U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Overview of ACMUI Activities

Darlene Metter, M.D.
ACMUI Chair/Diagnostic Radiologist
December 6, 2022

Today's Agenda

- Darlene Metter, MD (ACMUI Chair, Diagnostic Radiologist)
  - Overview of ACMUI Activities

- Michael O'Hara, PhD (FDA Representative)
  - ACMUI's Review of Yttrium-90 Medical Events

Today's Agenda (cont'd)

- Hossein Jadvar, MD PhD (ACMUI Nuclear Medicine Physician)
  - Emerging Radiopharmaceuticals in an Expanding Nuclear Arena
  - Impacts of the American Board of Radiology's Request to Terminate NRC Recognition of the American Board of Radiology's Board Certification Processes

Today's Agenda (cont'd)

- Megan Shober (Agreement State Representative)
  - ACMUI's Comments on the NRC Staff's Regulatory Basis for the Rulemaking on Emerging Medical Technologies and Rubidium-82 Generators

Overview of the ACMUI

- ACMUI Role
- Membership
- 2022 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 (13 members)

- Nuclear Medicine Physician (Dr. Hossein Jadvar)
- 2 Radiation Oncologists (Drs. Ronald Ennis & Harvey Wolkov)
- Nuclear Cardiologist (Vacant position)
- Diagnostic Radiologist (Dr. Darlene Metter)
- Nuclear Pharmacist (Mr. Richard Green)
- FDA Representative (Dr. Michael O'Hara)

ACMUI Membership (13 members) (cont'd)

- 2 Medical Physicists: Nuclear Medicine (Ms. Melissa Martin) & Radiation Therapy (Mr. Zoubir Ouhib)
- Patients' Rights Advocate (Mr. Josh Mailman)
- Agreement State Representative (Ms. Megan Shober)
- Healthcare Administrator (Ms. Rebecca Allen)
- Radiation Safety Officer (Dr. Richard Harvey)

ACMUI Consultant

- Interventional Radiologist (Dr. John Angle)

ACMUI Topics Dec 2021-Oct 2022

- Alpha Dart Licensing Guidance
- CivaDerm
- EMT/Rb-82 Generator Rulemaking
- Revision to Regulatory Guide 8.39 "Release of Patients Administered Radioactive Material"
- Training and Experience for All Modalities
- Impacts of ABR's termination of NRC recognition of ABR's Board Certification Processes

ACMUI Topics Dec 2021-Oct 2022 (cont'd)

- Y-90 Medical Events
- Non-Medical Events
- Minimizing Risk of Medical Events (Y-90 therapies)

ACMUI Topics in 2022 by Non-NRC Entities

- TheraSphere Y-90 Glass Microspheres by Boston Scientific
- SIR-Spheres Y-90 Resin Microspheres by Sirtex Medical
- CORAR Comments on the NIST Radioisotope Measurement Assurance Program (RMAP) by CORAR
- Update on NIST RMAP by NIST

Staff Presentations to the ACMUI (2022)

- Review of the Lu-177-PSMA Radiopharmaceutical
- Decommissioning Financial Assurance for Sealed and Unsealed Radioactive Materials
- Radioactive Source Security and Accountability
- Medical Related Events
- ACMUI Reporting Structure
- Medical Team Updates
- INFOSEC, Ethics and Allegations Training

Current ACMUI Subcommittees

- T&E for All Modalities
- Medical Events
- Y-90 Medical Events
- Infiltrations/Extravasations and ME Reporting
- Regulatory Guide 8.39 "Release of Patients Administered Radioactive Material"
- Liberty Vision
- Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics

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
- CORAR – Council on Radionuclides and Radiopharmaceuticals
- EMT – Emerging Medical Technologies
- FDA – U.S. Food & Drug Administration
- INFOSEC – Information Security
- Lu-177 – Lutetium-177
- ME – Medical Event

Acronyms

- NIST – National Institute of Standards and Technology
- NRC – U.S. Nuclear Regulatory Commission
- PSMA – Prostate-Specific Membrane Antigen
- RMAP – Radioisotope Measurement Assurance Program
- Ru-82 – Rubidium-82
- T&E – Training and Experience

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Y-90 Microsphere Medical Events Subcommittee Report

Michael O'Hara, PhD

Advisory Committee on the Medical Uses of Isotopes

December 6, 2022

Agenda

ACMUI Subcommittee Membership
ACMUI Subcommittee Charge
Key Messages
Background
Vendor Consultation
Vender Consultation – Sirtex Medical
Vendor Consultation – Boston Scientific
Further discussion with both vendors

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Subcommittee Members

John Angle
Vasken Dilsizian
Josh Mailman
Melissa Martin
Michael O'Hara (Chair)
Megan Shober

NRC Staff Resource: Katie Tapp

ACMUI Subcommittee Charge

To evaluate the issue of Y-90 microspheres medical events in more depth and, in consultation with the vendors, propose methods to decrease the number of Y-90 microsphere medical events

Key Message

- The reported number of medical events involving Y-90 microspheres is low compared to the number of treatments performed

- However, it is important to evaluate causes of events to find ways to minimize the chance of similar types of events from happening again

Background

- Hepatic radioembolization uses Y-90 microspheres for the treatment of primary and metastatic liver malignancies
- Currently 2 vendors: Boston Scientific and Sirtex Medical
- During the past few years, both vendors have increased their hepatic radioembolization business by approximately twenty percent.
- The MEs reported during 2020 were low compared to the number of treatments performed

Background (cont.)

- MEs involving Y-90 microsphere administration continues to be the most common MEs

- Types of MEs for Y-90 microspheres included:
  - >20% residual activity remaining in the delivery device,
  - delivery device setup error,
  - wrong dose given (treatment plan calculation error),
  - wrong site treated (catheter placement error, wrong dose vial selected and wrong site listed on WD)

Background (cont.)

- A past ACMUI MEs Subcommittee noted that performance of a "time out" and the use of a checklist immediately before administration of byproduct material could have prevented some MEs

- The NRC staff issued Information Notice 19-07 to inform licensees of past ACMUI recommendations

Vendor Consultation

- The ACMUI subcommittee contacted both Y-90 microsphere vendors, Sirtex Medical and Boston Scientific, to discuss possible methods to reduce MEs

- Both vendors voluntarily met and greatly supported the subcommittee in this effort

Vendor Consultation (cont.)

- Vendors were given
  - The ACMUI MEs Subcommittee Committee report presented on October 4, 2021,
  - general questions to start the conversation, and
  - ACMUI proposed recommendations to prevent 35.1000 Y-90 microsphere MEs

- The vendors were asked if these 3 actions are appropriate and if they had any further recommendations

Proposed Actions to Prevent Future MEs

The subcommittee proposed the following actions to the vendors as possible licensee actions to prevent future MEs:

- Review mechanics of Y-90 microsphere delivery device and setup procedures
- Confirm all data and calculations in the treatment plan
- Perform “time out” at the beginning of each procedure (name, date of birth, activity etc.)

Consultation – Sirtex Medical

- Sirtex evaluated the MEs reported by licensees in the 2021 ME Subcommittee report. They Identified 4 causes:
  - Greater than 20% residual activity remaining in the delivery device not due to vascular stasis
  - The wrong dose given (treatment plan calculation error)
  - The wrong site treated (catheter placement error)
  - The wrong site (written directive error)
- Sirtex agreed that greater use of the ACMUI recommendations by licensees may prevent MEs due to device set-up and procedural errors.

Consultation – Sirtex Medical (cont.)

Additional Actions Sirtex has taken that may reduce MEs

- Developed a Microsphere Activity Calculator
  - Second check against the activity identified in WD

Consultation – Sirtex Medical (cont.)

Actions Sirtex has taken that may reduce MEs

- Enhance Training Evaluation Certification Program
  - All necessary nuclear medical / radiation safety support is present
  - Includes in-service site visits and proctor assessments
  - Minimum frequency of use to continue treatments
  - More vendor staff in close contact with licensees

Consultation – Boston Scientific (cont.)

Vendor identified issues and currently available potential solutions:

- >20% volume Y-90 spheres left in delivery device – may need improved quality systems
- Events related to the delivery device – enhancements to the WD and /or increased familiarization with the device
- Wrong dose due to calculation errors, catheter placement errors or wrong dose vial – software tools

Consultation – Boston Scientific (cont.)

Resources provided to aid in the planning and facilitation of Y-90 treatments:

- Software tools to assist licensees in treatment planning and ordering Y-90 microspheres
  - TheraSphere Now® - online ordering tool
  - TheraSphere Treatment Window Illustrator® - spreadsheet ordering tool
  - TheraSphere iDoc® - online dose ordering tool

Consultation – Boston Scientific (cont.)

Resources provided to aid in the planning and facilitation of Y-90 treatments:

- IFU supported by training at new sites for physician authorized users, RSOs and support staff
- TheraSphere® Administration Checklist instructs users to confirm patient identity, instructions for administration set priming, dose vial preparation, administration set assembly final assembly before administration and disassembly and cleanup

ACMUI Recommendations

There should be further discussion with vendors to:

- Understand fully how these programs can reduce MEs
- How the vendor judges the effectiveness of these programs
- How the vendor tests the accuracy of spreadsheet or software tools
- What steps are being taken to minimize the chance of clogged microcatheters which causes residual activity to remain in delivery device

ACMUI Recommendations (cont.)

- Investigate the utility of software programs and checklists provided by the microsphere vendors with licensees.
- Issue information notice and speak at conferences to alert licensees of past MEs and share the ACMUI subcommittee recommended actions to reduce Y-90 microsphere MEs.

Acronyms

- ACMUI – Advisory Committee on the Medical Use of Isotopes
- MEs – Medical Events
- WD -Written Directive
- Y-90 –Yttrium 90
- IFU – Instructions for Use

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Emerging Radiopharmaceuticals in an Expanding Nuclear Medicine Arena

Hossein Jadvar, MD, PhD, MPH, MBA

Advisory Committee on the Medical Uses of Isotopes
December 6, 2022

Agenda

- Recent approvals
- PSMA Theranostics
  - Imaging trials
  - Therapeutic trials
- Summary
- Acronyms

Trends in Radiopharmaceuticals

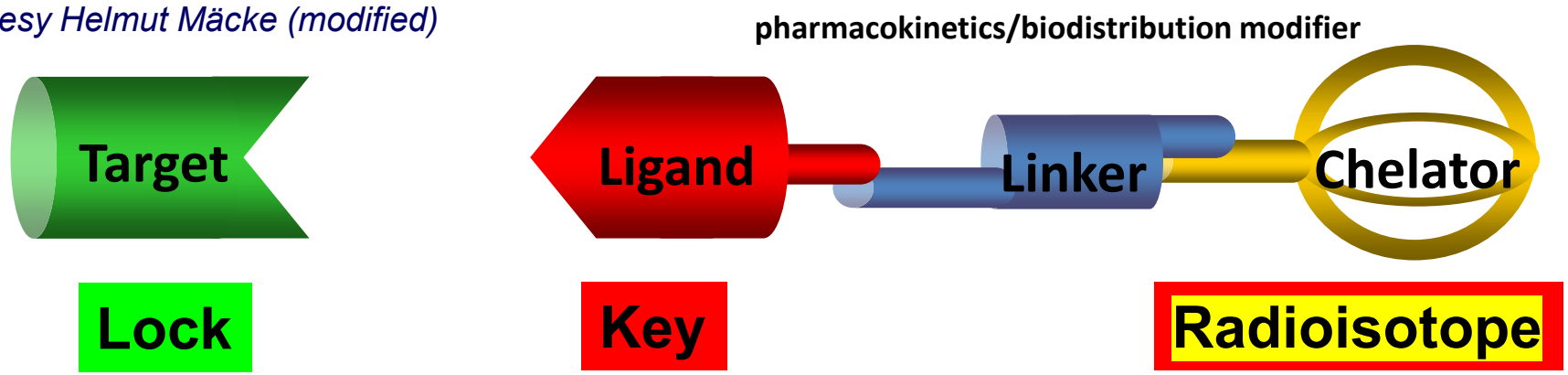
Recent Approvals

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}) ^{68}Ga-PSMA-11 *(UCSF, UCLA)*
2021		^{18}F-DCFPyL *(Pylarify*^{R}*)*
2022		*^{177}Lu*-vipivotide tetraxetan *(Pluvicto*^{R}*)*

THERANOSTICS
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Schematic Representation of an Agent for Imaging and Targeted Therapy

Courtesy Helmut Mäcke (modified)



Lock | **Key** | **Radioisotope**

Biological Targets

- antigens (e.g., CD20, HER2)
- GPCR (e.g. SSTR)
- enzymes & inhibitors (e.g., PSMA)
- transporters

Molecular Ligands

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

Reporting Unit

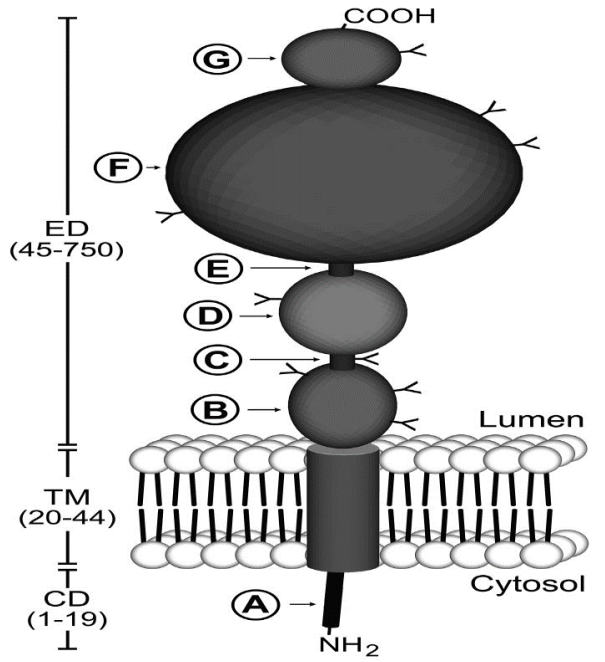
- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{18}F, ^{68}Ga
- Gd^{3+}

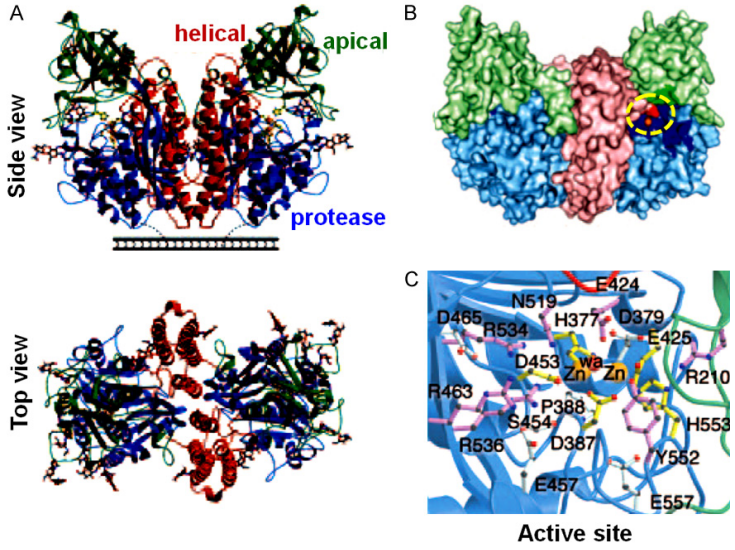
Cytotoxic Unit

- ^{90}Y, ^{177}Lu, ^{213}Bi, ^{225}Ac
- ^{105}Rh, ^{67}Cu, $^{186,188}Re$

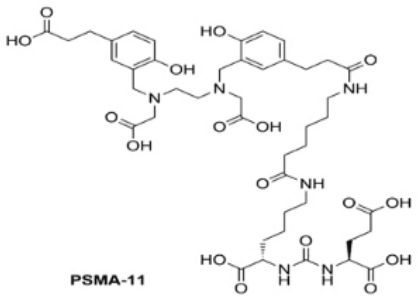
Prostate-Specific Membrane Antigen (PSMA)

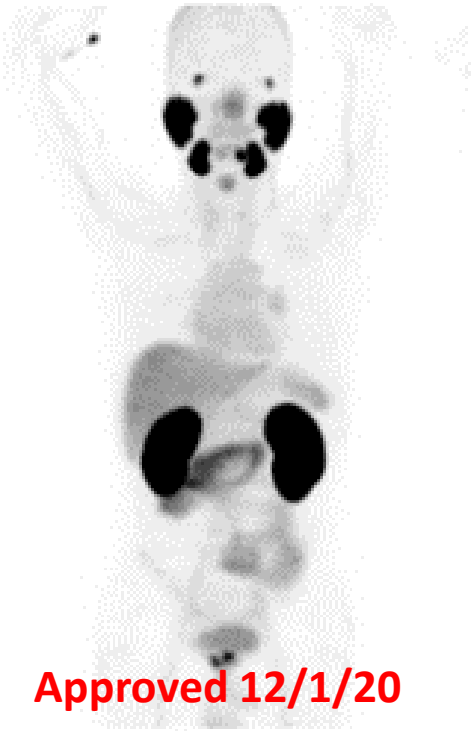
- Type II transmembrane enzyme (FOLH1; carboxypeptidase)
- Release of glutamate from folates, activation of glutaminergic system, redirecting cell survival signaling from MAPK pathway to PI3K/Akt oncogenic pathway
- LOW: secretory cells of prostate epithelium, brain
- MOD/HIGH: small bowel, proximal renal tubule, salivary glands, tumor neovasculature
- Undergoes internalization constitutively
- Over-expressed in aggressive PrCa, met/rec dz. (1000x nl./benign, ~2M/cell)
- 5-10% CAP no PSMA expression
- Intra- and inter-tumor heterogenous PSMA expression





PSMA PET

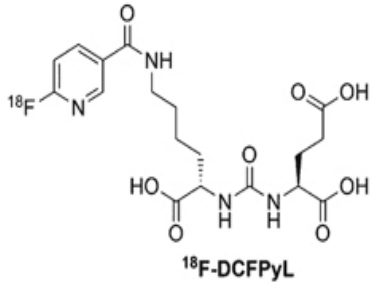


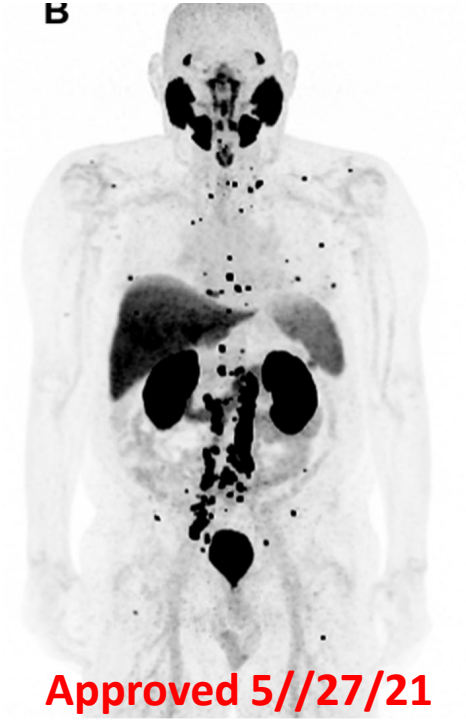


Approved 12/1/20

^{68}Ga-PSMA-11

(Illuccix; Locametz)

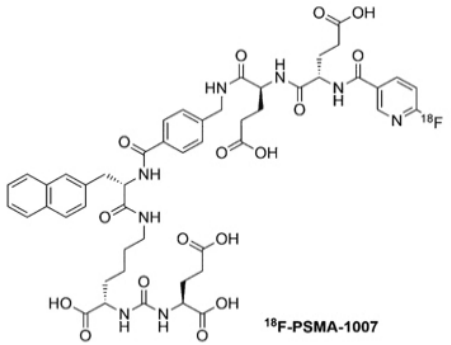


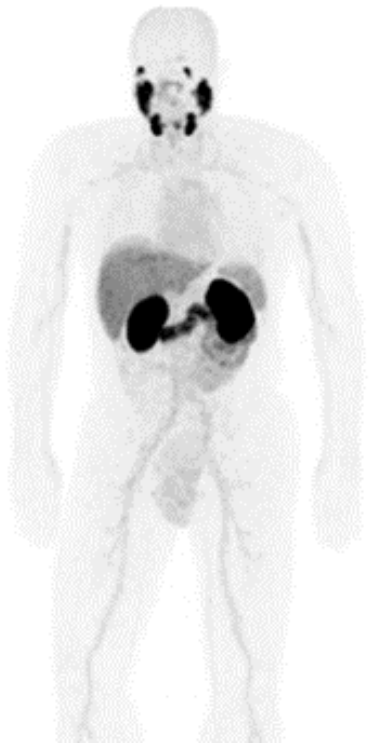


Approved 5//27/21

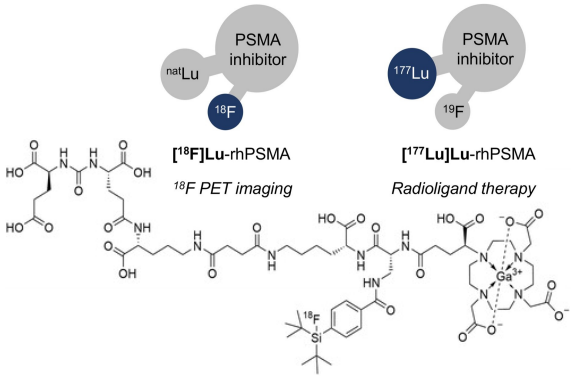
^{18}F-DCFPyL

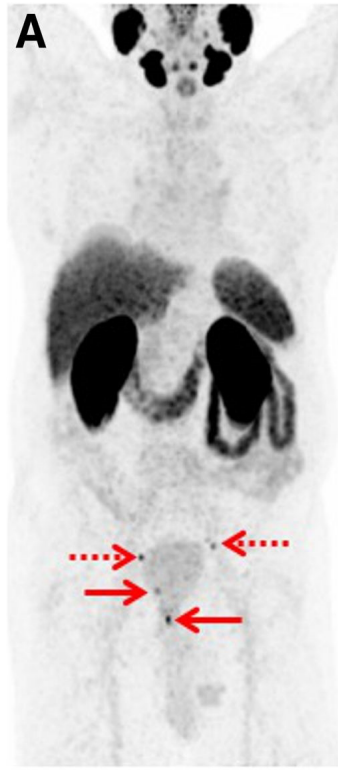
(Pylarify)





^{18}F-PSMA-1007

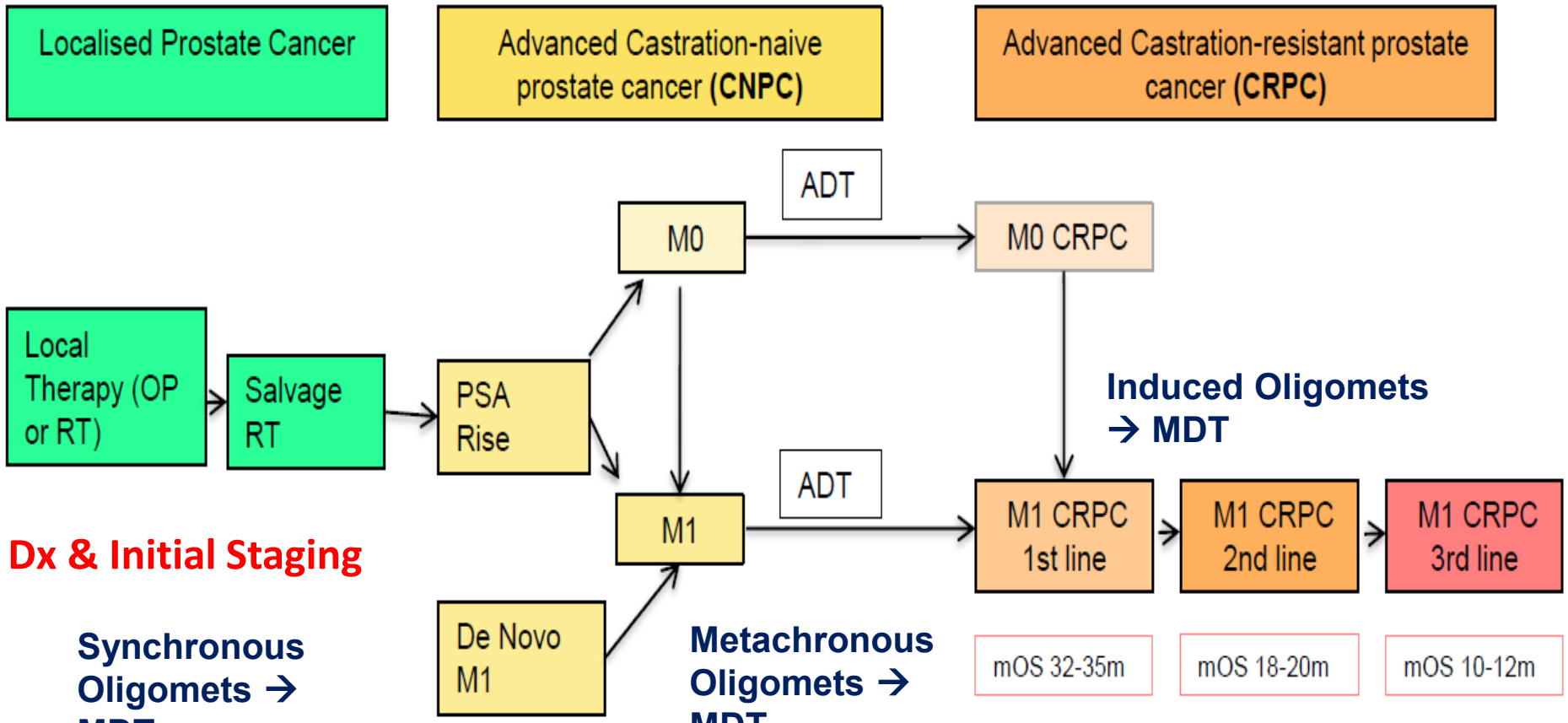




^{18}F-rhPSMA-7.3

Prostate Cancer

Natural History



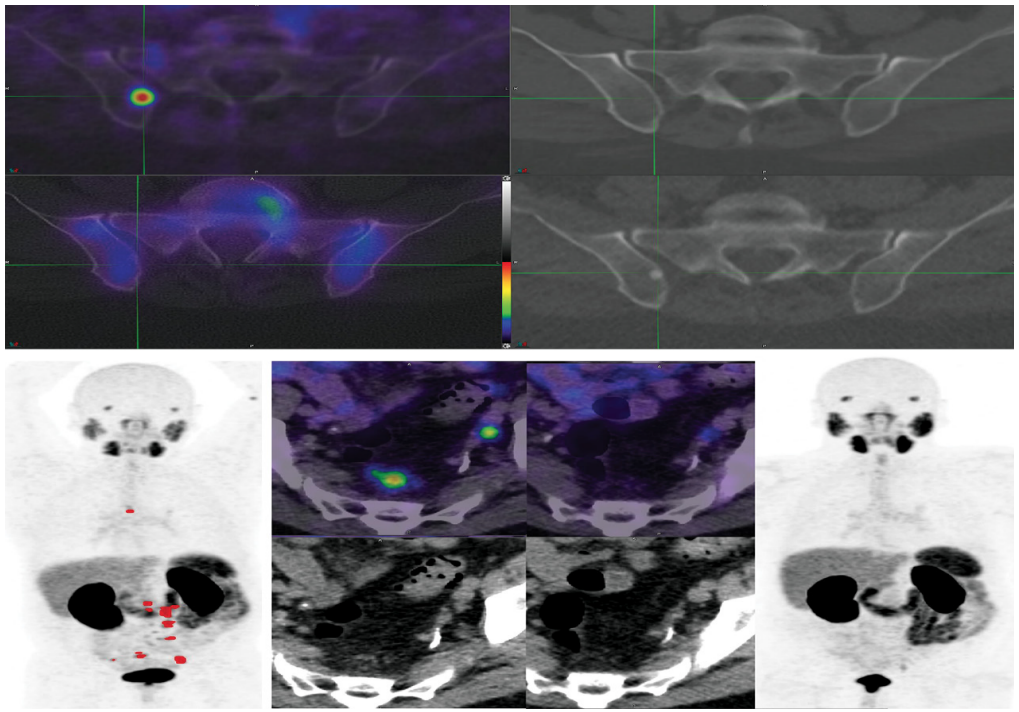
ADT: Androgen deprivation
M0: no evidence of metastatic disease
M1: metastatic disease on imaging

Omlin, 2016

proPSMA
Lancet 2020

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study

*Michael S Hofman, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators**



HiRsk: either of PSA≥20, ISUP 3-5, Clin Stage≥T3 PSMA PET-CT has better accuracy, with consequent management change, fewer equivocal results, and lower radiation exposure compared with CI → **CAN REPLACE CI**

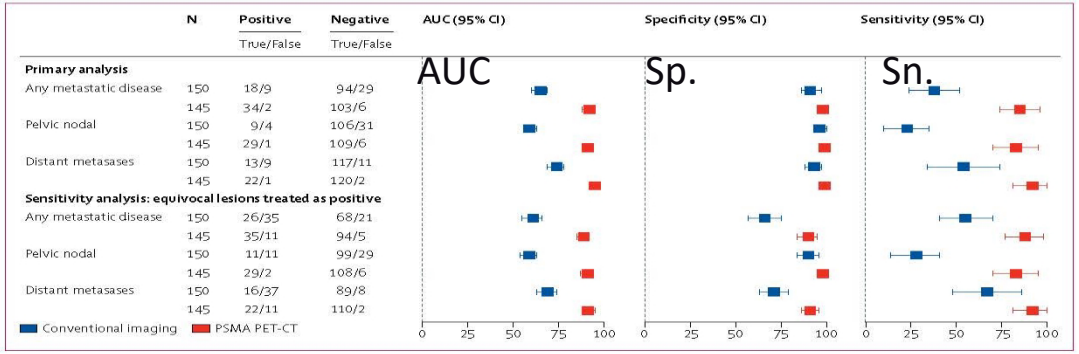


Figure 2: Accuracy, sensitivity, and specificity of conventional imaging compared with PSMA PET-CT
PSMA=prostate-specific membrane antigen. AUC=area under the curve.

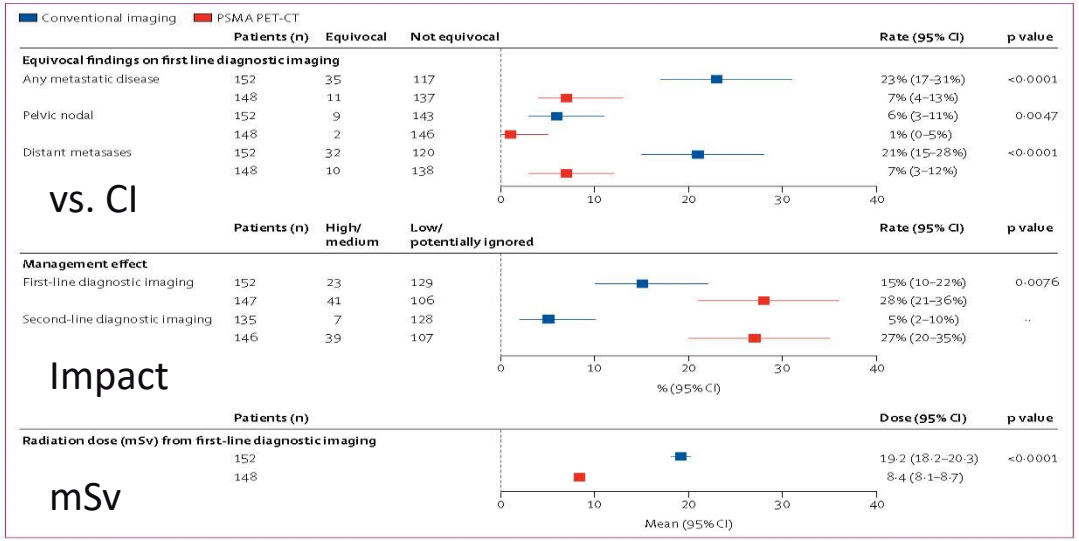


Figure 3: Equivocal findings, management effect, and radiation exposure of conventional imaging compared with PSMA PET-CT
PSMA=prostate-specific membrane antigen.

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OPEN

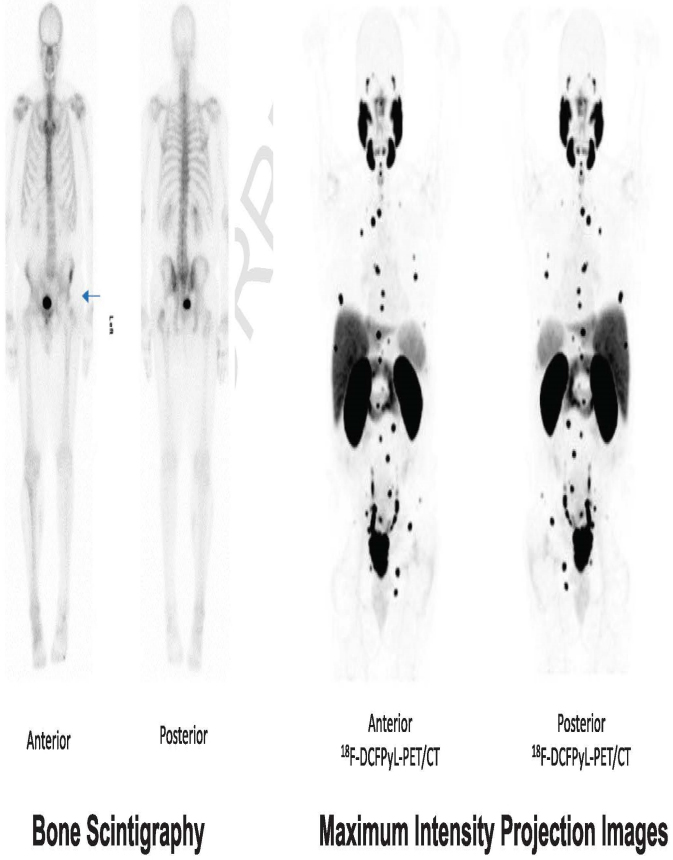
OSPREY

2021

A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with ^{18}F-DCFPyL in Prostate Cancer Patients (OSPREY)

Kenneth J. Pienta,* Michael A. Gorin,† Steven P. Rowe, Peter R. Carroll,‡ Frédéric Pouliot, Stephan Probst, Lawrence Saperstein, Mark A. Preston, Ajjai S. Alva,§ Akash Patnaik, Jeremy C. Durack,|| Nancy Stambler,¶ Tess Lin,¶ Jessica Jensen,¶ Vivien Wong,¶ Barry A. Siegel,¶,** Michael J. Morris¶,†† and OSPREY Study Group

- **Cohort A** (n=252) high-risk ca undergoing RP+PLND (SOT:+histo)
- Pelvic LN (sn 40.3%, sp 97.9%, ppv 86.7%, npv 83.2%); sn endpoint met w/ LN size > 5 mm
- **M0 to M1 12.3%**
- **Cohort B** (n=93) suspected rec/met on CI



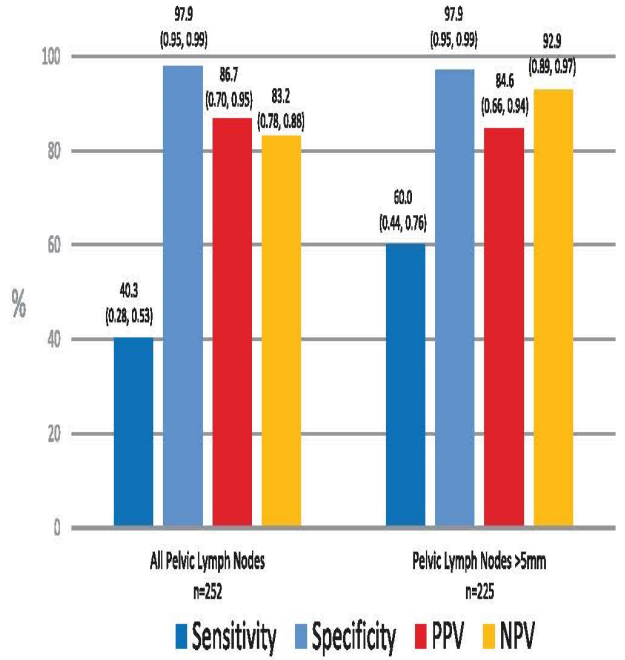


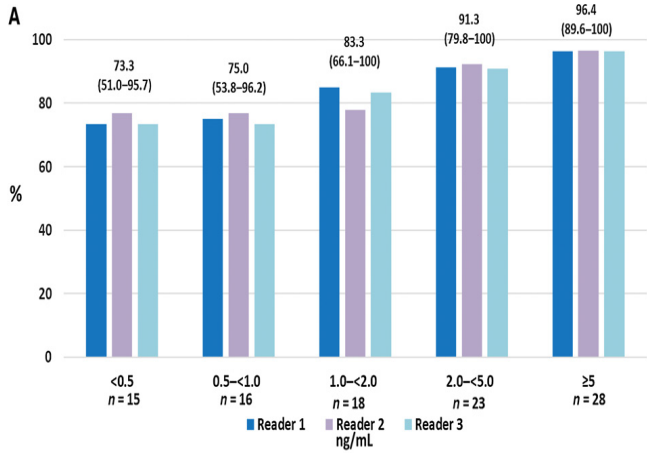
Figure 3. ^{18}F-DCFPyL-PET/CT diagnostic performance (median of 3 independent readers) in high-risk prostate cancer in cohort A.

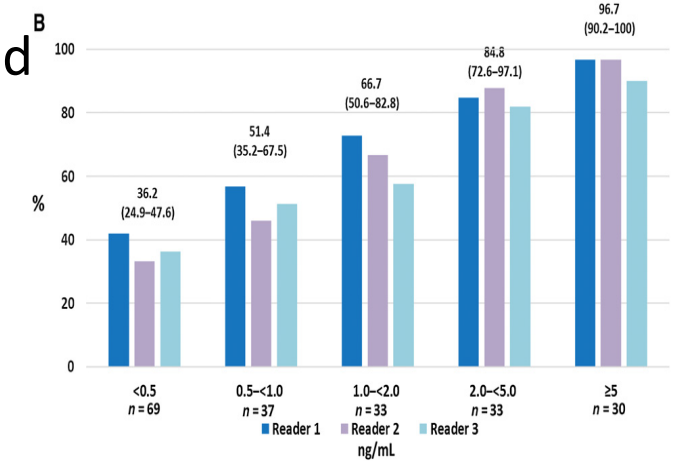
Diagnostic Performance of ^{18}F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study

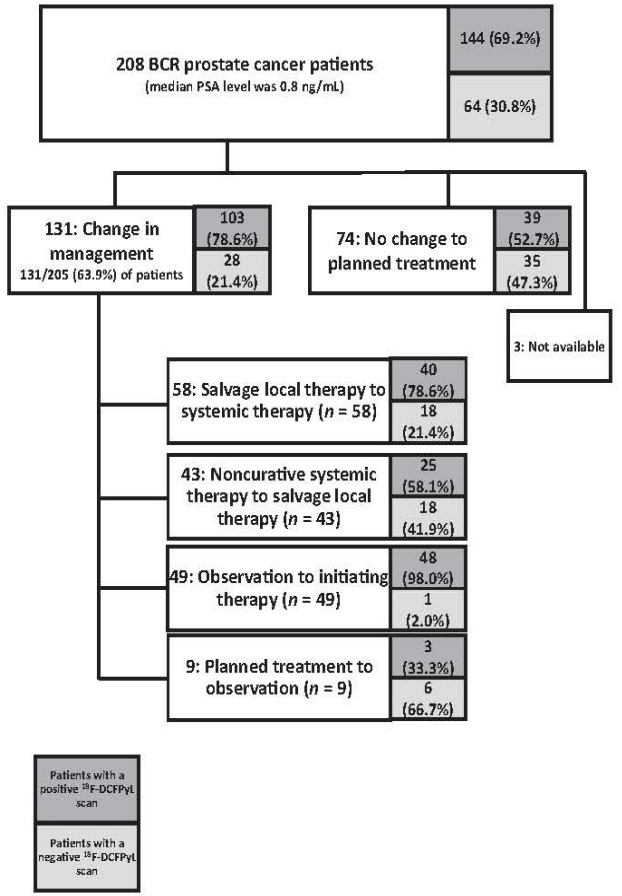
Michael J. Morris[1], Steven P. Rowe[2], Michael A. Gorin[3], Lawrence Saperstein[4], Frédéric Pouliot[5], David Josephson[6], Jeffrey Y.C. Wong[7], Austin R. Pantel[8], Steve Y. Cho[9], Kenneth L. Gage[10], Morand Piert[11], Andrei Iagaru[12], Janet H. Pollard[13], Vivien Wong[14], Jessica Jensen[14], Tess Lin[14], Nancy Stambler[14], Peter R. Carroll[15], Barry A. Siegel[16], and CONDOR Study Group

CONDOR

- 208 men with BCR per AUA/ASTRO-Phoenix criteria & uninformative CI
- Median PSA 0.8 ng/mL (0.2-98.4 ng/mL)
- 1º endpoint: CLR defined as PPV with anatomic colocalization & composite SOT with lower bound 95% CI for CLR>20% for 2/3 readers
- CLR 84.8%-87.0%
- **63.9% management change**







Trends in Radiopharmaceuticals

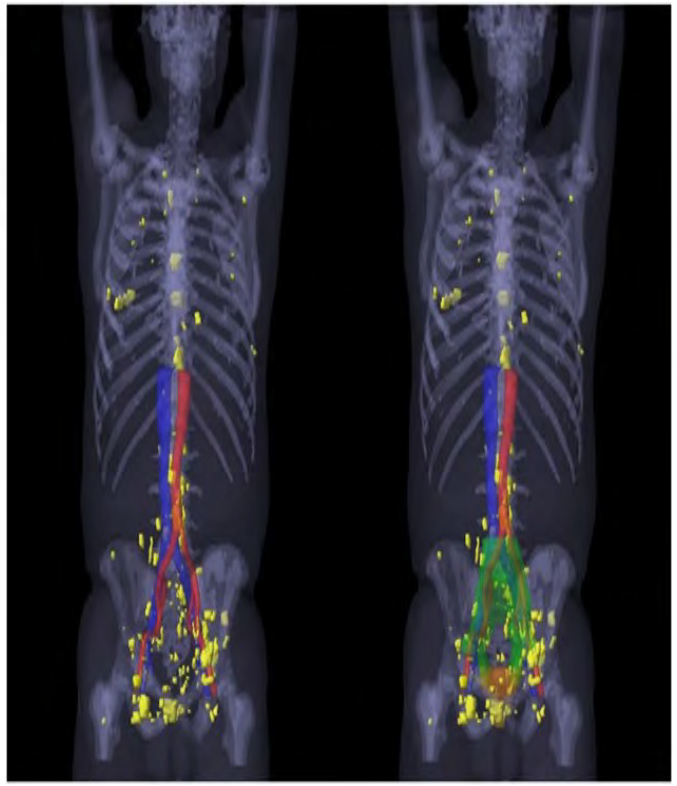
Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

JNM 2018

^{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

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

PSMA-SRT Trial

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

BMC Cancer

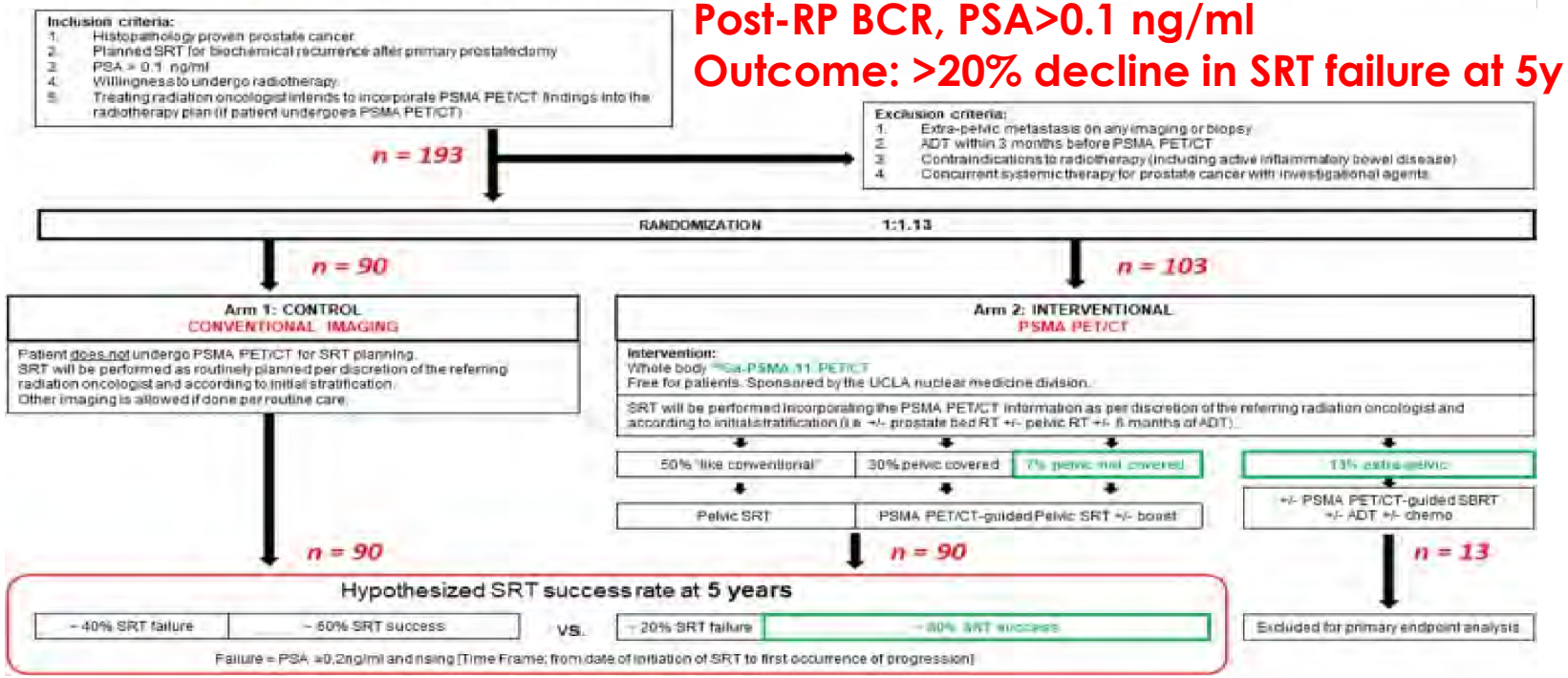
STUDY PROTOCOL Open Access

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



Jadvar H. et al. J Nucl Med
January 2022

Appropriate Use Criteria for Prostate-Specific Membrane Antigen PET Imaging

In this issue

Hossein Jadvar[1], Jeremie Calais[2], Stefano Fanti[3], Felix Feng[4], Kirsten L. Greene[5], James L. Gulley[6], Michael Hofman[7], Bridget F. Koontz[8], Daniel W. Lin[9], Michael J. Morris[10], Steve P. Rowe[11], Trevor J. Royce[12], Simpa Salami[13], Bital Savir-Baruch[14], Sandy Srinivas[15], and Thomas A. Hope[16]

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SNMMI, ACNM, ASCO, AUA, EANM, ACP, ANZSNM

NEWSLINE

Updates to Appropriate Use Criteria for PSMA PET

Thomas A. Hope, MD, University of California, San Francisco, CA; and Hossein Jadvar, MD, PhD, MPH, MBA, University of Southern California, Los Angeles, CA

As an indication of how quickly the field of nuclear medicine is advancing, the Appropriate Use Criteria (AUC) for Prostate-Specific Membrane Antigen (PSMA) PET document has been updated (*1*). This is due to the recent U.S. Food and Drug Administration (FDA) approval of ^{177}Lu-PSMA-617 (Pluvicto, ^{177}Lu-vipivotide tetraxetan; Novartis [Basel, Switzerland]/Advanced Accelerator Applications USA, Inc. [Millburn, NJ]) radiopharmaceutical therapy (RPT). Previously the AUC had scored the indication for a posttreatment prostate-specific antigen (PSA) rise in the metastatic castration-resistant prostate cancer (mCRPC) setting as "may be appropriate." This was because no available PSMA-targeted therapies would benefit from imaging using PSMA PET. With the approval of PSMA RPT, the PSMA PET AUC Working Group has split this indication into 2 distinct indications (see supplemental materials, available at http://ow.ly/ABfv30sh3uO). The first is "Posttreatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radiopharmaceutical therapy," which was again scored as "may be appropriate," because the clinical value of improved tumor localization in grossly metastatic disease is not clear in patients who are not being considered as candidates for PSMA RPT. The second indication is "Evaluation of eligibility for patients being considered for PSMA-targeted radiopharmaceutical therapy," which was scored as "appropriate" given the availability of a PSMA-targeted therapy.

An important point is that the AUC Working Group agreed that both ^{18}F-DCFPyL (Pylarify, ^{18}F-piflufolastat; Lantheus [Billerica, MA]) and ^{68}Ga-PSMA-11 (Illuccix and Locametz, ^{68}Ga-gozetotide; Telix Pharmaceuticals Ltd. [Melbourne, Australia], and Novartis/AAA, respectively) should be considered equivalent for selection of patients for treatment with ^{177}Lu-PSMA-617. In the prescribing information for ^{177}Lu-PSMA-617, the FDA recommended selection of "patients for treatment using Locametz or an approved PSMA-11 imaging agent based on PSMA expression in tumors." However, given the near equivalency of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, either of these radiotracers can be used for patient selection.

Another consideration for patient selection is what cutoff should make a patient eligible. Two randomized trials have evaluated ^{177}Lu-PSMA-617 therapy: the VISION and TheraP trials. Optimal PSMA PET criteria for patient selection are not yet well established. In the VISION trial, eligibility required uptake in disease greater than that in the liver, and no measurable disease with uptake less than that in the liver (*2*). Eligibility in the TheraP study required an SUV ≥20 at 1 site of disease, an SUV ≥10 at measurable soft tissue sites, and no ^{18}F-FDG–positive PSMA-negative sites of disease (*3*). It should be noted that, in general, the higher the uptake on PSMA PET, the better patients respond to treatment (*4,5*). PSMA PET is not only a prognostic biomarker but was shown to be predictive in the TheraP trial, with patients who had an SUV_{mean} ≥10 having a higher likelihood of PSA response compared to chemotherapy (cabazitaxel) (*6*). Although the decision in the VISION trial was binary, uptake may be used to help weigh various treatment options. The debate as to whether ^{18}F-FDG PET/CT should also be used to screen patients prior to PSMA RPT is outside of the scope of the PSMA PET AUC, although ^{18}F-FDG PET may provide additional value in identifying ^{18}F-FDG–positive/PSMA-negative sites of disease (*3*).

PSMA PET plays a significant role in the appropriate selection of patients for PSMA RPT. With the approval and availability of 2 PSMA PET agents, this imaging study should be widely available. Overall, these 2 imaging agents are considered equivalent for patient selection.

REFERENCES

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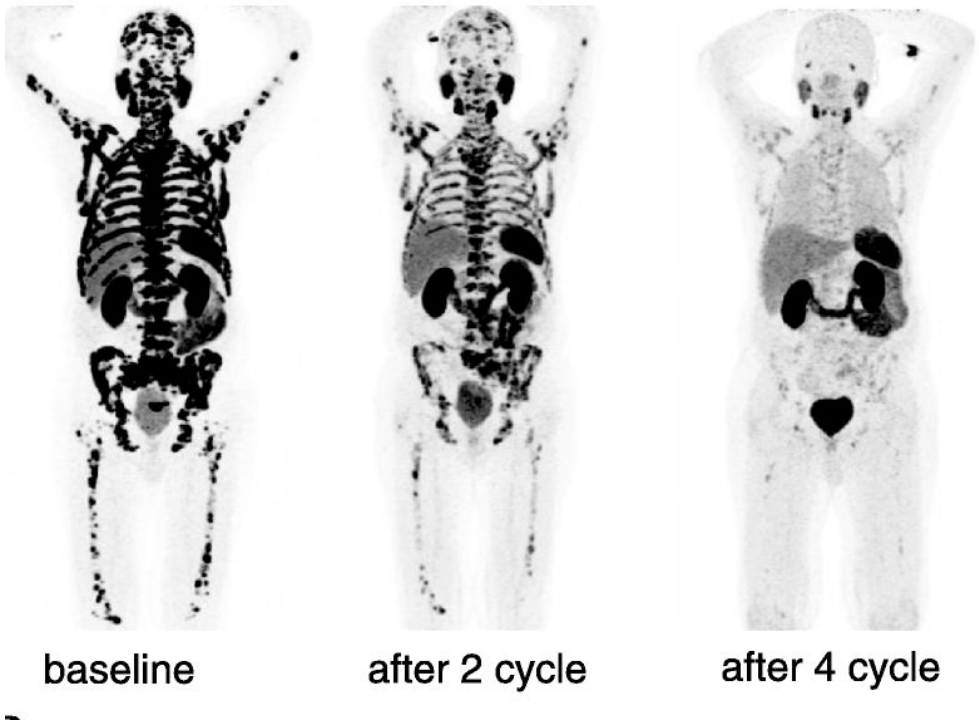
6. Buteau JP, Martin AJ, Emmett L, et al. PSMA PET and FDG PET as predictors of response and prognosis in a randomized phase 2 trial of ^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic, castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603) [abstract]. *J Clin Oncol.* 2022; 40(6; suppl):10-10.

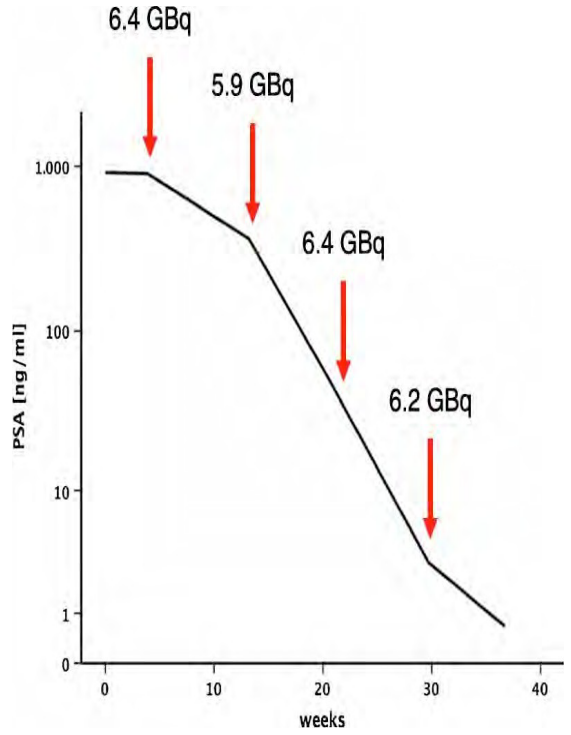
Hope & Jadvar. J Nucl Med
May 2022

Trends in Radiopharmaceuticals

Oncologic & Theranostics

^{177}Lu-PSMA-617





[^{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*

LuPSMA

Lancet Oncol 2018

- 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%)
- **PSA50 -- 57% of patients**
- 82% objective response
- 37% improvement in global health

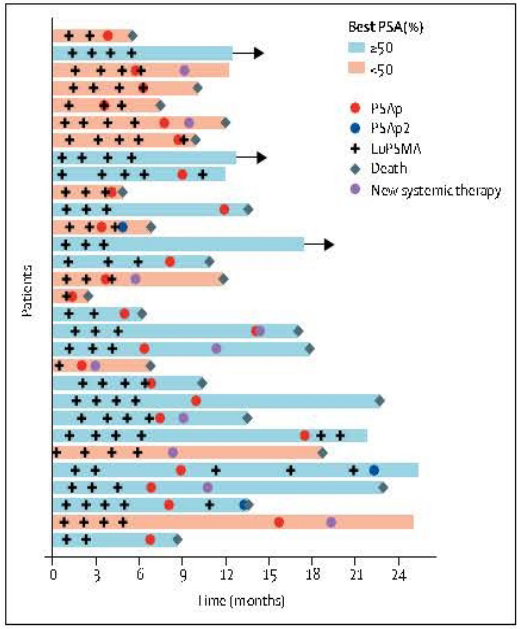


Figure 2: Patient events
Arrow indicates patients without PSA progression up to cut-off date. PSA=prostate-specific antigen. LuPSMA=lutetium-prostate-specific membrane antigen. PSAp2=second-PSA progression in patients with initial response who progressed after trial completion and responded to further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

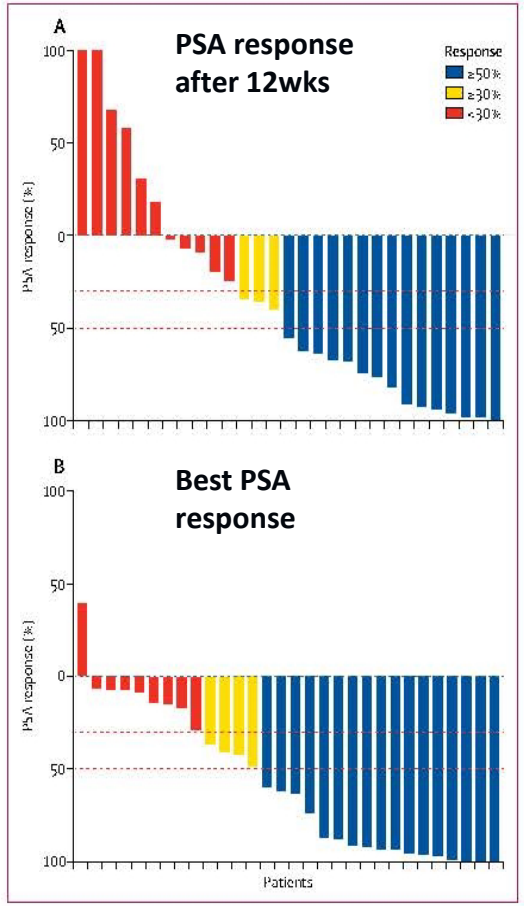


Figure 3: (A) PSA response after 12 weeks* and (B) best PSA response from

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

TheraP

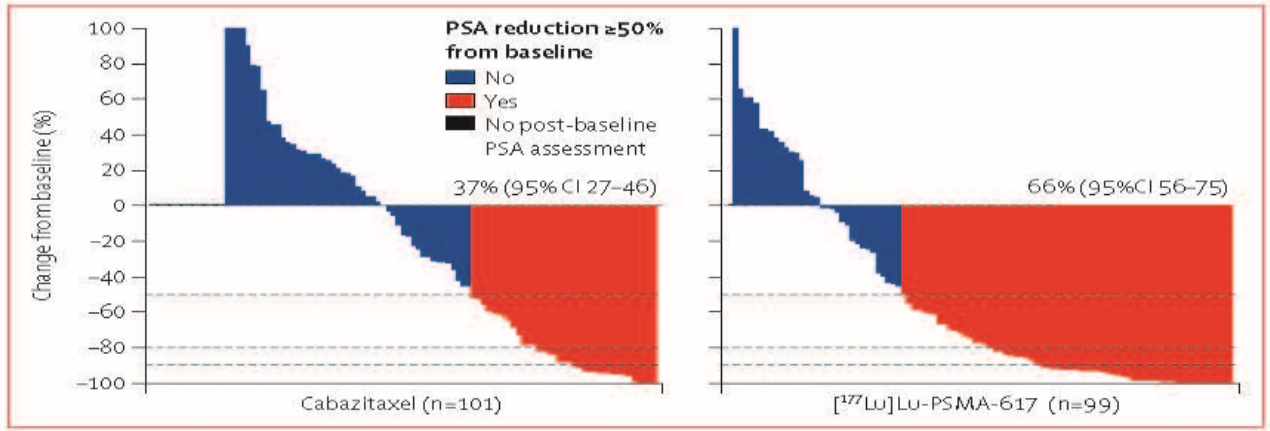
Lancet 2021

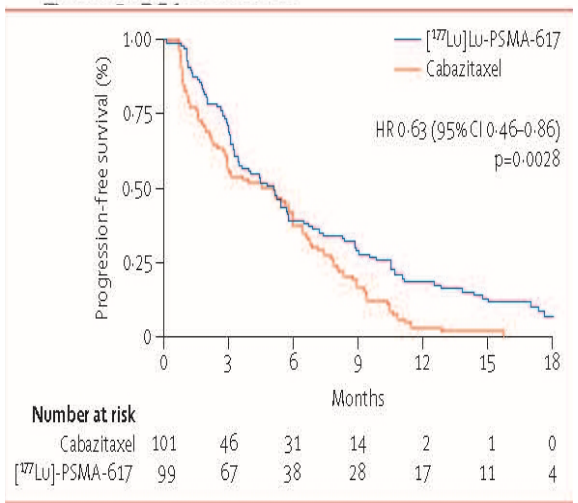
Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: Adverse events





-N: CBZ (85), Lu (98)

-No FDG+/PSMA - (28%)

-PSA50:

(**CBZ 44%** < **Lu 66%**)

-Gr. 3/4 AE (no xerostomia)

(**CBZ 53%** > **Lu 33%**)

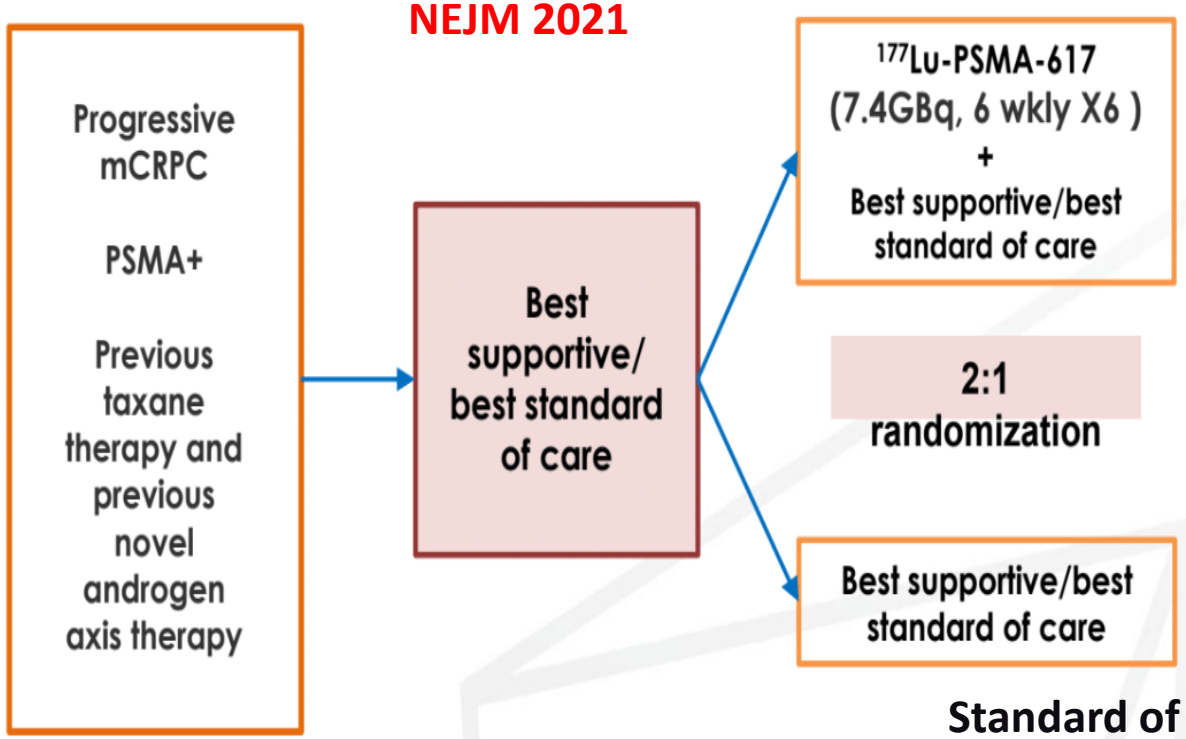
VISION Trial: ^{177}Lu-PSMA versus best supportive care

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., Alison Armour, M.B., Ch.B., M.D., Wendy J. Pérez-Contreras, M.P.A., Michelle DeSilvio, Ph.D., Euloge Kpamegan, Ph.D., Germo Gericke, M.D., Ph.D., Richard A. Messmann, M.D., M.H.S., Michael J. Morris, M.D., and Bernd J. Krause, M.D. et al., for the VISION Investigators*

NEJM 2021

- **40% decline in risk of death**
- **60% decline in radiographic progression**
- **4-m OS benefit; 5.3-m rPFS benefit**
- **More side effects but low grade and manageable**



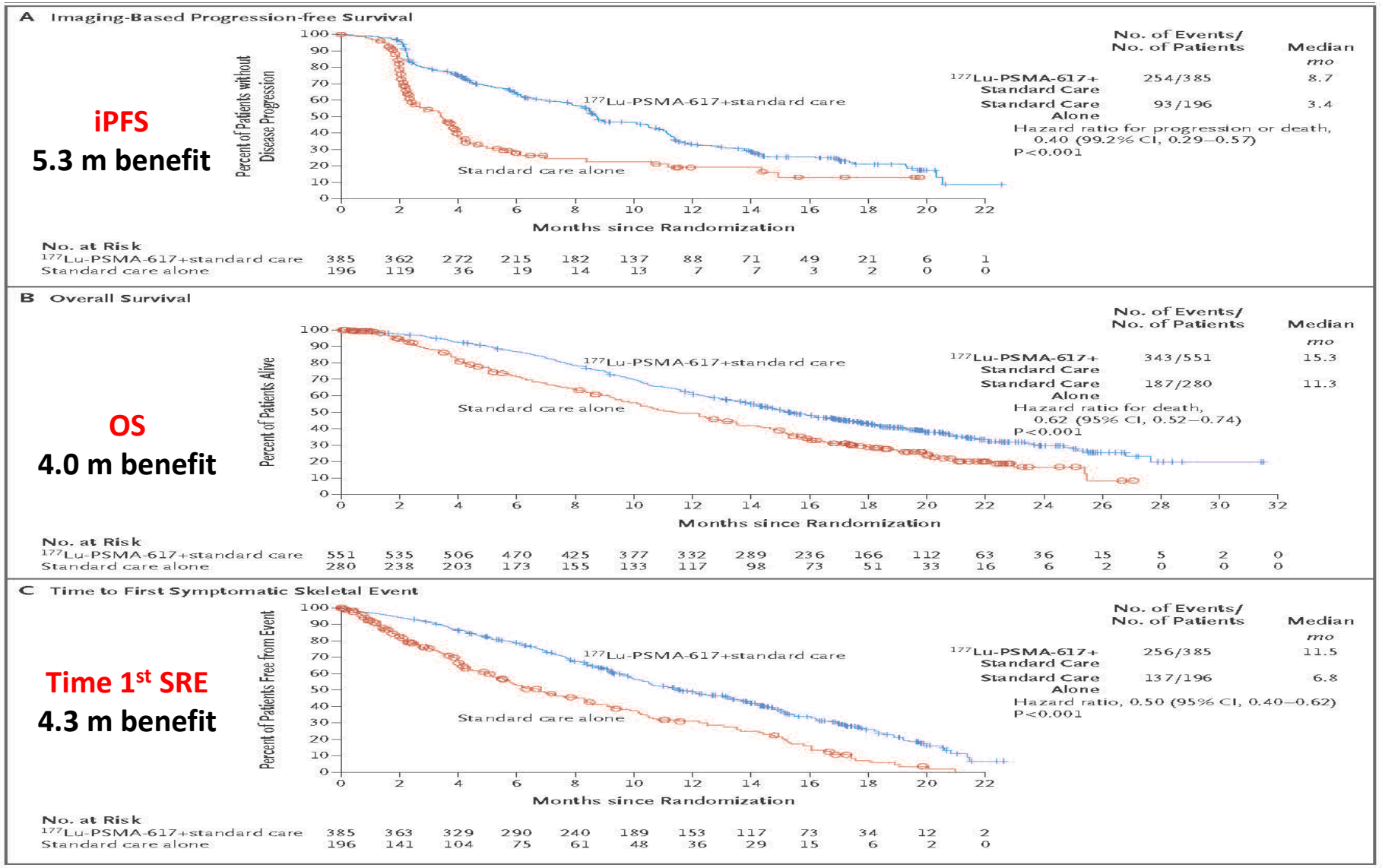
Primary Endpoint
- Overall survival

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

Standard of Care:
NOT ALLOWED - chemo, Ra, immunoRx, investigational drugs
ALLOWED: ADT, bone-directed Rx, palliative XRT

Enocyte/Novartis
NCT03511664



iPFS

5.3 m benefit

OS

4.0 m benefit

Time 1st SRE

4.3 m benefit

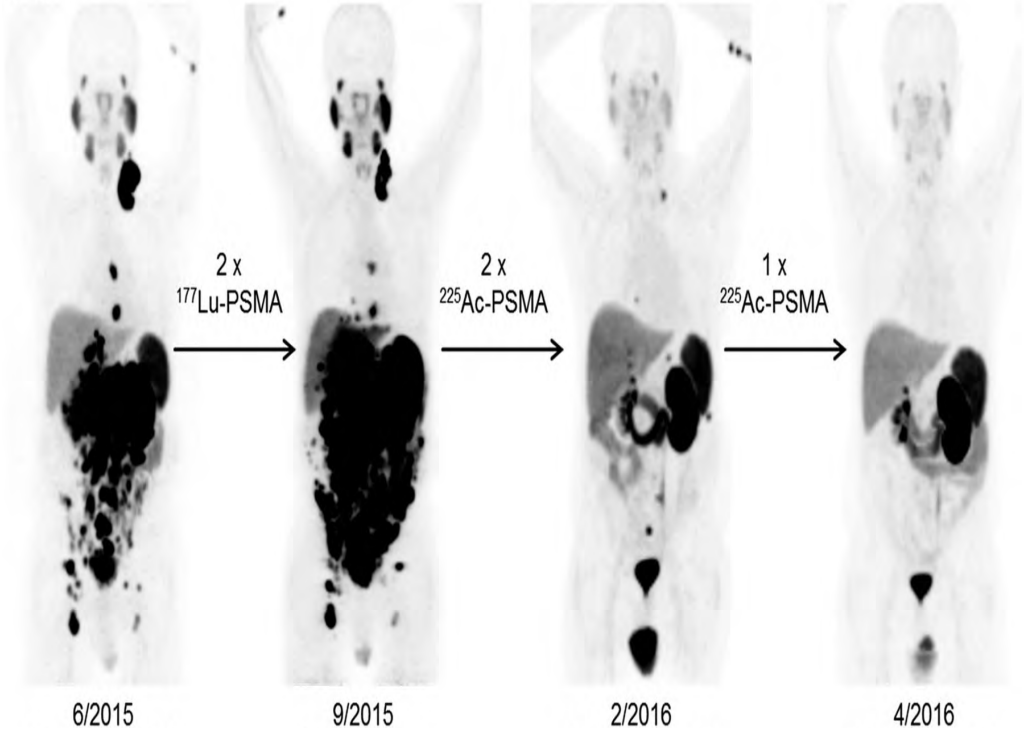
VISION: NEJM 2021

Trends in Radiopharmaceuticals

Oncologic & Theranostics

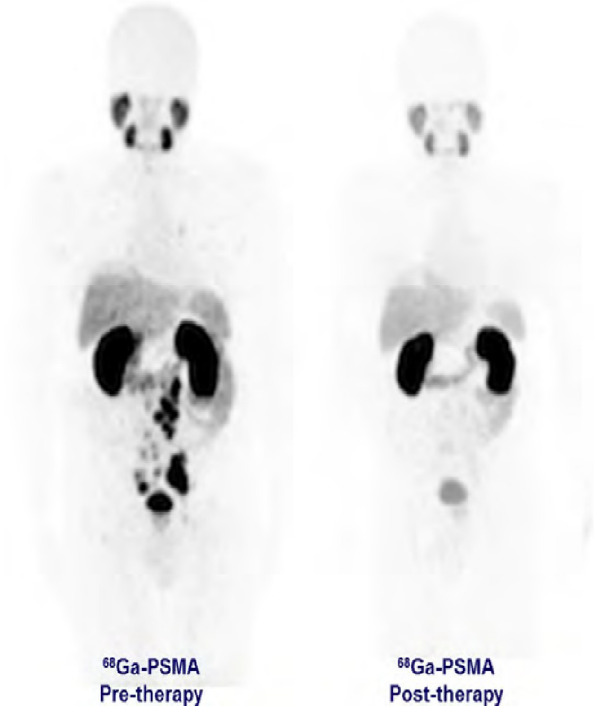
^{225}AC-PSMA-617

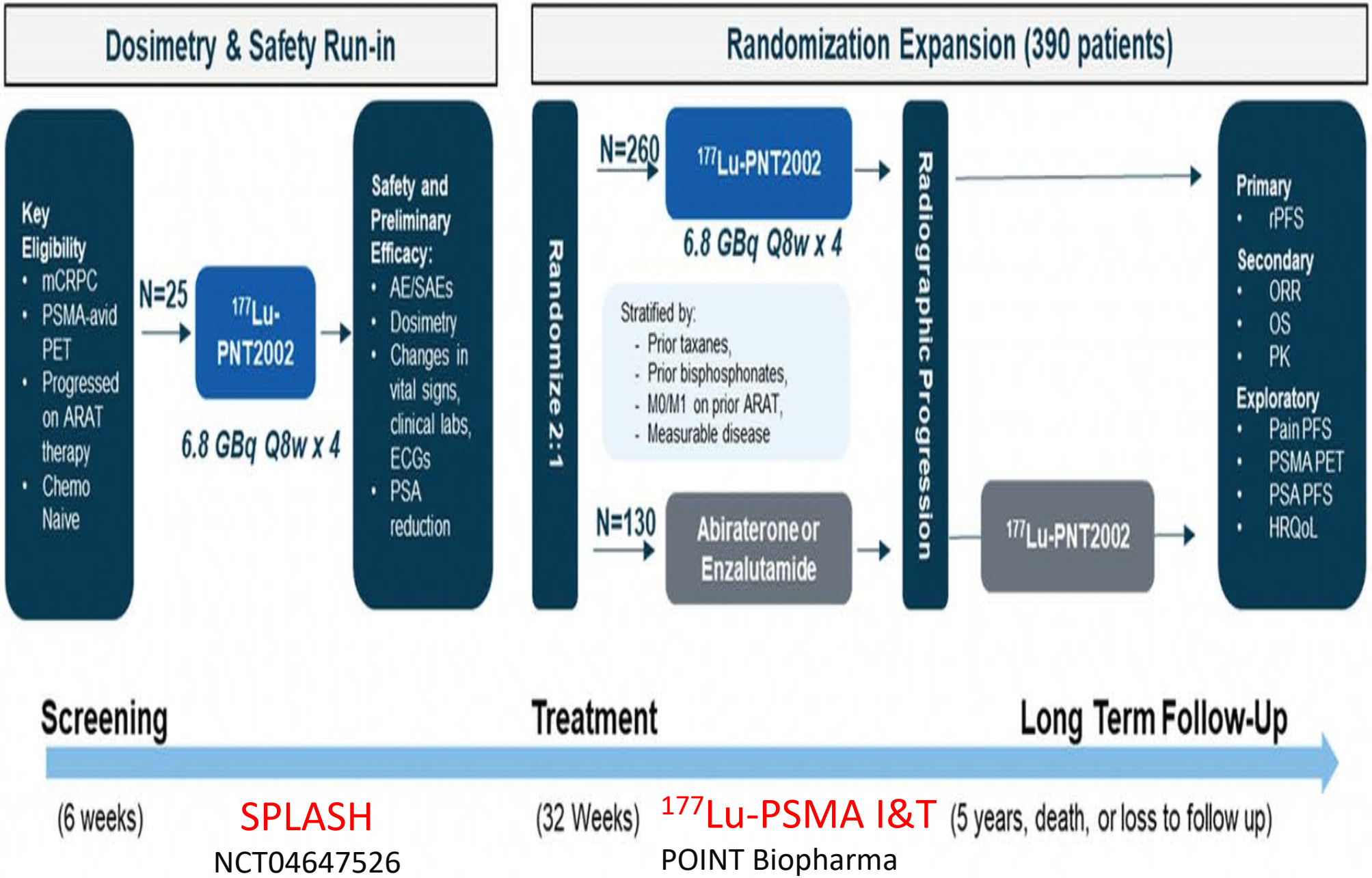
Kratochwil, JNM 2016



^{213}Bi-PSMA-617

Sathekge, EJNMMI 2018




Dosimetry & Safety Run-in
Randomization Expansion (390 patients)
Key Eligibility
• mCRPC
• PSMA-avid PET
• Progressed on ARAT therapy
• Chemo Naive
N=25
177Lu-PNT2002
6.8 GBq Q8w x 4
Safety and Preliminary Efficacy:
• AE/SAEs
• Dosimetry
• Changes in vital signs, clinical labs, ECGs
• PSA reduction
Randomize 2:1
N=260
177Lu-PNT2002
6.8 GBq Q8w x 4
Stratified by:
- Prior taxanes,
- Prior bisphosphonates,
- M0/M1 on prior ARAT,
- Measurable disease
N=130
Abiraterone or Enzalutamide
Radiographic Progression
177Lu-PNT2002
Primary
• rPFS
Secondary
• ORR
• OS
• PK
Exploratory
• Pain PFS
• PSMA PET
• PSA PFS
• HRQoL
Screening
Treatment
Long Term Follow-Up
(6 weeks)
SPLASH
NCT04647526
(32 Weeks)
177Lu-PSMA I&T
POINT Biopharma
(5 years, death, or loss to follow up)

PRINCE Trial

PSMA-lutetium **R**adionuclide therapy and ImmuNotherapy in prostate **C**anc**E**r

@UCSFImaging
NCT03805594
Dr Rahul Aggarwal
Dr Tom Hope

- Metastatic CRPC
- Progressed after enzalutamide, abiraterone or apalutamide

↓

PSMA + FDG PET/CT

↓

Pembroluzimab 200mg
3 weekly

+

^{177}Lu-PSMA-617
6 weekly, 4 cycles
Day 4 ± 2 days
8.5 GBq, ↓0.5 GBq/cycle

LuPARP Trial

Phase 1 trial of ^{177}Lu-PSMA-617 therapy and Olaparib (PARPi)

- Metastatic CRPC
- Progressed after 2nd generation AR-targeted agent
- Post taxane chemotherapy

↓

PSMA + FDG PET/CT

↓

^{177}Lu-PSMA-617	+	Olaparib day 2-15
6 weekly, 4 cycles		3+3 dose escalation design
7.4 GBq		50mg to 300mg bd
		(6 levels of increment)

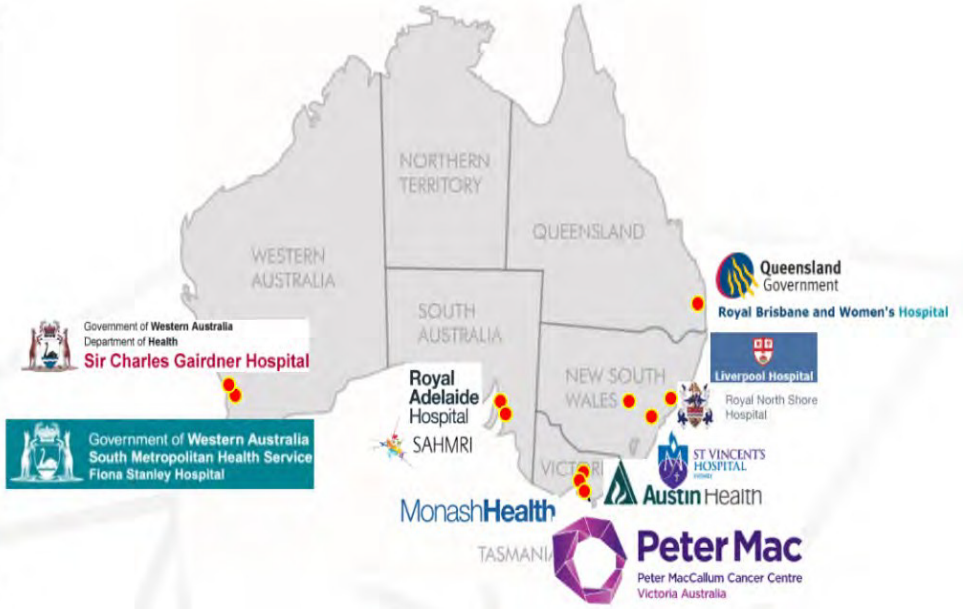
clinicaltrials.gov: NCT03874884
PI: A/Prof Shahneen Sandhu

#UpFrontPSMA: high-volume metastatic hormone naïve PC

ARM A (n = 70)
Upfront Lu-PSMA x 2-3 + ADT
followed by Docetaxel x 6

De novo High-Volume mHNPC
- ≥ 4 bone mets with ≥ 1 extra-axial AND/OR
- Visceral mets

ARM B (n = 70)
ADT + Docetaxel x 6



Primary endpoint: undetectable PSA at 12 months

PI: A/Prof Arun Azad

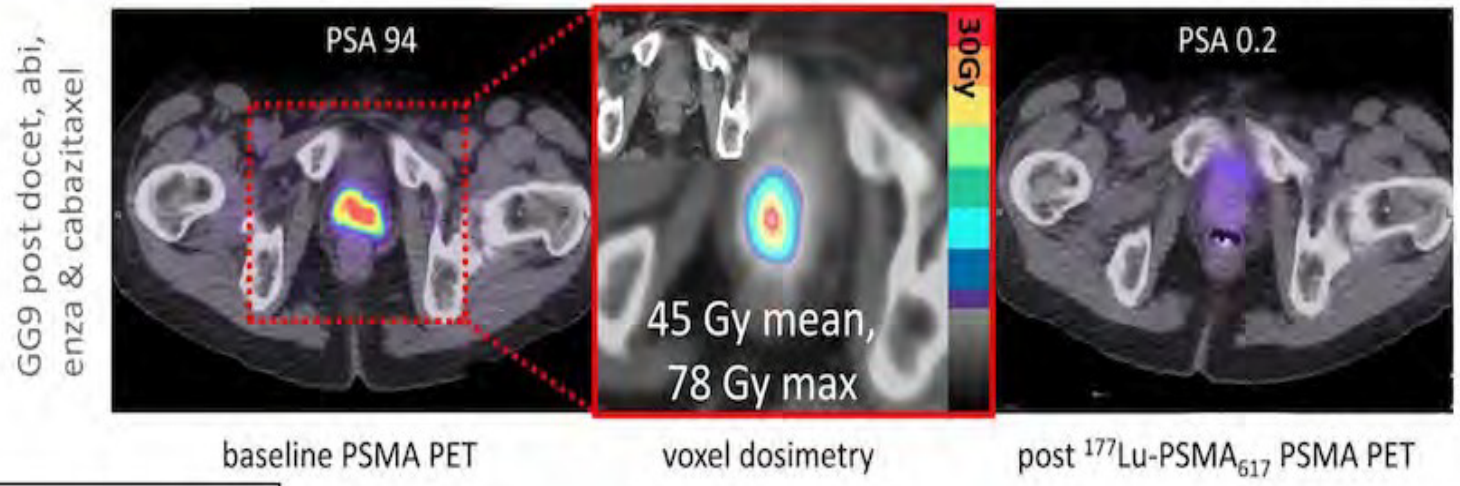
FUNDED BY MOVEMBER® FOUNDATION

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

Statistical assumptions
- P1 0.5, P2 0.25
- 2-sided alpha=0.05, beta=0.8

#LuTectomy: ^{177}Lu-PSMA prior to surgery

Hofman et al [unpublished)



High-risk localised prostate cancer ± N1

High PSMA Expression

→ **^{177}Lu-PSMA x 1-2 cycles**

→ **At 6-8 weeks:**
- **Prostatectomy + pelvic LN dissection**

Primary endpoints:
- **Dosimetry**

Key Secondary endpoints
- **Safety**
- **PSMA PET Response**

PI: Prof Declan Murphy

Correlative samples
- Tumour tissue
- PBMCs
- ctDNA, serum

TACTIST
^{225}Ac-PSMA I&T

Trial record **6 of 11** for: 225Ac prostate

Previous Study | Return to List | Next Study

Targeted Alpha Therapy With 225Actinium-PSMA-I&T of Castration-resISTant Prostate Cancer (TATCIST). (TATCIST)

ClinicalTrials.gov Identifier: NCT05219500

Recruitment Status : Recruiting
First Posted : February 2, 2022
Last Update Posted : February 2, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Sponsor:
Excel Diagnostics and Nuclear Oncology Center

Information provided by (Responsible Party):
Excel Diagnostics and Nuclear Oncology Center

US DOE Tri-Lab Production Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy: 2019 Update

Kevin John (LANL), Eva Birnbaum (LANL), Rose Boll (ORNL), Ariel Brown (ORNL, NIDC), Mark Brugh (LANL), Jason Cooley (LANL), Roy Copping (ORNL), Cathy Cutler (BNL), Ashley Dame (ORNL), Sandra Davern (ORNL), David Denton (ORNL), Michael Fassbender (LANL), Kevin Felker (ORNL, NIDC), Mitch Ferren (ORNL, NIDC), Jonathan Fitzsimmons (BNL), Kevin Gaddis (ORNL), Justin Griswold (ORNL), Dohyun Kim (BNL), Dmitri Medvedev (BNL), Saed Mirzadeh (ORNL), Karen Murphy (ORNL), F. Meiring Nortier (LANL), Eric Olivas (LANL), Allison Peacock (ORNL), David Reass (LANL), Karen Sikes (ORNL, NIDC), Daniel Stracener (ORNL), C. Etienne Vermeulen (LANL), Lance Wyant (ORNL)

LA-UR-19-25067

^{225}Ac Supply and Demand

^{225}Ac is a promising isotope for the treatment of cancer used in emerging Targeted Alpha Therapy (TAT) applications

Current worldwide supply of ^{225}Ac is estimated at 1200-1700 mCi/yr* derived from ^{229}Th/ ^{225}Ac generators

Patient doses, as informed by clinical trials, are estimated at:

- ^{225}Ac: 0.3-5 μCi per patient kg
- ^{213}Bi: 1 mCi per patient kg

*Projection of ^{225}Ac demand assuming multiple, approved ^{225}Ac and ^{213}Bi drugs and robust clinical R&D programs could be in the hundreds of Ci/year***

*International Atomic Energy Agency. Technical Meeting Report "Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy" IAEA Headquarters Vienna, Austria. 24-28 June **2013**

US DOE Offices of Nuclear Energy and Nuclear Physics "2008 Workshop on The Nation's Needs for Isotopes: Present and Future" Rockville, MD August **2008

^{225}Ac Supply Considerations

Facility	Nuclear Reaction
Reactor (thermal neutrons)	^{226}Ra(3n,γ)^{229}Ra →^{229}Ac→^{229}Th ^{228}Ra(n,γ)^{229}Ra →^{229}Ac→^{229}Th
Accelerator (electrons)	^{226}Ra(γ,n)^{225}Ra→^{225}Ac
Accelerator (low energy particles)	^{226}Ra(p,2n)^{225}Ac ^{226}Ra(α,n) ^{229}Th ^{226}Ra(p,pn) ^{225}Ra→^{225}Ac ^{232}Th(p,x) ^{229}Th
Accelerator (high energy protons)	**^{232}Th(p,x)^{225}Ac** ^{232}Th(p,x)^{225}Ra→^{225}Ac
Accelerator (high energy neutrons)	^{226}Ra(n,2n) ^{225}Ra→^{225}Ac
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

Current supply of ^{225}Ac is derived from the decay of ^{229}Th that was derived from limited stockpiles of ^{233}U

New sources of material are required to support ^{225}Ac-based pharmaceuticals

The high-energy accelerator route is of interest as it leverages unique US facility capabilities

Accelerator Production of ^{225}Ac

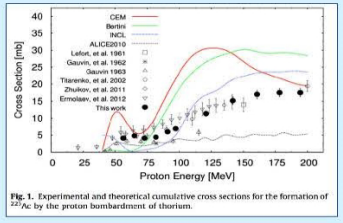


Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{227}Ac by the proton bombardment of thorium.

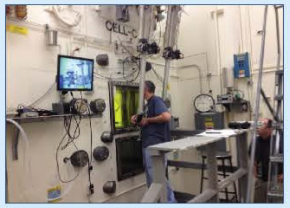
Facility	Anticipated Single Target Ac-225 Yields at EOB (10 day irradiation)
LANL (100 MeV, 250-450 μA)	**1.3-2.3* Ci**
BNL (200 MeV, 165 μA)	**2.2 Ci**

** Theoretical maximum value assumed for production with 450 μA on target.*

^{225}Ac yield curve based on measured cross sections show that Ci-scale production is feasible at LANL and BNL

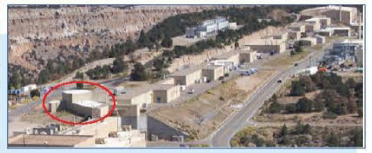
*J.W. Weidner et al. Appl. Radiat. Isot. 70 (**2012**) 2602*
*J.W. Engle et al. Phys. Rev. C. 88 (**2013**) 014604*
*J.W. Engle et al. Radiochim. Acta 102 (**2014**) 569*
*J.R. Griswold et al. Appl. Radiat. Isot. 118 (**2016**) 366*

The Tri-Lab Effort: Leveraging Unique National Resources



ORNL - Approximately 25 years of experience in the isolation of ^{225}Ac from fissile ^{233}U via ^{229}Th

LANL Isotope Production Facility (IPF) at LANSCE; 100 MeV incident energy up to 275 μA for routine production



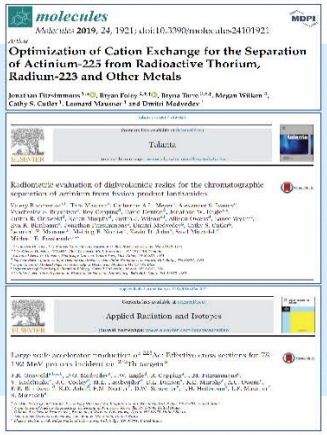
BNL Linac at the Brookhaven Linac Isotope Producer (BLIP) 165 μA intensity to targets at incident energies ranging from 66-202 MeV

Accelerator-Produced ^{225}Ac Overview

We've distributed over 275 mCi of accelerator produced ^{225}Ac/^{213}Bi as part of the Tri-Lab effort

19 separate batches have been processed (since the start of the effort) with multiple shipments per batch resulting in distribution to 15 different customers/evaluators

The Tri-Lab effort has generated multiple publications and patents (see US patents 9,951,399 and 9,555,140)



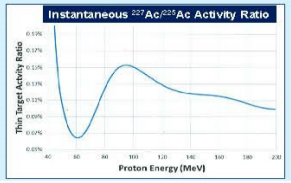
^{225}Ac Materials Evaluation Campaigns

Accelerator-produced ^{225}Ac/^{213}Bi generator performance is equivalent to generators produced from ^{229}Th-derived ^{225}Ac

Direct labeling studies of the accelerator-derived ^{225}Ac product are promising and are equivalent to ^{229}Th-derived ^{225}Ac

Supported three biodistribution/dosimetry/toxicity studies to assess impact of ^{227}Ac ($t_{1/2} \cong 22$ years)

"Our data demonstrates that accelerator-produced ^{225}Ac is suitable for the development of the pre-clinical and clinical targeted radionuclide therapy."



Accelerator-Produced ^{225}Ac Current Focus

General focus on increasing production frequency and volume in support of clinical R&D and clinical trials

Continued improvements to the design and preparation of thorium targets and radiochemical processing optimization

Continued improvement of shipping capabilities and shipping performance

Submittal of a Drug Master File to inform the FDA - helps our customer base, and protects our process

Starting to execute facility vision with eye toward Stage 3 large scale production

Continued focus on stakeholder and customer interactions

Approach to Routine Production for Use in Approved Drugs

We have positioned ourselves to ensure a strong, reliable supply that meets the quality requirements and quantities needed for clinical application

- ✓ - reliable, consistent and routine production
- ✓ - large quantities for meaningful impact to preclinical studies and clinical trials
- ✓ - experience with GMP production and regulatory compliance (as demonstrated by our ^{82}Sr production)

Please see US DOE Isotope Program booth # 467 for additional details

Summary and Acknowledgements

The Tri-Lab effort is routinely producing ^{225}Ac and ***product is available*** for end users and shipments to multiple users have been completed [please contact the National Isotope Development Center at (865) 574-6984 or see their website https://www.isotopes.gov/ for more details]

We have distributed over 275 mCi of accelerator produced ^{225}Ac to evaluators

^{227}Ac content is clinically insignificant from a dosimetry/toxicity perspective – but challenges with perception and regulatory compliance remain; we have a well-defined forward path to address these challenges with DOE

We are working with companies and research hospitals in preparation to support Phase I trials - DMF development is underway

This research is supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science for Nuclear Physics

Convergent Therapeutics and IONETIX Announce Supply Agreement for Therapeutic Radioisotope Actinium-225 (Ac-225)

NEWS PROVIDED BY
Convergent Therapeutics →
May 25, 2022, 08:00 ET

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IAEA

European Commission

REPORT ON JOINT IAEA-JRC WORKSHOP

"SUPPLY OF ACTINIUM-225"

IAEA, Vienna

October 2018

NorthStar Medical Radioisotopes and Convergent Therapeutics Announce Supply Agreement for Therapeutic Radioisotope Actinium-225 (Ac-225)

– NorthStar's high purity non-carrier-added (n.c.a.) Ac-225 to be used in Convergent's lead, dual-targeted radionuclide program for prostate cancer, CONV01-α –

Summary

- Theranostics is aligned with the concept of precision oncology
- Theranostics is growing rapidly with anticipated imaging-radiopharmaceutical therapy pairs targeted to new biological targets
- Theranostics will extend to other non-oncologic diseases
- Focus areas will be on education, physician/technologist/scientist/physicist pipeline, radioisotope supply, and potential regulatory ramifications

Acronyms

- CTV: clinical target volume
- FDG: fluorodeoxyglucose
- I&T: imaging and therapy
- PET: positron emission tomography
- PSMA: prostate-specific membrane antigen
- RT: radiation therapy
- RTOG: radiation therapy oncology group
- SPECT: single-photon emission computed tomography

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Impacts of the American Board of Radiology's Request to Terminate NRC Recognition of the American Board of Radiology's Board Certification Processes

Hossein Jadvar, MD, PhD, MPH, MBA

Advisory Committee on the Medical Uses of Isotopes (ACMUI)

December 6, 2022

Subcommittee Members

- Hossein Jadvar, MD, PhD (Nuclear Medicine Physician; Chair)
- Ronald D. Ennis, MD (Radiation Oncologist)
- Richard Harvey, DrPH (Radiation Safety Officer)
- Darlene F. Metter, MD (Diagnostic Radiologist)
- Megan L. Shober (Agreement State Representative)
- Melissa C. Martin (Medical Physicist, Nuclear Medicine)
- Maryann Ayoade (NRC Staff Resource)

Subcommittee Charge

- To identify any potential impacts of ABR's request to terminate NRC recognition and other inactive boards identified during the NRC's evaluation of specialty boards and provide recommendations to mitigate any potential impacts
- To review and evaluate the NRC's current board recognition criteria and provide any recommendations for action

NRC Recognized Boards
(certificate holder can request to NRC for granting AU status)

- American Board of Healthy Physics (ABHP)
- American Board of Science in Nuclear Medicine (ABSNM)
- American Board of Radiology (ABR)
- American Board of Medical Physics (ABMP)
- Canadian College of Physicists in Medicine (CCPM)
- Board of Pharmacy Specialties (BPS) [Formerly Board of Pharmaceutical Specialties]
- The American Board of Nuclear Medicine (ABNM)
- Certification Board of Nuclear Cardiology, Part of the Alliance for Physician Certification and Advancement™ Medical Specialty Boards and Certification Programs (CBNC)
- The American Osteopathic Board of Radiology (AOBR)
- The American Osteopathic Board of Nuclear Medicine (AOBNM) --- INACTIVE since March 5, 2019……recognition status under review
- Certification Board of Nuclear Endocrinology (CBNE) --- INACTIVE, no longer recognized

American Board of Radiology (ABR) Background

- Founded in 1934 as a non-for-profit organization and a member of the American Board of Medical Specialties (ABMS), one of 24 specialty certifying boards
- Certifying board for Diagnostic Radiology (DR), Interventional Radiology (IR), Medical Physics (Diagnostic, Nuclear, Therapeutic), Radiation Oncology (RO), and subspecialties (Nuclear Radiology, Neuroradiology, Pediatric Radiology)
- Mission
  - To certify that our diplomates demonstrate the requisite knowledge, skill, and understanding of their disciplines to the benefit of patients.

American Board of Radiology (ABR) Background

- Prior to 2005: ABR did not provide AU-E designation on board certificates
- 2005-2023: AU-E, AMP-E, & RSO-E designations was an option for candidates
- December 31, 2023: Last date for AU-E designation on certificates (DR, IR-DR, RO, Diagnostic MP (RSO-E), Nuclear MP (RSO-E), Therapeutic MP (AMP-E)
- 2024 and beyond: No AU-E designation option; candidates provide relevant T&E documentation through their employers directly to NRC to add the employee to employer's license
- REASONS (https://www.youtube.com/watch?v=hkRc9JzP2oA) March 30, 2022
  - not aligned with the core ABR mission; diverts limited resources
  - ABR has never issued AU status; most radiologists are not (and do not need to be) AUs
  - ABR merely passed along documentation of T&E and direct pathway to becoming AU exists
  - AU requirement for 700h T&E in nuclear radiology is an ACGME ("residency") requirement
  - IR-DR(Forms A & B), RO (2-page verification form) need not be submitted to ABR
  - RISE questions will not be scored separately
  - Trainees and programs should continue to keep T&E documentation
  - T&E docs needed for 16-m embedded NM/DR pathway and NR fellows to sit for NR CAQ exam

AJR FOCUS ON:

All You Need to Know as an Authorized User

Jon A. Baldwin[1]
Asim K. Bag
Sharon L. White
Fathima F. Palot-Manzil
Janis P. O'Malley

OBJECTIVE. The purpose of this article is to review the training requirements for practicing nuclear radiology, the scope of licensing, how to start a new practice, and the key concepts an authorized user needs to know for responsible use of radiopharmaceuticals.

CONCLUSION. Physicians responsible for the daily operations of nuclear medicine clinics often find the regulations concerning the safe handling and administration of radiopharmaceuticals daunting. Even experienced authorized users have concerns about handling many new therapeutic agents. Those studying for certifying and subspecialty examinations or for maintenance of certification for the American Board of Nuclear Medicine and the American Board of Radiology must clearly understand the overall process for becoming an authorized user.

SNMMI Newsline

Recognition of the ABNM by the NRC

George M. Segall - *Executive Director, American Board of Nuclear Medicine*

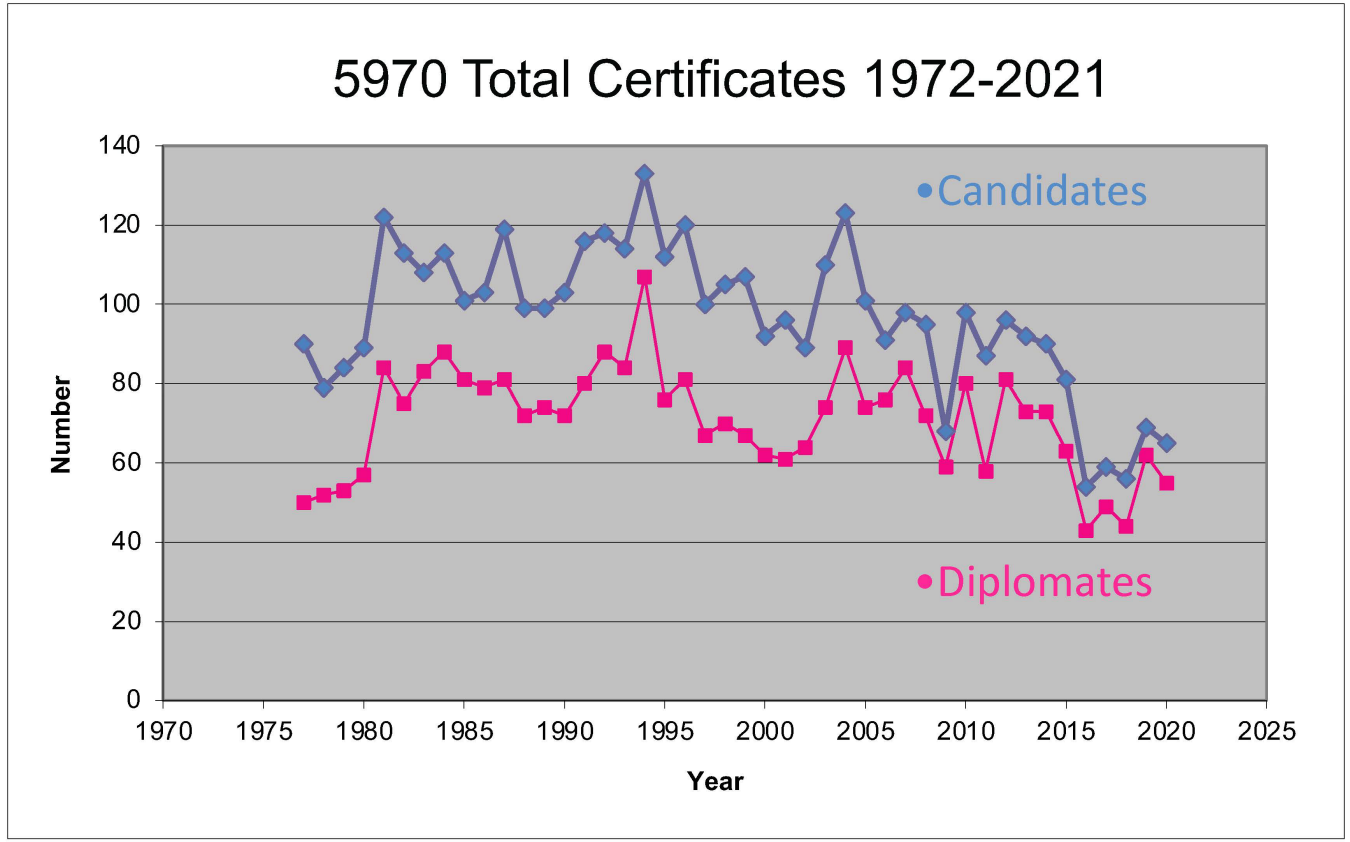
Reprinted with Permission J Nucl Med. 2022, 63 (7) 19N

Certification by the American Board of Nuclear Medicine (ABNM) is recognized by the U.S. Nuclear Regulatory Commission (NRC) as meeting the training and experience requirements to be an authorized user of byproduct material for medical use. The last time the ABNM's certification process was reviewed by the NRC was in 2005, following publication of the final rule 10 CFR Part 35, "Medical Use of Byprod-

long as the specific clock hour requirements are met and ject matter relates to radiation safety and safe han byproduct material for the uses for which authorization requested. Reviewing case histories or interpreting scan not be counted toward the minimum 200 hours of requir room and laboratory training in radiation safety and s dling of byproduct material.

ABNM Certification Examination

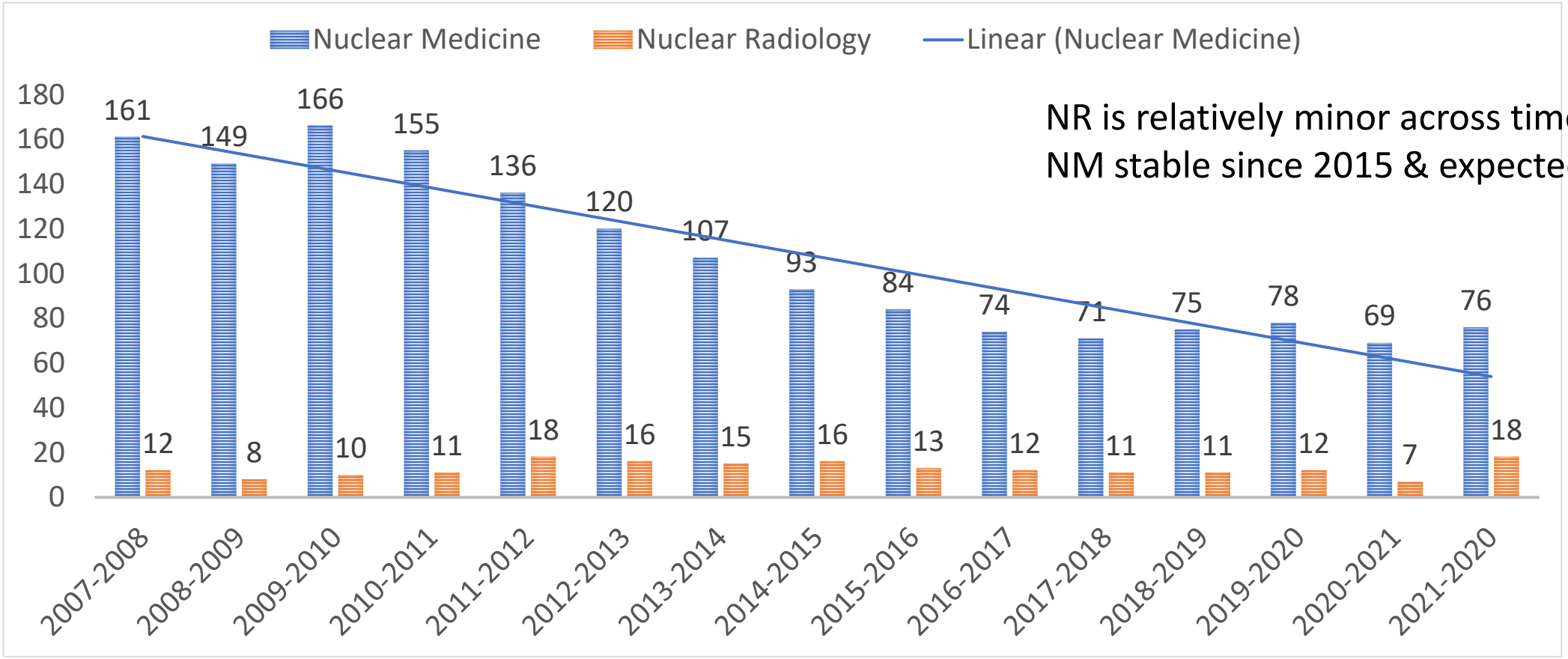
Number of Candidates and Diplomates



Average pass rate (2012 – 2021) = 82%

ABNM AMERICAN BOARD of NUCLEAR MEDICINE

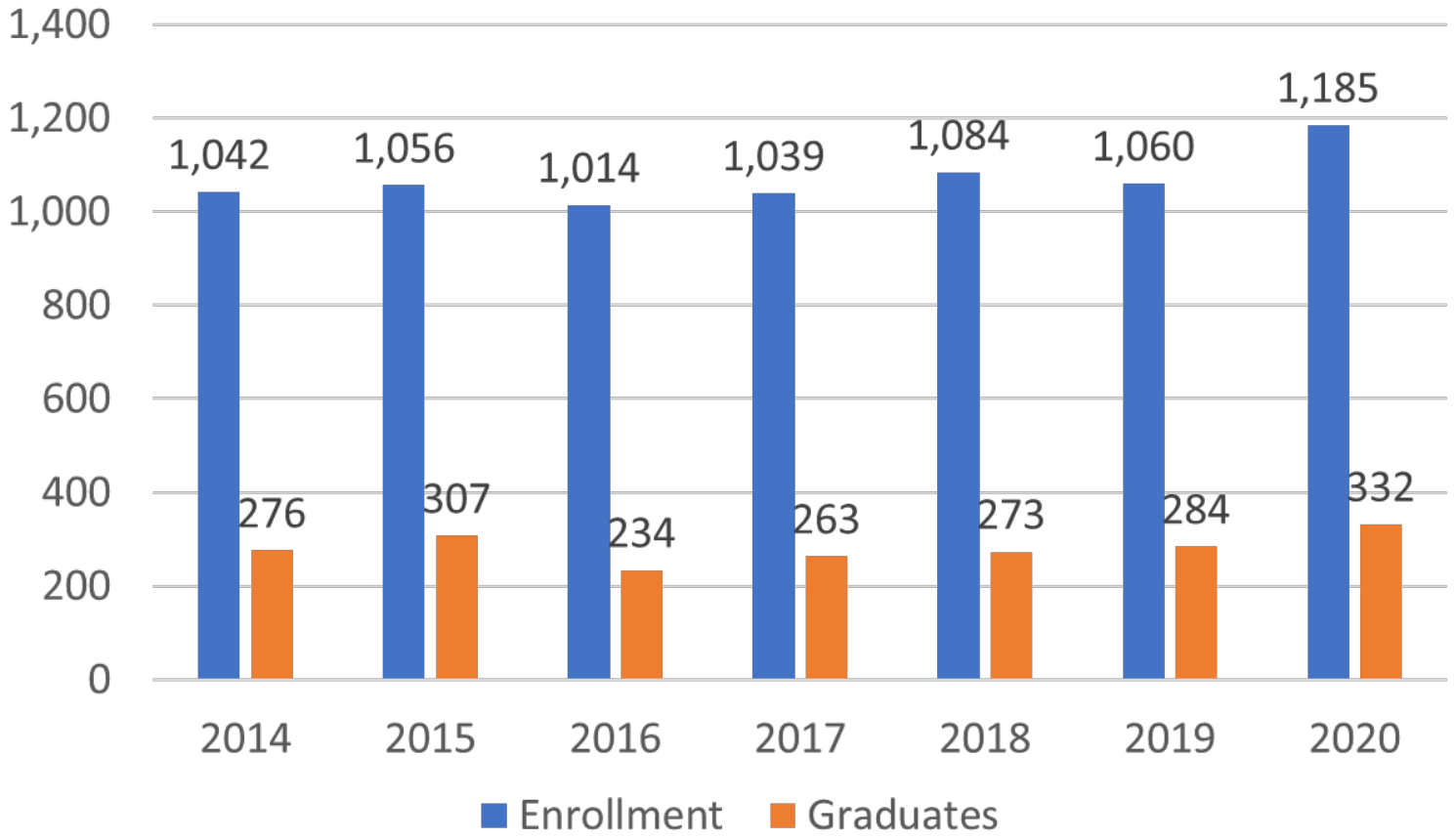
of Residents by Academic Year



NR is relatively minor across time
NM stable since 2015 & expected to rise

of Commission on Accreditation of Medical Physics Education Programs (CAMPEP) Accredited Program Graduates by Academic Year

+48 Graduates from 2019-2020



Reference: CAMPEP Graduate Program Report (July 26, 2021)

Ramifications & Potential Issues

- Potential confusion and challenges with burden on applicants and institutions for securing AU, AMP, or RSO status for new hires
  - AU-E board certification is rapid for proof of AU eligibility; ABR may have underestimated the burden being placed on the applicants, preceptors, and program directors
  - Deceased preceptors, unwilling preceptors to sign off if >7y window (per requirement in 10 CFR 35.59) or if preceptor was not involved with applicant's T&E
  - Potential increase in time reviewing T&E documentations (NRC & Agreement States); possible delays may impact practice of medicine (AU-E could function immediately)
    - California: 4h per license amendment; ~100 AUs added per year; no time difference between ABR certification v. alternate pathway
    - Wisconsin: no apparent adverse impact on regulatory agencies based on licensing databases for 2020/2021
    - SECY-20-0005: Rulemaking Plan for Training and Experience Requirements for Unsealed Byproduct Material (10 CFR Part 35), cost-benefit analysis, 15 hrs for NRC, 11 hrs for Agreement States, and 5 hrs for licensees

Ramifications & Potential Issues (cont.)

- ~80% of ABR certifications included AU-E; unknown what % become AUs on RAM licenses
- Alignment of ACGME / AAPM-CAMPEP and NRC T&E requirements for AU and AMP designations
- No indications that other NRC recognized entities will follow ABR's decision
  - CBNE (dissolved) and AOBNM (inactive and very small even when they were active)
- Association of University Radiologists (AUR) meetings may be appropriate venues for discussions and potential publication of recommendations in the AUR flagship journal, Academic Radiology

American Board of Radiology (ABR)
Questions

- Can ABR reveal time spent and/or expense for including AU-E designation vs. eliminating it?
- How do ABR members (applicants, preceptors and program directors) feel about the extra burden that will be placed on them by eliminating the AU-E designation on board certificates?
- Are there other options rather than eliminating the AU-E designation on the board certification?
- Did the AU-E to clinical AU conversion play into the ABR's decision, and if so, what was this estimate and how was this estimate obtained?
- How many ABR Certified Physicists get the RSO-E designation on their certificates/year?
- If there is a significant decrease in MPs approved to be RSOs, are they any plans to increase the number of radiologists who are prepared to become RSOs?

Acronyms

- AAPM – American Association of Physicists in Medicine
- ABR – American Board of Radiology
- ABNM – American Board of Nuclear Medicine
- ACGME – Accreditation Council for Graduate Medical Education
- AU-E – Authorized User-eligible
- AMP-E – Authorized Medical Physicist-eligible
- CAQ – Certificate of Added Qualification
- CAMPEP – Commission on Accreditation of Medical Physics Education Programs
- IR-DR – Interventional Radiology-Diagnostic Radiology
- MP – Medical Physicist

Acronyms (cont.)

- NM-DR – Nuclear Medicine – Diagnostic Radiology
- NR – Nuclear Radiology
- NRC – Nuclear Regulatory Commission
- RO – Radiation Oncology
- RISE – Radioisotope Safety Exam
- RSO-E – Radiation Safety Officer-eligible
- T&E – Training and Experience

ACMUI's Comments on the NRC Staff's Regulatory Basis for the Rulemaking on Emerging Medical Technologies and Rubidium-82 Generators

Commission Briefing | December 6, 2022 | Megan Shober

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BACKGROUND

The last major structural revision to 10 CFR Part 35 was in 2002.

- Energy Policy Act
- Stereotactic Devices
- Microsources
- Alpha-emitters
- Theranostics

BACKGROUND

10 CFR 35.1000 used when technologies don't "fit."

- Complex devices with new components
- Tiny sealed sources that behave like a liquid
- Unsealed brachytherapy sources
- Need for device-specific training
- Physical presence requirements
- Atypical authorized users

RULEMAKING TIMELINE

Rulemaking Plan
SECY-21-0013
2/9/2021

Commission Direction
1/13/2022

Draft Regulatory Basis
(to ACMUI)
9/27/2022

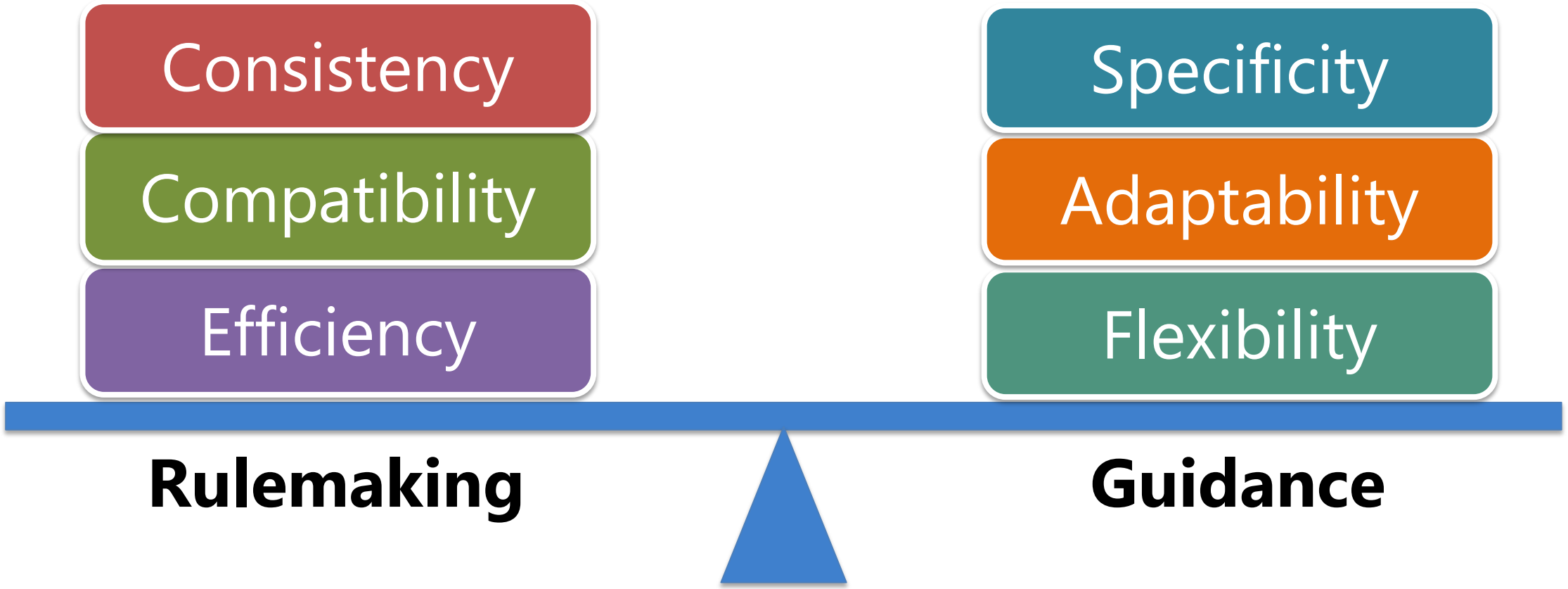
Regulatory Basis
(public comment)
Spring 2023

RULEMAKING PROGRESS

- ☒ Option 1: Rubidium-82 generators only
- ☒ Option 2: Rubidium-82 generators, limited EMTs
- ☑ Option 3: Rubidium generators-82, broadly incorporate EMTs

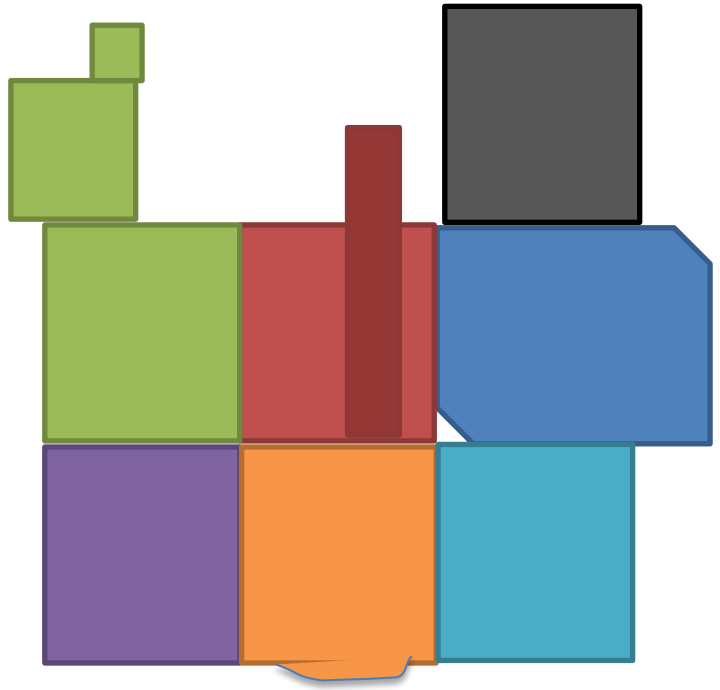
→ Staff developed draft regulatory basis.

REGULATORY ISSUES



PROPOSED CHANGES

- Add EMTs into the “best fit” Subpart and then expand regulations to accommodate differences
- New Subpart for microsources
- Device-specific training
- Conforming administrative updates



SUBCOMMITTEE EVALUATION

"Well-established technology"

- How widespread?
- How mature?
- How different?

SUBCOMMITTEE EMT EVALUATION

Well-established	Limited	Not Available
Ge-68 generators	Alpha DaRT™	ViewRay™
Intravascular brachy	GammaPod™	Epi-Rad90™
Seed localization	*RadioGenix™	GliaSite®
Gamma Knife®	**Liberty Vision	
Microspheres		

*NRC Staff chose to leave in 35.1000.

**Licensing guidance not yet published.

SUBCOMMITTEE RECOMMENDATIONS

- ☑ New Subpart for microsources
- ☑ Incorporate well-established EMTs into existing 10 CFR Part 35 Subparts
- ☑ Changes to Radiation Safety Committee membership, written directives
- ☑ Device-specific training
- ☑ Performance-based changes to 35.600

SUBCOMMITTEE RECOMMENDATIONS

- ✗ Do not add product-specific requirements in regulation unless EMT is well-established
- ✓ Add general requirements to address simple issues with EMTs
- ? Re-evaluate ophthalmic sources
- ? Re-evaluate authorized medical physicists
- ? Broadly consider training for atypical AUs

SUBCOMMITTEE CONCLUSIONS

- Many of the current EMTs are well-established and should be moved out of 35.1000.
- Some EMTs should stay in 35.1000 due to limited operating experience.
- NRC should periodically assess whether EMTs are still in use.
- Thanks to Staff for their efforts on this project!

ACRONYMS

- ACMUI: Advisory Committee on the Medical Uses of Isotopes
- AUs: Authorized Users
- CFR: Code of Federal Regulations
- EMTs: Emerging Medical Technologies
- Ge-68: Germanium-68
- NRC: Nuclear Regulatory Commission