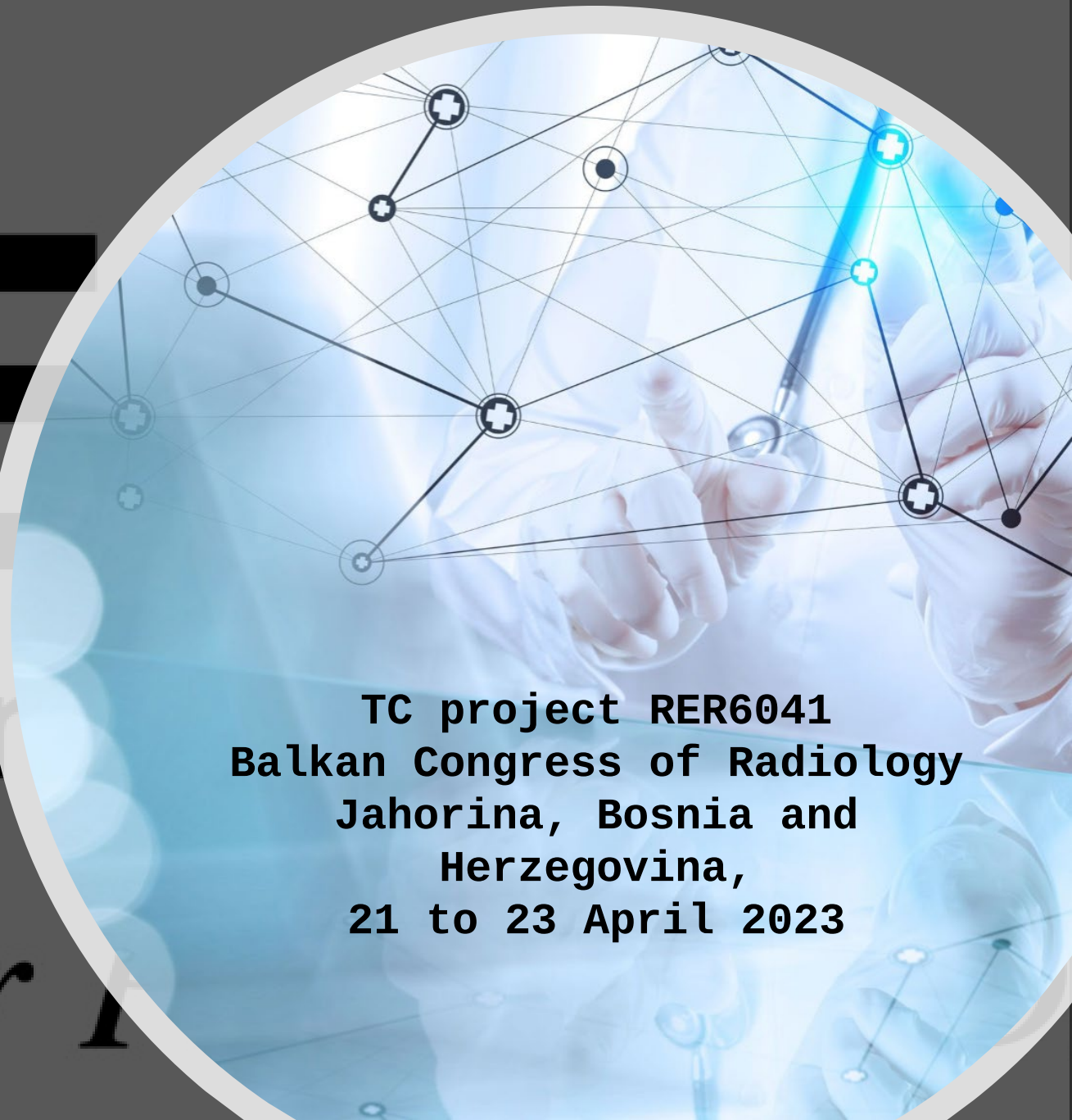
New Trends in Medical Imaging for the Management of Cancer

The Role of IAEA in Supporting the Development of Radiology and Nuclear Medicine in Member States



TC project RER6041
Balkan Congress of Radiology
Jahorina, Bosnia and Herzegovina,
21 to 23 April 2023

IAEA
International Atomic Energy Agency
Atoms for Peace and Development

Enrique Estrada-Lobato

Nuclear Medicine and Diagnostic Imaging Section

Division of Human Health

Department of Nuclear Sciences and Applications

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Main Activities Implemented by the Professional in a Technical Department

- Education and Training
- Guidelines/Recommendations
- Quality Assurance/Improvement & Management
- Research
- Dosimetry Lab Activities
- Technical Cooperation (TC) Program Support
- Collaboration with other Relevant Organizations

Act as technical Officers is one of the many activities of the professionals working in technical departments

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Technical Cooperation Programme

Through the TC programme, the IAEA helps Member States to build capacities in safe and peaceful use of nuclear technology for sustainable socioeconomic development

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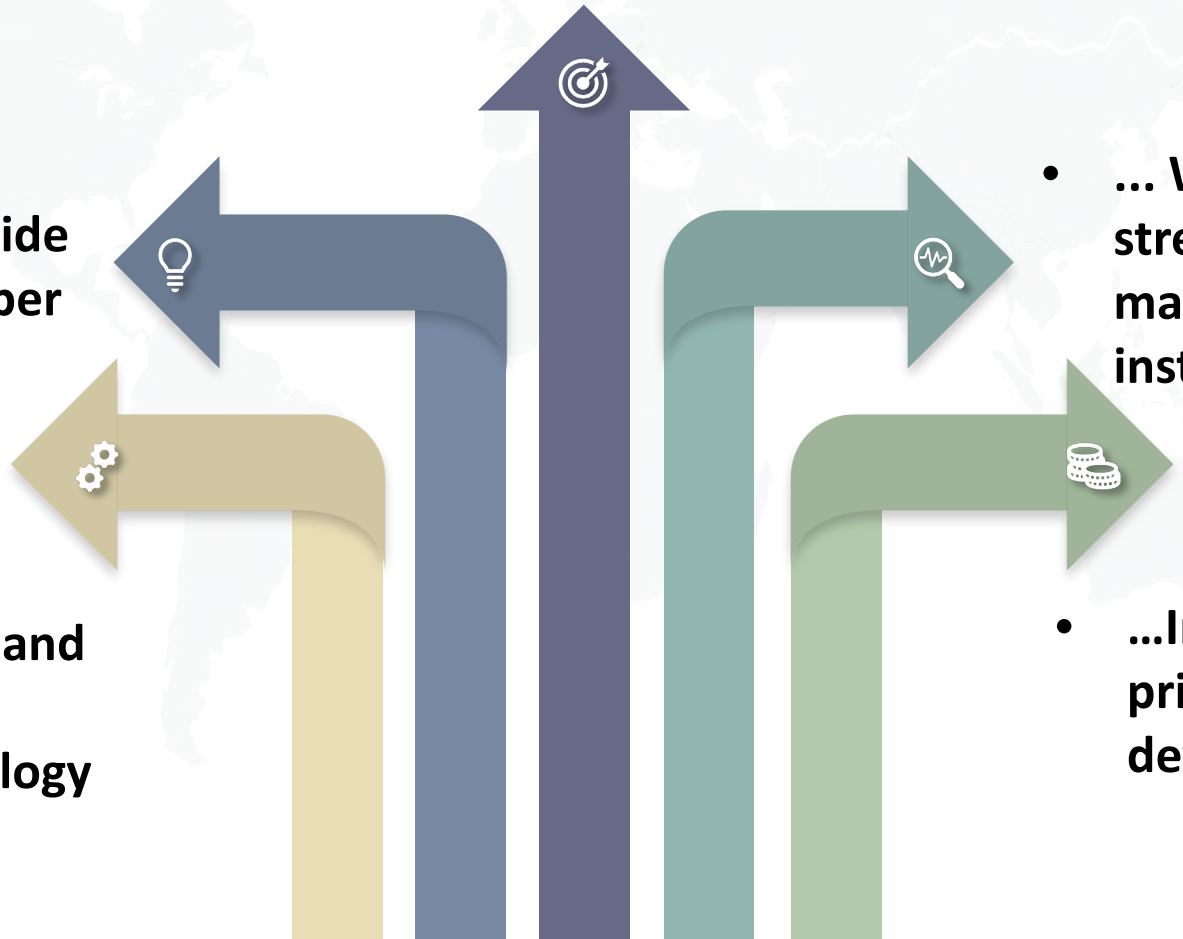
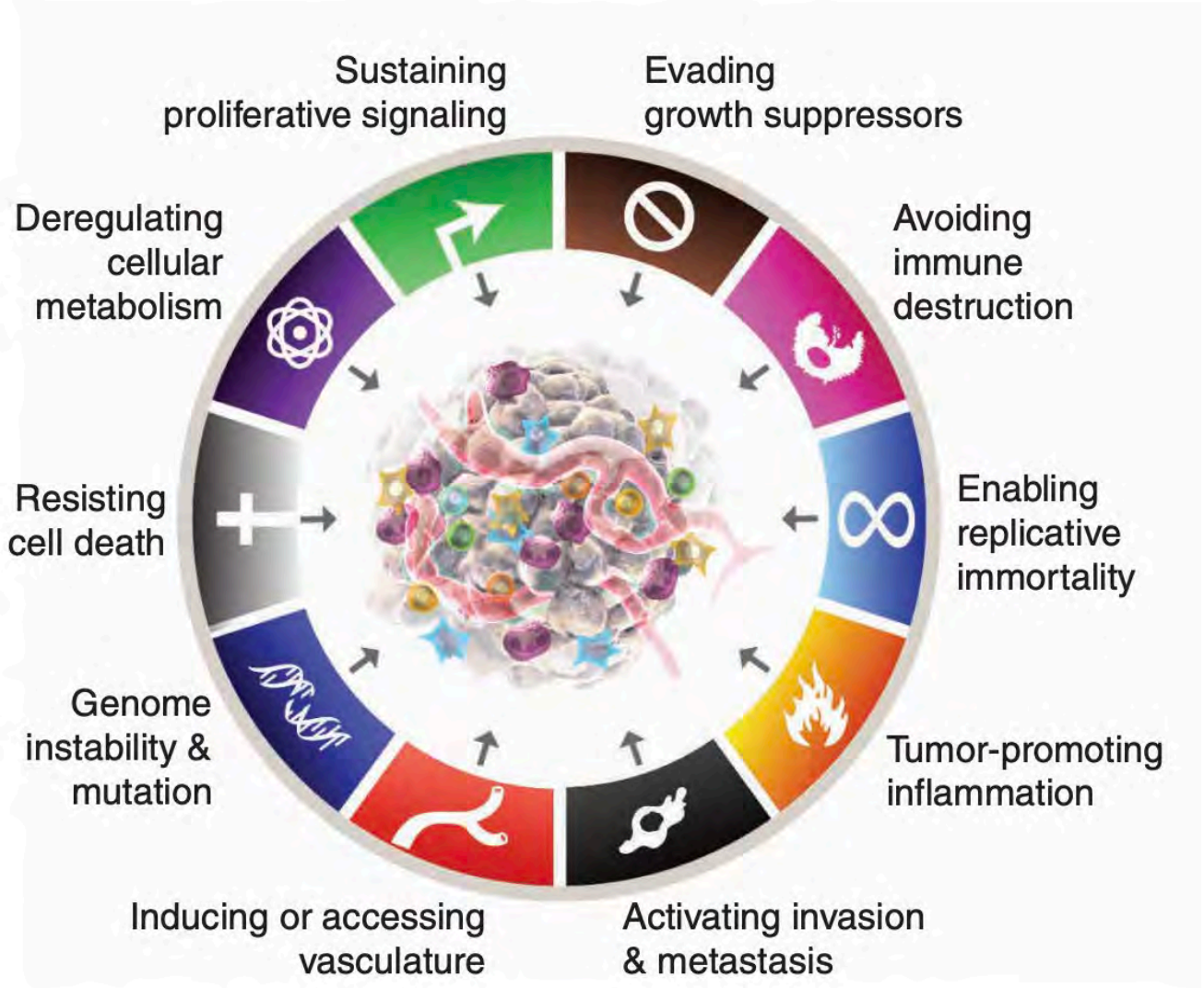
Technical Cooperation Programme

- **…It is the main mechanism to provide assistance to Member States.**
- **... For the peaceful and safe use of nuclear science and technology**

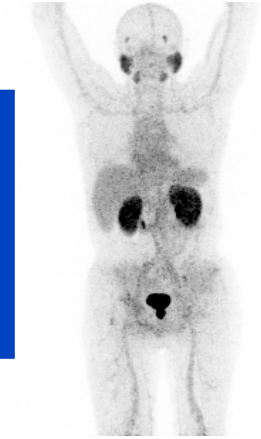


- **... With the aim of creating, strengthening and maintaining human and institutional capacities**
- **…In support of national priorities for sustainable development**

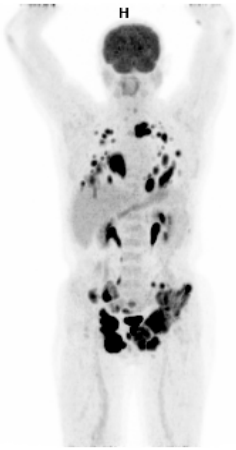
Hallmarks of Cancer



Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. 4.



^{68}Ga-PSMA



^{18}F-FDG

^{68}Ga-DOTATOC

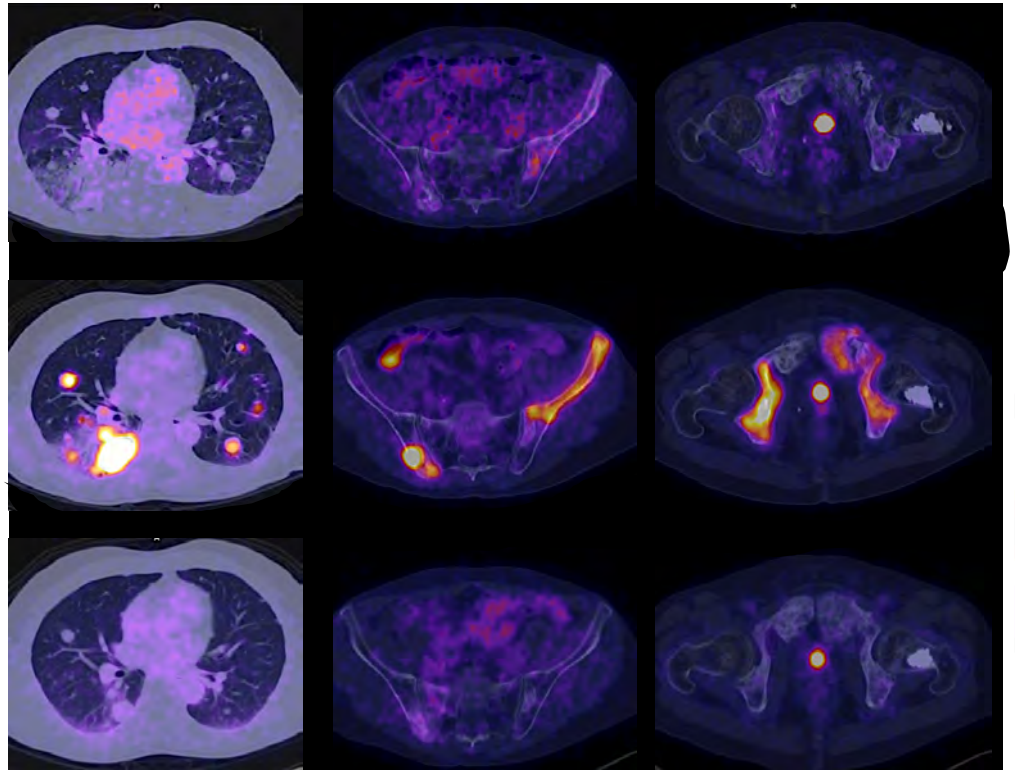
diagnostics

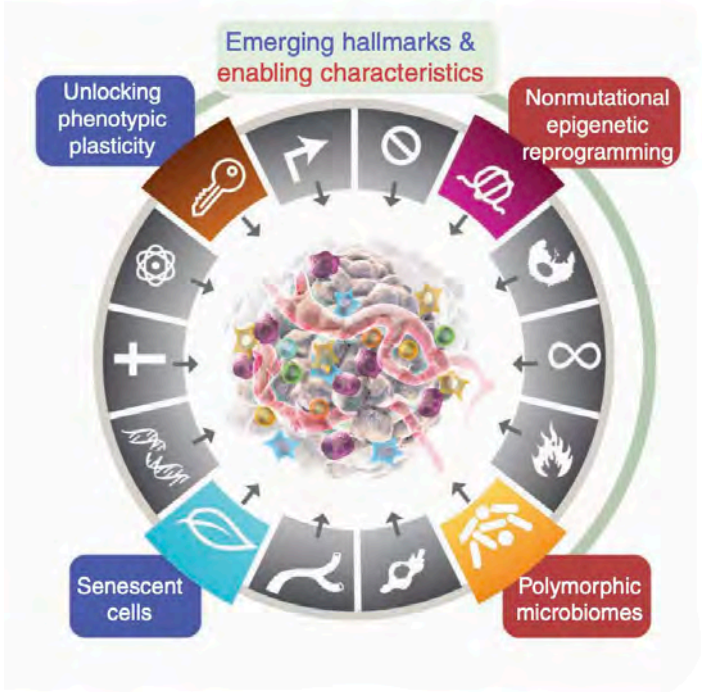
MDPI

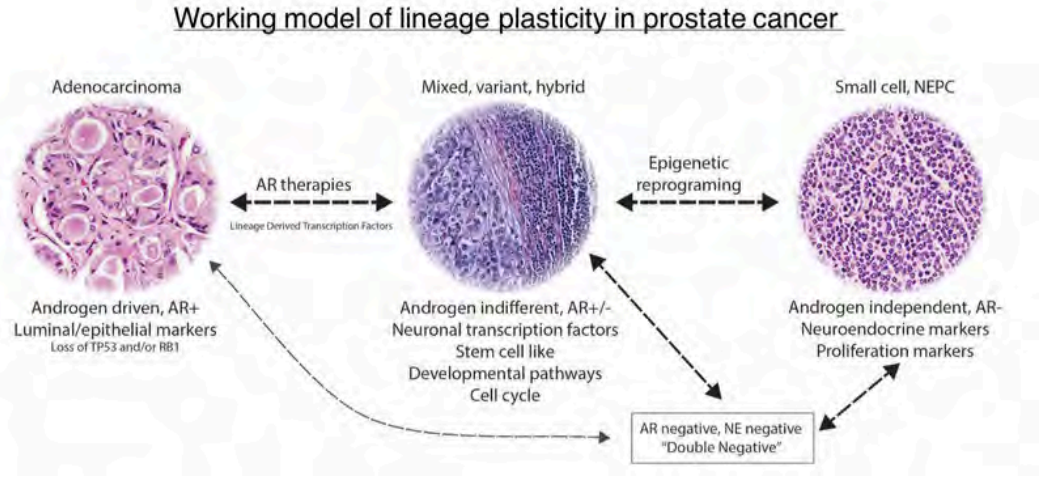
Article

Multitarget Molecular Imaging in Metastatic Castration Resistant Adenocarcinoma Prostate Cancer with Therapy Induced Neuroendocrine Differentiation

Joel Vargas Ahumada [1], Sofía D. González Rueda [1], Fabio A. Sinisterra Solís [1], Quetzali Pitalúa Cortés [1], Liliana P. Torres Agredo [2], Jimenez Ríos Miguel [3], Ana Scabuzzo [3], Irma Soldevilla-Gallardo [1], Miguel A. Álvarez Avitia [4], Nora Sobrevilla [4] and Francisco Osvaldo García Pérez [1,*]







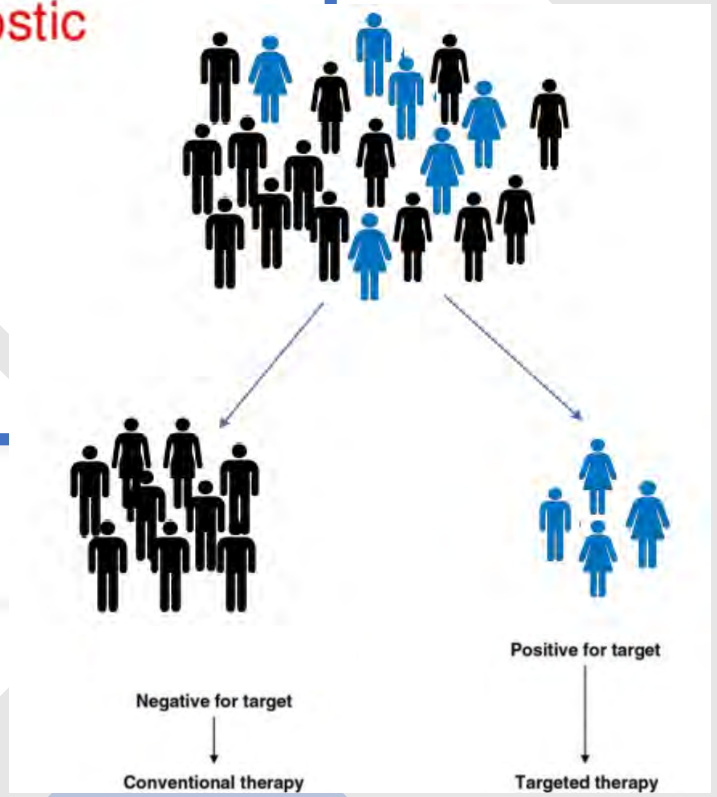
Vargas & Garcia. Multitarget Molecular Imaging in Metastatic Castration Resistant Adenocarcinoma Prostate Cancer with Therapy Induced Neuroendocrine Differentiation. Diagnostics 2022, 12, 1387.

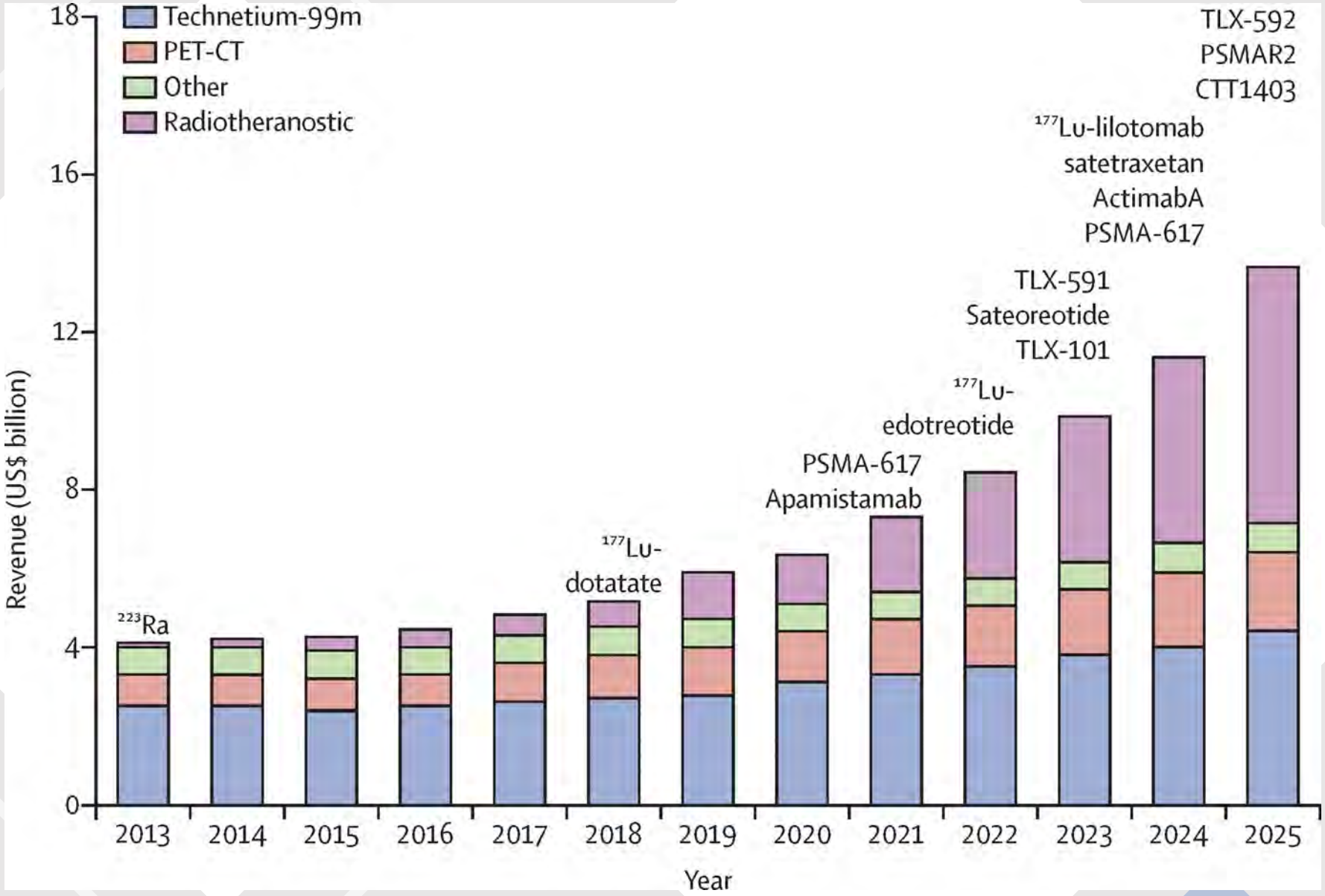
Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. 4.

Theranostics

Combination of two words:

- Therapeutic + Diagnostic





Lancet Oncol. 2020 Mar;21(3):e146-e156

131 Iodine 1st Theranostic agent

RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

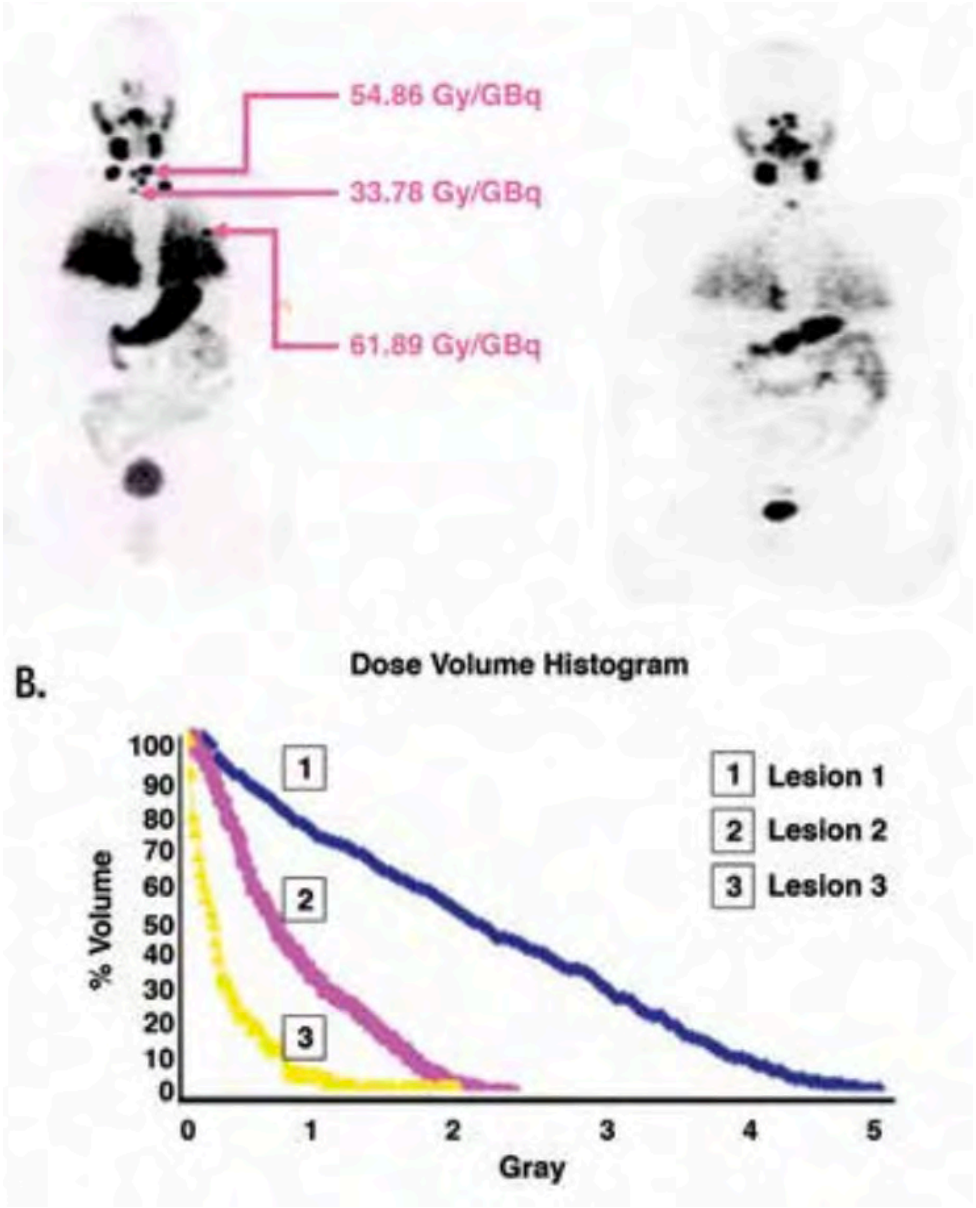
BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

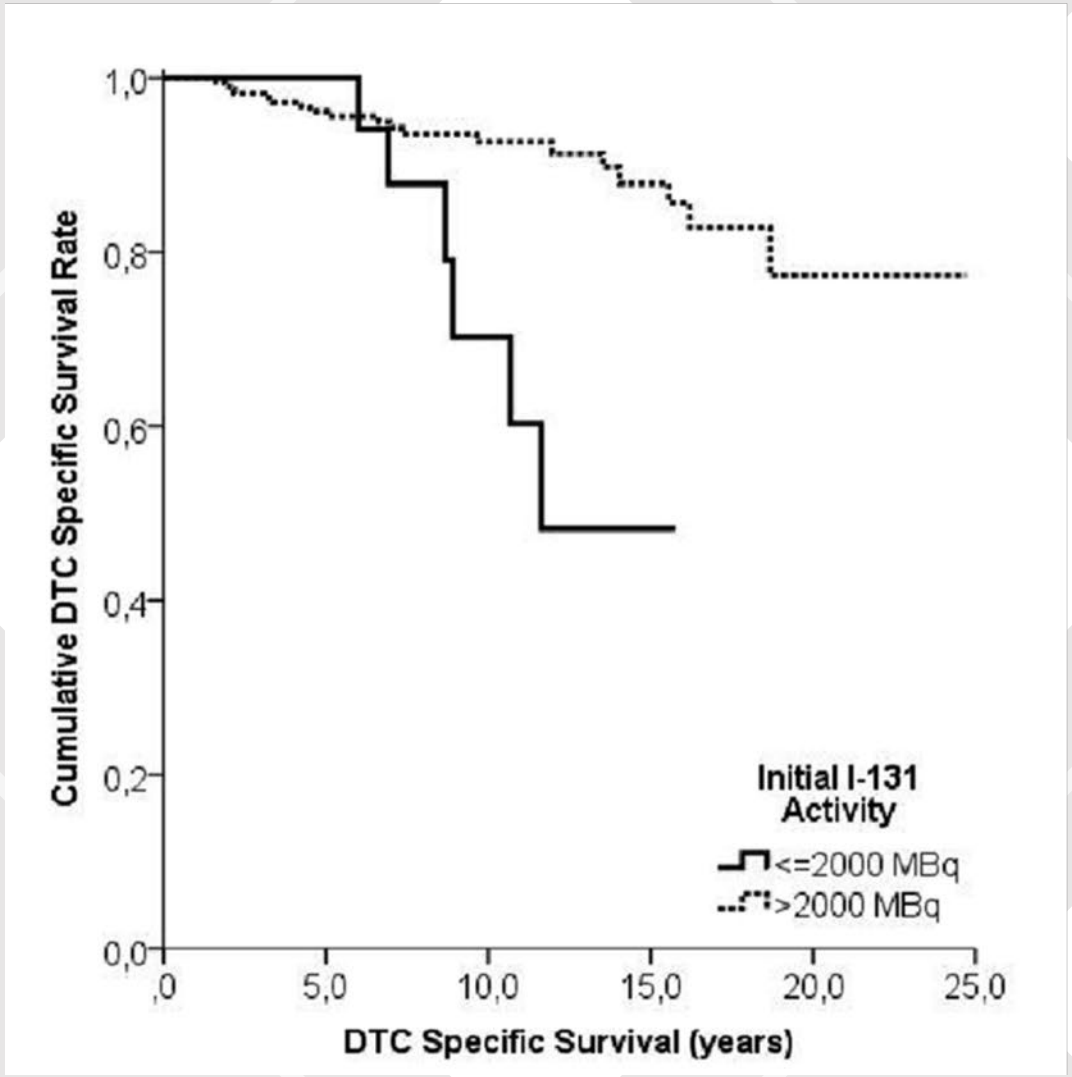
When Brunstein was admitted to New York's Montefiore Hospital seven years ago he appeared to be suffering from an overactive thyroid gland rather than from cancer. He had a very fast heart and quivering hands, and he was weak and emaciated. But examination revealed that he had no thyroid gland: it had been removed by surgery 19 years before when it had become cancerous. Apparently some of the cancer cells had sloughed off, however, and had been carried through the circulatory system to other parts of his body: eight cancerous tumors were found growing into the patient's lungs, ribs, femur, spine, pelvis and skull. The tumors, composed of malignant thyroid tissue, were secreting hormones and were otherwise behaving like thyroid glands.

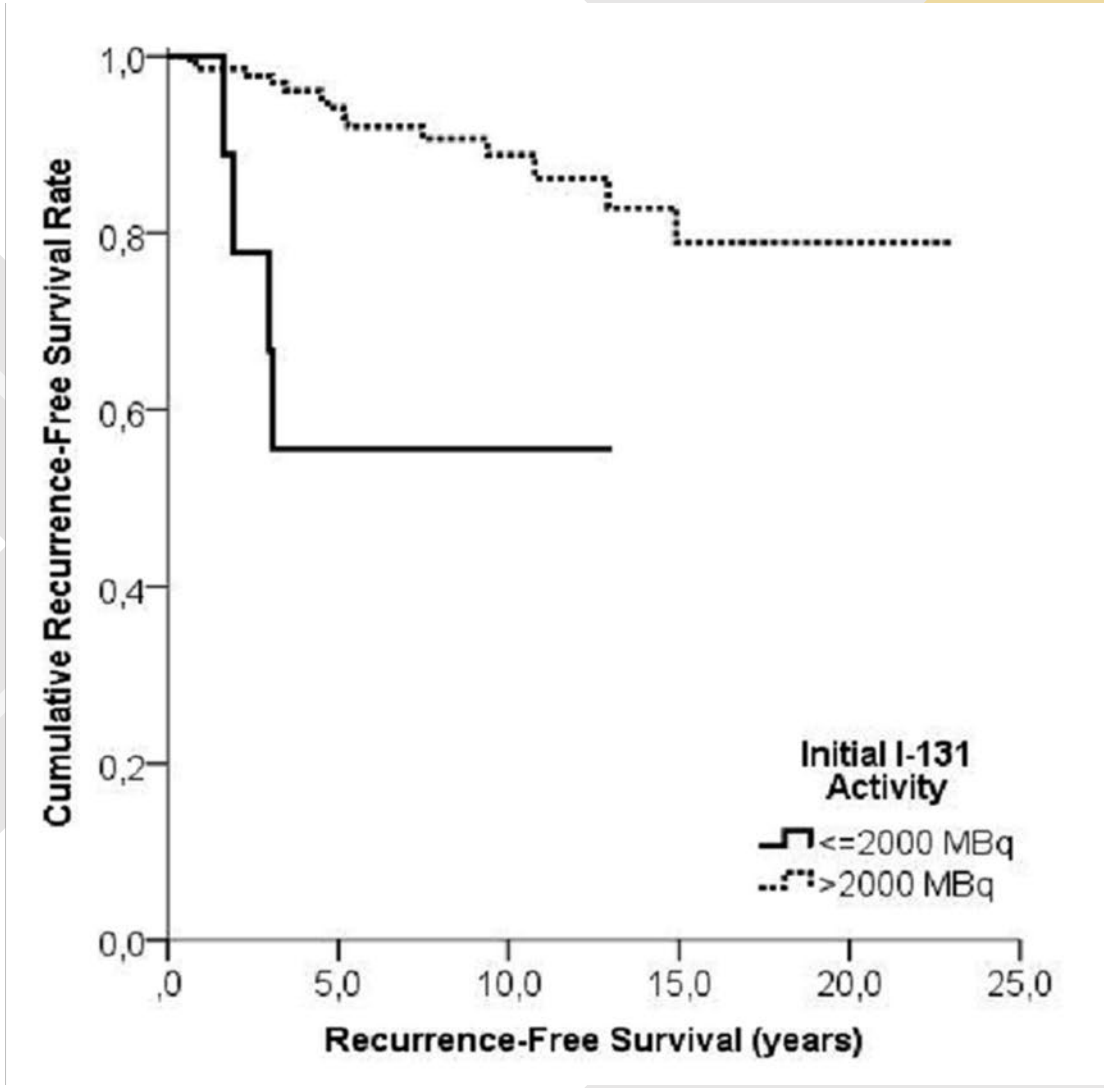
Radio-iodine was given to Brunstein on the theory that his thyroid-like tumors would absorb the drug just as a normal thyroid gland picks up ordinary iodine. If they did, they would be destroyed. For while radio-iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether. Last May a section of Brunstein's skull was removed for a microscopic examination of the site of one of his tumors. Only scar tissue and dead cells remained, and not a single living cancer cell was found (*left*).

From his experience with Brunstein and subsequent cases Dr. S. M. Seidlin of Montefiore Hospital, an endocrinologist and a pioneer in radiotherapy, has deduced that radio-iodine does not work in many ordinary thyroid cancer cases because most of the chemical is picked up by the thyroid gland itself, and little of it gets to distant tumors. But if the gland is destroyed, the medicine has a better chance of reaching the diseased areas. Of a group of 12 patients treated by Seidlin since 1942, five appear to be recovering and in two others the tumors have stopped growing. Of the five who died, two had their lives prolonged several years, two were near death when treatment was started, and one died of a different disease.

Life Magazine, Oct 1949 Edition







J Clin Endocrinol Metab 99: 4487– 4496, 2014

Molecular Imaging

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Introduction

Theranostics in Nuclear Medicine: Emerging and Re-emerging Integrated Imaging and Therapies in the Era of Precision Oncology

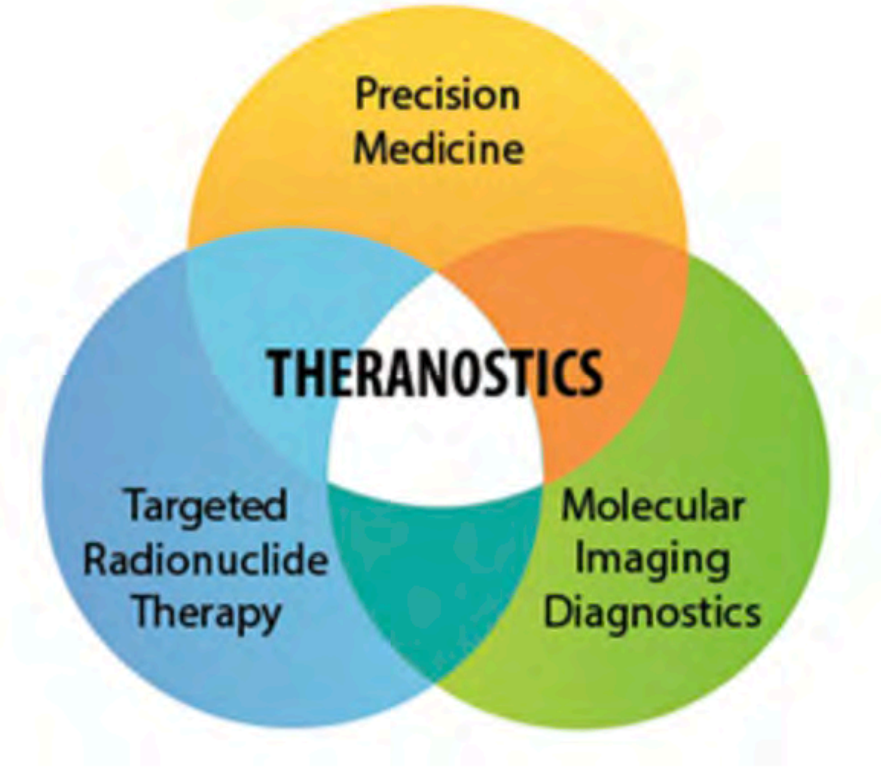
Paul Ehrlich proposed the term *"magic bullet"*

↓

Chemotherapy & Target Therapies

↓

Personalized, targeted and/or precision medicine



RadioGraphics 2020; 40: 1715-1740

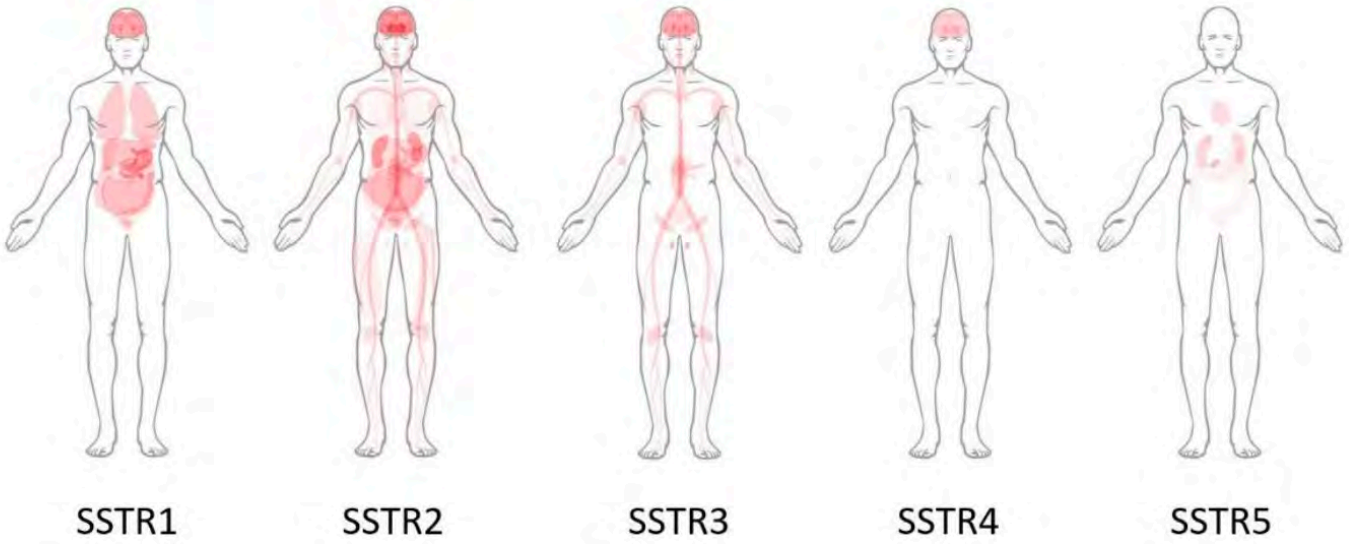
molecules

MDPI

Review

Overview of Radiolabeled Somatostatin Analogs for Cancer Imaging and Therapy

Romain Eychenne [1,2,3], Christelle Bouvry [4,5], Mickael Bourgeois [2,3], Pascal Loyer [6], Eric Benoist [1] and Nicolas Lepareur [4,6,*]



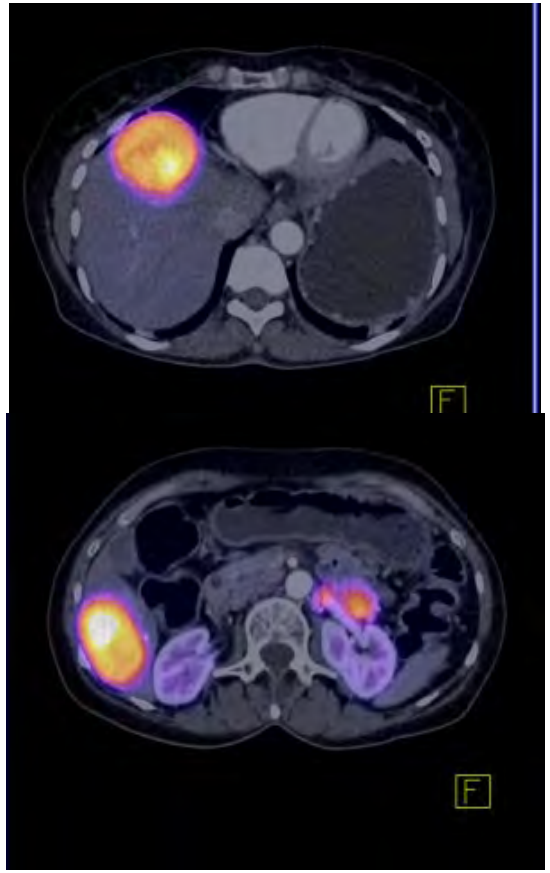
Peptide	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
DOTANOC	>10,000	1.9+/-0.4	4.0+/-5.8	260+/-74	7.2+/-1.6
DOTATOC	>10,000	2.5+/-0.5	613+/-140	>1000	73+/-21
DOTATATE	>10,000	0.2+/-0.04	>1,000	300+/-140	377+/-18

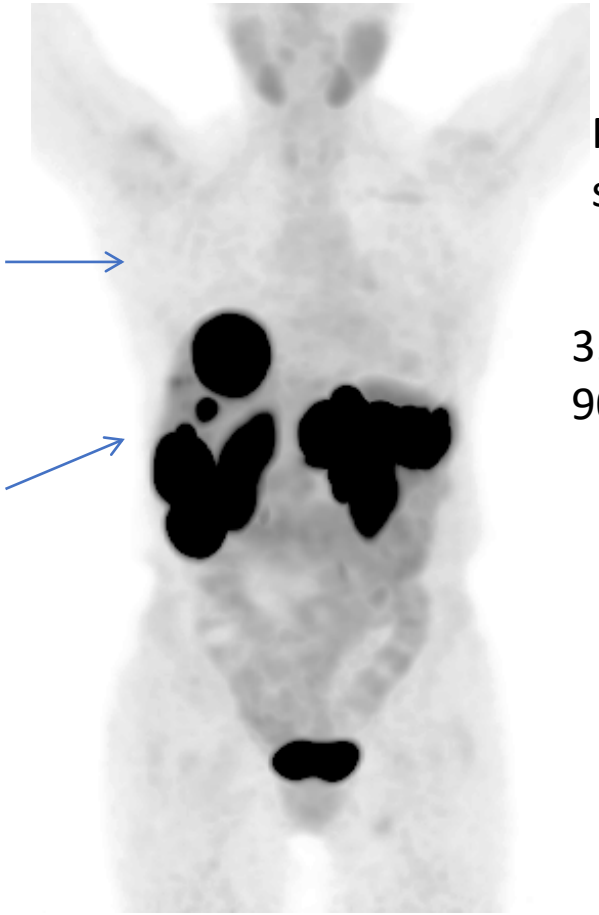
Tumor Type	SSTR Expression
Growth hormone-producing pituitary adenoma	**+** (SSTR2, SSTR5)
Gut carcinoid	**+** (SSTR2 > SSTR1, SSTR5)
Hepatocellular carcinoma	+ (SSTR2, SSTR5)
Insulinoma	+ (SSTR1, SSTR2, SSTR3)
Leiomyoma	+
Lymphoma	+ (SSTR2)
Medullary thyroid carcinoma	+ (SSTR2)
Medulloblastoma	**+** (SSTR2)
Meningioma	**+** (SSTR2)
Neuroblastoma	**+** (SSTR2)
Non-functioning pituitary adenoma	+ (SSTR3 > SSTR2)
Non-small cell lung cancer	-
Ovarian carcinoma	+
Paraganglioma	**+** (SSTR2)
Pheochromocytoma	**+** (SSTR1, SSTR2)
Prostate carcinoma	+ (SSTR1)
Renal cell carcinoma	+ (SSTR2)
Small cell lung cancer	+ (SSTR2)
Urinary bladder carcinoma	-

Molecules. 2020;25(17):4012.

Terminal Carcinoid Tumor of the Ileum
75% reduction in lesion metabolism 18 months post-therapy with radiolabelled peptides.

January 2015



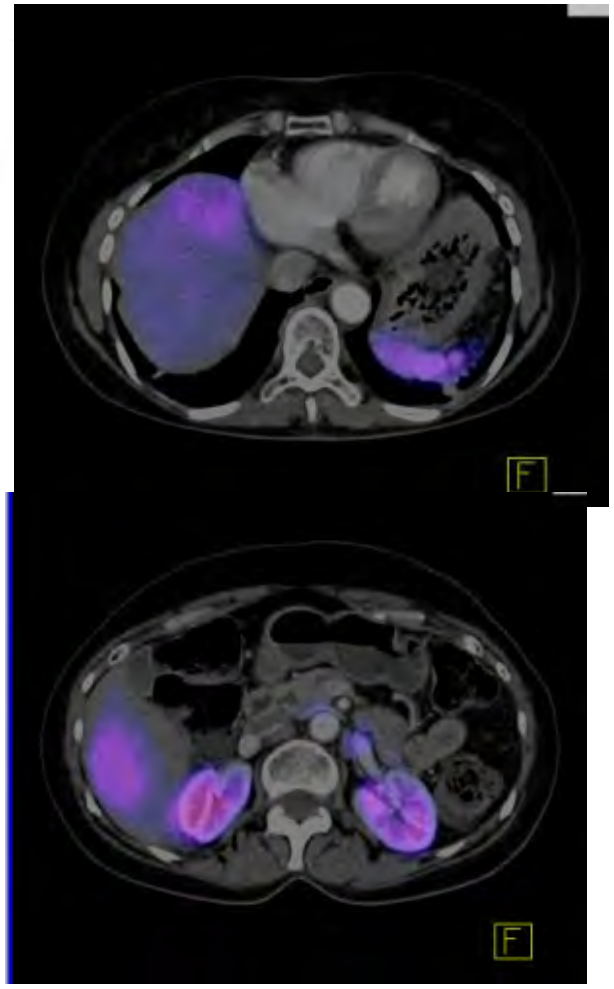


Progression to sandostatin

3.7 GBq (100 mCi)
90 Y DOTATOC
+

200 mCi
177 Lu DOTATOC

July 2016



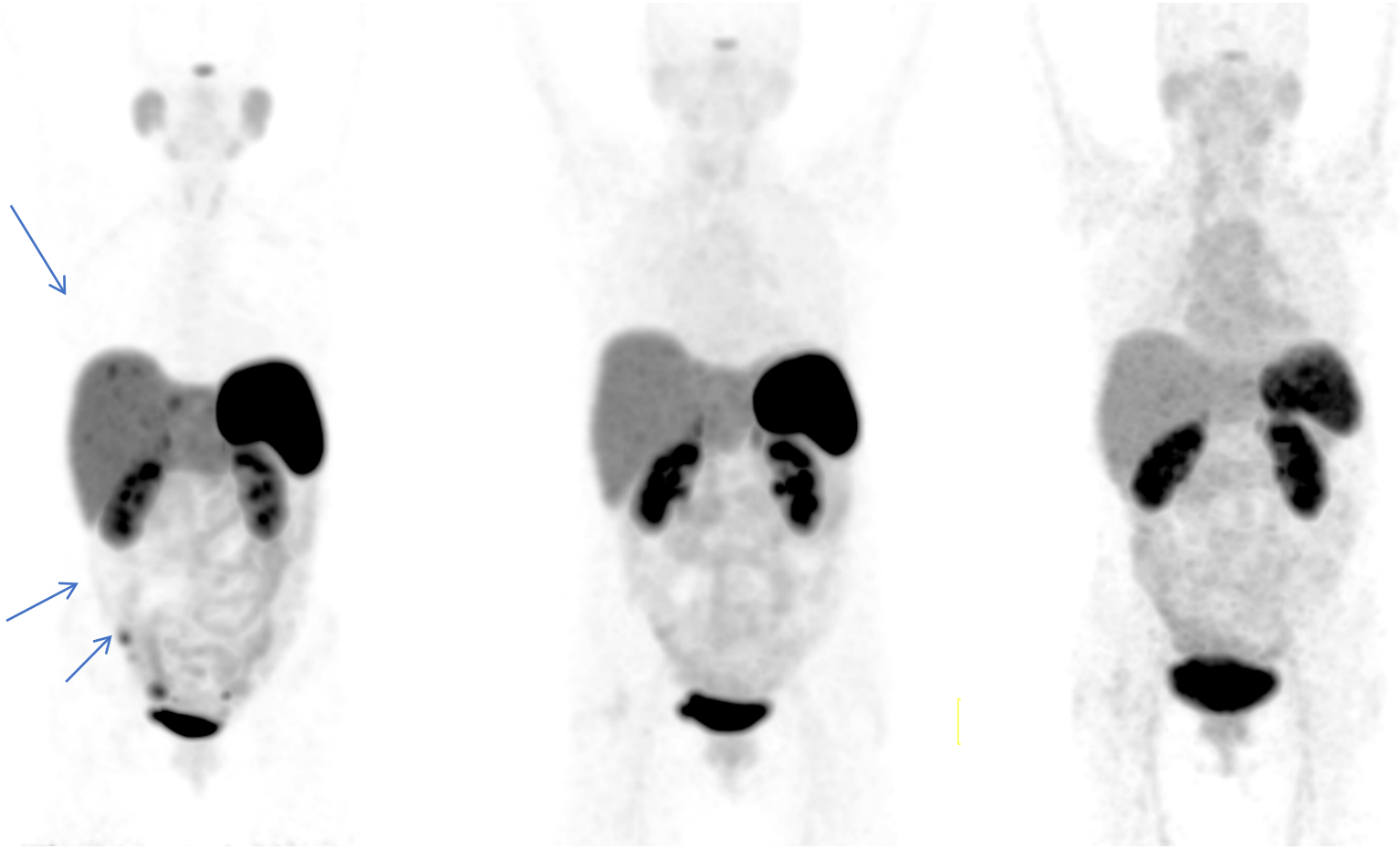
INCan Archive

68 Ga DOTATOC → 68 Ga DOTATOC

METASTATIC pancreas-to-liver NETs
Complete response 12 months post therapy with radiolabeled peptides.

200 mCi
177 Lu DOTATOC

200 mCi
177 Lu DOTATOC



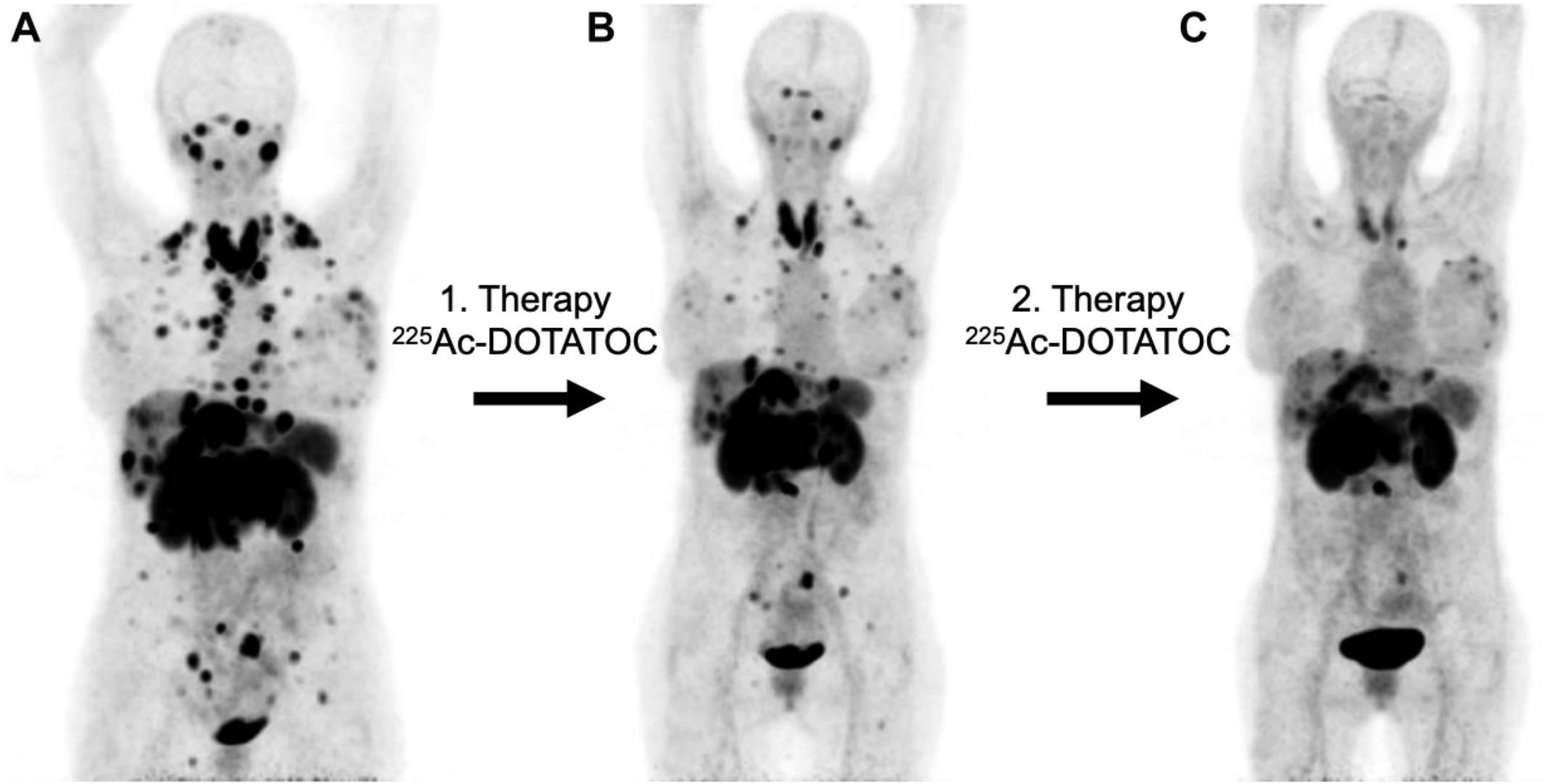
68 Ga DOTATOC

68 Ga DOTATOC

68 Ga DOTATOC

INCan Archive

NET
^{225}Ac-DOTATE



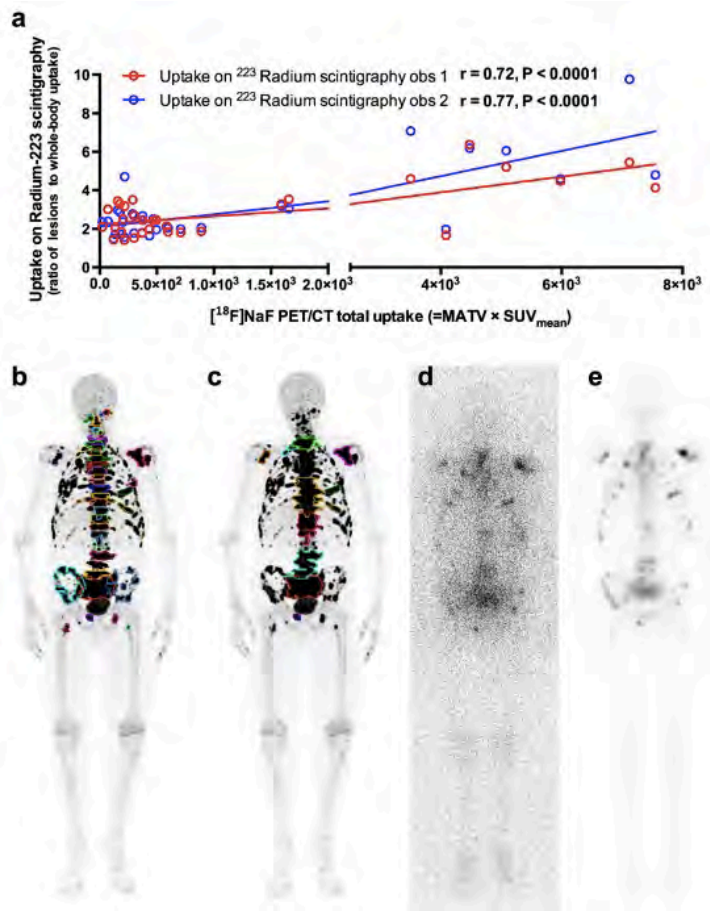
Ballal S et al. EJNMMI 2020

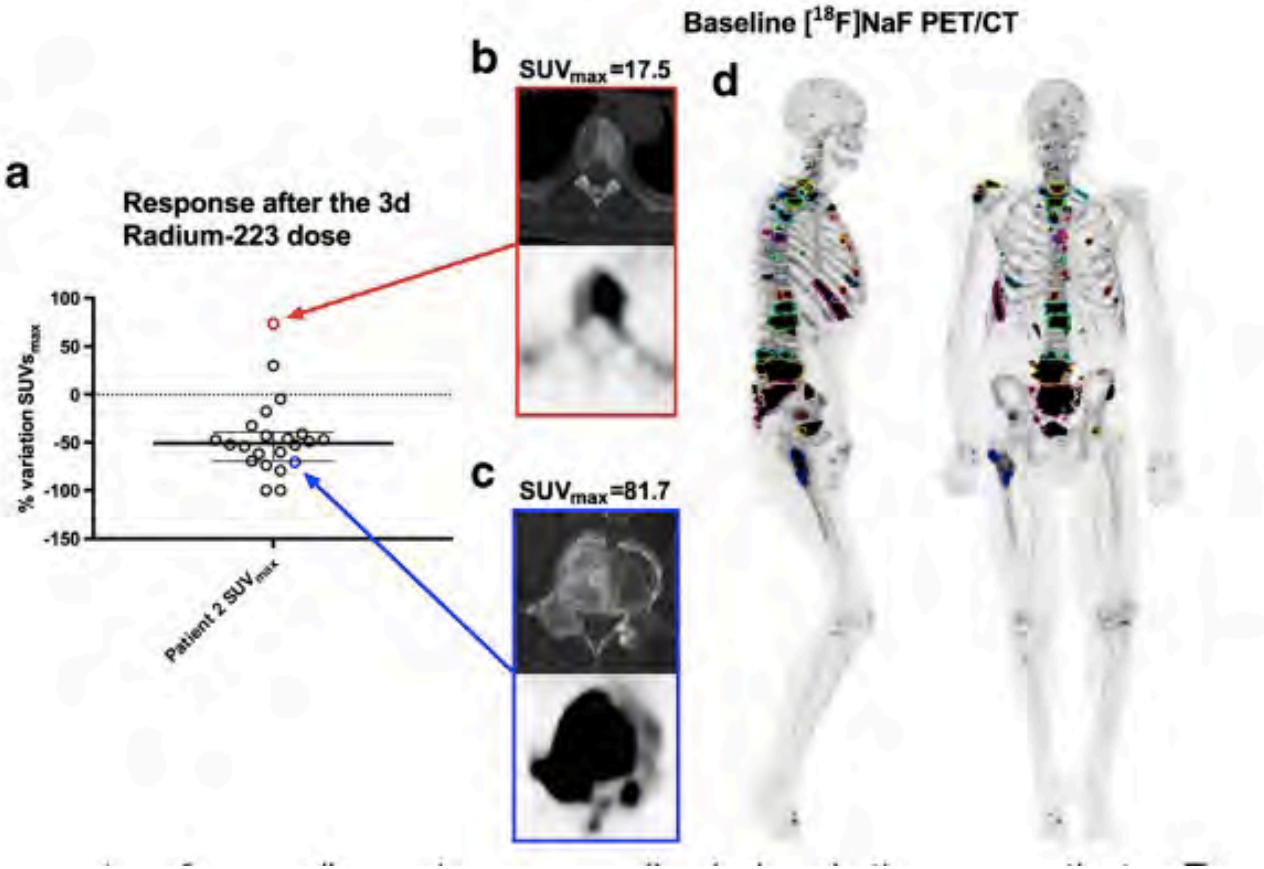

Prostate

RESEARCH ARTICLE

Uptake of Radium-223 Dichloride and Early [^{18}F]NaF PET Response Are Driven by Baseline [^{18}F]NaF Parameters: a Pilot Study in Castration-Resistant Prostate Cancer Patients

18 NaF PET is a predictor of response to at least three doses of Ra 223

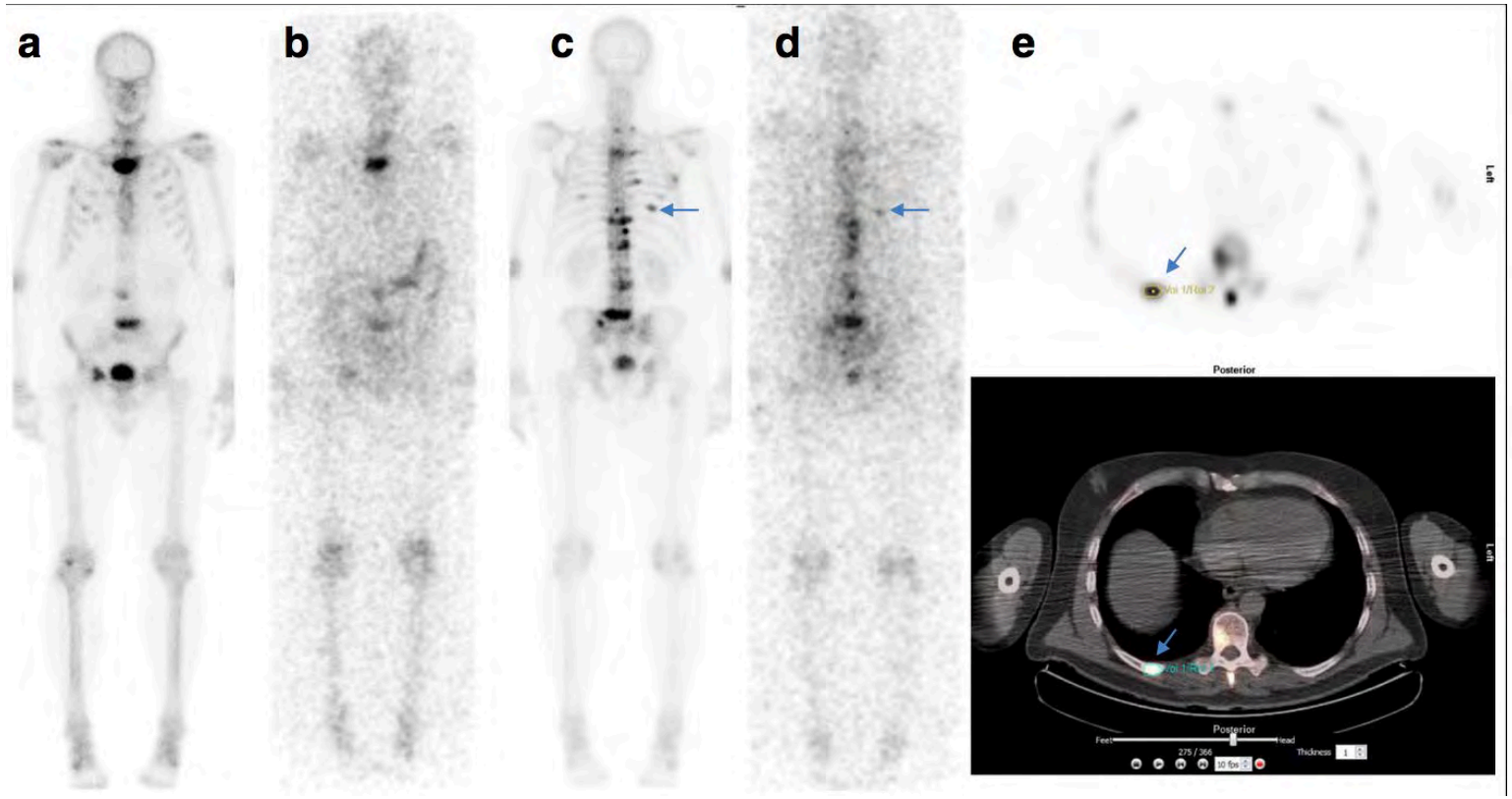


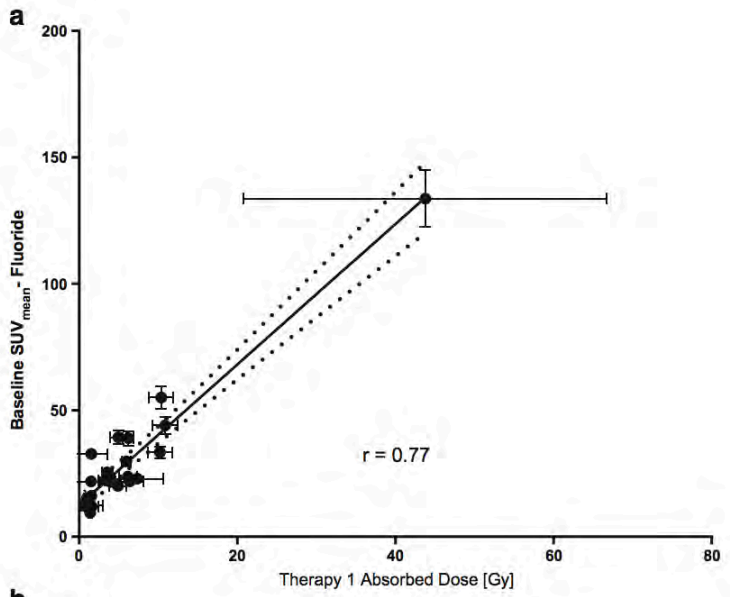


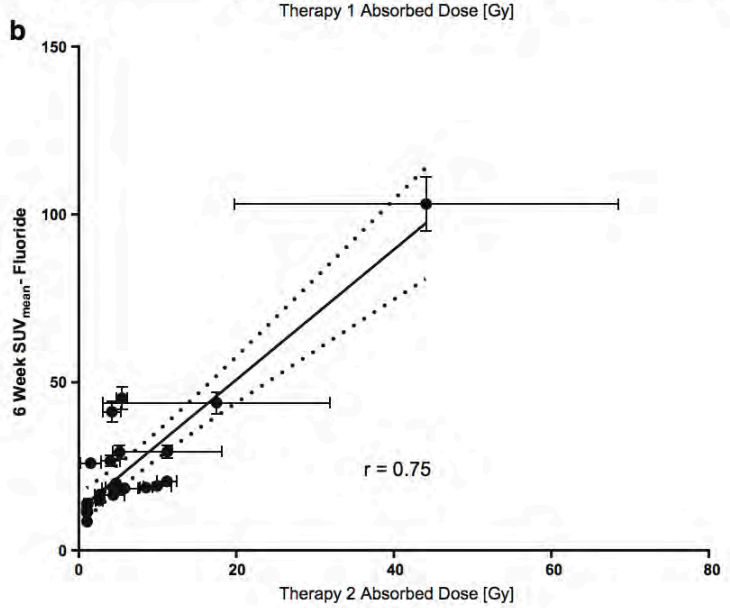
Letellier A, Uptake of Radium-223 Dichloride and Early [18F]NaF PET Response Are Driven by Baseline [18F]NaF Parameters: a Pilot Study in Castration-Resistant Prostate Cancer Patients. Mol Imaging Biol. 2018 Jun;20(3):482-491.

The potential of ^{223}Ra and ^{18}F-fluoride imaging to predict bone lesion response to treatment with ^{223}Ra-dichloride in castration-resistant prostate cancer

Iain Murray[1,2] · Sarah J. Chittenden[1,2] · Ana M. Denis-Bacelar[1,2] · Cecilia Hindorf[1,2,3] · Christopher C. Parker[4] · Sue Chua[5] · Glenn D. Flux[1,2]

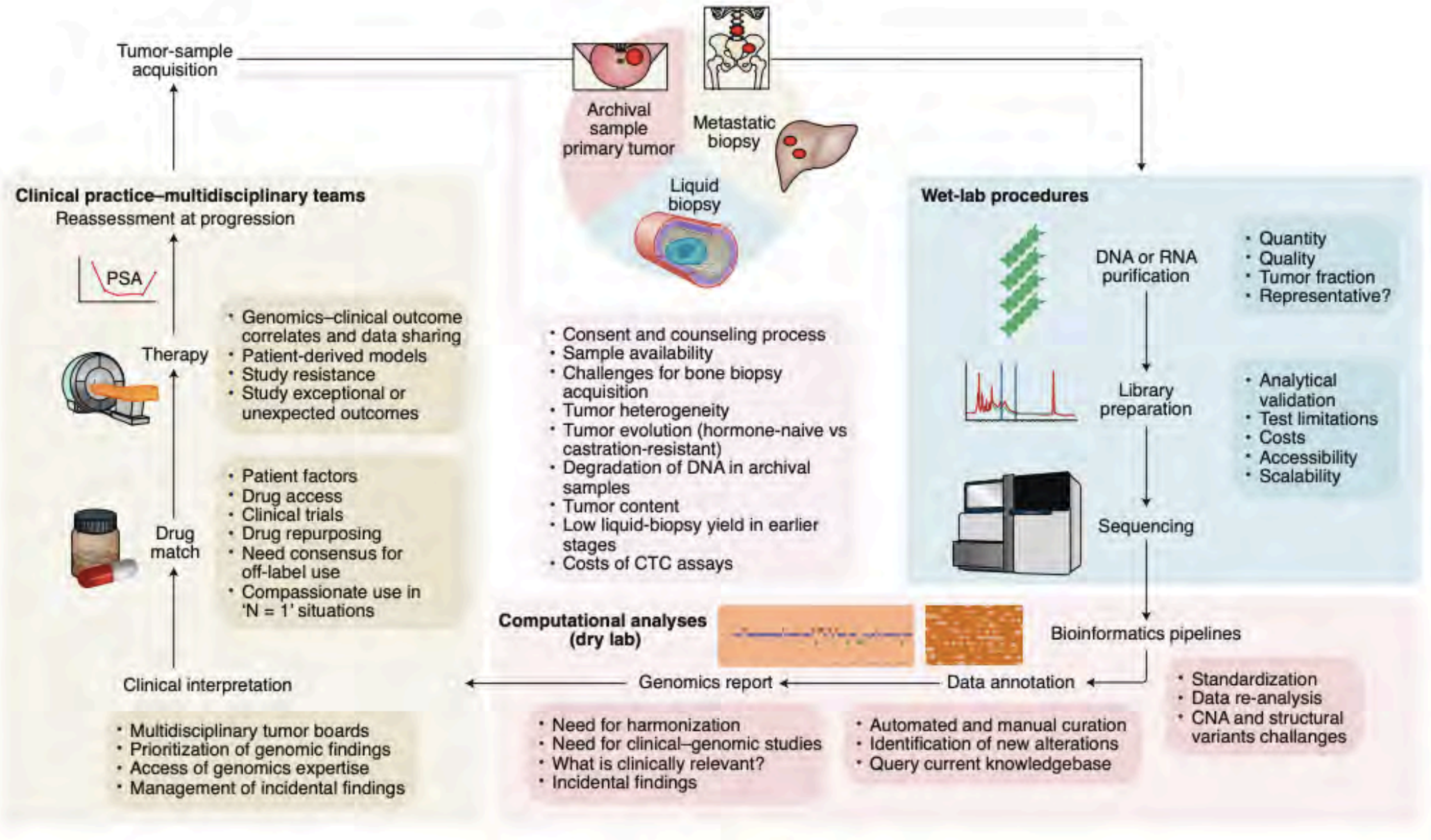






Eur J Nucl Med Mol Imaging. 2017 October ; 44(11): 1832–1844.

Precision Oncology



Nat Cancer **1,** 1041–1053 (2020).

Therapies

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Prostate

RESEARCH ARTICLE

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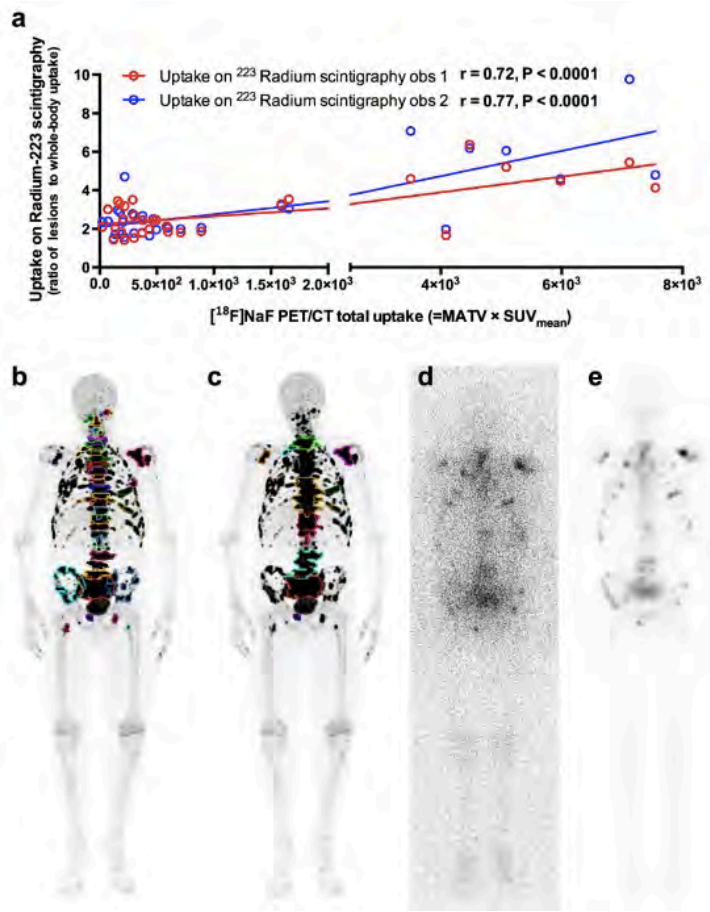

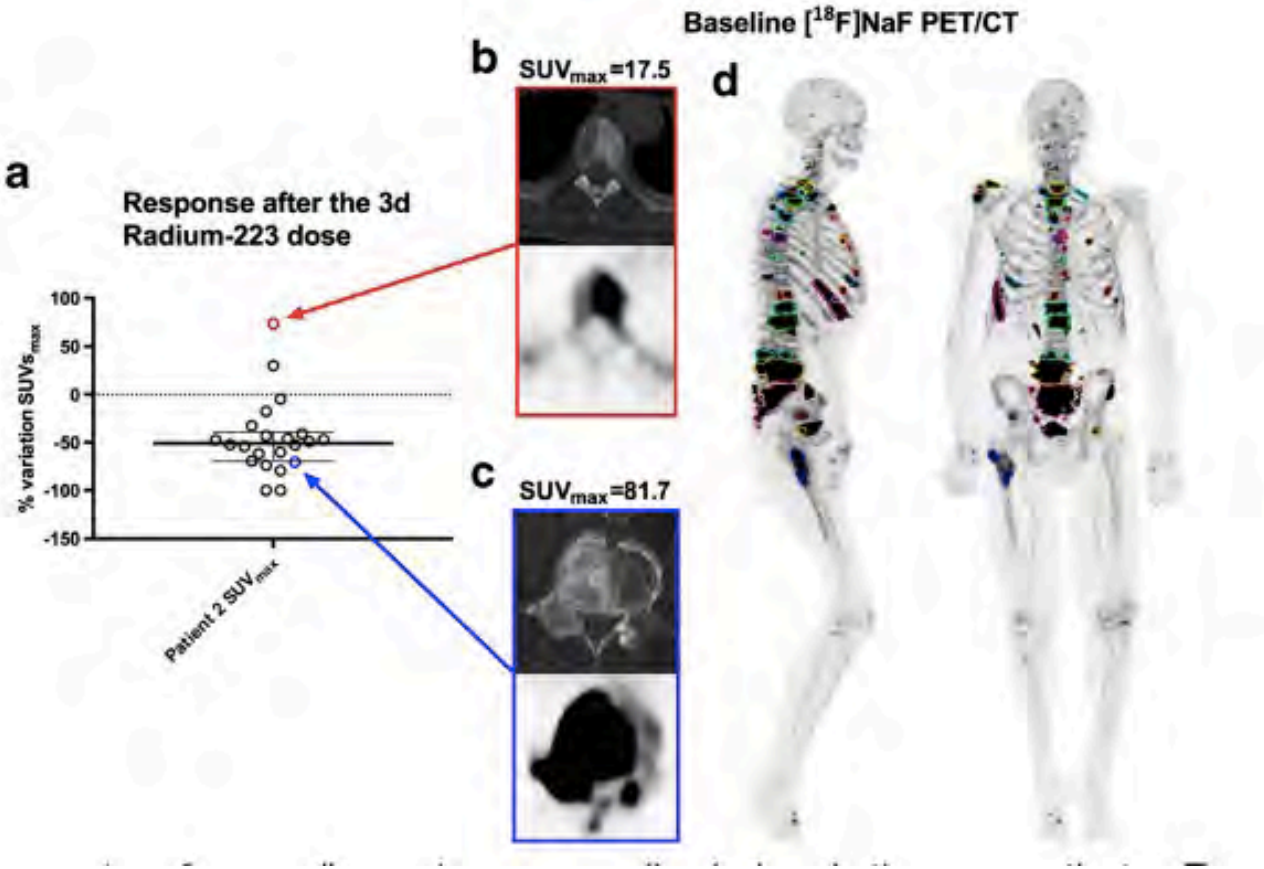

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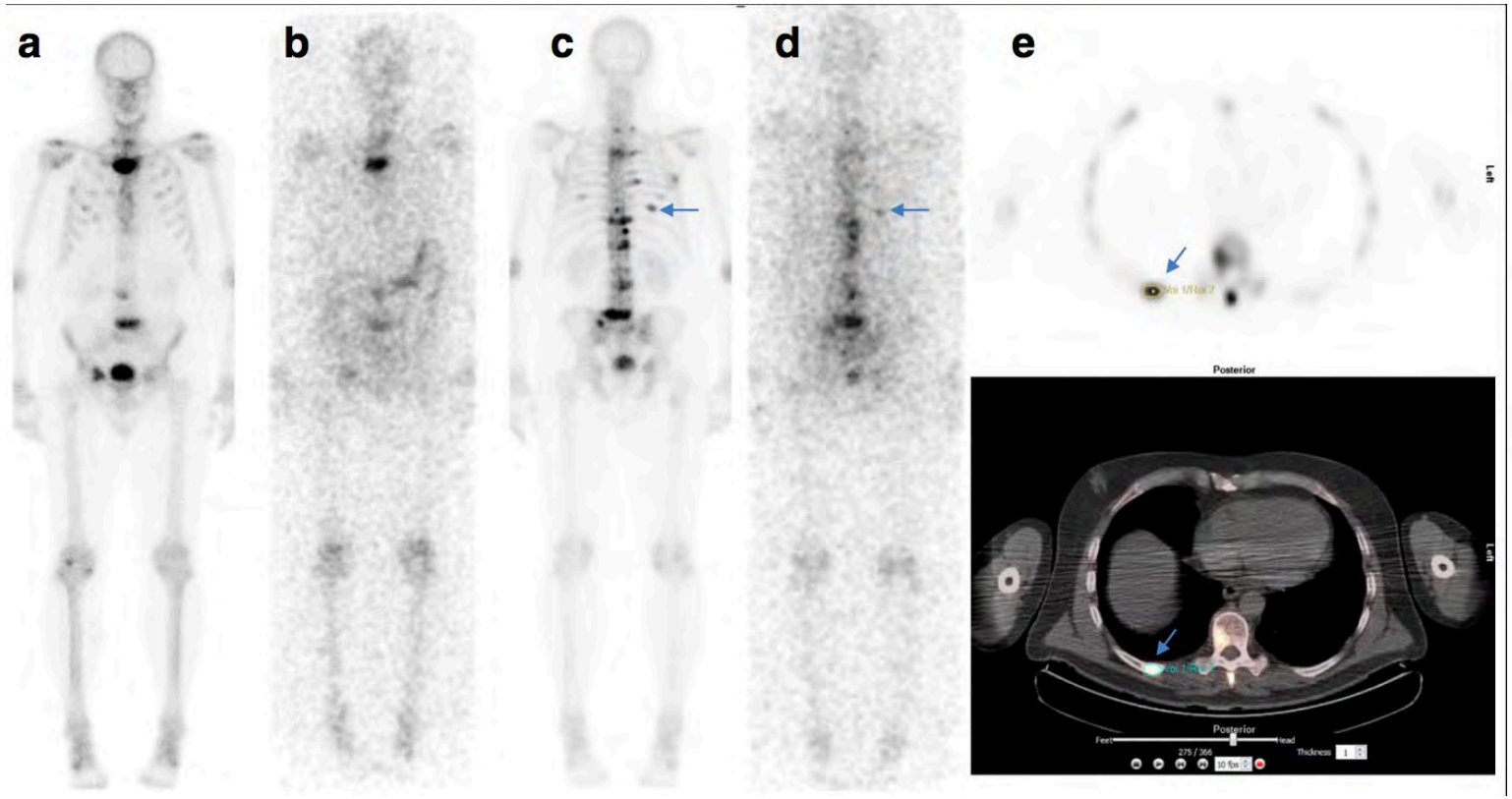

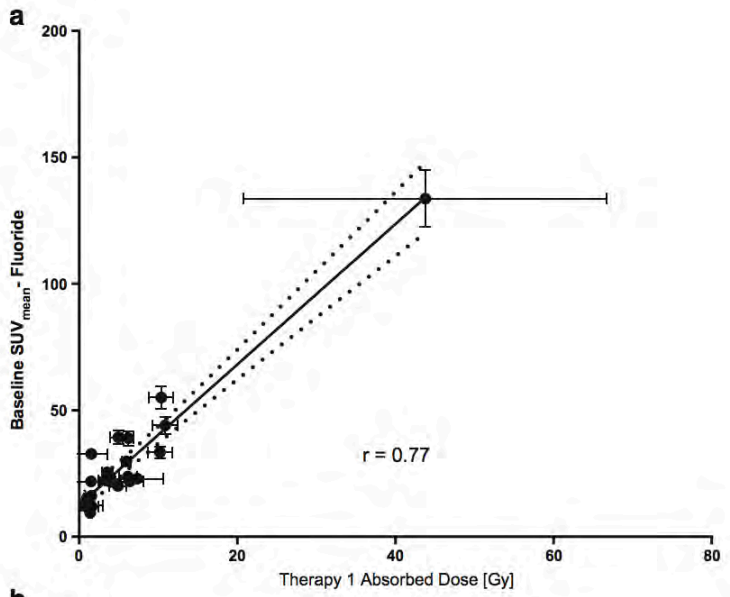

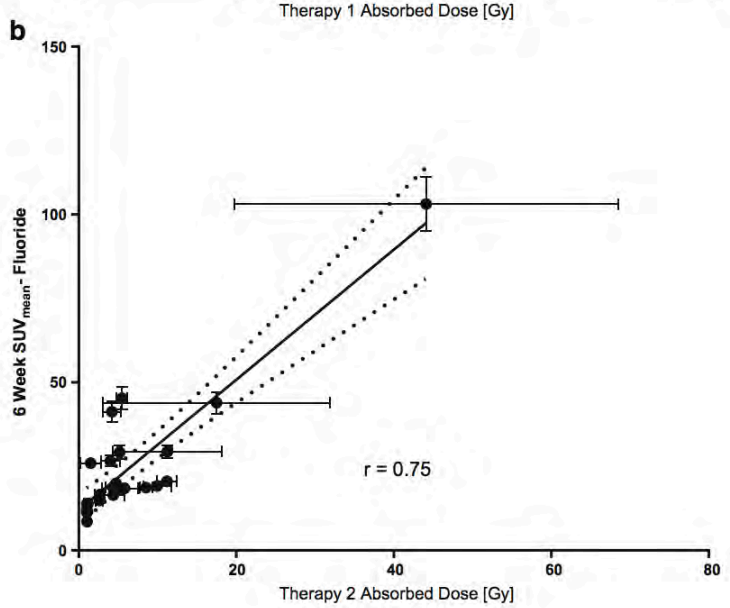

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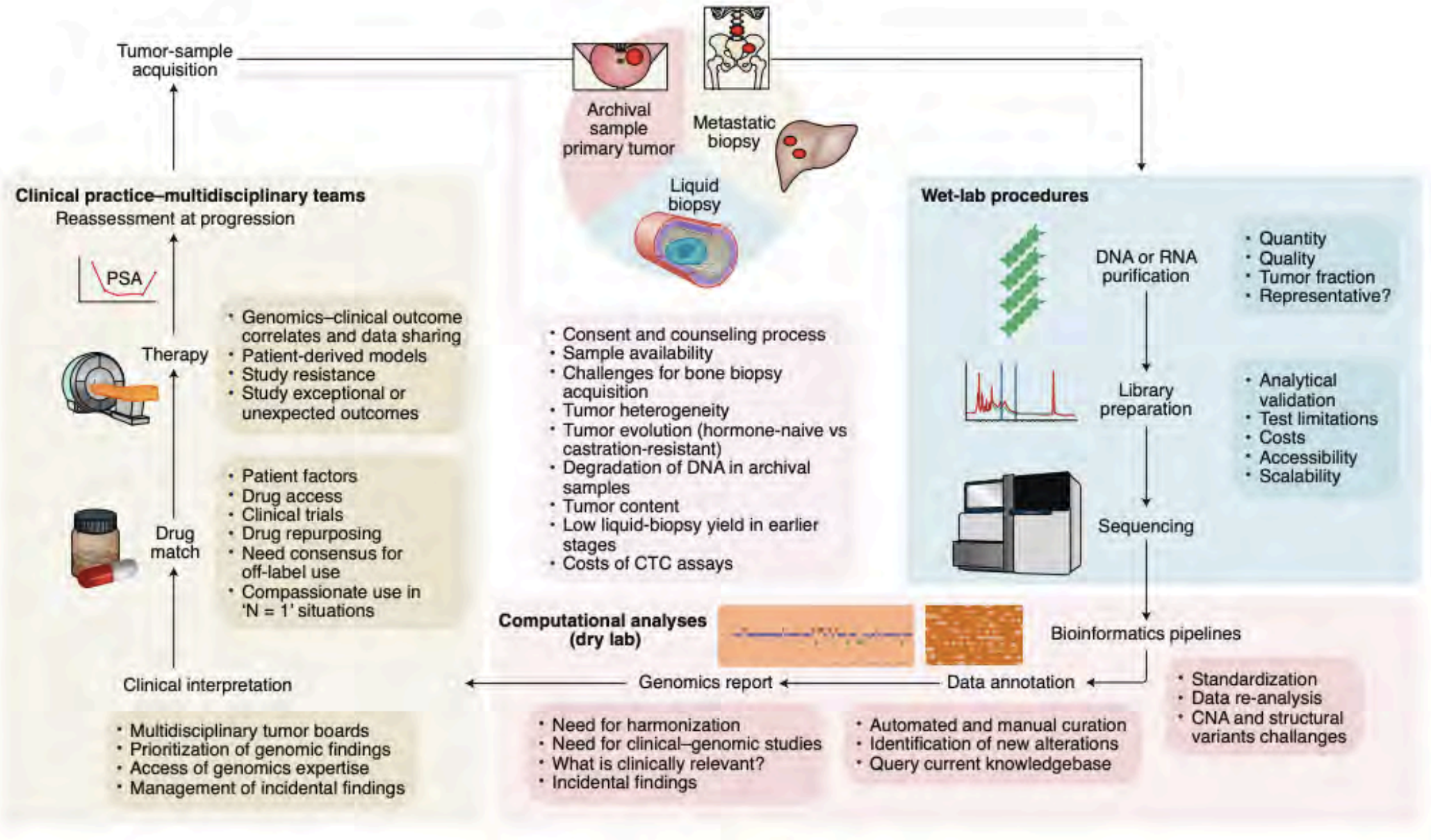

Nat Cancer **1,** 1041–1053 (2020).

Therapies

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Review

Preclinical and Clinical Status of PSMA-Targeted Alpha Therapy for Metastatic Castration-Resistant Prostate Cancer

Asta Juzeniene [1,*], Vilde Yuli Stenberg [1,2,3], Øyvind Sverre Bruland [3,4] and Roy Hartvig Larsen [2]

	α	β
Relative mass of the particle	7300	1
Reach in tissues (µm)	50	1700
LET	100 KeV/µm	0.2 KeV/µm
DNA damage	Double chain break	Breaking a chain
Impacts on DNA to induce cell death	1-10	100-1000

Cancers 2021, 13, 779

I-131 - MIP 1095

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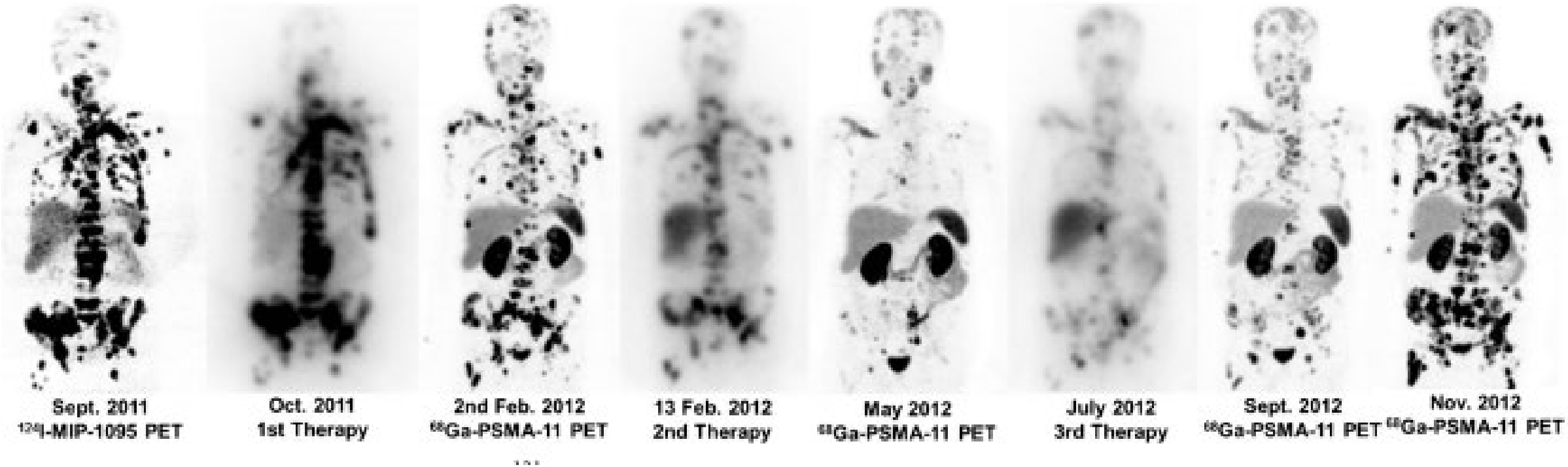
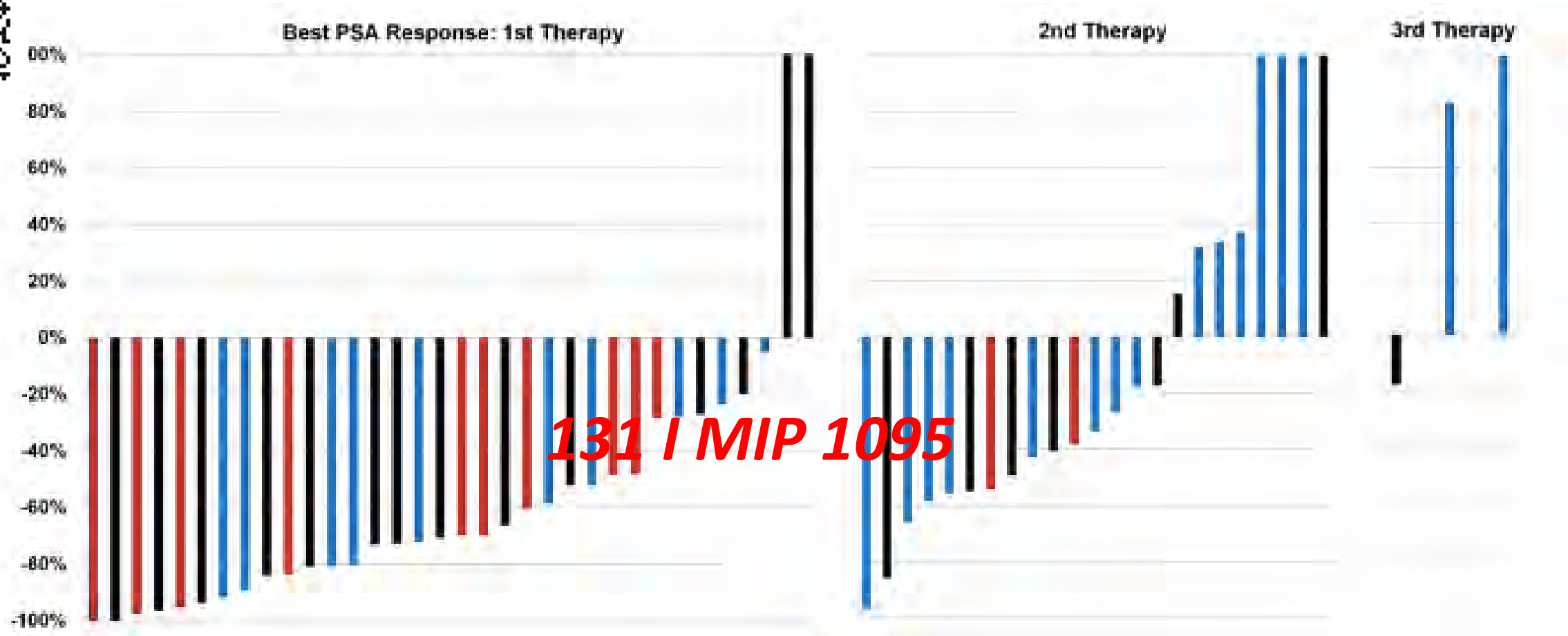
Repeated PSMA-targeting radioligand therapy of metastatic prostate cancer with ^{131}I-MIP-1095

Ali Afshar-Oromieh[1,2] · Uwe Haberkorn[1,2] · Christian Zechmann[1] · Thomas Armor[3] · Walter Mier[1] · Fabian Spohn[1] · Nils Debus[1] · Tim Holland-Letz[4] · John Babich[5,6,7] · Clemens Kratochwil[1]

34 pacientes CPRCm



Eur J Nucl Med Mol Imaging (2017) 44:950–959



< 3,5 GBq Blue
3.5-5 GBq Black
>5.0 GBq Red

Median Survival from first therapy 17 months

Afshar et al Eur J Nucl Med Mol Imaging (2017) 44:950–959

177-Lu PSMA

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International Atomic Energy Agency
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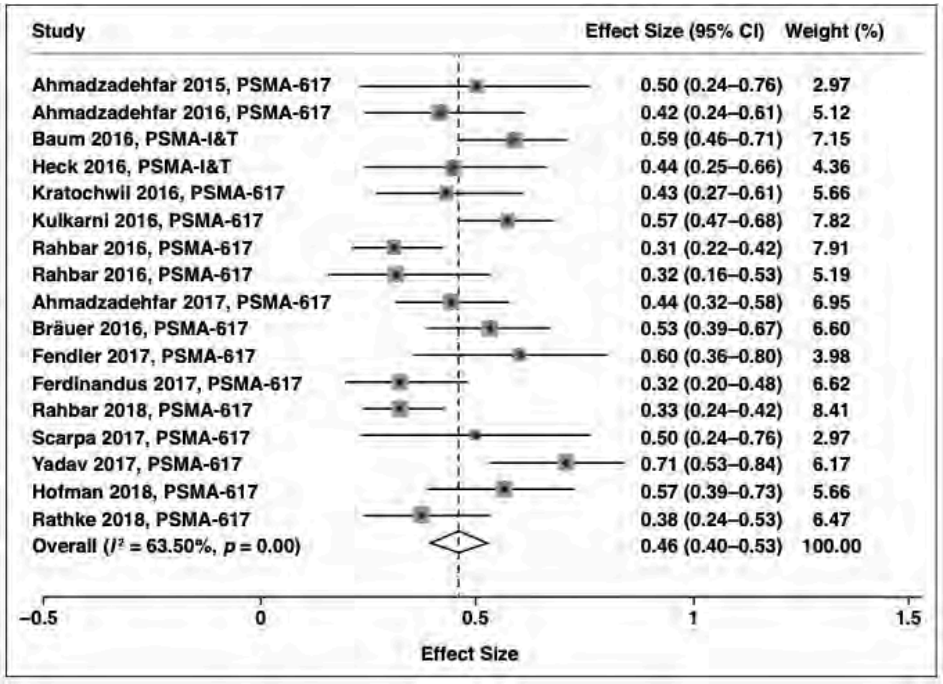
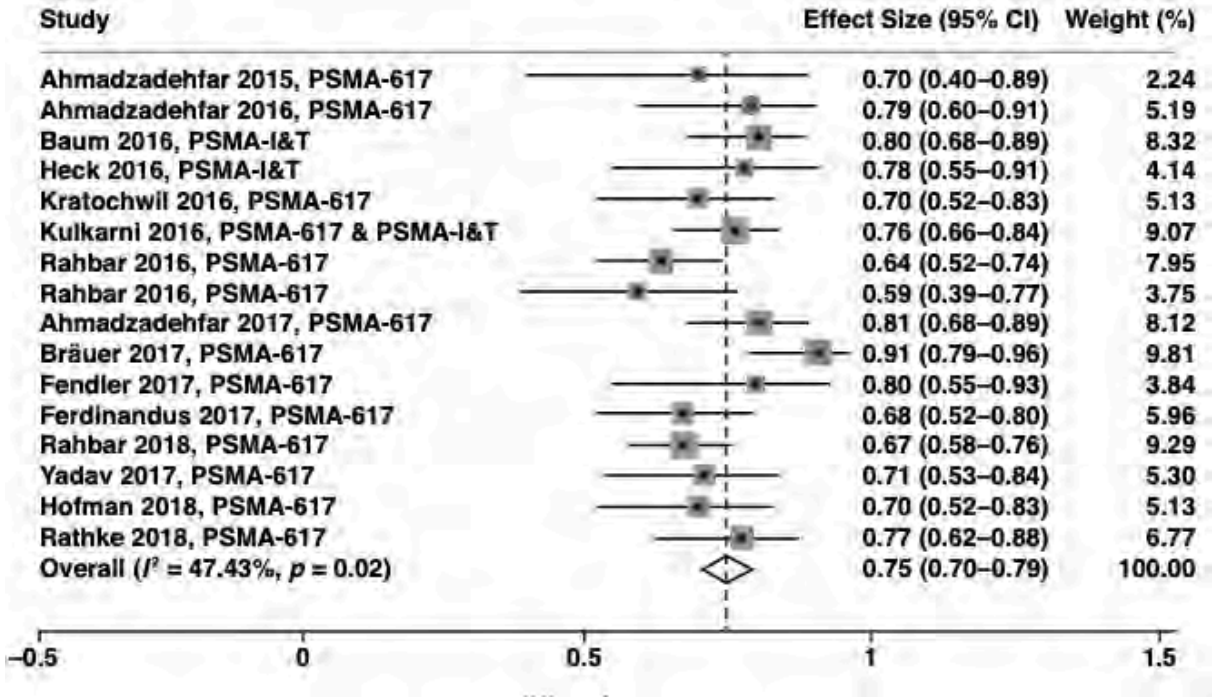
AJR FOCUS ON:

Radioligand Therapy With ^{177}Lu-PSMA for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

17 articulos
704 pacientes

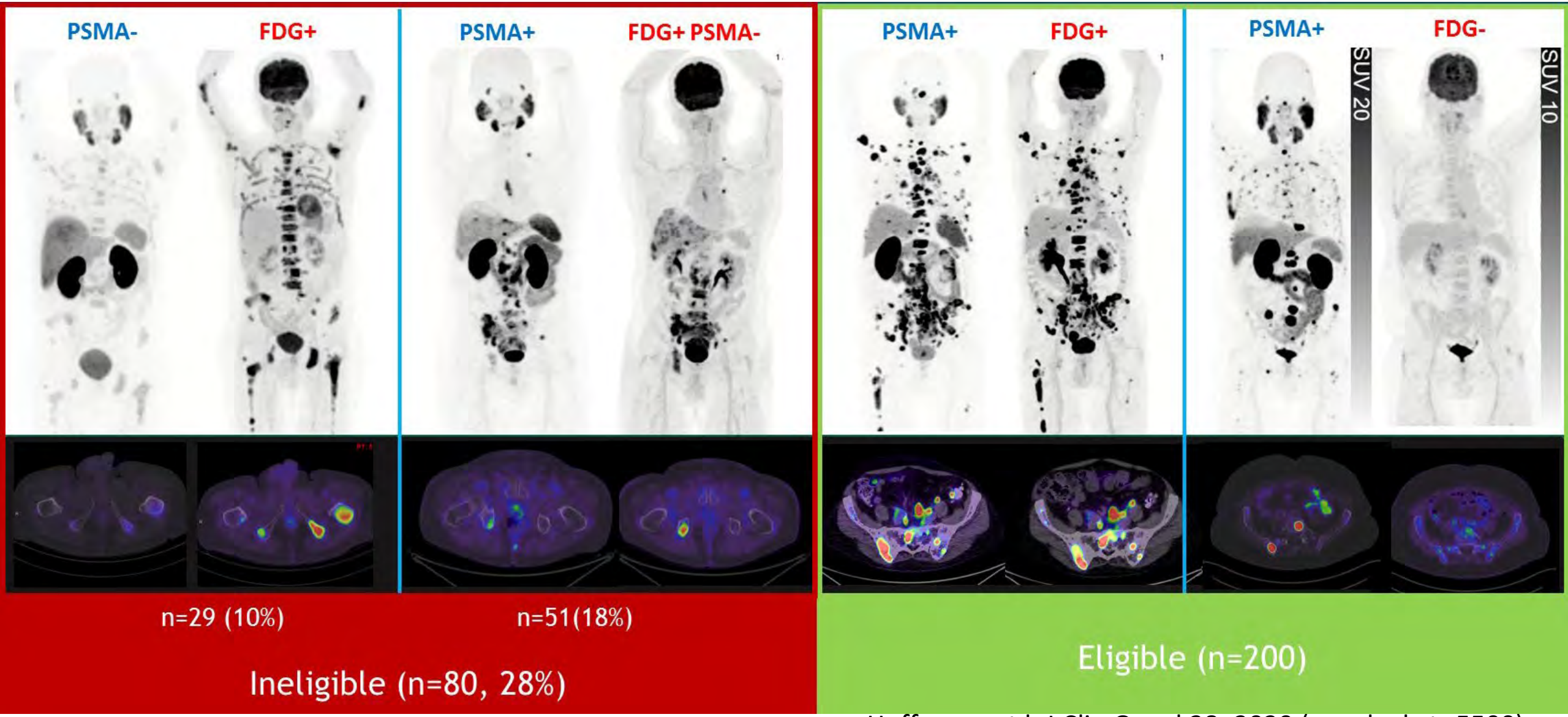




Reduction > 50% PSA 46%

Any PSA Reduction 75%

AJR 2019; 213:275–285



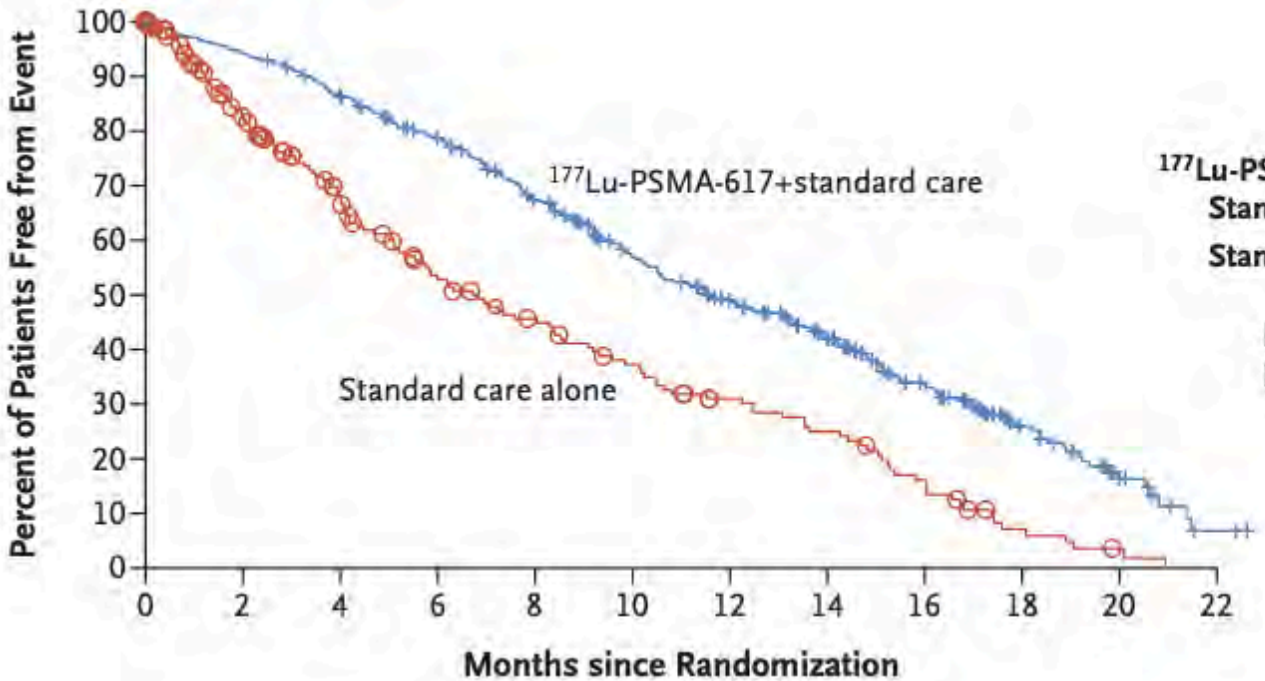
Hoffmann et l. J Clin Oncol 38: 2020 (suppl; abstr 5500)

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

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

831 pacientes

C Time to First Symptomatic Skeletal Event



	No. of Events/ No. of Patients	Median mo	n
^{177}Lu-PSMA-617+ Standard Care	256/385	11.5	
Standard Care Alone	137/196	6.8	

Hazard ratio, 0.50 (95% CI, 0.40–0.62)
P<0.001

N Engl J Med. 2021 Jun 23.

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

N Engl J Med. 2021 Jun 23.

Re-treatment

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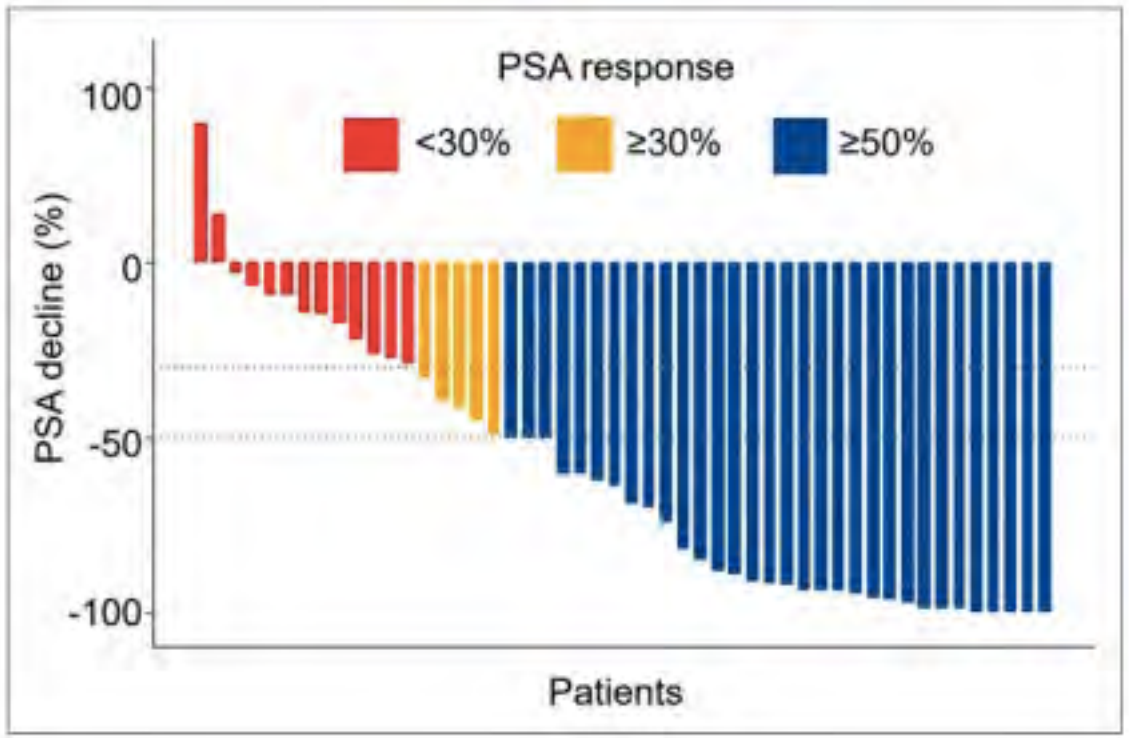
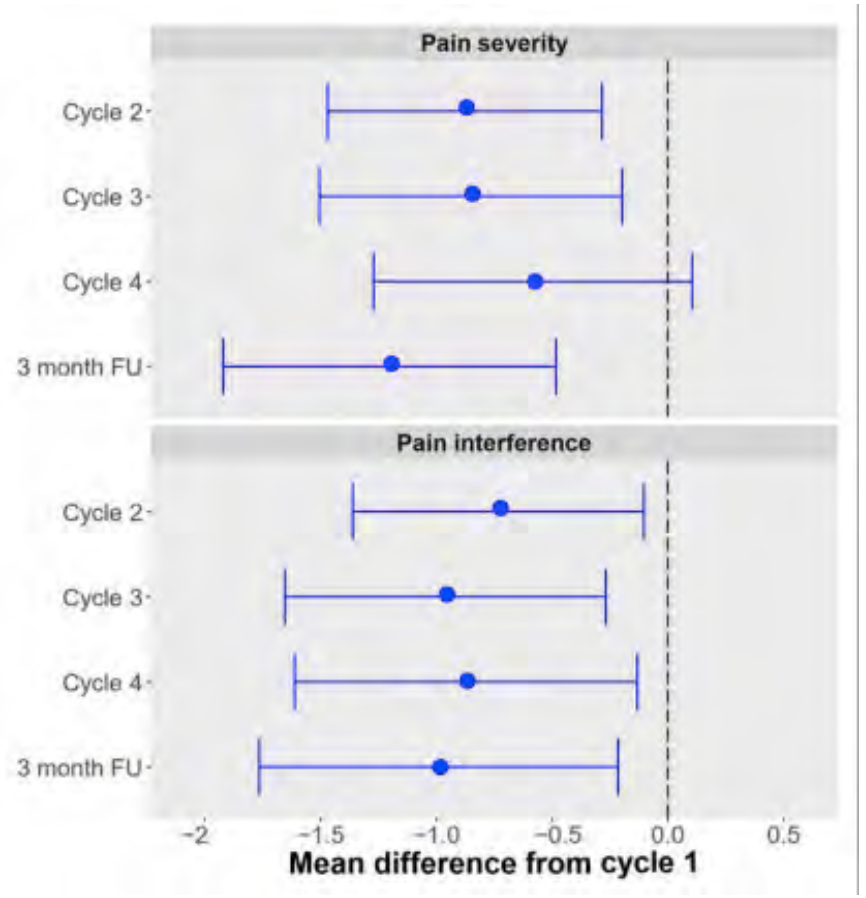
Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of ^{177}Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer

50 Pacientes



64% had a reduction in the PSA > 50%



Violet et al. J Nucl Med 2020; 61:857–865

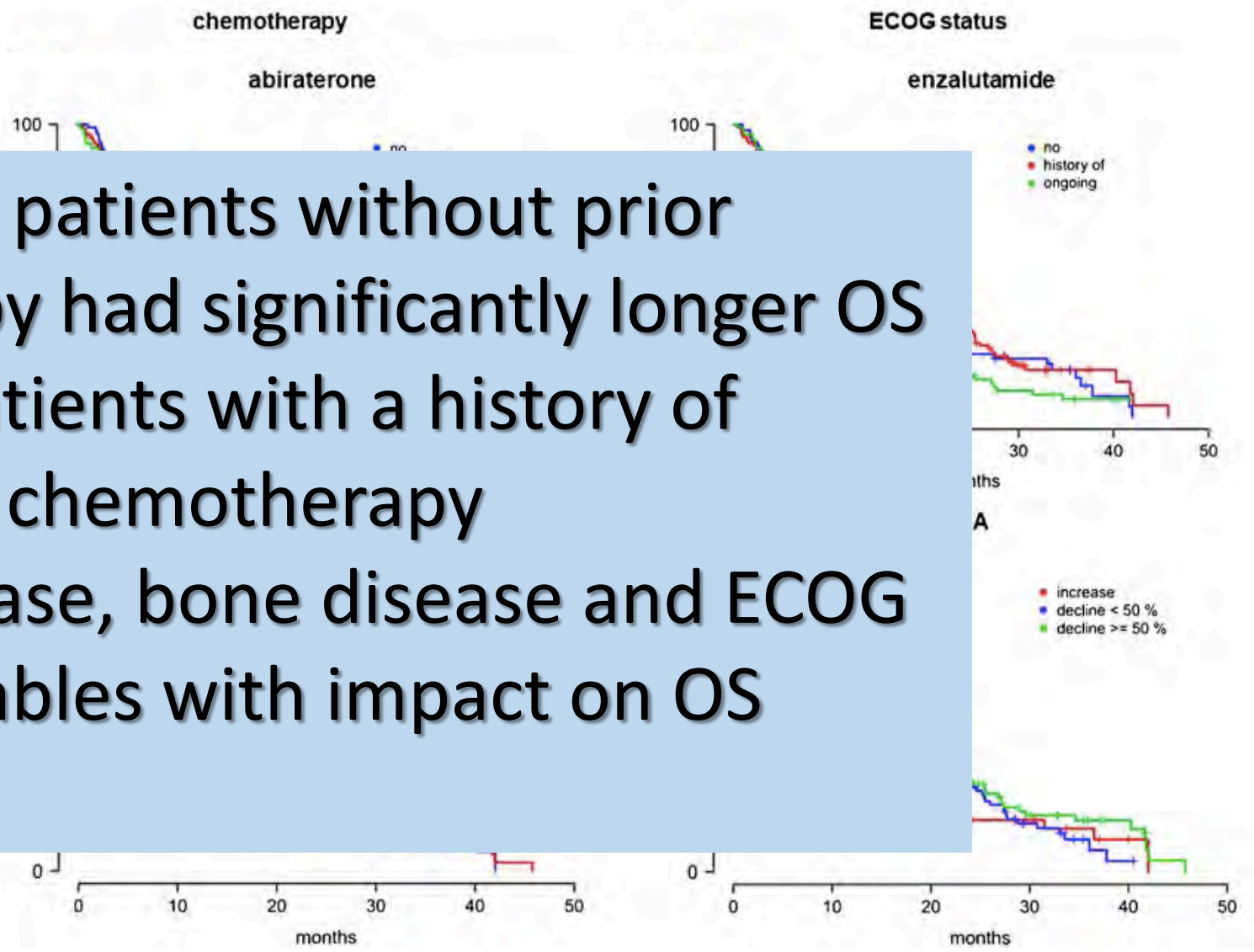
Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with [^{177}Lu] Lu-PSMA-617. A WARMTH multicenter study (the 617 trial)

Hojjat Ahmadzadehfar[1,2] · Kambiz Rahbar[3] · Richard P. Baum[4] · Robert Seifert[3] · Katharina Kessel[3] · Martin Bögemann[5] · Harshad R Kulkarni[4] · Jingjing Zhang[4] · Hendrik Rathke[7] · Harun Ilhan[8] · Johanna Maffey-Steffan[9] · Francisco Osvaldo Garcia-Perez[12] · Kalevi Kairemo[13] · Masha

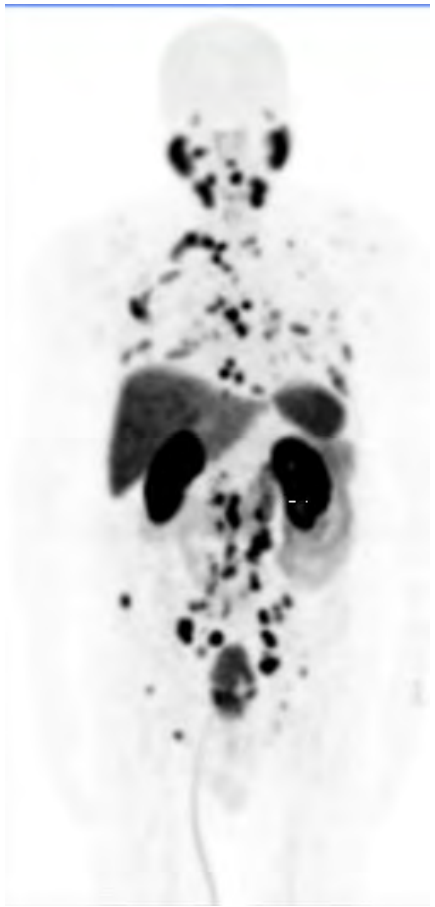
631 metastatic

mCRPC patients without prior chemotherapy had significantly longer OS than patients with a history of chemotherapy

Visceral disease, bone disease and ECOG are variables with impact on OS



Eur J Nucl Med Mol Imaging. 2021 Jan;48(1):113-122.



July 2017
PSA 782 ng/l

Sep 2017
PSA 71 ng/l

Nov 2017
PSA 0.64 ng/l

Jun 2018
PSA 0.07 ng/l

May 2018
PSA 0.04 ng/l

Eur J Nucl Med Mol Imaging. 2019 Jan;46(1):129-138.

Future

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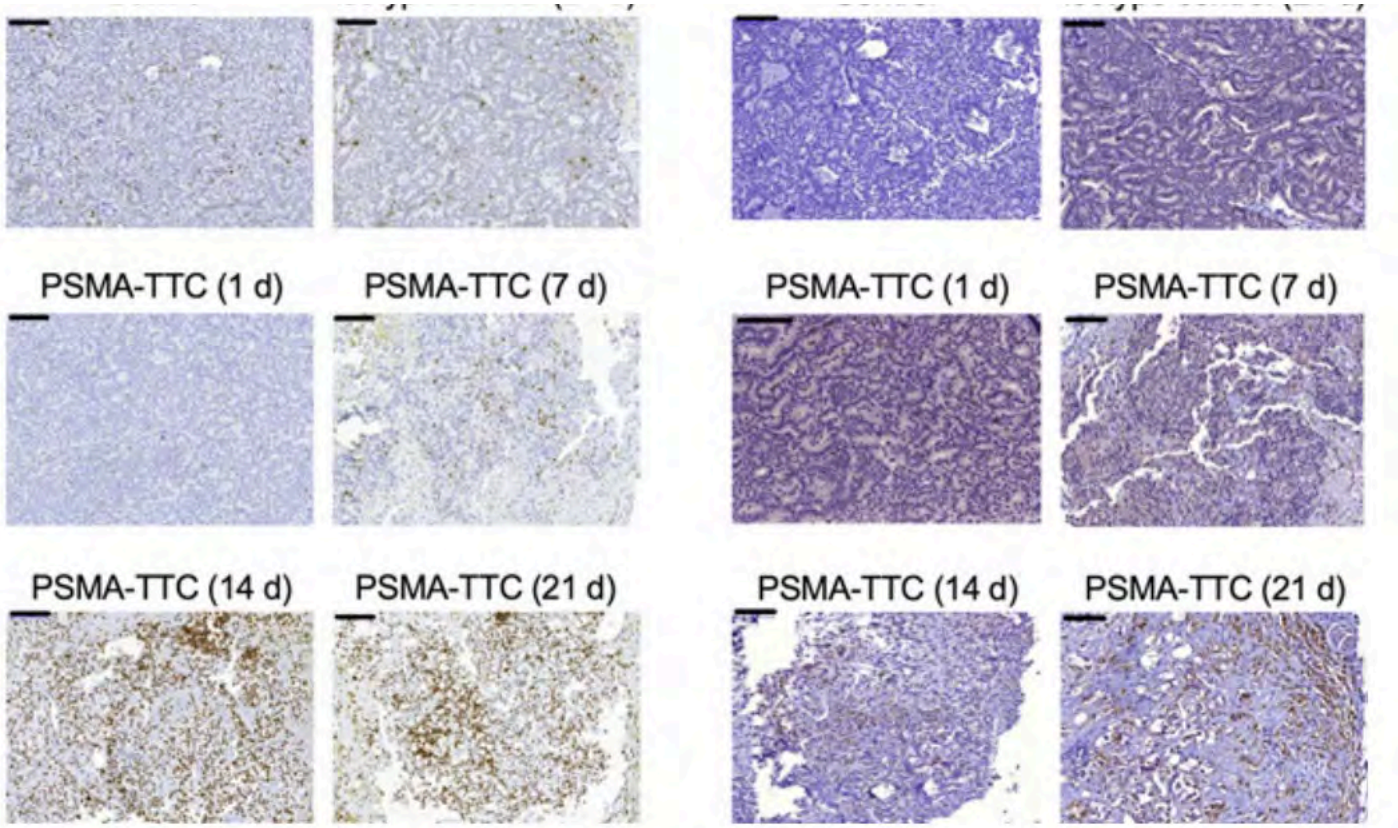
Preclinical Efficacy of a PSMA-Targeted Thorium-227 Conjugate (PSMA-TTC), a Targeted Alpha Therapy for Prostate Cancer AC

γHA2X

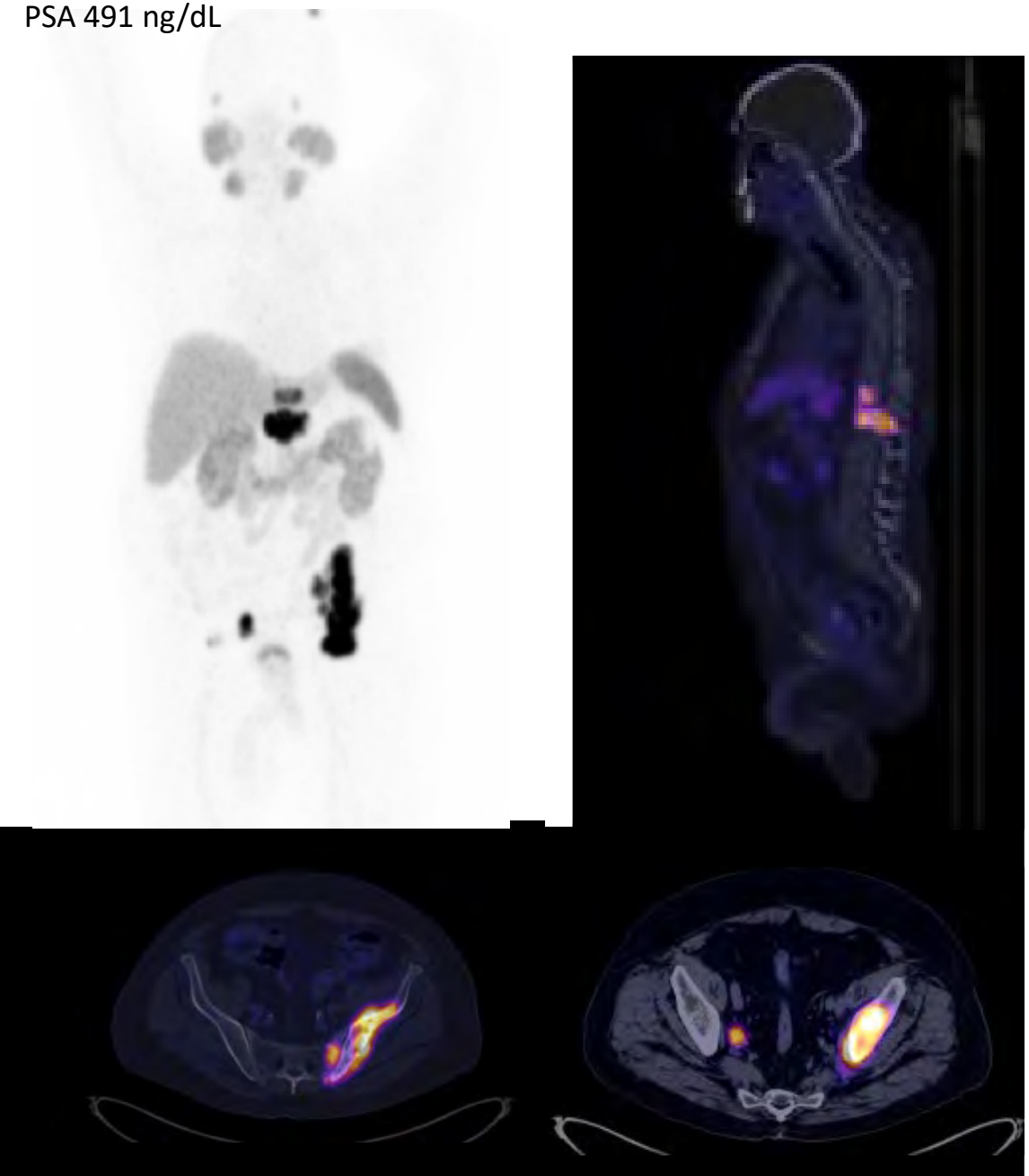
Caspasa



Hammer et al Clin Cancer Res 2020;26:1985–96

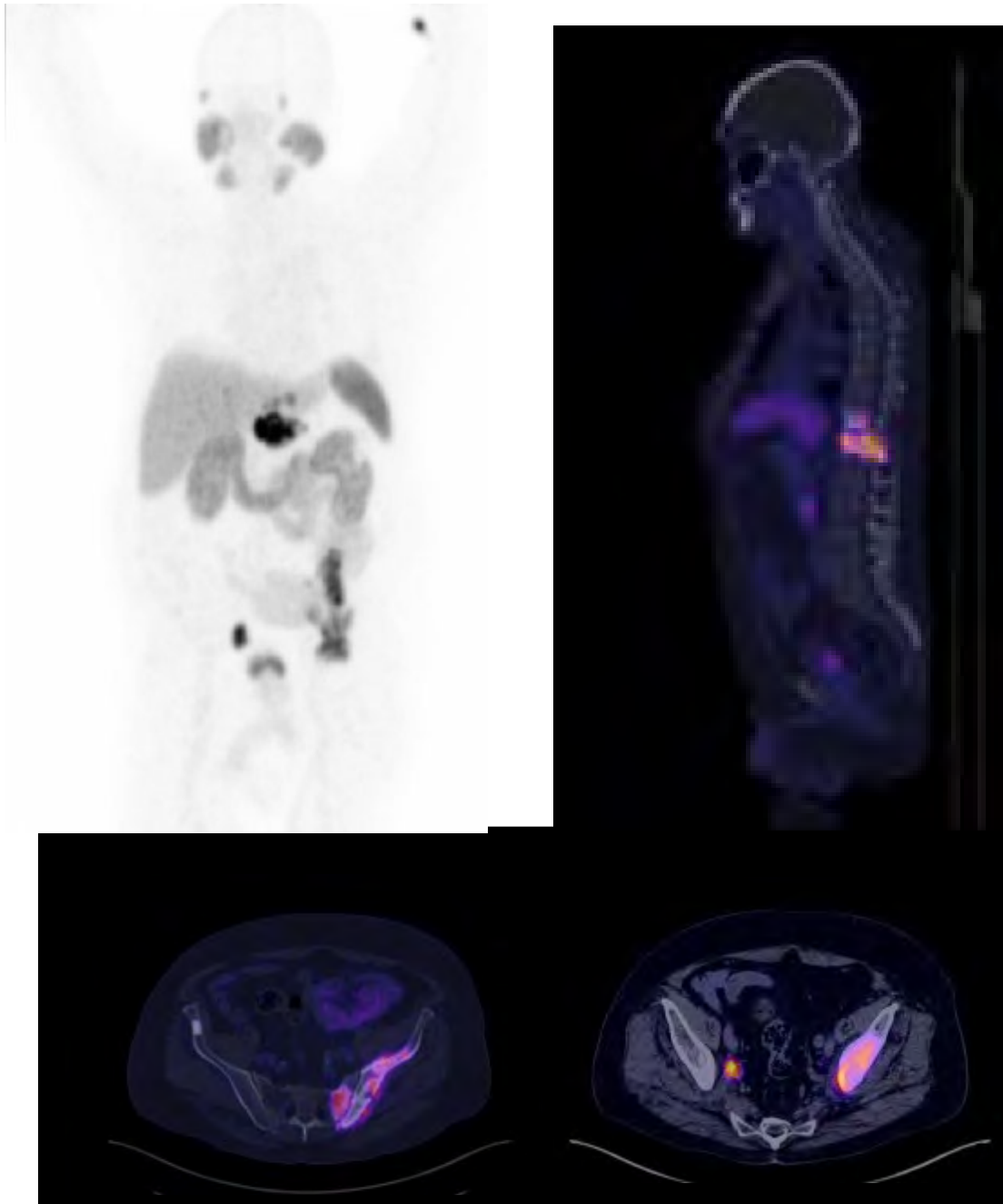
Patient 1

68 Ga PSMA-11
PSA 491 ng/dL



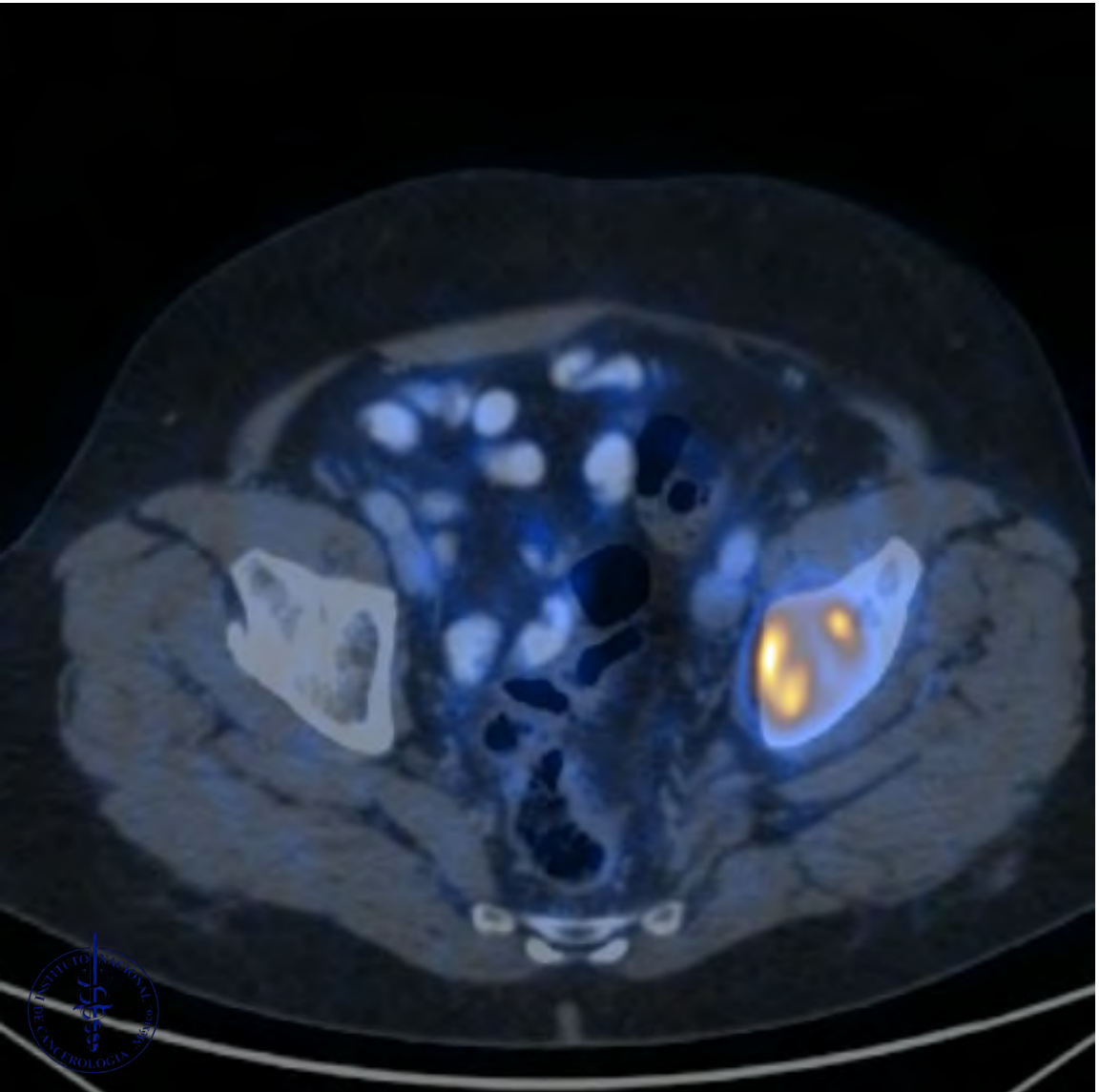
4 cycles 177 Lu iPSMA

68 Ga PSMA 11
PSA 19.4 ng/dL



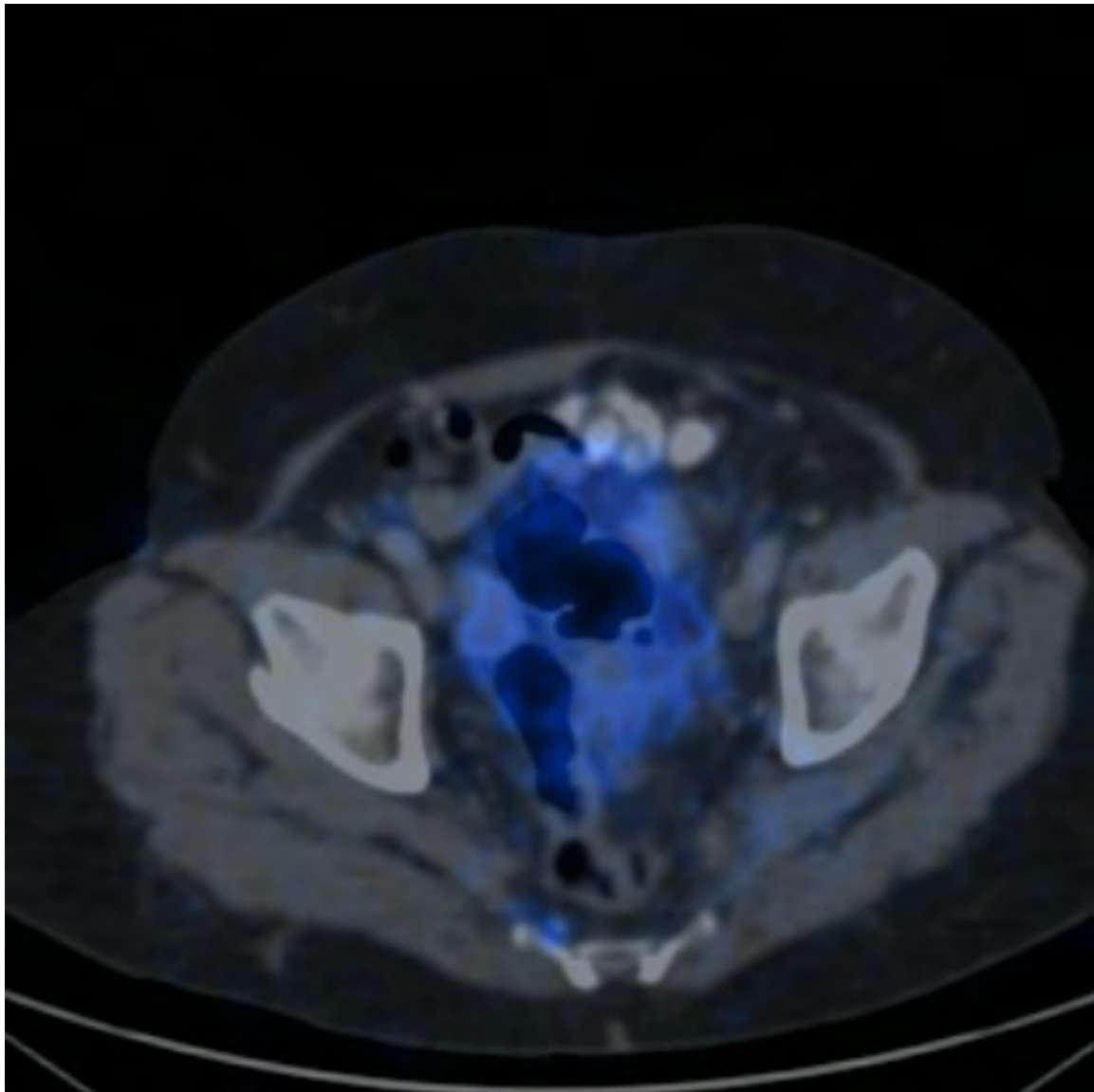
Patient 5

68 Ga PSMA-11
PSA 194 ng/dL



4 cycles 177 Lu iPSMA

18 F PSMA 1007
PSA 21.6 ng/dL



Theranostics: Future of the PSMA

last line to first line

Trial	Summary	Men with	Funded by	Investigator	Commenced
PRINCE	Lu-PSMA + **immunotherapy** (pembroluzimab)	mCRPC	VCA	Sandhu Hofman	Jun 2019
LuPARP	Lu-PSMA + **PARPi** (olaparib)	mCRPC	PCF	Sandhu Hofman	Jun 2019
ENZA-P	Lu-PSMA vs Lu-PSMA + **enzalutamide**	mCRPC	Movember	Emmett	soon
UpFront PSMA	Lu-PSMA followed by chemotherapy (docetaxel) vs. chemotherapy alone	**mCSPC**	Movember DoD	Azad Hofman	Apr 2020
LuTectomy	Lu-PSMA prior to prostatectomy	**High-risk localised PC**	Movember	Hofman Violet Murphy	Jun 2020

Conclusions

- Previous chemotherapies do not impact response significantly
- DHL decrease in PSA prognostic factors >> therapy with 177-Lu
- Use of biomarkers to improve efficiency
- Total tumour burden
- Potential re-treatment
- Patients with diffuse infiltration
- Resistance to 177-Lu >> considere Alphas
- Ac-225 promising results
- New Alpha emmiters
- Other theranostic options

TC Principles

- Respond to Member States' needs
- Contribute to development goals
- Peaceful use undertaking
- Safety
- Shared responsibility
- Non-discrimination
- Transparency
- Partnership building

A Shared Responsibility

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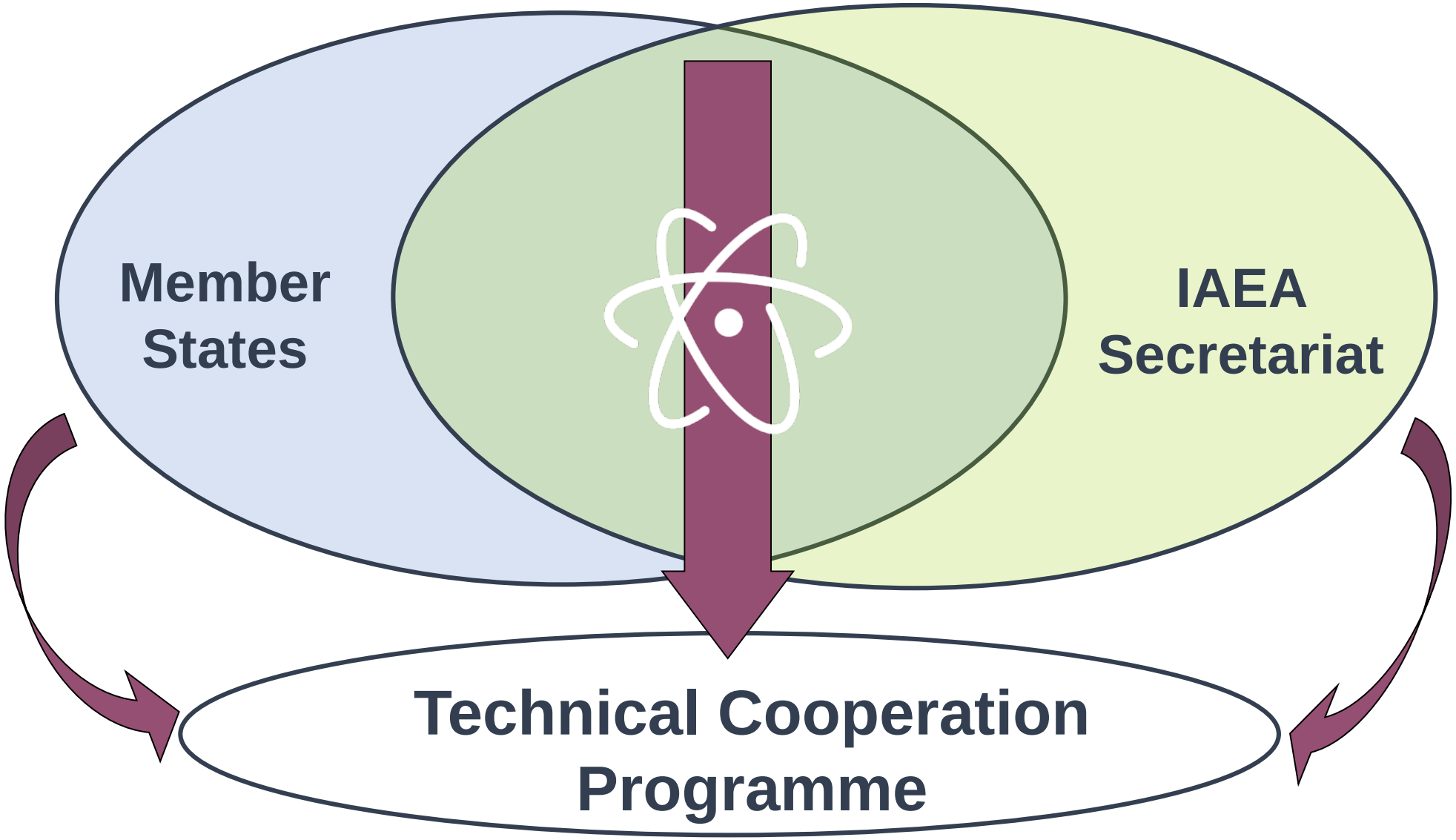




Member States' role

- Set policy framework
- Guide TC activities
- Fund TC programme
- Define national and regional priorities
- Participate in and benefit from the TC programme
- Offer training and technical support to other Member States

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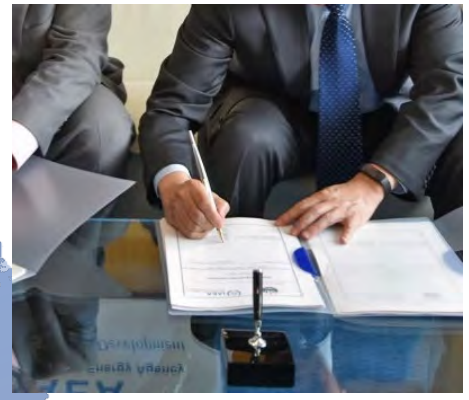
Alignment with Member States' priorities

- Country Programme Framework (CPF)
  - Identify national priorities
  - Link TC programme with national development plans

- Other important planning input
  - Regional agreements
  - United Nations Development Assistance Framework (UNDAF)



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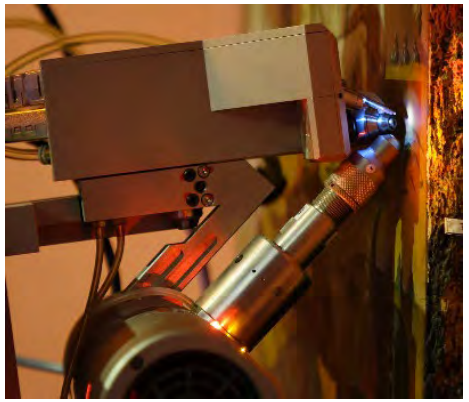

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