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Advances in Targeted Radiopharmaceuticals Therapy Using Isotopes to Fight Cancer

Jacek Capala

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Theranostic

Therapeutic + Diagnostic = Theranostic

- diagnostic test to identify patients that might respond to a specific treatment
- diagnostic test to monitor early response to treatment and predict efficacy

History

- Radioiodine for the diagnosis and treatment of thyroid cancer (1940's)
- Measuring estrogen and progesterone receptors and HER2 expression in breast cancer to guide hormonal and targeted therapy

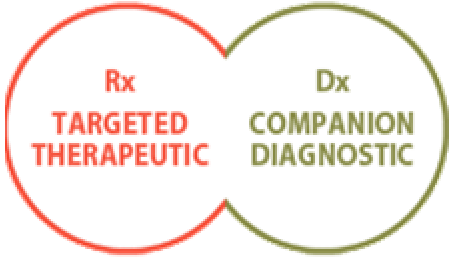
In nuclear medicine, the same or very similar agent can serve as both a diagnostic and therapeutic agent

- whole body imaging to assess the entire tumor burden
- diagnostic imaging to assess the distribution of targeted epitopes

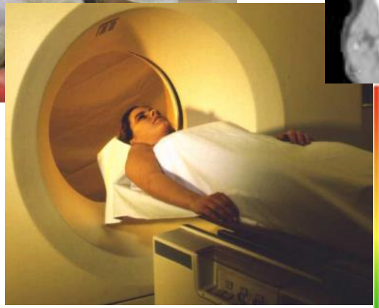
TRT Advantages

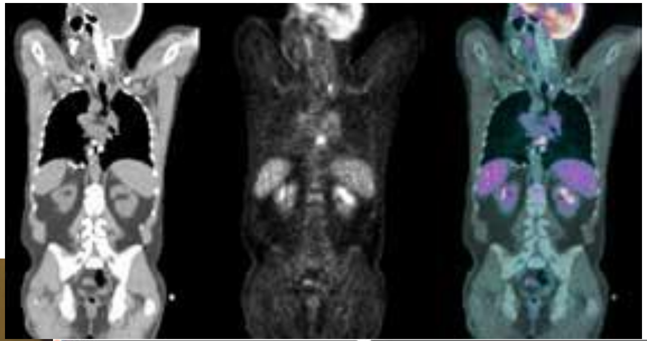
- Arming molecularly targeted agents, including those that are currently used, with therapeutic radionuclides enables:
- Cell killing by DNA strand breaks
- Non-invasive monitoring of biodistribution
- Estimation of dose to tumor and normal tissue
- Selective targeting of occult metastatic lesions
- Cross-fire irradiation; circumventing the local heterogeneity problem

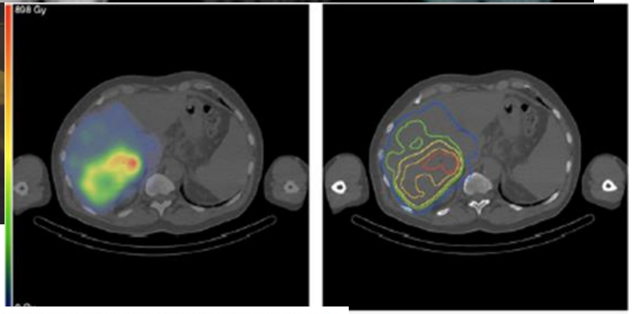
Targeted Radionuclide Therapy (TRT)

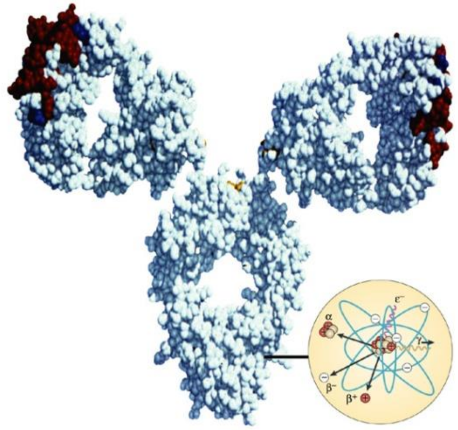


theranostics

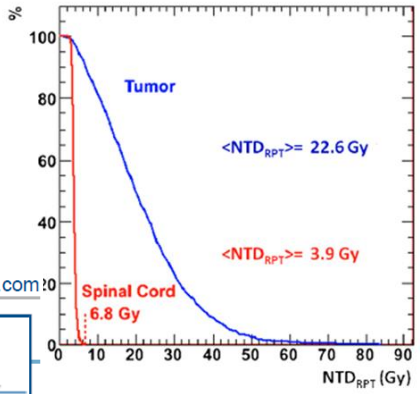








Nature Reviews | Drug Discovery



www.medscape.com

The New Golden Era for Radioimmunotherapy

Not Just for Lymphomas Anymore

Michael B. Tomblyn, MD, MS, Michael J. Katin, MD, Paul E. Wallner, DO

Cancer Control. 2013;20(1):60-71.

Cancer Control

Journal of the Moffitt Cancer Center

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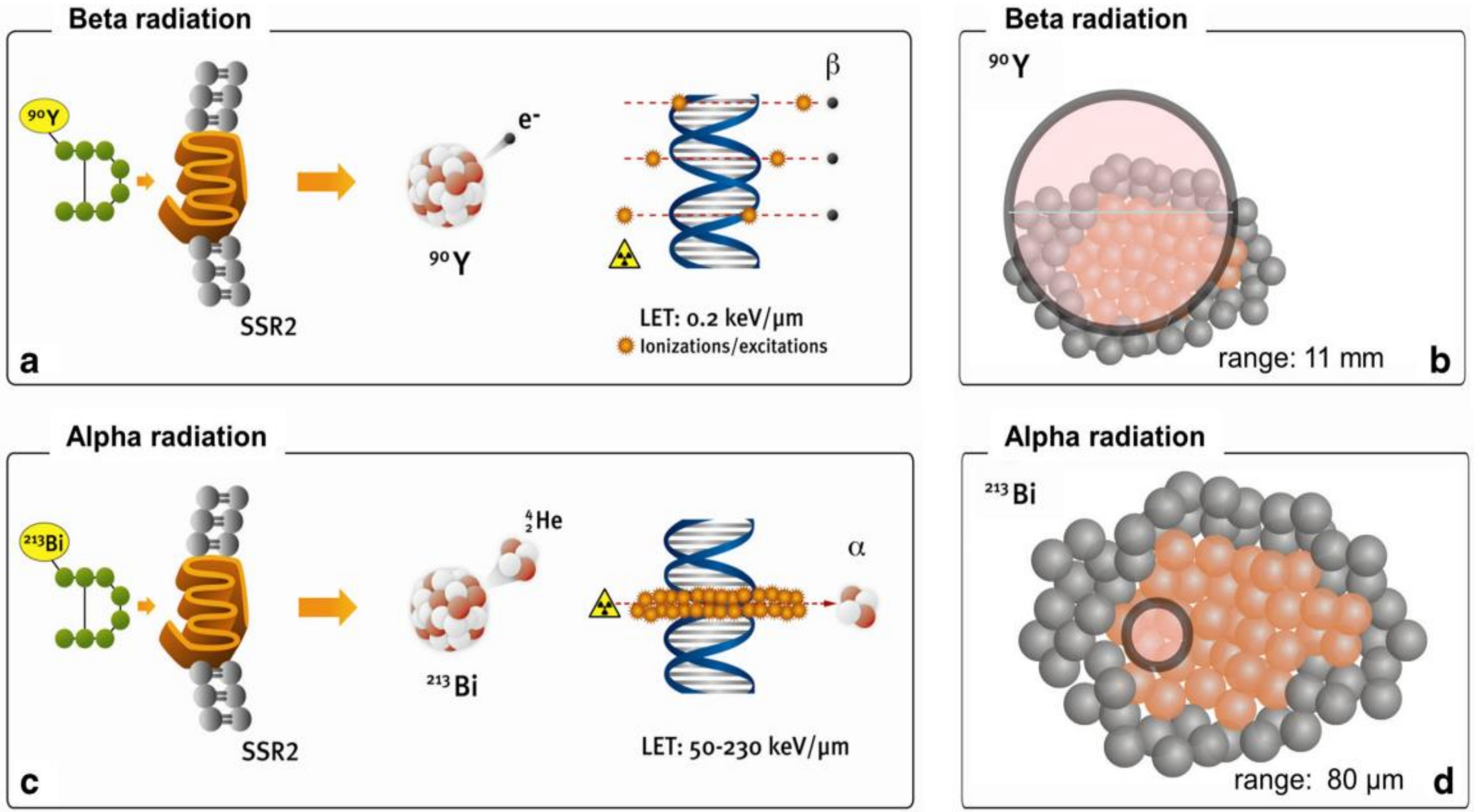
Therapeutic Radiopharmaceuticals – Beta vs Alpha Emitters



Sr-89
Y-90
I-131
Sm-153
Lu-177

At-211
Ra-223
Ac-225

Kratochwil C, et al., 2014. ^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging, 41: 2106-19.

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Beta Emitters

Radio-nuclide	Half-life (d)	E_{mean} (MeV)	Range mean (mm)	E_{max} (MeV)	Range max (mm)	E_{γ} (keV)	I_{γ} (%)
P-32	14.3	0.7	3	1.71	9.1		-
Sr-89	50.6	0.59	2.3	1.5	7.8		-
Y-90	2.67	0.93	4.4	2.28	12		-
I-131	8.03	0.18	0.39	0.81	3.7	284 364 637	6.1 81.5 7.2
Sm-153	1.94	0.22	0.55	0.81	3.7	103	29.3
Ho-166	1.12	0.67	2.8	1.85	10	81	6.6
Lu-177	6.65	0.13	0.23	0.50	1.9	113 208	6.2 10.4
Er-169	9.39	0.10	0.14	0.35	1.1		-
Re-186	3.72	0.35	1.1	1.07	5.2	137	9.5
Re-188	0.71	0.76	3.3	2.12	12	155	15.6

Alpha Emitters

Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_α mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219 Po-215 *Pb-211* Bi-211	4 s 1.8 ms *0.6 h* 130 s	4	6.59	>50
Ra-224	3.66 d	Rn-220 Po-216 *Pb-212* Bi-212	56 s 0.15 s *10.6 h* 1.01 h	4	6.62	>50
Ac-225	10.0 d	Fr-221 At-217 *Bi-213* Po-213	294 s 32 ms *0.76 h* 4 μs	4	6.88	>50
Th-227	18.7 d	Ra-223 Rn-219 Po-215 *Pb-211* Bi-211	11.4 d 4 s 1.8 ms *0.6 h* 130 s	5	6.45	>50
U-230	20.8 d	Th-226 Ra-222 Rn-218 Po-214	0.51 h 38 s 35 ms 0.16 ms	5	6.71	>50

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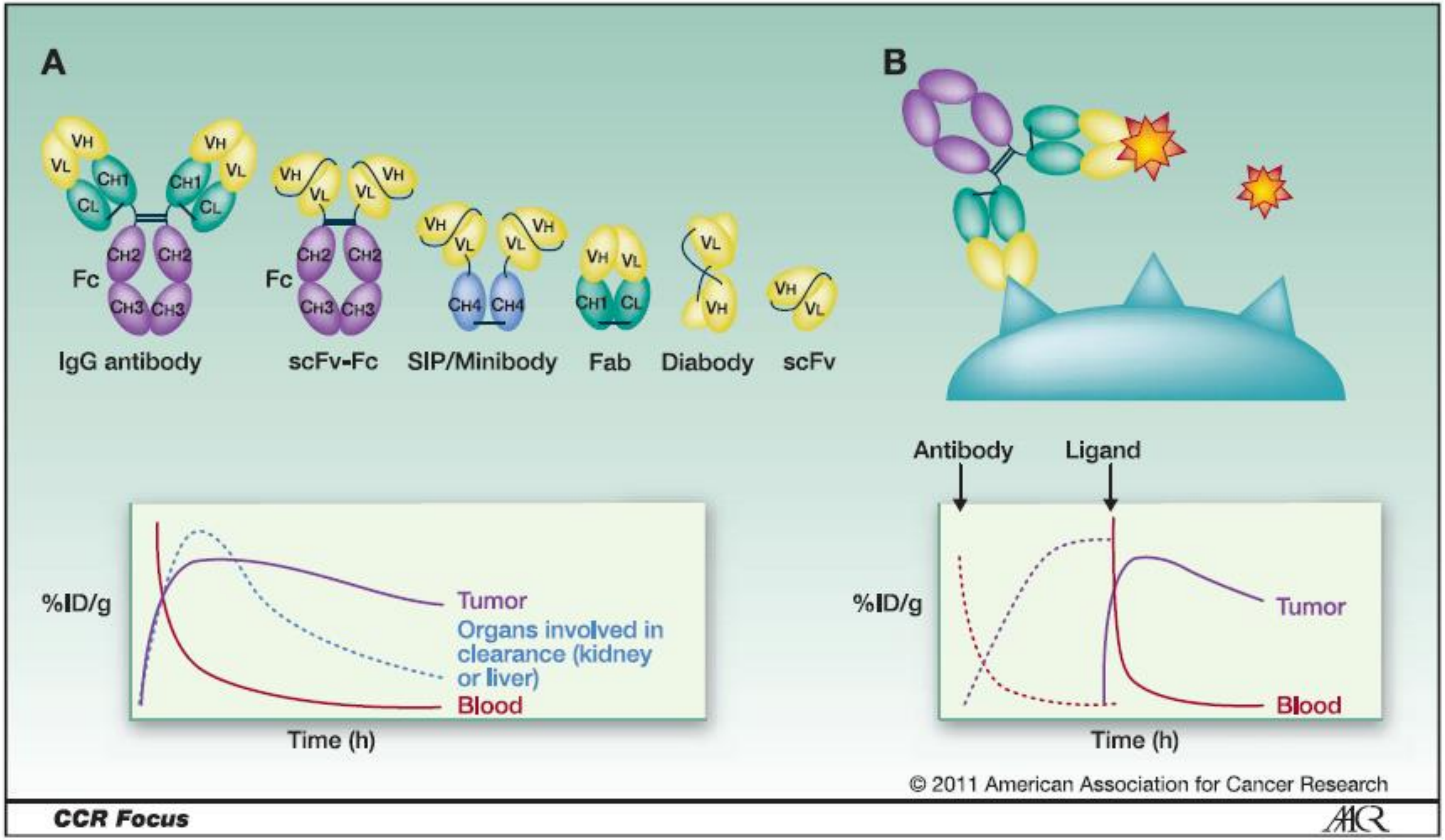
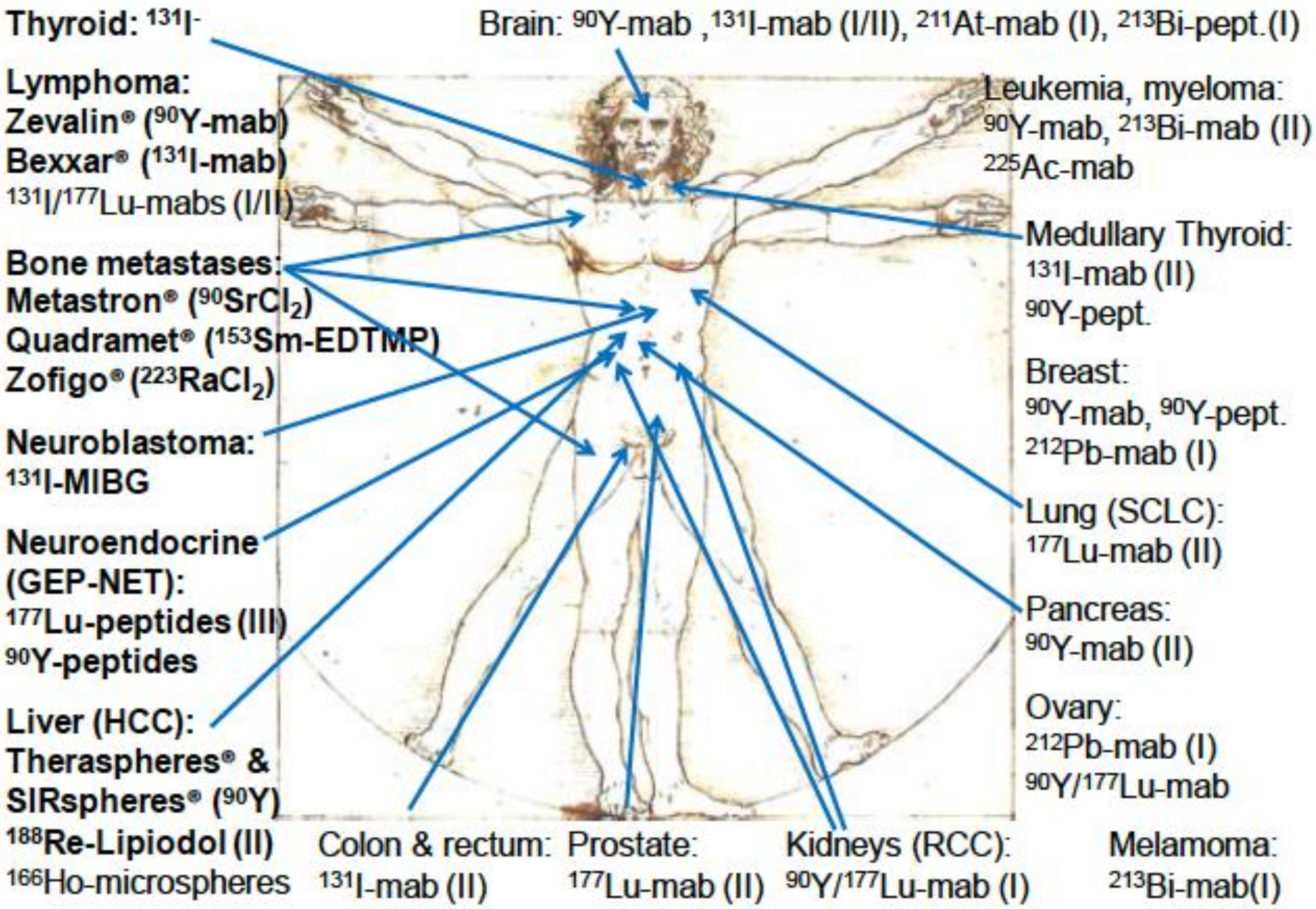
Targeting Agents



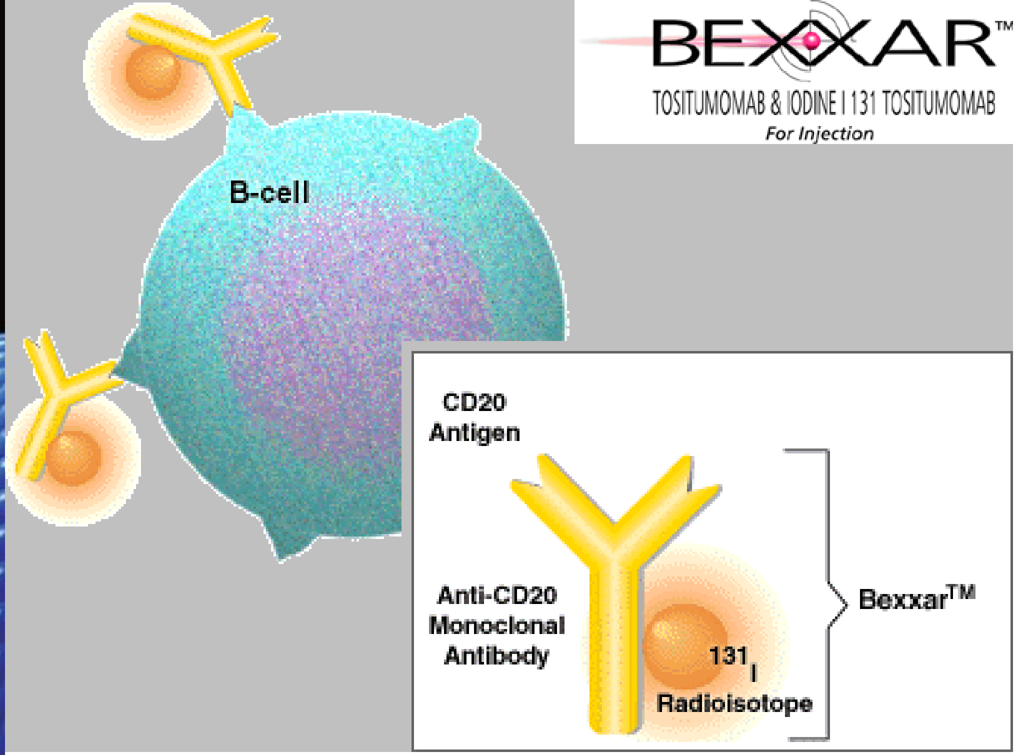
Application

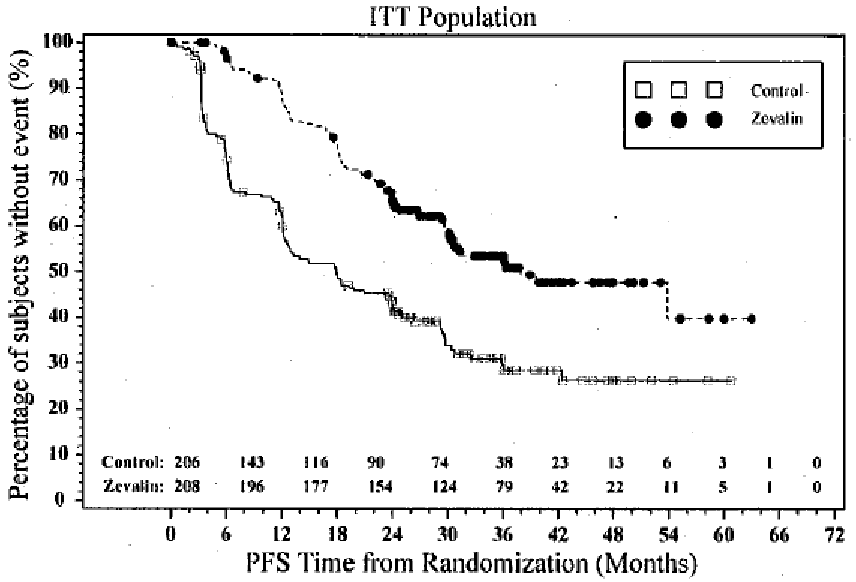


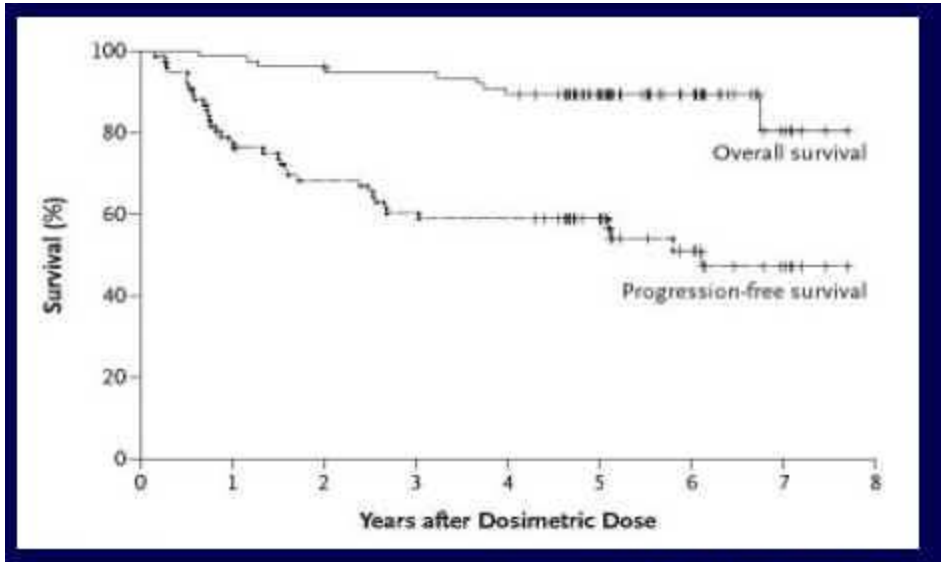
Selumetinib-enhanced Radioiodine Uptake in Thyroid Cancer

before seluemetanib treatment

post four week MEK treatment

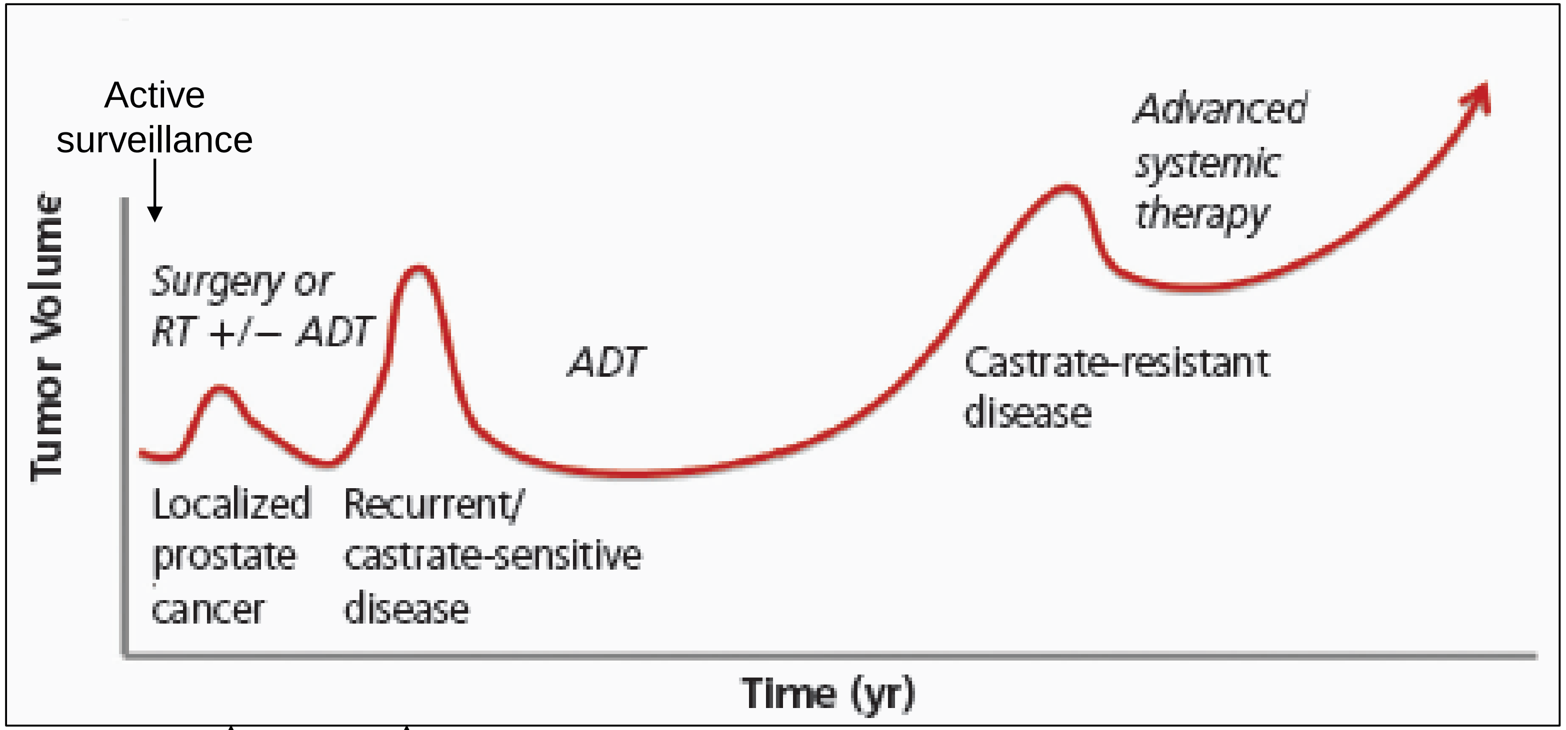






Kaminski et al, NEJM 2005, 352: 441

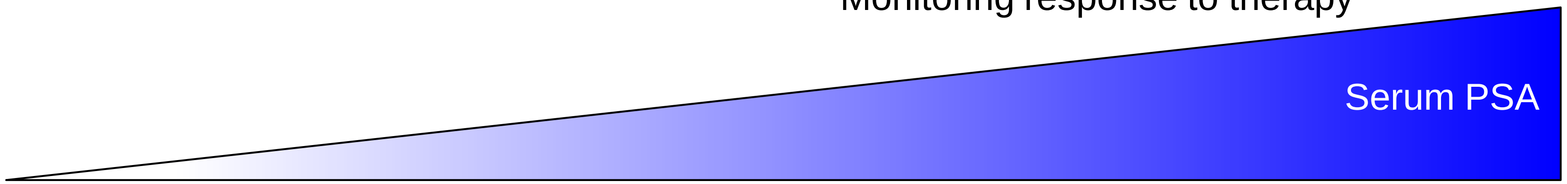
Prostate Cancer Continuum



Initial diagnosis, staging, and biopsy guidance

Detection and restaging of recurrence

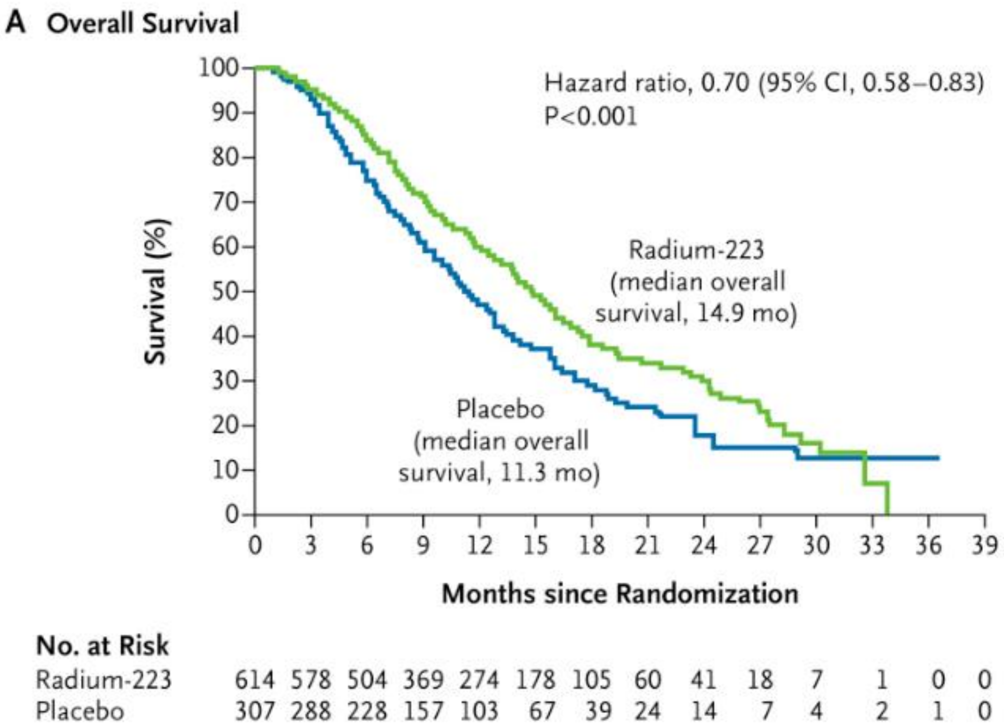
Selection of appropriate therapy
Monitoring response to therapy

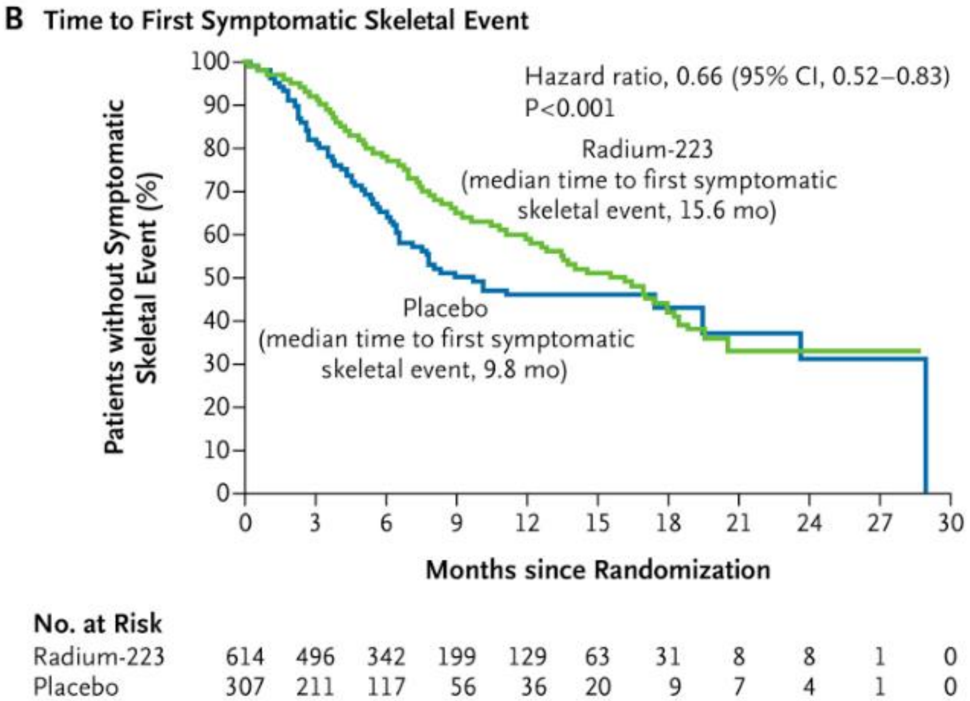


Higher serum PSA and faster PSA doubling time are associated with higher yield of PET imaging for biochemical recurrence

cernetwork.com/oncology-journal/what-should-we-tell-patients-about-physical-activity-after-prostate-cancer-diagnosis

$^{223}RaCl_2$ for Metastatic Castration-Resistant Prostate Cancer





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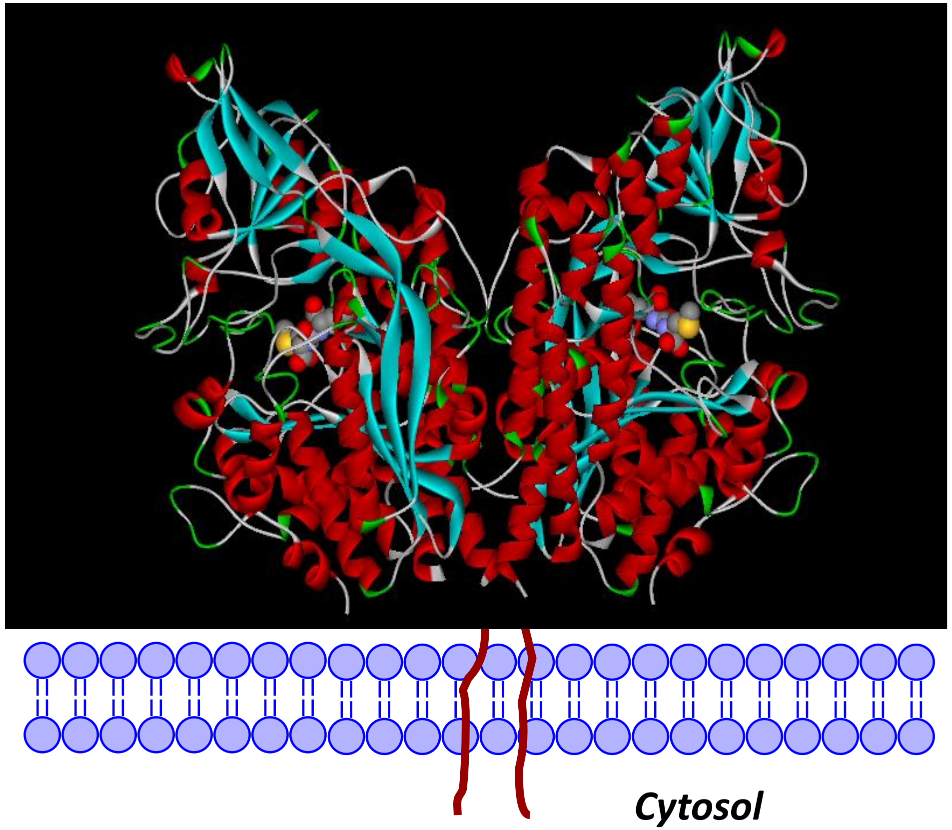
Prostate-specific Membrane Antigen (PSMA)



Curr Med Chem 2012

- Type II transmembrane protein
- Glutamate carboxypeptidase
- Associated with aggressive disease
- Present in solid tumor neovessels
- Marker of androgen signaling

Slide courtesy of Marty Pomper MD, PhD (Johns Hopkins) and Steve Cho MD (University of Wisconsin-Madison)

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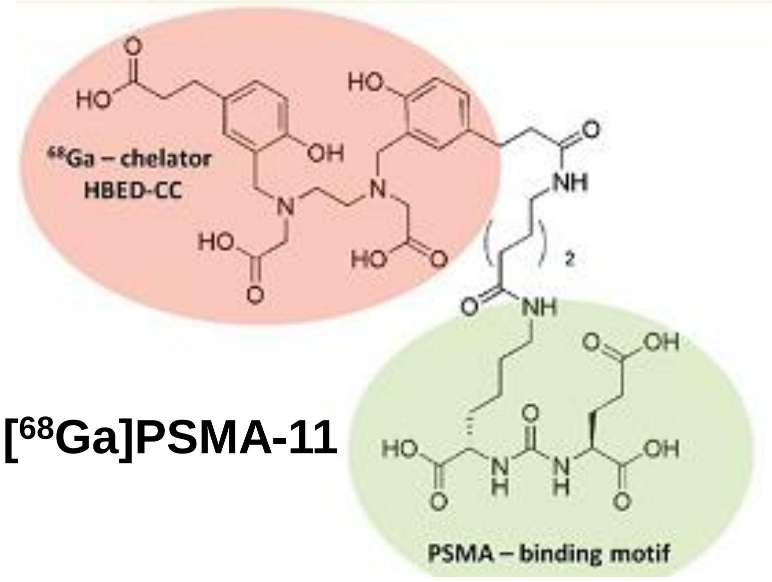
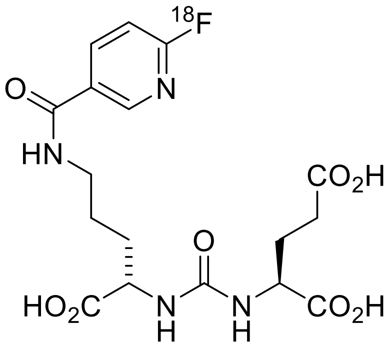
Selected PET Tracers Targeting PSMA

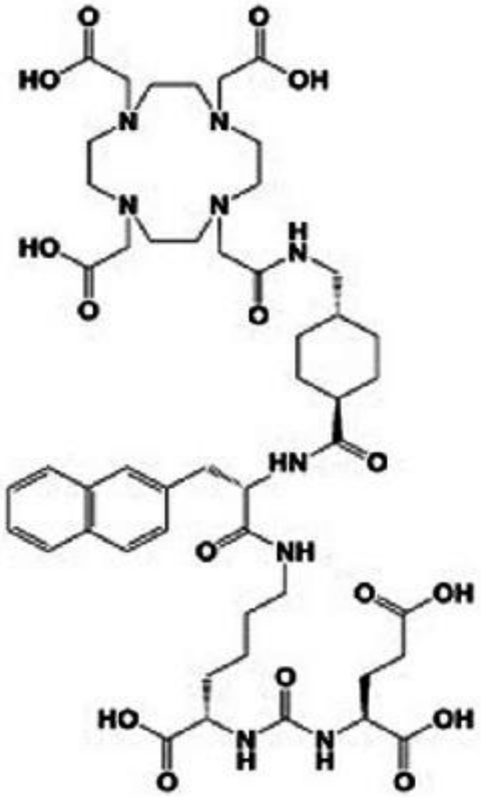


[^{68}Ga]PSMA-11

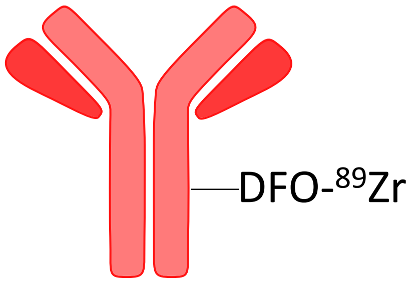
Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)]



[^{18}F]DCFPyl

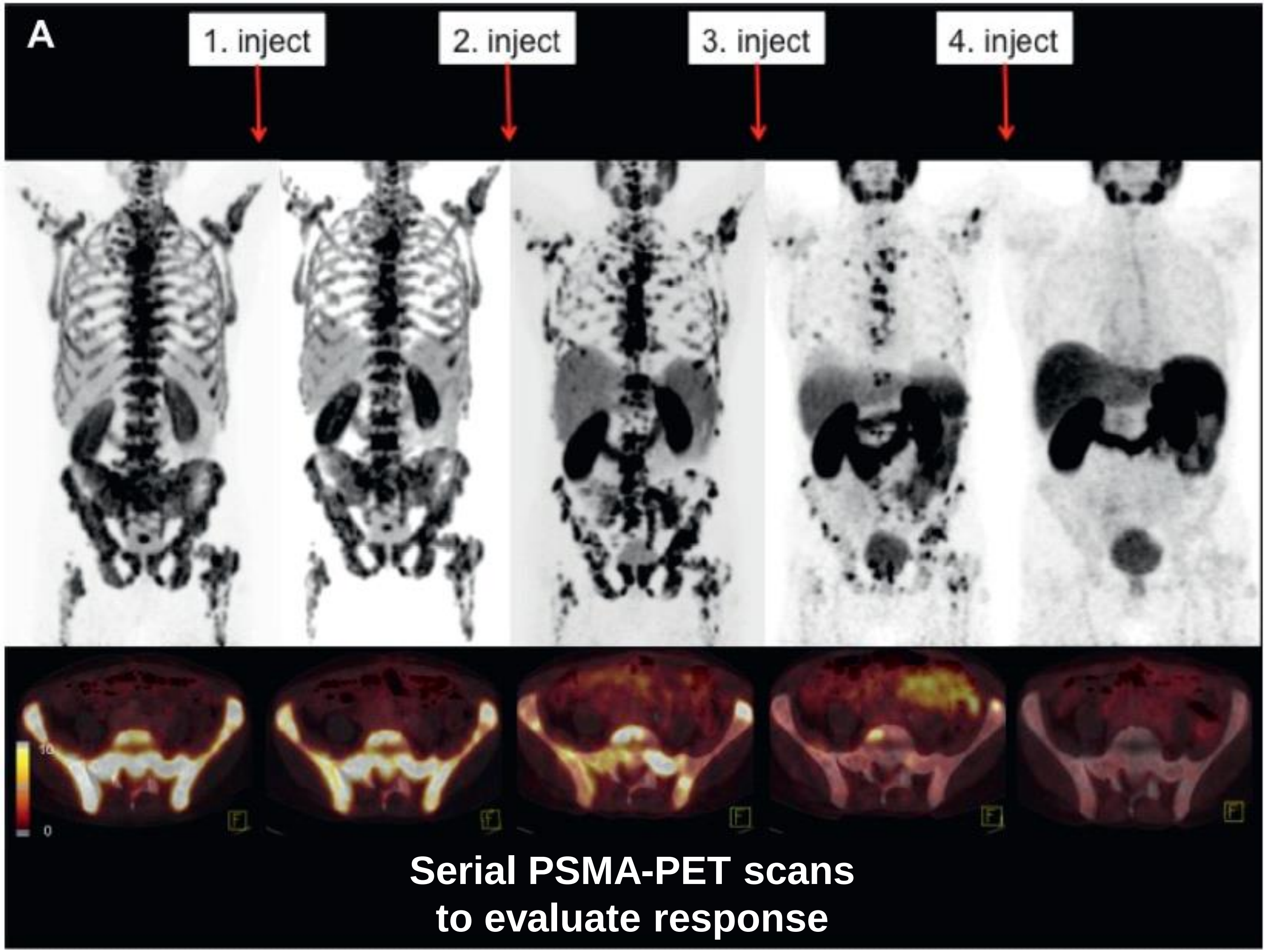


[^{177}Lu]PSMA-617



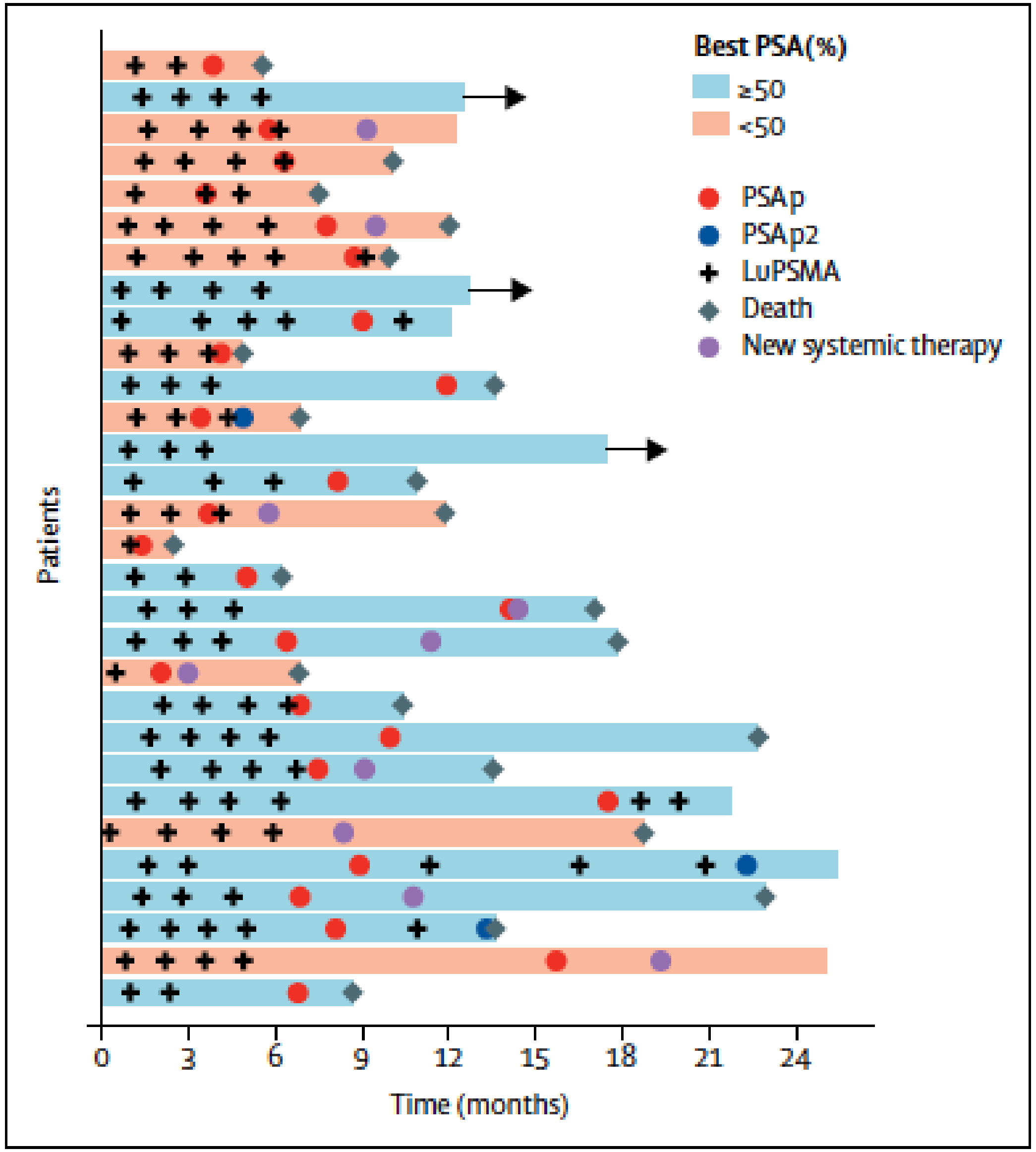
[^{89}Zr]DFO-J591

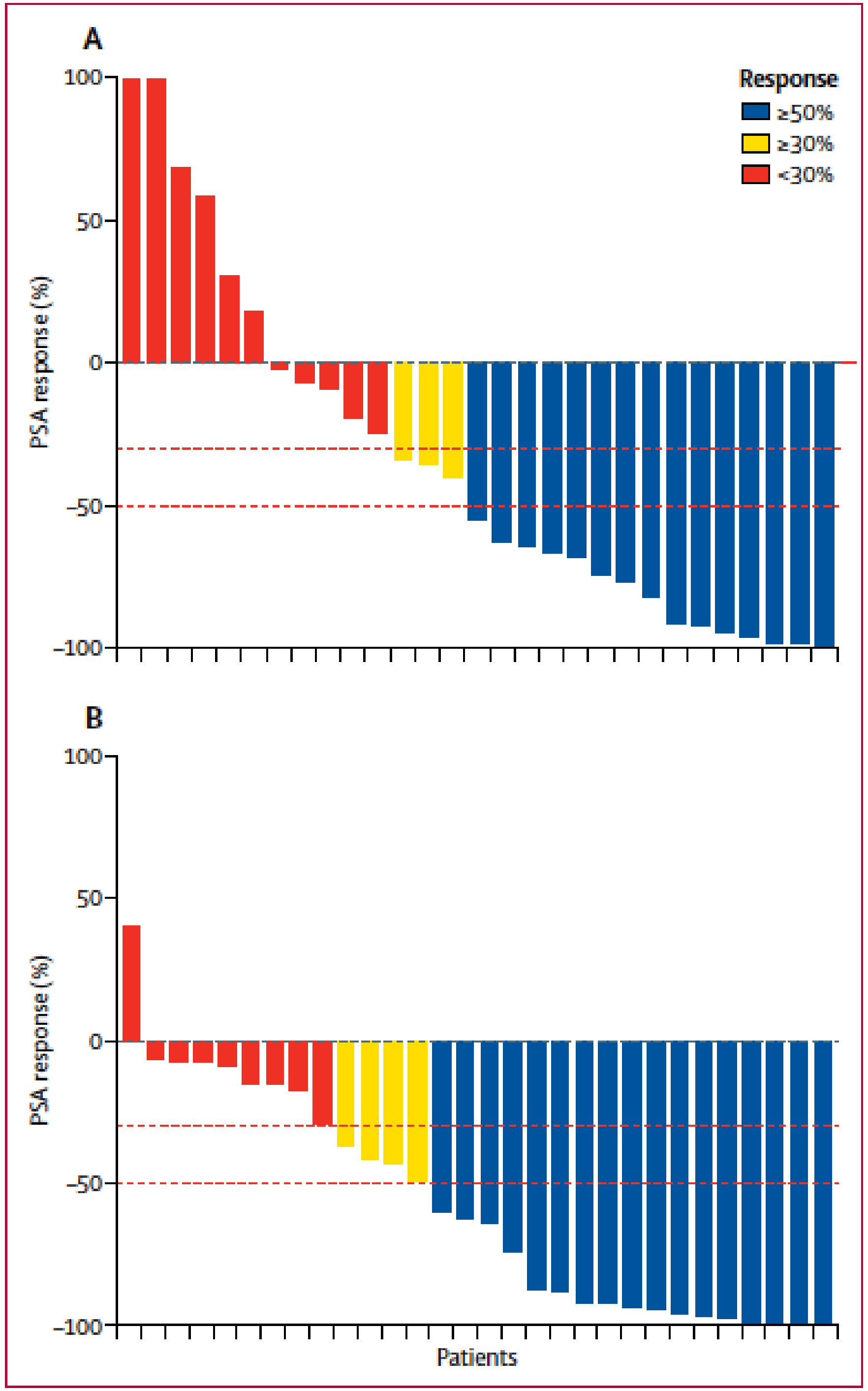
Lu-177 PSMA for TRT



Heck, MM, et al., 2016. Systemic Radioligand Therapy with ^{177}Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer. J Urol, 196: 382-91.

Lu-177 PSMA for TRT





www.thelancet.com/oncology Published online May 8, 2018

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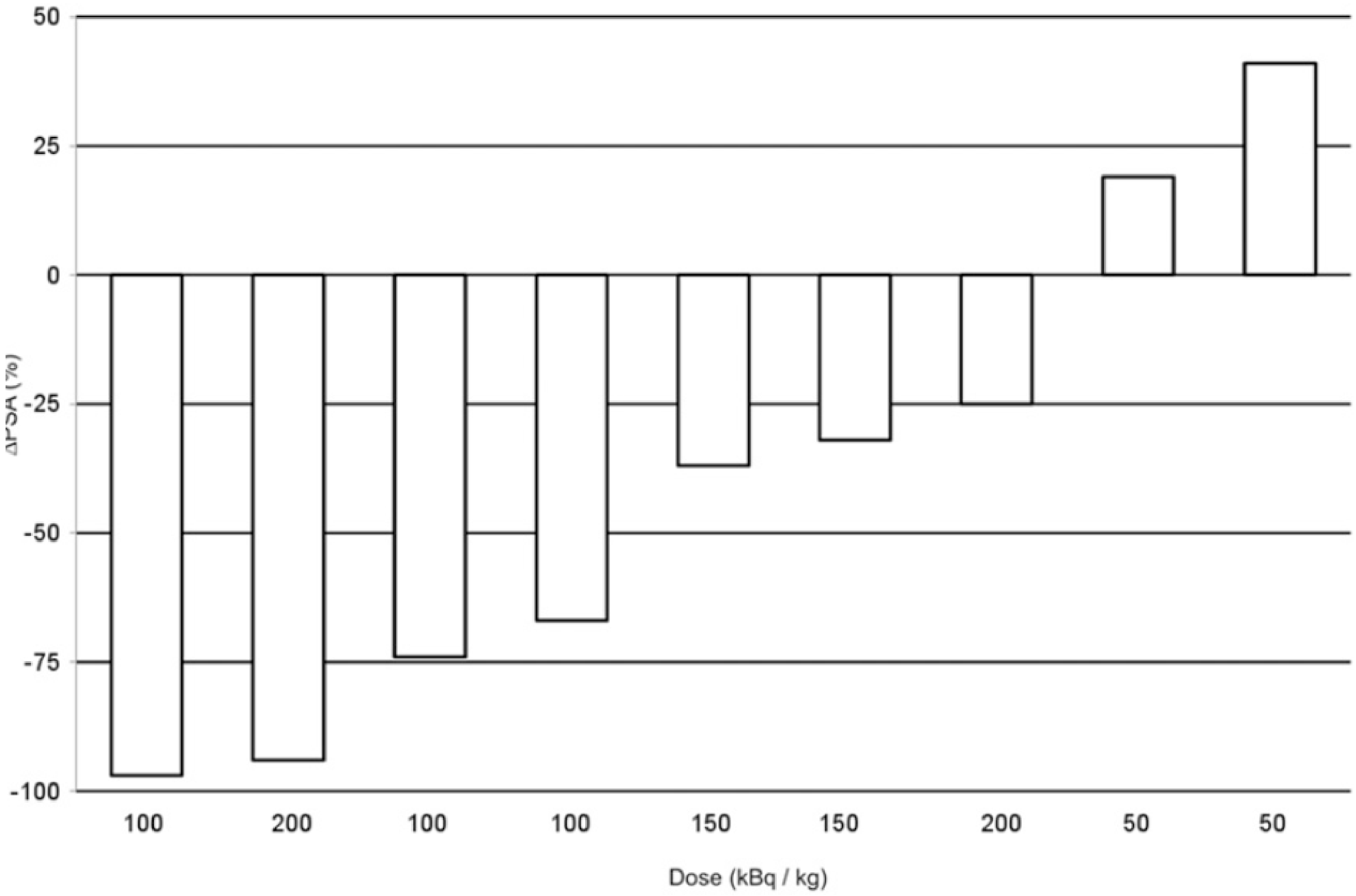
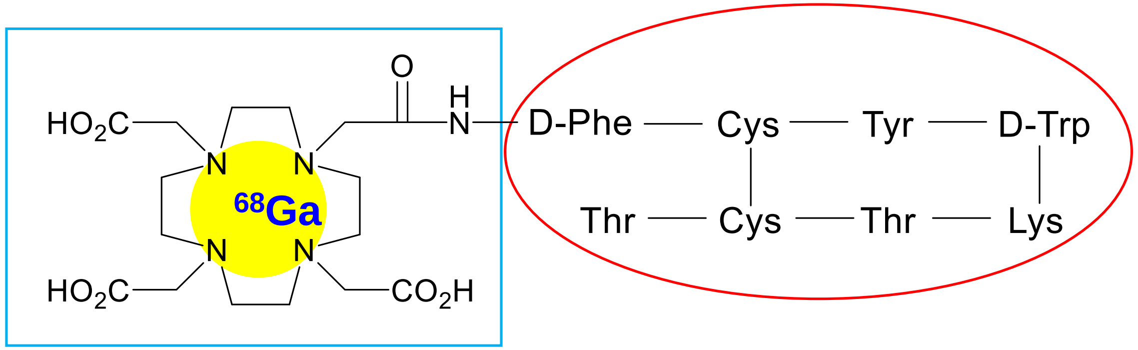
^{225}Ac-PSMA-617 for TRT



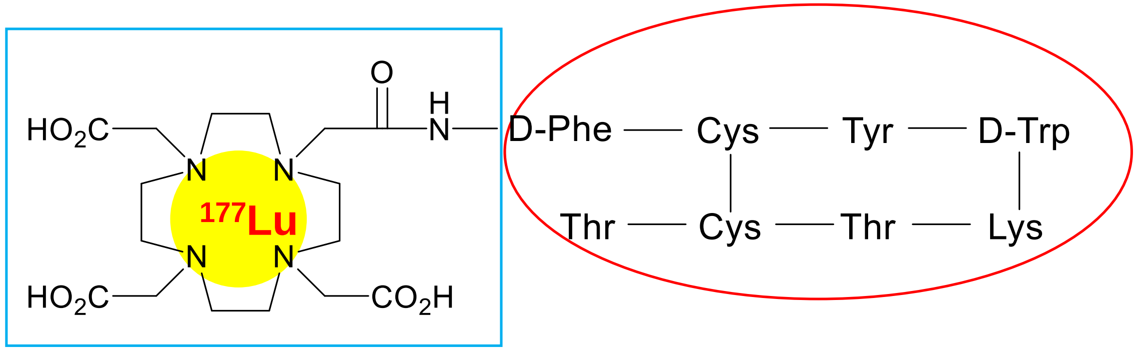
Waterfall graph of PSA response in evaluable patients. PSA response was observed in 75% of patients. No dose–response correlation was observed the 100–200 kBq/kgBW treatment activities

Recently Approved Theranostic Approach

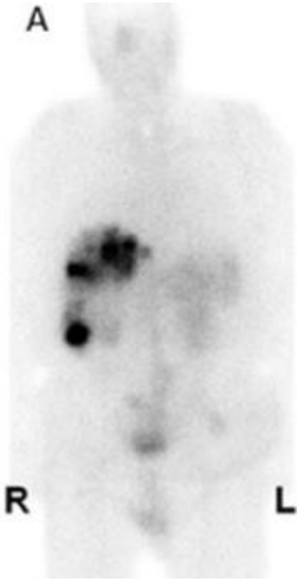
[^{68}Ga]DOTATATE for imaging (NETSPOT)



[^{177}Lu]DOTATATE for imaging (Lutathera)



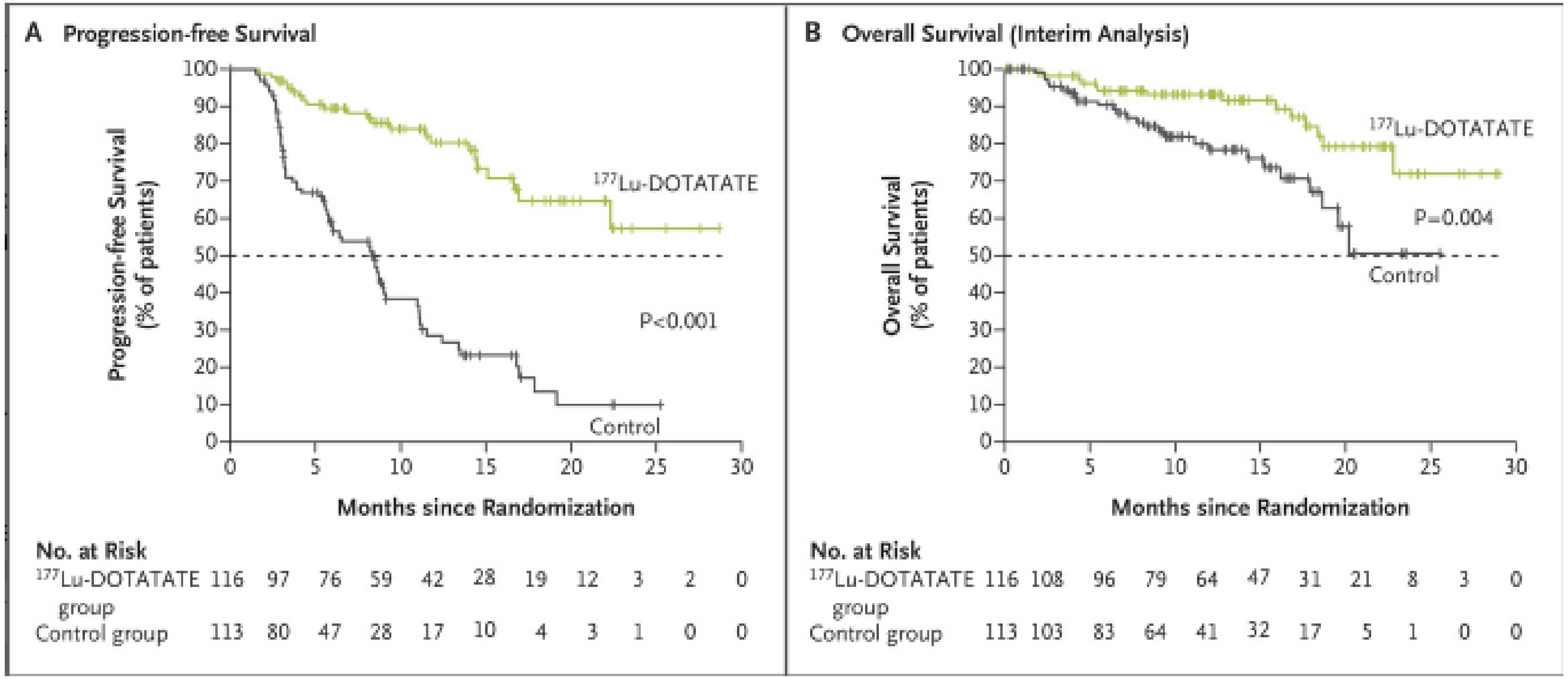
[^{68}Ga]DOTATATE



[^{177}Lu]DOTATATE

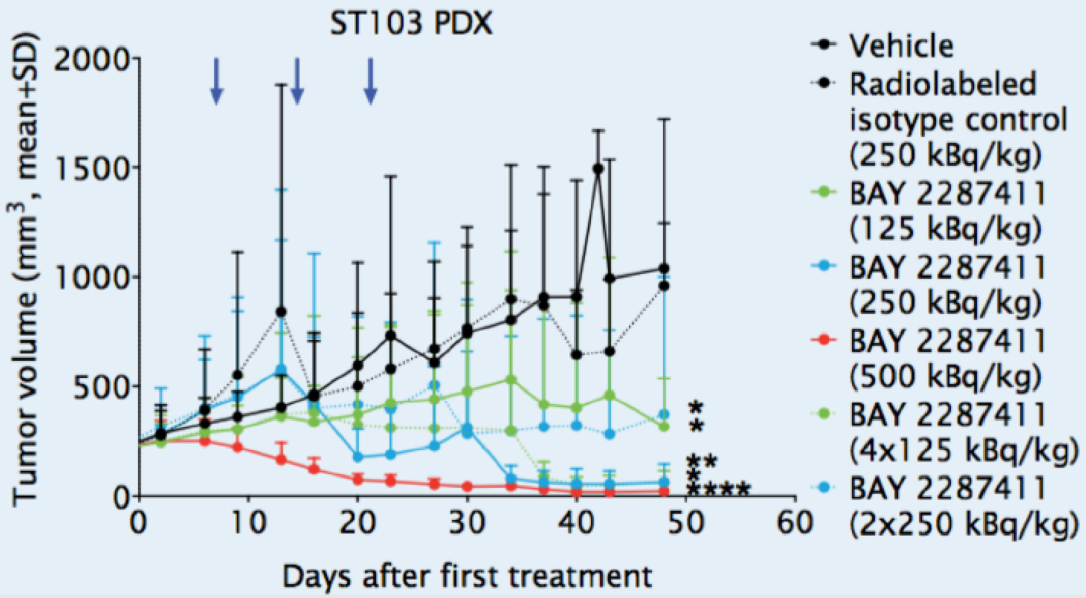
Sainz-Esteban, A, et al., 2012. Eur J Nucl Med Mol Imaging, 39: 501-11.

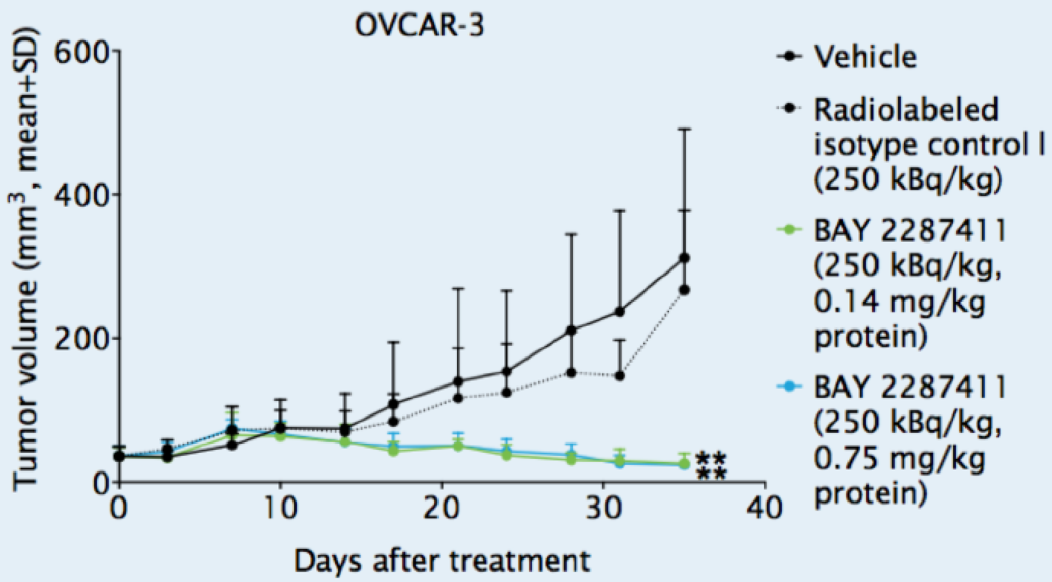
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors



N Engl J Med 2017; 376:125-135January 12, 2017 DOI: 10.1056/NEJMoa1607427

Mesothelin-Targeted Th-227 Radioconjugtes





850

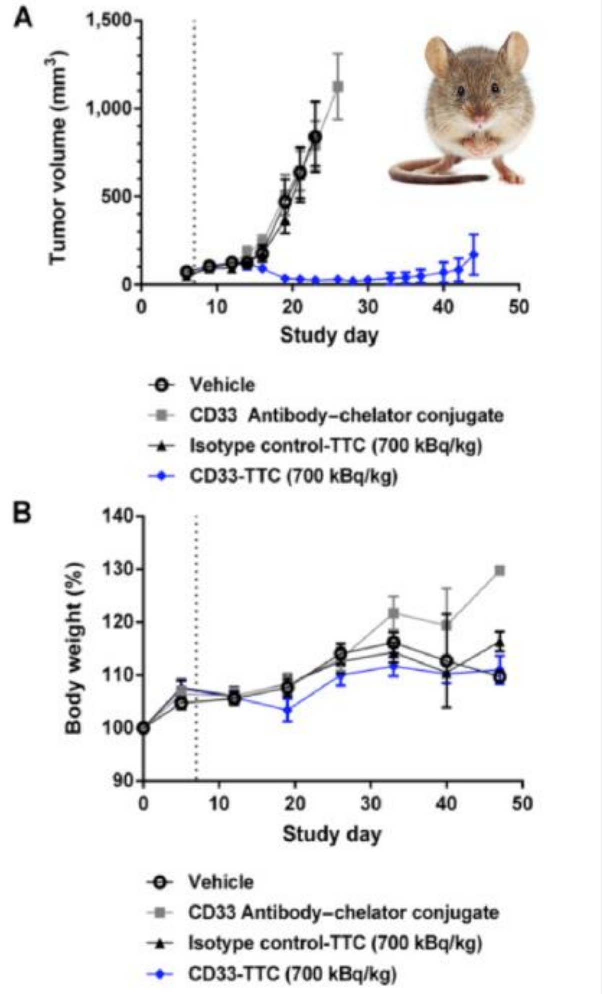
Mesothelin-Targeted Thorium-227 Conjugate (MSLN-TTC; BAY 2287411): Preclinical evaluation of a new targeted alpha therapeutic in mesothelin-positive cancers

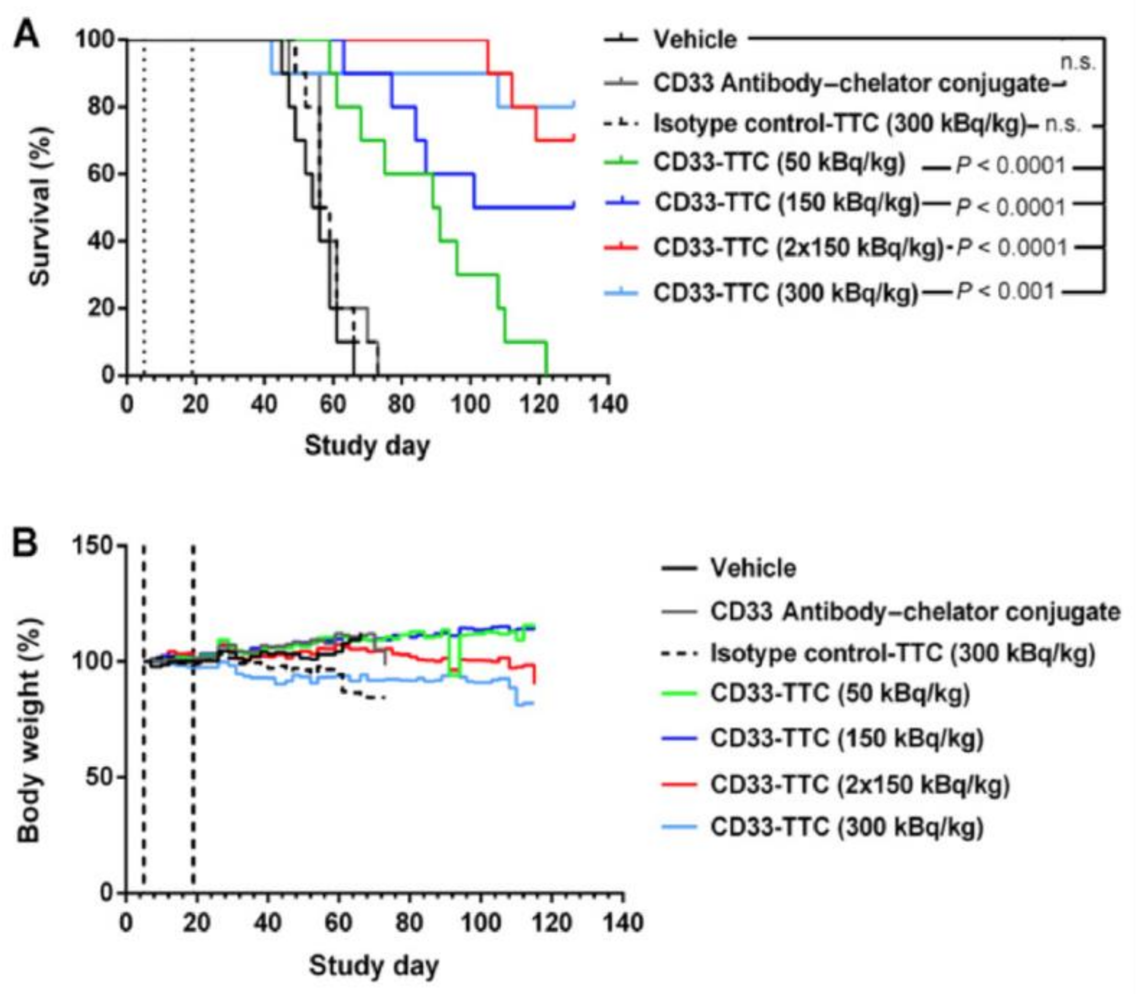
Urs B Hagemann[1], Alexander Kristian[2], Christine Ellingsen[2], Veronique Cruciani[2], Katrine Wickstroem[2], Anne Mobergslien[2], Jenny Karlsson[2], Roger M Bjerke[2], Christoph Schatz[1], Christoph Kneip[1], Joachim Schuhmacher[1], Liv-Ingrid-Oedegaardstuen[2], Hartwig Hennekes[1], Anna Tafuri[1], Dominik Mumberg[1], Hanno Wild[3], Karl Ziegelbauer[1] and Alan Cuthbertson[2]

[1]Bayer AG, Pharmaceutical Division, Berlin, Germany; [2]Bayer AS, Pharmaceutical Division, Oslo, Norway; [3]Bayer AG, Pharmaceutical Division, Wuppertal, Germany

American Association for Cancer Research, 2018

CD33-Targeted Th-227 Radioconjugate





Large Molecule Therapeutics

Molecular Cancer Therapeutics

***In Vitro* and *In Vivo* Efficacy of a Novel CD33-Targeted Thorium-227 Conjugate for the Treatment of Acute Myeloid Leukemia**

Urs B. Hagemann, Katrine Wickstroem, Ellen Wang, Adam O. Shea, Kristine Sponheim, Jenny Karlsson, Roger M. Bjerke, Olav B. Ryan, and Alan S. Cuthbertson

Mol Cancer Ther. 2016 Oct;15(10):2422-2431

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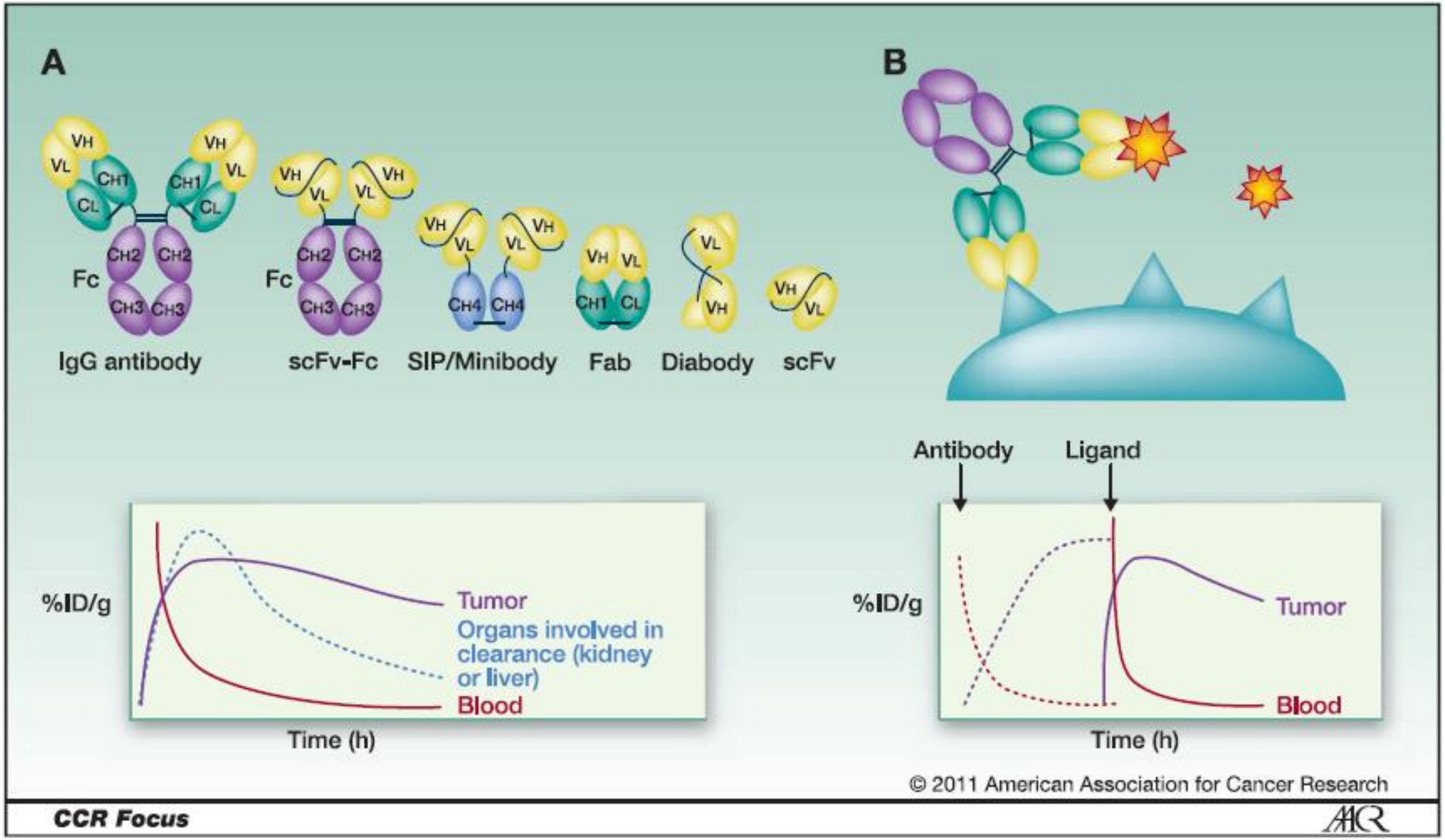
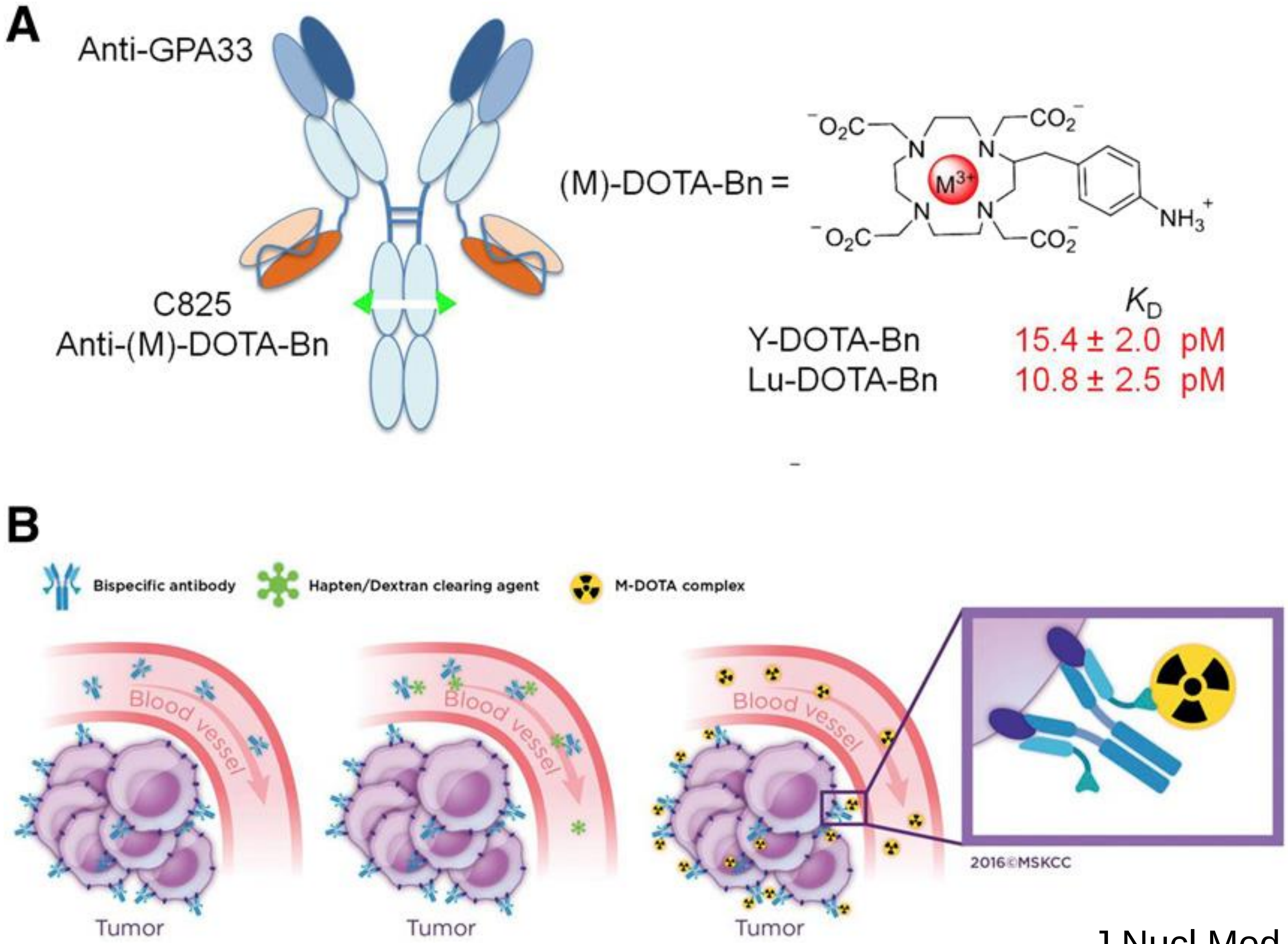
Targeting Agents

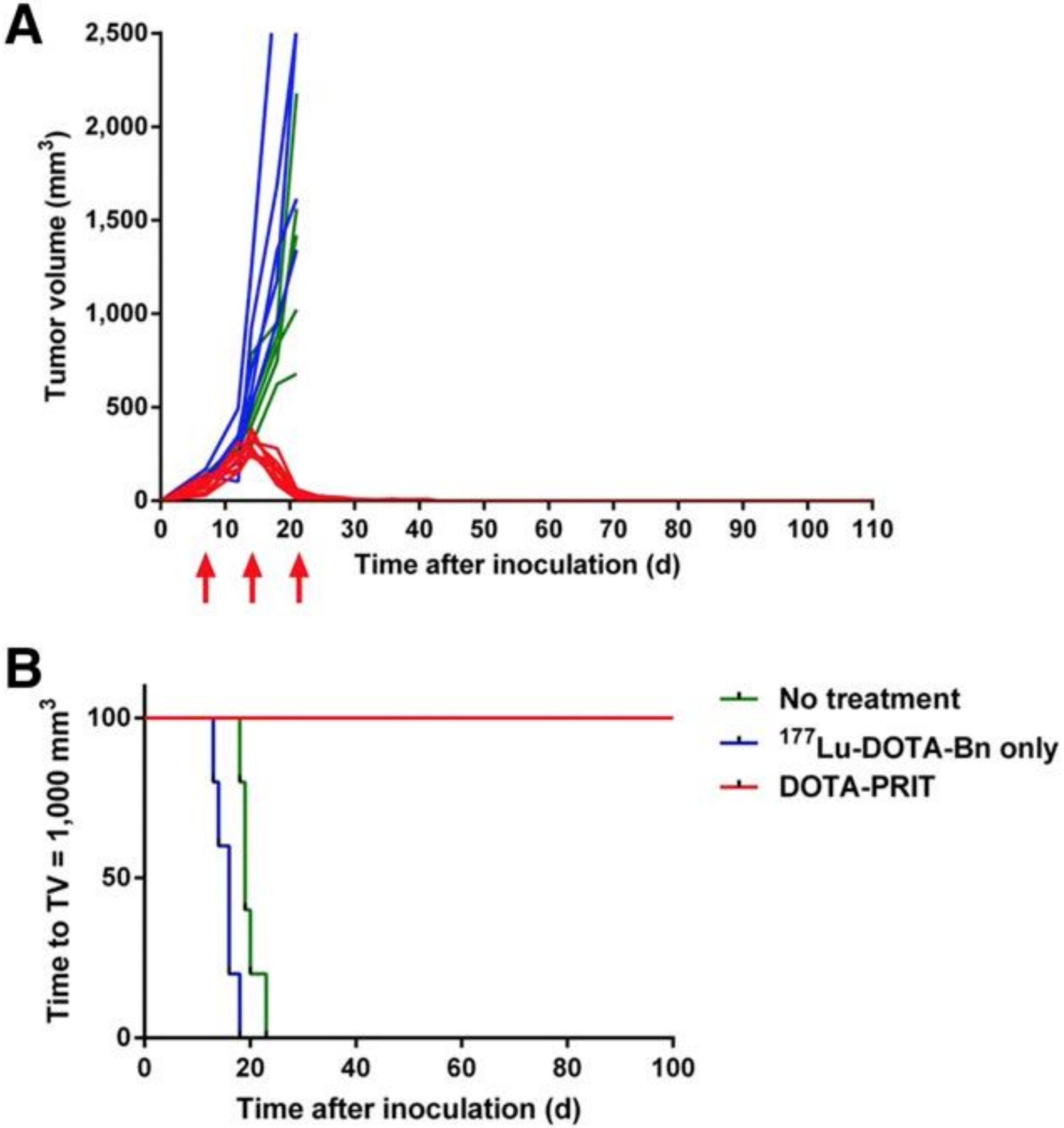


Pre-targeting



J Nucl Med 2017; 58:1735–1742

Pre-targeting



J Nucl Med 2017; 58:1735–1742

Summary

Approved

- Sodium Iodine-131
  - Thyroid cancer
  - Hyperthyroidism
- Ra-223 dichloride for CRPC
- Sm-153 EDTMP, Sr-89 for osseous metastases
- I-131 tositumomab, Y-90 ibritumomab tiuxetan for lymphoma
- Intracavitary therapy with P-32 colloid
- Hepatic arterial radioembolization with Y-90 microspheres
- I-131-MIBG
- Lu-177-DOTATATE for NETs

Investigational

- PRRT
  - Y-90 DOTATOC
  - Lu-177 antagonists
- PSMA
  - I-131, Lu-177, Bi-213, Ac-225
- Ra-223 dichloride outside CRPC
- Radiolabeled antibodies
  - I-131 or Ac-225 antibody for leukemia
- At-211 MABG
- Mesothelin-Targeted or CD33-Targeted Th-227
- HER2-targeted Pb-212
- Many, many others

Challenges and opportunities

- Reliable and economically viable supply chain of radionuclides for theranostics for preclinical research, clinical trials, and routine use
- Funding to support preclinical and early translational theranostic development
- Regulatory approval pathways for theranostics that address both the imaging and therapeutic aspects of the agent
- Adequate reimbursement for FDA-approved diagnostic and therapeutic agents
- Clinical adoption of approved theranostic agents
- Potential competition with other cancer therapies
- Incorporation earlier in cancer treatment and combination with other disease-specific treatments
- Individual treatment planning

Treatments historically governed by activity administered:

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi Y-90 microspheres for treatment of liver metastases
- 200 mCi I-131 mIBG for neuroendocrine tumours
- 200 mCi x 4 for Y-90 DOTATATE of neuroendocrine tumours
- 200 mCi x 4 for Lu-177 DOTATATE for neuroendocrine tumours
- 200 mCi x 4 for Lu-177 PSMA for bone metastases
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Empirical (chemotherapy) paradigm – learning from observation and experience…

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Chemotherapy-like approach leading to significant differences in the dose delivered to tumor and normal tissues

I-131 NaI for DTC (mGy / MBq)	Ra-223 for bone metastases (mGy / MBq)	Lu-177 PRRT (mGy / MBq) from Eberlein Et al J Nucl Med 2017
Red marrow: Bianchi (2012) 0.04 – 0.4	Red marrow: Chittenden (2015) 177-994	Red marrow: 0.1 - 0.13
Metastatic lesions: Kolbert (2007) 0.03 – 2.6	Lesions: Pacilio (2016) 0.9 – 8.9	Tumor 3.9 - 37.9 0.1 - 20.0 1.4 - 23
Salivary glands: Jentzen (2006) 0.2 - 1.2	Kidneys: Chittenden (2015) 2-15	Kidneys: 0.33 - 2.4 0.27 - 1.35
Thyroid remnants: Minguez (2016) 0.2 - 160	Bone surfaces Chittenden (2015) 2331 – 13118	

Absorbed doses from fixed activities of I-131 NaI, Ra-223 and Lu-177 vary by ~1 order of magnitude for organs at risk and 2 orders of magnitude for target volumes

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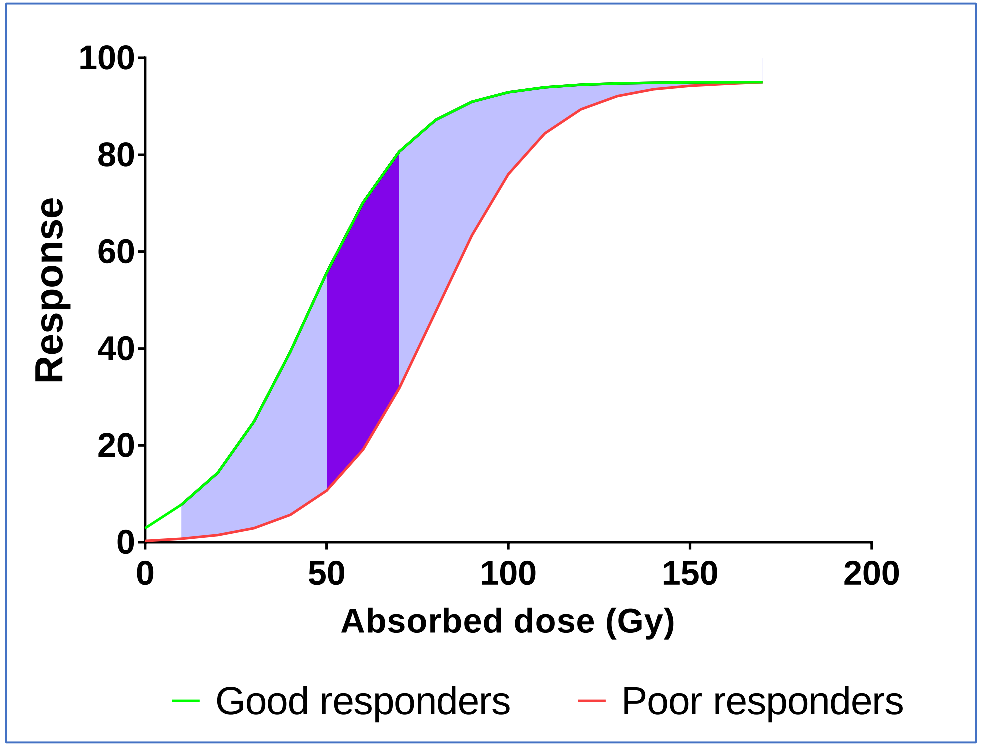
Clinical trials

Treatment according to Gy, even with an uncertainty on the absorbed dose, will deliver a narrower range of responses.



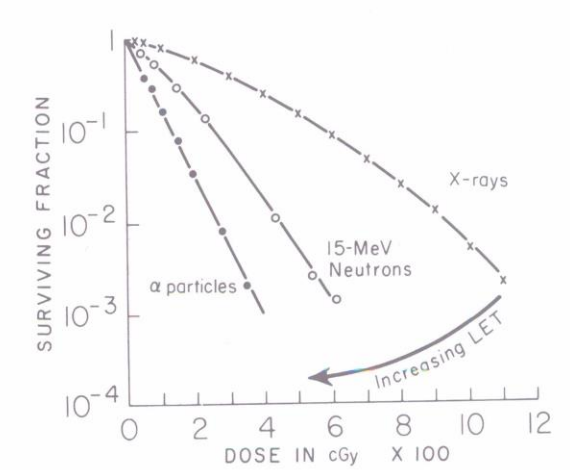
Example:

Target absorbed dose 60 Gy, with a 30% uncertainty.

An RCT would be comparing a large range of unknown doses with a narrow range of known doses

Randomising between knowledge vs ignorance…

The need to optimize the treatment



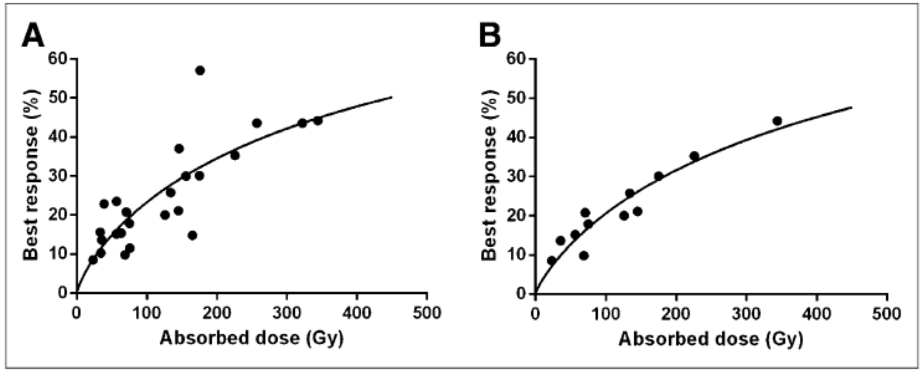
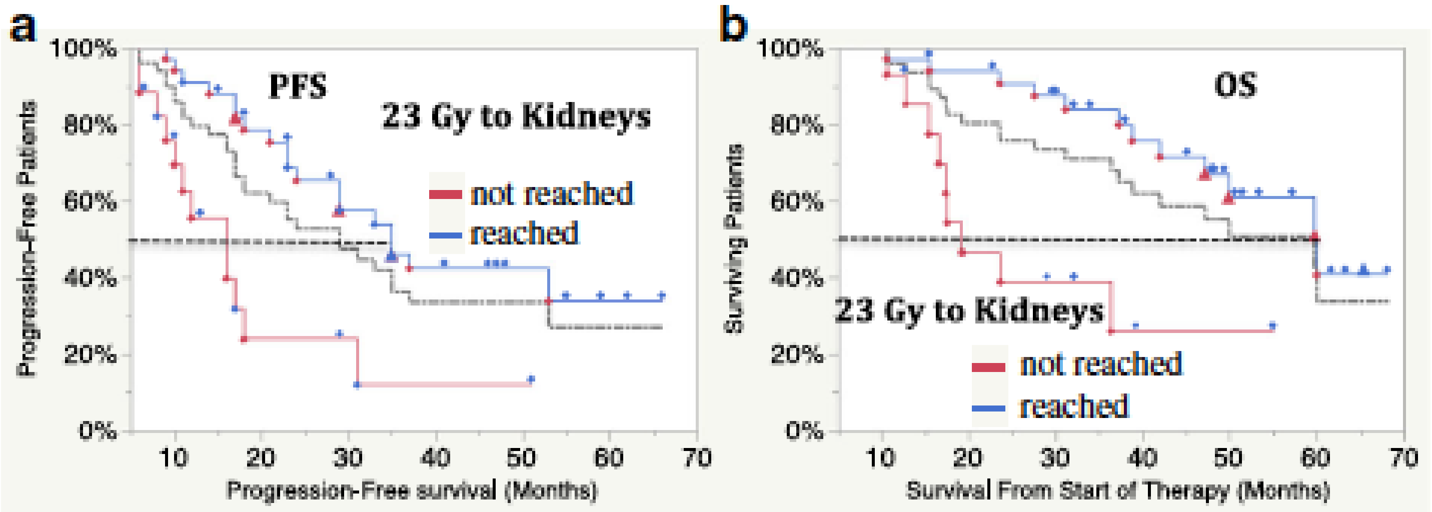


FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using ^{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B).



50 patients who received prescribed four cycles of 177Lu-DOTAoctreotate.

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:970–988

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TO DO OR NOT TO DO DOSIMETRY?

That is *not* the question:

- Patient safety
- Treatment justification (patient selection)
- Treatment optimisation
- Health economics

Just a matter of time and effort

Thank you

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