Theranostics in Precision Oncology

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USC Norris Comprehensive Cancer Center

Part of the Keck School of Medicine of USC

USC University of Southern California

Disclosures:

- Investigator
  - NIH
  - Ming Hsieh Institute
- Advisory Board
  - Lantheus
  - Pharmalogic
- Consultant
  - Bayer
  - Siemens
- Speaker’s Bureau
  - Blue Earth Diagnostics
  - Lantheus

Outline

- Theranostics (definition & goal)
- **FRONTIERLAND**
  - Radioiodine (thyroid cancer)
  - SSTR (NET)
  - PSMA (prostate cancer)
- **TOMORROWLAND**
  - FAP (pan-cancer)
  - CXCR4 (lymphoma/myeloma)
  - GRPR (prostate cancer)

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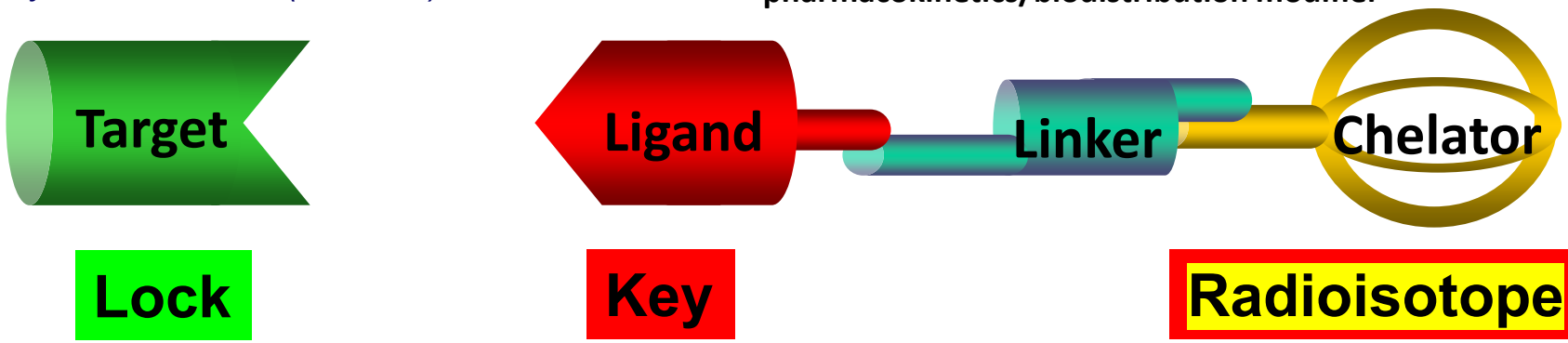
THERANOSTICS
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Schematic Representation of an Agent for Imaging and Targeted Therapy

Courtesy Helmut Mäcke (modified)



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, ^{89}Zr
- Gd^{3+}

Cytotoxic Unit

- ^{177}Lu, ^{90}Y, ^{67}Cu ^{225}Ac, ^{212}Pb, ^{227}Th
- ^{213}Bi, ^{211}At

nature communications

Article

https://doi.org/10.1038/s41467-024-55291-x

The *Theranostic Genome*

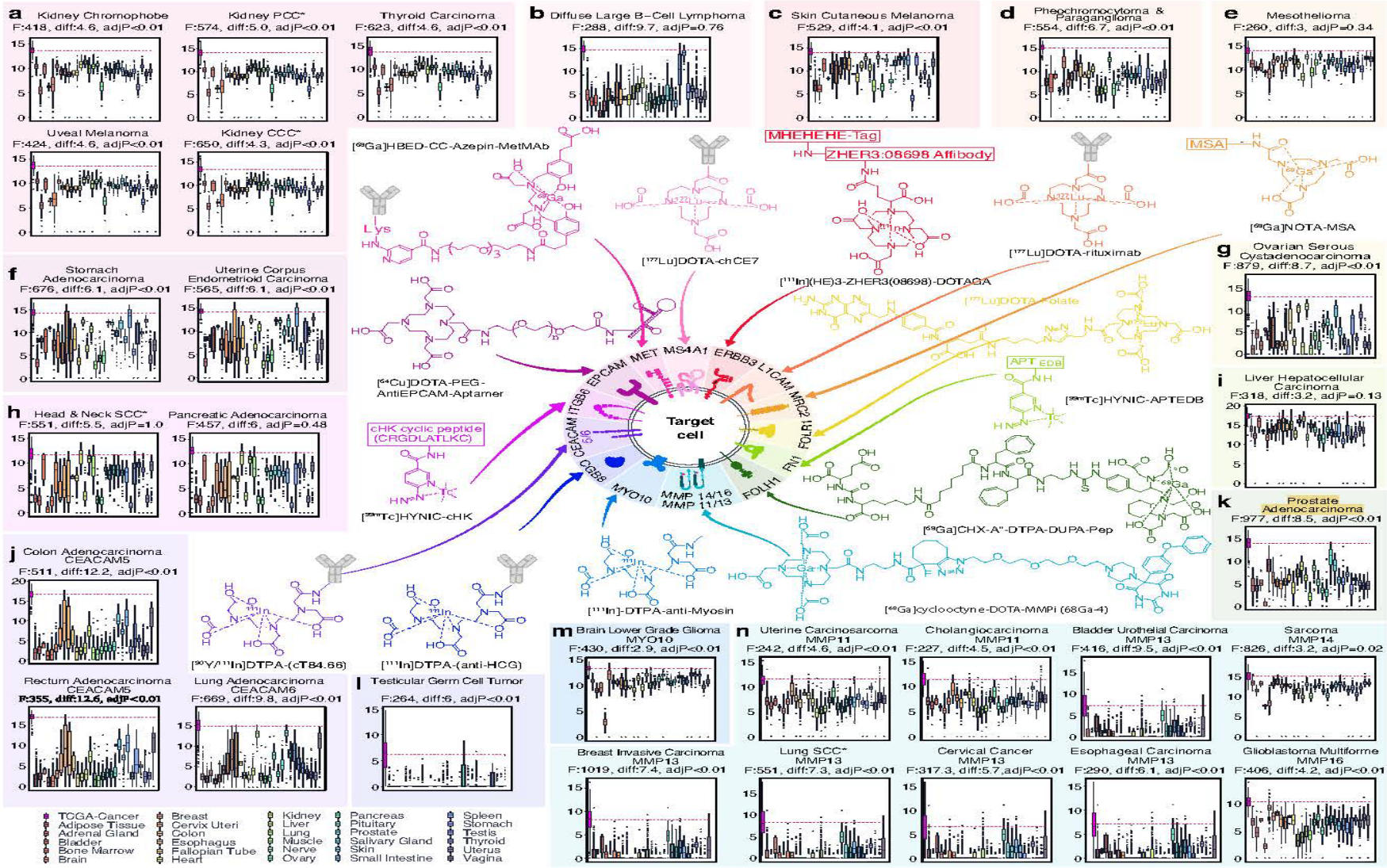
Received: 25 January 2024

Accepted: 5 December 2024

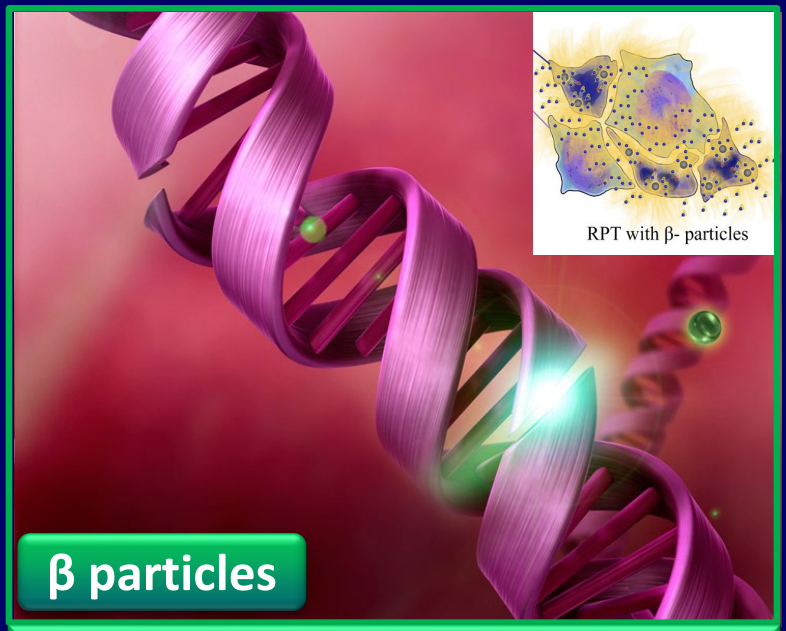
Xiaoying Xu[1,8], Pablo Jané[2,3,8], Vincent Taelman[1,8], Eduardo Jané[4], Rebecca A. Dumont[1], Yonathan Garama[1], Francisco Kim[1], María del Val Gómez[5], Karim Gariani[6] & Martin A. Walter[1,7]

Applicability of Theranostic Genome to Human Cancers

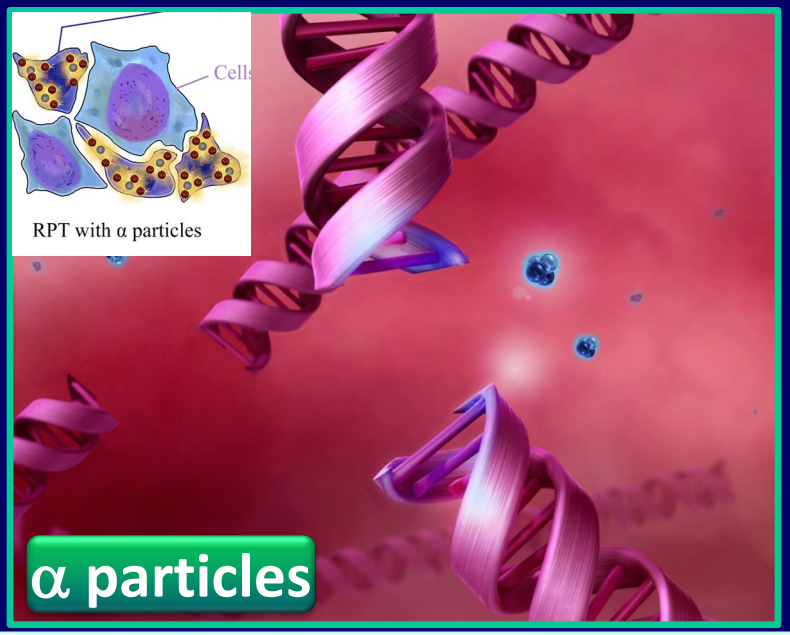
(cross-ref PubMed, MICAD, TCGA, GEO databases; 0.4% genome; 1.3% protein-coding genome)



Particle Radiation Effects on DNA



- **Long range:** ≤ 12 mm; "e-"
- Traverses ~30 cells
- 98% speed of light
- **Low-LET** (~0.2 keV/um)
- **Single-strand DNA breaks**
- DNA breaks easily repaired
- Suited for medium-large tumors



- **Short range:** 50-100 μm; "He (2p,2n)"
- Traverses ~2-5 cells
- 6% of speed of light
- **High-LET** (80 keV/um)
- **Double-strand DNA breaks**
- DNA breaks difficult to repair, lethal
- Suited for small tumors, micromets

Kassis, Semin Nucl Med 2008; Ritter, Nature 1977; Sedlack, Radiographics 2024

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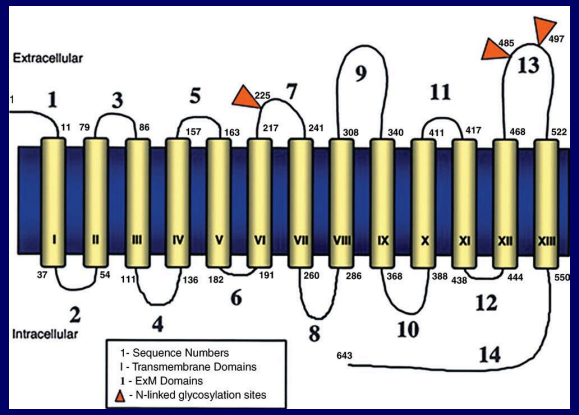
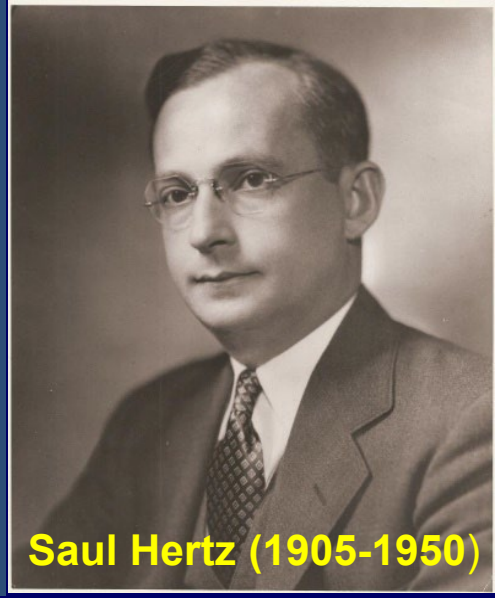
Radiotheranostics

Radioiodine



Harvard Medical School – Vanderbilt Hall

Saul Hertz spontaneously posed the seminal question that launched the RAI research.



Saul Hertz (1905-1950)

- Radioiodine as classic radiotheranostic agent (*NaI symporter*)
- *Saul Hertz* at MGH performed first radioiodine (^{130}I, $t_{1/2}$=12h) Rx in thyrotoxicosis in 1941
- *S.M. Seidlin* performed first radioiodine Rx in thyroid CA in 1946
- First experience with radioiodine Rx published in *J Clin Invest* in 1942
- SNMMI celebrated 75th anniversary of 1st therapeutic use of radioiodine in 2016
- SNMMI Therapy COE established Saul Hertz award

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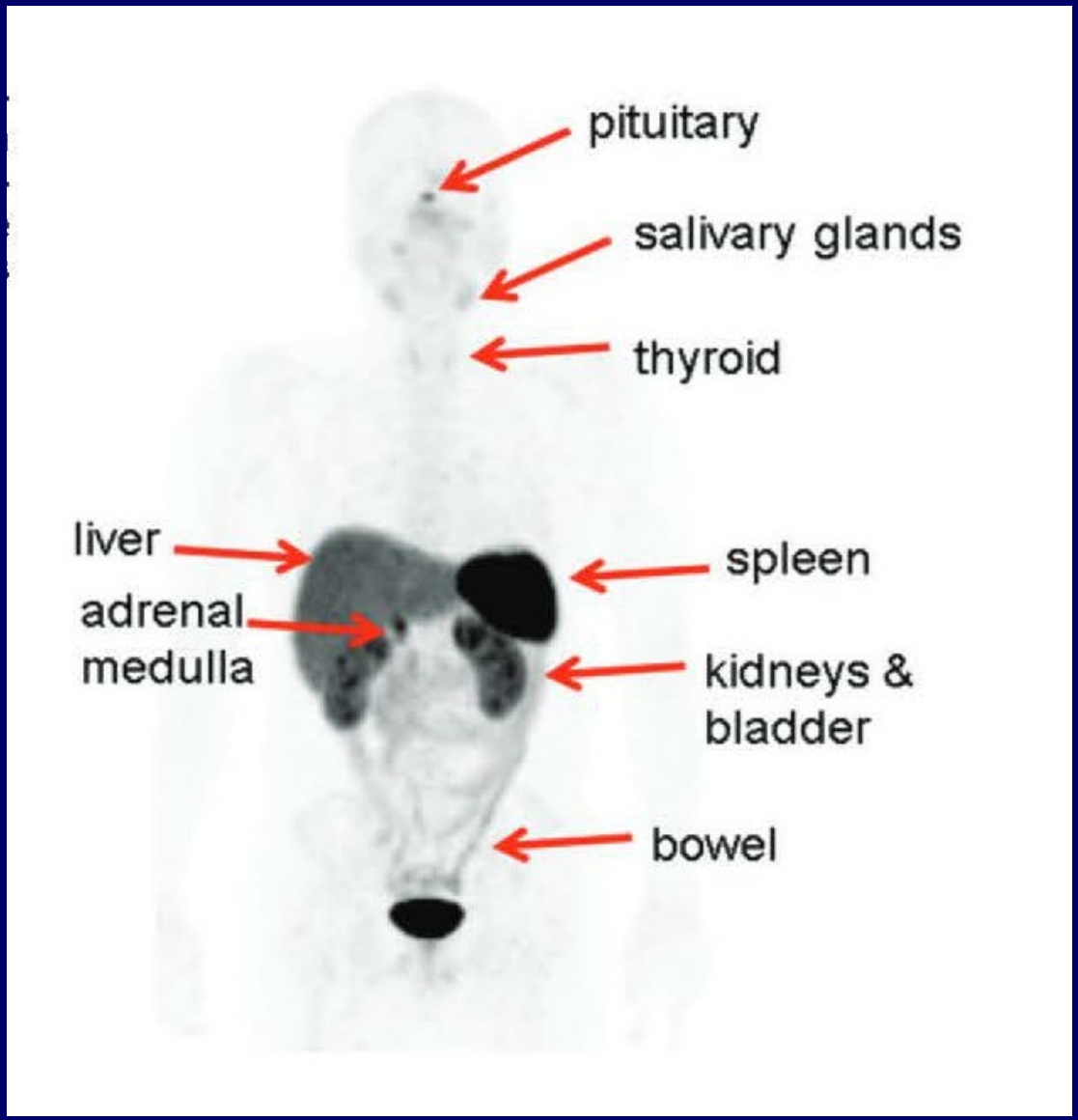
Normal Biodistribution of ^{68}Ga-DOTATATE

Hofman MS et al. Radiographics 2015



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The NEW ENGLAND JOURNAL of MEDICINE

NETTER-1

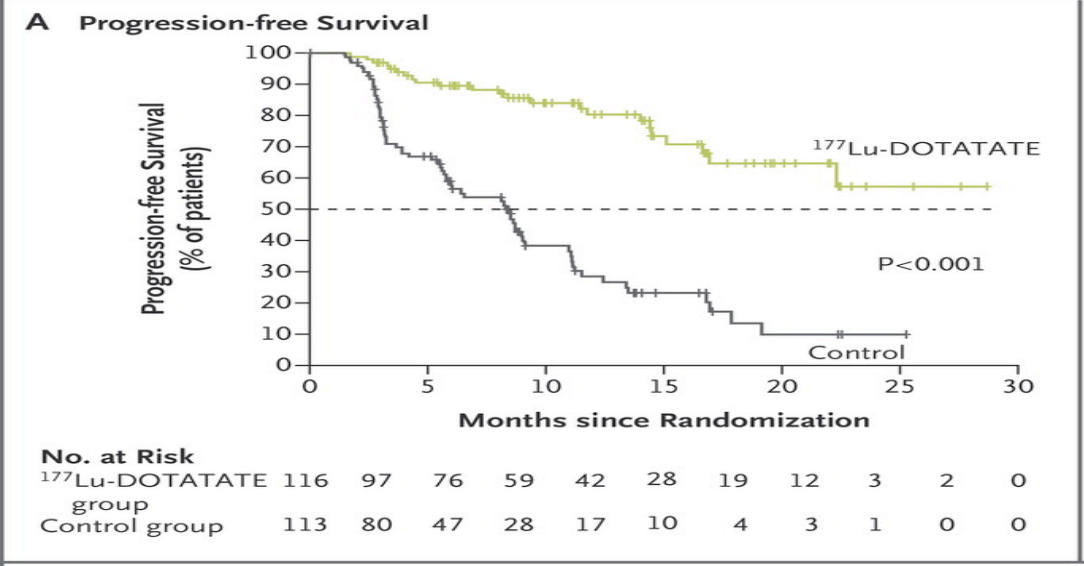
ORIGINAL ARTICLE

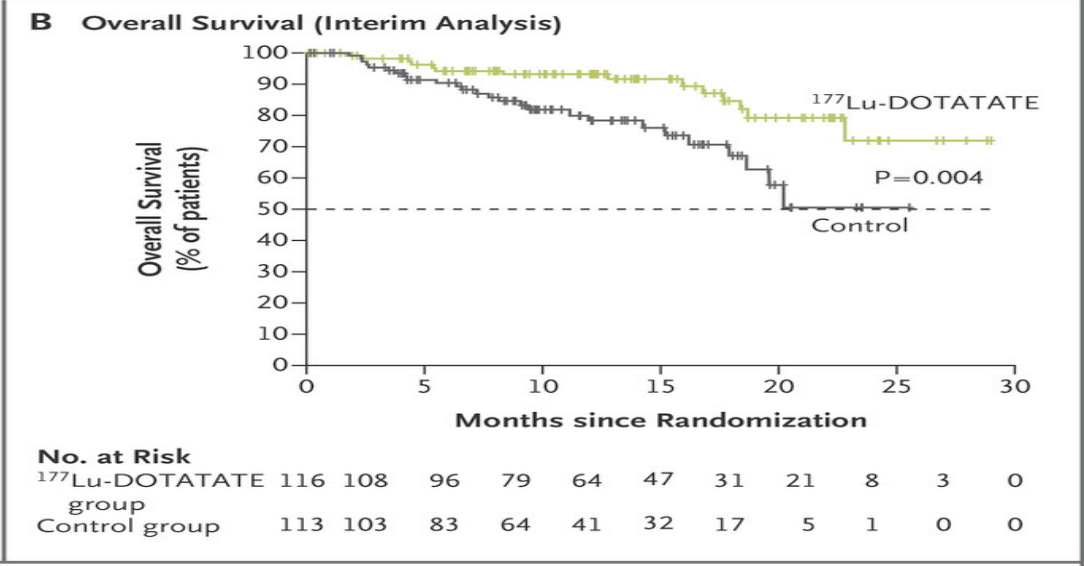
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

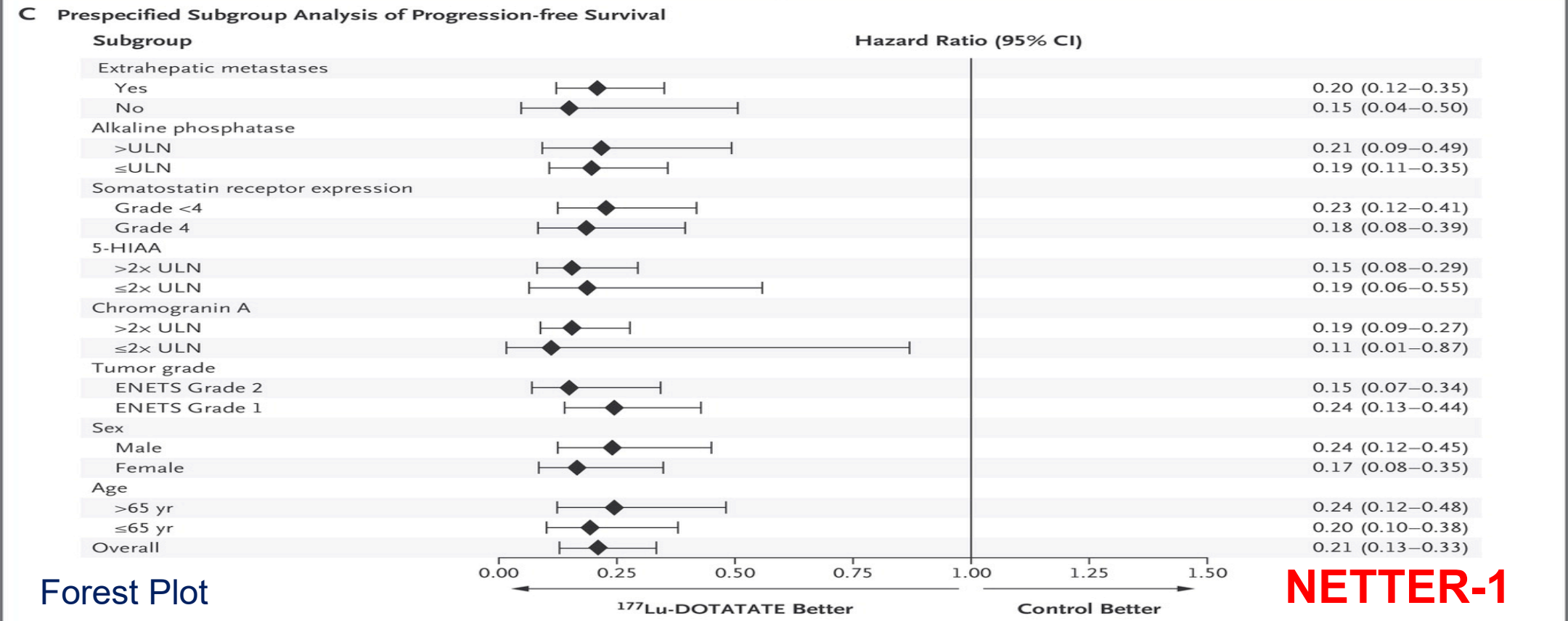
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

2017 ABSTRACT NCT01578239

- n=229 with WD (Ki67<20%) inoperable, metastatic or progressive (on octreotide LAR 20-30 mg q3-4w for >12 wks) midgut NET randomly assigned
  - n=116 LuTATE 7.4GBq IV q8 weeks x 4 + BSC (IV octreotide LAR 30 mg)
  - n=113 BSC (IV octreotide LAR 60 mg q4 weeks)
  - Primary outcome: PFS
  - Secondary outcome: OS, ORR, safety, adverse events







Forest Plot

NETTER-1

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

NETTER-2

2024

Neuroendocrine/Carcinoid | January 22, 2024

[^{177}Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: Primary analysis of the phase 3 randomized NETTER-2 study.

Authors: Simron Singh, Daniel M. Halperin, Sten Myrehaug, Ken Herrmann, Marianne Pavel, Pamela L. Kunz, Beth Chasen, Jaume Capdevila, Salvatore Tafuto, Do-Youn Oh, Changhoon Yoo, Stephen Falk, Thorvardur Ragnar Halfdanarson, Ilya Folitar, Yufen Zhang, Paola Santoro, Paola Aimone, Wouter W. de Herder, and Diego Ferone SHOW FEWER | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 3_suppl
https://doi.org/10.1200/JCO.2024.42.3_suppl.LBA588

NCT03972488

- G2/3 (Ki67 10%-55%; G3 tumors 35%)
- 1L Rx; n=226 randomization 2:1 (primary outcome: PFS)
- LuTATAE arm (n=151): 4 cycles IV LuTATE 7.4 GBq + 30 mg octreotide LAR q8wks, then q4Wks post-LuTATE
- Control arm (n=75): 60 mg octreotide LAR q4wks
- PFS: 22.8 m vs. 8.5 m (gain of 14.3 m in LuTATE arm)
- BM AE in 3 pts, MDS in 1 pt (LuTATE arm)

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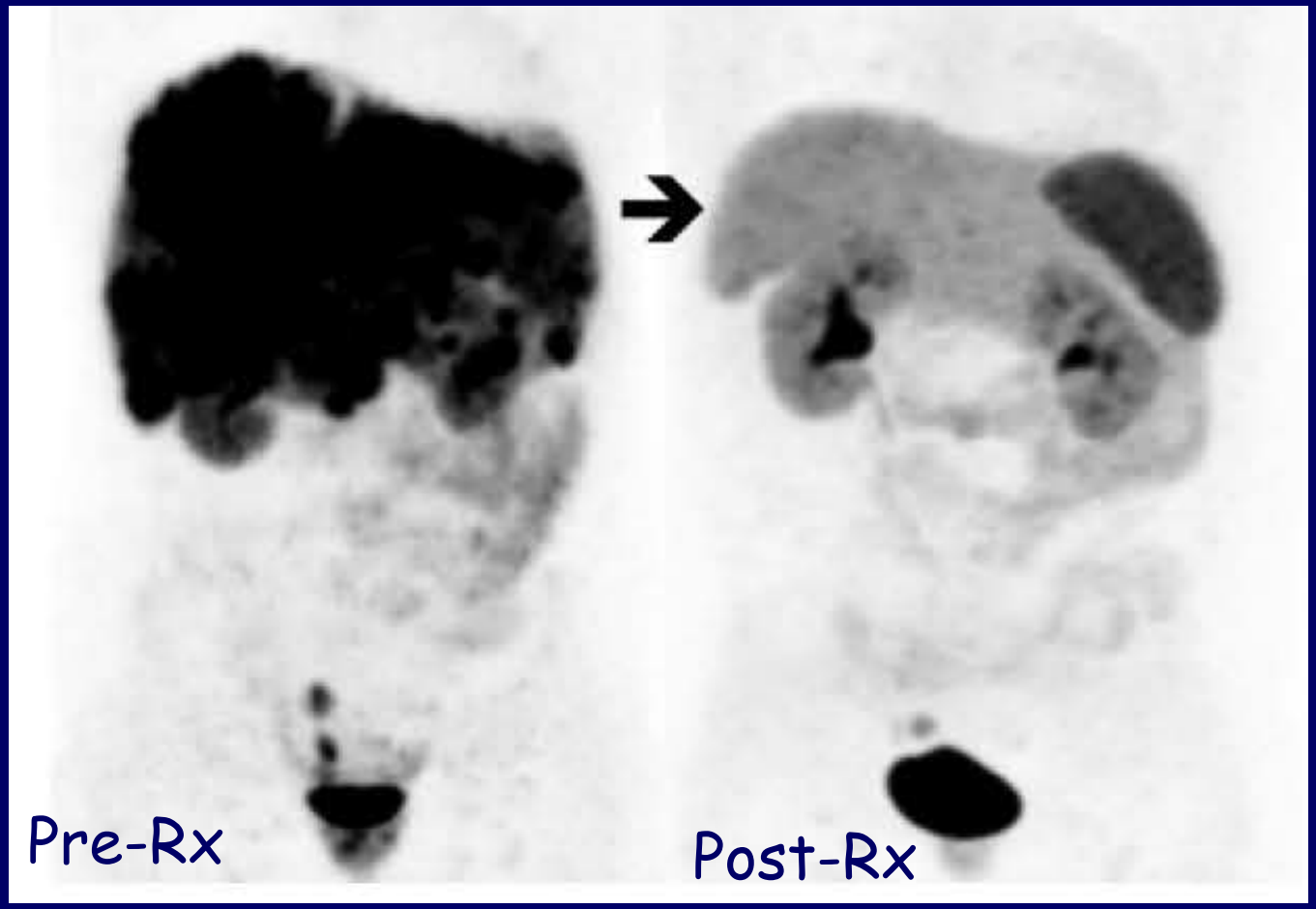
Metastatic Rectal NET

Hofman, Radiographics 2015



Pre- and Post 4 cycles of ^{177}Lu-DOTA-octreotate + 5FU

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USC Theranostics Center

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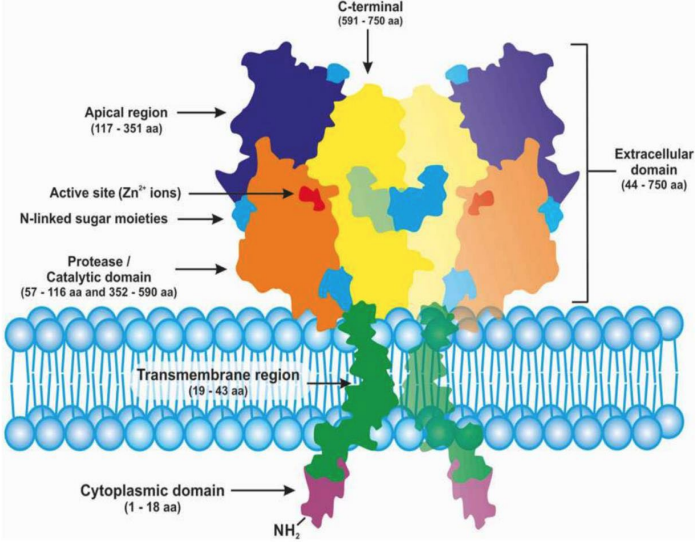
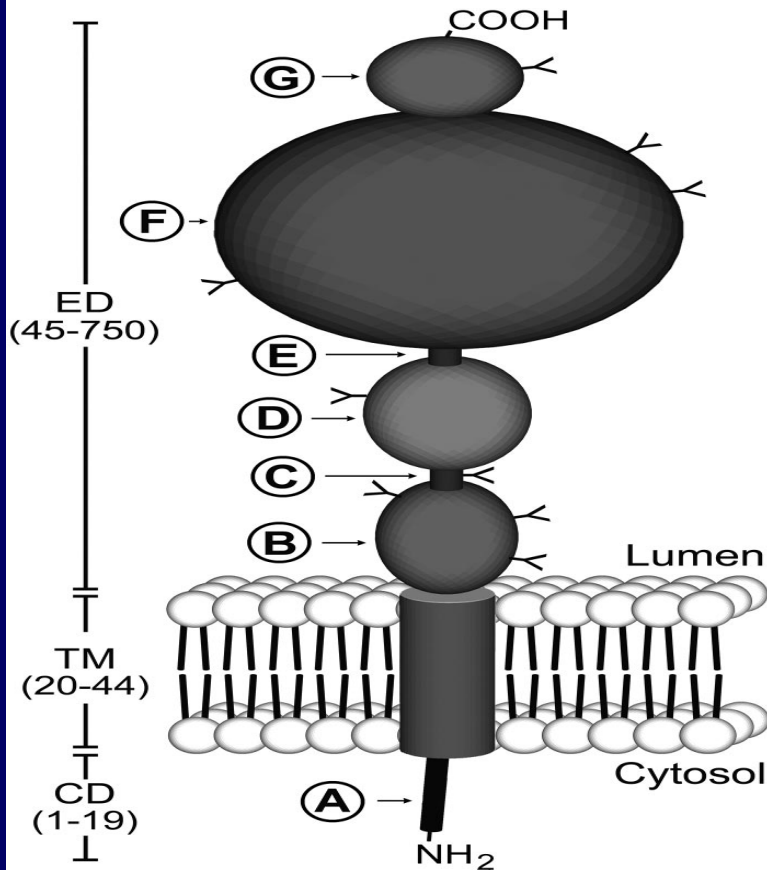
PSMA

Prostate-Specific Membrane Antigen

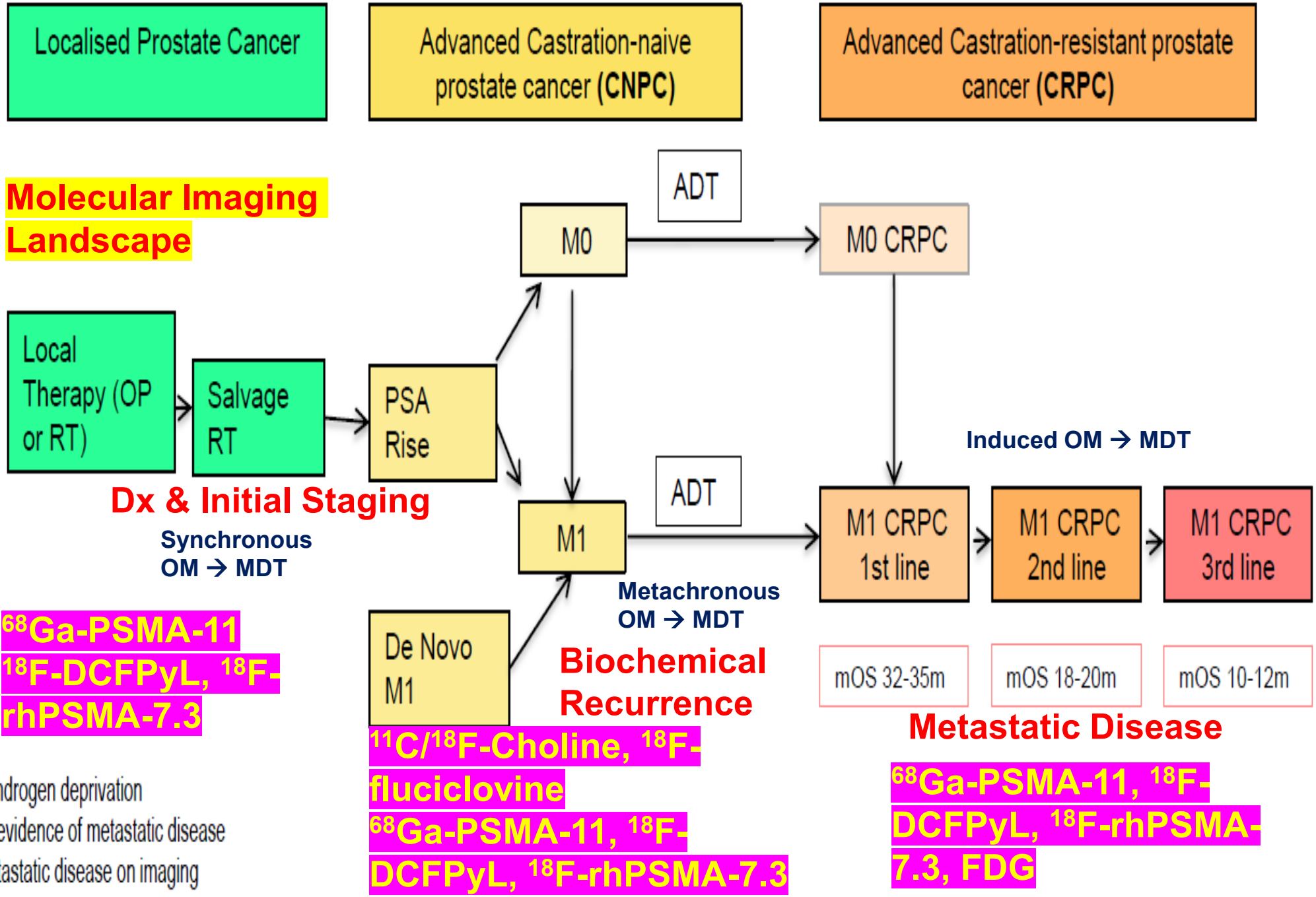
- Neither prostate nor cancer specific
- Type II TM enzyme (glutamate carboxypeptidase II, folate hydrolase 1)
- Secretory cells of prostate epithelium, SB, proximal renal tubule, SG, tumor neovasculature
- Undergoes *internalization* constitutively
- Overexpressed heterogeneously in met. / rec. prostate CA (1000x, ~2M/cell)
- Associated with DNA repair defects
- No expression in 5-10% of prostate CA

O'DriscottC, *Br J Pharm* 2016; Paschalis, *Eur Urol* 2019; Ferraro, *Theranostics* 2020

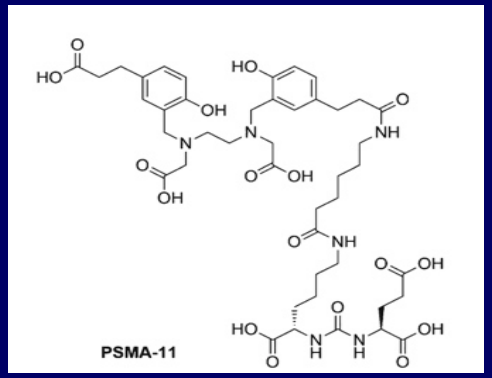


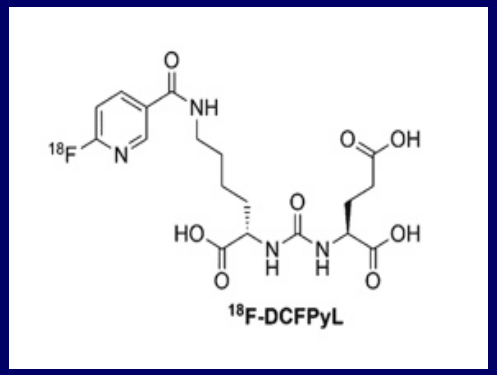


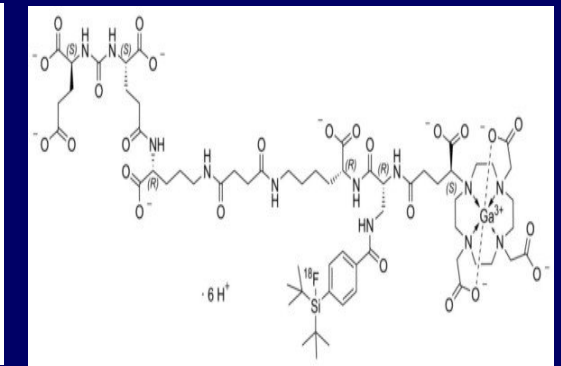
Omlin, 2016 (adapted)

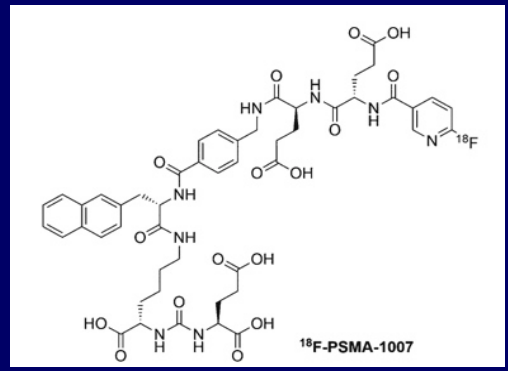


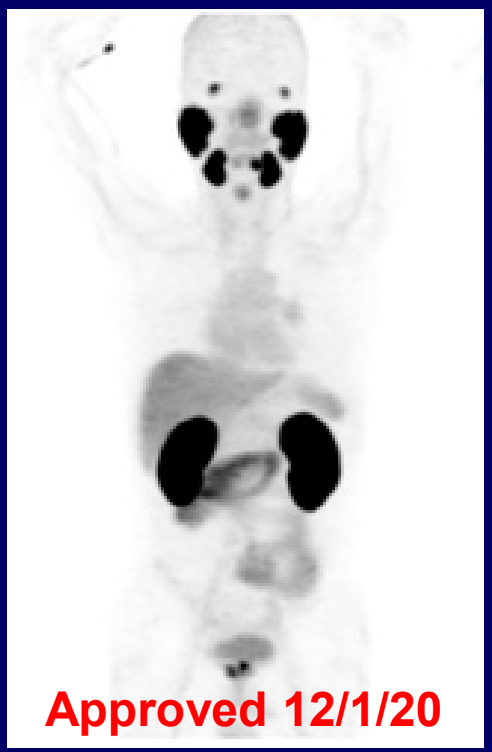
PSMA PET



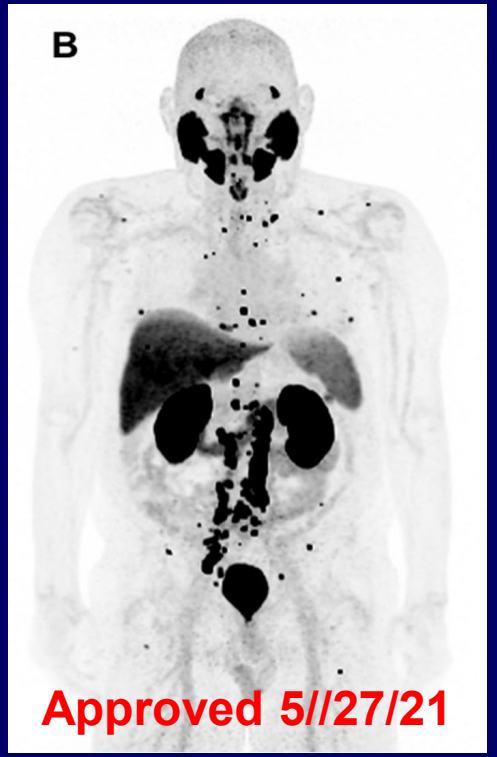




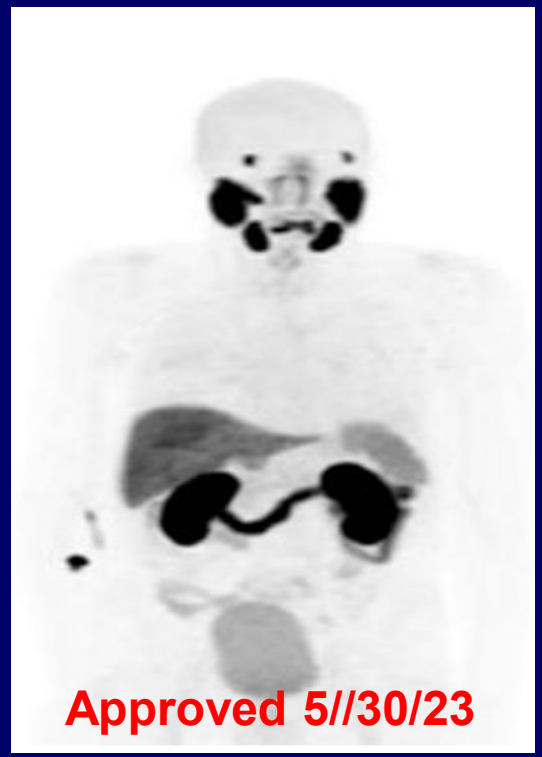




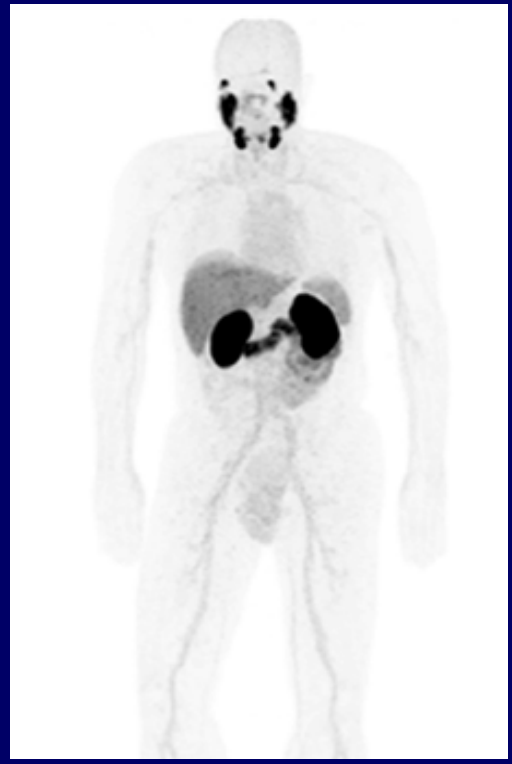
Approved 12/1/20



Approved 5//27/21



Approved 5//30/23



^{68}Ga-PSMA-11 ***(Locametz; Illuccix)***

^{18}F-DCFPyL ***(Pylarify)*** ***(CONDOR, OSPREY)***

^{18}F-rh-PSMA-7.3 (*Posluma*) ***(LIGHTHOUSE, SPOTLIGHT)***

^{18}F-PSMA-1007

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 1.2025 — December 4, 2024

NCCN.org

At this time, the NCCN Guidelines only recommend the currently FDA-approved PSMA agents: F-18 piflufolastat PSMA (also known as F-18 DCFPyL), F-18 flotufolastat PSMA (also known as rh-PSMA-7.3), and Ga-68 PSMA-11. Throughout these Guidelines, "PSMA-PET" refers to any of these FDA-approved PSMA ligands.

- **Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to CT, MRI, and bone scan at both initial staging and BCR, PSMA-PET/CT or PSMA-PET/MRI can serve as a more effective frontline imaging tool for these patients.**

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Jadvar,…..,Hope. J Nucl Med
January 2022

Table 2

Clinical Scenarios for PSMA PET

Scenario no.	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	Posttreatment PSA rise in the mCRPC setting in a patient not being considered for PSMA-targeted radioligand therapy	May be appropriate	5
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

JNM The Journal of NUCLEAR MEDICINE

Stanford

Prospective Evaluation in an Academic Center of ^{18}F-DCFPyL PET/CT in Biochemically Recurrent Prostate Cancer: A Focus on Localizing Disease and Changes in Management

Hong Song, Caitlyn Harrison, Heying Duan, Kip Guja, Negin Hatami, Benjamin Franc, Farshad Moradi, Carina Mari Aparici, Guido Davidzon and Andrei Iagaru

J Nucl Med.
Published online: October 18, 2019.
Doi: 10.2967/jnumed.119.231654

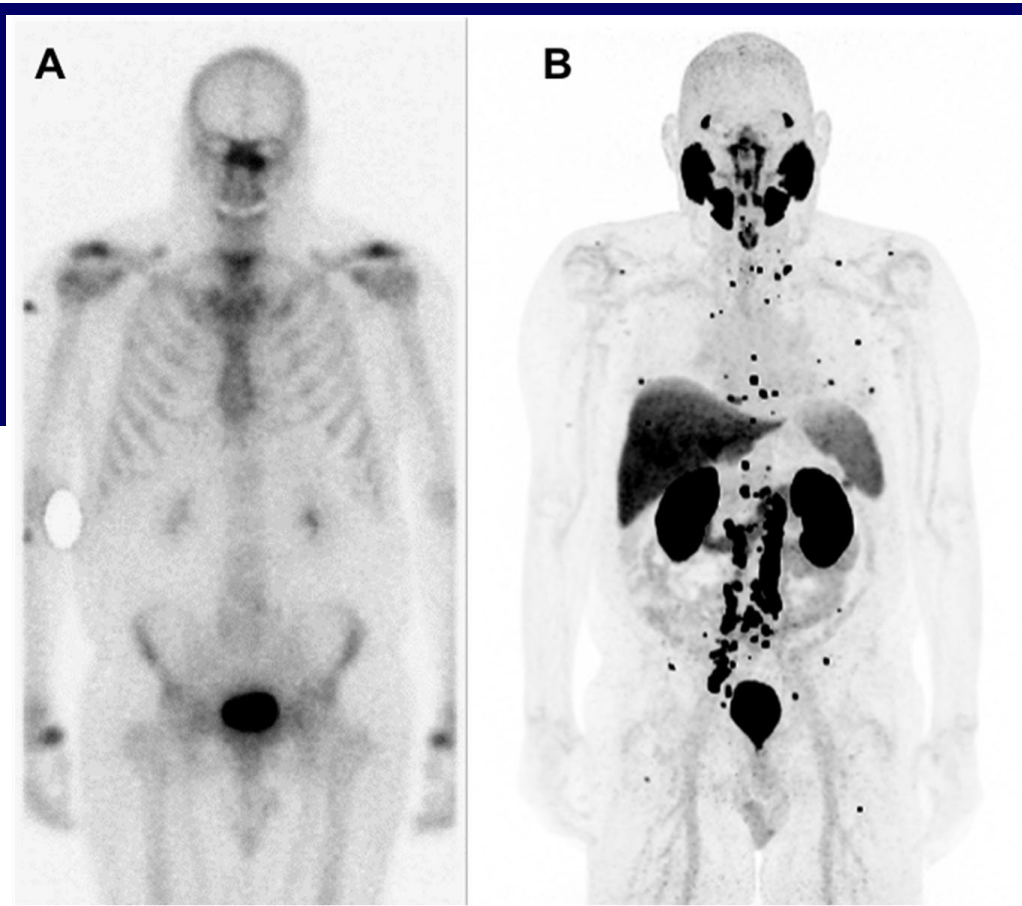
^{18}F-DCFPyL, BCR

- N= 72 BCR s/p RP or RT
- PSA (0.2-698.4 ng/ml; 15.8±83.2)
- 24% PSMA+ but CI-
- 60% change in management

Supplemental Table 2: Impact of ^{18}F-DCFPyL PET/CT on Patient Management

Number of patients (% total patients)	Positive ^{18}F-DCFPyL PET				Negative ^{18}F-DCFPyL PET
	Total	Prostatectomy	Radiation therapy	Negative conventional imaging†	Total
Radiation with or without ADT	20 (28)	15 (21)	5 (7)	6 (8)	3‡ (4)
ADT	23 (32)	12 (17)	11 (15)	11 (15)	3 (4)
Surveillance	5 (7)	3 (4)	2 (3)	3 (4)	5 (7)
Other	13* (18)	5 (7)	8 (11)	6 (8)	

*Six patients with no documented follow up management plan yet. Three patients started ADT before the scan and continued afterwards. Three patients need additional work-up. One patient had ^{18}F-DCFPyL PET as a requirement to participate in a clinical trial.
†Eight patients had not had any documented conventional imaging.
‡Two patients with negative ^{18}F-DCFPyL PET scans received radiation therapy to prostate bed and pelvic lymph nodes. One patient who had negative ^{18}F-DCFPyL PET but prostate bed uptake on ^{18}F-Fluciclovine PET received radiation therapy.

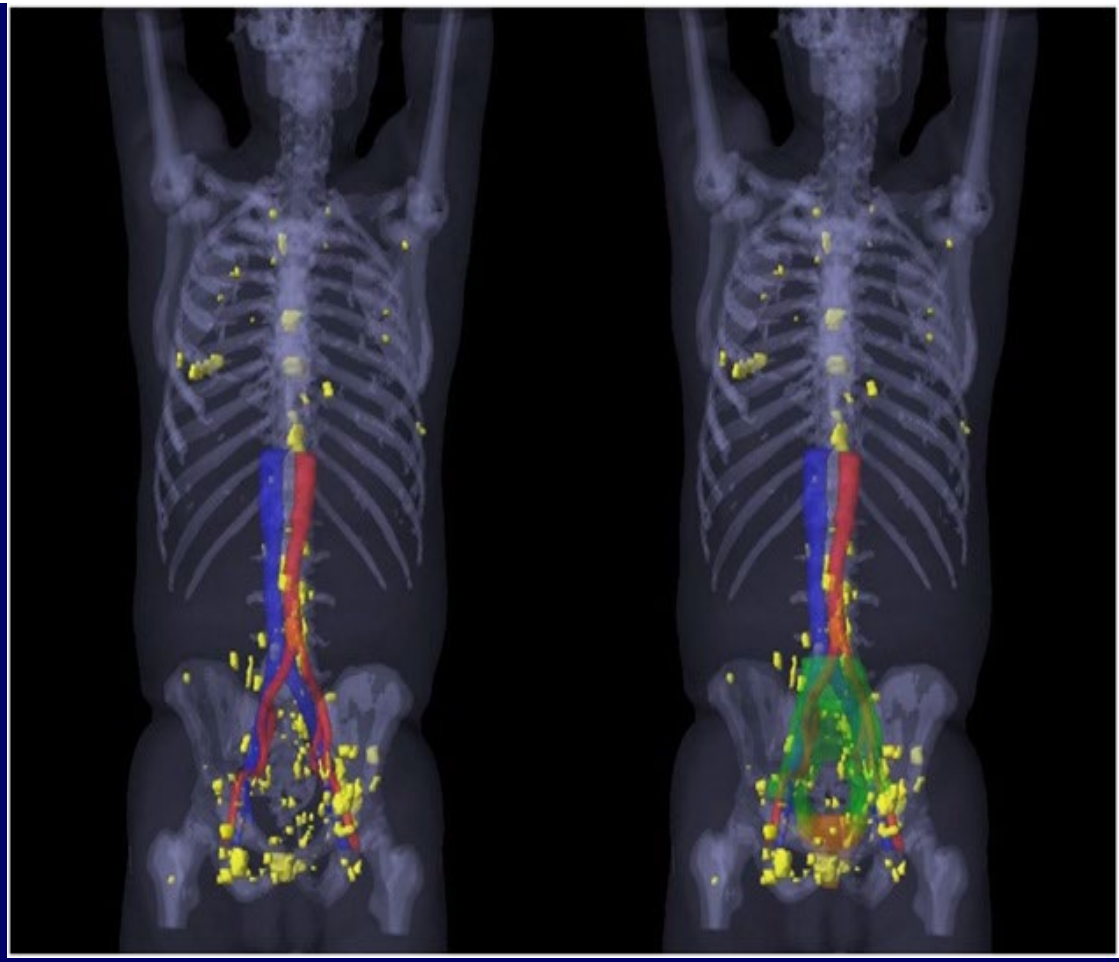


^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning

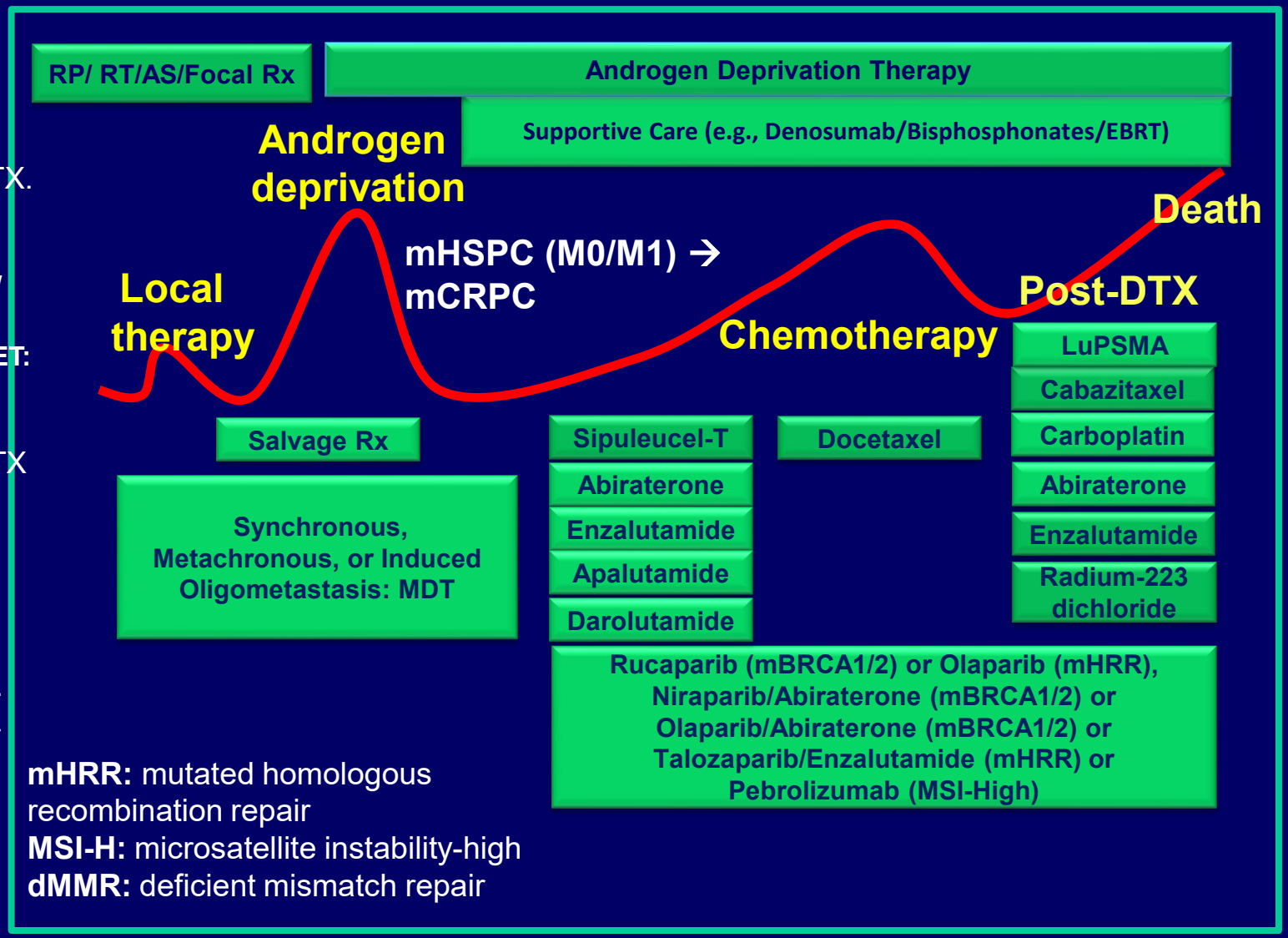
JNM 2018

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

- 49% pts +PSMA
- 19% pts with at least 1+ lesion not covered by RTOG guidelines CTVs



Prostate Cancer
Evolving Treatment Landscape



mHRR: mutated homologous recombination repair
MSI-H: microsatellite instability-high
dMMR: deficient mismatch repair

mHSPC (M1)
CHAARTED: DTX.
STAMPED (C): DTX
STAMPEDE(G) / LATITUDE: Abi.
ARCHES/ENZAMET: Enz.
TITAN: Apal.
PEACE1: Abi/DTX
ARASENS: DTX+Darl.

mHSPC (M0)
ARAMIS: Darl.
PROSPER: Enz.
SPARTAN: Apal.

mCRPC1
TAX327: DTX.
COU-AA-302: Abi.
PREVAIL: Enz.
IMPACT: SipT
PROpel: Olap.
TRITON3: Rucap.
MAGNITUDE: Nirap.
TALAPRO-2: Talaz.

mCRPC2
TROPIC: Cabaz.
COU-AA-302: Abi.
AFFIRM: Enz.
PROfound: Olap.
ALSYMPCA: Ra.

mCRPC3
VISION: LuPSMA
PSMFore: LuPSMA
CARD: cabz.
KEYNOTE: Pemb.
TRITON2: Rucap.

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

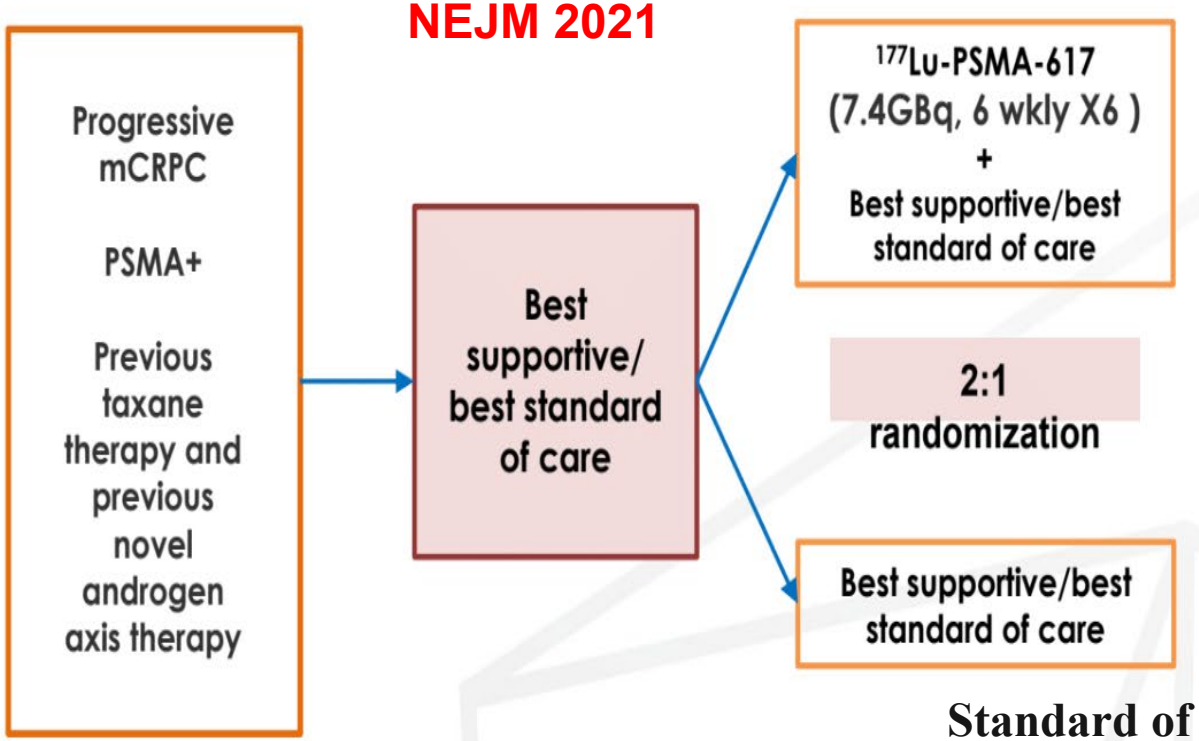
Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

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

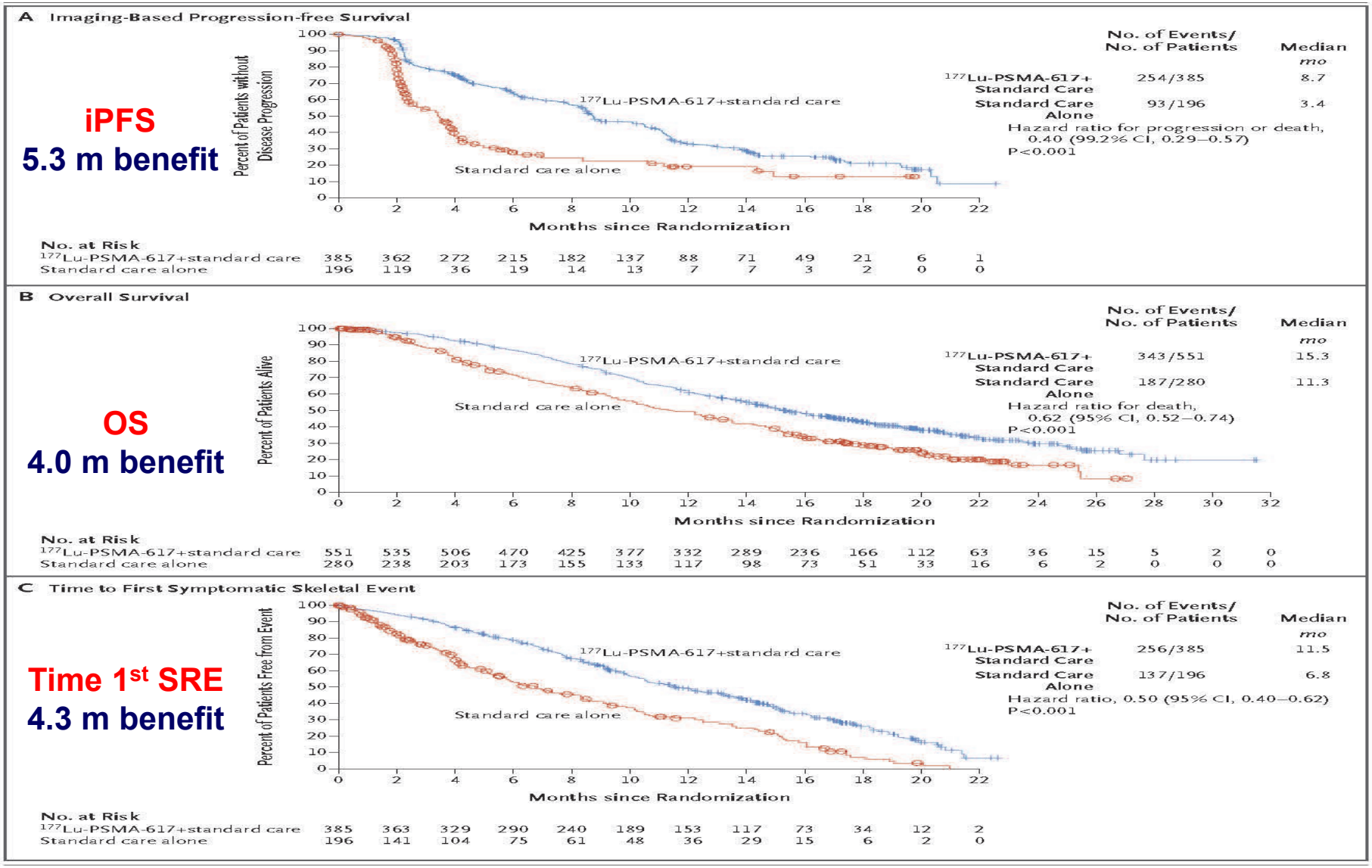
Key Secondary Endpoints
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

- 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

Metastatic Castrate Resistant Prostate Cancer (mCRPC, pre-chemo)

PSMAfore

NCT04689828

Patient population

- mCRPC with disease progression on previous ARPI therapy[a]
- No previous taxane in CRPC or HSPC setting
- PSMA-positive on [^{68}Ga]Ga-PSMA-11 PET/CT[b]

Stratification factors

- Previous ARPI use in CRPC vs HSPC
- Asymptomatic/mildly symptomatic vs symptomatic patients

R 1:1

^{177}Lu-PSMA-617 Q6W × 6

Crossover allowed upon radiographic progression

Primary endpoint: radiographic PFS

Change in ARPI treatment

84% cross-over from ARPI to LuPSMA at 2nd interim analysis

Secondary/exploratory endpoints

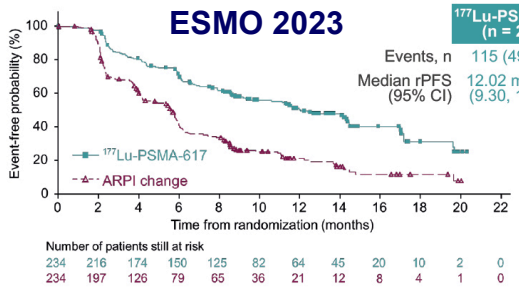
- OS (key secondary endpoint)
- Safety
- PFS
- rPFS2 for crossover patients
- ORR, DCR (RECIST 1.1)
- Duration of response
- PSA50 response rate
- Time to first symptomatic skeletal event
- Time to PSA progression
- Time to soft tissue progression
- Time to pain progression
- HRQoL (FACT-P, EQ-5D-5L, BPI-SF)

rPFS: primary endpoint was met

Primary HR:0.41 (95% CI: 0.29, 0.56); $p < 0.001$

Updated HR:0.43 (95% CI: 0.33, 0.54)

ESMO 2023



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

Novartis

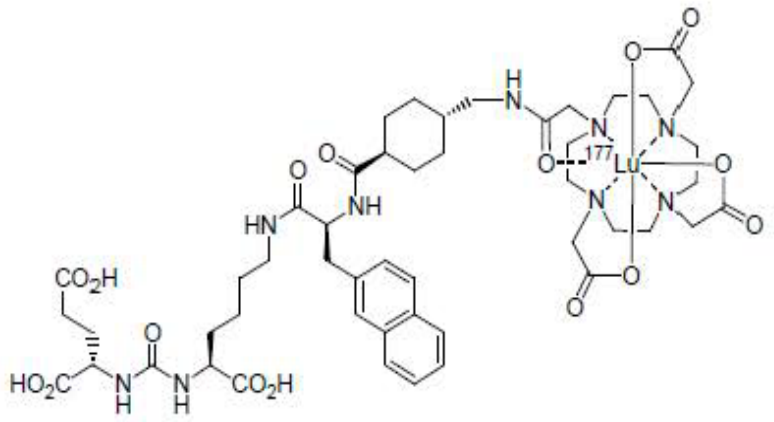
^{177}Lu-vipivotide tetraxetan (Pluvicto^{TM})

FDA Approved Indications

Treatment of PSMA+ mCRPC post ARPI therapy:

- PSMAFore: appropriate to delay taxane-based chemotherapy (2025)
- VISION: received prior taxane-based chemotherapy (2022)

$C_{49}H_{68}{}^{177}LuN_9O_{16}$



Jadvar

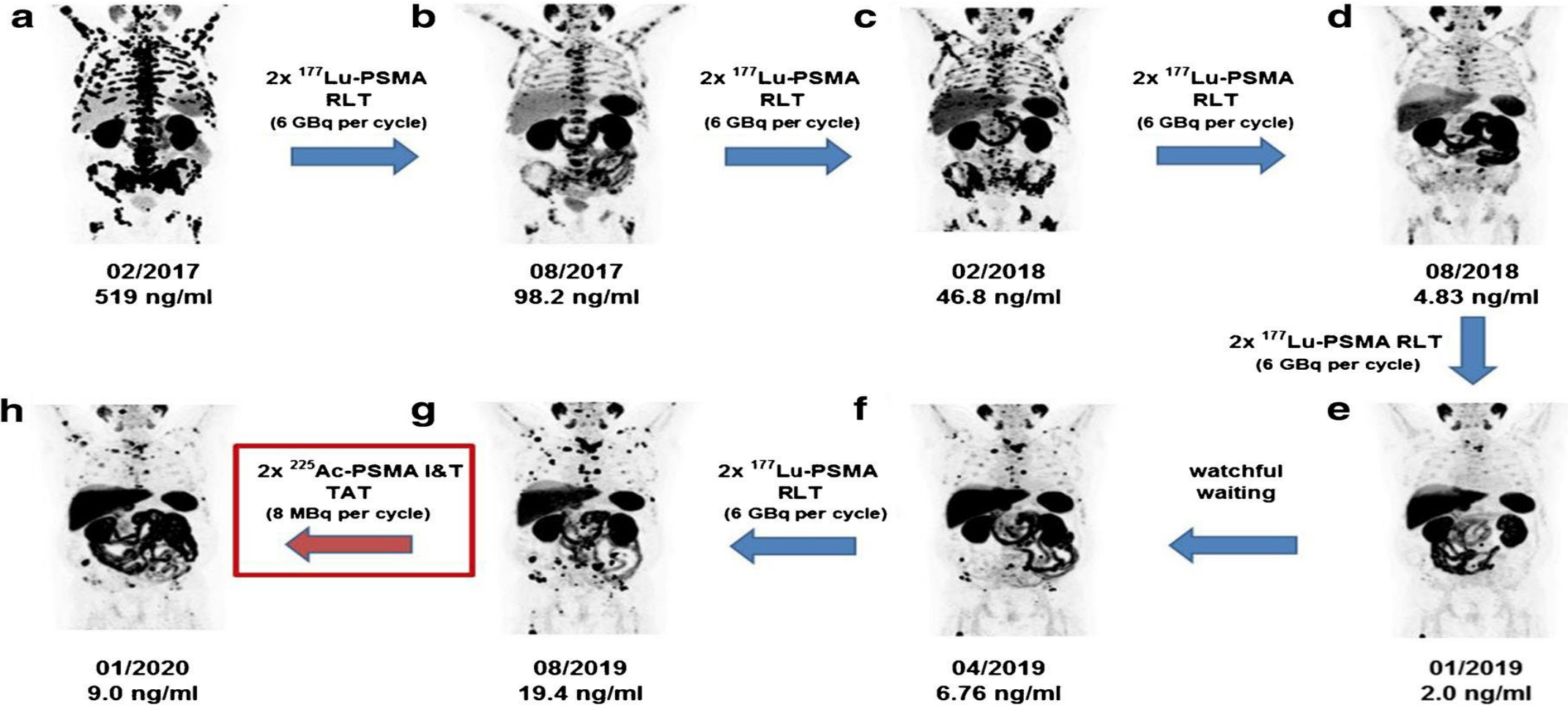
European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:1262–1263
https://doi.org/10.1007/s00259-020-05023-2

IMAGE OF THE MONTH

EJNMMI 2021

Response to ^{225}Ac-PSMA-I&T after failure of long-term ^{177}Lu-PSMA RLT in mCRPC

Harun Ilhan[1] · Astrid Gosewisch[1] · Guido Böning[1] · Friederike Völter[1] · Mathias Zacherl[1] · Marcus Unterrainer[2] · Peter Bartenstein[1] · Andrei Todica[1] · Franz Josef Gildehaus[1]



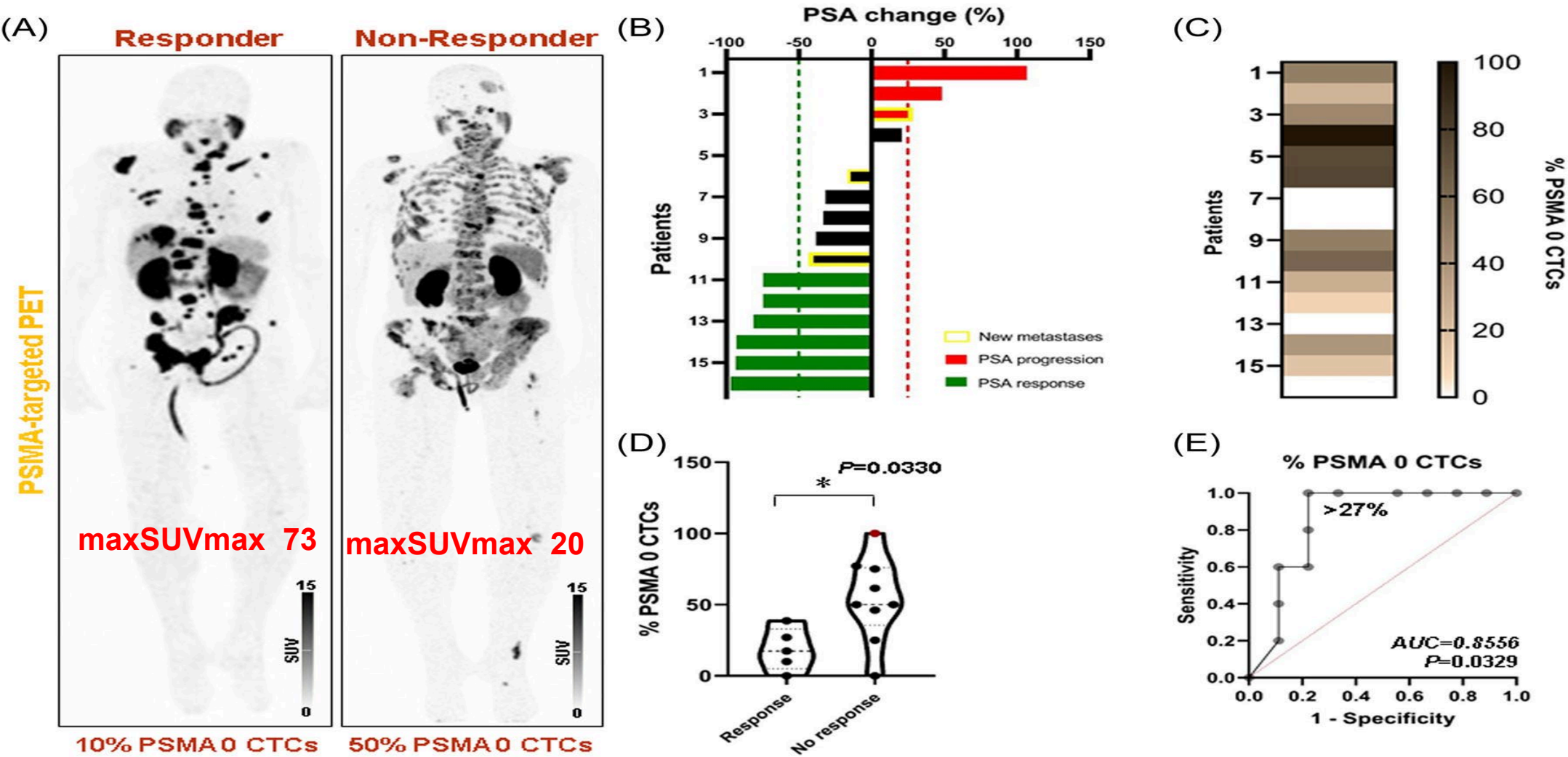
ORIGINAL ARTICLE

The Prostate WILEY

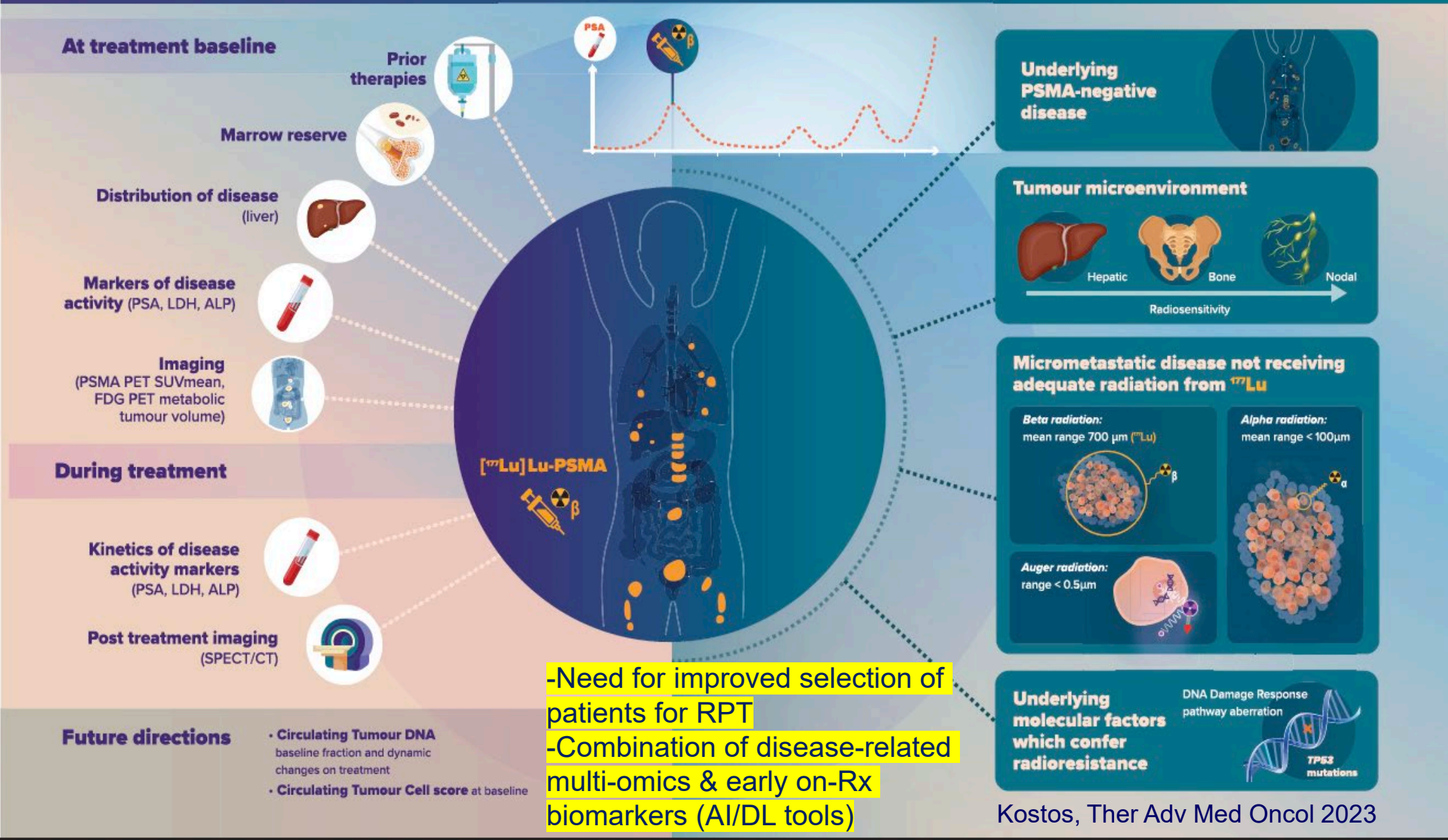
PSMA-heterogeneity in metastatic castration-resistant prostate cancer: Circulating tumor cells, metastatic tumor burden, and response to targeted radioligand therapy

PROSTATE 2023

Thorsten Derlin MD[1] | Sabine Riethdorf PhD[2] | Udo Schumacher MD[3,4] | Marcel Lafos MD[5] | Sven Peine MD[6] | Cornelia Coith[2] | Tobias L. Ross PhD[1] | Klaus Pantel MD[2] | Frank M. Bengel MD[1]



Potential Predictors of Response to PSMA-based Radionuclide Therapy & Mechanisms of Resistance in patients with metastatic castration-resistant prostate cancer



-Need for improved selection of patients for RPT

-Combination of disease-related multi-omics & early on-Rx biomarkers (AI/DL tools)

Kostos, Ther Adv Med Oncol 2023

Outline

- Theranostics (definition & goal)
- **FRONTIERLAND**
  - Radioiodine (thyroid cancer)
  - SSTR (NET)
  - PSMA (prostate cancer)
- **TOMORROWLAND**
  - FAP (pan-cancer)
  - CXCR4 (lymphoma/myeloma)
  - GRPR (prostate cancer)

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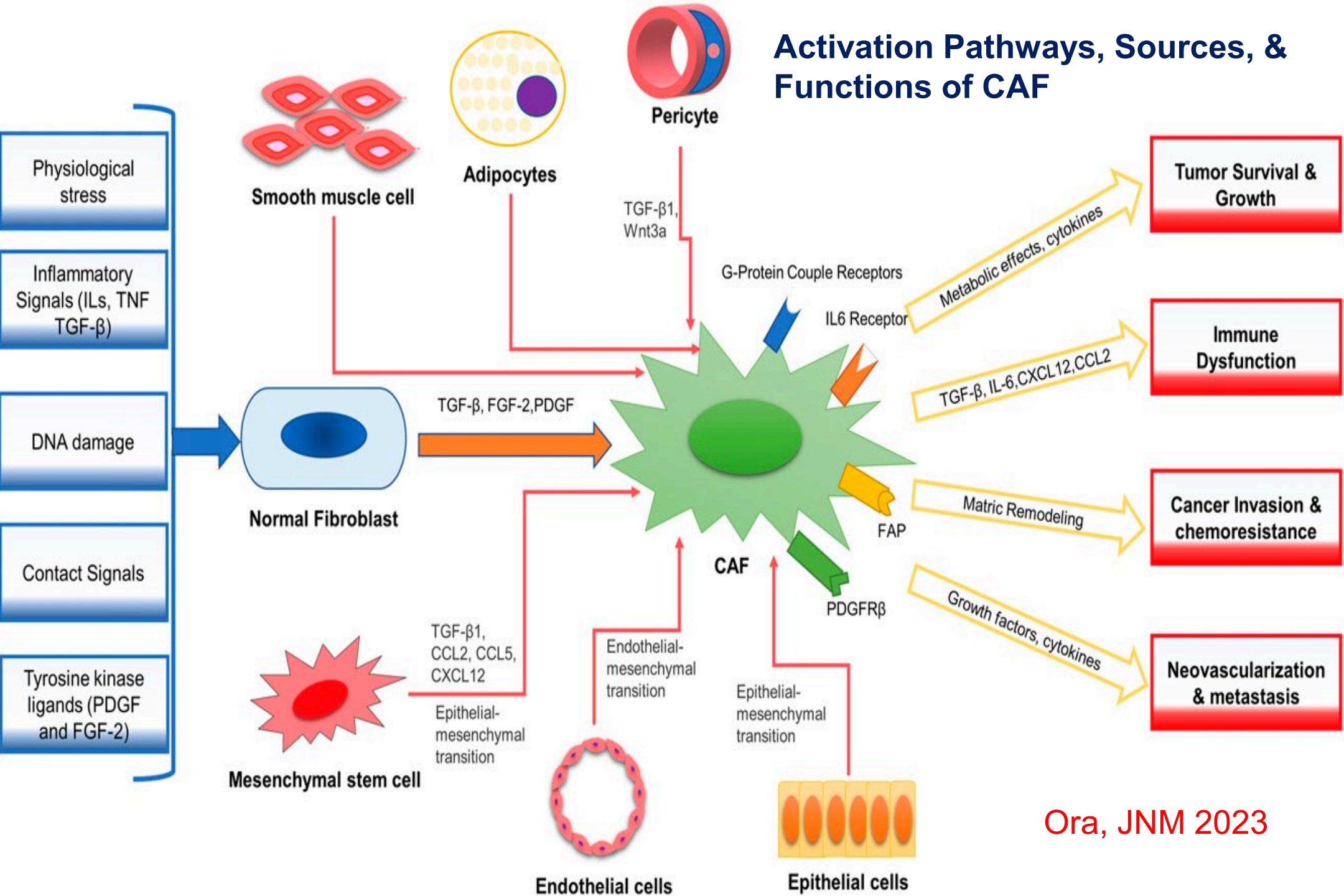
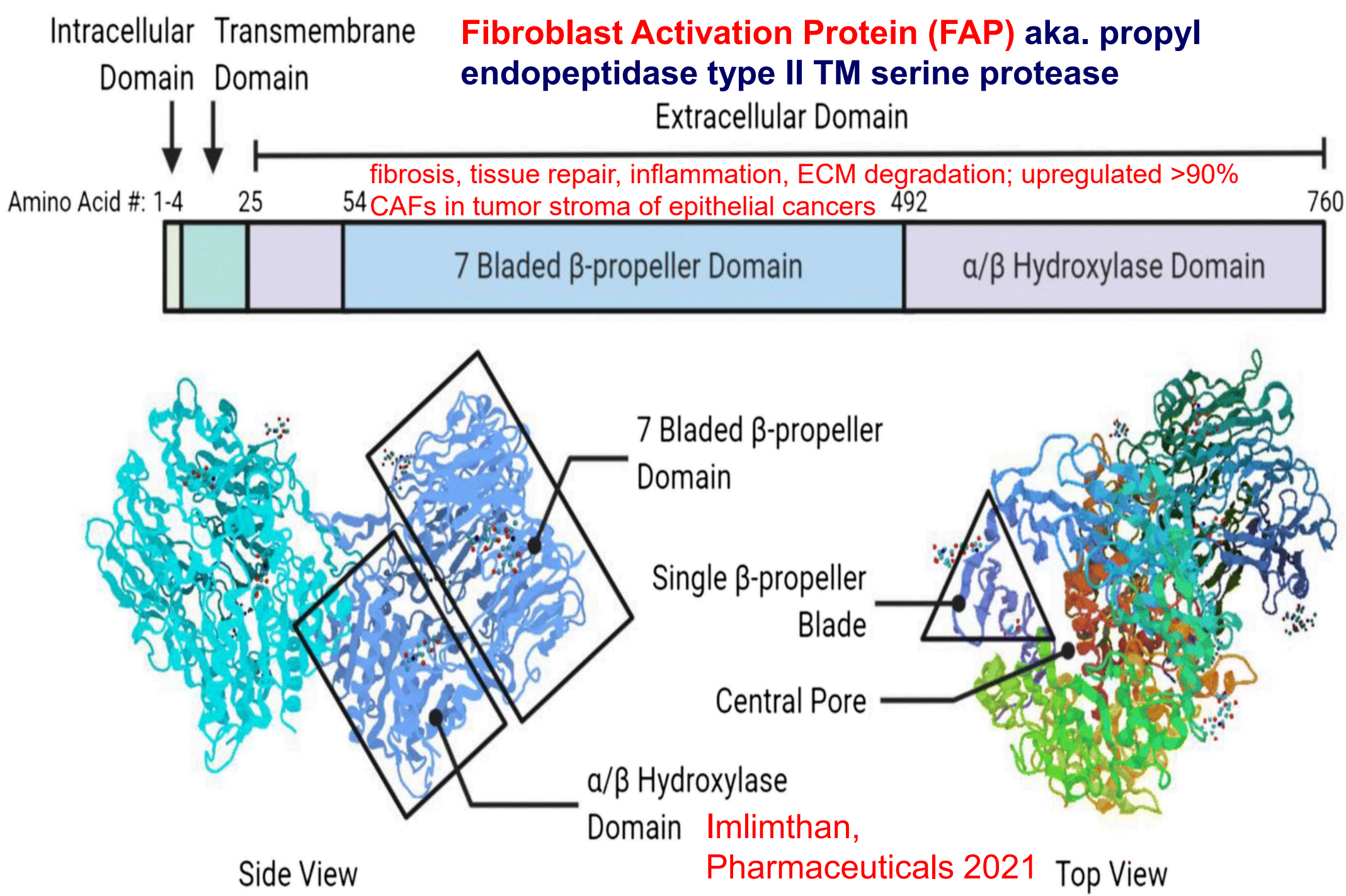
Activation Pathways, Sources, & Functions of CAF

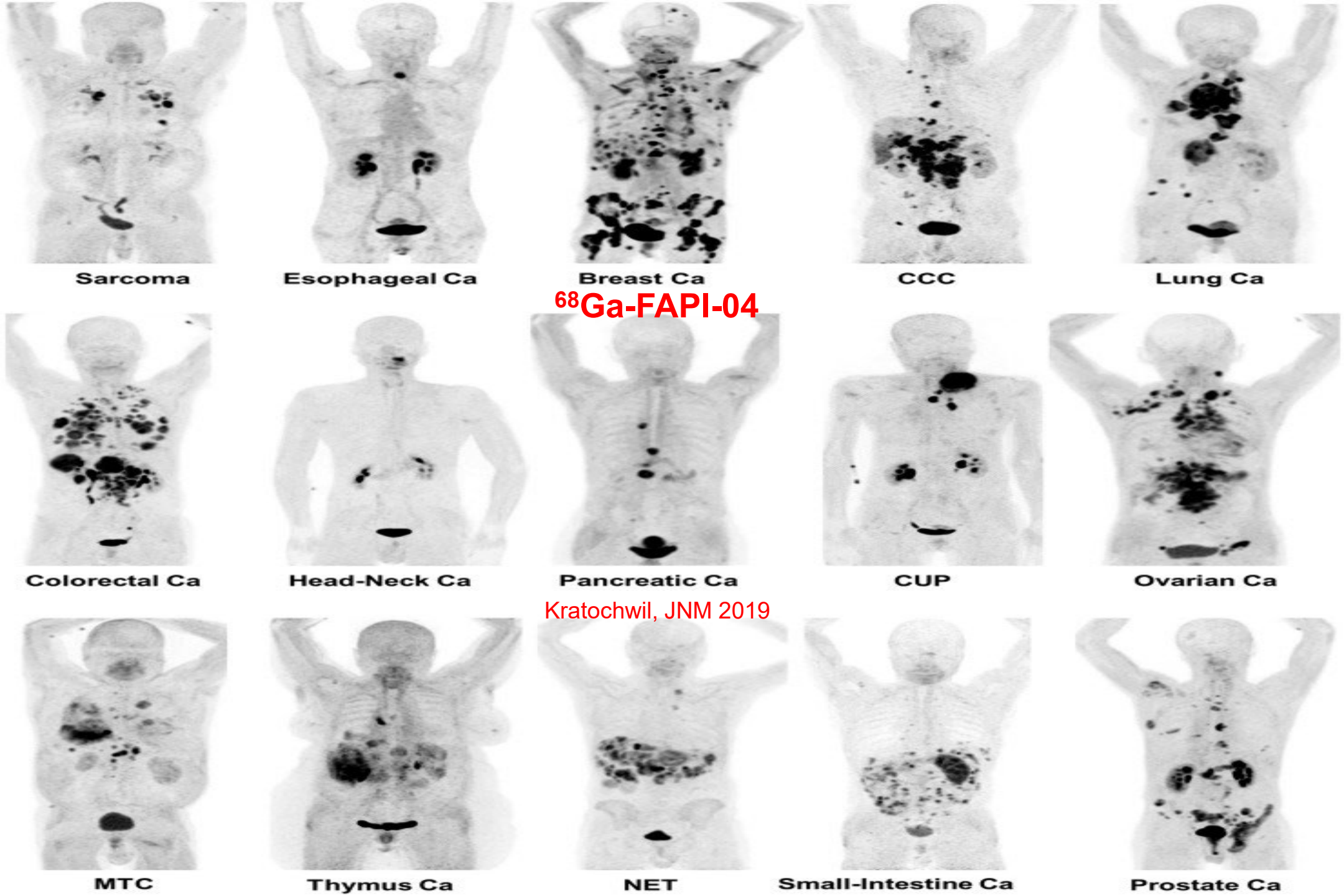


Ora, JNM 2023

Fibroblast Activation Protein (FAP) aka. propyl endopeptidase type II TM serine protease



Imlimthan, Pharmaceuticals 2021

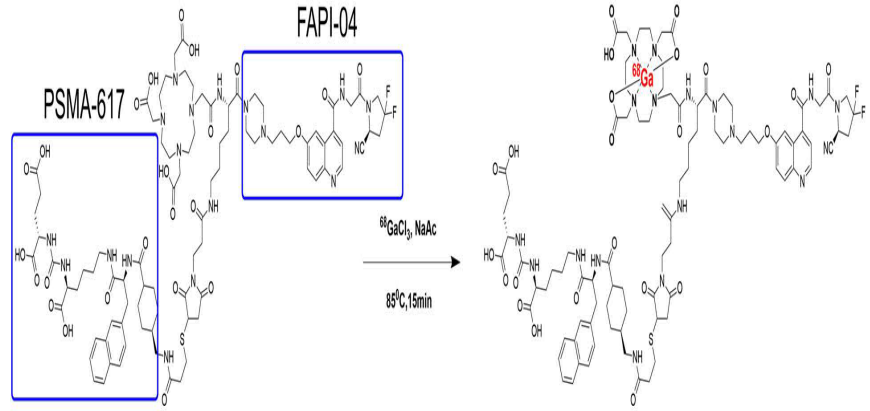

Sarcoma
Esophageal Ca
Breast Ca
CCC
Lung Ca
68Ga-FAPI-04
Colorectal Ca
Head-Neck Ca
Pancreatic Ca
CUP
Ovarian Ca
Kratochwil, JNM 2019
MTC
Thymus Ca
NET
Small-Intestine Ca
Prostate Ca

molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics

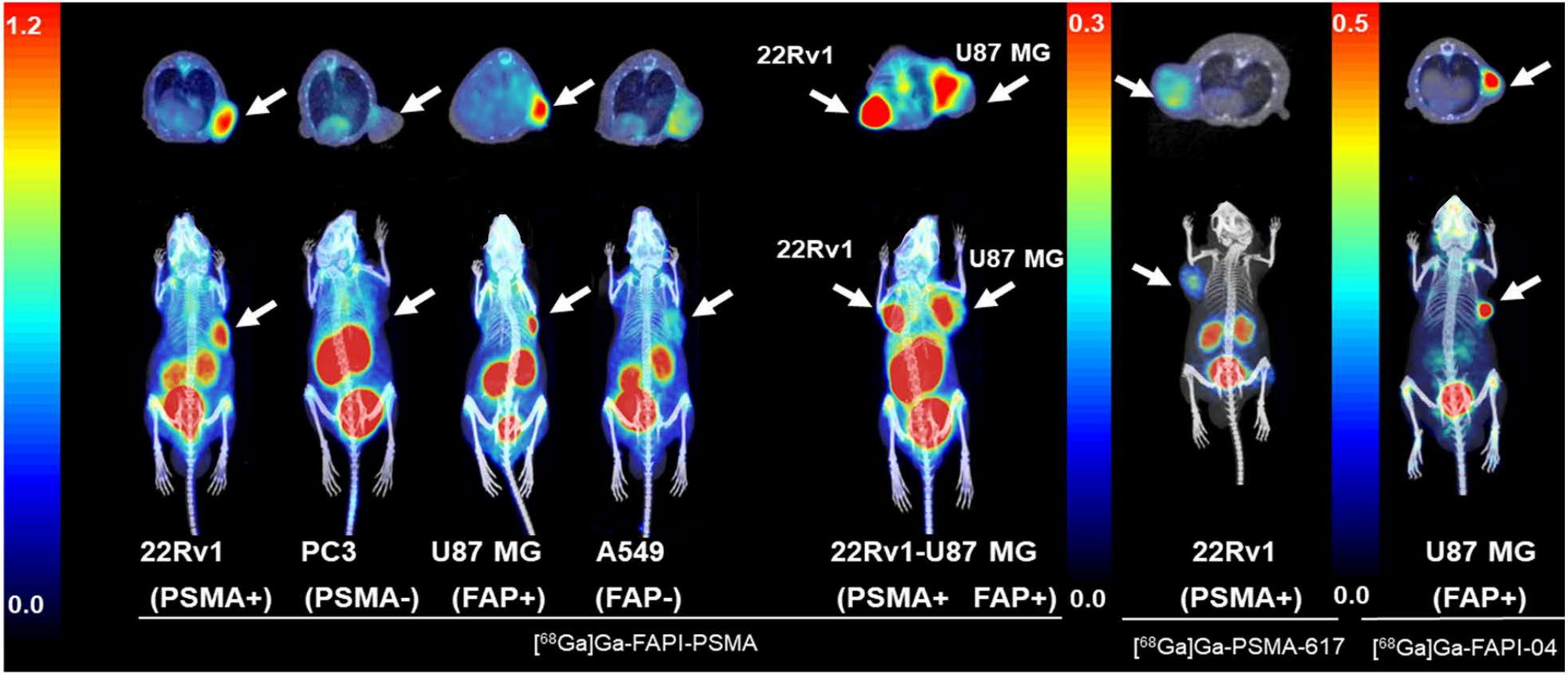
Article

^{68}Ga-FAPI-PSMA



Preclinical Evaluation of a Fibroblast Activation Protein and a Prostate-Specific Membrane Antigen Dual-Targeted Probe for Noninvasive Prostate Cancer Imaging

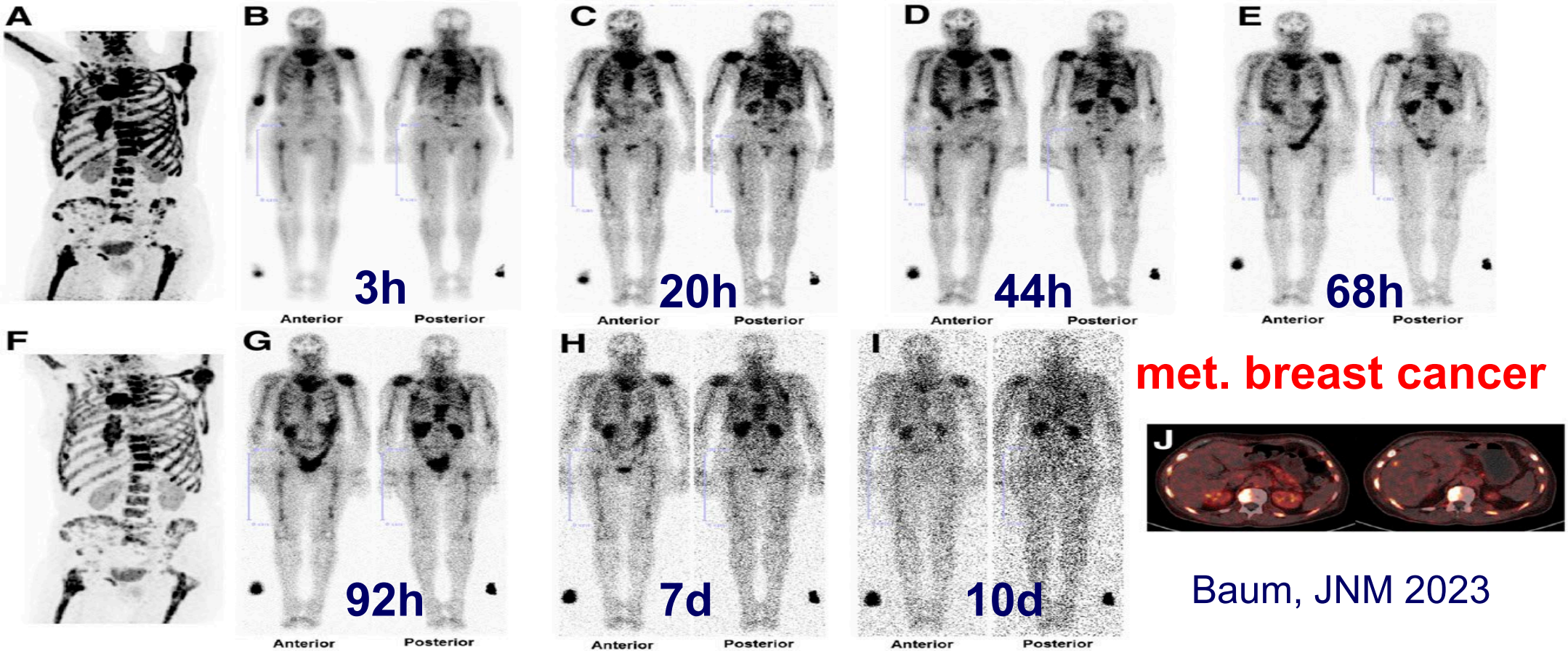
Pei Wang,[§] Shuailiang Wang,[§] Futao Liu,[§] Ya'nan Ren, Qian Guo, Qian Zhang, XingGuo Hou, Yuan Yao, Hua Zhu,* and Zhi Yang*



Feasibility, Biodistribution, and Preliminary Dosimetry in Peptide-Targeted Radionuclide Therapy of Diverse Adenocarcinomas Using ^{177}Lu-FAP-2286: First-in-Humans Results

^{68}Ga-FAP-2286
^{177}Lu-FAP-2286 (2.4 GBq)

Richard P. Baum*[1,2], Christiane Schuchardt[1], Aviral Singh[1], Maythinee Chantadisai[1,3], Franz C. Robiller[1], Jingjing Zhang[1,4], Dirk Mueller[1], Alexander Eismant[1], Frankis Almaguel[1,5], Dirk Zboralski[6], Frank Osterkamp[6], Aileen Hoehne[6], Ulrich Reineke[6], Christiane Smerling[6], and Harshad R. Kulkarni*[1]

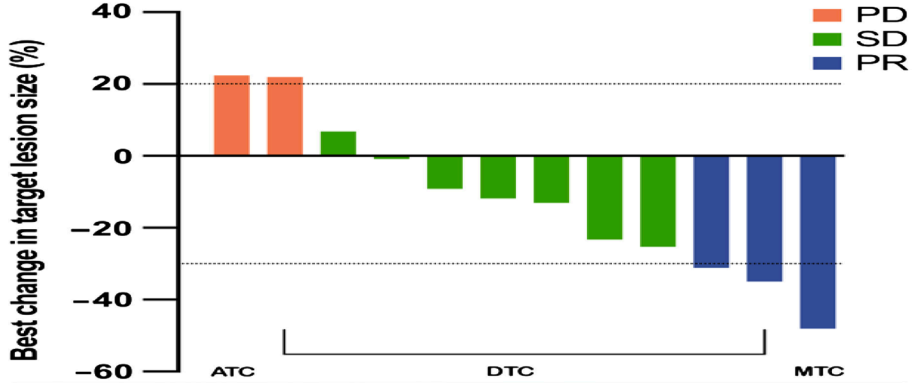


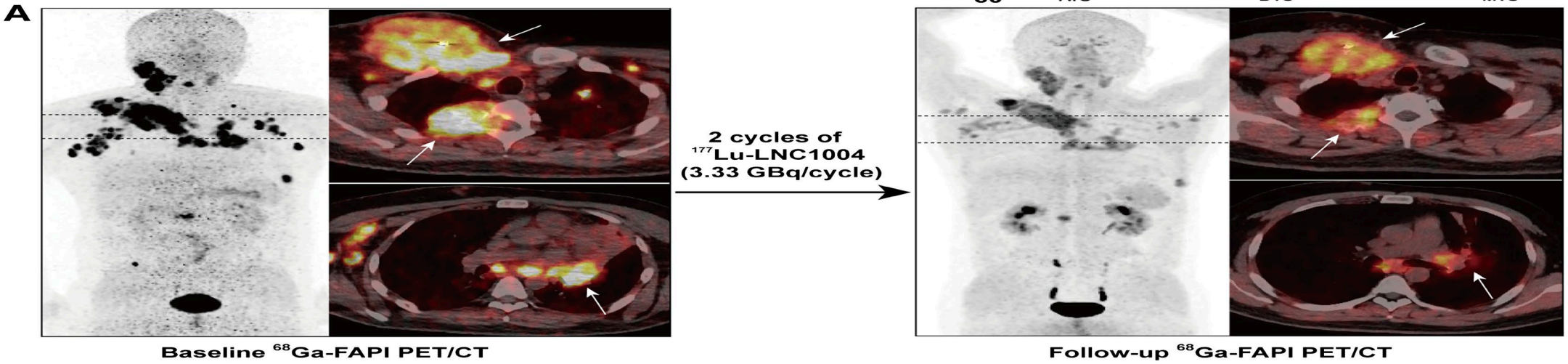
Baum, JNM 2023

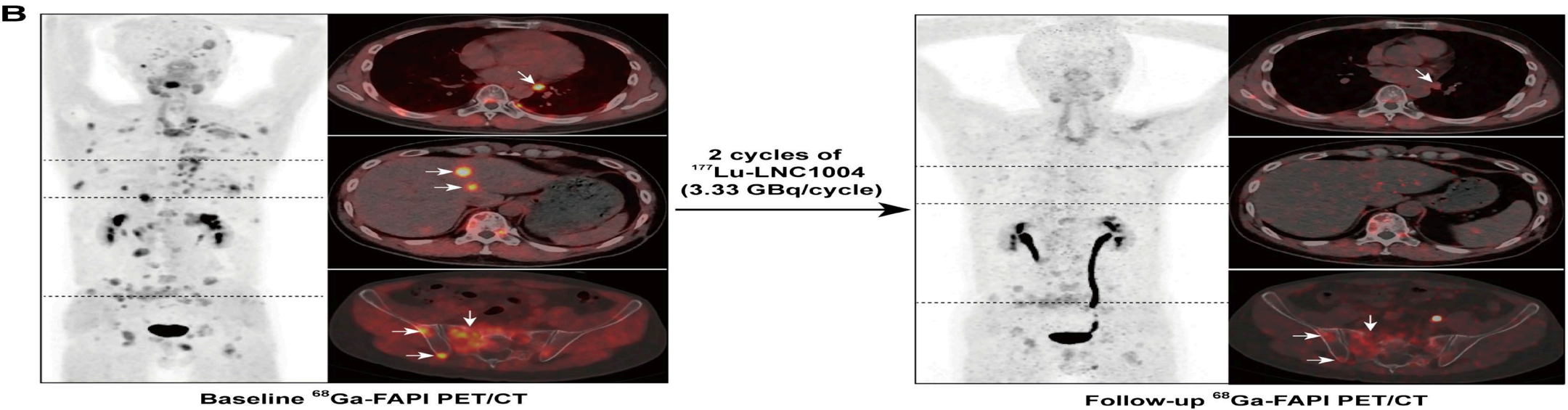
Fibroblast Activation Protein-Targeted Radioligand Therapy with ^{177}Lu-EB-FAPI for Metastatic Radioiodine-Refractory Thyroid Cancer: First-in-Human, Dose-Escalation Study

Hao Fu[1], Jingxiong Huang[1], Tianzhi Zhao[2,3,4,5,6,7], Hongjian Wang[8], Yuhang Chen[8], Weizhi Xu[1], Yizhen Pang[1], Wei Guo[1], Long Sun[1], Hua Wu[1], Pengfei Xu[2,3,4,5,6,7], Bishan Su[1], Jingjing Zhang[2,3,4,5,6,7], Xiaoyuan Chen[2,3,4,5,6,7], and Haojun Chen[1]

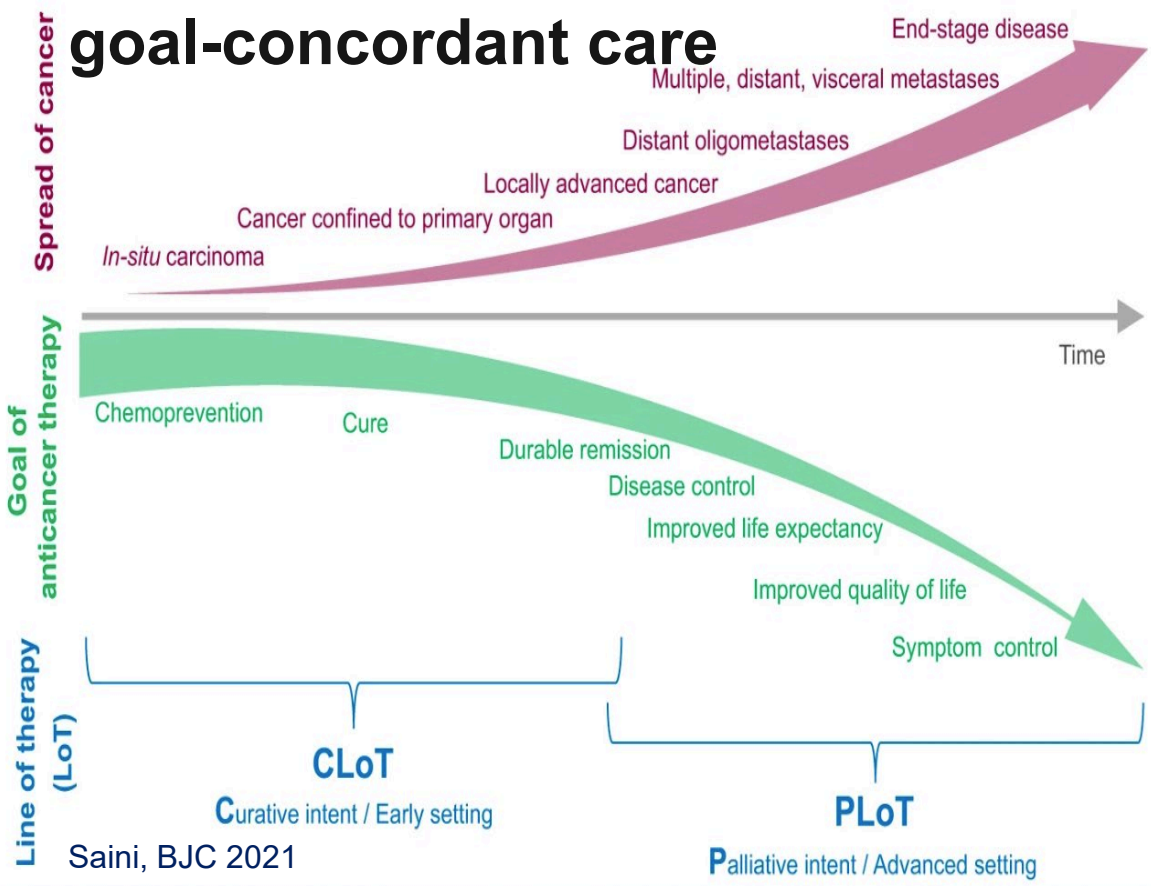
2023







goal-concordant care



Saini, BJC 2021

- **Unmet clinical need for new treatment options**
  - Chimeric antigen receptor T cells (CAR-T)
  - Antibody-drug conjugates (ADCs)
  - Radiopharmaceutical therapy (RPT)

The Pillars of Cancer Treatment

Acknowledgement

NIH / NCI / NIBIB

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R21-EB017568

P30-CA014089

SC CTSI Southern California Clinical and Translational Science Institute

The Ming Hsieh Institute

for Research on Engineering-Medicine for Cancer

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USC University of Southern California