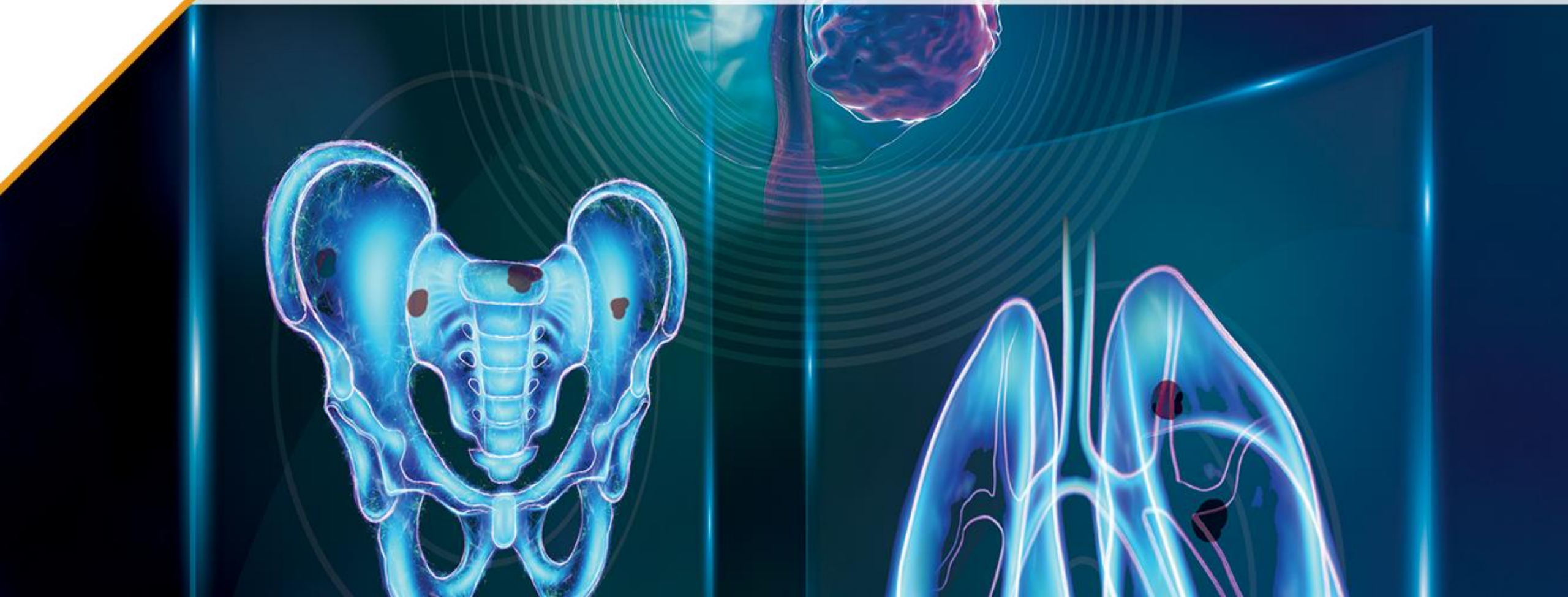
AXIS
Medical Education

Improved Outcomes in mCRPC with PSMA-Directed Diagnostics and Therapies



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Disclosure of Conflicts of Interest

Ayse Tuba Kendi, MD

Reported a financial interest/relationship or affiliation in the form of *Advisory board*; Novartis Pharmaceuticals Corporation. *Research grant*; Novartis Pharmaceuticals Corporation.

A. Oliver Sartor, MD

Reported a financial interest/relationship or affiliation in the form of *Consultant*: Advanced Accelerator Applications; Astellas Pharma US, Inc; AstraZeneca Pharmaceuticals LP; Bayer; Blue Earth Diagnostics, Inc; Bavarian Nordic; Bristol-Myers Squibb Co; Clarity Pharmaceuticals; Clovis Oncology; Constellation, Dendreon Corp; EMD Serono, Inc; Fusion; Isotopen Technologien Meunchen; Janssen; Myovant; Myriad; Noria Therapeutics, Inc; Novartis Pharmaceuticals Corp; Noxopharm; Progenics Pharmaceuticals, Inc; POINT Biopharma; Pfizer, Inc; Sanofi; Tenebio; Telix; and Theragnostics. *Research grant*: Advanced Accelerator Applications; Amgen, Inc; AstraZeneca Pharmaceuticals LP; Bayer; Constellation; Endocyte; Invitae; Janssen; Lantheus; Merck & Co, Inc; Progenics; and Tenebio.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Describe the clinical significance of the background and use of PSMA-based imaging for PET/CT for diagnosis of mCRPC
- Evaluate clinical trial data and research findings in the determination of best-practice selection and sequencing of available and emerging treatment modalities for patients with mCRPC
- Recognize the potential application of both PSMA-directed PET for diagnostics and PSMA-directed RLT for treatment
- Identify patients most likely to benefit from a theranostic approach to slow tumor progression
- Apply strategies to identify and manage adverse events associated with PSMA-targeted therapies for mCRPC
- Summarize the potential impact of QoL improvements and other clinical challenges in patients with heavily pretreated mCRPC

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CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; QoL, quality of life; RLT, radioligand therapy.

Overview of Theranostics, PSMA, and PSMA Imaging

Dr. Tuba Kendi

PSMA, prostate-specific membrane antigen.

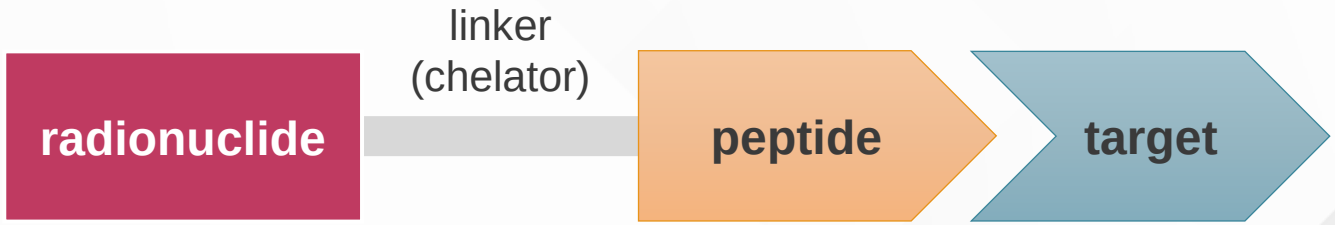
Outline

- Discuss concept of thera(g)nostics
- Understand appropriate use of PSMA agents
- Compare PSMA imaging agents
- Understand role of PSMA imaging before RLT
- Review of alpha emitters

PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

What is Thera(g)nostics?

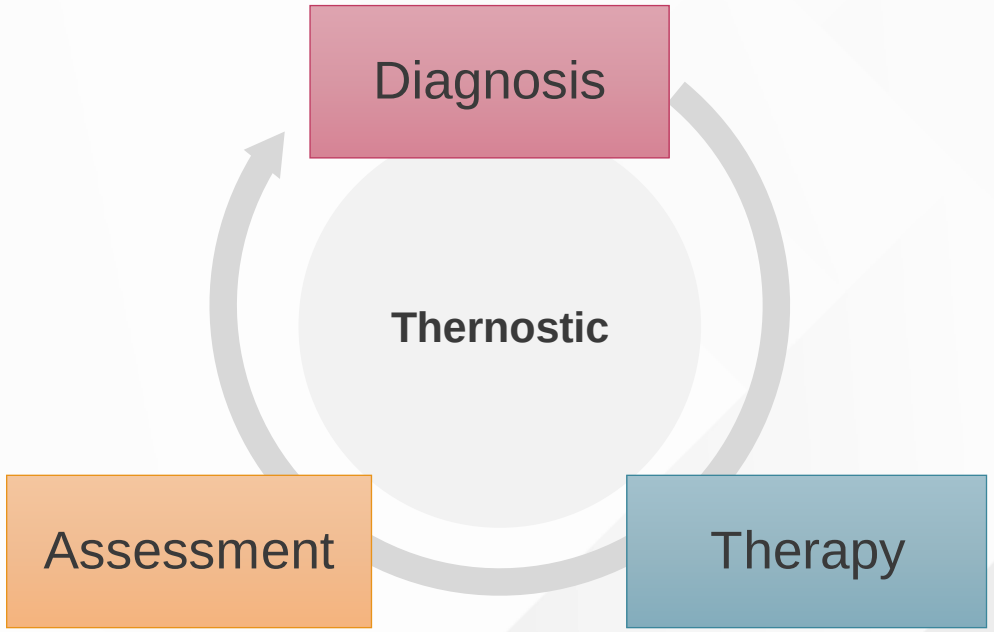
Theranostic combines the words “therapy” and “diagnostics"



Hofman et al. *Radiographics* 2015;35;500-516. Frangos and Buscombe *Eur J Nucl Med Mol Imaging* 2019;46:519.

Thera(g)nostics (from imaging to therapy)

If you can see it,
you can treat it



Kumar et al. *Chem Soc Rev*. 2015;44:6670-6683.

Prostate Cancer

Introduction

- Most common cancer diagnosed in men in the United States
  - Approximately 268,490 men will be diagnosed with prostate cancer in 2022
  - About 1 man in 8 will be diagnosed with prostate cancer during his lifetime
- The second most common cause of cancer mortality in the United States is from metastatic, castrate-resistant prostate cancer that no longer responds to hormonal therapy
  - About 34,500 men will die from prostate cancer

American Cancer Society. January 12, 2022; https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html;
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf

Prostate Cancer

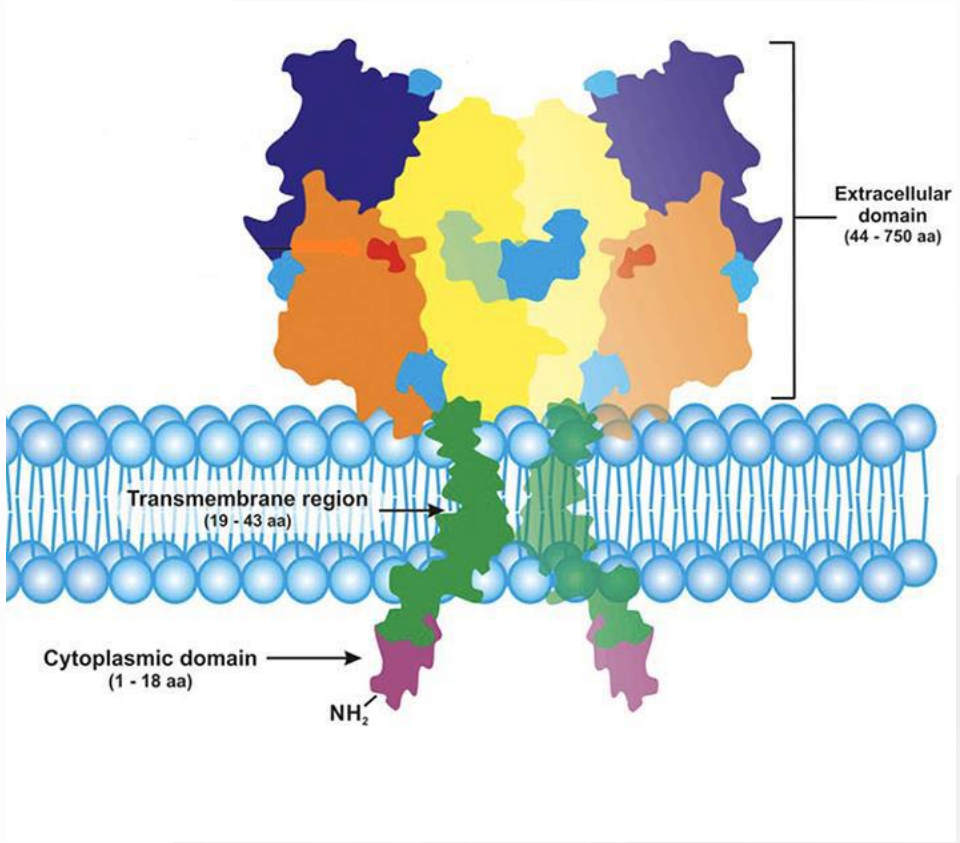
Current treatment landscape

- Radical prostatectomy or radiotherapy (local disease)
- Hormonal therapy (androgen deprivation)
- Enzalutamide and abiraterone (androgen receptor inhibitors)
- Chemotherapy (docetaxel/cabazitaxel) + prednisone
- Sipuleucel-T (cell-based immunotherapy)
- Radium-223 (alpha particle-emitting radioactive therapeutic agent)

Schaeffer et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate cancer. V.4.2022.
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prostate-Specific Membrane Antigen

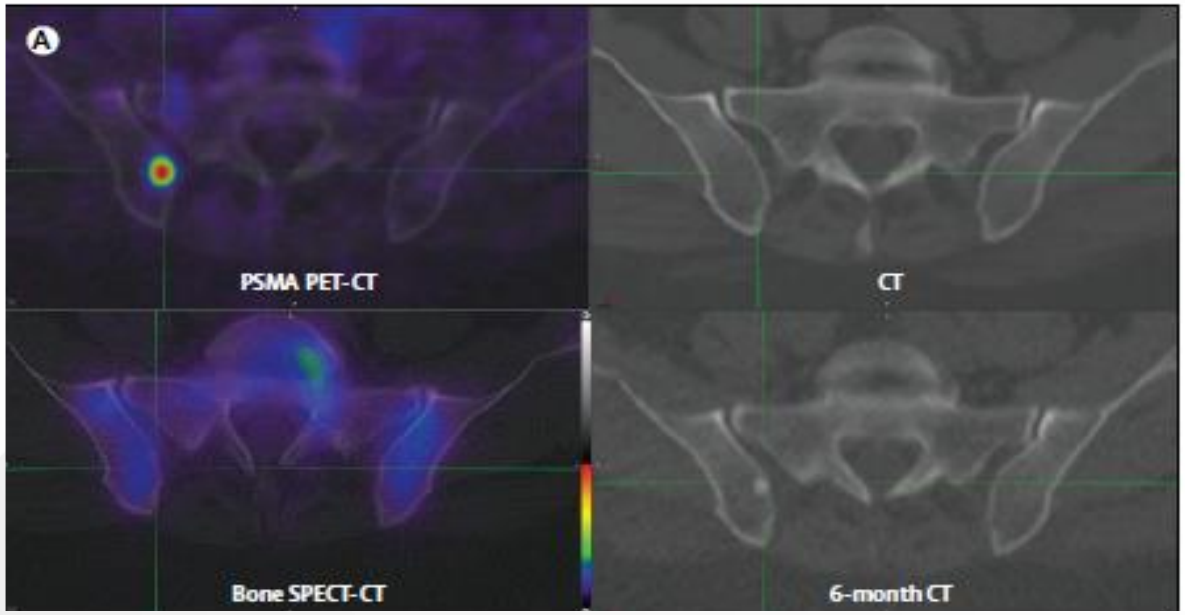
- A glutamate carboxy peptidase/folate hydrolase cell surface enzyme
- Overexpressed on the surface of prostate cancer cells (up to 100-1000 fold)
- Highly attractive target for imaging and therapy

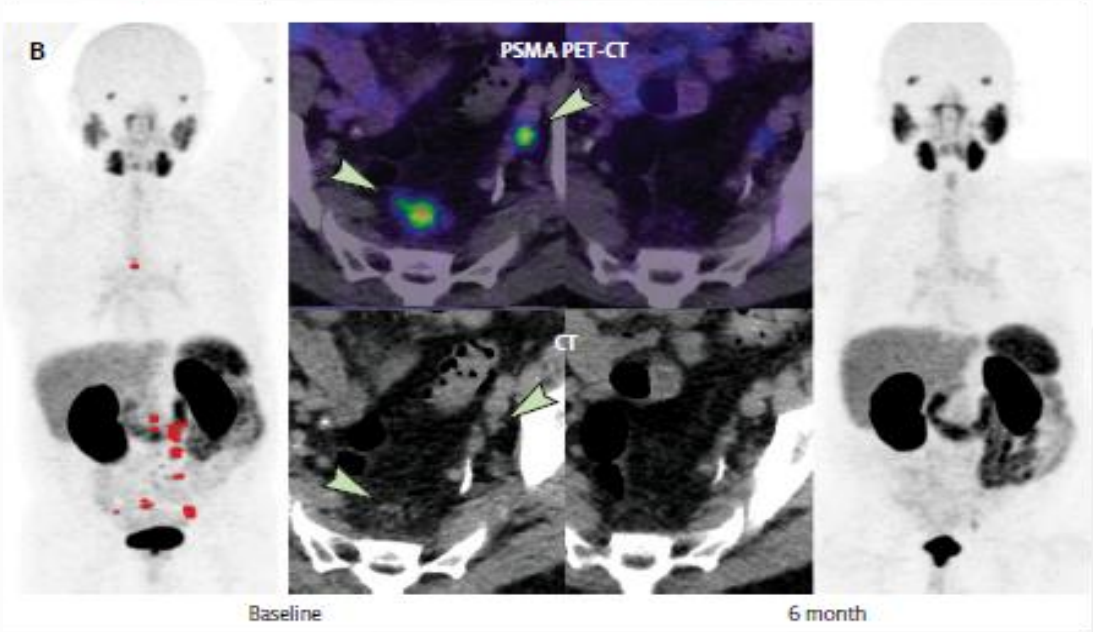


Evans et al. *Br J Pharmacol*. 2016;173:3041-3079.

Why PSMA Imaging?

PSMA PET in High-Risk Prostate Cancer

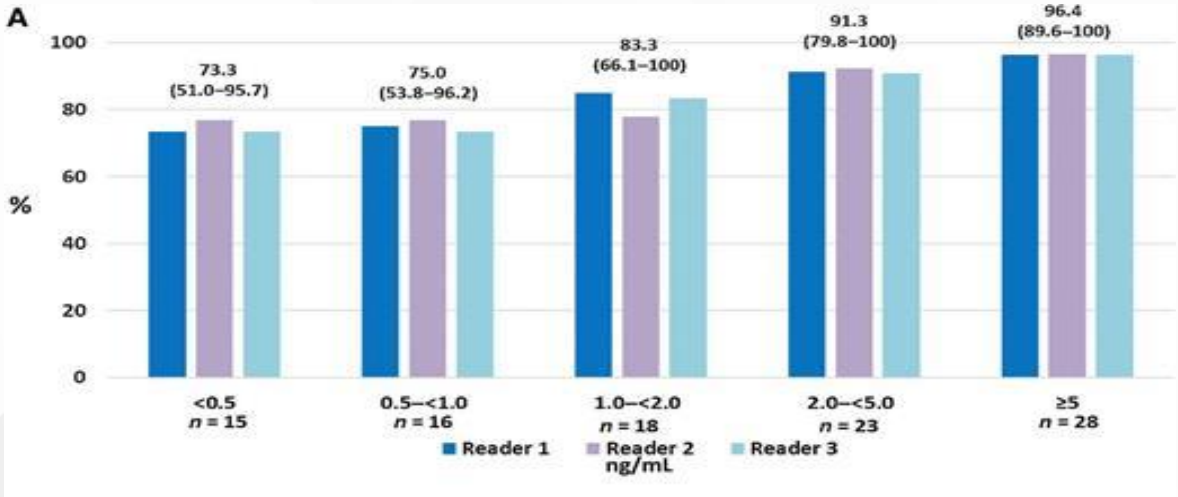




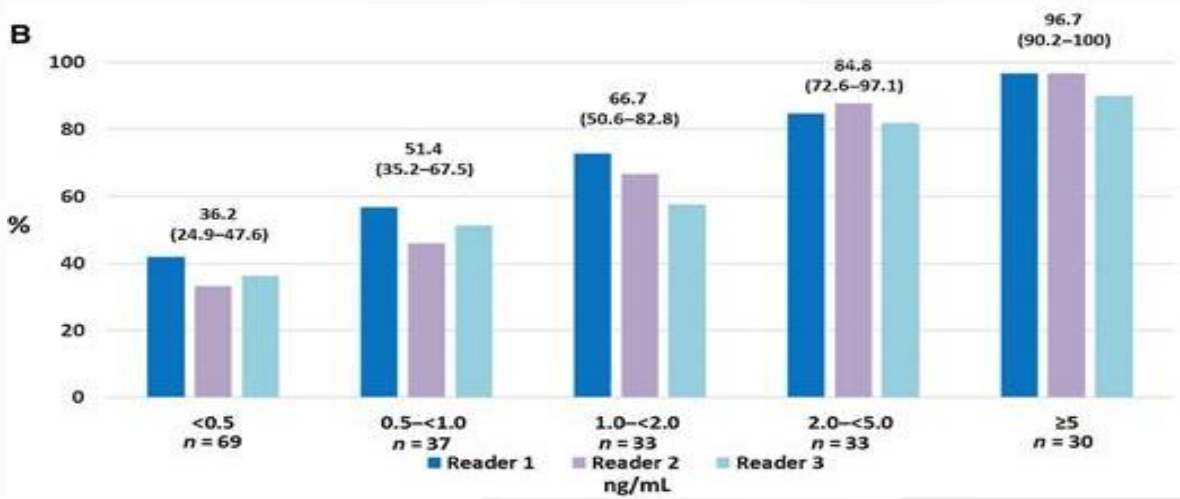
PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Hofman et al. *Lancet* 2020;395:1208-1216.

CONDOR Study: ^{18}F-DCFPYL-PET

Correct Localization Rate by Baseline PSA levels



Detection Rate by Baseline PSA levels



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^{18}F-DCFPYL, F-DCFPyL=fluorine, 2-(3-{1-carboxy-5-[(6-[(18)F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid;
PET, positron emission tomography; PSA, prostate-specific antigen.
Morris et al. *Clin Cancer Res*. 2021;27(13):3674-3682.

Benefit of PSMA Imaging

- High detection rate and diagnostic accuracy
- Results frequently result in changing management plans
- Assesses patients for eligibility for PSMA RLT

PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

Indications for PSMA PET

Clinical Scenarios for Prostate Cancer

Scenario #	Description	Appropriateness	Score
1	Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor	Rarely Appropriate	3
2	Patients with very low, low, and favorable intermediate-risk prostate cancer	Rarely Appropriate	2
3	Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer	Appropriate	8
4	Newly diagnosed unfavorable intermediate, high-risk, or very high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging	Appropriate	8
5	Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging	May be Appropriate	4
6	PSA persistence or PSA rise from undetectable level after radical prostatectomy	Appropriate	9
7	PSA rise above nadir after definitive radiotherapy	Appropriate	9
8	PSA rise after focal therapy of the primary tumor	May be Appropriate	5
9	nmCRPC (M0) on conventional imaging	Appropriate	7
10	Post-treatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radioligand therapy	May be Appropriate	6
11	Evaluation of eligibility for patients being considered for PSMA-targeted radioligand therapy	Appropriate	9
12	Evaluation of response to therapy	May be Appropriate	5

mCRPC, metastatic castration-resistance prostate cancer; nm, non-metastatic; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; PET, positron emission tomography.

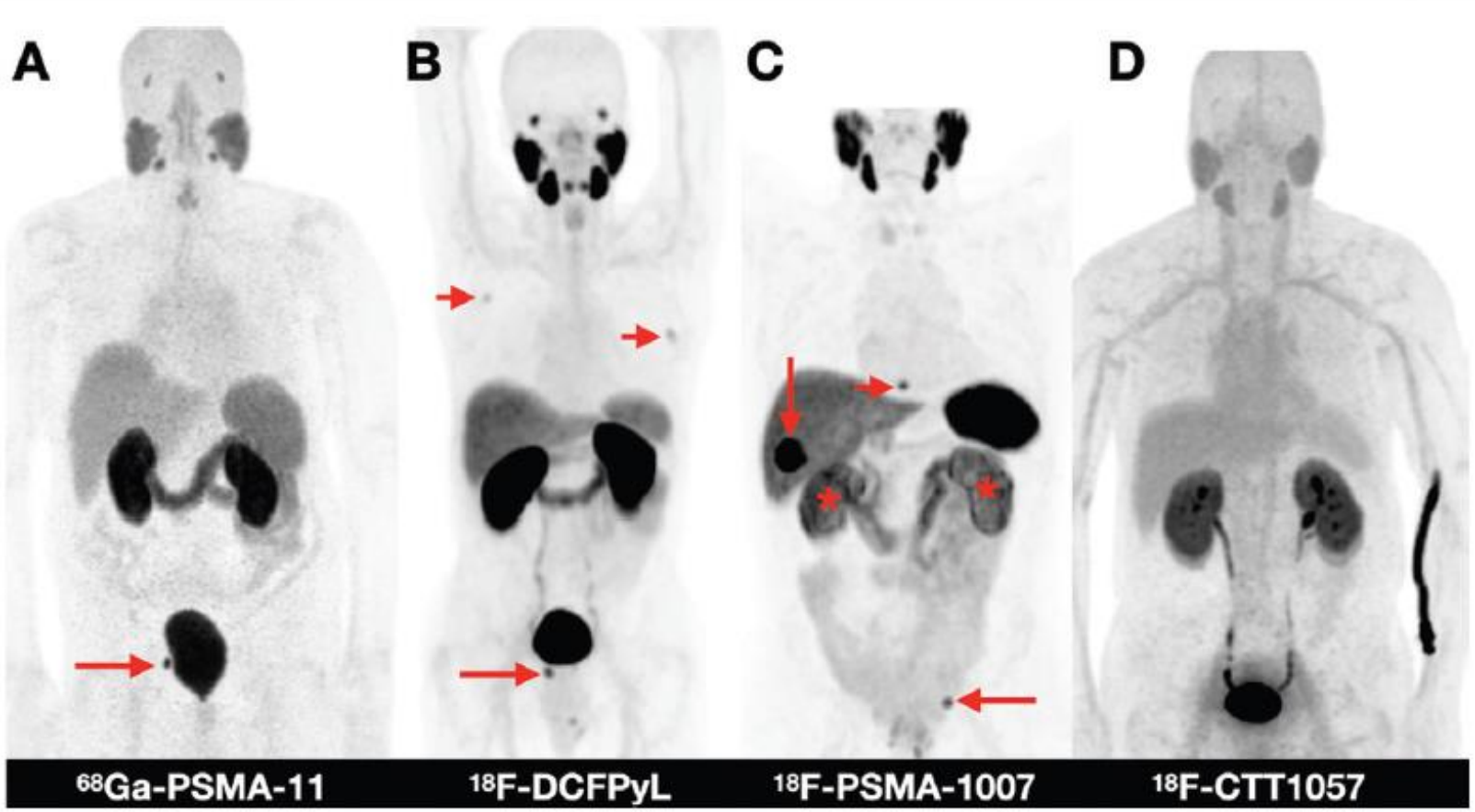
Jadvar et al. *J Nucl Med*. 2022;63:59-68.

PSMA Imaging Agents

Which One to Choose?

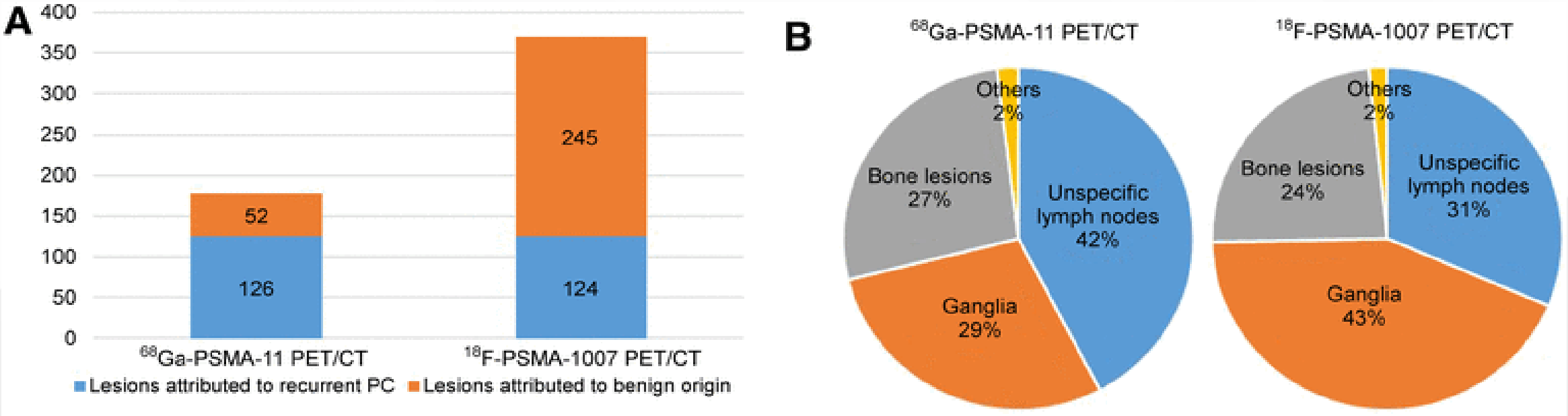
Do We Need to Choose?

PSMA Radiopharmaceuticals



PSMA, prostate-specific membrane antigen; Ga, Gallium, F, Piflufolastat;
F-DCFPyL, fluorine, 2-(3-{1-carboxy-5-[(6-[(18)F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid; F-CTT1057, fluorine cancer-targeted technology.
Lawhn-Heath et al. *Radiology* 2021; 299:248-260.

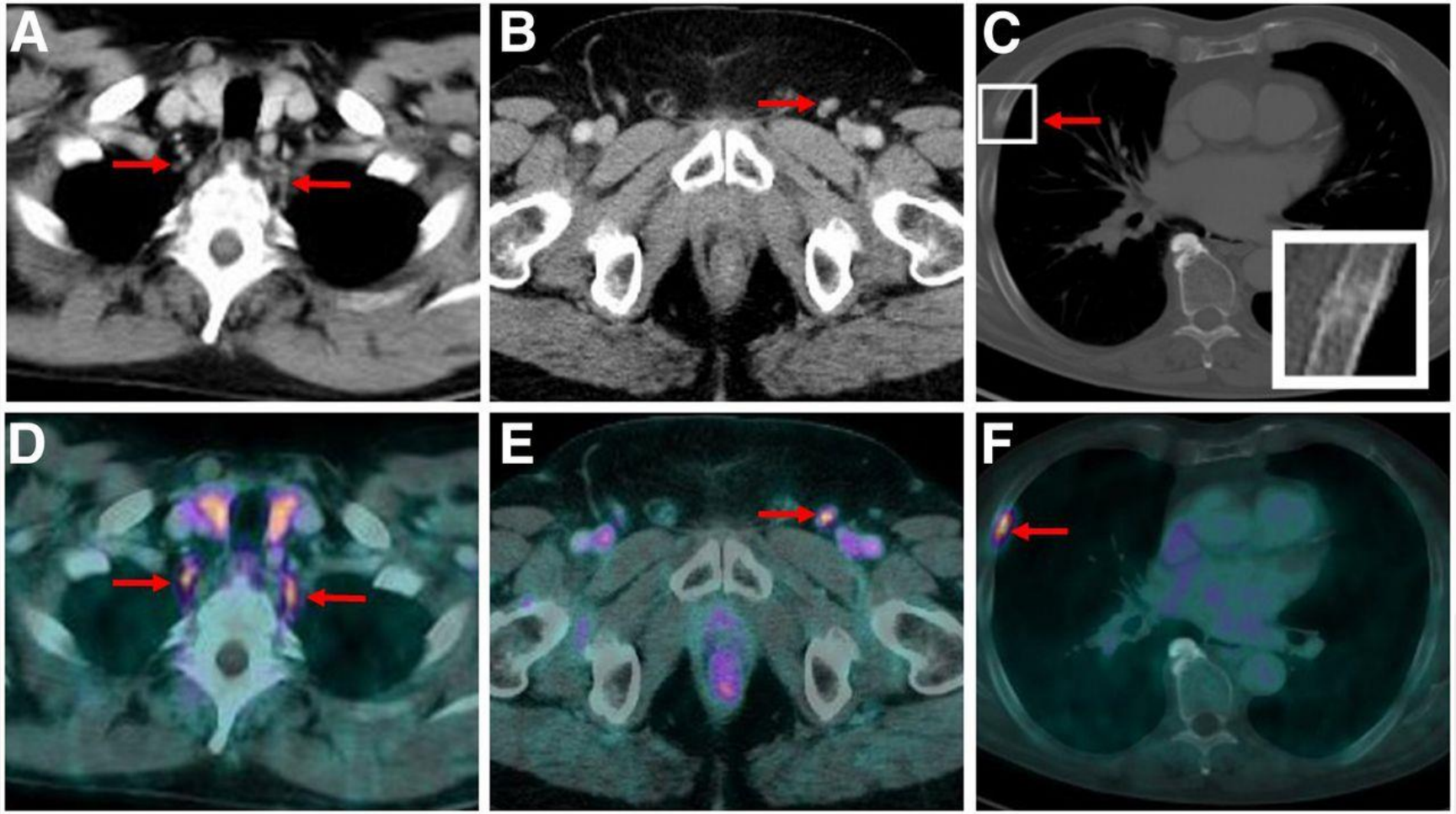
^{68}Ga-PSMA-11 vs ^{18}F-PSMA-1007 PET



CT, computed tomography; Ga, Gallium; F, Piflufolastat; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; PC, prostate cancer.

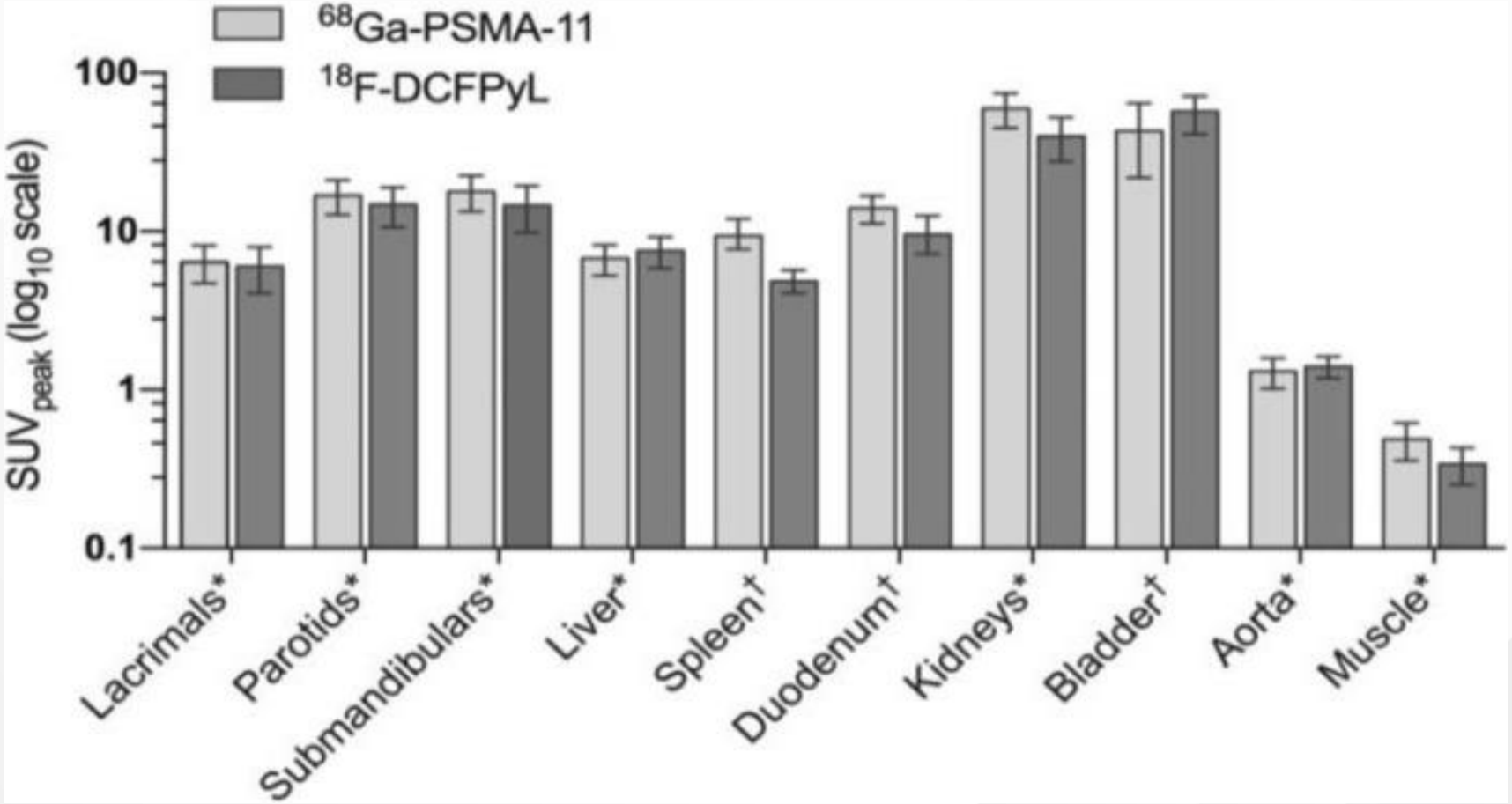
Rauscher et al. *J Nucl Med*. 2020;61:51-57.

CT vs ^{18}F-PSMA-1007 PET



CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Rauscher et al. *J Nucl Med*. 2020;61:51-57.

^{68}Ga-PSMA-11 vs ^{18}F-DCFPyL



Ga, Gallium; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value.
Ferreira et al. *Cancer Imaging* 2019;19(1):23.

Choosing PSMA PET Agents

- All agents equally effective for assessing metastasis
- All agents equally effective as radiotracers for PSMA radioligand therapy

PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Jadvar et al. *J Nucl Med*. 2022;63:59-68.

PSMA PET Imaging

How Do We Assess Patients for RLT Now?

PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

^{177}Lu-PSMA 617 Indication

- FDA approved, March 2022
- Patients with metastatic castration-resistant prostate cancer previously treated with taxane-based chemotherapy and androgen receptor pathway inhibitors

FDA, U.S. Food & Drug Administration; Lu, Lutetium; PSMA, prostate-specific membrane antigen.

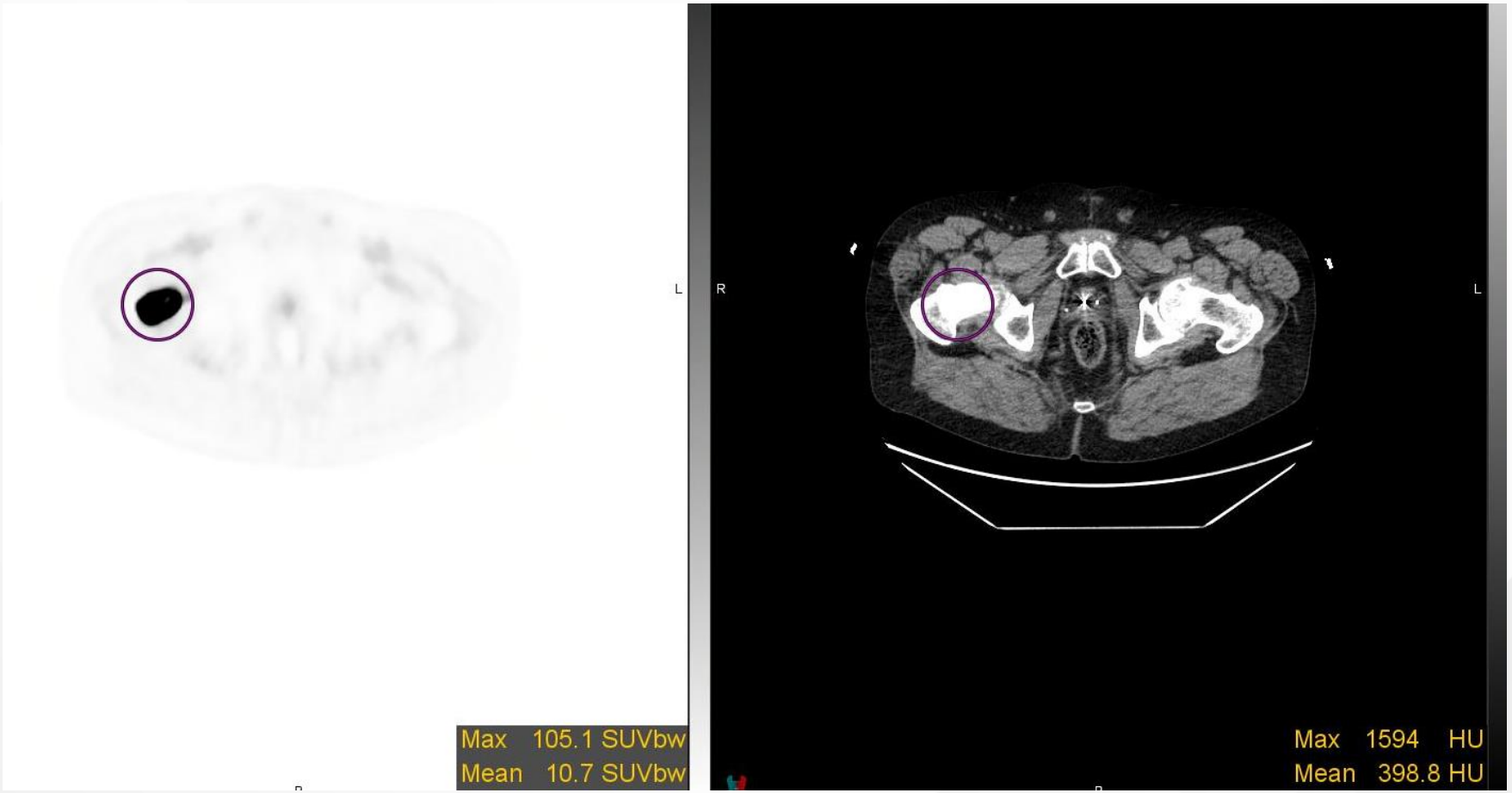
PSMA Imaging Results Criteria for Selection of Lu-PSMA 617 Therapy

- Lu-PSMA 617 eligible: PSMA uptake greater than liver uptake in one or more metastatic lesions of any size in any organ
- Lu-PSMA 617 ineligible: PSMA uptake equal or lower than uptake in liver in any lymph node with short axis measuring at least 2.5 cm or in any solid organ with a lesion measuring at least 1 cm in the short axis

- 87% qualified by imaging criteria for enrollment in the VISION trial
- 13% did not qualify

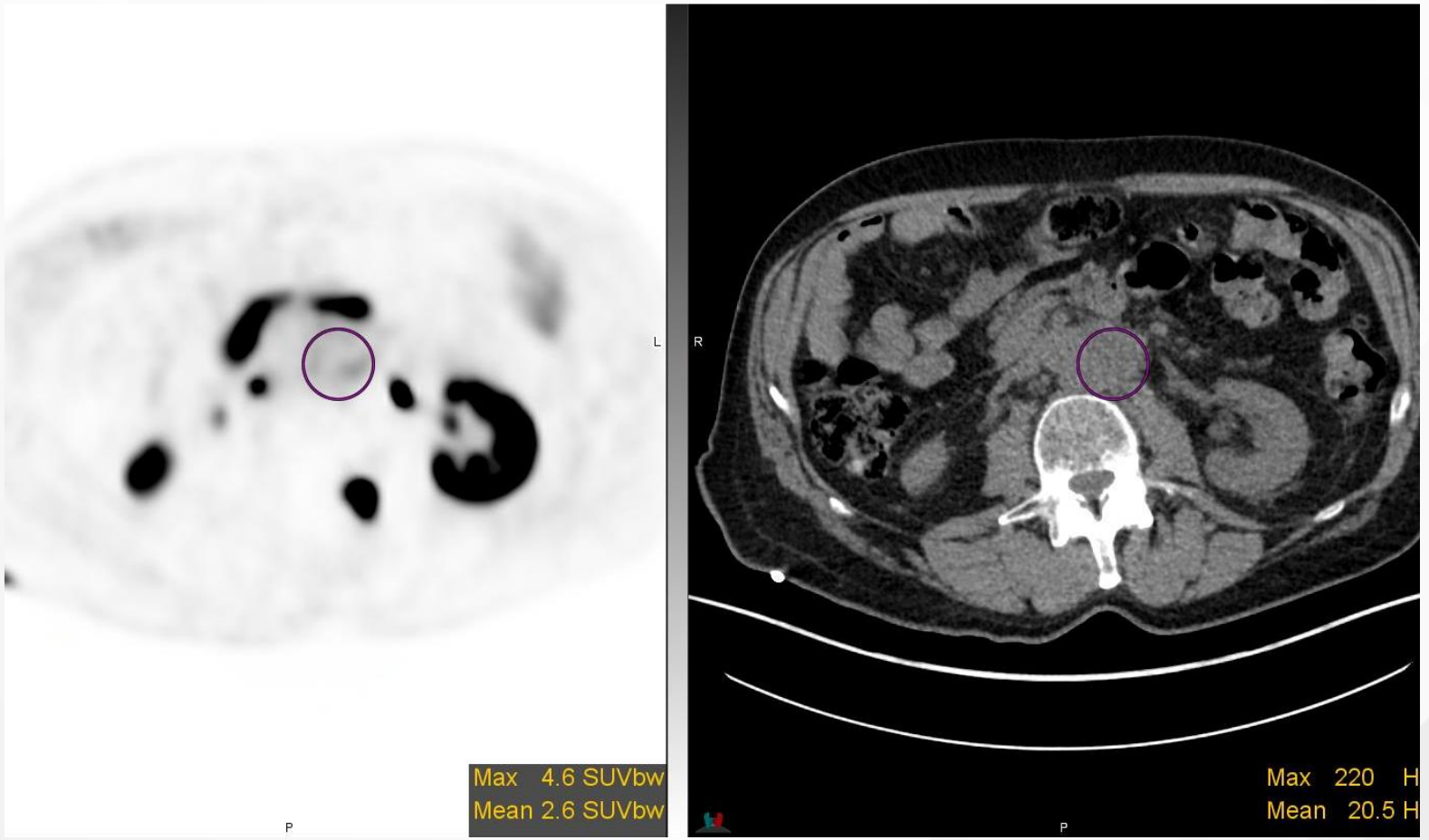
Lu, lutetium; PSMA, prostate-specific membrane antigen.

PSMA-Positive Disease



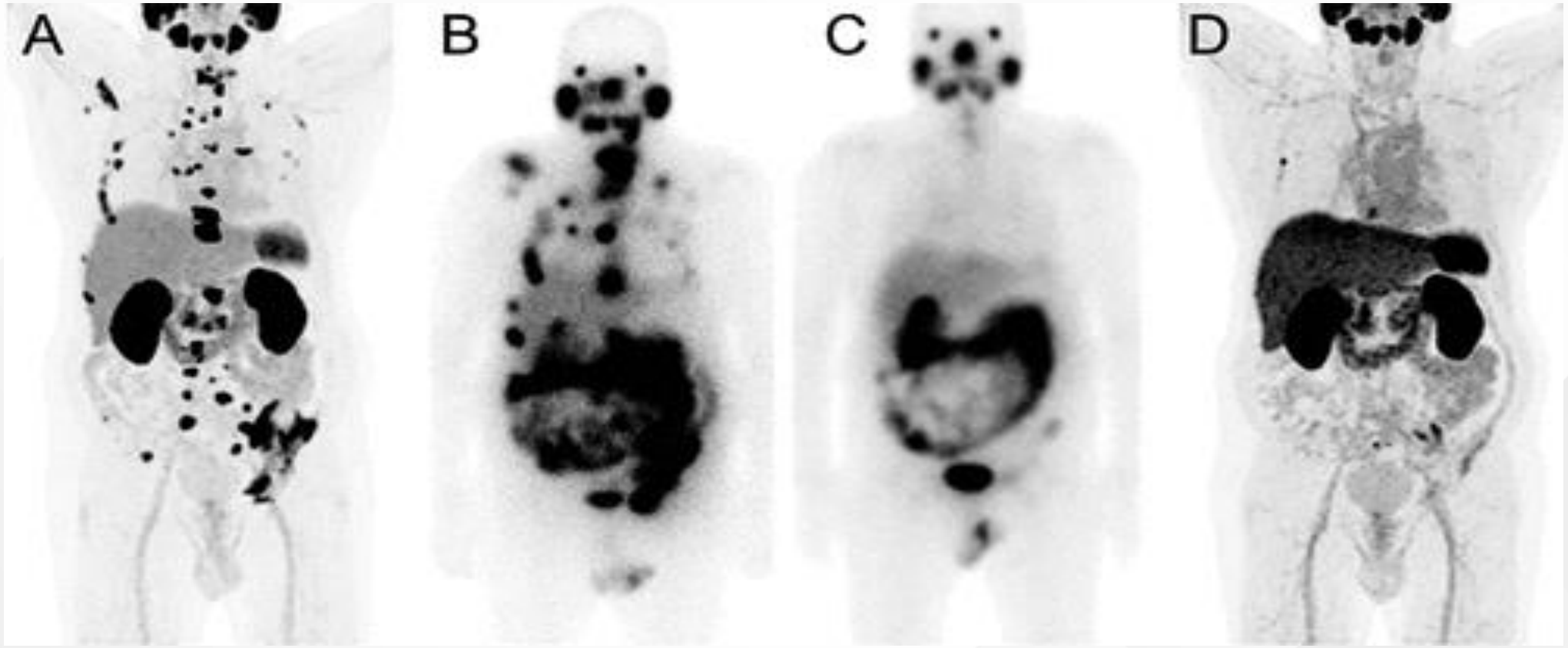
PSMA, prostate-specific membrane antigen.
Slide courtesy of Dr. Ayse Kendi.

PSMA-Negative Disease



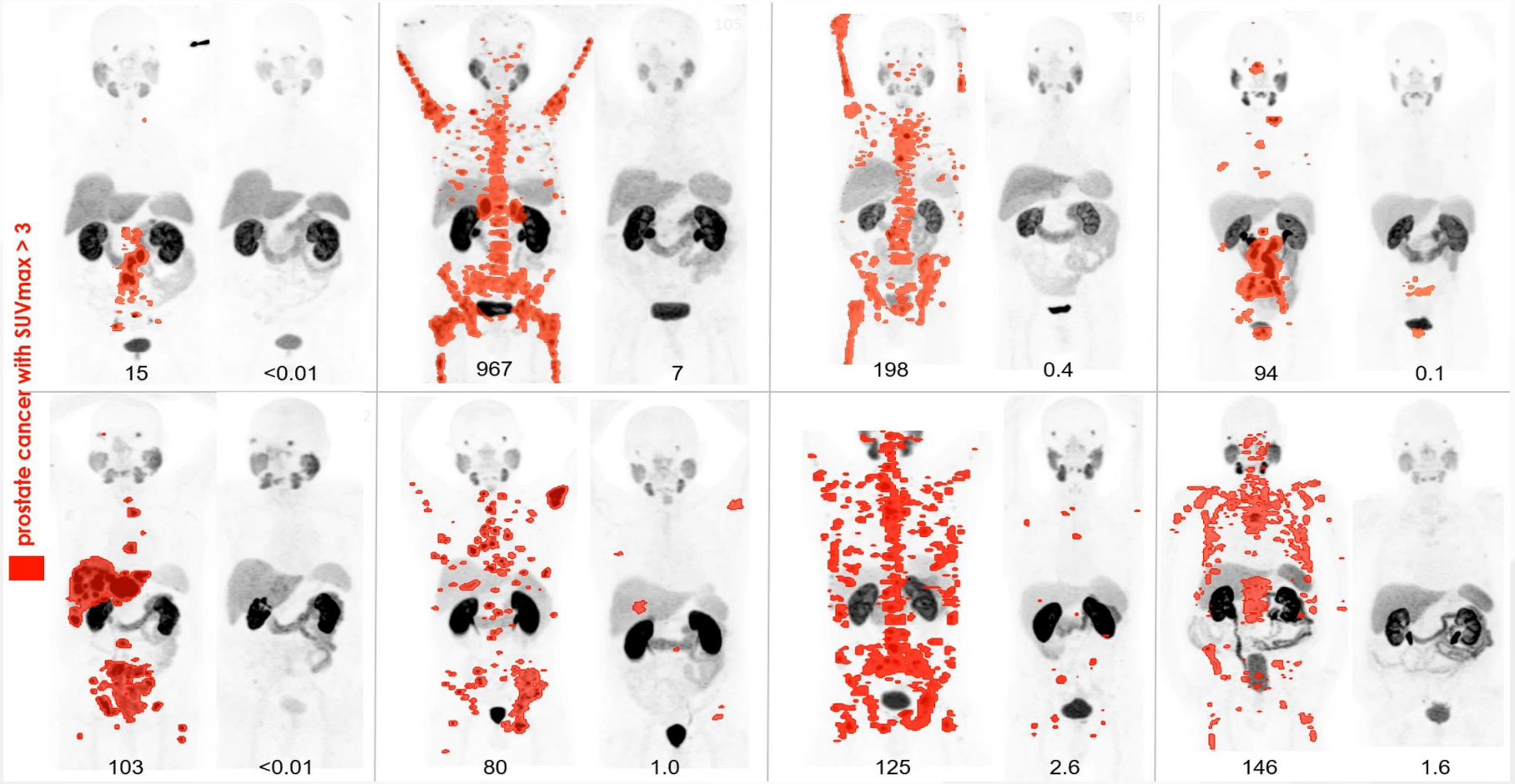
PSMA, prostate-specific membrane antigen.
Slide courtesy of Dr. Ayse Kendi.

PSMA Therapy Response



PSMA, prostate-specific membrane antigen.
Lawhn-Heath et al. *Radiology* 2021;299:248-260.

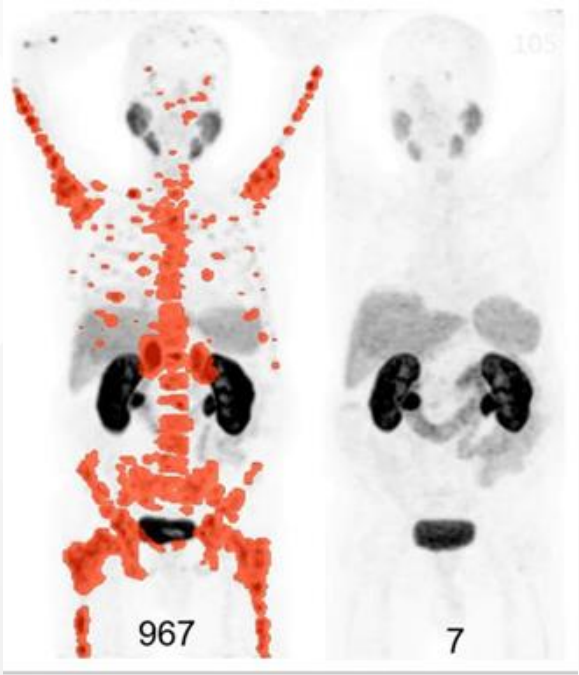
^{177}Lu-PSMA-617 Treatment



Lu, lutetium; PSMA, prostate-specific membrane antigen.
Miyahira et al. *Prostate* 2020;80:1273-1296.

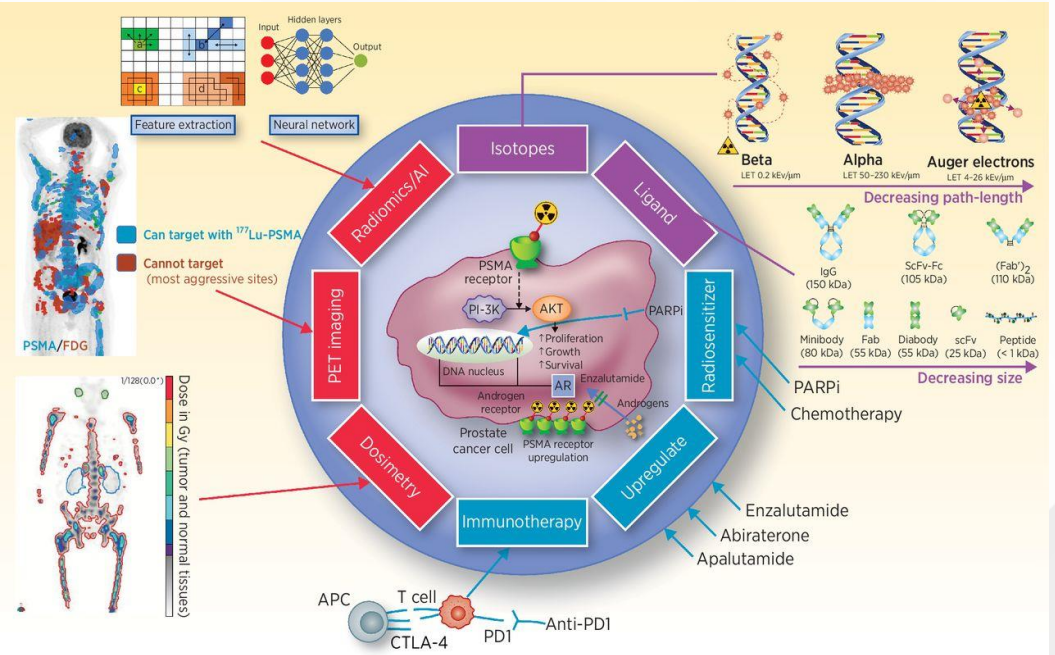
PSMA Theranostics

Current State



- High response rate
- Low toxicity
- Significant improvement of clinical symptoms
- Well-tolerated

Potential Mechanisms to Optimize



- Given the large number of patients with metastatic prostate cancer, it is projected that 160,000 cycles of Lu-PSMA will be administered annually
- Discovery → Research → Education → Application

Lu, lutetium; PSMA, prostate-specific membrane antigen.
Miyahira et al. *Prostate* 2020;80:1273-1296; Kumar and Hofman. *Clin Cancer Res.* 2020;26:2774-2776.

If Patients Don’t Respond or Stop Responding to Beta Emitters, What’s Next?

Alpha Emitters vs Beta Emitters

Alpha Emitter

- LET: 50-230 keV/microm
- Shorter range (less than 0.1 mm)
- Induces double DNA breaks
- Targets micrometastatic disease more efficiently

Beta Emitter

- LET: 0-2 keV/microm
- Range is up to 2 mm
- Mostly induces single DNA breaks

DNA, deoxyribonucleic acid; LET, linear energy transfer.

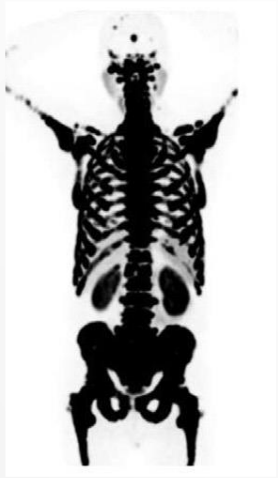
Alpha Emitters

- Prior RLT failure (primarily due to progression of micrometastases)
- Diffuse bone marrow infiltration
- Limited availability
- Challenging radiochemistry
- Toxicity (salivary glands)

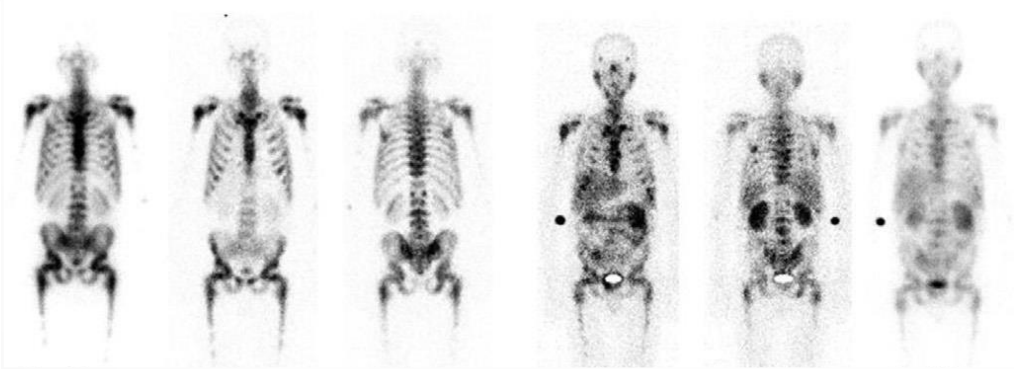
RLT, radioligand therapy.

^{225}Ac-PSMA Diffuse Type Red Marrow Infiltration

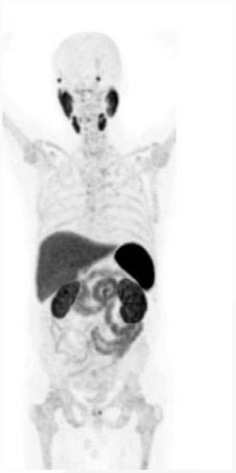
PSMA-PET



Planar-Emission Scans



PSMA-PET



Lab test:
[prior PSMA-Tx]

PSA 722.5 / AP 639
LDH 425 / PLT 55 / Hb 6.8
Leucoerythroblastic cell-count:
10% Progenitor cells (1% meta myelocytes, 7% myelocytes, 2% blasts)

1. Cycle
[1.5 GBq ^{177}Lu-PSMA+ 8 MBq ^{225}Ac-PSMA]

2. Cycle
[2 GBq ^{177}Lu-PSMA+ 6 MBq ^{225}Ac-PSMA]

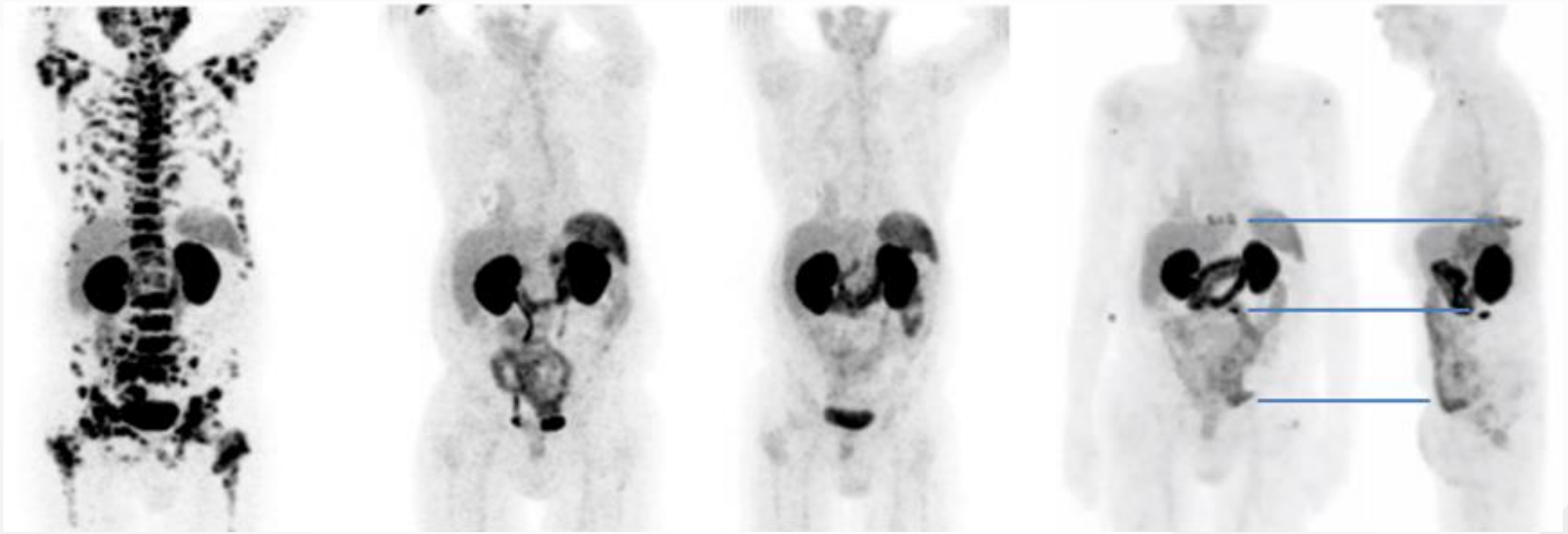
Lab test:
[after PSMA-Tx]

PSA 0.4 / AP 144
LDH 232 / PLT 146 / Hb 9.7
Leucoerythroblastic cell-count:
0% Progenitor cells

Ac, actinium; Hb, hemoglobin; LDH, lactate dehydrogenase; Lu, lutetium; PET, positron emission tomography; PLT, platelets; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; Tx, treatment.

Kratochwil et al. *Semin Nucl Med*. 2020;50(2):133-140.

^{225}Ac-PSMA Therapy



12/2014
PSA > 3,000.0 ng/mL

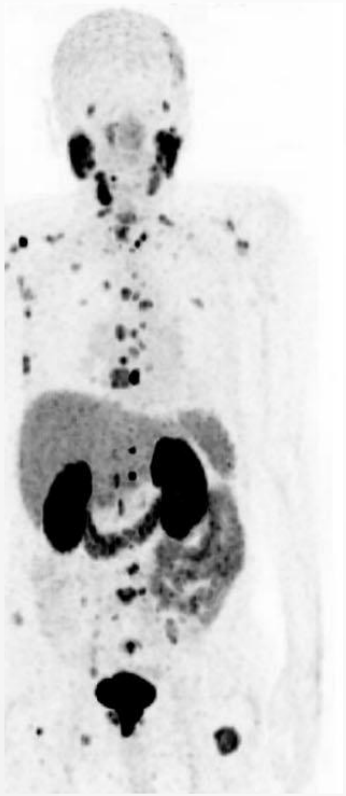
08-11 / 2015
PSA < 0.1 ng/mL

12 / 2015
PSA 0.2 ng/mL

12 / 2016
PSA 192 ng/mL

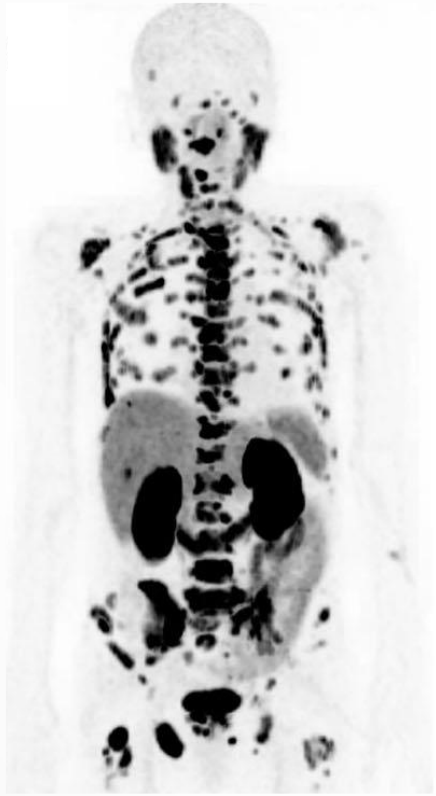
Ac, actinium; PSMA, prostate-specific membrane antigen.
Kratochwil et al. *Semin Nucl Med*. 2020;50(2):133-140.

Tandem Therapy (Ac-225-PSMA/Lu-PSMA-617)



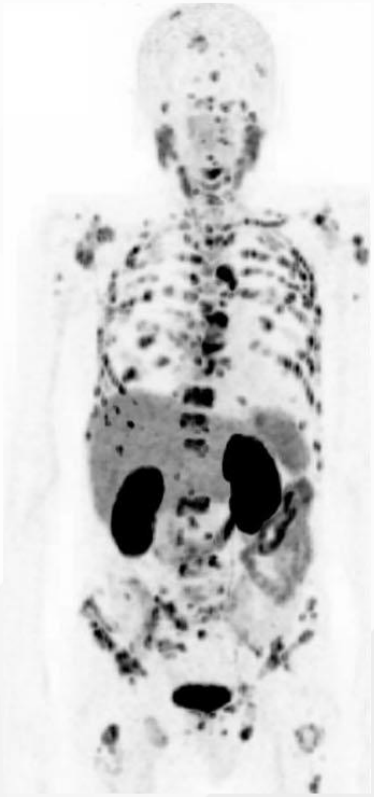
5/2017
PSA = 142 ng/ml

3x cycles
^{177}LuPSMA



2/2018
PSA = 486 ng/ml

1x Tandem
^{225}Ac/^{177}LuPSMA



5/2018
PSA = 213 ng/ml

Ac, actinium; Lu, lutetium.
Khreish et al. *Eur J Nucl Med Mol Imaging* 2020;47:721-728.

PSMA-Directed RLT is Teamwork and Requires a Dedicated Multidisciplinary Team

- Urology
- Radiology/Nuclear Radiology
- Radiation Oncology
- Medical Oncology
- Surgery

PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

Conclusions

- PSMA imaging is superior to conventional imaging
- PSMA imaging is appropriate for unfavorable intermediate and high-risk patients after RP or RT
- PSMA imaging results in appropriate selection for PSMA-directed RLT
- Current PSMA agents are comparable to each other
- ^{18}F-DCFPyL and ^{68}Ga-PSMA-11 are FDA approved for PSMA-directed RLT, and are suitable for patient selection for RLT
- Alpha-emitters are appropriate for patients with diffuse bone marrow infiltration and following failure of prior beta emitter RLT

BM, bone marrow; FDA, US Food & Drug Administration; Ga, Gallium; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy; RP, radical prostatectomy; RT, radiotherapy.

Radioligands Targeting PSMA: Challenges, Current Data, and Opportunities

Dr. Oliver Sartor

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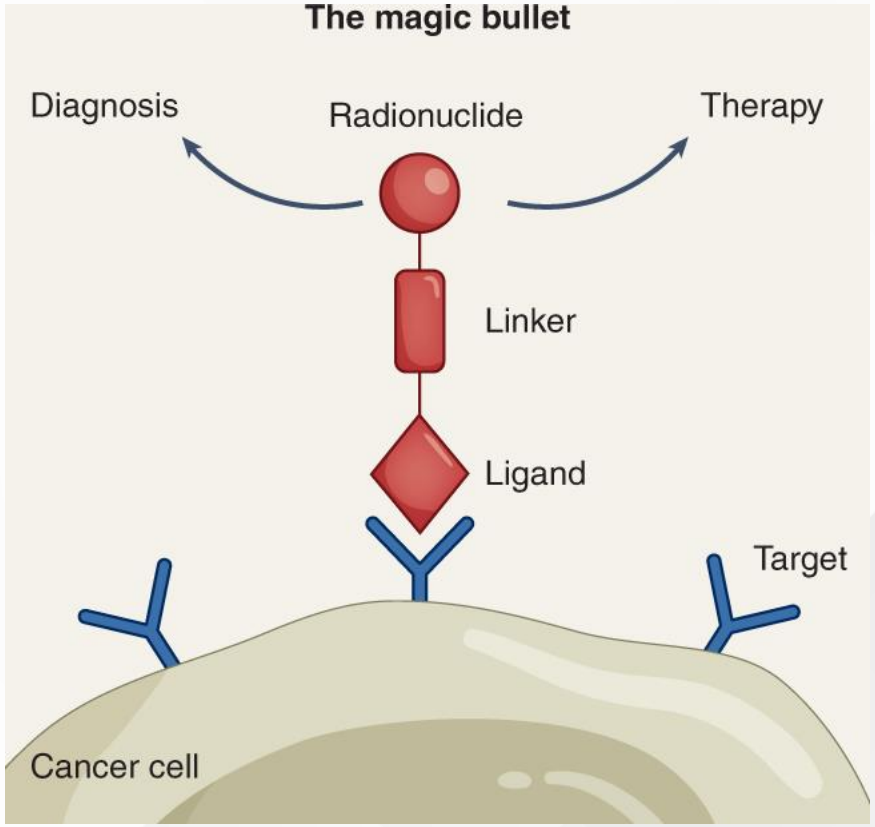
Theranostics: See it... Treat it

- Cell surface target
- A ligand
- A linker
- An isotope



Some Targets of Note

- SST2R (NETs)-proven success with isotopes
- PSMA (prostate)-proven success with isotopes
- CD19 (leukemia/lymphoma)-proven success with CAR-T
- CD37 (lymphoma)
- HER2 (breast)-notable recent success with new ADC
- HK2 (prostate)-interesting new target
- IGFR-1 (multiple)
- FAP (huge number of tumors for a stromal target)
- MC1R (melanoma)
- CA IX (renal)

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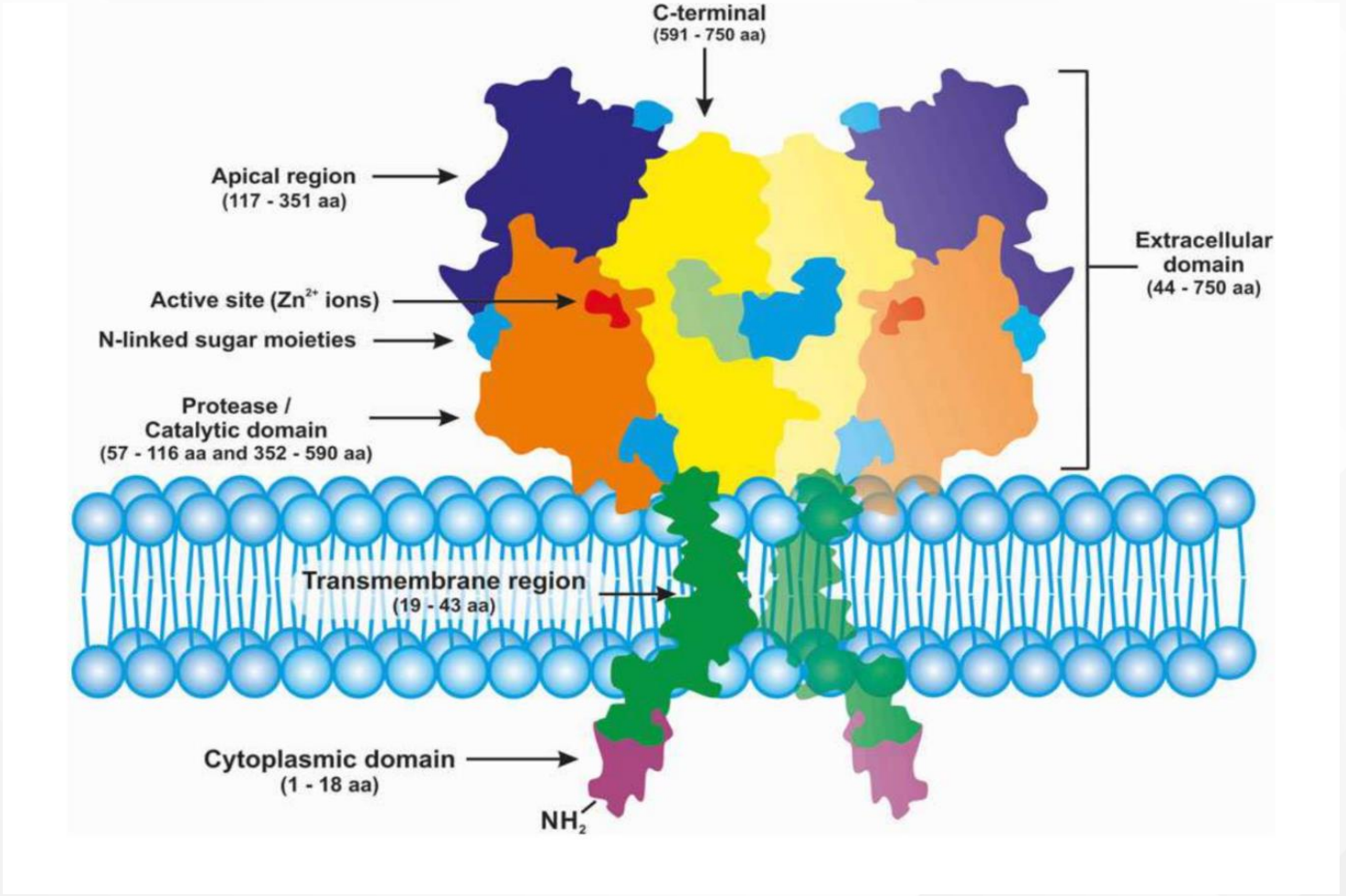
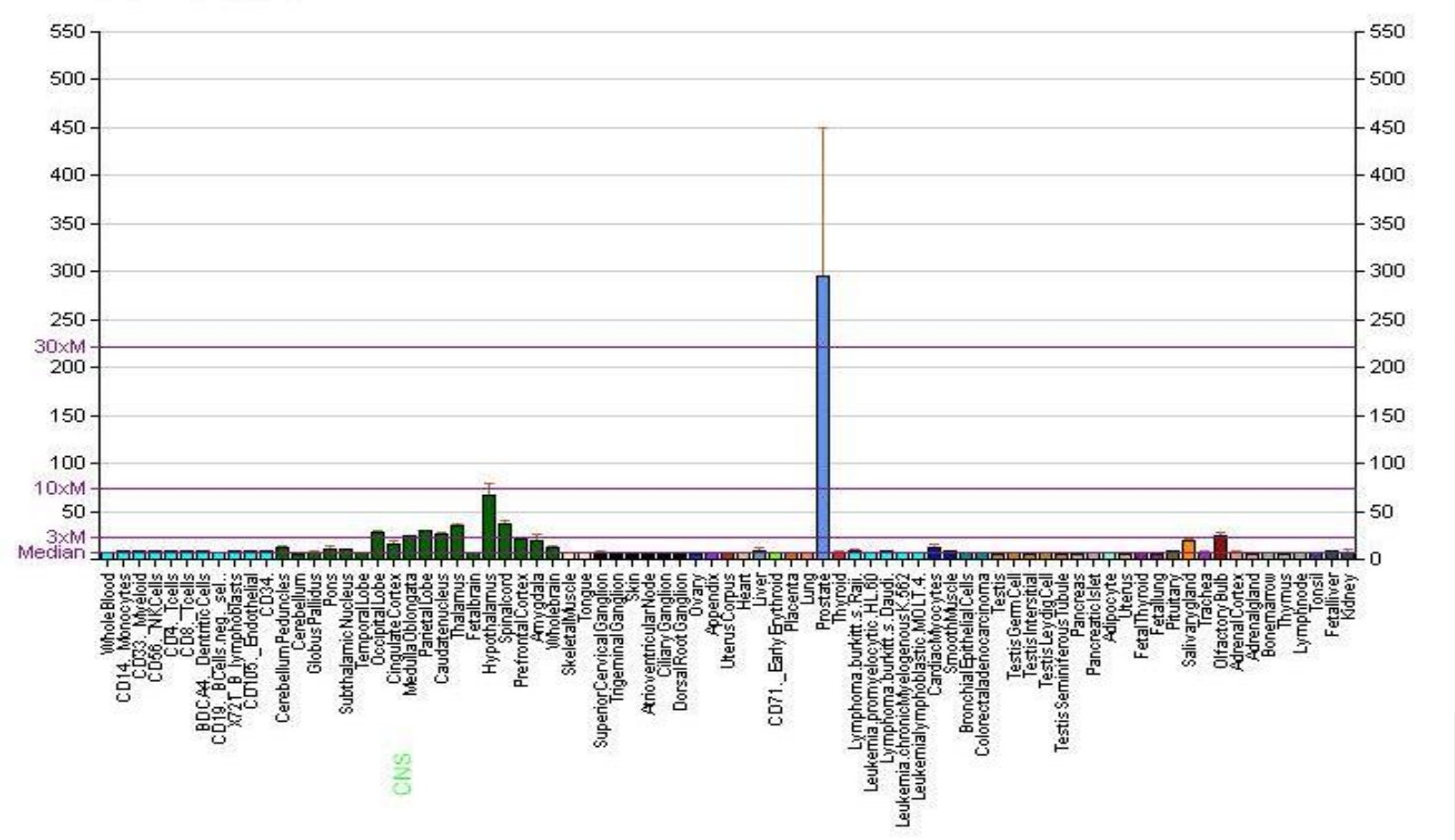
SST2R, somatostatin receptor 2; PSMA, prostate-specific membrane antigen; CD, cluster of differentiation; HER2, human epidermal growth factor receptor; HK2, hexokinase 2; IGFR, insulin-like growth factor receptor; FAP, fibroblast activation protein; CA IX, carbonic anhydrase IX.; NETs, neuroendocrine tumors; CAR-T, chimeric antigen receptor **T**-cell therapy; ADC, antibody-drug conjugate; MC1R, melanocortin receptor-1.

PSMA: Transmembrane Protein



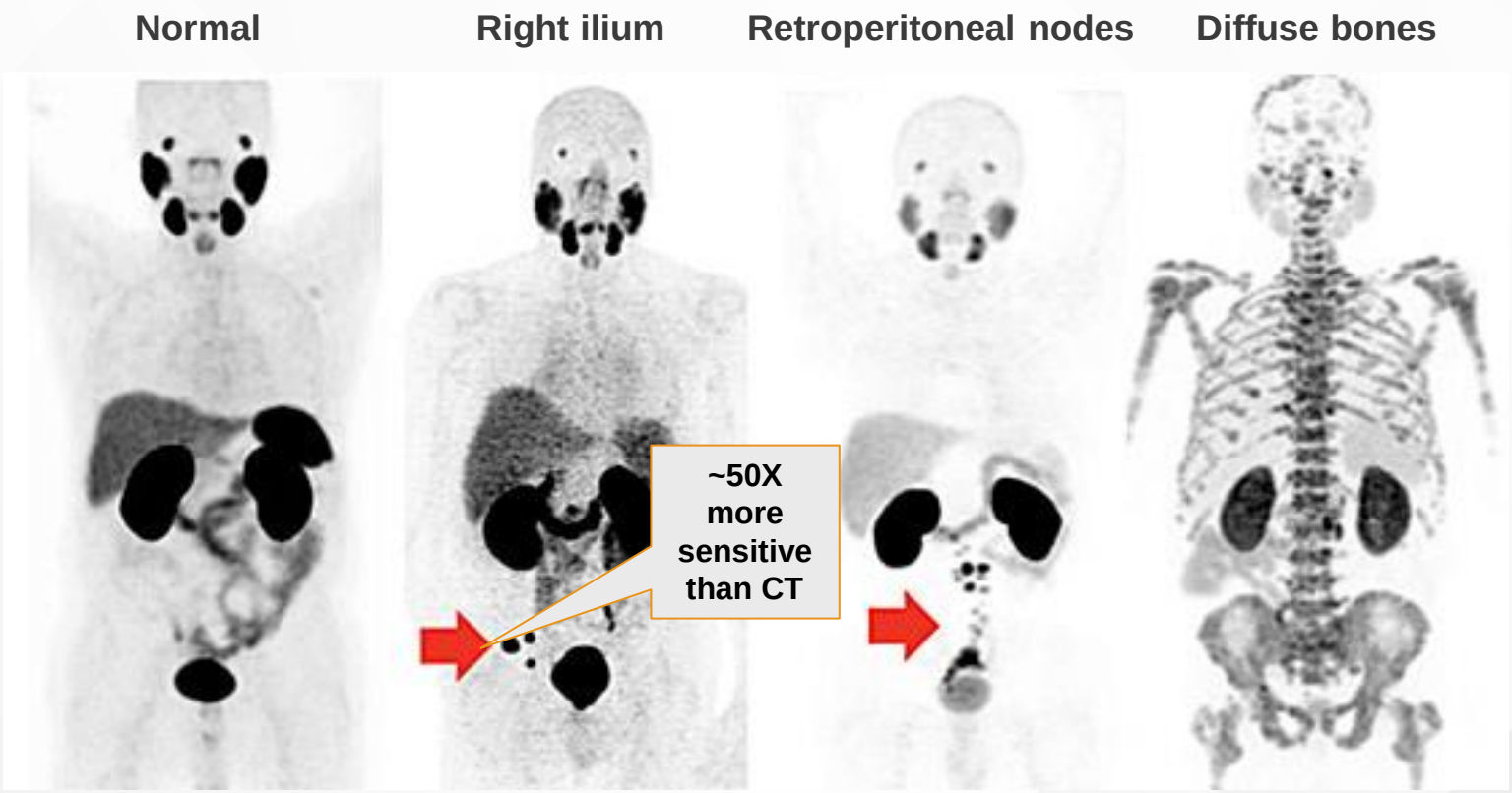
PSMA, prostate-specific membrane antigen.
Evans et al. *Br J Pharmacol*. 2016;173:3041-3079.

PSMA: Gene Expression High in the Prostate



PSMA, prostate-specific membrane antigen.
Genomics Institute of the Novartis Research Foundation.

PSMA PET (Molecular Imaging): A Disruptive Force Across the Spectrum of Prostate Cancer



CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Courtesy of Oliver Sartor, MD.

PSMA PET Imaging Is Redefining Staging for All Manner of Prostate Cancer Patients (both at diagnosis and in the recurrent setting)

FDA approvals for 18F-DCFPyL and 68Ga-PSMA-11 in 2021

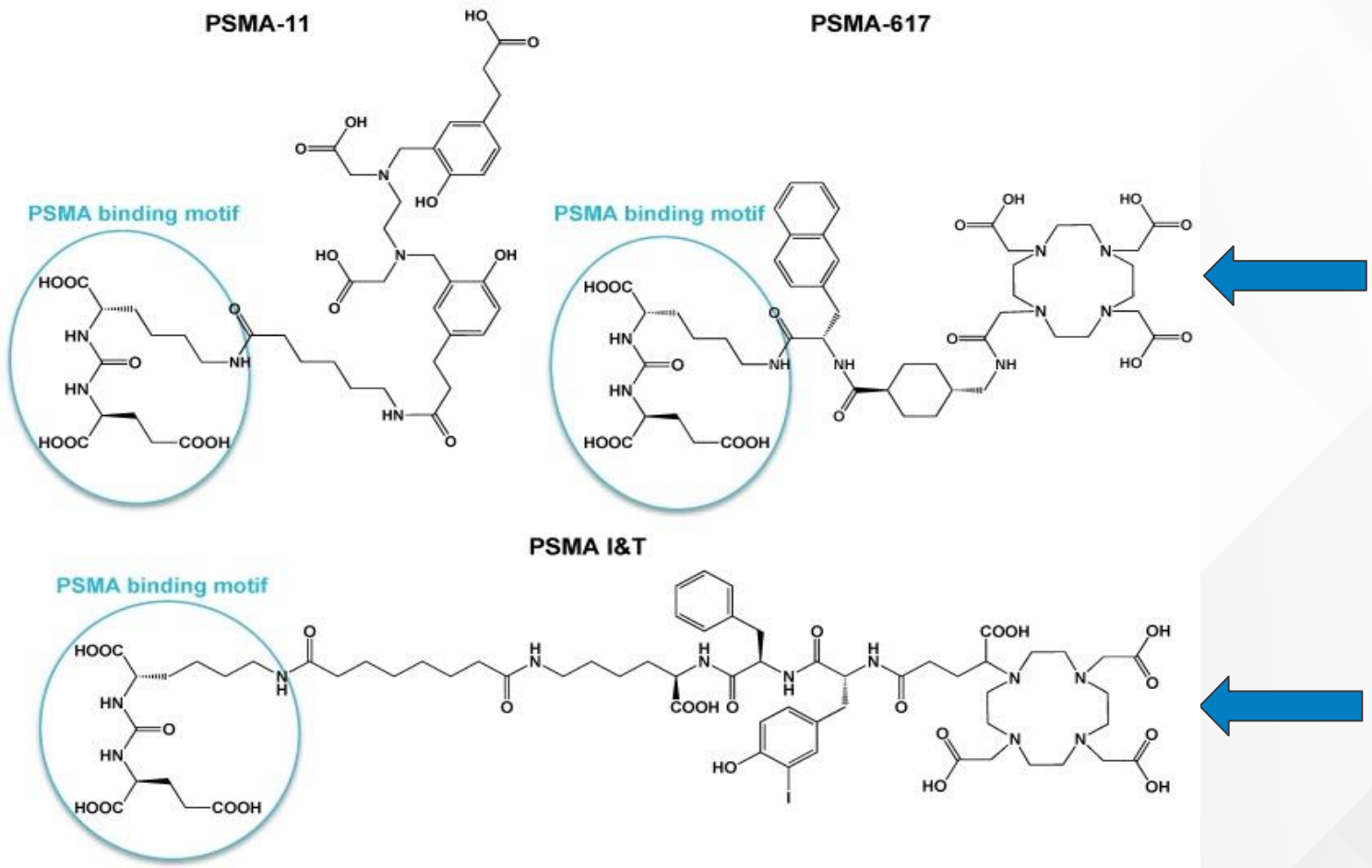
AXIS Medical Education

FDA, US Food & Drug Administration; Ga, Gallium; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

Molecularly Targeted Isotopic Therapy

Small molecules, peptides, antibodies, minibodies, aptamers, and radionuclides

PSMA Binding Ligands Can Be Linked to Therapeutic Agents via a Chelator



PSMA, prostate-specific membrane antigen; I&T, imaging and therapy.
Chatalic et al. *Theragnostics* 2016;6:849-861.

Large Number of Beta Emitters in Human Studies

Radionuclide	Half-life	Maximum Energy (MeV)	Mean Energy	Average Penetration
Strontium-89	50.5 days	1.46	0.58	2.4 mm
Samarium-153	1.9 days	0.81	0.22	0.5 mm
Phosphorus-32	14.3 days	1.71	0.69	3.0 mm
Ytrium-90	2.7 days	2.27	0.93	4.0 mm
Lutetium-177	6.7 days	0.49	0.14	0.3 mm
Iodine-131	8.0 days	0.61	0.19	0.8 mm
Rhenium-186	3.8 days	1.07	0.33	1.0 mm
Rhenium-188	0.7 days	2.12	0.64	3.8 mm
Holmium-166	1.1 days	1.84	0.67	3.3 mm
Tin-117m*	13.6 days	0.15	0.14	0.2 mm

* Conversion electron

PSMA Targeted Therapy: The Beginning

Radiation Dosimetry and First Therapy Results with a $^{124}I/^{131}I$-labeled Small Molecule (MIP-1095) Targeting PSMA for Prostate Cancer Therapy

Christian M Zechmann, Ali Afshar-Oromieh, Tom Armor, James B Stubbs, Walter Mier, Boris Hadaschik, John Joyal, Klaus Kopka, Jürgen Debus, John W Babich, Uwe Haberkorn

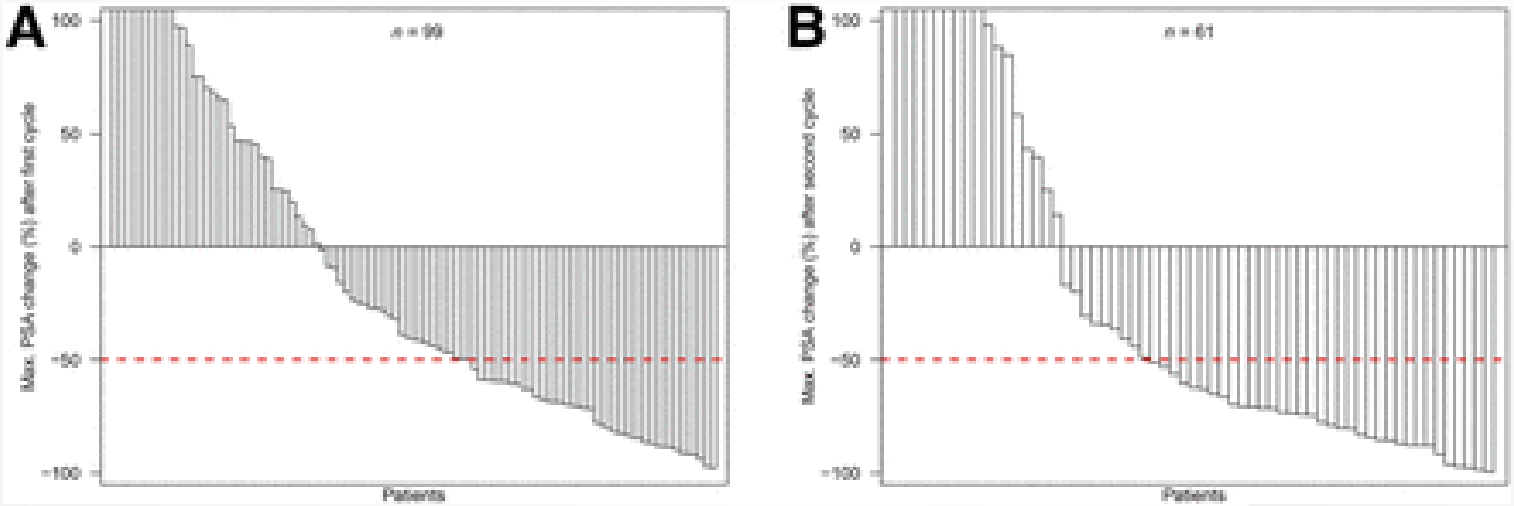
PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013

Harshad R. Kulkarni, Aviral Singh, Christiane Schuchardt, Karin Niepsch, Manal Sayeg, Yevgeniy Leshch, Hans-Juergen Wester and Richard P. Baum

PSMA, prostate-specific membrane antigen.
Zechmann et al. *Eur J Nucl Med Mol Imaging* 2014;41:1280-1292; Kulkarni et al. *J Nucl Med*. 2016;57(suppl 3):97S-104S.

German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients

Optimal dose and schedule not established

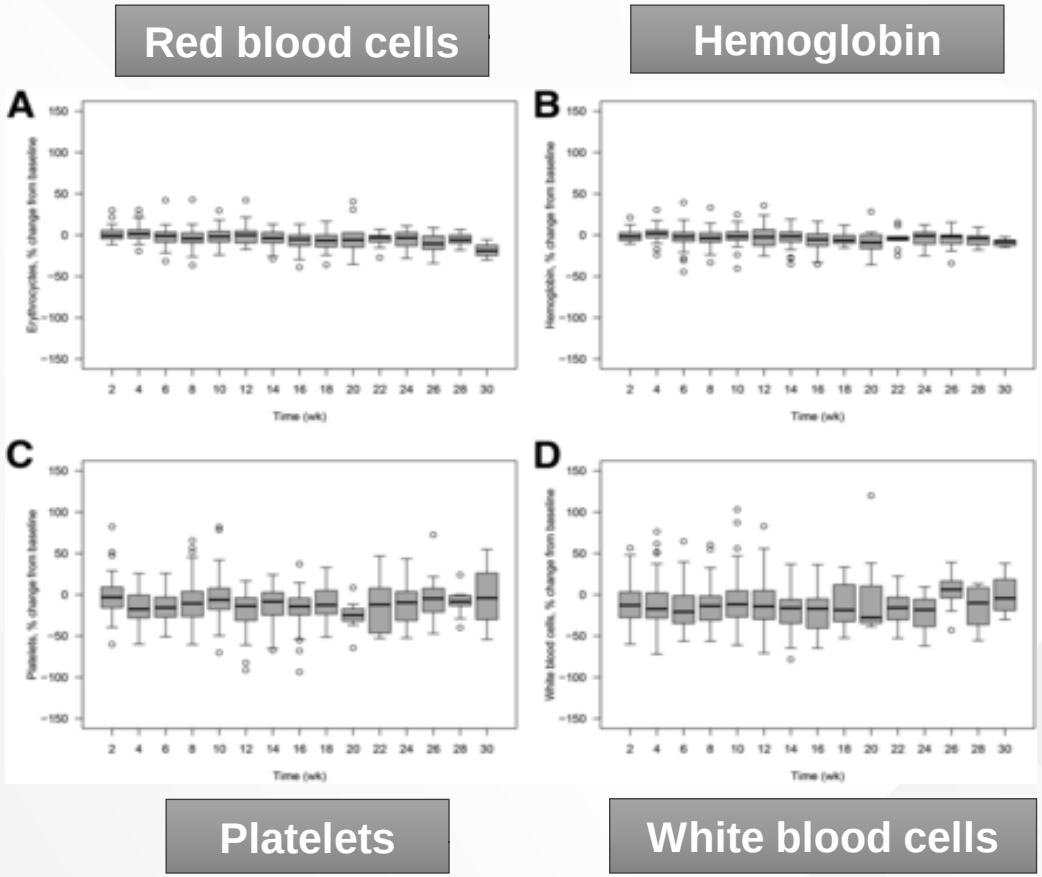


First Cycle **Second Cycle**

^{177}Lu-PSMA, lutetium-177–prostate-specific membrane antigen.

Rahbar et al. *J Nucl Med.* 2017;58:85-90.

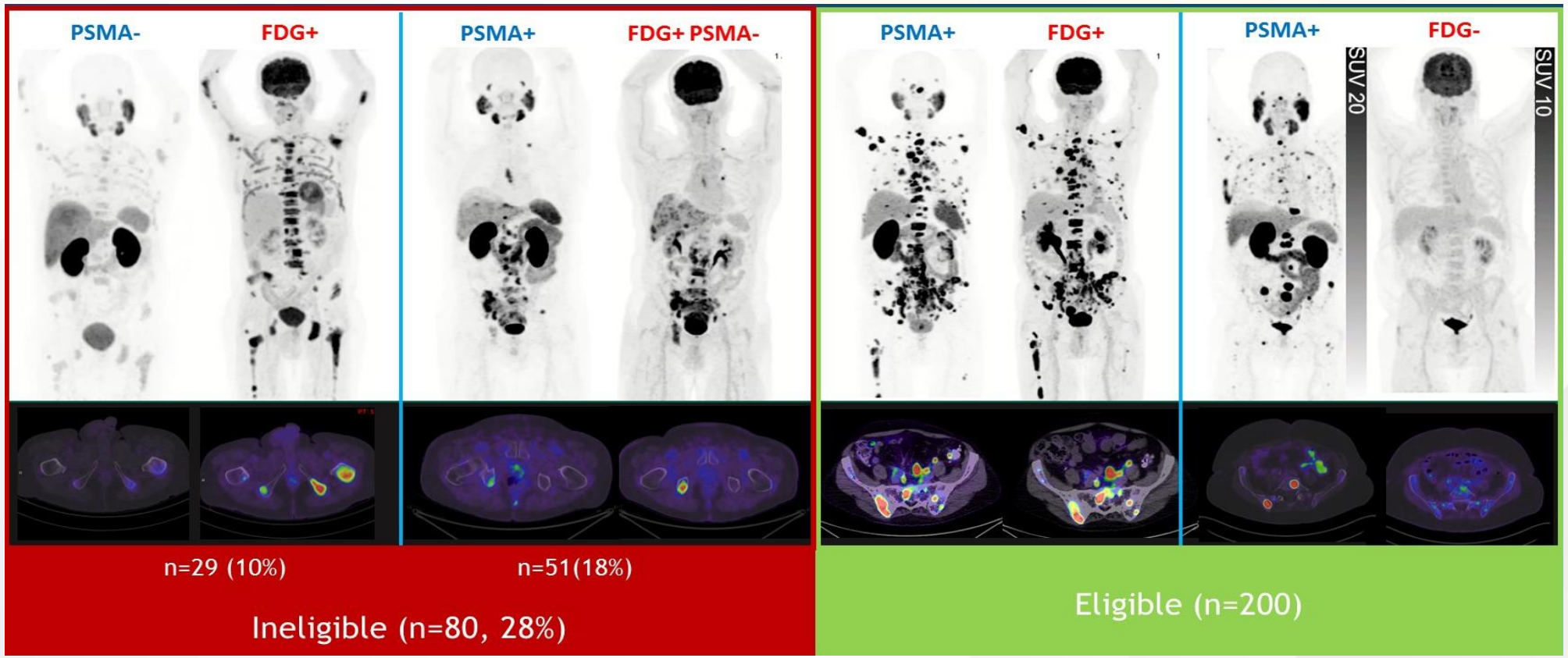
German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients



^{177}Lu-PSMA, lutetium-177–prostate-specific membrane antigen.

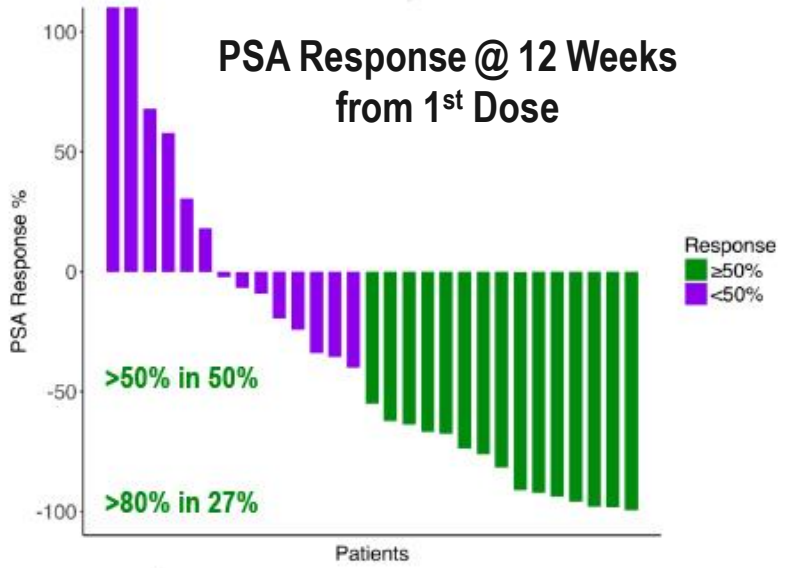
Rahbar et al. *J Nucl Med.* 2017;58:85-90.

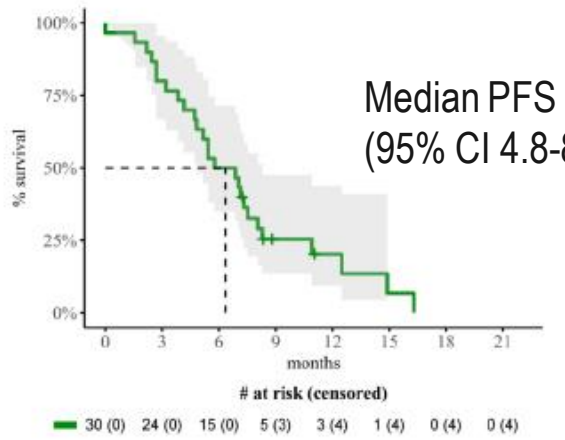
Patient Selection in Australian PSMA 617 Trials: PSMA and FDG PET/CT



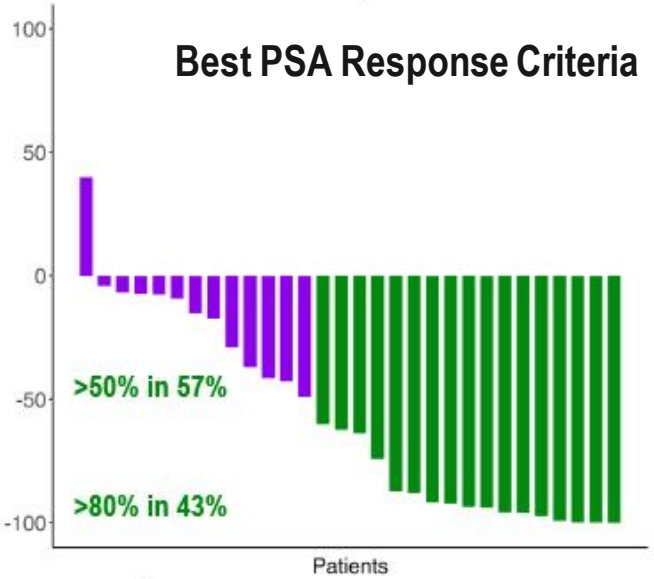
PSMA, prostate-specific membrane antigen; FDG PET/CT, fluorodeoxyglucose-positron emission tomography.
Hofman et al. *J Clin Oncol*. 2020;38(15):5500.

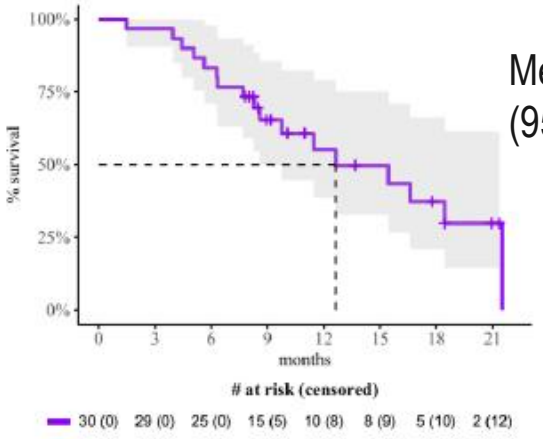
LuPSMA Trial: ^{177}Lu-PSMA-617 in a Single-arm, Single-center, Phase 2 Trial





Median PFS 6.3 months
(95% CI 4.8-8.3)





Median OS 12.7 months
(95% CI 9.9 - not reached)

AXIS Medical Education

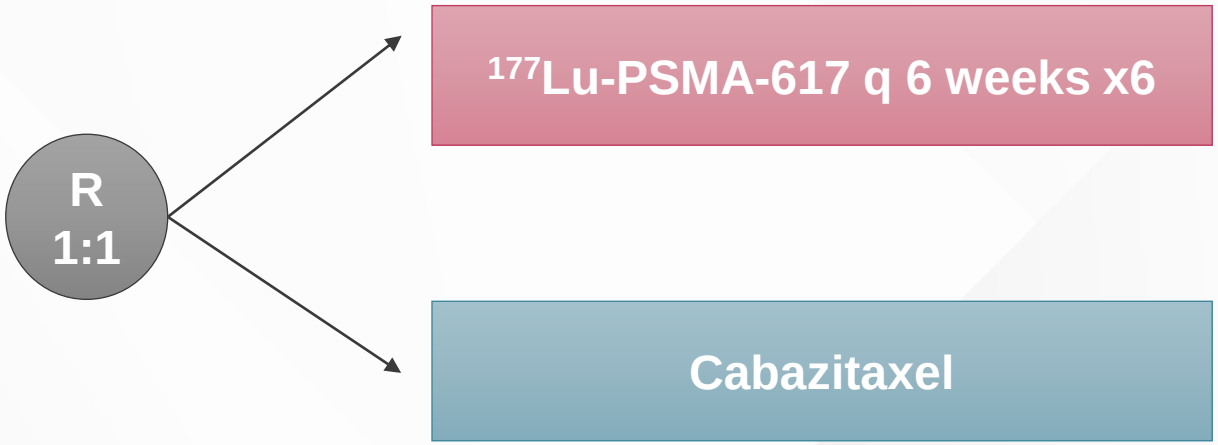
^{177}Lu-PSMA, lutetium-177–prostate-specific membrane antigen; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
Adapted from Hofman et al. *Lancet Oncol.* 2018;19:825-833.

TheraP Trial: Randomized Phase 2 Trial Comparing Cabazitaxel to ^{177}Lu-PSMA-617 (ANZUP 1603)

Key Eligibility Criteria

- Progressive mCRPC after docetaxel treatment
- ^{68}Ga-PSMA-11 PET/CT positive scan and no discordant sites by ^{18}F-FDG PET determined by central reader
- ECOG PS 0-2

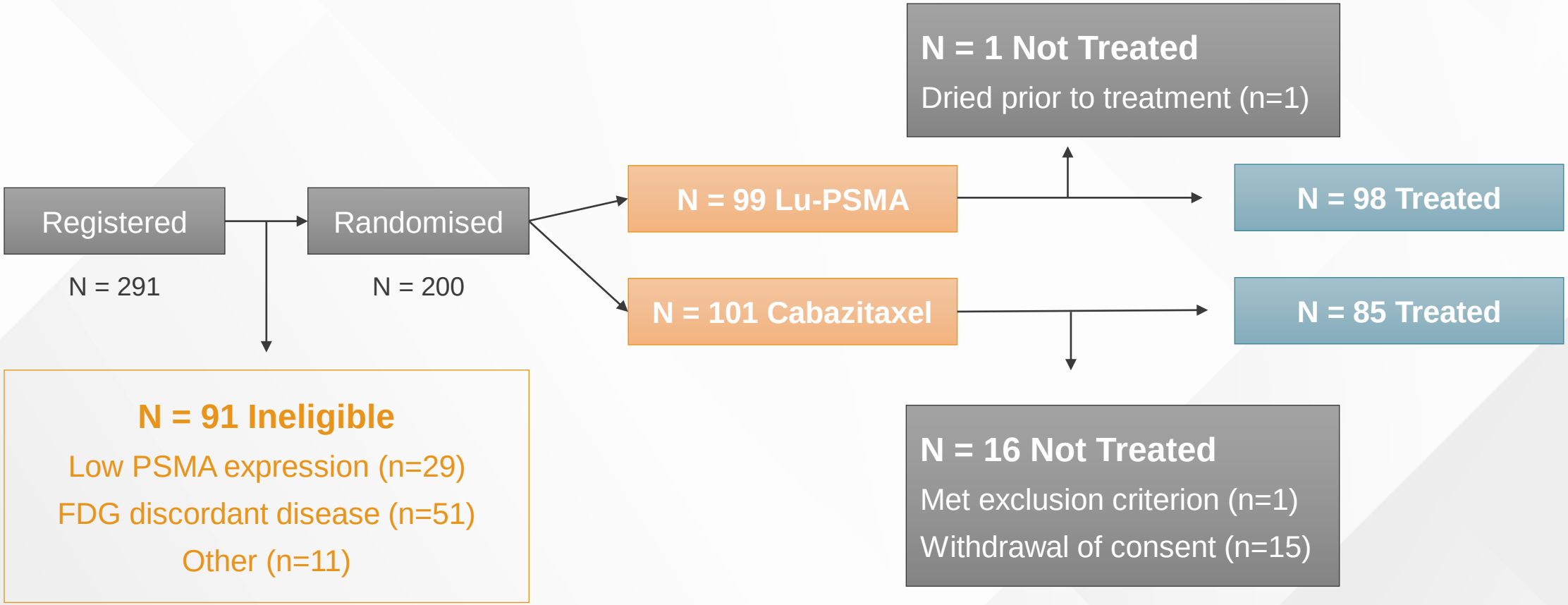
N = 200



Primary Endpoint: PSA response

^{68}Ga, gallium-68; ^{177}Lu, lutetium-177; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
Hofman et al. *BJU Int*. 2019;124:5-13.

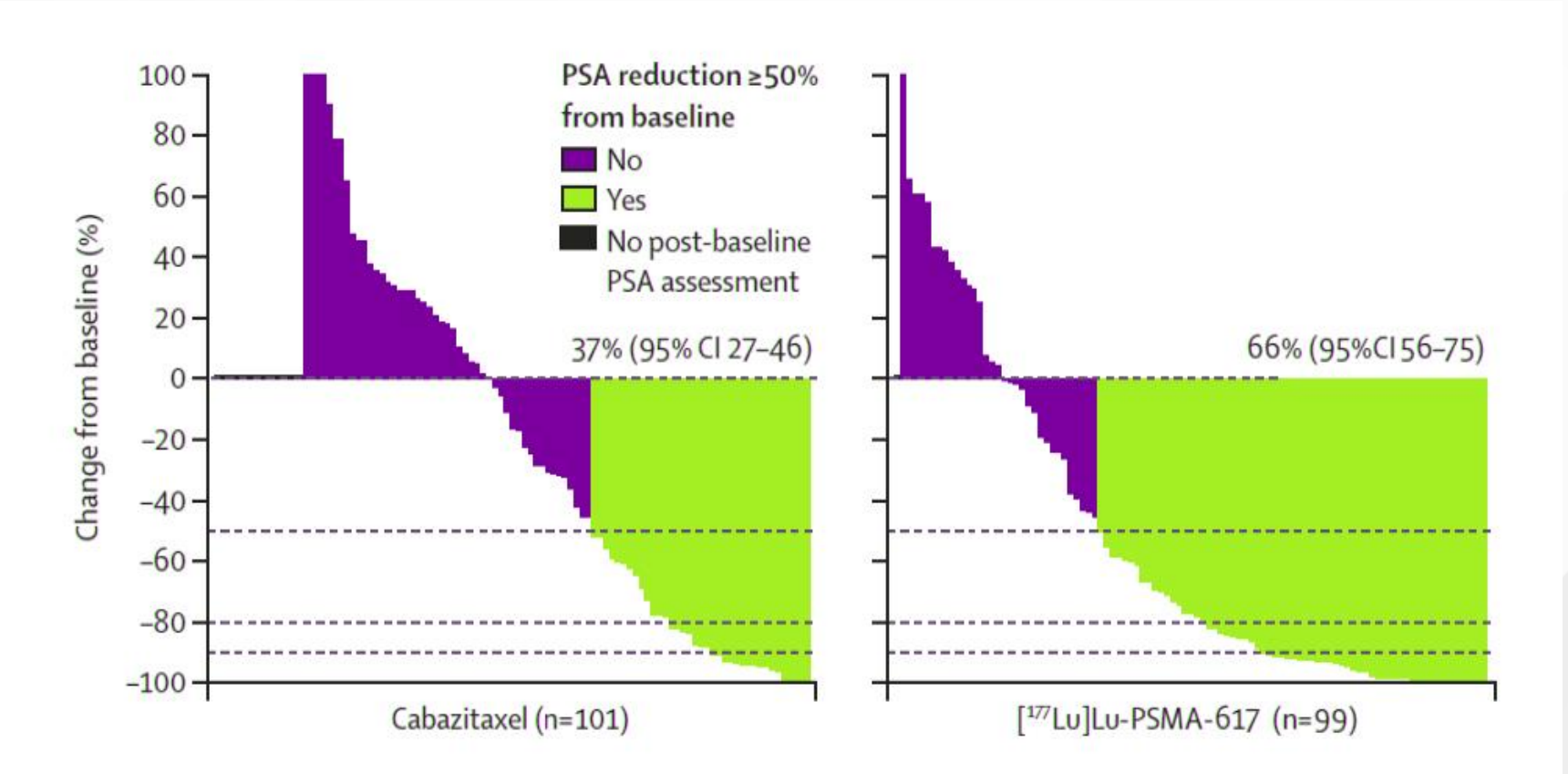
TheraP Trial: CONSORT Diagram for Key Details



Intention-to-treat analysis + sensitivity analysis for per-protocol analysis

Lu, lutetium; PSMA, prostate-specific membrane antigen; FDG, fluorodeoxyglucose.
Hofman et al. *J Clin Oncol*. 2020;38(15):5500.

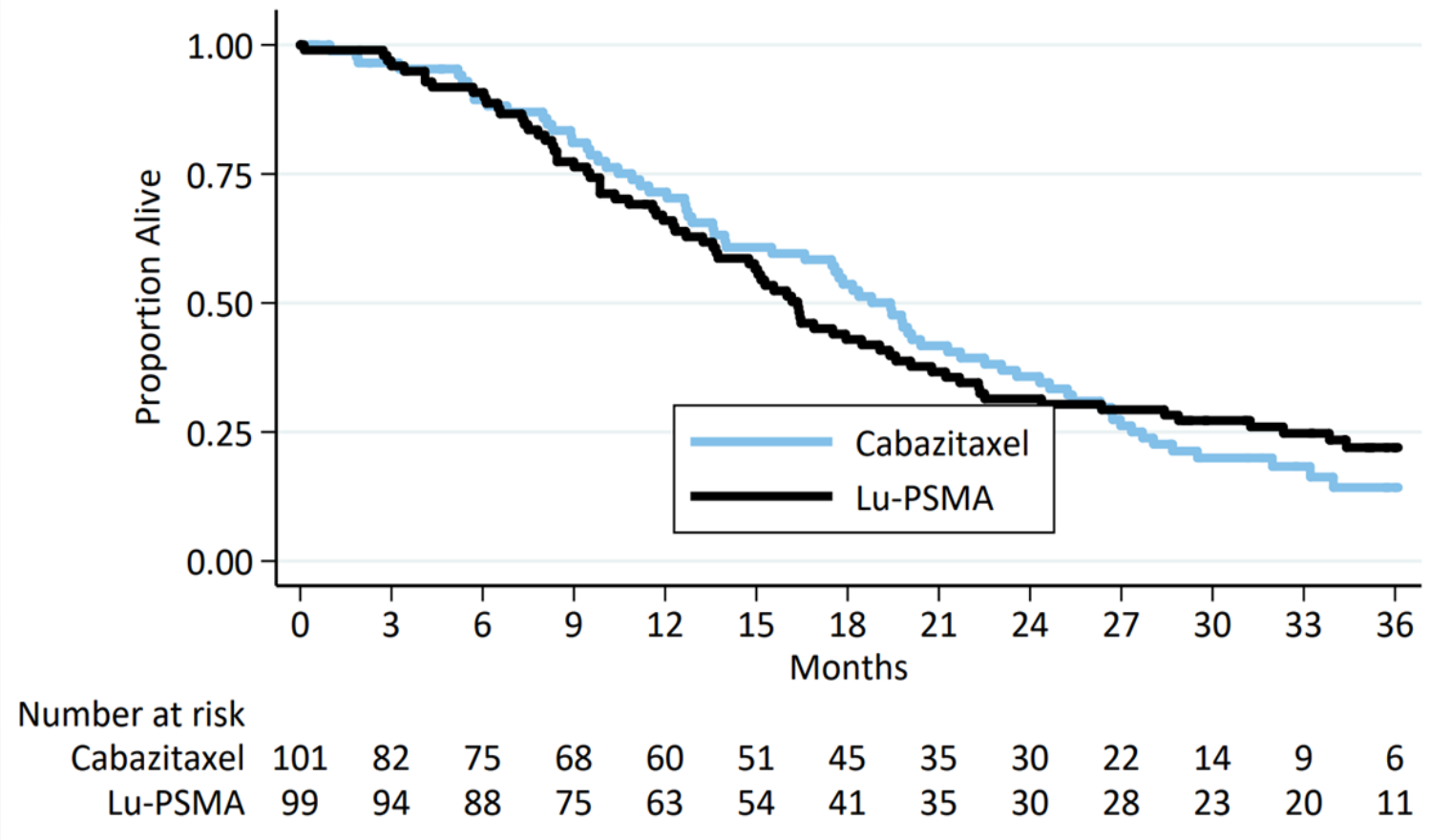
[^{177} Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial



^{177}Lu, lutetium-177; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
Adapted from Hofman et al. *Lancet* 2021;397:797-804.

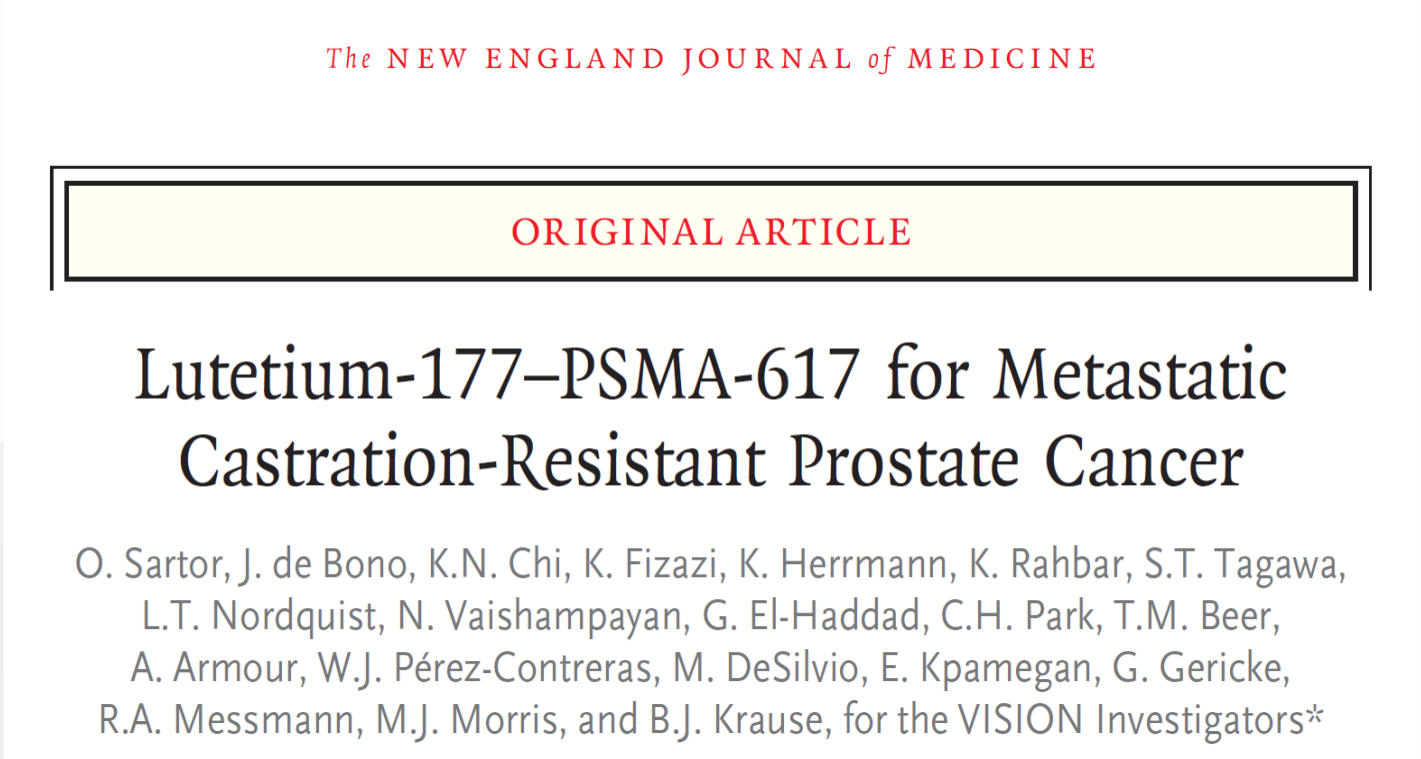
Survival in TheraP After 3 Years

- HR 0.97
- (95% CI, 0.70-1.4)
- *P* = .99
- Median not stated but approximately 17 months for ^{177}Lu-PSMA and approximately 20 months for cabazitaxel



^{177}Lu, lutetium-177; PSMA, prostate-specific membrane antigen.
Hofman et al. *J Clin Oncol*. 2022;40(16):5000.

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



Published
6/23/2021

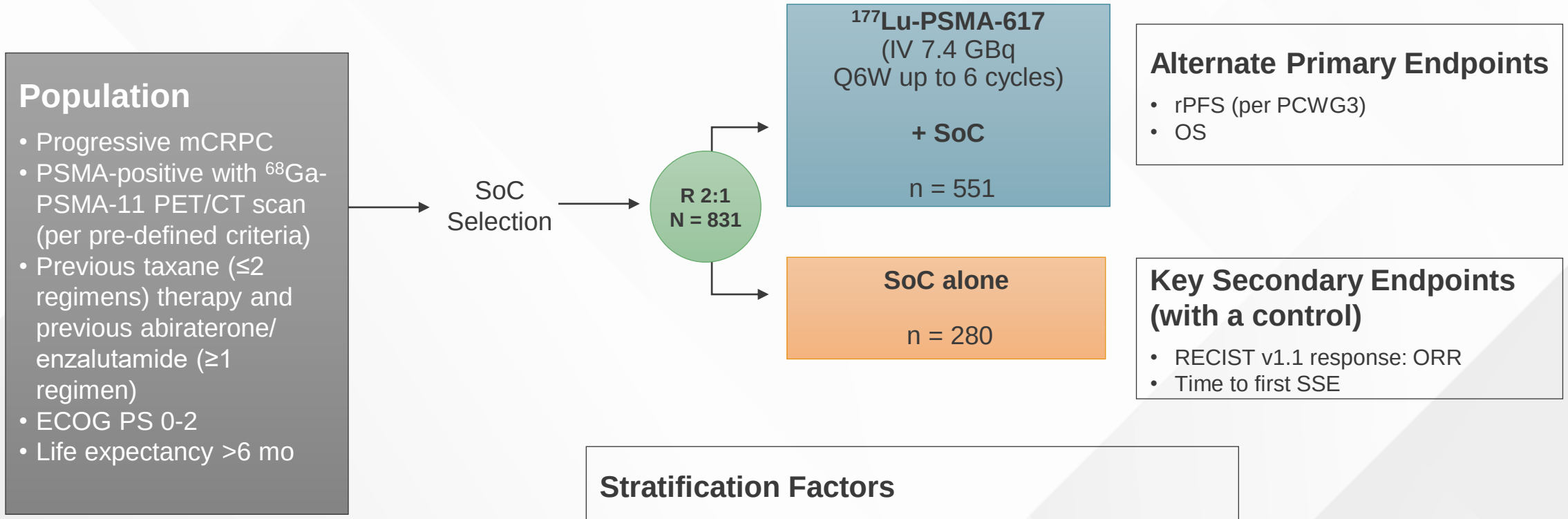
FDA approved
3/23/2022

Supply chain issues
5/5/2022

Resumed
6/30/22

FDA, U.S. Food and Drug Administration.
Sartor et al. *N Engl J Med*. 2021;385(12):1091-1103.

VISION: ^{177}Lu-PSMA-617 Phase 3 Trial Study Design



AXIS Medical Education

^{68}Ga, gallium-68; ^{177}Lu, lutetium-177; ARPI, androgen receptor pathway inhibition; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3. PET, positron emission tomography; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care; SSE, symptomatic skeletal event.

VISION Trial: Patient Selection with PSMA PET

Prespecified criteria for PSMA positivity

- PSMA-positive metastatic lesion
  - PSMA PET positivity defined as uptake ≥ liver
- No size criteria for PSMA-positive lesions
- No PSMA negative visceral or lytic bone lesions ≥1 cm
- No PSMA negative lymph node lesions ≥2.5 cm

AXIS Medical Education

^{68}Ga, gallium-68; ^{177}Lu, lutetium-177; CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

VISION Trial: Logistical Issues

- Shortly after accrual began, dropout problems immediately evident in control group among certain sites
  - Sites where nuclear medicine doctors were leading the trial
- Patients disappointed not to be receiving ^{177}Lu-PSMA
- Sites were closed, remaining sites further educated, the FDA consulted, and statistics reassessed

^{177}Lu-PSMA, lutetium-177–prostate-specific membrane antigen; FDA, US Food & Drug Administration.

VISION Trial: Baseline Patient Characteristics

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N = 581)		All Patients Who Underwent Randomization (N = 831)	
	^{177}Lu-PSMA-617 plus Standard Care (N = 385)	Standard Care Alone (N = 196)	^{177}Lu-PSMA-617 plus Standard Care (N = 551)	Standard Care Alone (N = 280)
Previous prostatectomy – no. (%)	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous androgen-receptor–pathway inhibitor – no. (%)				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy – no. (%)				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

AXIS Medical Education

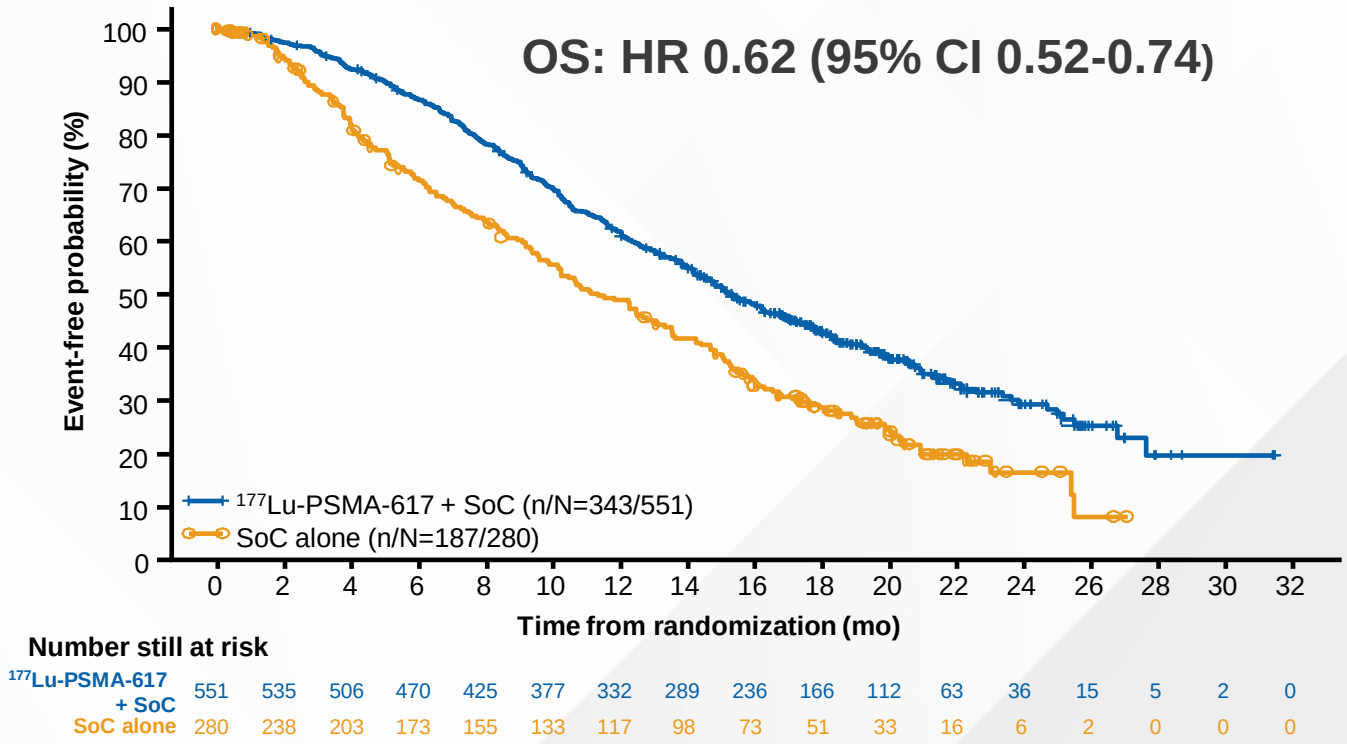
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617.

Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

VISION Trial: Primary Efficacy Outcomes Imaging-based OS

VISION met both primary endpoints of OS and rPFS

	^{177}Lu-PSMA-617 + SoC (n = 551)	SoC alone (n = 280)
Median OS, mo	15.3	11.3
HR (95% CI)	0.62 (0.52-0.74)	
***P*, one-sided**	<.001	



Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

AXIS Medical Education

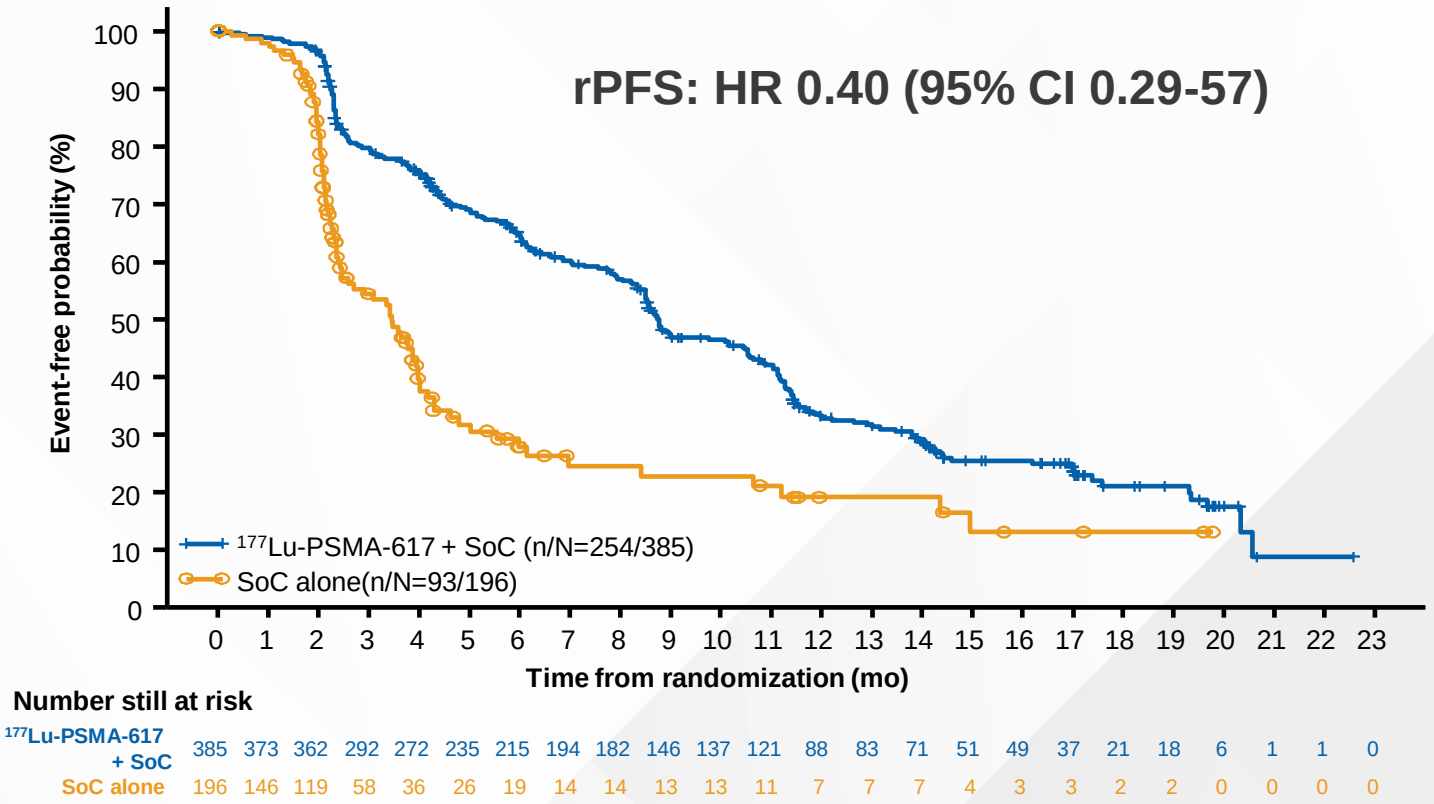
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.

Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

VISION Trial: Primary Efficacy Outcomes Imaging-based PFS

VISION met both primary endpoints of OS and rPFS

	^{177}Lu-PSMA-617 + SoC (n = 385)	SoC alone (n = 186)
Median rPFS, mo	8.7	3.4
HR (95% CI)	0.40 (0.29-0.57)	
***P*, one-sided**	<.001	



Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

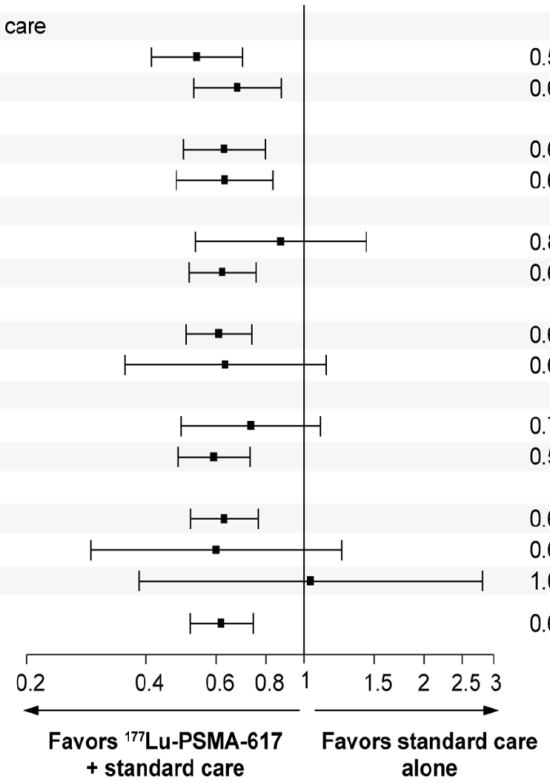
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.

Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

VISION Trial: Prespecified Subgroup Analyses of Imaging-based PFS and OS

B Overall survival (N=831)

Subgroup	^{177}Lu-PSMA-617 + standard care (N=551) n/N (%)	Standard care alone (N=280) n/N (%)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned standard care			
Yes	135/243 (55.6)	96/146 (65.8)	0.54 (0.41, 0.70)
No	208/308 (67.5)	91/134 (67.9)	0.68 (0.53, 0.87)
LDH			
≤260 IU/L	202/368 (54.9)	107/182 (58.8)	0.63 (0.50, 0.80)
>260 IU/L	140/182 (76.9)	80/97 (82.5)	0.63 (0.48, 0.84)
Liver metastases			
Yes	40/48 (83.3)	28/34 (82.4)	0.87 (0.53, 1.43)
No	303/503 (60.2)	159/246 (64.6)	0.62 (0.51, 0.76)
ECOG score			
0 or 1	305/510 (59.8)	170/258 (65.9)	0.61 (0.50, 0.74)
2	38/41 (92.7)	17/22 (77.3)	0.63 (0.35, 1.13)
Age			
<65 years	82/145 (56.6)	38/60 (63.3)	0.73 (0.49, 1.10)
≥65 years	261/406 (64.3)	149/220 (67.7)	0.59 (0.48, 0.73)
Race			
White	300/486 (61.7)	159/235 (67.7)	0.63 (0.52, 0.77)
African American or Black	20/34 (58.8)	12/21 (57.1)	0.60 (0.29, 1.24)
Asian	9/9 (100)	7/11 (63.6)	1.04 (0.38, 2.81)
All patients	343/551 (62.3)	187/280 (66.8)	0.62 (0.52, 0.74)

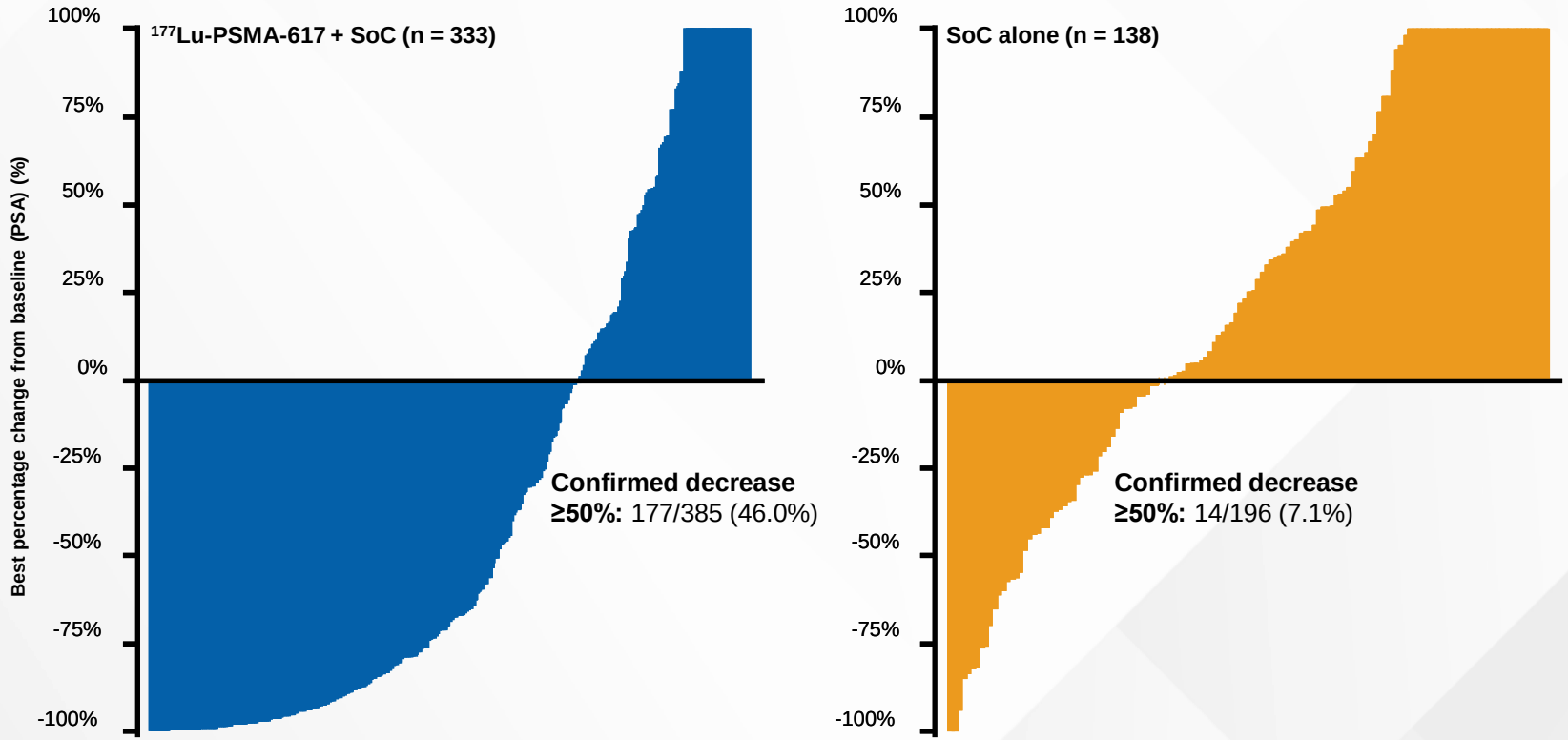


^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; OS, overall survival.

Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

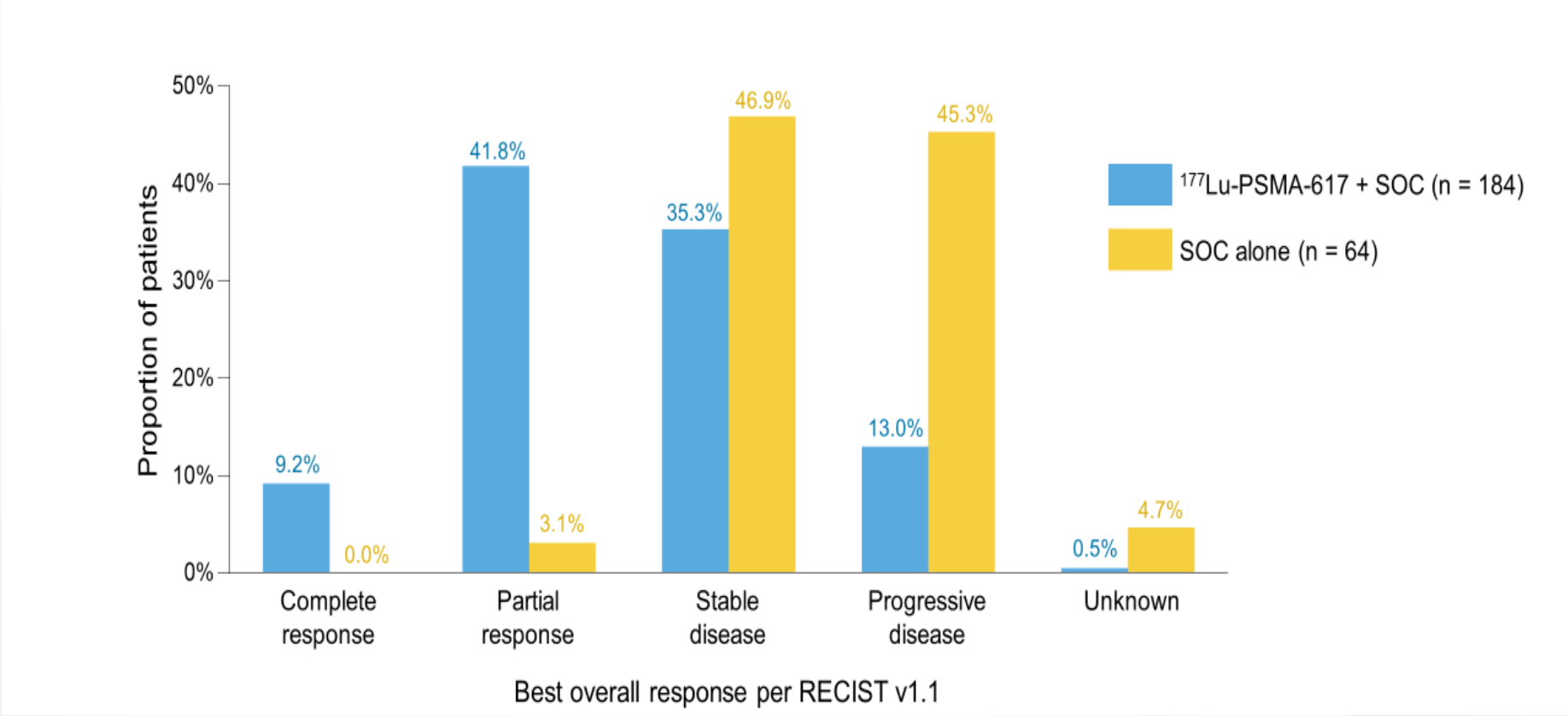
VISION Trial: Prostate-Specific Antigen Responses

PSA waterfall plot



177Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; PSA, prostate-specific antigen; SoC, standard of care.
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

Secondary Endpoint: RECIST v1.1 Responses Favored the ^{177}Lu-PSMA-617 Arm in Patients with Measurable Disease

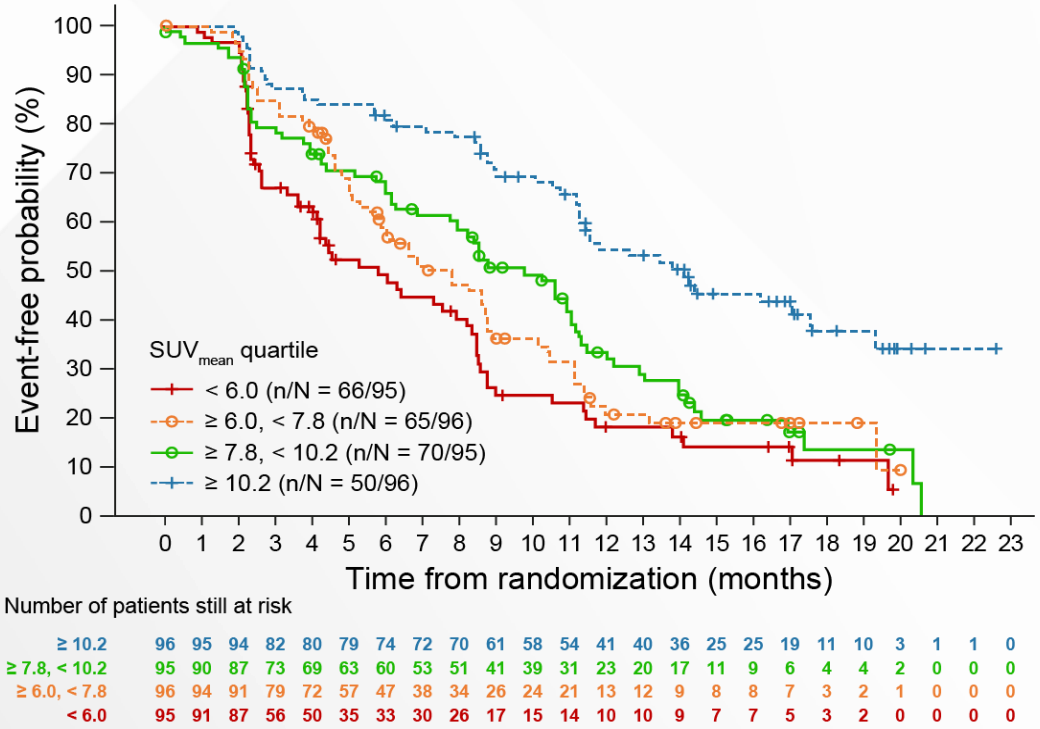


^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; SOC, standard of care; RECIST, Response Evaluation Criteria in Solid Tumors.

Morris et al. *J Clin Oncol*. 2021;39(18):LBA4.

rPFS by Whole-body SUVmean Quartiles (PFS-FAS)

Higher whole-body SUV_{mean} was associated with prolonged rPFS



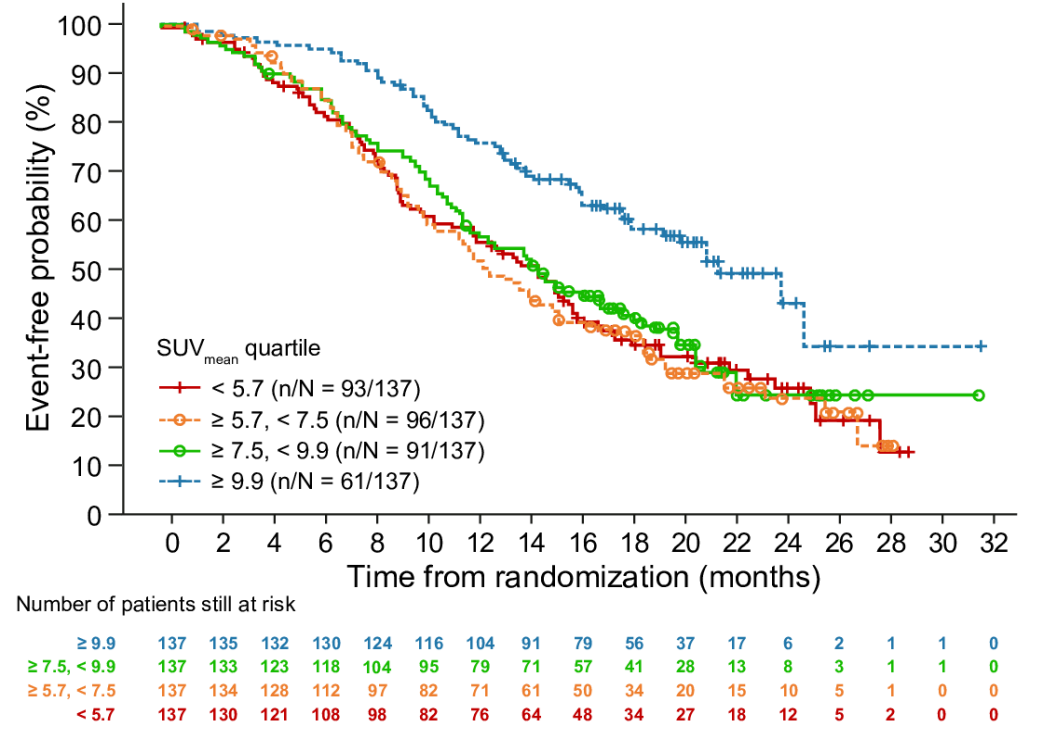
SUV_{mean} quartile	Median rPFS (mo)
≥10.2 (highest)	14.1
≥7.8, <10.2	9.8
≥6.0, <7.8	7.8
<6.0 (lowest)	5.8

SUV_{mean}	rPFS
	HR [95% CI], *P*
Univariate analysis	**0.88** [0.84-0.91], <.001
Multivariate analysis	**0.86** [0.82-0.90], <.001

PFS-FAS, progression-free survival-full analysis set; rPFS, radiographic progression-free survival; SUV, standardized uptake value.
Kuo et al. *J Clin Oncol*. 2022;40:5002.

OS by Whole-body SUVmean Quartiles (FAS)

Higher whole-body SUV_{mean} was associated with improved OS



SUV_{mean} quartile	Median OS (mo)
≥9.9 (highest)	21.4
≥7.5, <9.9	14.6
≥5.7, <7.5	12.6
<5.7 (lowest)	14.5

SUV_{mean}	OS
	HR [95% CI], *P*
Univariate analysis	**0.92** [0.89-0.95], <.001
Multivariate analysis	**0.88** [0.84-0.91], <.001

FAS, full-analysis set; OS, overall survival; SUV, standardized uptake value.
Kuo et al. *J Clin Oncol*. 2022;40:5002.

VISION Trial: Adverse Events

TEAEs Occurring in ≥5% of Patients, n (%)	Safety Set (N = 734)			
	All Grades		Grade 3-5	
	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC alone (n = 205)	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC alone (n = 205)
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anaemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopaenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Lymphopaenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopaenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)

AXIS Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; SoC, standard of care; TEAEs, treatment-emergent adverse effects.

Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

What We Know From VISION

- ^{177}Lu-PSMA-617 is effective and well tolerated in heavily pretreated mCRPC
- The trial would have been positive without patient selection using PSMA PET
  - OS HR 0.62 (95% CI 0.52-0.74)
- Nuclear medicine sites not well partnered with oncology had difficulty managing the control group in this randomized trial
  - Multidisciplinary care is **required!!!**
- This therapy will be adopted rapidly after regulatory approvals and will be used earlier in the treatment paradigm
- March 2022: FDA approved lutetium-177 vipivotide tetraxetan for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy

AXIS Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; FDA, US Food & Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SoC, standard of care.

What We Do Not Know From VISION

- What is the optimal patient selection criteria when using PSMA PET? FDG PET?
- What is the optimal dose and schedule for this therapy?
- What is the relationship between PSA progression and/or response and survival benefit?
  - Extremely good!!!
- Can re-treatment at progression make a positive impact?
- Does treatment with “SoC” + ^{177}Lu-PSMA-617 add to that of the isotope alone?
- What about trials in the pre-chemotherapy space?
- What type of therapies might be synergistically combined with this therapy?

AXIS Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; FDG, fluorodeoxyglucose; PET, positron emission tomography; PSA, prostate-specific antigen; SoC, standard of care.

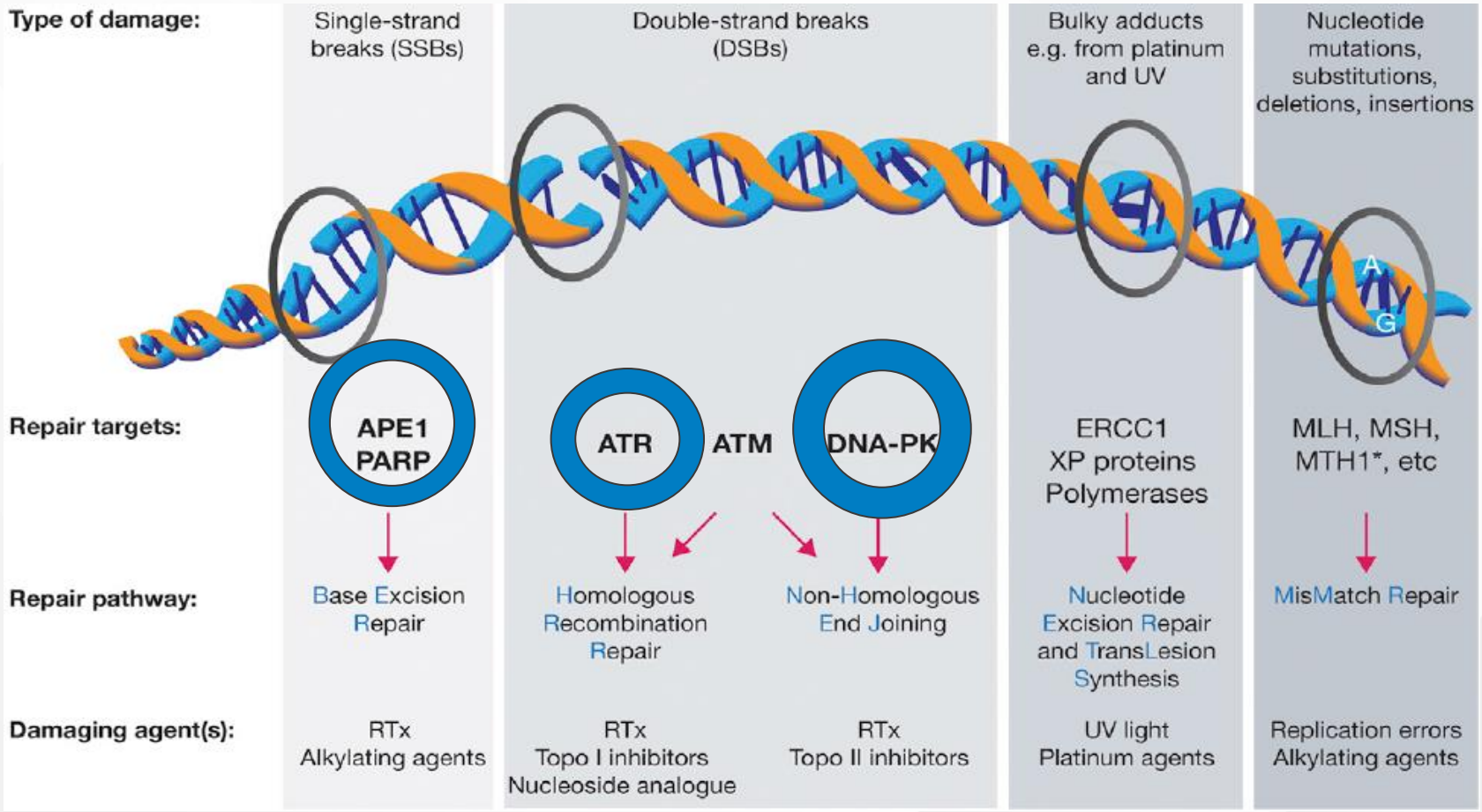
New Important Trials in Metastatic Prostate Cancers

Trial Name	Phase	Prostate Cancer Type	Details
PSMAfore	3	mCRPC	Open-label, Multi-Center, Randomized Study Comparing ^{177}Lu-PSMA-617 vs. a Change of Androgen Receptor-directed Therapy in the Treatment of Taxane Naïve Men With Progressive mCRPC
SPLASH	3	mCRPC	Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment
ECLIPSE	3	mCRPC	Open-Label, Multi-Center, Randomized Trial Comparing the Safety and Efficacy of ^{177}Lu-PSMA-I&T Versus Hormone Therapy in Patients With mCRPC
PSMAddition	3	mHSPC	International Prospective Open-label, Randomized, Study Comparing ^{177}Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in mHSPC

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; SoC, standard of care.

Synergistic Opportunities for Radiopharmaceuticals

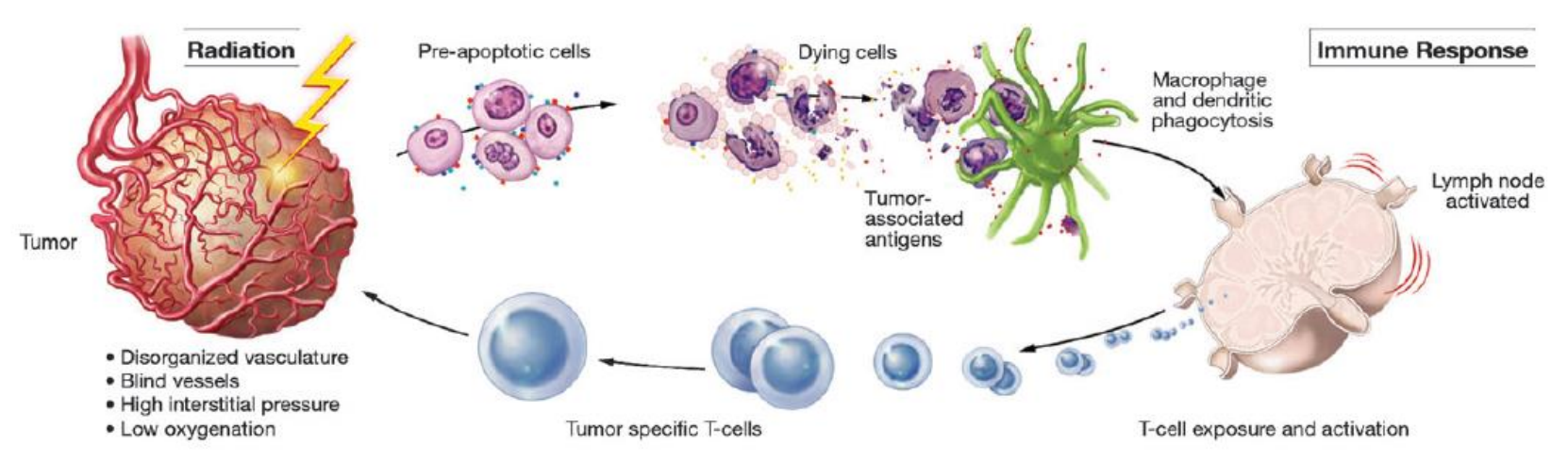
Targeting DNA Damage Repair Pathways in Combination With Radionuclides



APE1, AP endonuclease 1; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and Rad3-related; DNA-PK, DNA-dependent protein kinase; PARP, poly(ADP-ribose) polymerase; RTx, radiotherapy; Topo, topoisomerase; UV, ultraviolet.

O'Connor. *Mol Cell* 2015;60:547-560.

Antigen Release From Radiated Tumor: Synergy With Immunotherapies?



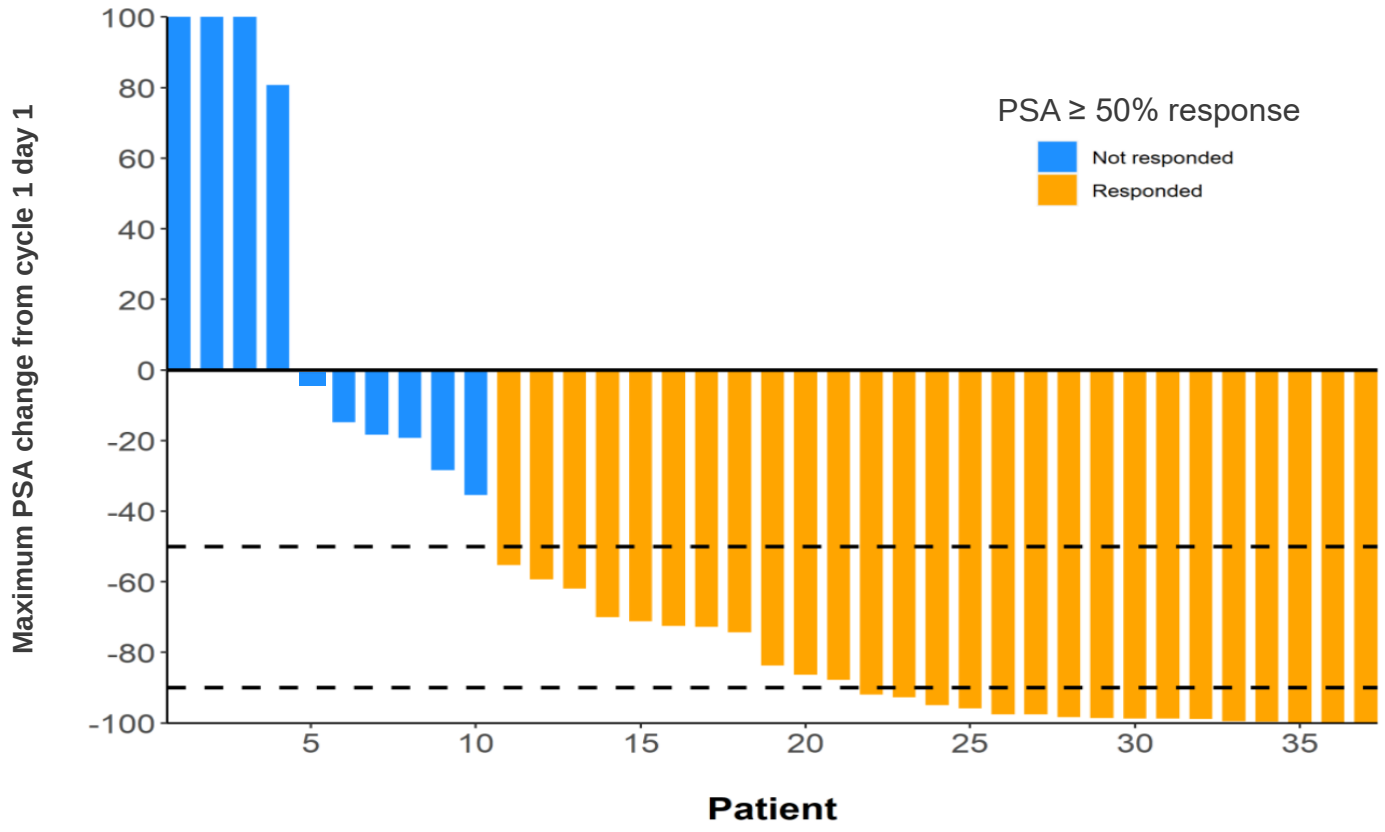
Systemic/local immune enhancement

- Vaccine
- Checkpoint Inhibitors
  - Anti-CTLA-4
  - Anti-PD-L1
  - Anti-PD-1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-GITR
  - Anti-CD27
  - Anti-CD40
- Exogenous Cytokines
  - IL-2
  - IL-7
  - IL-12
  - IL-15
  - IL-21
  - GM-CSF

CTLA, cytotoxic T-lymphocyte–associated antigen; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

Kamrava et al. *Mol BioSyst* 2009;5:1249-1372.

Waterfall Plot for PSA Declines on PRINCE Trial: ^{177}Lu-PSMA-617 + Pembrolizumab



This may be selection bias

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; PSA, prostate-specific antigen.
Sandhu et al. *Ann Oncol*. 2021;32:S626-S677.

What About PSMA Radiopharmaceutical Studies With Ligands Other Than PSMA-617?

- Antibodies
  - J591 anti-PSMA antibody with ^{177}Lu and ^{225}Ac
  - PSMA-directed antibody (PSMA TTC): phase 1 with ^{227}Th
- Small molecules
  - PSMA I&T: two phase 3 trials with ^{177}Lu
  - PSMA I&T with ^{225}Ac
  - PSMA-R2: phase 1 trial with ^{177}Lu
  - MIP-1095: phase 2 trial with ^{131}I
  - SAR-PSMA entering phase 1 trial with ^{67}Cu
  - ITM-22 with ^{225}Ac in phase 1 trial
  - NG001 with ^{212}Pb about to enter the clinic
  - And more……

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; ^{212}Pb, lead-212; ^{225}Ac, actinium-225; I&T, imaging and therapy; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Alphas

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Radium-223 Only Goes to Bone!

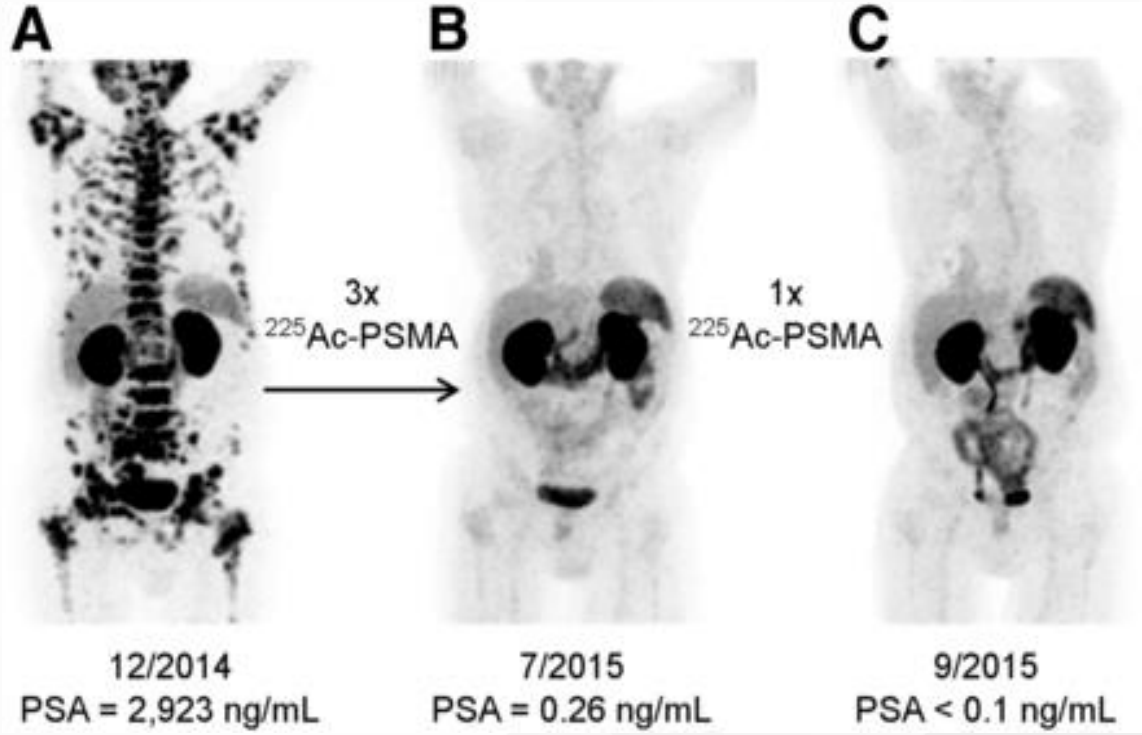
- This agent does an excellent job in treating bone but tumors in other locations cannot be neglected

Alphas

Radionuclide	Chelate	Half life	Total alpha	"Long lived" Intermediate	Final
Terbium-149	DOTA	4.1 hours	1 alpha		Nd-145
Astatine-211	Various	7.2 hours	1 alpha		Pb-207
Bismuth-212	C-DEPA/ DTPA/DOTA	61 minutes	1 alpha 1 beta		Pb-208
Lead-212	TCMC and more	10.6 hours	1 alpha 2 beta		Pb-208
Bismuth-213	C-DEPA/ DTPA/DOTA	46 minutes	1 alpha 2 beta		Bi-209
Radium-224	None	3.6 days	4 alpha	Lead-212	Pb-208
Actinium-225	DOTA and more	10.0 days	4 alpha 2 beta	Bismuth-213	Bi-209
Radium-223	None	11.4 days	4 alpha 2 beta		Pb-207
Thorium-227	DOTA	18.7 days	5 alpha	Radium-223	Pb-207

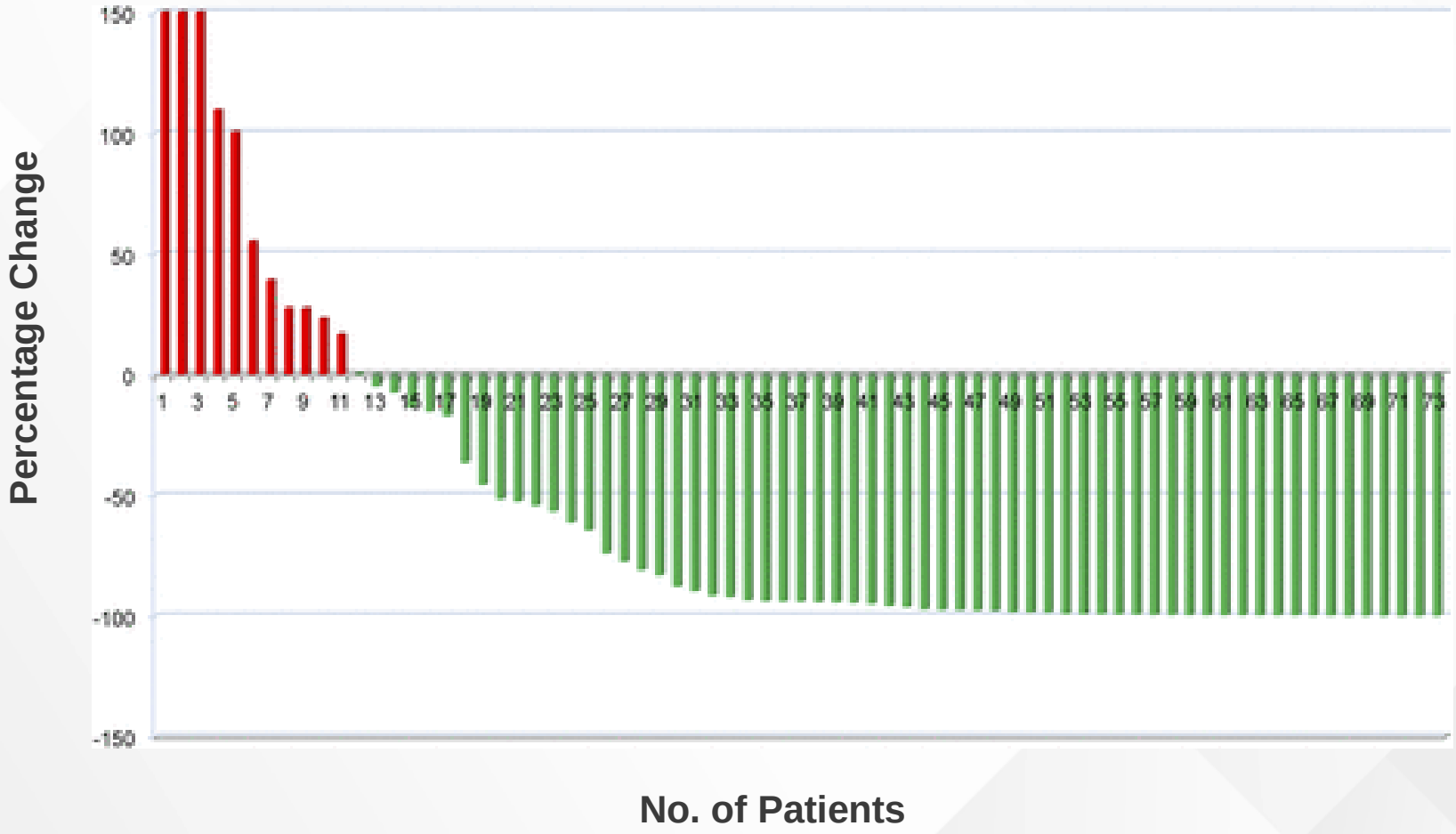
Radio-Conjugates: PSMA-Targeted Alpha Emitters (Actinium-225) as Ninth-Line Treatment

Patient A
Leuprorelin
Zoledronate
Docetaxel (50 cycles)
Carmustine/epirubicin in hyperthermia
Abiraterone
Enzalutamide
^{223}Ra (6 cycles)
Abiraterone reexposition
Estramustine



^{225}Ac-PSMA, actinium-225–prostate-specific membrane antigen; ^{223}Ra, radium-223; PSA, prostate-specific antigen.
Kratochwil et al. *J Nucl Med*. 2016;57:1-4.

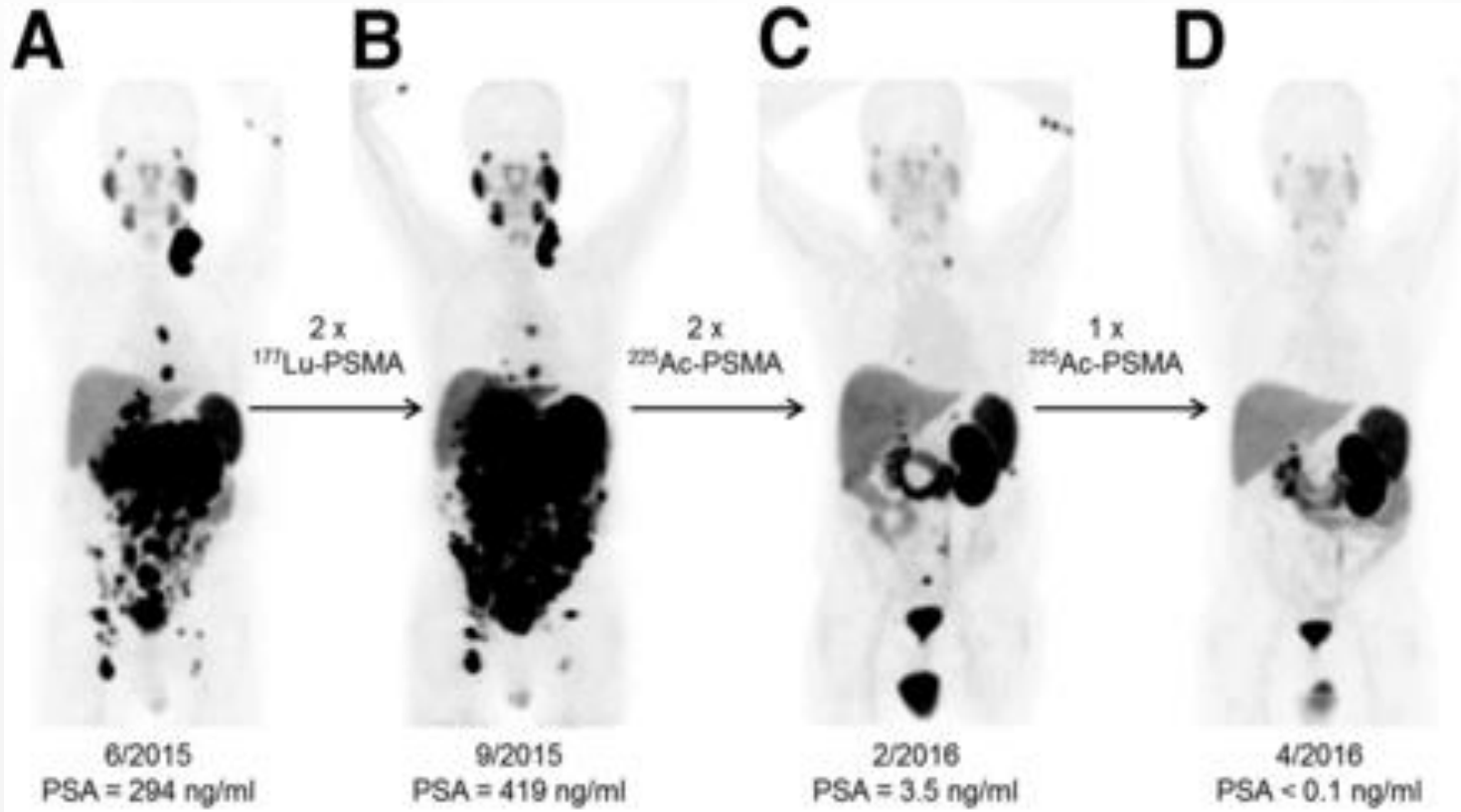
Percentage Change in PSA After ^{225}Ac-PSMA-617



^{225}Ac-PSMA 617, actinium-225–prostate-specific membrane antigen; PSA, prostate-specific antigen.

Sathekge et al. *J Nucl Med*. 2020;61:62-69.

Alpha Post-Beta Failure



^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; ^{225}Ac-PSMA, actinium-225–prostate-specific membrane antigen; PSA, prostate-specific antigen.
Kratochwil et al. *J Nucl Med*. 2016;57:1-4.

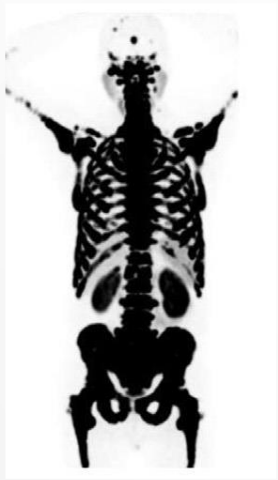
Current “Combination” Explorations

- Isotopes: Alphas and Betas in combination
- Isotopes and various hormonal therapies
  - Novartis “mHSPC” phase 3 trial
- Isotopes and PARPi and other inhibitors of DNA repair
- Isotopes and high-dose testosterone
- Isotopes and 5-FU infusion low dose (radiosensitizer)
- Isotopes and immunotherapy (anti-PD-1, etc)

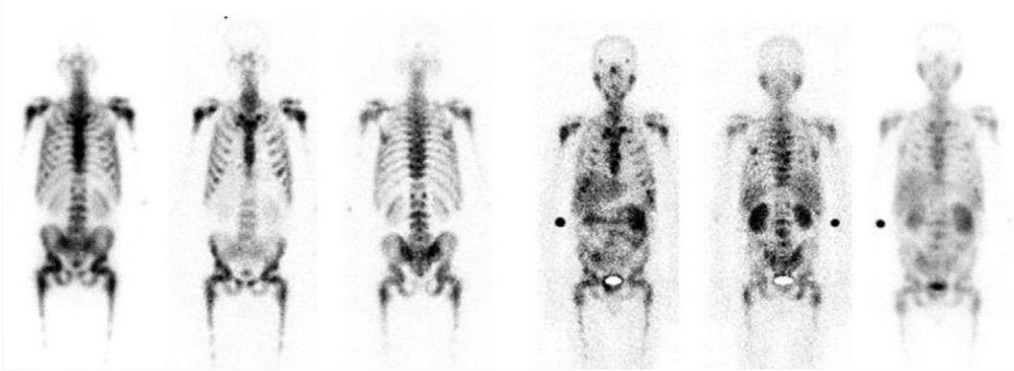
5-FU, 5-fluorouracil; mHSPC, metastatic hormone-sensitive prostate cancer; PARPi, pol (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1.

Alpha/Beta Combo

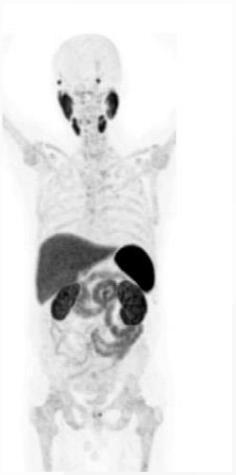
PSMA-PET



Planar-Emission Scans



PSMA-PET



Lab test:
[prior PSMA-Tx]

PSA 722.5 / AP 639
LDH 425 / PLT 55 / Hb 6.8
Leucoerythroblastic cell-count:
10% Progenitor cells (1% meta myelocytes, 7% myelocytes, 2% blasts)

1. Cycle
[1.5 GBq ^{177}Lu-PSMA+ 8 MBq ^{225}Ac-PSMA]

2. Cycle
[2 GBq ^{177}Lu-PSMA+ 6 MBq ^{225}Ac-PSMA]

Lab test:
[after PSMA-Tx]

PSA 0.4 / AP 144
LDH 232 / PLT 146 / Hb 9.7
Leucoerythroblastic cell-count:
0% Progenitor cells

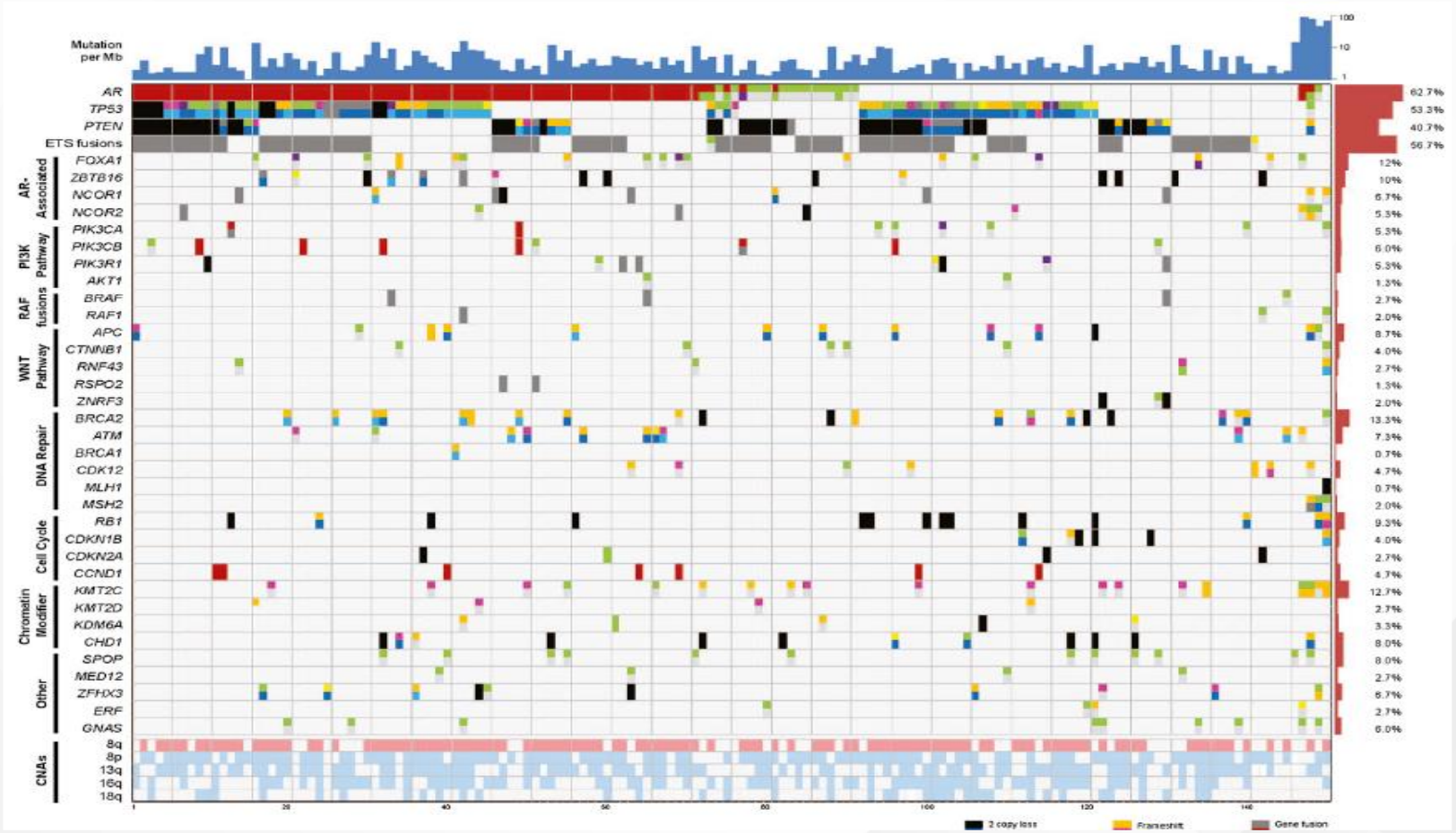
Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; ^{225}Ac-PSMA, actinium-225–prostate-specific membrane antigen; AP, alkaline phosphatase; Hb, hemoglobin; LDH, lactate dehydrogenase; PET, positron emission tomography; PLT, platelets; PSA, prostate-specific antigen; Tx, treatment.
Kratochwil et al. *Semin Nucl Med*. 2020;50:133-140.

Why Isotopes?

- Tremendous acceleration of drug development when you can see your target and the ratio of tumor uptake to non-tumor tissues
  - Imaging key!
- Ability to treat the “umbra and penumbra” around the area of “drug” deposition
  - The ability to overcome heterogeneity is key to success

Challenges: Metastatic Prostate Cancer Is a Heterogeneous Group of Diseases, but Radiation Can Kill Them All!



Robinson et al. *Cell* 2015;161:1215.

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Medical Education

Improved Outcomes in mCRPC with PSMA-Directed Diagnostics and Therapies