would create an additional alternate pathway in which T&E requirements for AUs would be reduced based on pairing AUs with other individuals with radiation safety T&E.

-While a licensee must have an RSO knowledgeable in the applicable regulations, radiation safety requirements, and emergency procedures; the AU should also be independently knowledgeable in these areas for the modalities in which they practice.

-Safety may be compromised when the physician is not sufficiently knowledgeable of the dangers of radioactive materials in patient care.

Option 2d. cont'd

Option 2d. "Team-Based Requirements," would create an additional alternate pathway in which T&E requirements for AUs would be reduced based on pairing AUs with other individuals with radiation safety T&E.

-Given the hierarchical culture in medicine, an authorized nuclear pharmacist (ANP) or authorized administrator may not have the freedom or authority to assure safety when the physician does not fully appreciate the dangers inherent in radioactive materials use, or the required mitigating procedures.

-Other considerations for a partnered or multiple AU team approach (in its execution and its regulation) are the asymmetric scopes of practice and authority, and associated legal and reimbursement issues.

ACMUI Training and Experience Subcommittee Perspective

Approach One: Removal of Prescriptive T&E requirements and NRC Review and Approval of AUs

The Subcommittee does not support Options 1a or 1b.

Option 1c may be feasible if the appropriate level of training and experience is required. If the NRC applies sufficient rigor in evaluating radiation-related content and competencies as discussed above, new boards could possibly provide an appropriate level of radiation protection regarding public health and safety.

As mentioned earlier, Option 1c does not provide an alternate pathway. The Subcommittee recognizes the value and flexibility of the alternate pathway.

ACMUI Training and Experience Subcommittee Perspective

Approach Two: Maintain or Enhance the Existing T&E Framework

Currently, and with the advent of new and emerging radiopharmaceuticals, Option 2a, (maintaining the current T&E or *status quo* for AUs under 10 CFR 35.390) appears to be the best approach.

In Option 2b (tailored T&E), the AU applicant should acquire a fundamental base in radiation related topics; including comprehensive radiation protection training equivalent to 10 CFR 35.390. Subsequently, the individual must attain the clinical experience for the requested therapy.

This seems likely to create a chaotic system with significant burden on the NRC to develop T&E requirements for each agent, and confusion among regulators and AUs about which agents each AU is authorized to use.

ACMUI Training and Experience Subcommittee Perspective

Approach Two: Maintain or Enhance the Existing T&E Framework

The Subcommittee does not support Option 2c. Evaluation of all emerging radiopharmaceuticals under 35.1000 guidance would be overly burdensome and time-intensive.

Option 2d, a team-based, “partnered AU” approach to radionuclide therapy, may be problematic for reasons stated above.

ACMUI Training and Experience Subcommittee Recommendations

-Recommends maintaining the *status quo* under 10 CFR 35.390

-While strongly affirming the structural superiority of the status quo over the other options proposed in the draft paper, we acknowledge there is room for a comprehensive review of the specific requirements in 35.390 such as the seemingly arbitrary requirement of 700 hours. The Subcommittee (and likely, ACMUI) would welcome the opportunity to critically assess these details.

-If the NRC proceeds to grant AU status by NRC-recognized specialty boards, the T&E should be equivalent to 35.390.

-The Subcommittee recognizes the value of an alternate pathway, and is willing to review and evaluate the requisite knowledge, preceptor-reviewed experience, and competency assessments.

ACMUI Training and Experience Subcommittee

SUBCOMMITEE - minority opinion excerpts:

-NRC should shift its T&E regulatory framework to focus on T&E for individuals who *handle* or *administer* 10 CFR 35.300 radiopharmaceuticals. To move toward this shifted framework, I support a hybrid of Option 1b and Approach 2, where authorized user physicians are not individually listed on a license but are subject to training and certification requirements in 10 CFR 35. For comparison, NRC regulates high-risk industrial uses of radioactive material, and a very similar user training model has been in place for industrial radiography licensees for many years

-This hybrid option would lessen the administrative burden on licensees and NRC to amend licenses to track specific physician authorizations, an effort which currently consumes an enormous amount of regulatory resources but has only an indirect link to radiation safety at most medical institutions

Post-Subcommittee Report Landscape

The next several slides report on recent factors related to the T&E report, and are not that of the convened Subcommittee.

A. Robert Schleipman, PhD.

Post-Subcommittee Report Landscape

NRC staff submitted SECY-20-0005, "Rulemaking Plan for Training and Experience Requirements for Unsealed Byproduct Materials" (January 13, 2020)

- The rulemaking plan considered varied options for T&E

- Staff endorsed Option 3, "*National Materials Program-Recognized Specialty Board Credentialing*," a performance-based approach that would remove review and approval of T&E for AUs by the NRC and Agreement States, and instead would require that physicians be certified by a medical specialty board recognized by the NRC or an Agreement State.

SECY-20-0005

Rulemaking Plan for Training and Experience Requirements for Unsealed Byproduct Material (10 CFR Part 35)

The ACMUI has not formally reviewed this proposal, though note that Option 3 within the rulemaking proposal is congruent with Option 1c of the previously discussed draft paper; wherein the T&E Subcommittee remarked:

"Option 1c may be feasible if the appropriate level of training and experience is required. If the NRC applies sufficient rigor in evaluating radiation-related content and competencies as discussed above, new boards could possibly provide an appropriate level of radiation protection regarding public health and safety.

"*As mentioned earlier, Option 1c does not provide an alternate pathway. The Subcommittee recognizes the value and flexibility of the alternate pathway."*

Training and Experience Questions

Commission's Public Meeting on the Discussion of Medical Use of Radioactive Material, 28 Jan. 2020

Operational questions arose:

i. *Removal of alternate pathway- access issues?*
ii. *What if no new boards are developed by other specialties?*
iii. *Cost prohibitive for other specialties to develop/administer new boards?*
iv. *Post-board certification competency requirements?*
v. *Must AUs be listed on the license?*

T&E COVID-19 Adaptations: Accrediting Boards

American Board of Nuclear Medicine (ABNM), March 25, 2020

ABNM has made a one-time modification of the case experience requirements in 2020 for all COVID-19 related reasons, as follows:

- Cardiovascular stress test supervision (exercise or pharmacologic) -75 studies (normally 100 studies)
- Pediatric nuclear medicine -75 studies (normally 100 studies)
- Radiotherapy with I-131 - 20 cases (at least 10 benign plus 10 malignant, including 3 ≤ 33 mCi and 3 > 33 mCi) (normally 30 cases)
- Parenteral therapies requiring a written directive – 3 cases (normally 5 cases)

T&E COVID-19 Adaptations: Accrediting Boards

American Board of Radiology (ABR) website:

As the organization responsible for establishing post-graduate training requirements, the **ACGME has made it clear that case log numbers are suggested targets and not absolute requirements**, and that the absolute *sine qua non* of satisfactory completion of a post-graduate training program is consensus of the program's Clinical Competency Committee that an individual trainee has satisfied all required milestones inherent in that program, and attestation to that consensus by the program director.

T&E COVID-19 Adaptations: Accrediting Boards

American Board of Radiology (ABR) website:

As the organization responsible for establishing post-graduate training requirements, CAMPEP (Commission on Accreditation of Medical Physics Education Programs) has made it clear that the absolute *sine qua non* of satisfactory completion of a post-graduate training program is attestation by a program director that an individual trainee has satisfied all required activities inherent in that program.

T&E COVID-19 Adaptations: Accrediting Boards

American Board of Radiology (ABR) website:

In certain instances, such as U.S. Nuclear Regulatory Commission (NRC) requirements for authorized user-eligibility, neither the ACGME nor the ABR have the authority to waive those requirements.

NRC T&E COVID-19 Adaptations

Medical Use Licensee Temporary Exemptions During the Emergency Caused by the COVID-19 Public Health Emergency Updated: May 8, 2020

Formally lists temporary regulatory relief for inspection/calibration frequency, annual occupational dosimetry notices, refresher training; though does not address T&E requirements (September 6, 2020)

As health care and educational institutions adapt and evolve in the pandemic/post-pandemic setting, is there an opportunity to streamline regulations via rulemaking or other instruments?

Conclusion

The ACMUI T&E Subcommittee looks forward to continuing its review of T&E requirements.

Acronyms

- ABNM – American Board of Nuclear Medicine
- ABR – American Board of Radiology
- ACGME – Accreditation Council for Graduate Medical Education
- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- ANP – authorized nuclear pharmacist
- AU – authorized user
- CAMPEP – Commission on Accreditation of Medical Physics Education Programs
- RSO – Radiation Safety Officer
- T&E – training and experience

ACMUI Evaluation of Extravasations

Melissa C. Martin

ACMUI Nuclear Medicine Physicist

November 18, 2020

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Disclosures

None

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Subcommittee Members

- Vasken Dilsizian, M.D.
- Richard Green
- Melissa Martin (Chair)
- Michael Sheetz
- Megan Shober
- Laura Weil (former member)

- NRC Staff Resource: Maryann Ayoade and Said Daibes, Ph.D.

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Subcommittee Charge

Re-evaluate and provide recommendations on the NRC decision on infiltrations and extravasations published in the *Federal Register*, Volume 45, No. 95, on May 14, 1980.

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Purpose of the Subcommittee

Subcommittee and its Chair were appointed by ACMUI Chairman, Dr. Christopher Palestro, at the ACMUI meeting on April 3, 2019, to review the NRC current decision on infiltrations and extravasations when radionuclides are injected into patients.

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Criteria for Misadministration from May 14, 1980 *Federal Register* (45 FR 95)

- Misadministration means the administration of:
  - wrong source
  - wrong patient
  - wrong route of administration
  - diagnostic dose differing by more than 50% from prescription
  - therapeutic dose differing by more than 10% from prescription

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Exclusion of Extravasation from Misadministration Definition

- Specific request for the NRC to review this exclusion as stated in the May 14, 1980 FR:
  - "Extravasation is the infiltration of injected fluid into the tissue surrounding a vein or artery.
  - Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections.
  - It is virtually impossible to avoid.
  - Therefore, the Commission does not consider extravasation to be a misadministration."

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Medical Event Definition: 10 CFR 35.3045

- 10 CFR 35.3045 "Report and Notification of a Medical Event" (published in 2002) changed "misadministration" to "medical event."

- Medical event is defined as a discrepancy of a total dosage of +/- 20% delivered dose.

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Prior Discussions of Extravasation of Radiopharmaceuticals

- Clinical aspects of extravasation of radiopharmaceuticals has been discussed previously by the ACMUI at the December 18, 2008 and May 8, 2009 meetings.

- Decisions at both of these meetings was that extravasation of radiopharmaceuticals not be considered to be a medical event at that time.

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Technology Presentation at April 3, 2019 ACMUI Meeting

At the April 3, 2019 ACMUI meeting, a technology was presented that identifies:

- Extravasations of PET radiopharmaceutical injection sites early in the process.
- The effect on the Standardized Uptake Value (SUV) of tumors or organs when extravasation occurs.

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Clinical Aspects of Extravasation

- Main point of discussion of extravasation of radiopharmaceuticals is that the denominator for this problem is several million injections per year of **ALL** radiopharmaceuticals injected.
- Extravasation problem is **NOT LIMITED to PET** isotopes only.
- Prevention of extravasation is a medical training issue for the Authorized User (AU) physician and the technologist under the supervision of the AU, which is considered medical practice.

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SUV of F-18 PET Isotopes

- Currently, 48 radiopharmaceuticals approved by the FDA, including five IV therapeutic drugs.

- Extravasation of the 6 fluorinated compounds, including the F-18 PET drugs, can bring about discrepancies in the SUV.

- SUV value is **NOT** relied on solely.

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Isotopes Other than F-18

- For isotopes other than FDG isotopes used for PET, it is difficult to quantify non-F-18 drugs left at the injection site and difficult to assign the radiation dose attributable to it.
- When extravasation of radiopharmaceuticals occurs, there is a variable delay in the biodistribution of the isotope after injection.
- **NONE** of the total doses in these extravasations meet the NRC's medical event criteria.

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Extravasation Occurrences

- This subcommittee does not consider extravasation a de facto medical event.
- Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid.
- Not all nuclear medicine cameras in use today (PET and SPECT) can quantify the amount of radiopharmaceutical localized in the extravasation site.
- Subcommittee members are unaware of any cases of documented patient harm due to extravasation as of today.

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Subcommittee Conclusion

Extravasation is a practice of medicine issue and not an item that needs to be regulated by the NRC.

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Subcommittee Recommendations

- There is no evidence at this time for the subcommittee to recommend a reclassification of extravasation at the injection site for radiopharmaceuticals to be considered a medical event.
- The subcommittee recommends that extravasations that lead to “unintended permanent functional damage” be reported as a Medical Event under 10 CFR 35.3045(b).

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Subcommittee Recommendations

The subcommittee recommends that extravasations be considered a type of passive "patient intervention," similar to the recommendations from the ACMUI Subcommittee (Presented during the ACMUI public meeting in October 2015 and referenced in the Patient Intervention Subcommittee report dated April 27, 2017) and should be captured in the NRC's current definition of patient intervention under 10 CFR 35.2.

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Minority Opinion

- One member of the subcommittee had a different perspective on potential medical event reporting due to extravasation.
  - This member wants extravasation occurrences that trigger ME criteria of >50 rem tissue dose or <80% of the prescribed dose delivered to the patient, to be reported as a Medical Event. This would be consistent with all other MEs that cause no patient harm and are currently required to be reported. The exclusion of extravasation is inconsistent with other regulation and is unwarranted.

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- AU – authorized user
- FDA – U.S. Food and Drug Administration
- FDG – fluorodeoxyglucose
- FR – *Federal Register*
- IV – intravenous therapy
- ME – medical event
- NRC – U.S. Nuclear Regulatory Commission
- PET – positron emission tomography
- SPECT – single-photon emission computed tomography
- SUV – Standardized Uptake Value

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ACMUI's Comments on Patient Intervention and Other Actions Exclusive of Medical Events

Michael Sheetz
ACMUI Radiation Safety Officer
November 18, 2020

Subcommittee Members

- Mr. Gary Bloom
- Dr. Vasken Dilsizian
- Dr. Ronald Ennis
- Mr. Mike Sheetz (chair)

- NRC Staff Resource: Dr. Said Daibes-Figueroa

Issue

Determine what types of events are intended to be captured by the term “patient intervention” and what should or should not be reported as a Medical Event

Revised Medical Event Reporting Requirement (2002)

- Medical Event (ME) criteria revised to include a dose threshold and be more risk based
- Purpose of reporting ME
  - To evaluate if there was a breakdown in the licensee's program
  - Take corrective action If there was a generic issue that should be reported to other licensees

Specific Exclusions to Medical Event Reporting Requirement

- Extravasation - the infiltration of injected fluid into the tissue surrounding a vein or artery (1980)
- Brachytherapy sources implanted in the correct site but migrated outside the treatment site (2002)
- Patient Intervention - actions by the patient, whether **intentional** or **unintentional**, such as dislodging or removing treatment devices or prematurely terminating the administration (2002)

Specific Exemptions to Medical Event Reporting in 10 CFR 35.1000

- RSL Licensing Guidance, Revision 1
  - Patient fails to return for explant surgery
  - Determination not to explant seed due to various patient conditions
- Y-90 Microsphere Licensing Guidance, Revision 10
  - Emergent patient conditions (artery spasm or sudden change in blood pressure)
  - Stasis or dose to wrong treatment site due to shunting

Types of Patient Intervention

- **Intentional or "voluntary" physical actions** taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment

- **Unintentional or "involuntary" actions** resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment

Extravasation - Type of Patient Intervention

- Contributing factors
  - Injection technique
  - Patient anatomy
- Exceeding ME dose threshold doesn't indicate error or harm
- Controlling for extravasation is a medical practice issue

ACMUI Position on Medical Events and Patient Intervention

- Purpose of ME reporting is to evaluate problem in licensee program, or generic issue that should be reported to other licensees
- Unanticipated event that occurs during properly performed clinical procedure, that results from actions taken by the patient which could not have been reasonably prevented, or results from anatomical or physiological condition of the patient, should not need to be reported as a ME
- Reporting such unavoidable patient specific events will not help to prevent such events in the future, and doing so would potentially infringe on the practice of medicine

ACMUI Recommendations

- Current definition of “patient Intervention” should be interpreted to include both **intentional (or voluntary)** actions taken by the patient, and **unintentional (or involuntary)** actions
- Medical Events resulting from “patient intervention” should not need to be reported as it would potentially infringe on the practice of medicine, and it will not help to prevent such events in the future
- Medical Events resulting from patient intervention which result in unintended permanent functional damage to an organ or a physiological system should be reported as required by 10 CFR 35.3045(b)

Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- ME – medical event
- RSL – radioactive seed localization
- Y-90 – yttrium-90

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Trends in Radiopharmaceuticals

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ACMUI Nuclear Medicine Physician

November 18, 2020

Disclosures

Agents covered in this presentation are investigational and not currently approved for clinical use

Outline

- Recent approvals
- Focus on oncologic & theranostic agents
- Summary

Trends in Radiopharmaceuticals

YEAR	Neuropsychiatric	Oncologic
2012	^{18}F-florbetapir (*Amyvid*^{R})	^{11}C-choline
2013	^{18}F-futemetamol (*Vizamyl*^{R})	^{223}Ra dichloride (*Xofigo*^{R})
2014	^{18}F-florbetaben (*NeuraCeq*^{R})	
2016		^{18}F-fluciclovine (*Axumin*^{R}) ^{68}Ga-DOTATATE (*Netspot*^{R})
2018		^{177}Lu-DOTATATE (*Lutathera*^{R}) ^{131}I-Iobenguane (*Azedra*^{R})
2019	^{18}F-fluorodopa	^{68}Ga-DOTATOC
2020	^{18}F-flortaucipir (*Tauvid*^{R})	^{64}Cu-DOTATATE (*Detectnet*^{R}) ^{18}F-fluoroestradiol (*Cerianna*^{R})

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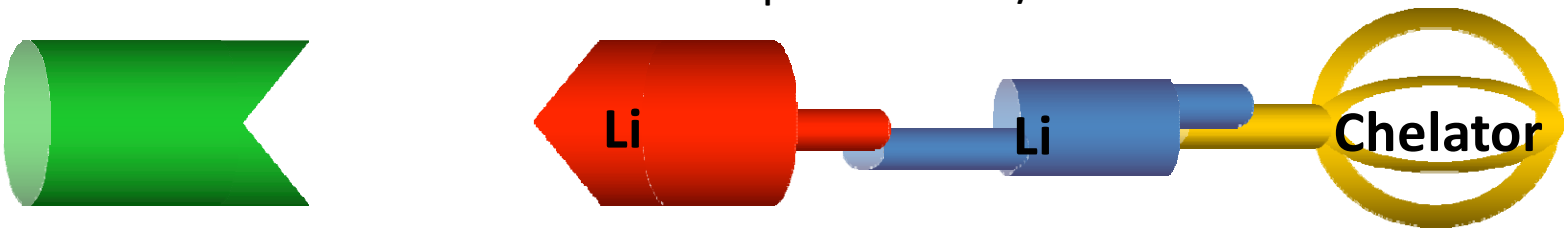
THERANOSTICS
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Radioactive Drugs for Imaging and Targeted Therapy



Targets
- antigens (e.g. CD8, HER2)
- receptors (e.g. SSTR)
- Enzymes (e.g. PSMA)
- transporters

Molecular Address
- antibodies, minibodies, affibodies, aptamers
- peptides (agonists & antagonists)
- amino acids

Reporting Unit
- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga, ^{18}F

Cytotoxic Unit
- ^{90}Y, ^{177}Lu, ^{67}Cu, ^{131}I
- ^{213}Bi, ^{225}Ac, ^{227}Th
- ^{212}Pb, ^{211}At, ^{149}Tb

Courtesy R. Baum (modified)

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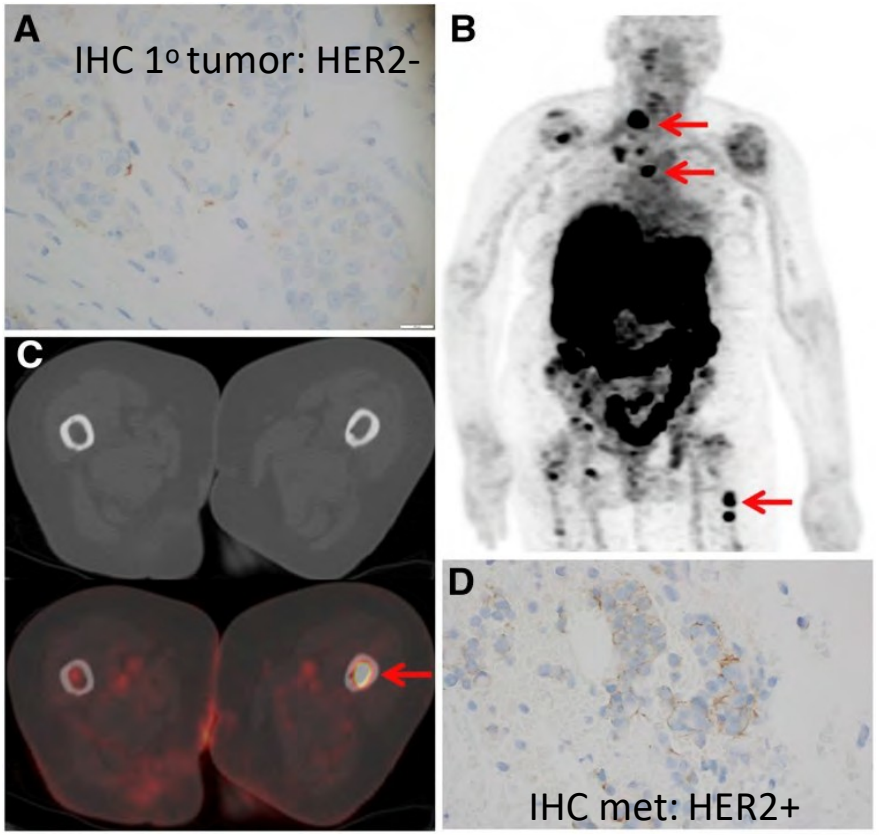
Oncologic & Theranostics

^{89}Zr-trastuzumab

- Human epidermal growth factor receptor 2 (HER2)– targeted PET tracer
- HER2-positive metastases in patients with HER2-negative primary breast cancer
- HER2-targeted imaging can identify additional candidates for HER2-targeted therapy



Ulaner GA, JNM 2016

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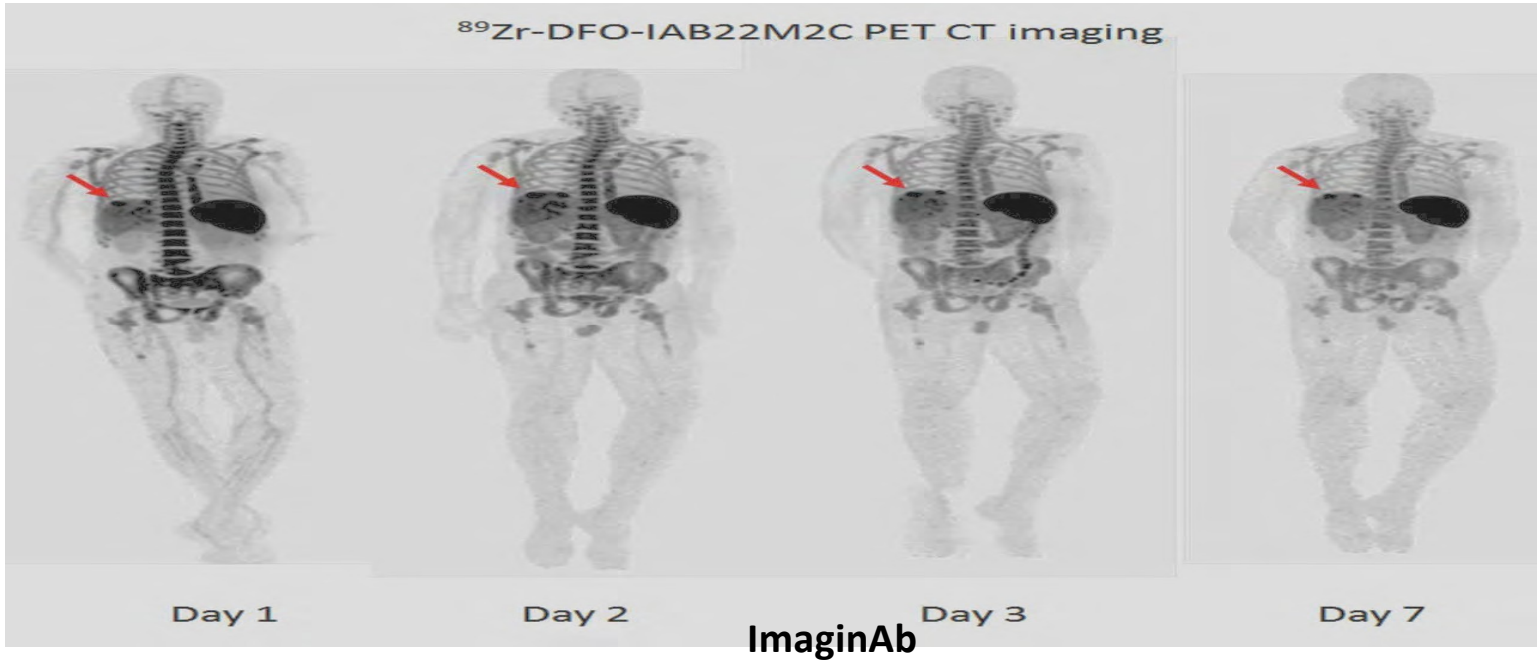
Oncologic & Theranostics

^{89}Zr-IAB22M2C anti-CD8 Minibody



ClinicalTrials.gov Identifier NCT03802123: Phase II, Open Label, Multi-Dose Study of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) for PET/CT in Patients with Metastatic Solid Tumors; N=40 (recruiting); 3 mCi (±20%) IV before & 4-5 wks after Rx; RECIST 1.1/iRECIST – Pandit-Taskar N, JNM 2020

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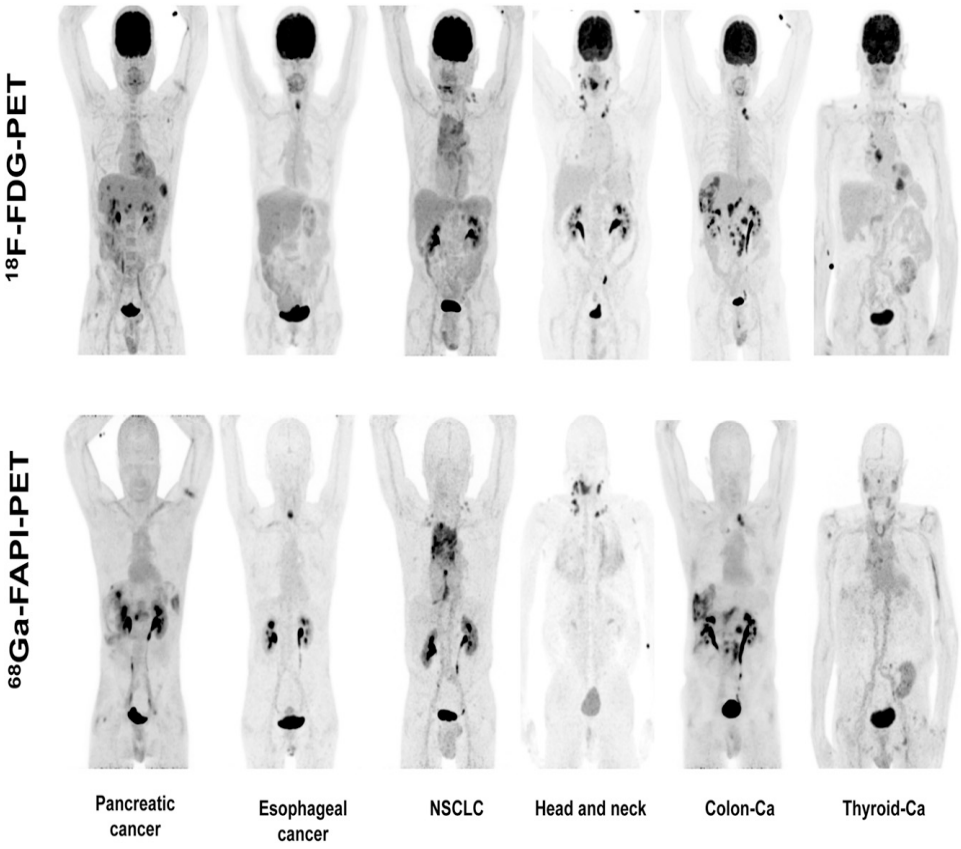
Oncologic & Theranostics

^{68}Ga-FAPI

- Fibroblast activation protein inhibitor (FAPI)
- FAP: type II membrane-bound glycoprotein enzyme with peptidase activity; highly expressed on cell surface of activated fibroblasts (wound healing, inflammation, fibrosis, *cancer associated fibroblasts*)
- **FAP-targeted theranostics**



Kratochwil C, JNM 2019

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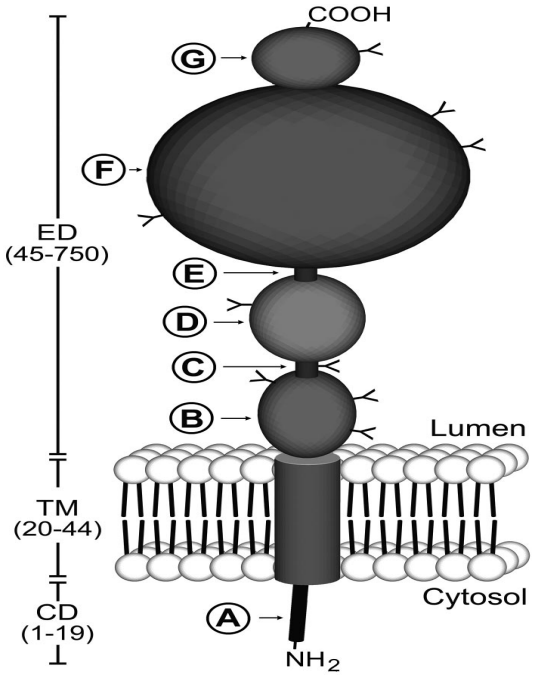
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

- Transmembrane enzyme (folate hydrolase 1 (FOLH1); carboxypeptidase)
- Expressed in secretory cells of prostate epithelium, small bowel, proximal renal tubule, salivary glands, brain, neovasculature of many tumors
- Undergoes internalization constitutively
- Over-expressed in aggressive tumors, met/rec dz. (1000x nl./benign, ~2M/cell)



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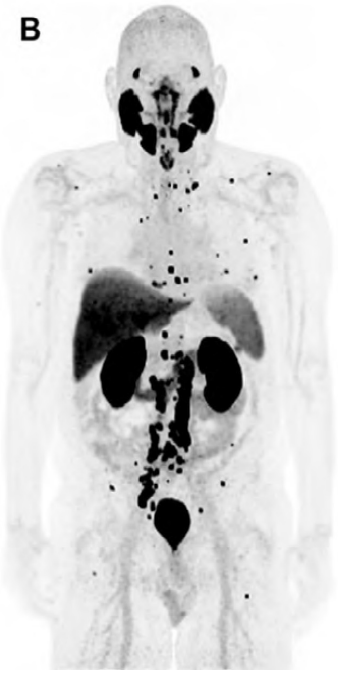
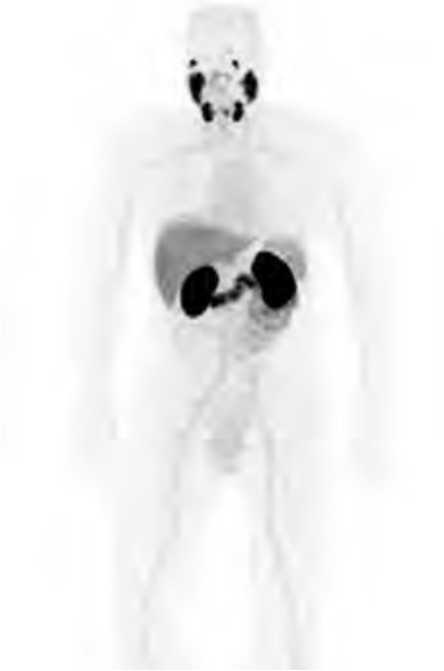
Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

^{68}Ga-PSMA-11



^{18}F-DCFPyL



^{18}F-PSMA-1007

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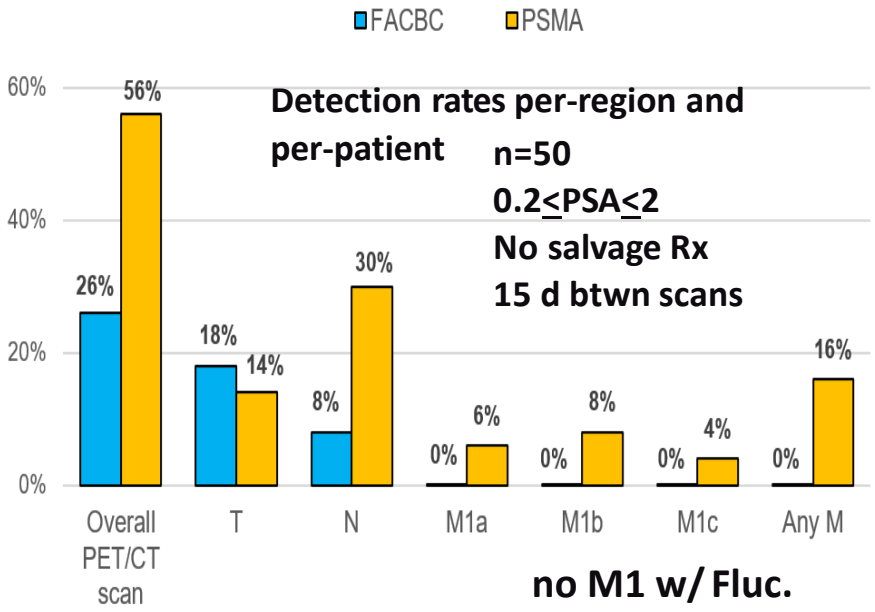
^{68}Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to ^{18}F-Fluciclovine PET/CT in a prospective head-to-head comparative phase 3 study

Calais J, Ceci F, Eiber M, Elashoff D, Grogan T, Dahlbom M, Slavik R, Gartmann J, Nguyen K, Lok V, Reiter RE, Rettig MB, Jadvar H, Bach-Gansmo T, Savir-Barush B, Nanni C, Rischpler C, Hofman M, Hope TA, Fendler WP, Czernin J



	Multi-rater Kappa (95% CI)		
Region	PSMA	^{18}F-fluciclovine	p
Tr	0.65 (0.49,0.81)	0.43 (0.27,0.59)	0.046
N	0.76 (0.60,0.92)	0.05 (-0.11,0.21)	<0.001
M1a	0.60 (0.44,0.76)	-0.02 (-0.18,0.14)	<0.001
M1b	0.46 (0.30,0.62)	-0.03 (-0.19,0.13)	0.003
M1c	0.65 (0.49,0.81)	-0.01 (-0.17,0.15)	0.004
AnyM	0.60 (0.44,0.76)	-0.07 (-0.23,0.09)	<0.001
PET/CTscan	0.67 (0.51,0.83)	0.20 (0.04,0.36)	0.015

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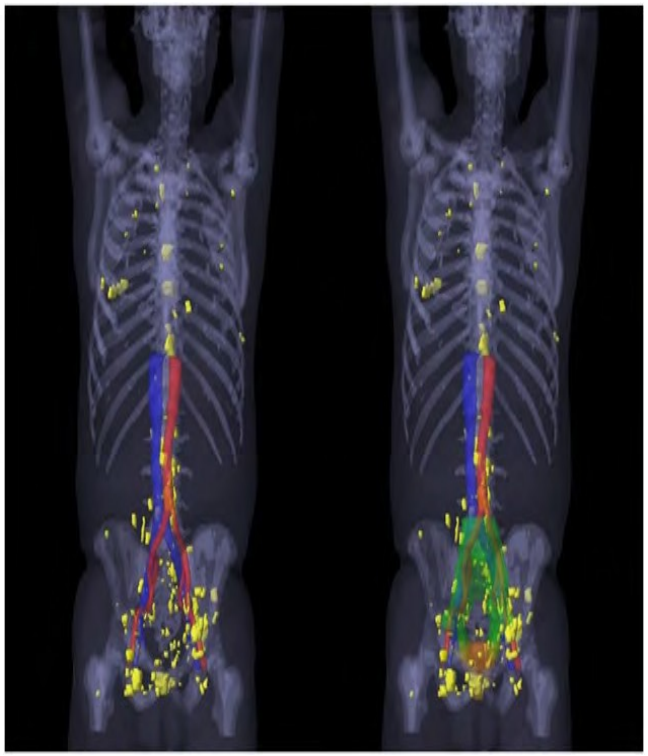
Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning

JNM 2018

Jeremie Calais[1], Johannes Czernin[1], Minsong Cao[2], Amar U. Kishan[2], John V. Hegde[2], Narek Shaverdian[2], Kiri Sandler[2], Fang-I Chu[2], Chris R. King[2], Michael L. Steinberg[2], Isabel Rauscher[3], Nina-Sophie Schmidt-Hegemann[4], Thorsten Poeppel[5], Philipp Hetkamp[5], Francesco Ceci[1], Ken Herrmann[1,5], Wolfgang P. Fendler[1,6], Matthias Eiber[1,3], and Nicholas G. Nickols[2,7]



49% pts +PSMA

19% pts with at least 1+ lesion not covered by RTOG guidelines CTVs

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PSMA-SRT Trial

Calais *et al. BMC Cancer* (2019) 19:18
https://doi.org/10.1186/s12885-018-5200-1

BMC Cancer

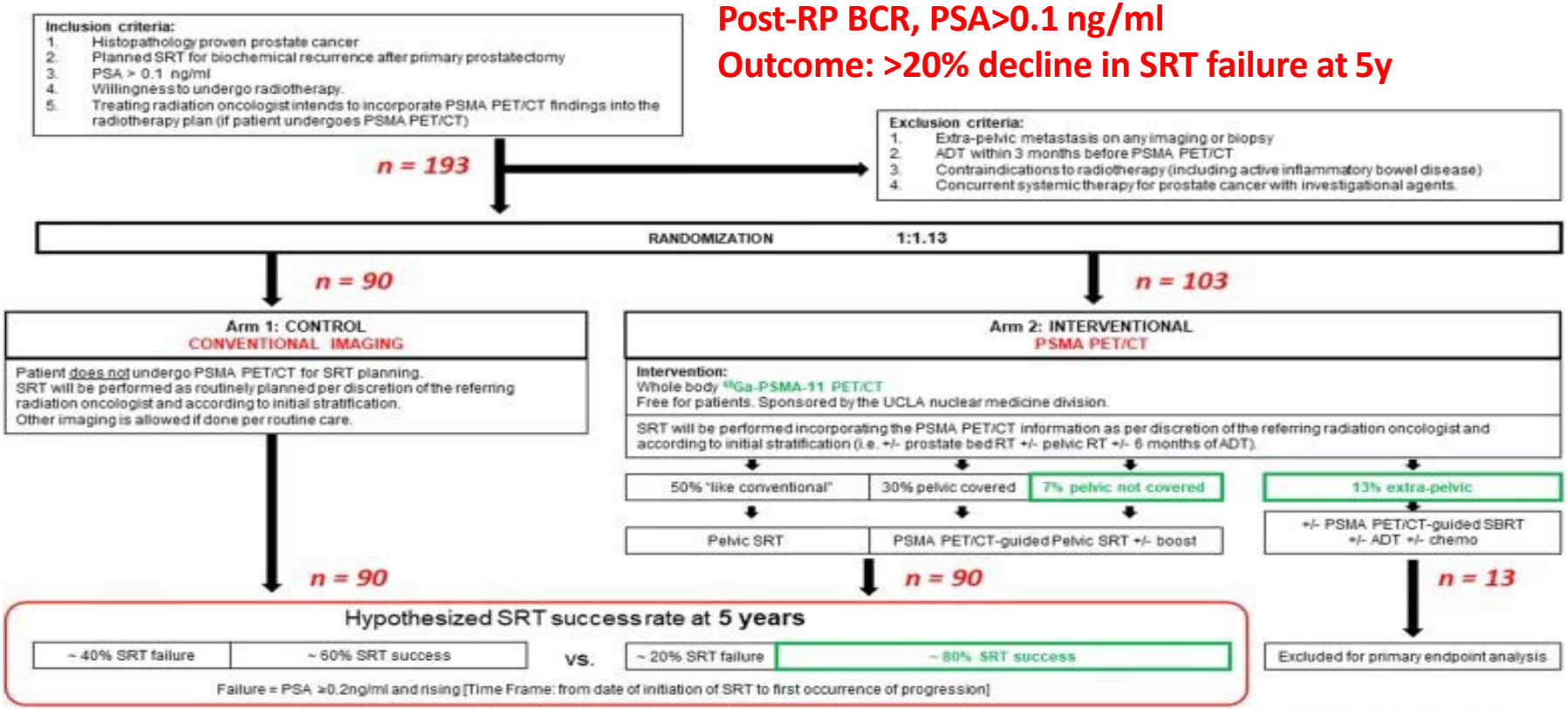
STUDY PROTOCOL Open Access

Randomized prospective phase III trial of ^{68}Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]

Jeremie Calais[1*], Johannes Czernin[1*], Wolfgang P. Fendler[1,2], David Elashoff[3] and Nicholas Nicholas G. Nickols[4,5]

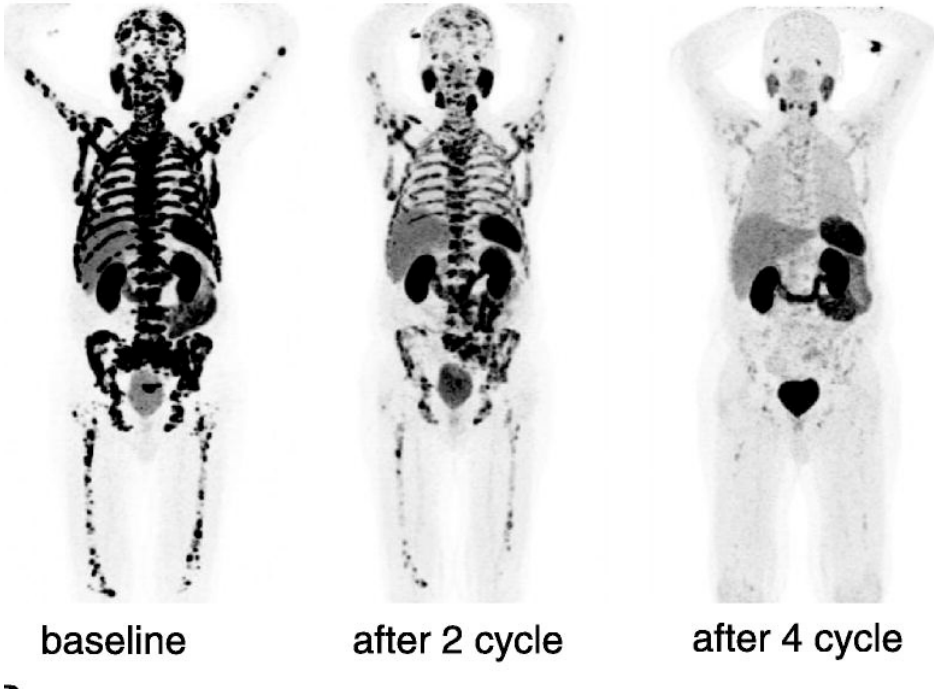
Post-RP BCR, PSA>0.1 ng/ml

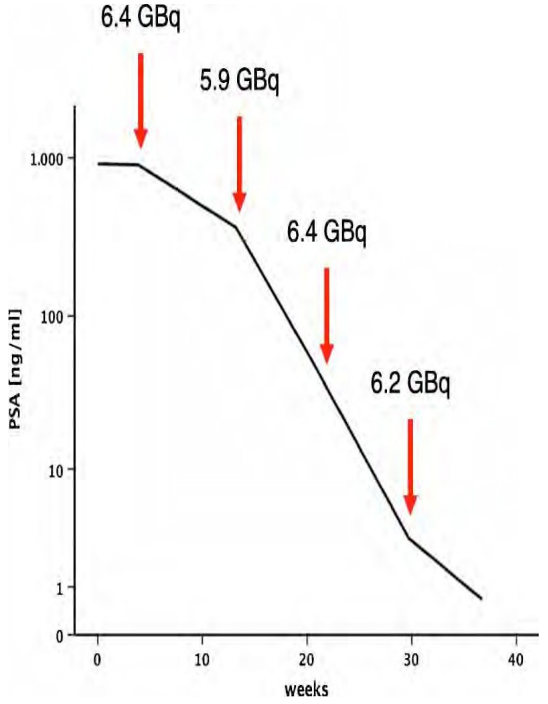
Outcome: >20% decline in SRT failure at 5y



Oncologic & Theranostics

^{177}Lu-PSMA-617





Roll W, CNM 2017

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[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Michael S Hofman, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu*

- 30 men mCRPC
- Prior Rx: 87% chemo, 83% ADT
- PSMA+ / FDG-
- RLT: 7.5 GBq/cycle x 4 cycles q6w
- 1 (100%), 2 (93%), 3 (80%), 4 (47%)
- **PSA decline ≥50% -- 57% of patients**
- 82% objective response
- 37% improvement in global health

Lancet Oncol 2018

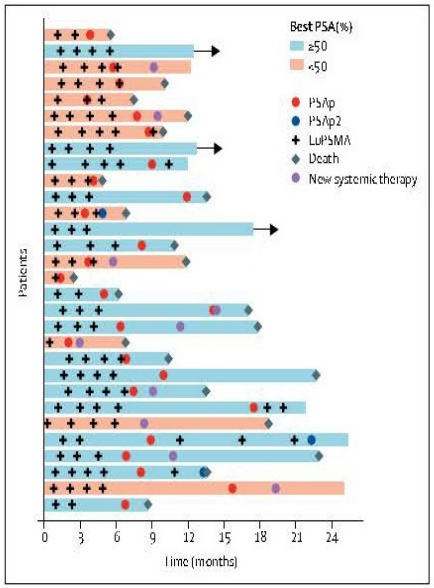


Figure 2: **Patient events**
Arrow indicates patients without PSA progression up to cut-off date. PSA=prostate-specific antigen. LuPSMA=lutetium-prostate-specific membrane antigen. PSAp2=second-PSA progression in patients with initial response who progressed after trial completion and responded to further LuPSMA.

study was sponsored by the Peter MacCallum Cancer Centre (Melbourne, Australia). All authors had full access to all of the data. The corresponding author takes final responsibility for the analysis and decision to submit for publication.

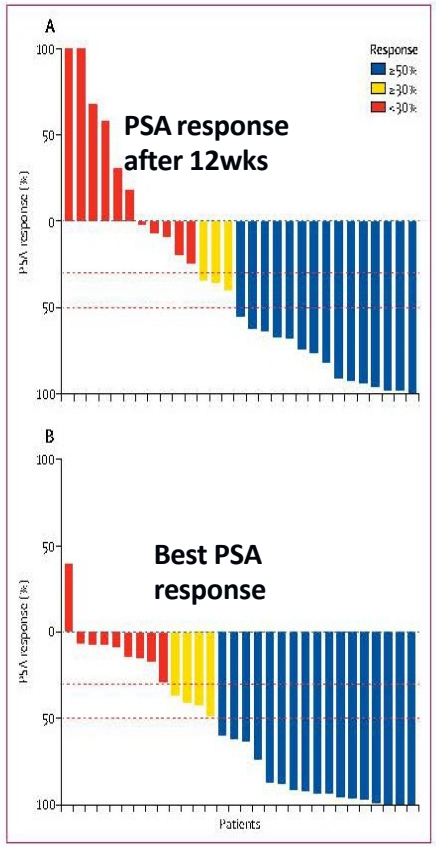
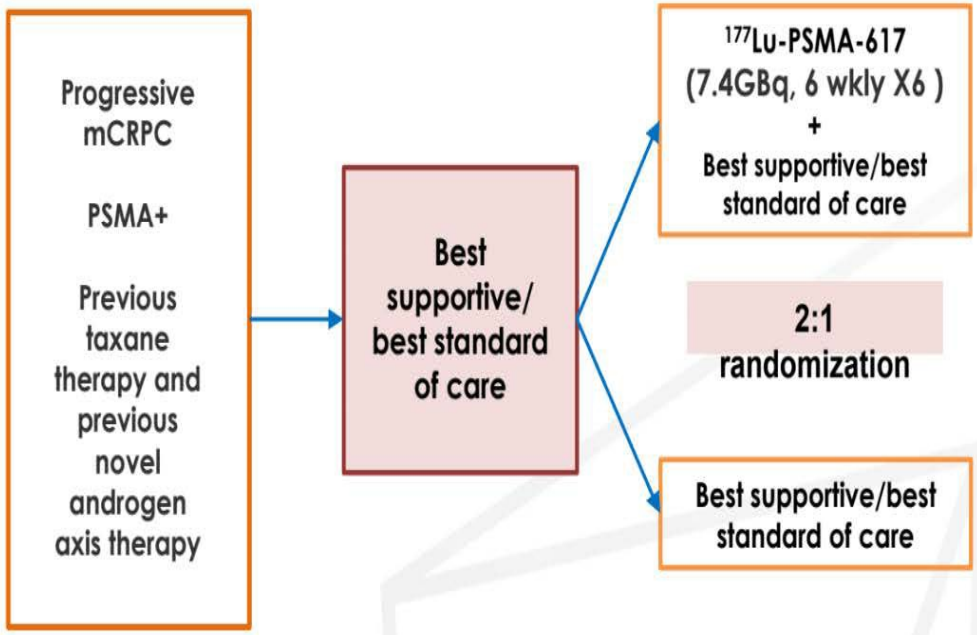


Figure 3: (A) PSA response after 12 weeks* and (B) best PSA response from

VISION Trial: ^{177}Lu-PSMA versus best supportive care

Phase III



Primary Endpoint
- Overall survival

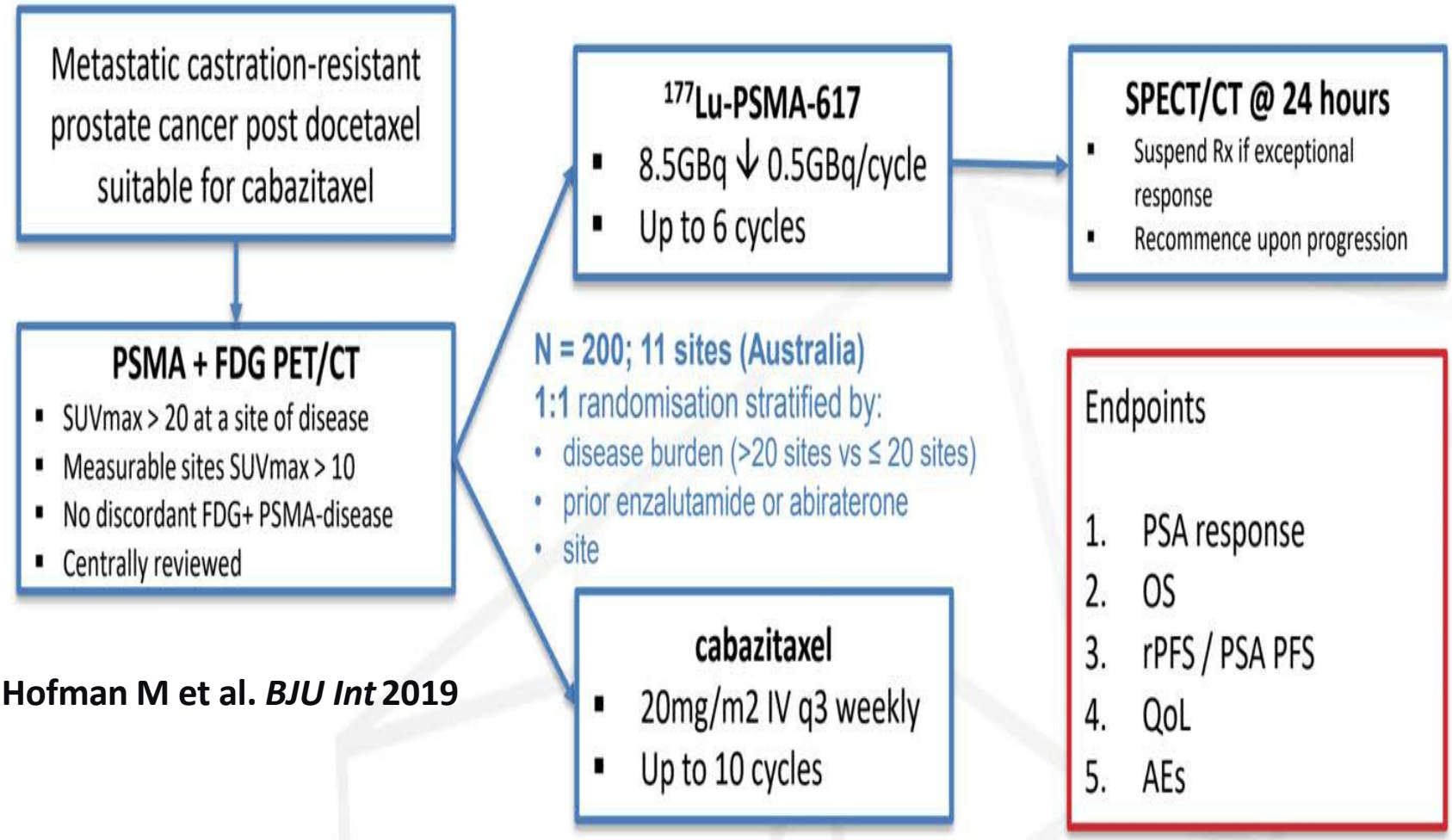
Key Secondary Endpoints
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

- 9 Countries (NA and EU)
- >750 patients recruited
- 12-14 months FU min 15 month

Enocyte/Novartis
NCT03511664
Rahbar et al, *J Nucl Med* 2019

TheraP Trial: ^{177}Lu-PSMA-617 vs. cabazitaxel

Phase II, ANZUP 1603

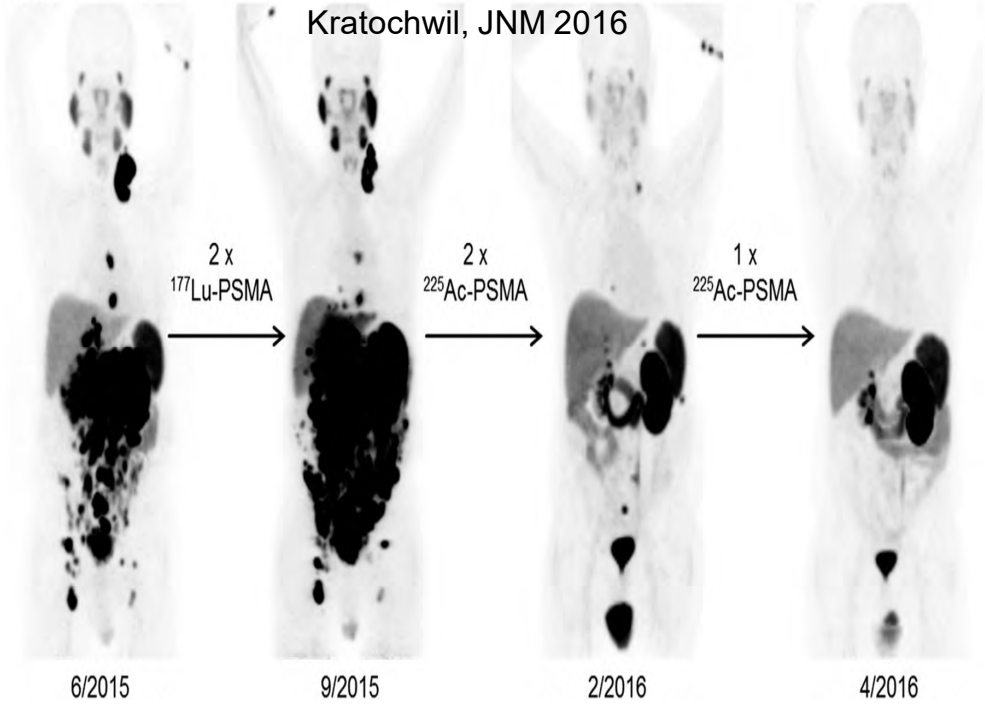


Hofman M et al. *BJU Int* 2019

Oncologic & Theranostics

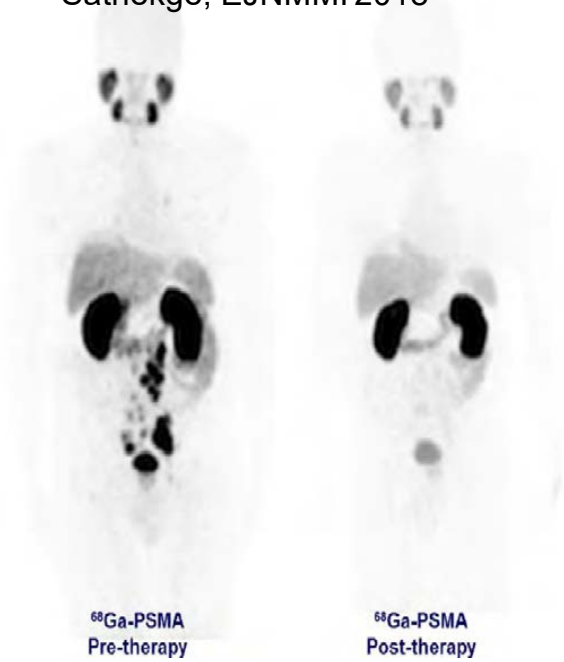
^{225}AC-PSMA-617

Kratochwil, JNM 2016



^{213}Bi-PSMA-617

Sathekge, EJNMMI 2018



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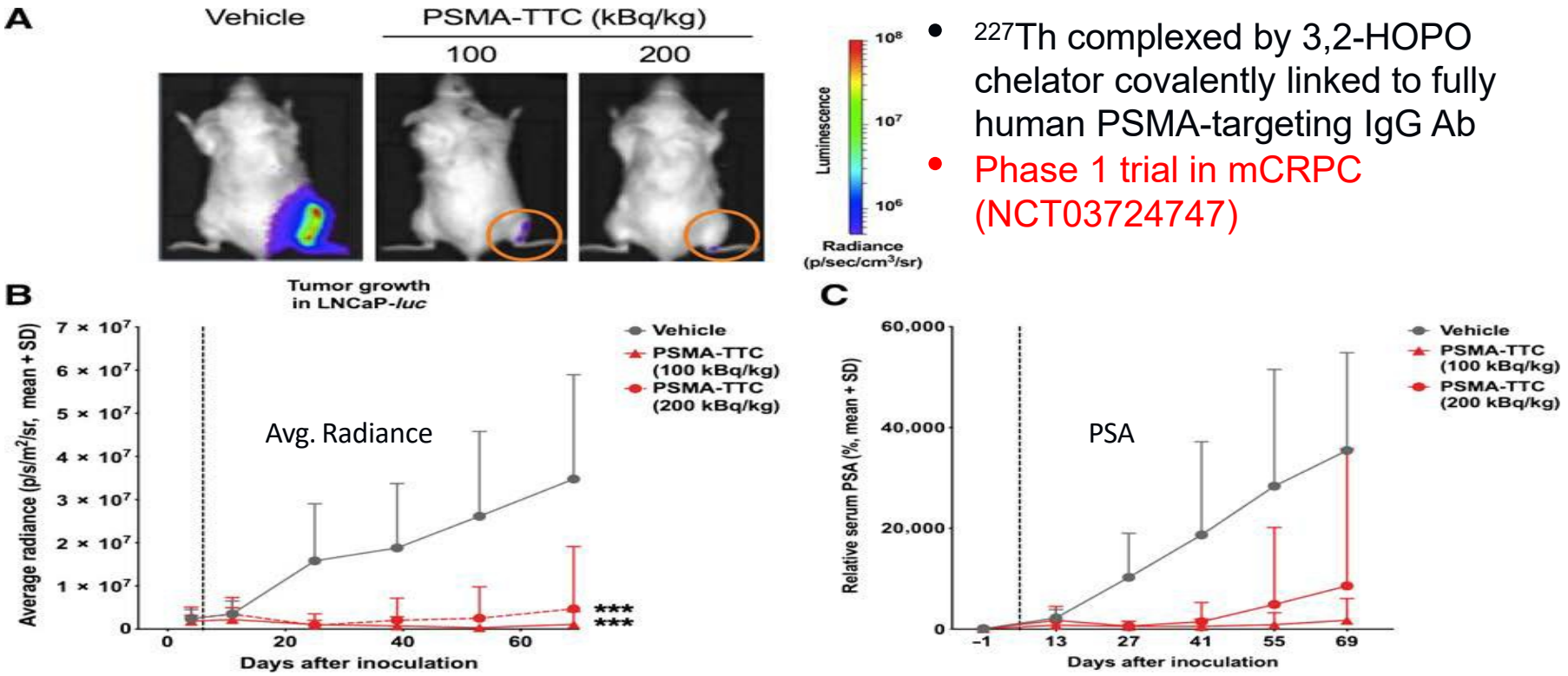
Preclinical Efficacy of a PSMA-Targeted Thorium-227 Conjugate (PSMA-TTC), a Targeted Alpha Therapy for Prostate Cancer

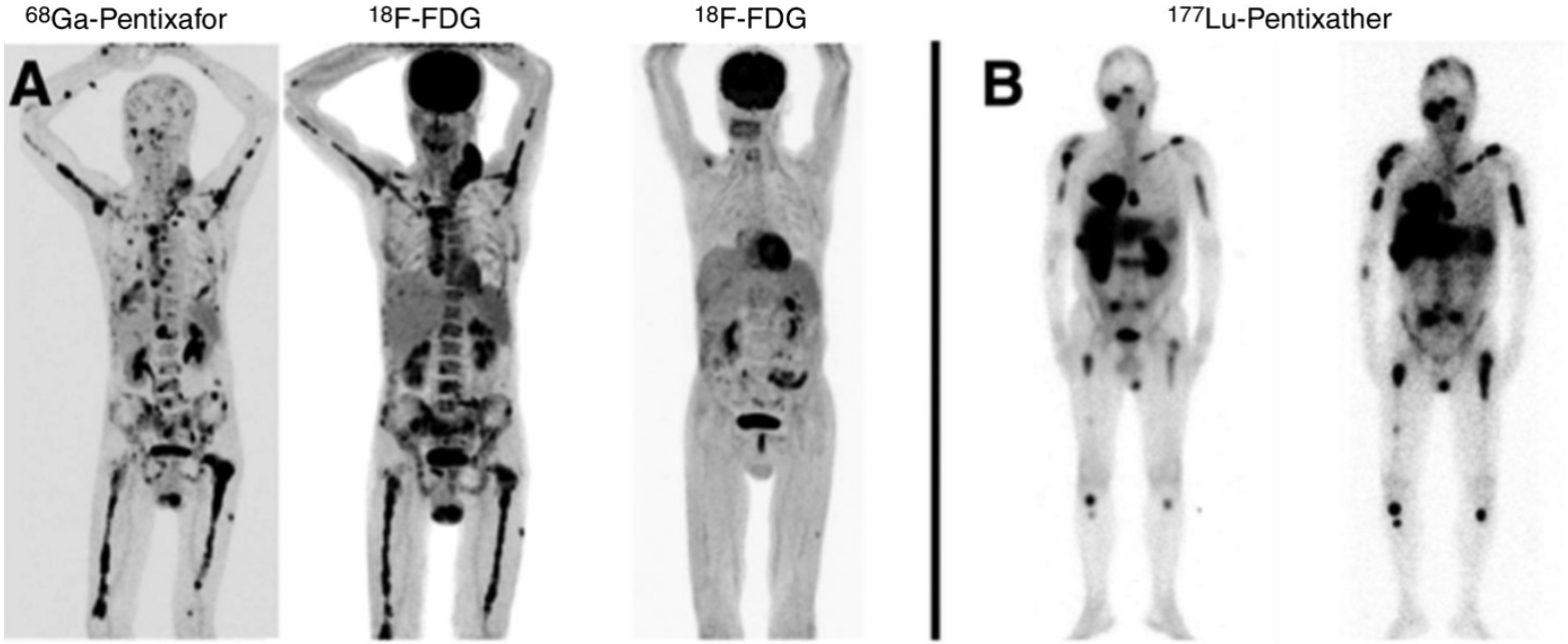
Stefanie Hammer[1], Urs B. Hagemann[1], Sabine Zitzmann-Kolbe[1], Aasmund Larsen[2], Christine Ellingsen[2], Solene Geraudie[2], Derek Grant[2], Baard Indrevoll[2], Roger Smeets[2], Oliver von Ahsen[1], Alexander Kristian[2], Pascale Lejeune[1], Hartwig Hennekes[1], Jenny Karlsson[2], Roger M. Bjerke[2], Olav B. Ryan[2], Alan S. Cuthbertson[2], and Dominik Mumberg[1]



- ^{227}Th complexed by 3,2-HOPO chelator covalently linked to fully human PSMA-targeting IgG Ab
- Phase 1 trial in mCRPC (NCT03724747)

C-X-C Motif Chemokine Receptor 4 (CXCR4)

Roles in tumor initiation, progression, and metastasis in many cancers (lung, breast, colorectal, pancreas, prostate, **multiple myeloma**)



Herrmann K, J Nucl Med 2016

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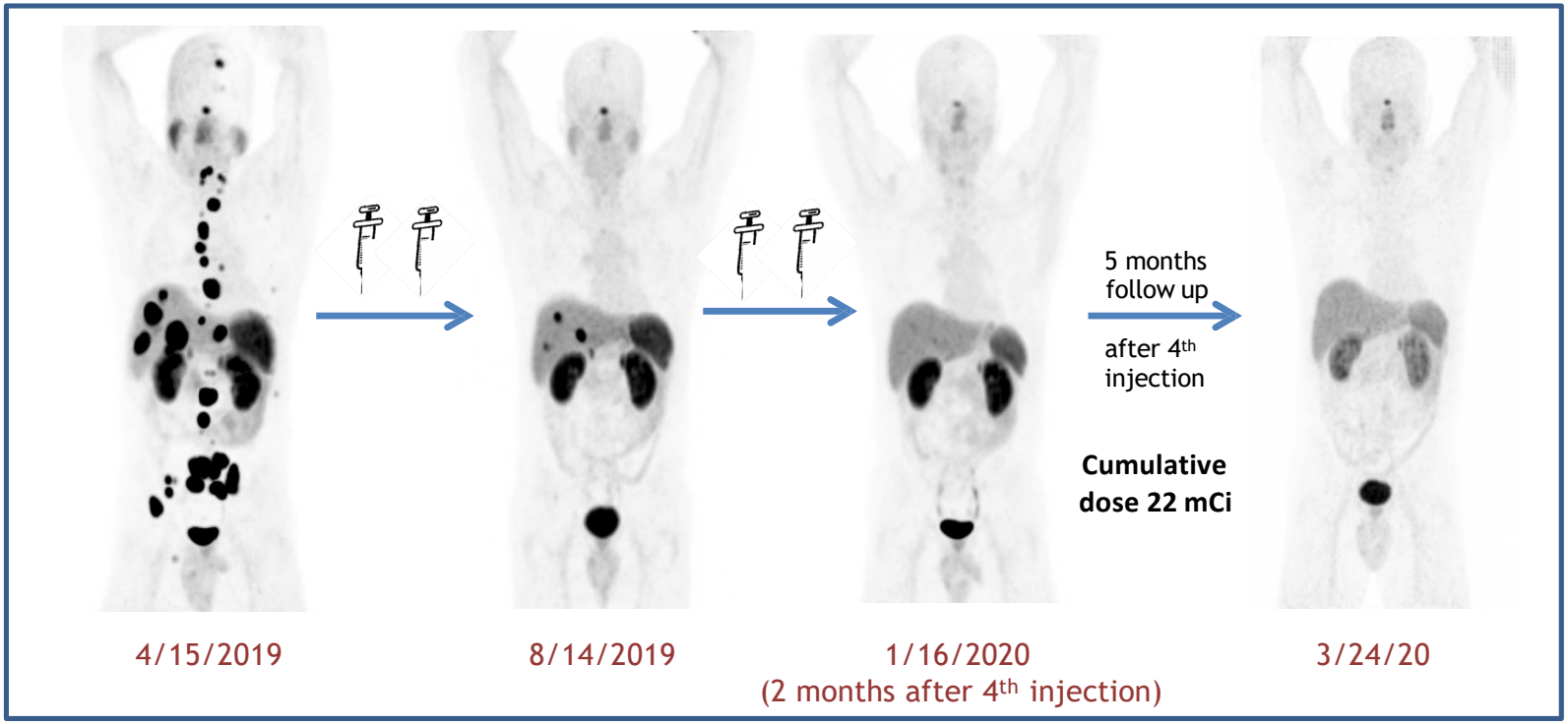
^{212}Pb-DOTAMTATE Alpha Therapy in NET

^{68}Ga-DOTATATE PET/CT scans



A Phase 1, Non-Randomized, Open-Label, Dose Escalation, Single-Center Study to Determine the Safety and Bio-distribution and Preliminary Effectiveness of Pb^{212}-DOTAMTATE (AlphaMedix™) in Adult Subjects with Somatostatin Receptor Expressing Neuroendocrine Tumors (NET) – IND #133661

Delpassand ES et al. (Radiomedix Inc.)

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Summary

Theranostics will continue to grow with the approval and clinical introduction of agents for targeted imaging and radioligand therapy of cancer.

Acronyms

- CT: computed tomography
- CXCR4: C-X-C motif chemokine receptor 4
- FAPI: fibroblast activation protein inhibitor
- FDG: fluorodeoxyglucose
- HER2: human epidermal growth factor receptor 2
- PET: positron emission tomography
- PSMA: prostate-specific membrane antigen
- SSTR: somatostatin receptor