International Atomic Energy Agency Scientific Forum

A Decade of Action on Cancer Control and the Way Forward

IAEA
International Atomic Energy Agency
Atoms for Peace and Development

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Vienna International Centre
Board Room D, C Building, 4th Floor

Impact of radiopharmaceutical development on the management of cancer

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Acknowledgments

IAEA

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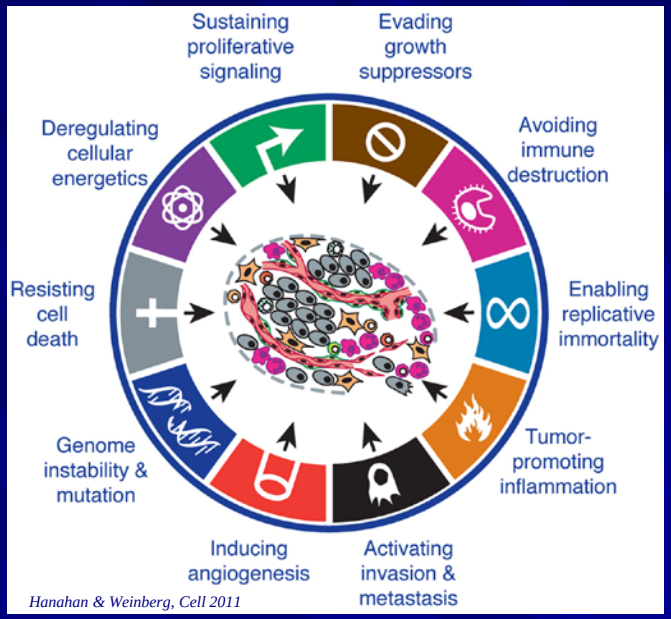
NM UP/SBAH

Nonjola L, Ebenhan T, Mahlangu Z, D Van Wyk, L Boshoff, C van Raven, AM Koegelenberg, M Mekwa, Kleynhans J, Zeevaart JR & NECSA radiochemist staff, Maes A, Van de Wiele C, Buscombe J

Radiopharmaceuticals: Targeting of the Hallmarks of Cancer

- Metabolism
  - Glucose
  - Cell membrane
  - Proteins
  - Bone
- Tumor specific agents
- Proliferation
- Angiogenesis
- Apoptosis
- Vascularization
- Hypoxia



✓ Characterization of tumor biology - image-based “biomarker”

✓ Identification of therapy targets - Theranostics and treatment planning

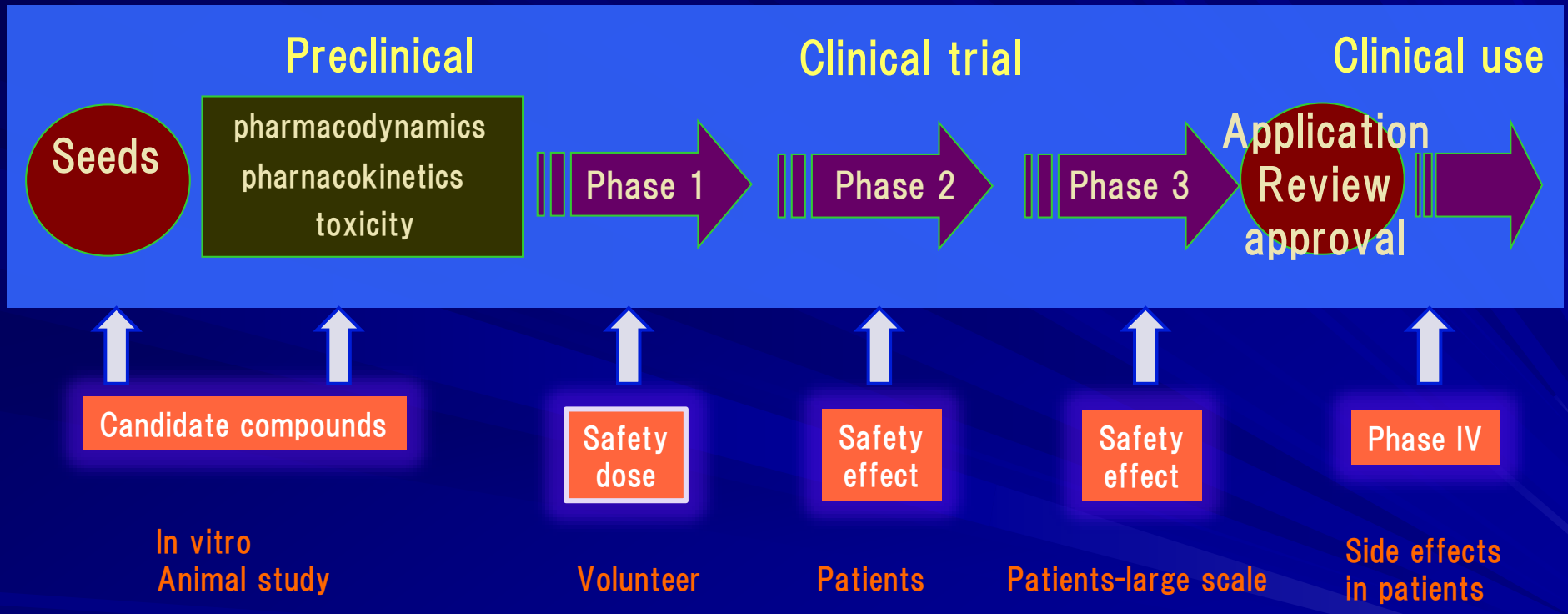
✓ Early Indicator of Tumor Response - patient-specific effect on outcome

Process of New Drug Development

Duration of new drug development: 12 years

Cost of new drug development: ???>R800million

Successful compounds: only 8% of candidate compounds



Screening of compounds

Pharmacokinetics urinary or biliary excretion unexpected accumulation

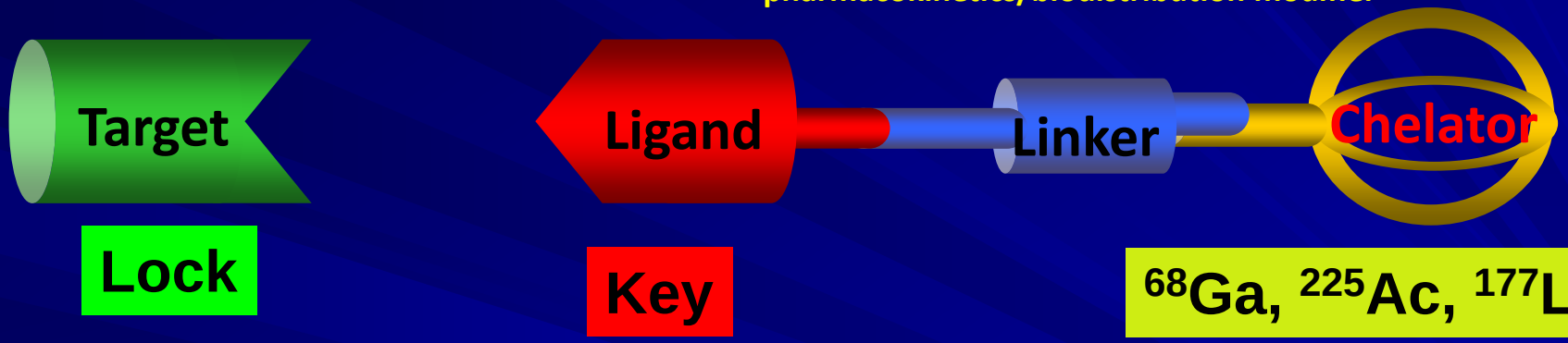
Dose setting

Screening of patients

effectiveness

THERANOSTIC PAIRS
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Schematic Representation of a Drug for Imaging and Targeted Therapy



Targets

- **Antigens**
  e.g. **CD20**, HER2)
- **GPCR** e.g. **SSTR**
- Enzymes & inhibitors
  e.g. **PSMA**
- **Transporters**

Molecular Address

- Antibodies, minibodies, Affibodies, aptamers
- **Regulatory peptides** (agonists & antagonists)
- Amino Acids

Reporting Unit

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

Cytotoxic Unit

- ^{225}Ac, ^{177}Lu, ^{213}Bi, ^{131}I
- ^{105}Rh, ^{67}Cu, ^{188}Re, ^{90}Y

Modified form: Helmut Mäcke & Rich Baum

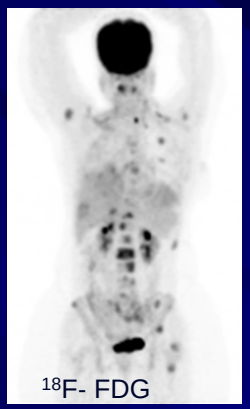
Androgen Receptors

^{18}F- FDHT

PARP inhibitors

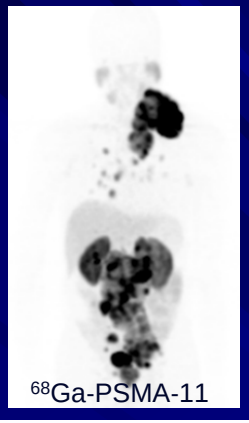
^{18}F-PARPi

Glucose metabolism



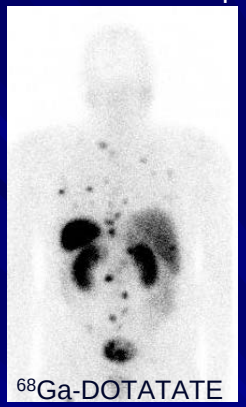
^{18}F- FDG

Prostate Cancer



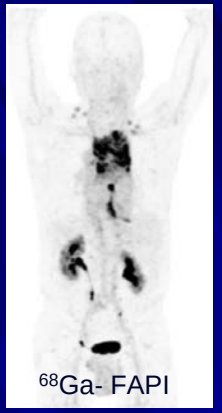
^{68}Ga-PSMA-11

Somatostatin Receptor



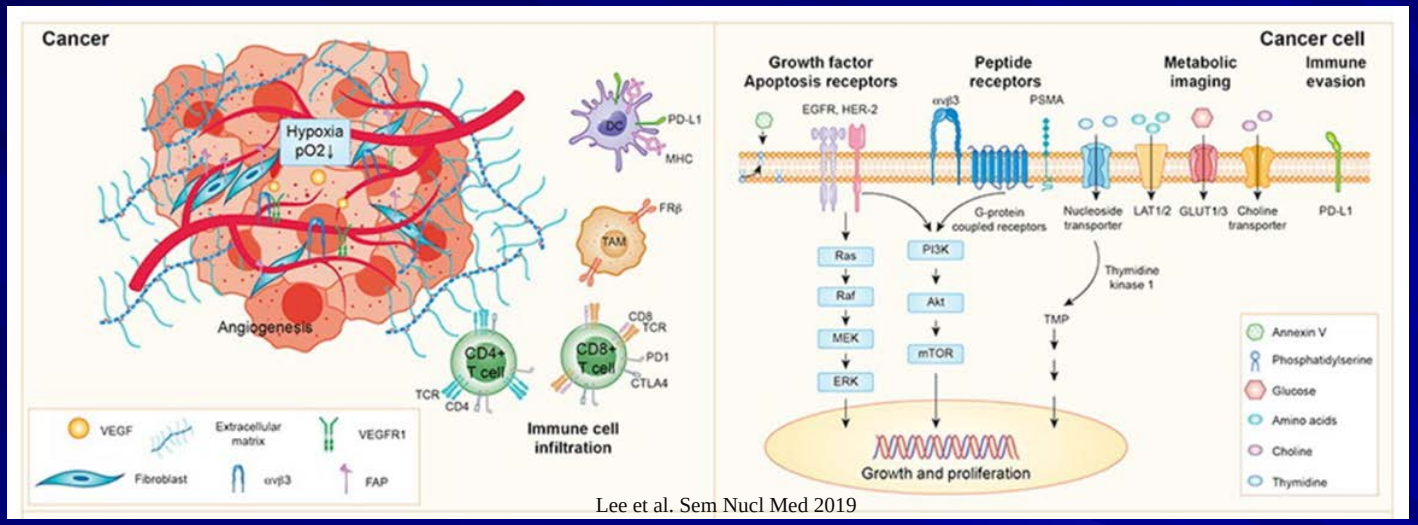
^{68}Ga-DOTATATE

Cancer-Fibroblasts



^{68}Ga- FAPI

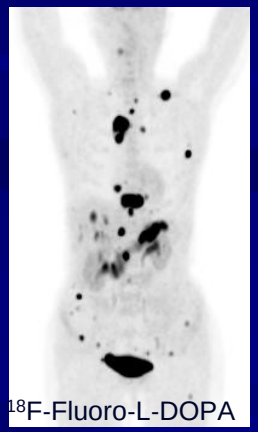
Tumor
- Detection
- Staging
- Recurrence



Lee et al. Sem Nucl Med 2019

Tumor
- Biology
- Targets
- Response

Proteins metabolism

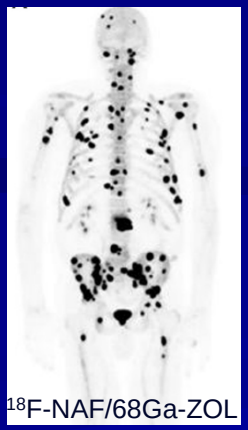


^{18}F-Fluoro-L-DOPA

Cell Membrane

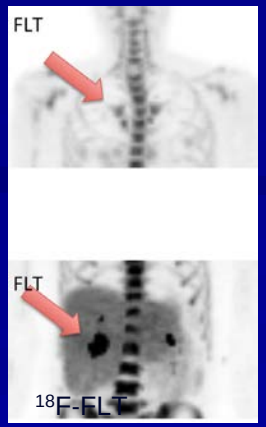
^{18}F-CHOLINE

Bone



^{18}F-NAF/68Ga-ZOL

Proliferation

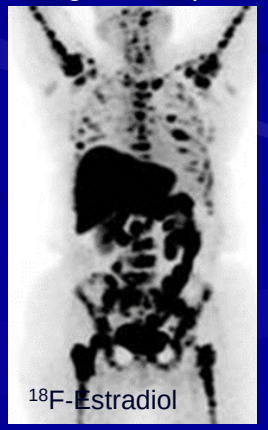


^{18}F-FLT

Angiogenesis

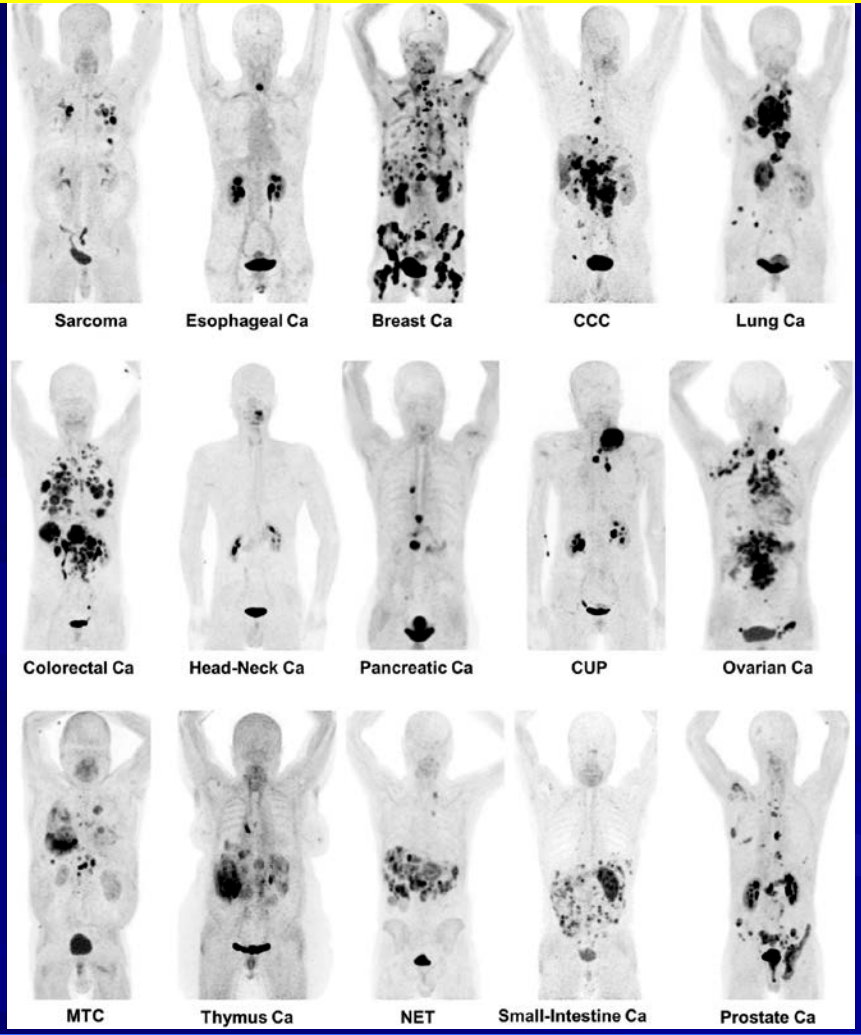
^{68}Ga- RGD

Estrogen Receptors



^{18}F-Estradiol

68Ga-FAPI PET/CT in patients reflecting 15 different Cancers



- ✓ Fibroblast activation protein (FAP) is overexpressed in cancer associated fibroblasts of several tumor entities (15).
- ✓ 90% of the gross tumor-mass can consist from stromal but not tumor cells
- ✓ FAPI-tracers contain the universal DOTA-chelator: theranostic approach

Kratochwil et al. J Nucl Med 2019

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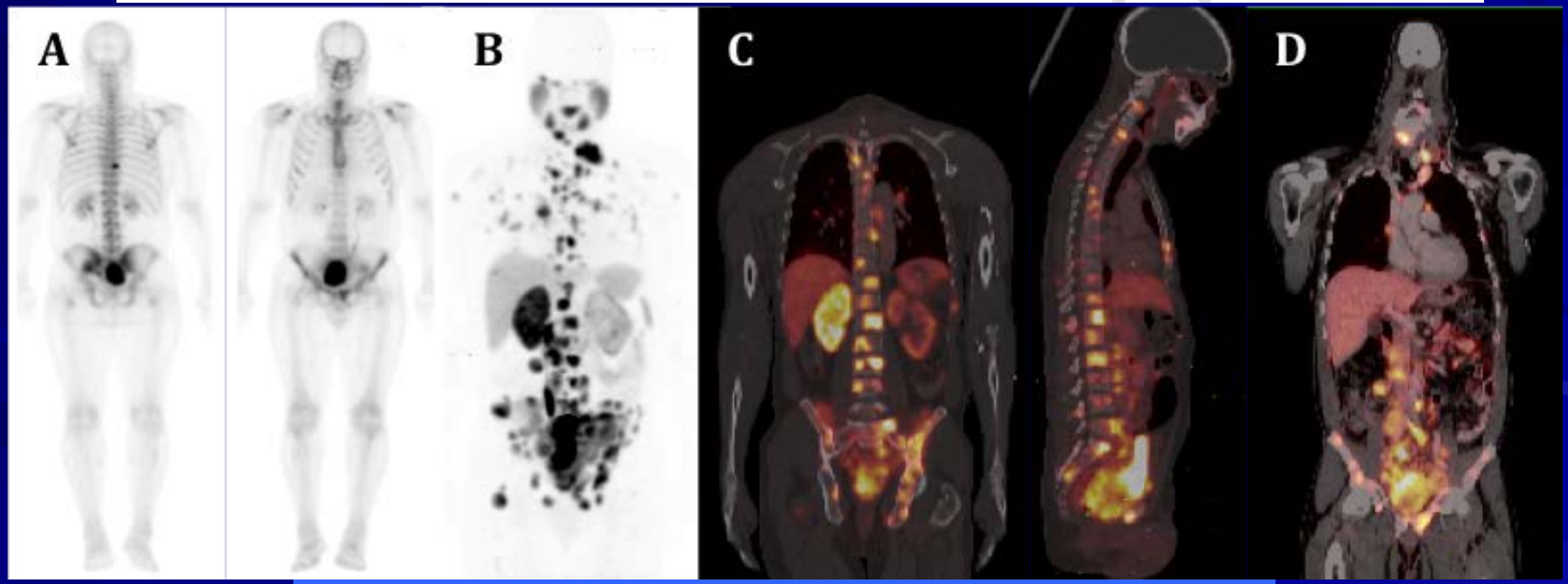
Original Study

^{68}Ga-PSMA PET/CT Replacing Bone Scan in the Initial Staging of Skeletal Metastasis in Prostate Cancer: A Fait Accompli?

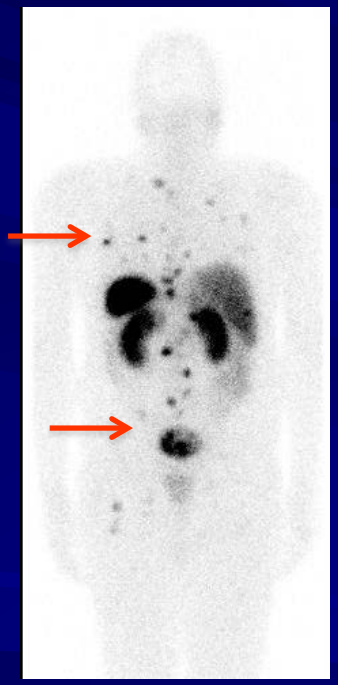
Thabo Lengana,[1] Ismaheel O. Lawal,[1] Tebatso G. Boshomane,[1] Gbenga O. Popoola,[2] Kgomotso M.G. Mokoala,[1] Evelyn Moshokoa,[3] Alex Maes,[1,4] Neo P. Mokgoro,[1] Christophe Van de Wiele,[1,5] Mariza Vorster,[1] Mike M. Sathekge[1]



Planned clinical management altered in 52%

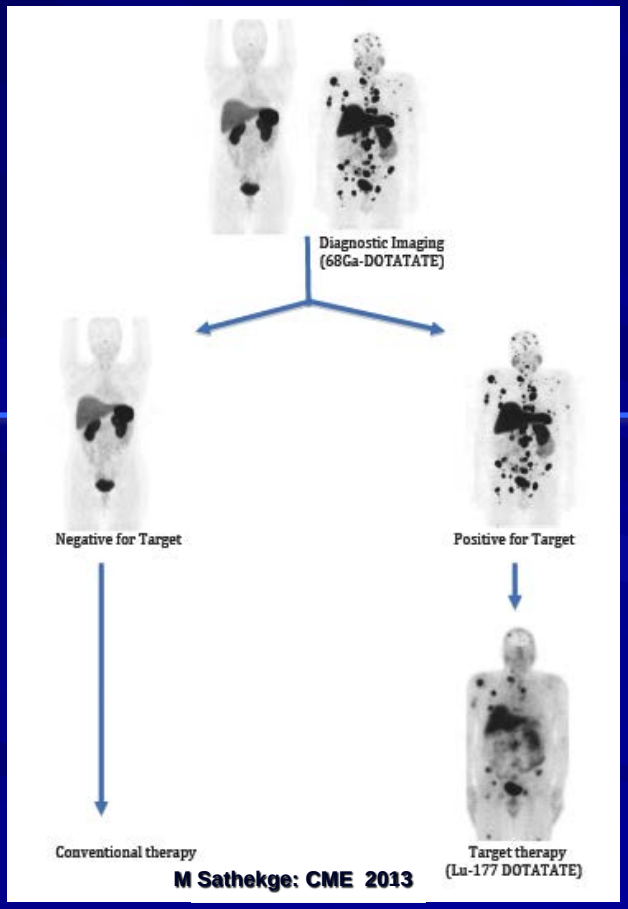
Theranostics

Find



68Ga-DOTATATE/PSMA

Fight



Lu-177/Bi213 DOTATATE/PSMA

Follow-up

68Ga- DOTATATE/PSMA

Theranostics: Personalized Medicine

Table 1 Overview of theranostic agents

Theranostic molecule	Iodine	mIBG	SSA	PSMA-ligands	Benzamide/ arylcarboxamide
Target	Thyroid cancer cells	Neurosecretory granules	SSTR, especially the subtype SSTR2	PSMA	Melanin
Planar imaging/ SPECT or	^{131}I and ^{123}I	[^{131}I]I-mIBG, [^{123}I]I-mIBG	SSA labeled with indium-111	[^{123}I]I-MIP-1072	[^{123}I]I-BA52
PET	^{124}I	[^{124}I]I-mIBG	[^{68}Ga]Ga-DOTA-TATE [^{68}Ga]Ga-DOTA-TOC [^{68}Ga]Ga-DOTA-NOC	[^{68}Ga]Ga-PSMA-11 [^{68}Ga]Ga-PSMA-617	[^{18}F]F-ICF15002
Therapeutic agent	^{131}I	[^{131}I]I-mIBG	[^{177}Lu]Lu-DOTA-TATE [^{177}Lu]Lu-DOTA-TOC [^{90}Y]Y-DOTA-TOC [^{90}Y]Y-DOTA-TATE	[^{177}Lu]Lu-J591 [^{90}Y]Y-J591 [^{131}I]I-MIP-1095 [^{177}Lu]Lu-PSMA-617	[^{131}I]I-BA52 [^{131}I]I-ICF15002
Indication	Thyroid cancer	Neuroblastomas, pheochromocytomas, paragangliomas, medullary thyroid carcinomas, and other NEN	NEN, especially GEP-NEN	Metastatic prostate cancer	Metastatic melanoma

Abbreviations: mIBG, metaiodobenzylguanidine; SSA, somatostatin analogs; SSTR, somatostatin receptors; NEN, neuroendocrine neoplasia; GEP, gastroenteropancreatic system; SPECT, single photon emission computed tomography; PET, positron emission tomography.

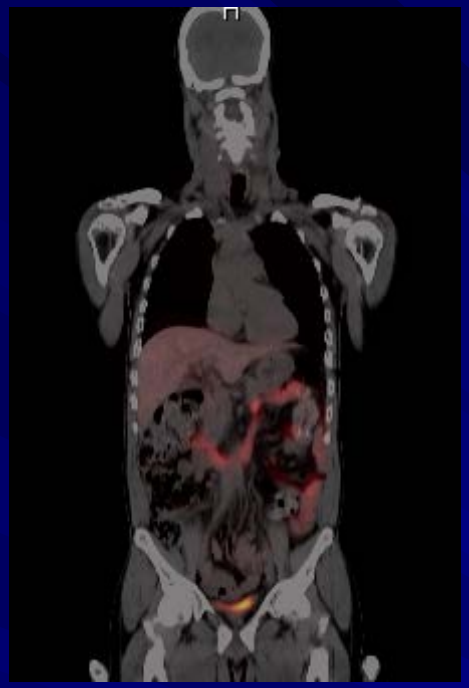
Yordanova et a 2017

A Morgernstern et al. 2018

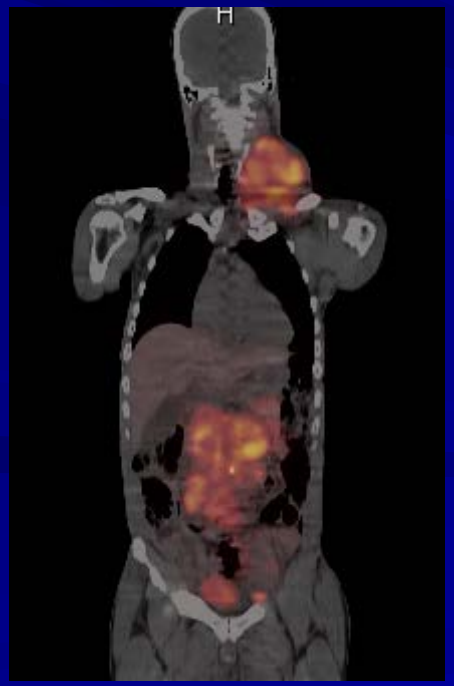
Cancer type	Radioconjugate	Patients	Reference
Leukemia	^{213}Bi-HuM195mAb	49	**[38,39]**
	^{225}Ac-HuM195mAb	36	**[40]**
Lymphoma	^{213}Bi-anti-CD20-mAb	12	**[41]**
Melanoma	^{213}Bi-9.2.27mAb	54	**[42-44]**
Bladder Cancer	^{213}Bi-anti-EGFR-mAb	12	**[32,45]**
Glioma	^{213}Bi-Substance P	68	**[46-48]**
	^{225}Ac-Substance P	19	**[48]**
Neuroendocrine tumors	^{213}Bi-DOTATOC	25	**[4]**
	^{225}Ac-DOTATOC	39	**[49]**
Prostate cancer	**^{225}Ac-PSMA-617**	**190**	**[5,50,51]**

Remission for 26 Months

Post-Tx



Pre-Tx



Radiopharmaceuticals: Targeting of the Hallmarks of Cancer

	Pretoria cohort	Heidelberg cohort		Munich cohort	
Castrate-resistant	70 % (51/73) 29% CR PFS 15.2 mo	8/8/8 MBq	63% (24/38) 13% CR PFS 7.0 mo		
Chemo naive	88% (15/17) 41% CR	8/6/4-6 MBq	63% (19/30) 10% CR		
		6/6/6 MBq	44% (7/16) 12% CR		
		4 GBq Lu / 4 MBq Ac	76% (13/17) 0% CR		
		Ac post Lu	62 % (21/34) 3% CR PFS 4.0 mo	Ac post Lu	33% (5/15) 0% CR

Sathekge……Kratochwil ……Heck……
Morgenstern & Bruchertseifer

- ✓ Characterization of tumor biology - image-based “biomarker”
- ✓ Identification of therapy targets - Theranostics and treatment planning
- ✓ Early Indicator of Tumor Response - patient-specific effect on outcome