Memorial Sloan Kettering Cancer Center

National Cancer Policy Forum

Understanding Biological Activity to Inform Drug Development

December 12, 2016

Wolfgang Weber
Molecular Imaging and Therapy Service
Department of Radiology

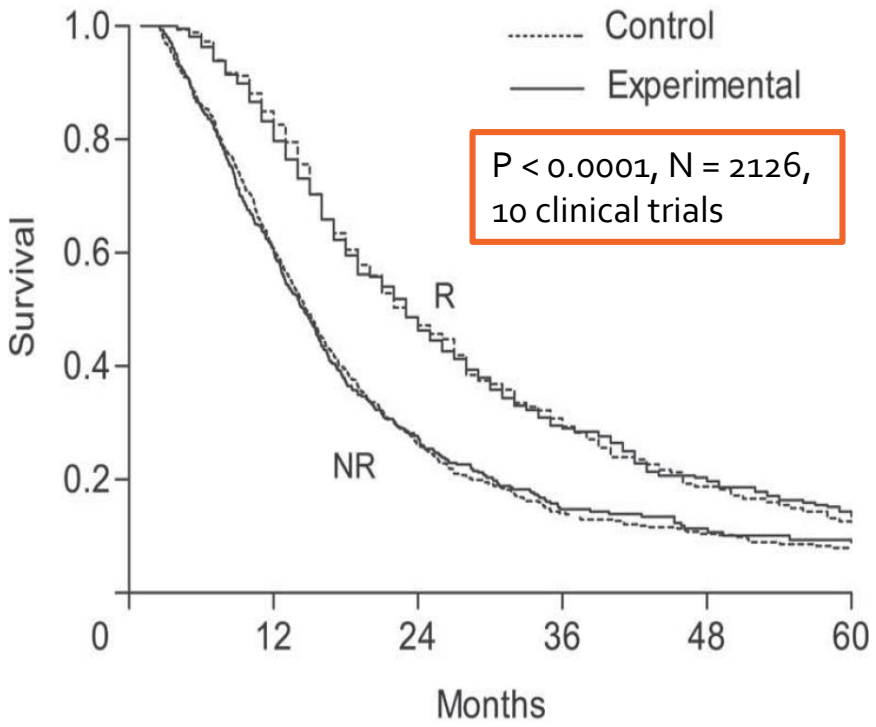
RECIST – Response evaluation criteria in solid tumors

- Tumor response defined by number and size of tumor lesions
- Criteria developed in the seventies (WHO criteria) for technologies available at this time (palpation and planar x-rays)
- Refined/simplified for broad use in clinical trials as RECIST 1.0 and RECIST 1.1
  (decrease of the number of lesions measured, one-dimensional instead of bi-dimensional measurements)
- Correlation of RECIST response with patient outcome has been demonstrated by analyses of imaging data from multiple clinical trials
- Modified (but not fundamentally different) systems for response assessment are used in specific tumor types/treatments (e.g. immune-related response criteria)

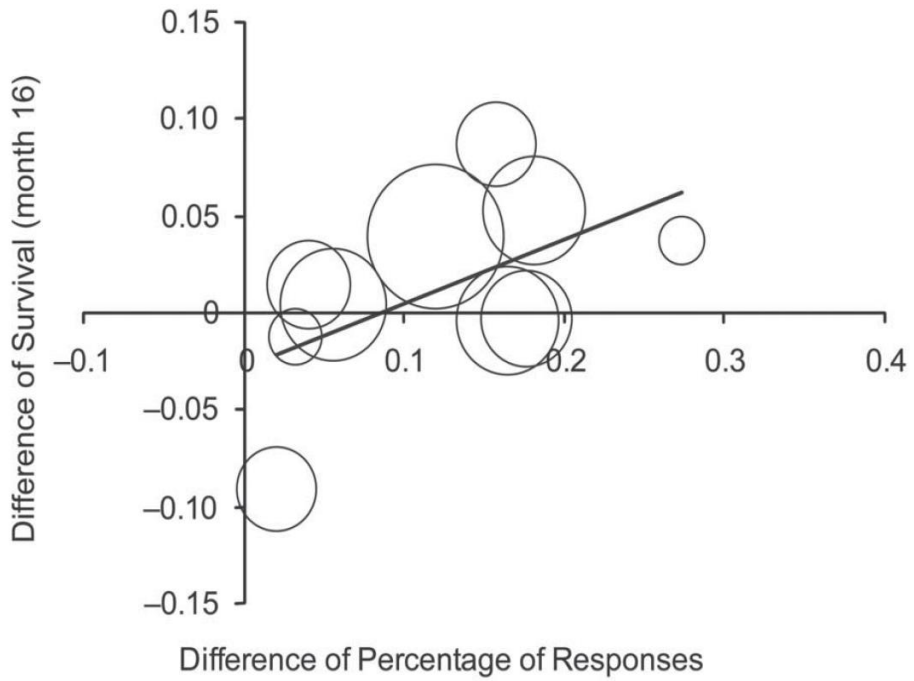
Miller et al. Cancer (1981) 47:207-214
Therasse et al. J Natl Cancer Inst (2000) 92:205-216
Eisenhauer et al. Eur J Cancer (2009) 228-247
Wolchok et al. Clin Cancer Res (2009) 15:7412 – 7420

RECIST and patient survival in metastatic breast cancer

Overall survival on patient level



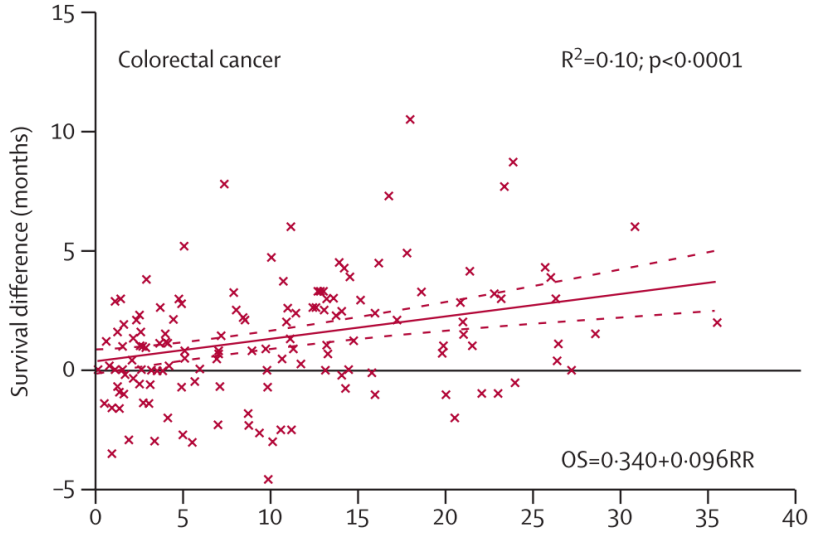
Correlation between response and Survival on the trial level

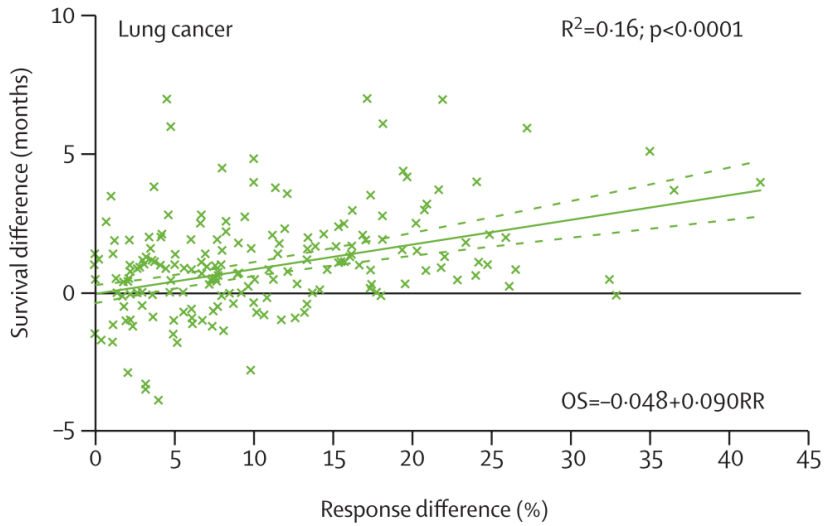


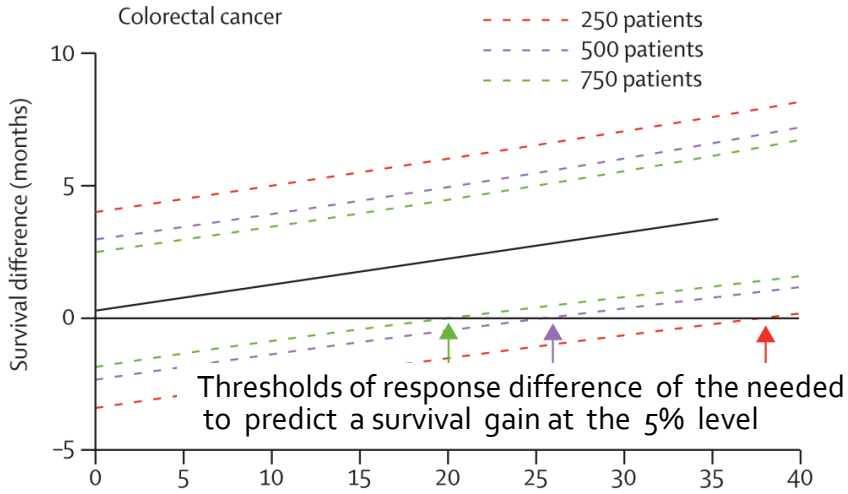
Bruzzi et al. J Clin Oncol (2005) 5117-5125, Figure 3 (edited) and Figure 4

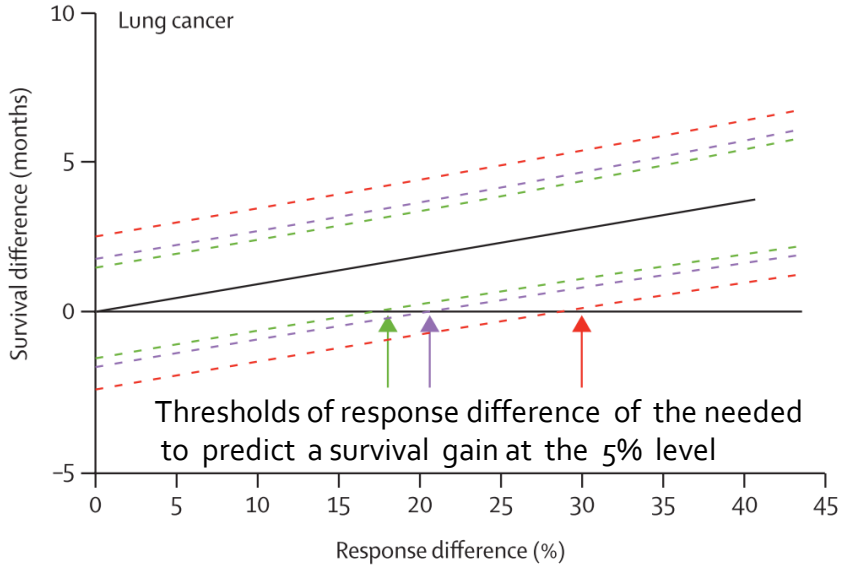
Memorial Sloan Kettering Cancer Center

Prediction of survival by RECIST response









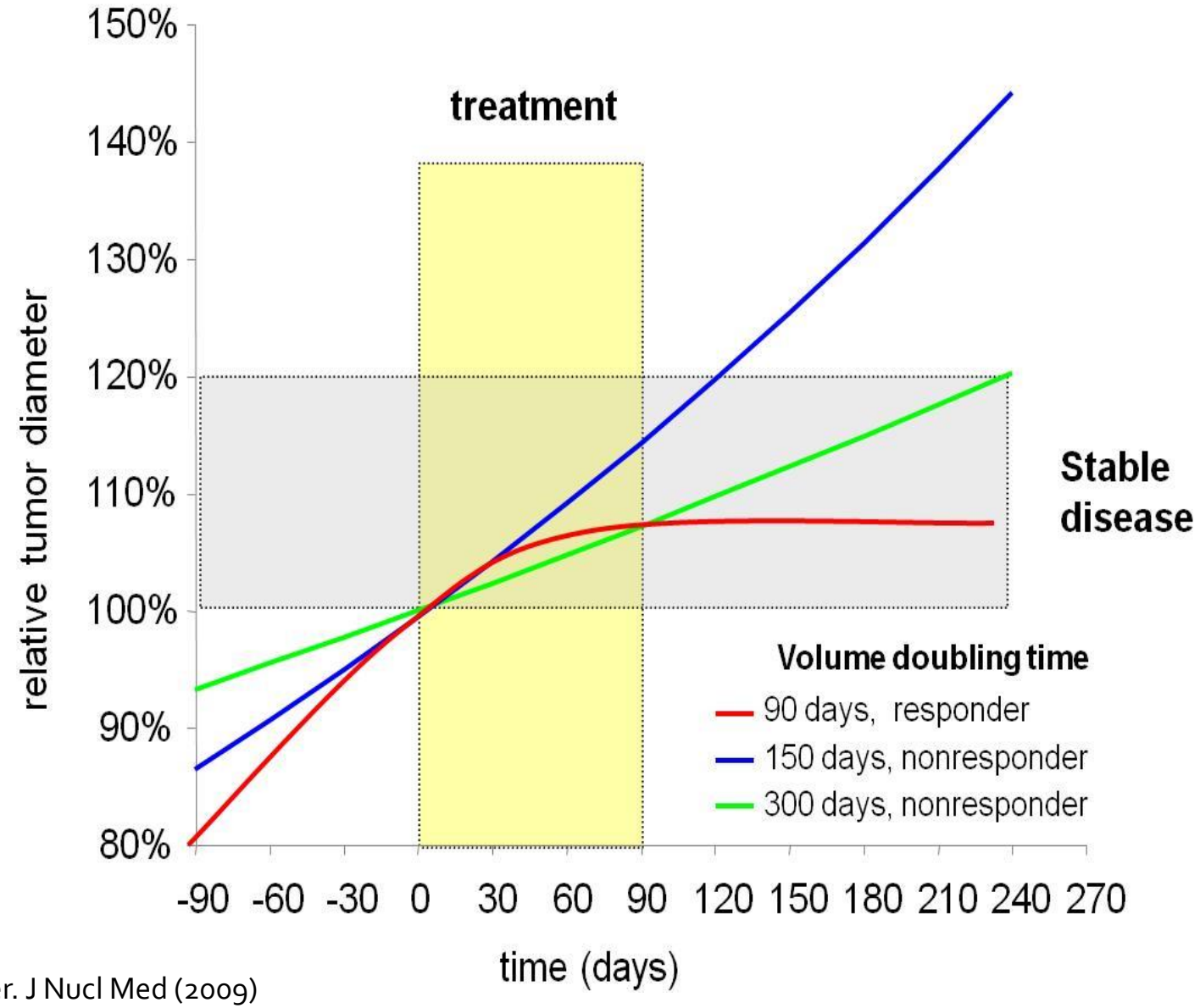
Johnson et al. Lancet Oncol 2006; 7: 741–46, Figures 1 & 3

Memorial Sloan Kettering Cancer Center

Limitations of RECIST

- Inability to differentiate between "viable tumor" and "treated disease (scar)
- Not all metastatic sites are considered measurable (e.g. bone metastases)
- Criteria for response assessment are more or less arbitrary for current imaging technologies
- Parts of the RECIST assessment are subjective, e.g. selection of the "target lesion", "unequivocal progression of non-target lesion"
- "Stable disease" is problematic in non-randomized clinical trials.

Tumor Control (SD) and Prognosis



Weber. J Nucl Med (2009)

Memorial Sloan Kettering Cancer Center

Stable Disease in NSCLC Patients Treated with Placebo

	Gefitinib (n=1129)	Placebo (n=563)
Reason for failure of last chemotherapy		
Refractory‡	1011 (90%)	512 (91%)
Intolerant	114 (10%)	48 (9%)
Unknown	4	3

ISEL Study

	Number of patients	
	Gefitinib (n=959)	Placebo (n=480)
Objective response	77 (8%)	6 (1%)
Complete response	1	0
Partial response	76 (8%)	6 (1%)
Stable disease	304 (32%)	148 (31%)
Progressive disease	360 (37%)	232 (48%)

Thatcher et al. Lancet (2005) 366:1527-1537, Tables 1 and 2

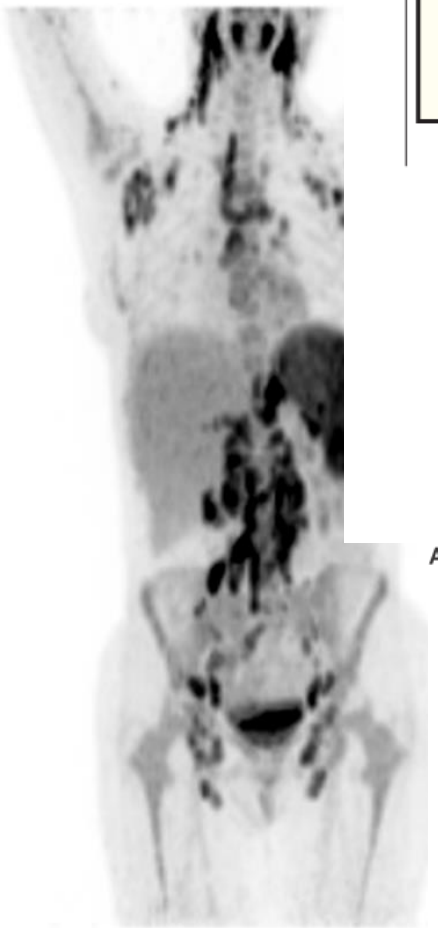
Memorial Sloan Kettering Cancer Center

Functional imaging to assess tumor response

- Differentiation between "treated disease" and viable tumor tissue
- Monitoring tumor response in body areas that cannot be assessed by RECIST, e.g. bone, esophageal wall
- Quantification of changes in physiologic/biochemical parameters
- Examples
  - DCE MRI to assess tumor vascularization and perfusion
  - FDG PET to assess tumor glucose metabolism

FDG-PET for monitoring tumor response

Hodgkin

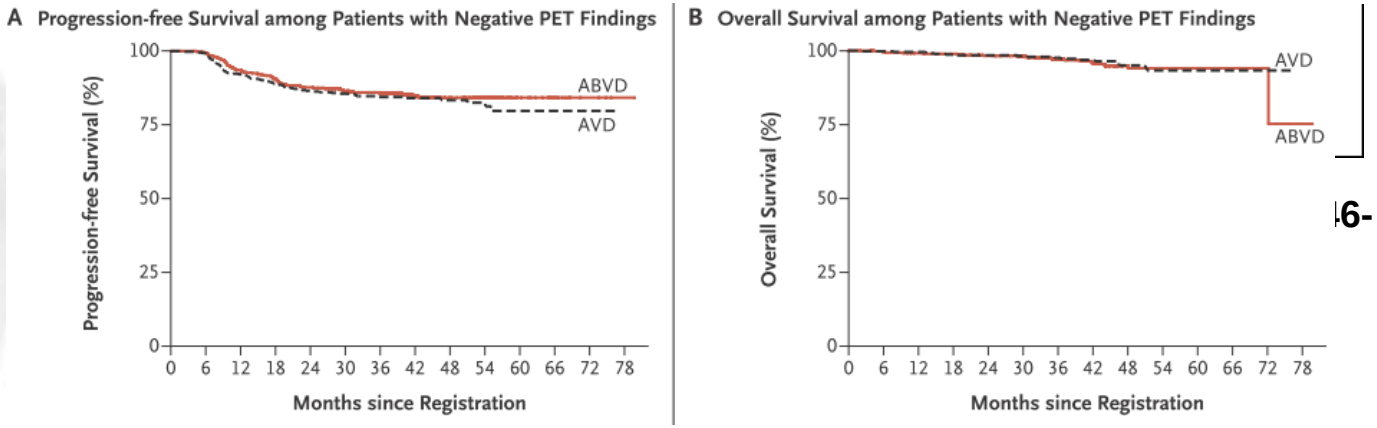


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2016 VOL. 374 NO. 25

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

Peter Johnson, M.D., Massimo Federico, M.D., Amy Kirkwood, M.Sc., Alexander Fosså, M.D., Leanne Berkahn, M.D., Angelo Carella, M.D., Francesco d'Amore, M.D., Gunilla Enblad, M.D., Antonella Franceschetto, M.D., Michael Fulham, M.D., Stefano Luminari, M.D., Michael O'Doherty, M.D., Pip Patrick, Ph.D., Thomas Roberts, B.Sc., Gamal Sidra, M.D., Lindsey Stevens, Paul Smith, M.Sc., Judith Trotman, M.D., Zaid Viney, M.D., John Radford, M.D., and Sally Barrington, M.D.



-6-

Before Ctx **During Ctx**

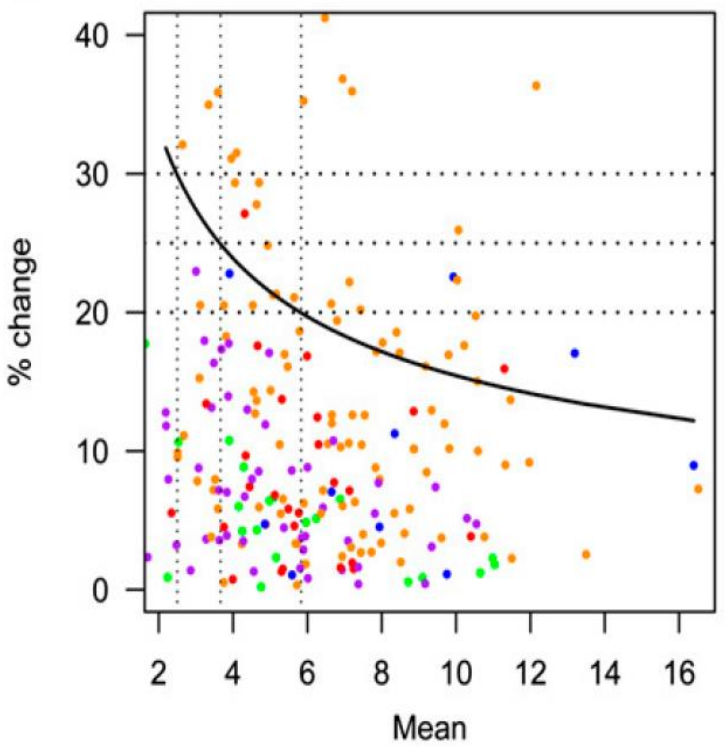
Memorial Sloan Kettering Cancer Center

PET Response Criteria in Solid Tumors

PERCIST 1.0

- CR – Disapereance of all lesions
- PR – At least 30% decrease of SUV
- SD – Neither response or PD
- PD – At least 30% increase of SUV or increase in tumor size or new lesions

Repeatability of measurements of tumor FDG uptake



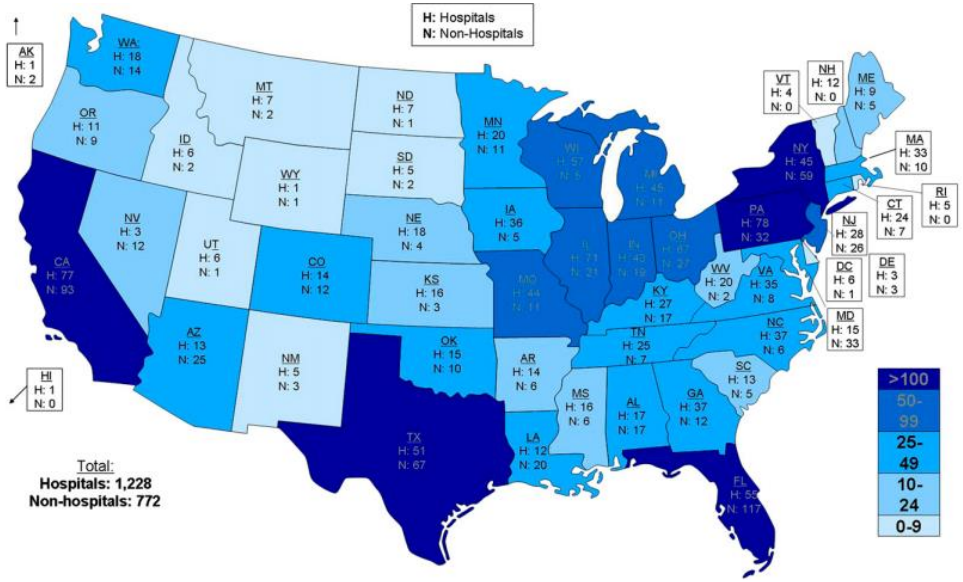
Meta-analysis of 5 studies on

Wahl et al. J Nucl Med (2009) 50 Suppl 1: 122S-150S
de Langen et al. J Nucl Med (2012) 53:701-708, Figure 2, page 705

Memorial Sloan Kettering Cancer Center

PET/CT imaging technology

- Widely available in the US due to th success of FDG PET/CT
- Established infrastructure for production and distribution of PET tracers
- Simple, robust image acquisition
- Inherently quantitative data
- Whole body imaging in ~ 15 min (with current scanners)



Scanners installed in 2009: **~ 2000**

Capacity: **5-7 Million/ year**

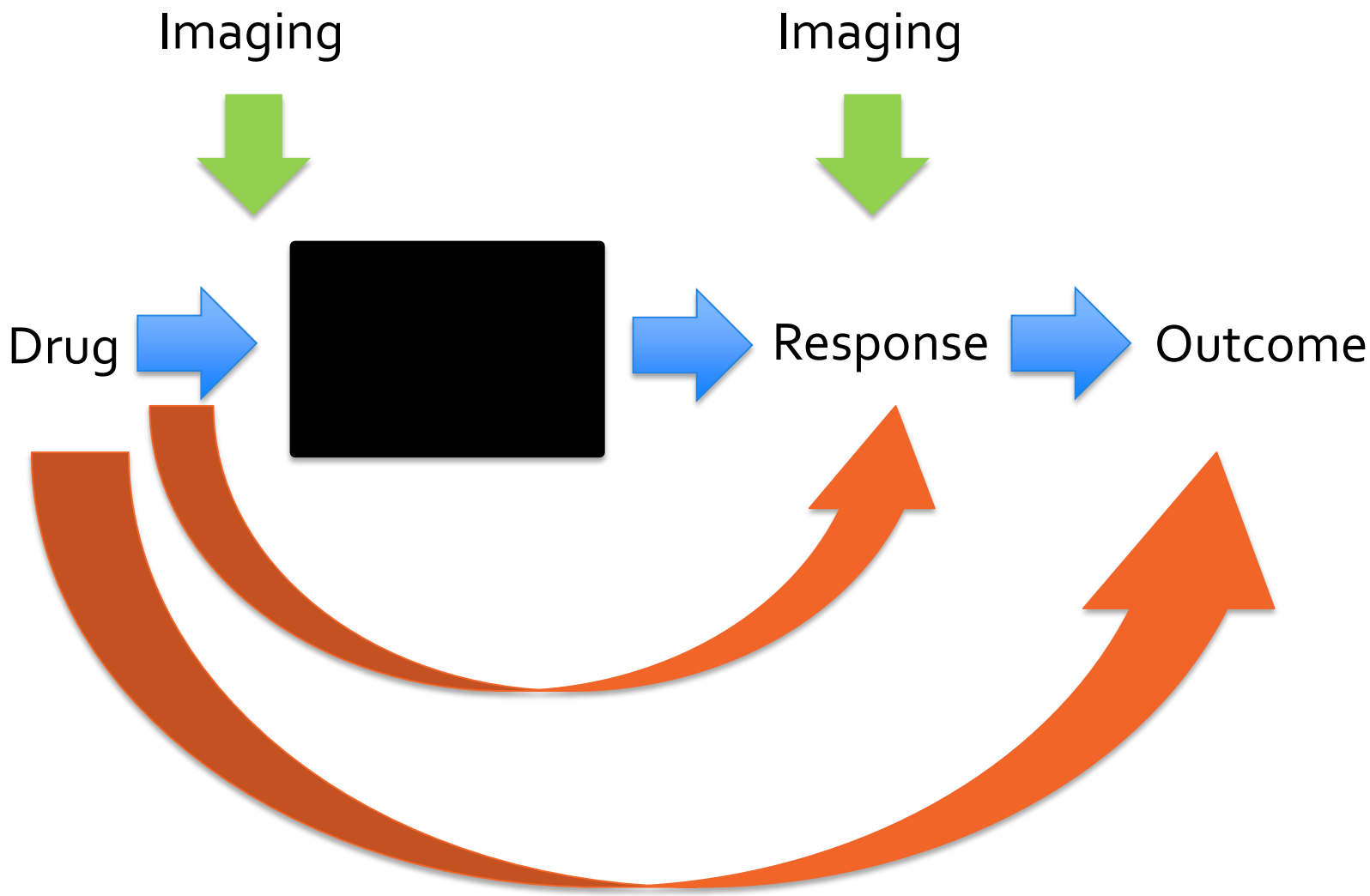
(10-15 scans/day/scanner)

- **Significant installed infrastructure that is only partially utilized by FDG imaging**
- **New imaging agents are of great clinical interest**

Buck et al. J Nucl Med (2010) 51:401-412, Figure 1, edited

Memorial Sloan Kettering Cancer Center

Using imaging to go beyond assessment of response



Biomarker Definitions Working Group
Clinical Pharmacology & Therapeutics (2001), modified

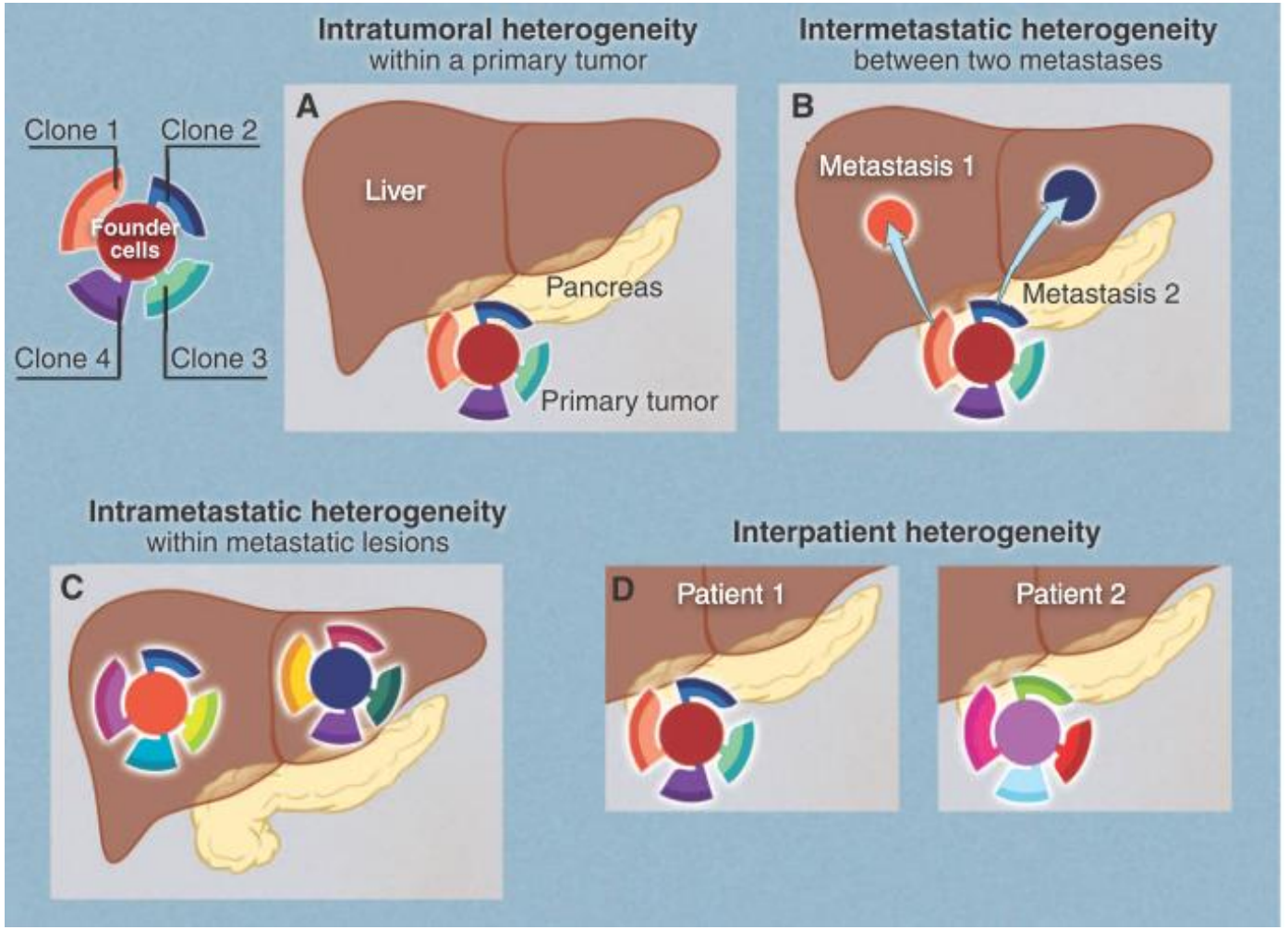
Memorial Sloan Kettering Cancer Center

Imaging of biological activity

Key questions:

- **Is the drug target present (at all disease sites, at high concentration)?**
- **What is the concentration of the drug at the site of the target?**
- **Does the drug interact with the target?**

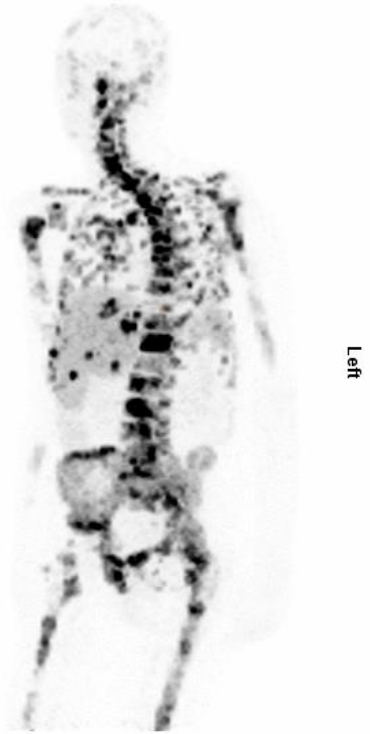
Genetic heterogeneity of metastatic cancer



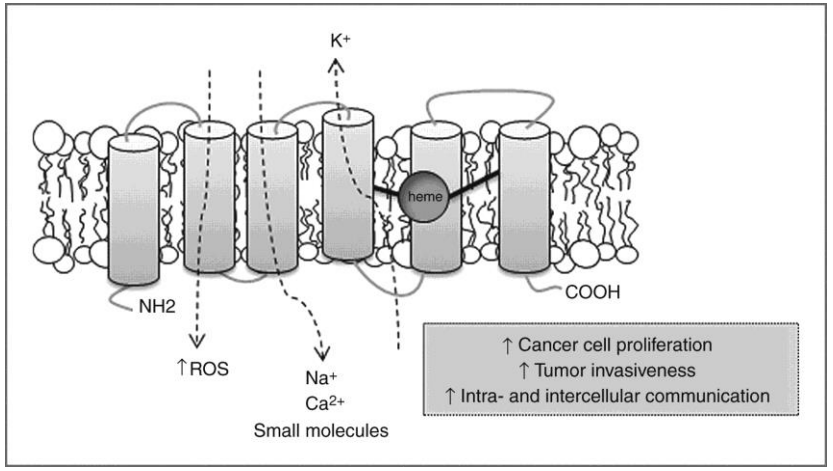
B. Vogelstein. Science 339, 1546 (2013), figure 6

Memorial Sloan Kettering Cancer Center

Imaging STEAP1 with Zr-89 DFO-MSTP2109A



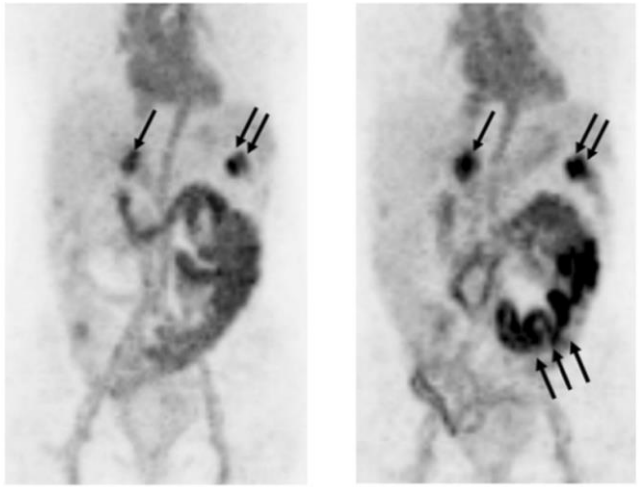
- First member of the six-transmembrane epithelial antigen of prostate (STEAP) family
- New target for therapy of prostate cancer: use of antibody drug conjugates



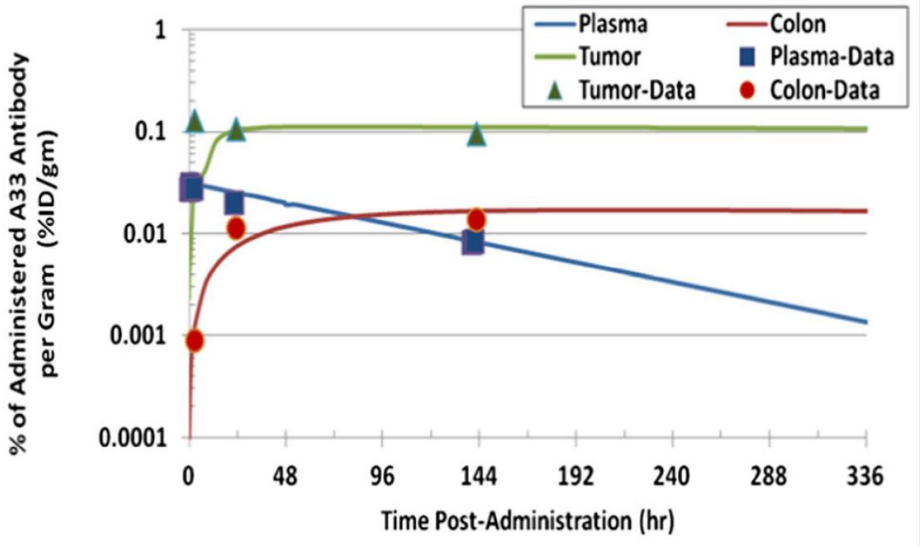
Carrasquillo et al. AACR 2014

Predicting the concentration of antibody drug conjugates

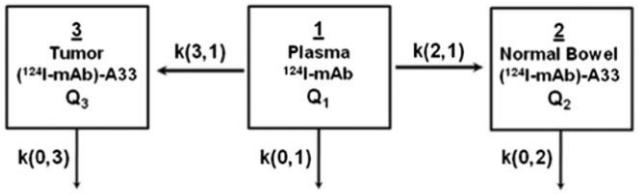
^{89}Zr-A33 antibody PET



2 days 7 days



Prediction of tumor concentrations



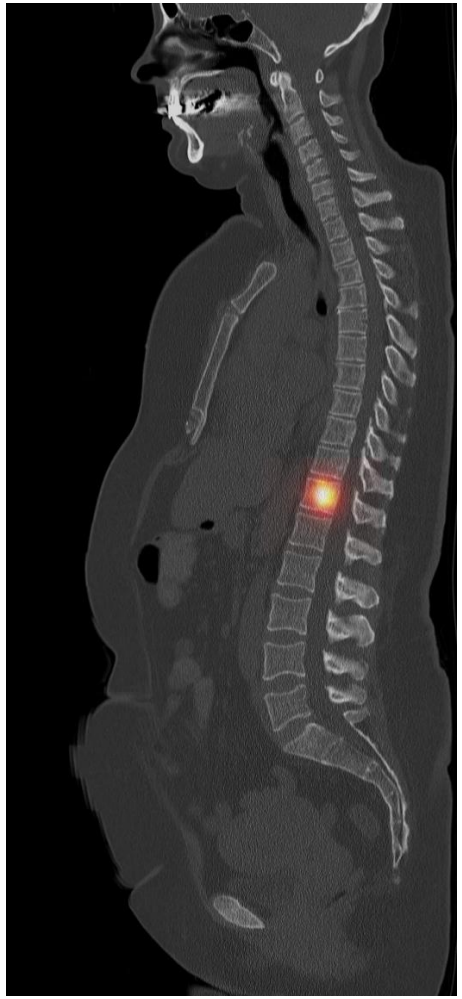
Compartmental model

Zanzonico et al. Eur J Nucl Med Mol Imaging, 2015

Memorial Sloan Kettering Cancer Center

"Theranostic" compounds

- Use of the same (or very similar) molecule for imaging and therapy
- Well established for radioiodine therapy of thyroid cancer (radioiodine imaging and therapy)
- The principle is to concentrate a radioactive isotope in the tumor for targeted radiotherapy
- Recently this concept has been expanded to several other malignancies

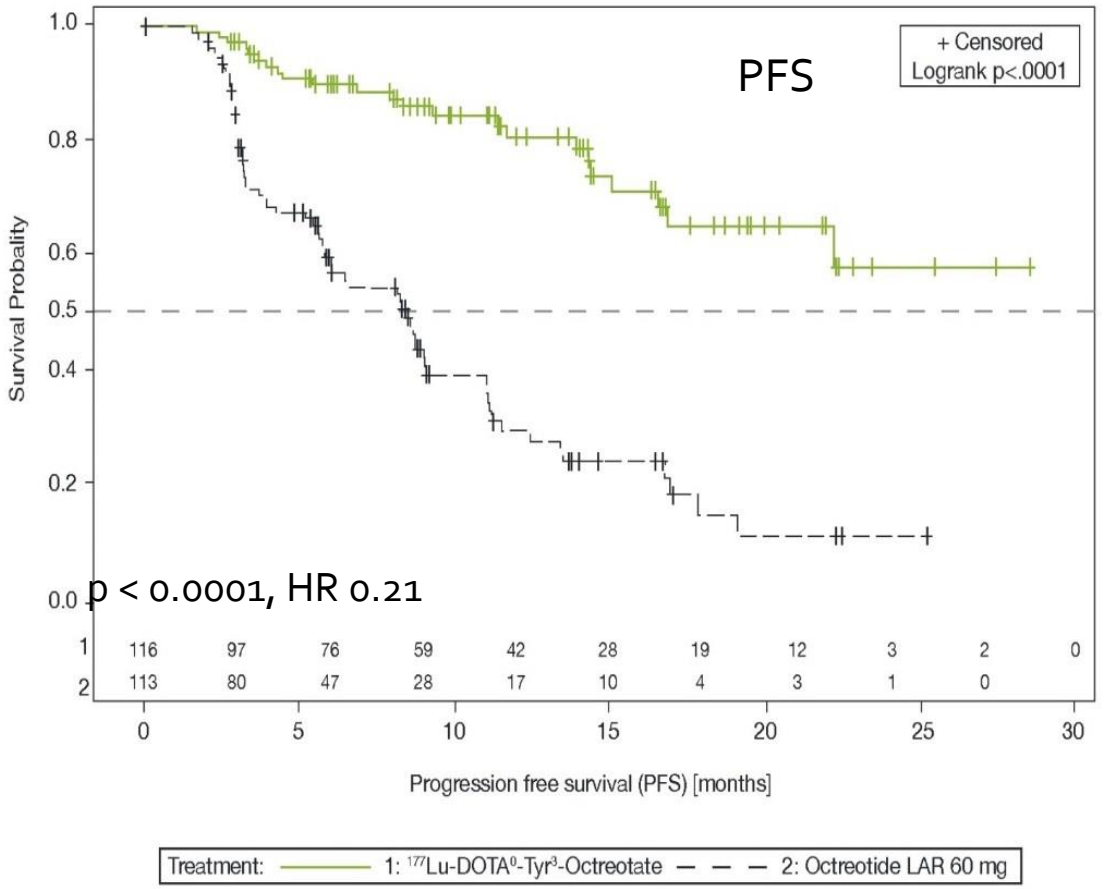


Iodine-131 SPECT/CT

Treatment of NETs with radiolabeled somatostatin analogs

NETTER-1 trial

- Randomized comparison of
  - ^{177}Lu-DOTATATE
    (4 cycles of 7.4 GBq every 8 weeks)
  - Octreotide LAR
    (60 mg every 4 weeks)
- 230 patients with grade 1-2 metastatic midgut NETs
- Median PFS (primary endpoint)
  - Not reached for ^{177}Lu-DOTATATE
  - 8.4 months for Octreotide
- Deaths: 14 for ^{177}Lu-DOTATATE vs. 26 for octreotide LAR
  (p = 0.0043, interim analysis)



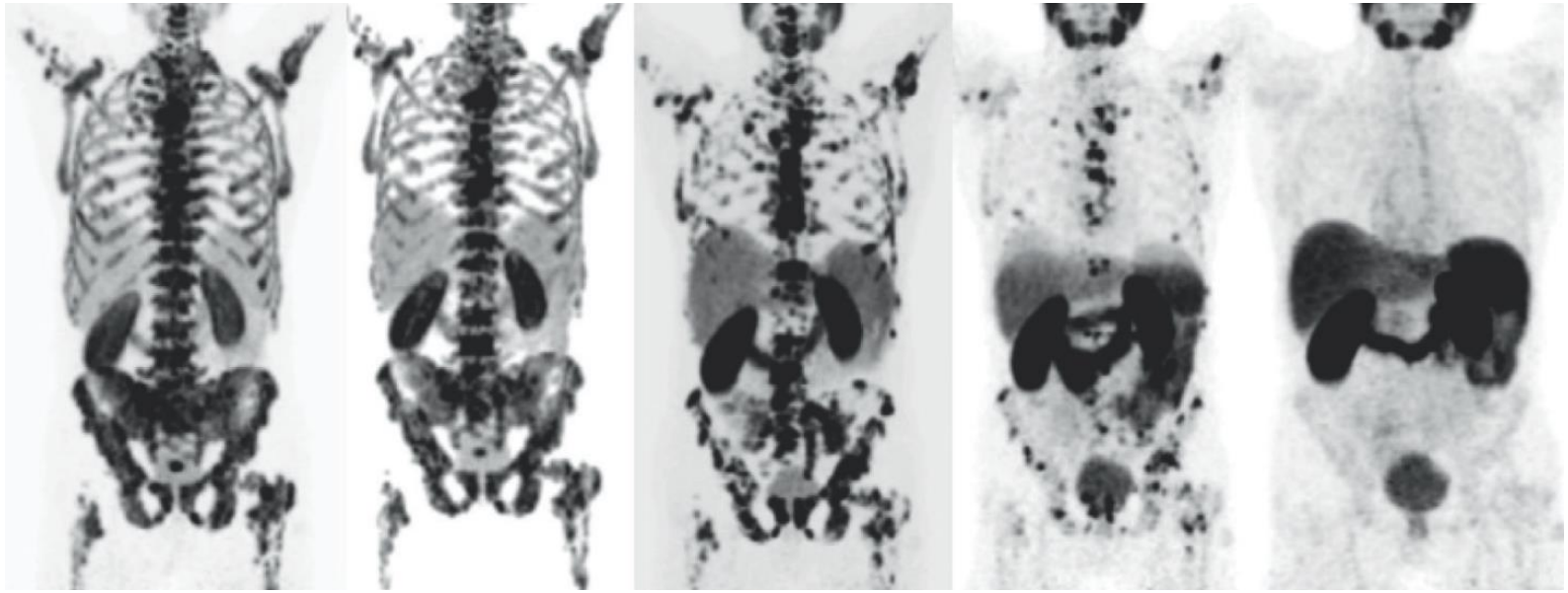
Strosberg et al. ECCO Congress 2015

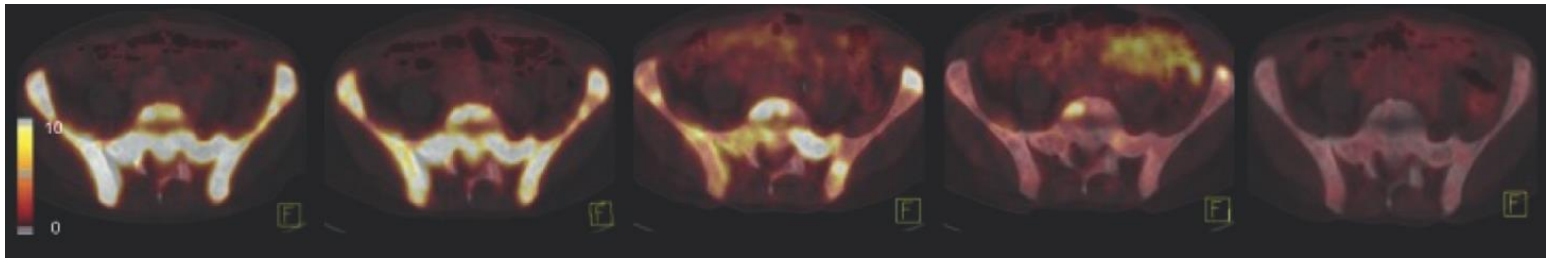
Memorial Sloan Kettering Cancer Center

Therapy of metastatic prostate cancer with a ^{177}Lu labeled -PSMA ligand

71y/o patient, s/p Doc/Abi/Enza/Ra-223

Before therapy PSA = 755 ng/mL	Cycle 1	Cycle 2	Cycle 3	Cycle 4 PSA < 0.2 ng/mL





^{68}Ga-PSMA-11 PET/CT

Heck et al. J Urol (2016) 196:382–391, Figure 4, edited

Memorial Sloan Kettering Cancer Center

Importance of an in-vivo pharmacodynamics marker

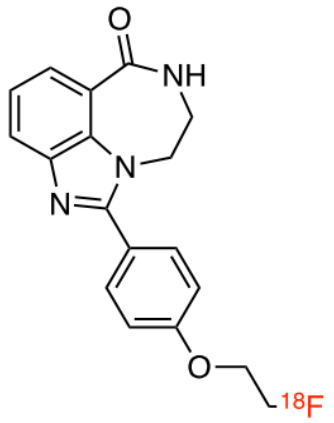
NH_2

Iniparib is not a PARP1 inhibitor at clinically relevant dose levels in patients!

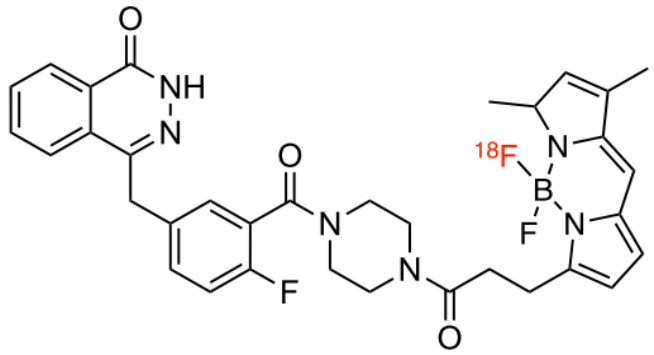
PARP = poly ADP ribose polymerase

Memorial Sloan Kettering Cancer Center

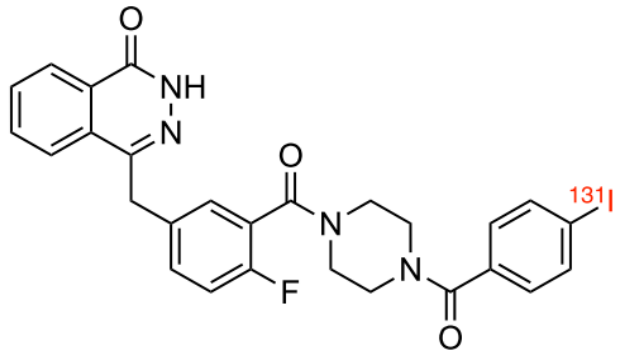
Radiolabeled PARP inhibitors for imaging PARP expression



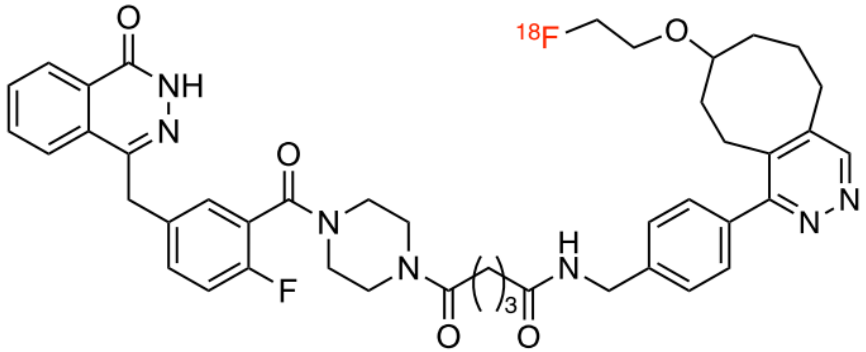
Zhou, D. et al. *Bioorganic & Medicinal Chemistry.* 2014
Edmonds, C. E. et al. *Am J Nucl Med Mol Imaging.* 2016



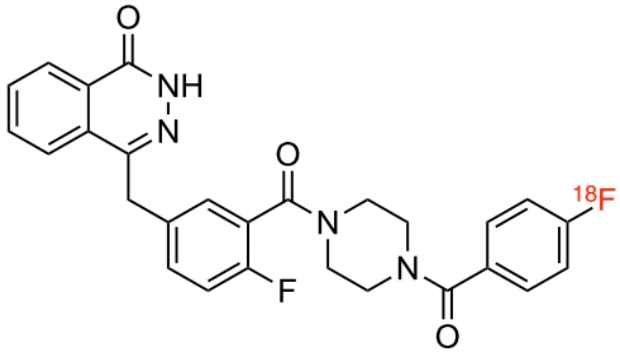
Keliher, E. J. et al. *ChemMedChem.* 2014
Carlucci, G. et al. *Mol Imaging Biol.* 2015



Salinas, B. et al. *EJNMMI Res.* 2015
Zmuda, F. et al. *J Med Chem* 2015



Keliher, E. J. et al. *ChemMedChem.* 2011
Reiner, T. et al. *Neoplasia.* 2012

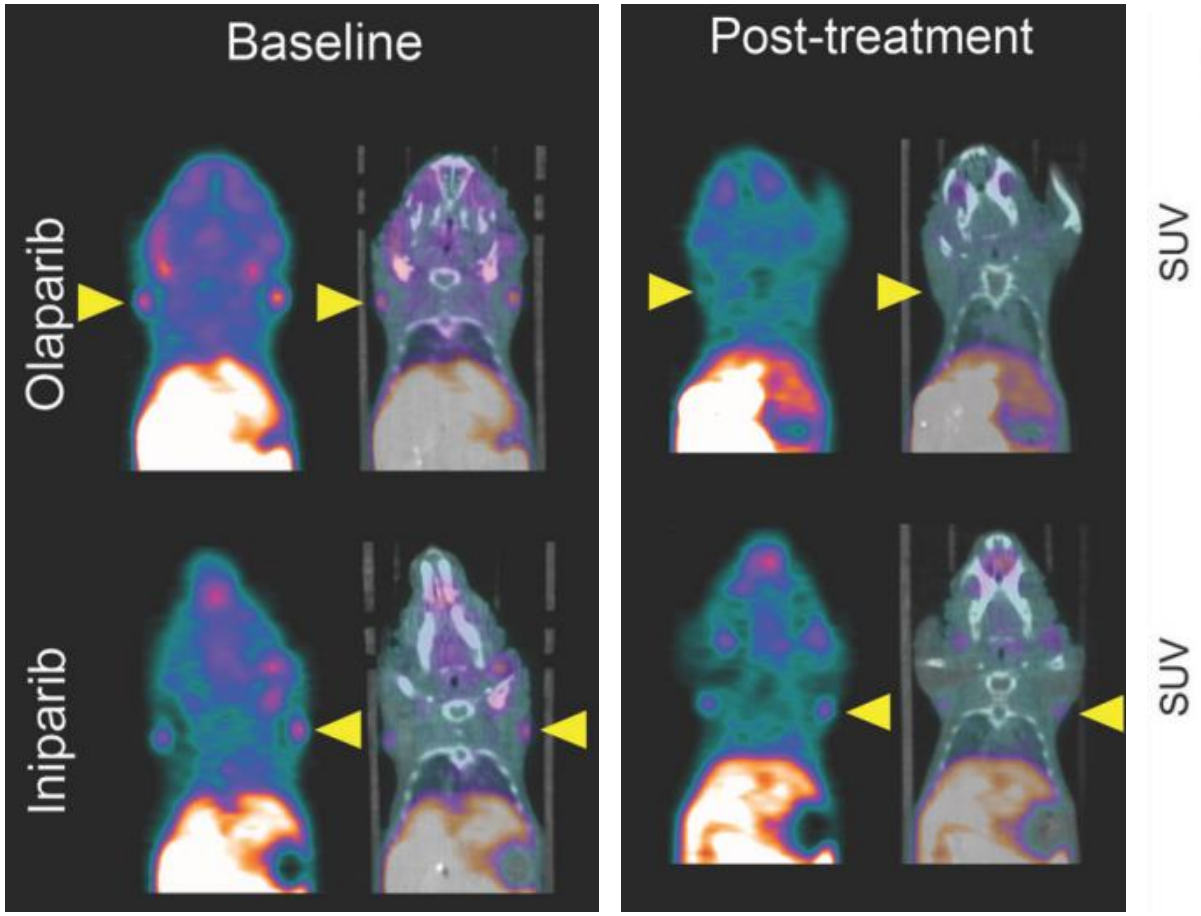


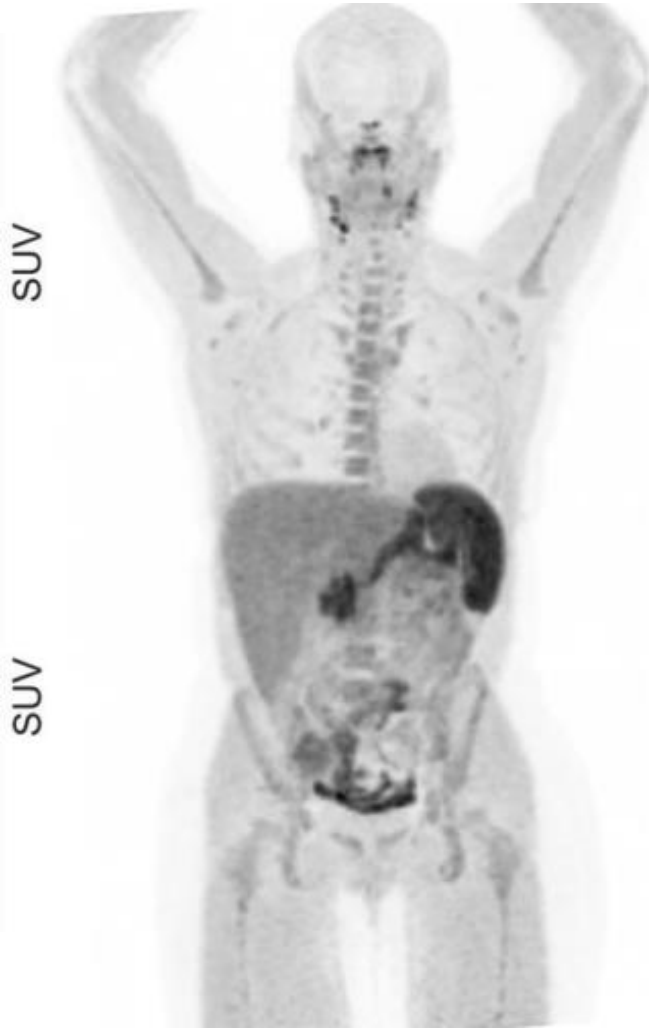
Carney, B. et al. *Mol Imaging Biol.* 2015

Carney, Reiner

Memorial Sloan Kettering Cancer Center

Imaging Interaction of Olaparib and Iniparib with ^{18}F-FTT





Washington University; Michel et al. Radiology (2016) online

Memorial Sloan Kettering Cancer Center

Summary/Conclusions

- Morphologic assessment by RECIST remains an important tool for drug development, but has well-known limitations
- Functional imaging techniques can overcome some of these limitations by using physiologic/biochemical parameters to monitor tumor response
- Molecular imaging allows for
  - Visualization and quantification of drug target expression in whole body imaging studies
  - Monitoring the interaction between drug and target

  -> Definition of the biologically relevant dose
- "Theranostic drugs", combine imaging and therapy and have recently shown promise in neuroendocrine tumors and prostate cancer