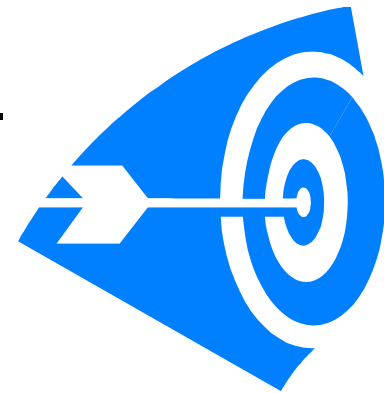


PSMA:
Prostate Cancer's
Molecular Bull's-eye



Neil H Bander, MD
Bernard & Josephine Chaus Professor
of Urologic Oncology
Weill Medical College of Cornell University

Disclosure

Dr. Bander is the inventor of patents related to anti-PSMA Antibodies. Those patents are assigned to Cornell Research Foundation. Dr. Bander is eligible to receive royalty payments if any of those antibodies are commercially marketed.

Outline

- **PSMA**
- **PSMA: an Ideal Molecular Target**
- **PSMA-targeted Imaging**
- **PSMA-targeted Therapy**

PSMA is an Unparalleled Target in PC

- PSMA is the single most well-established, prostate-restricted, cell membrane antigen known
- 90-95% of PC are PSMA-positive
- Highly PC-specific
- ↑ PSMA \cong ↑ lethality
- Expression levels are increased by hormonal Rx
- Rapidly internalized

PSMA Expression in Prostate Cancer Patients

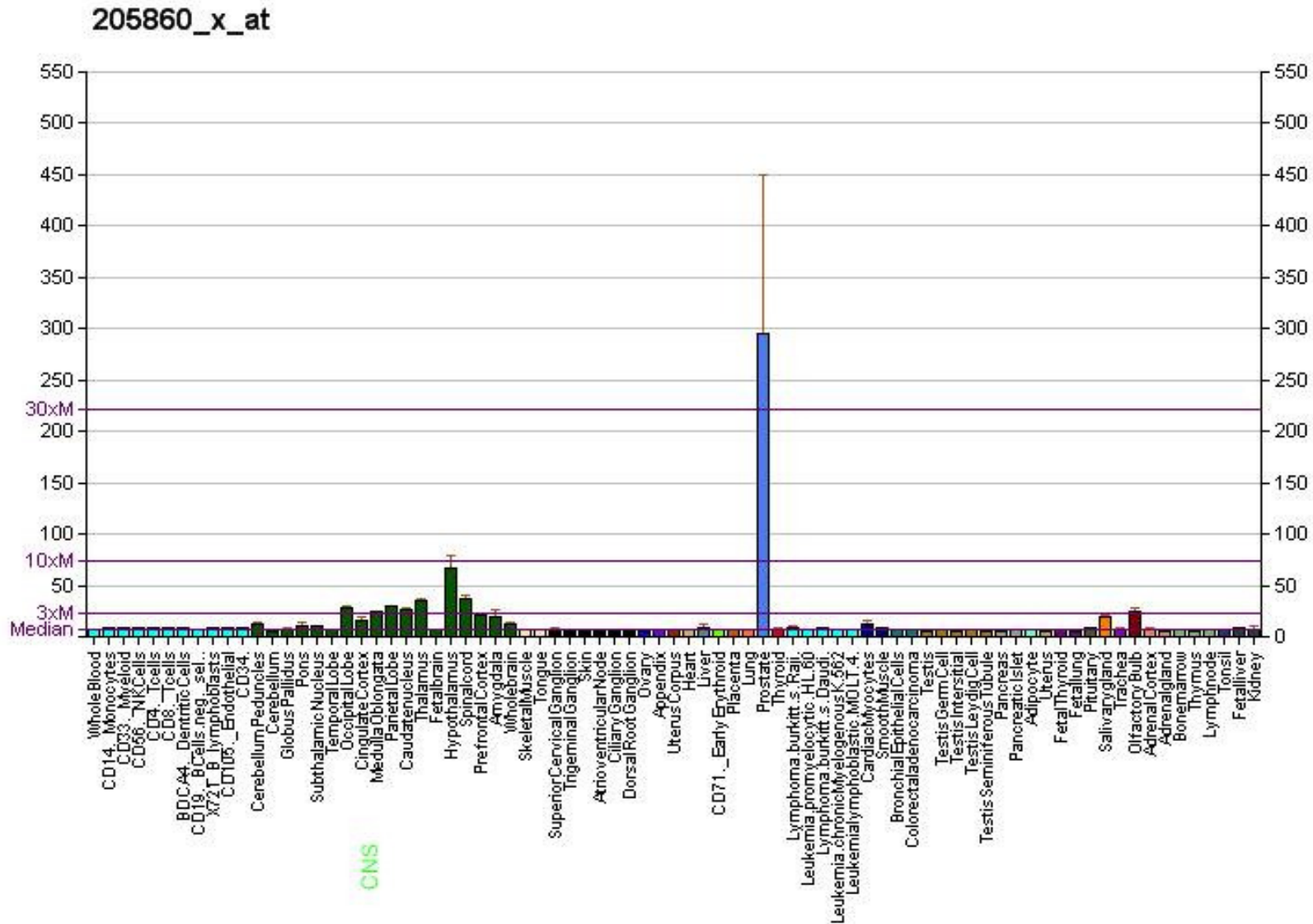
Reference	Adeno-carcinoma	Lymph node metastases	Bone metastases	Other or unspecified metastases	Total
Horoszewicz et al., Anticancer Res 1987; 7:927	9/9	2/2			11/11
Lopes et al., Cancer Res 1990; 50:6423	10/10				10/10
Israeli et al., Cancer Res 1994; 54:1807	1/1				1/1
Troyer et al., Int J Cancer 1995; 62:552	3/4				3/4
Wright et al., Urology 1996; 48:326	25/25				25/25
Silver et al., Clin Cancer Res 1997; 3:81	33/35	7/8	8/18		48/61
Liu et al., Cancer Res 1997; 57:3629	21/21				21/21
Kawakami et al., Cancer Res 1997; 57:2321	15/15				15/15
Sweat et al., Urology 1998; 52:637	232/232	227/232			459/464
Bostwick et al., Cancer 1998; 82:2256	129/129	184/184			313/313
Chang et al., Cancer Res 1999; 59:3192	12/12				12/12
Chang et al., Urology 2001; 57:1179		6/6	7/7	9/9	22/22
Ross et al., Clin Cancer Res 2003; 9:6357	138/138				138/138
Birtle et al. BJUI 2005; 96:303	30/33				30/33
Kinoshita et al., World J Surg 2006; 30:628	19/19				19/19
Kusumi et al., Pathology Int 2008; 58:687	42/42				42/42
Hull et al., BJUI 2009; 104:915	85/90				85/90
Mannweiler et al., Pathol Oncol Res 2009; 15:167	49/51	3/3	25/31	15/17	92/102
Ananias et al., Prostate 2009; 69:1101		21/21	17/17		38/38
Ben Jemaa et al., J Exp Clin Cancer Res 2010; 29:171	38/39				38/39
Zhang et al., PLoS ONE 2011; 6:e27970				83/100	83/100
Minner et al., Prostate 2011; 71:281	1606/1700				1606/1700
TOTAL	2590/2746	450/456	57/73	107/126	3204/3401

22 refs

	76 – 100%
	51 – 75%
	26 – 50%
	0 – 25%
% of tumors stained positive for PSMA	

94%

PSMA: Gene Expression Highly Prostate-specific



Protein Expression Profile

THE HUMAN PROTEIN ATLAS

ABOUT & HELP

PSMA Search Clear Fields

GENE: **FOLH1**

SUMMARY

INFO

GENE/PROTEIN

ANTIBODY/ANTIGEN

EXPRESSION

SUBCELLULAR LOCATION

NORMAL TISSUE

CANCER TISSUE

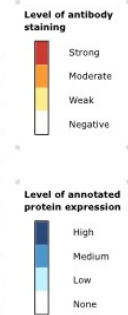
CELL LINE

RNA

NORMAL TISSUE ? »
Expression summary High and selective cytoplasmic expression in prostate gland.
Reliability (APE) High
Antibodies in assay CAB001451, HPA010593

Tissue presentation order Organ Cell type Alphabetical

Tissue	Organ	Cell type	Antibody staining	Annotated expression	Tissue	Organ	Cell type	Antibody staining	Annotated expression
Central nervous system (Brain)					Respiratory system (Lung)				
Cerebral cortex		Neuronal cells	<input type="checkbox"/>	<input type="checkbox"/>	Nasopharynx		Respiratory epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>
Cerebral cortex		Glial cells	<input type="checkbox"/>	<input type="checkbox"/>	Bronchus		Respiratory epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>
Hippocampus		Neuronal cells	<input type="checkbox"/>	<input type="checkbox"/>	Lung		Pneumocytes	<input type="checkbox"/>	<input type="checkbox"/>
Hippocampus		Glial cells	<input type="checkbox"/>	<input type="checkbox"/>	Lung		Macrophages	<input type="checkbox"/>	<input type="checkbox"/>
Lateral ventricle		Neuronal cells	<input type="checkbox"/>	<input type="checkbox"/>	Cardiovascular system (Heart and blood vessels)				
Lateral ventricle		Glial cells	<input type="checkbox"/>	<input type="checkbox"/>	Heart muscle		Myocytes	<input type="checkbox"/>	<input type="checkbox"/>
Cerebellum		Purkinje cells	<input type="checkbox"/>	<input type="checkbox"/>	Breast and female reproductive system (Female tissues)				
Cerebellum		Cells in granular layer	<input type="checkbox"/>	<input type="checkbox"/>	Breast		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Cerebellum		Cells in molecular layer	<input type="checkbox"/>	<input type="checkbox"/>	Vagina		Squamous epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>
Blood and immune system (Hematopoietic)					Cervix, uterine		Squamous epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>
Bone marrow		Hematopoietic cells	<input type="checkbox"/>	<input type="checkbox"/>	Cervix, uterine		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Lymph node		Germinal center cells	<input type="checkbox"/>	<input type="checkbox"/>	Uterus, pre-menopause		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Lymph node		Non-germinal center cells	<input type="checkbox"/>	<input type="checkbox"/>	Uterus, pre-menopause		Cells in endometrial stroma	<input type="checkbox"/>	<input type="checkbox"/>
Tonsil		Germinal center cells	<input type="checkbox"/>	<input type="checkbox"/>	Uterus, post-menopause		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Tonsil		Non-germinal center cells	<input type="checkbox"/>	<input type="checkbox"/>	Uterus, post-menopause		Cells in endometrial stroma	<input type="checkbox"/>	<input type="checkbox"/>
Tonsil		Squamous epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>	Fallopian tube		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Spleen		Cells in white pulp	<input type="checkbox"/>	<input type="checkbox"/>	Ovary		Follicle cells	<input type="checkbox"/>	<input type="checkbox"/>
Spleen		Cells in red pulp	<input type="checkbox"/>	<input type="checkbox"/>	Ovary		Ovarian stroma cells	<input type="checkbox"/>	<input type="checkbox"/>
Liver and pancreas					Placenta				
Liver		Hepatocytes	<input type="checkbox"/>	<input type="checkbox"/>	Placenta		Trophoblastic cells	<input type="checkbox"/>	<input type="checkbox"/>
Liver		Bile duct cells	<input type="checkbox"/>	<input type="checkbox"/>	Placenta		Decidual cells	<input type="checkbox"/>	<input type="checkbox"/>
Gall bladder		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Male reproductive system (Male tissues)				
Pancreas		Exocrine glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Testis		Cells in seminiferous ducts	<input type="checkbox"/>	<input type="checkbox"/>
Pancreas		Islets of Langerhans	<input type="checkbox"/>	<input type="checkbox"/>	Testis		Leydig cells	<input type="checkbox"/>	<input type="checkbox"/>
Digestive tract (GI-tract)					Epididymis		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Oral mucosa		Squamous epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>	Prostate		Glandular cells	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Salivary gland		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Seminal vesicle		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
Esophagus		Squamous epithelial cells	<input type="checkbox"/>	<input type="checkbox"/>	Urinary tract (Kidney and bladder)				
Stomach, upper		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Kidney		Cells in glomeruli	<input type="checkbox"/>	<input type="checkbox"/>
Stomach, lower		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Kidney		Cells in tubules	<input type="checkbox"/>	<input type="checkbox"/>
Duodenum		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Urinary bladder		Urothelial cells	<input type="checkbox"/>	<input type="checkbox"/>
Small intestine		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Skin and soft tissues				
Appendix		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Skin		Epidermal cells	<input type="checkbox"/>	<input type="checkbox"/>
Appendix		Lymphoid tissue	<input type="checkbox"/>	<input type="checkbox"/>	Vulva/anal skin		Epidermal cells	<input type="checkbox"/>	<input type="checkbox"/>
Colon		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Skeletal muscle		Myocytes	<input type="checkbox"/>	<input type="checkbox"/>
Rectum		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>	Smooth muscle		Smooth muscle cells	<input type="checkbox"/>	<input type="checkbox"/>
Endocrine glands					Thyroid gland		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
					Parathyroid gland		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>
					Adrenal gland		Glandular cells	<input type="checkbox"/>	<input type="checkbox"/>



PSMA

← Prostate

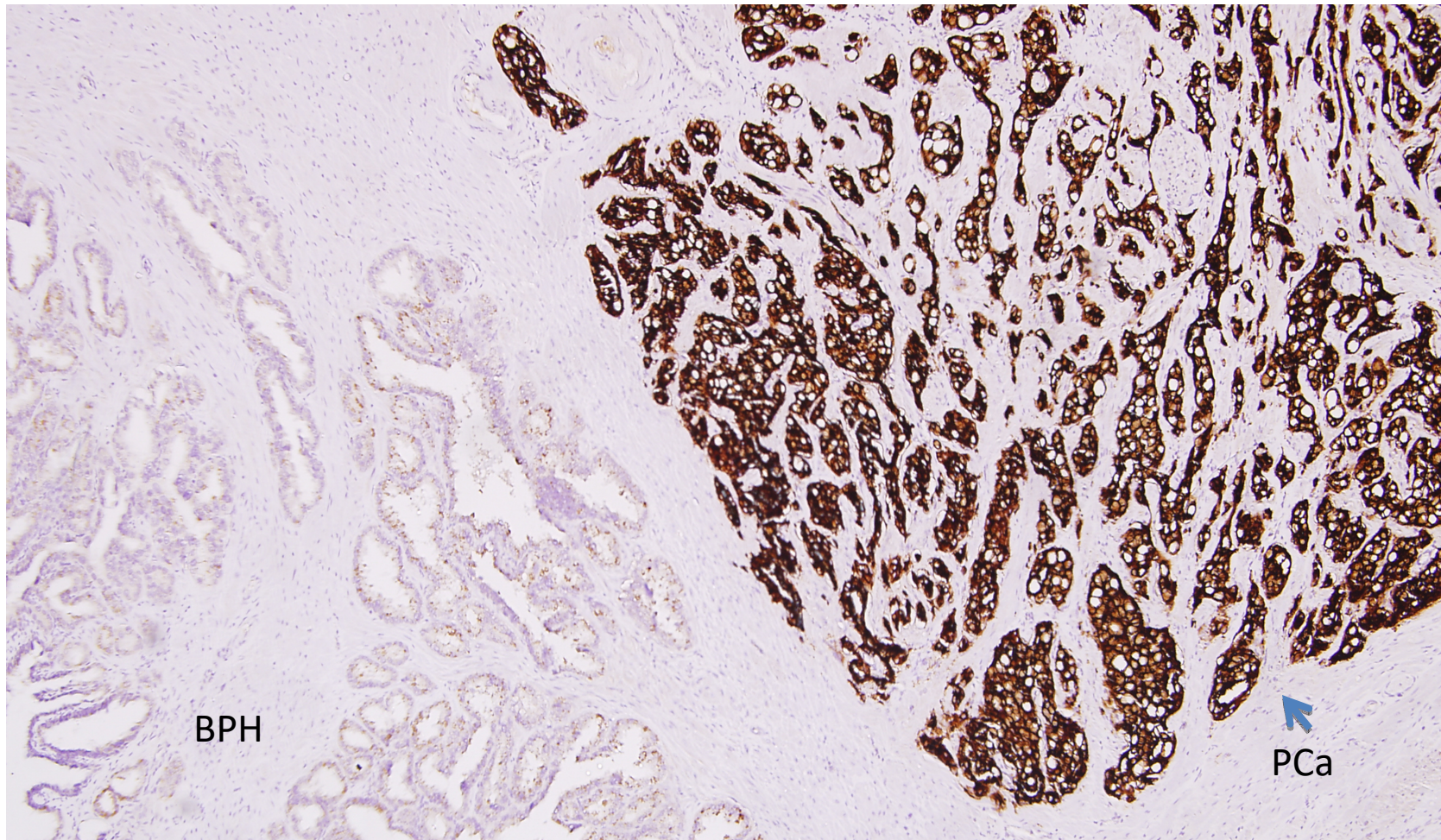
CAB001451

HPA010593

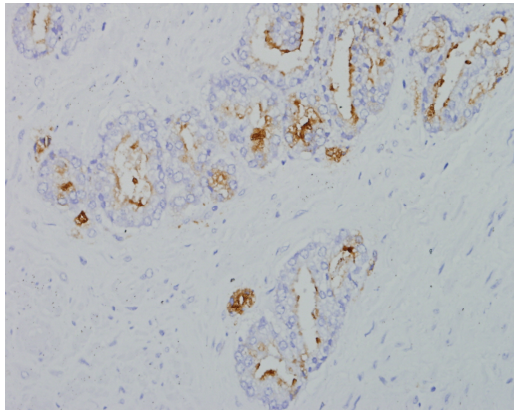
CAB001451

HPA010593

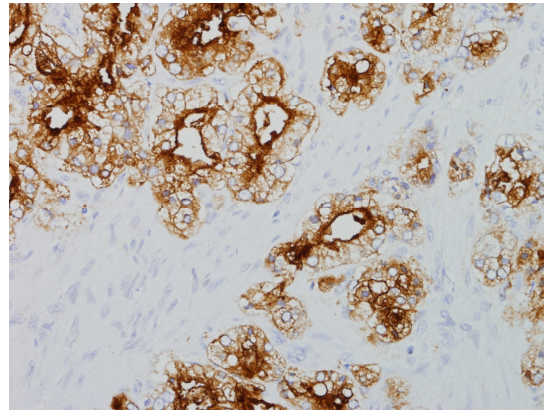
PSMA: Highly Over-Expressed in PC



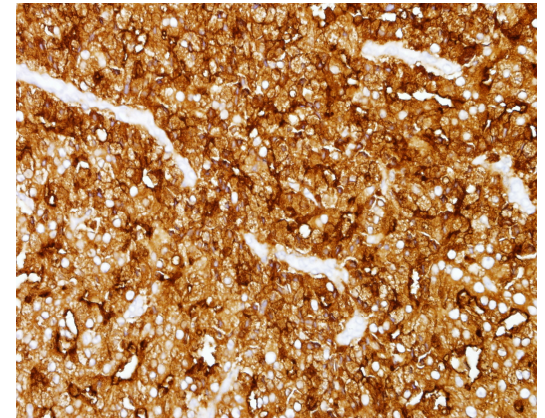
- \uparrow tumor grade = \uparrow PSMA
- PSMA level is prognostic



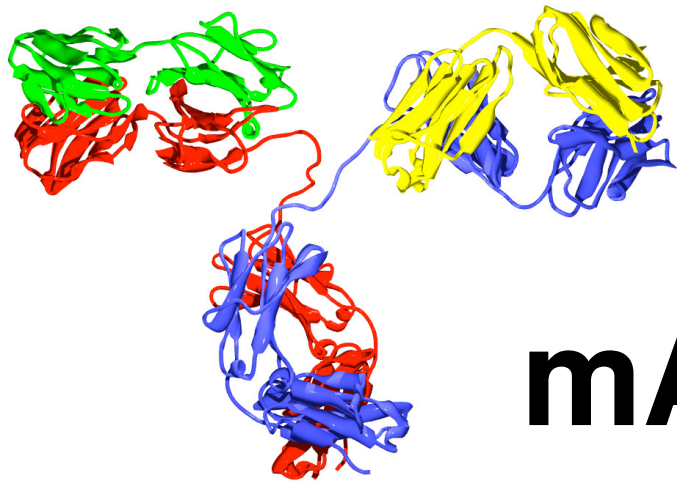
Gleason 3



Gleason 4



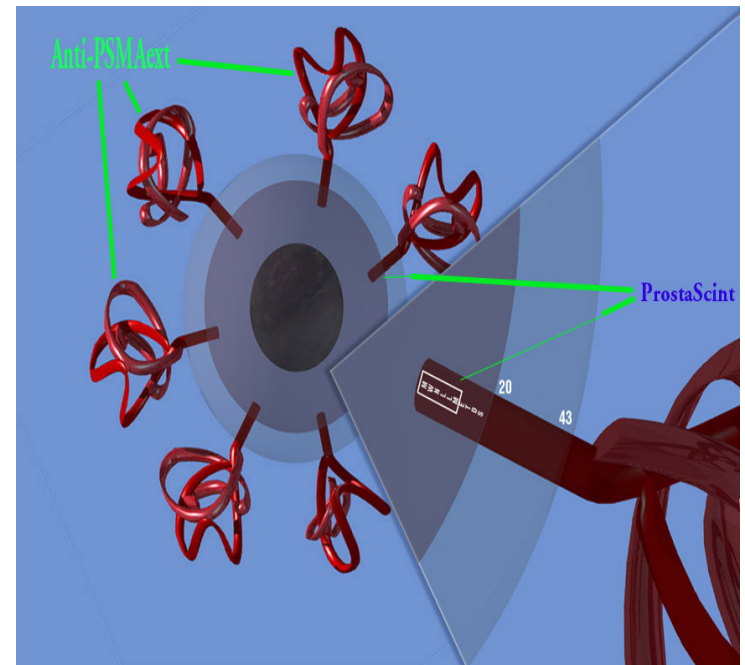
Gleason 5



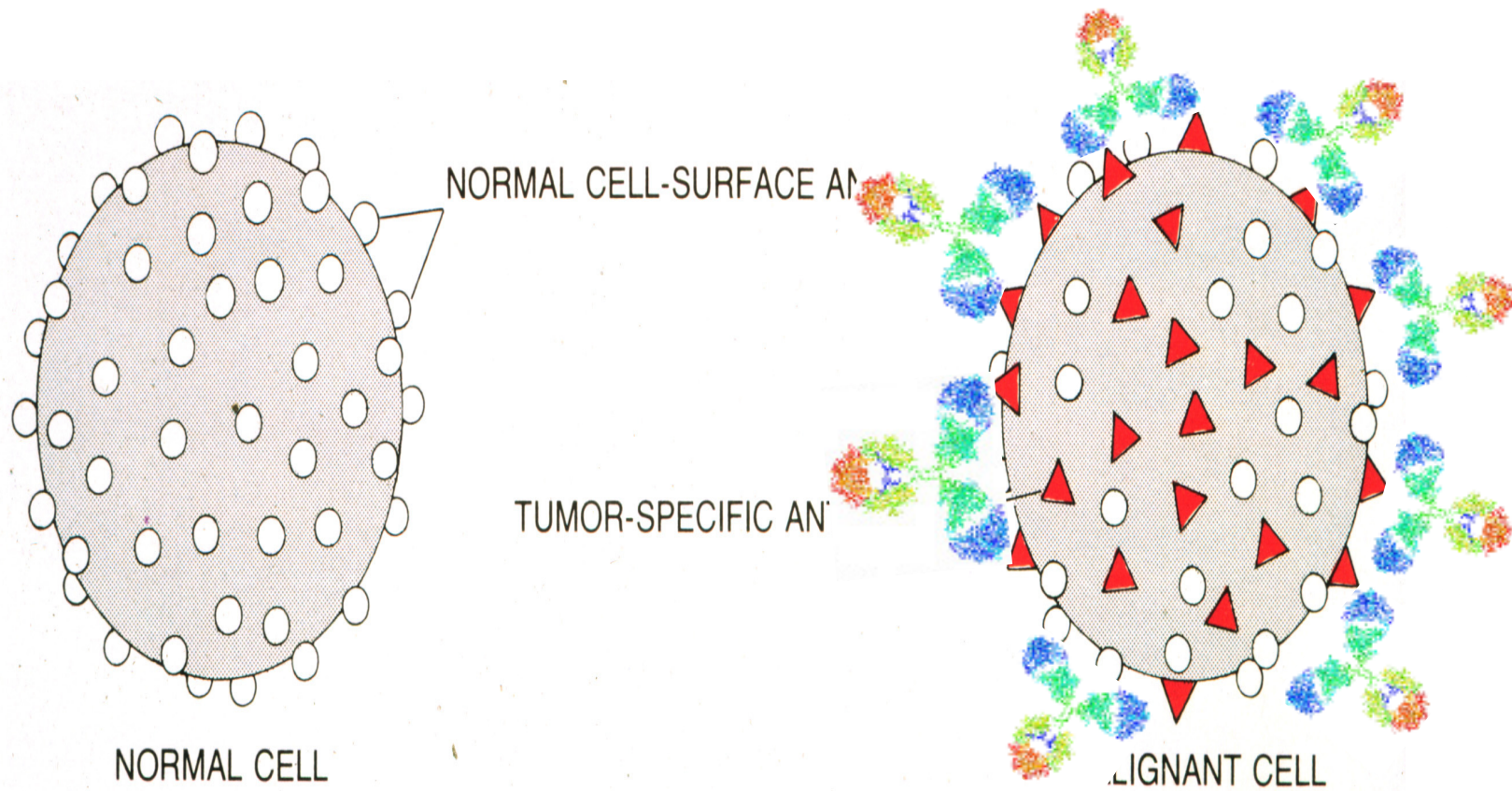
mAbs to PSMA

1st mAbs to PSMA_{ext}

Weill/Cornell group
1st to make mAbs to
PSMA able to bind
living PC cells

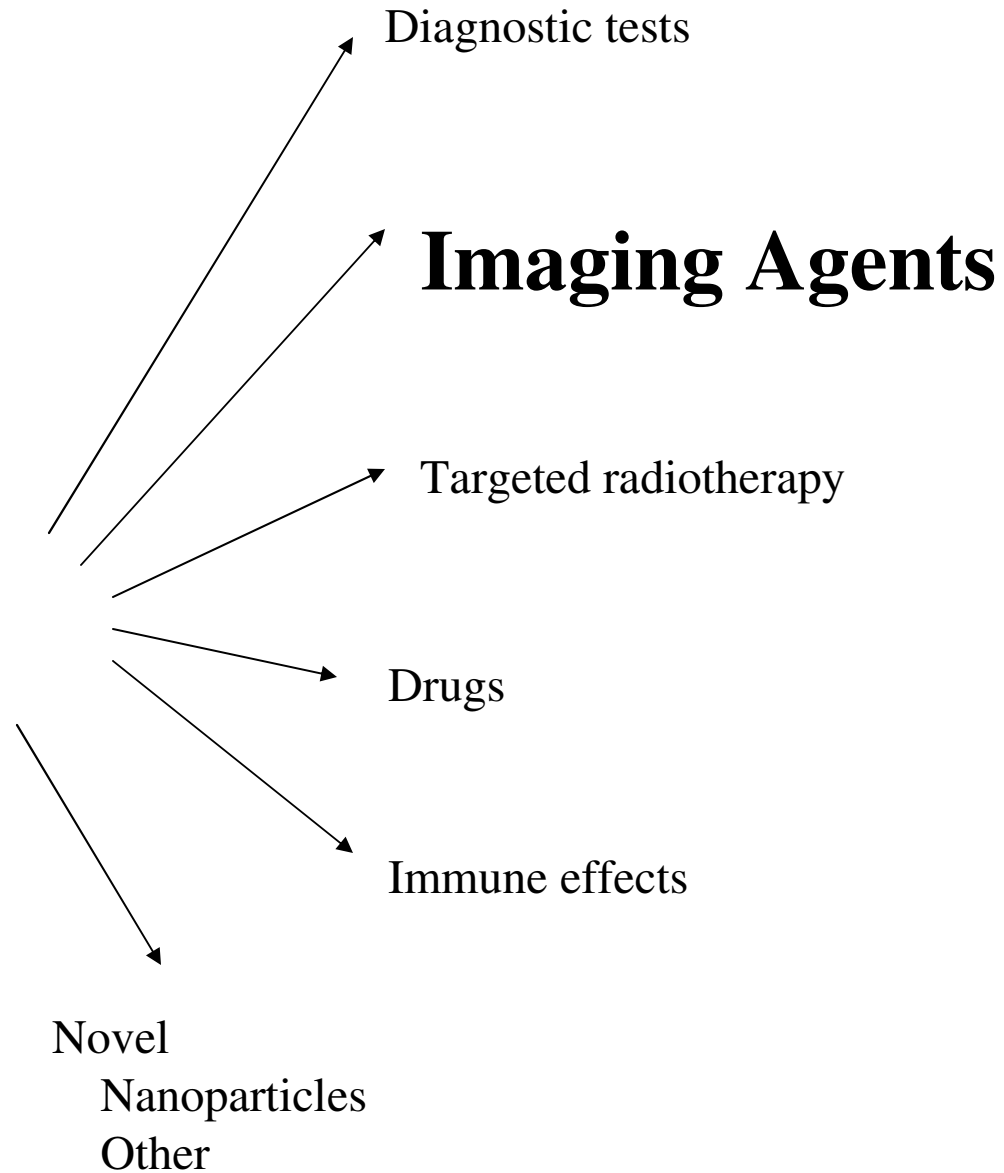


Pca Target: PSMA





Selectively target
cancer cells



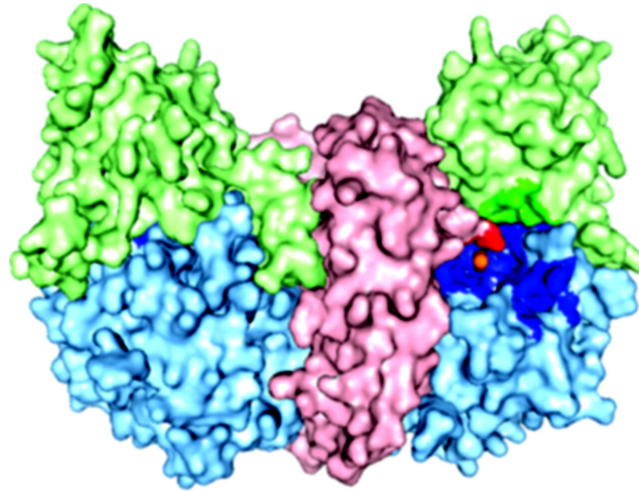
Standard imaging techniques

- **Bone scan**
- **CT/MR**
- **Ultrasound**

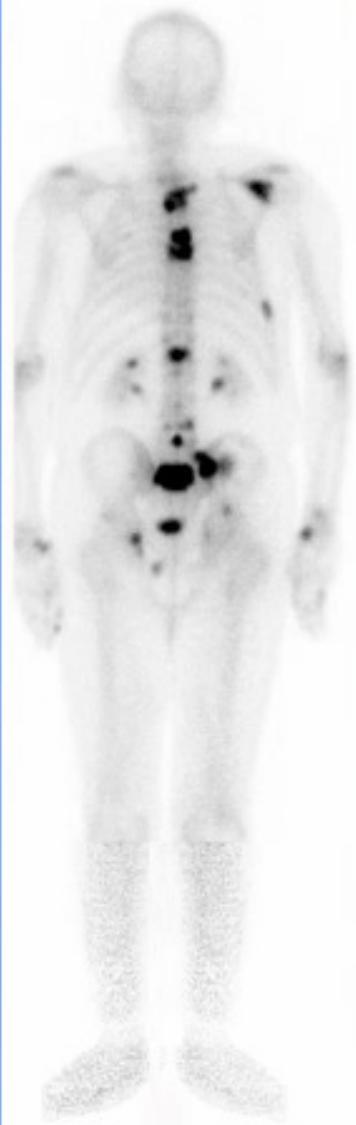
- NaF PET
- FDG PET
- Choline PET

2 ways to target PSMA

- Abs that bind the molecule (e.g., J591)
- Inhibitors/agents that bind the enzymatic 'pocket'



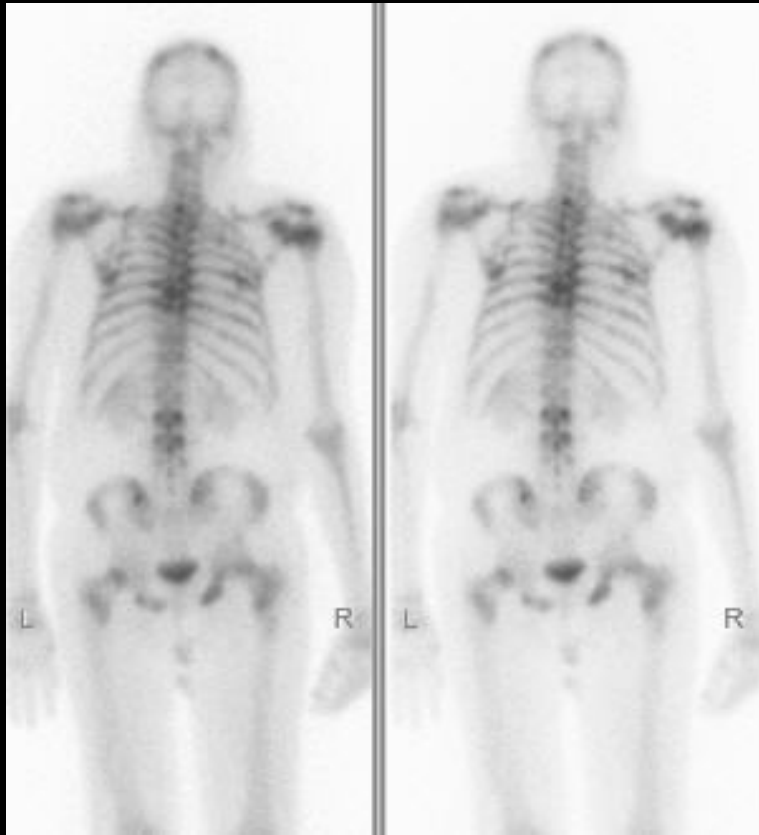
PSMA



Positron Emission Tomography (PET)

- Radioisotope based
- High resolution
- High sensitivity
- Quantitative

Case 1- Comparison of Bone Scan and ^{89}Zr -J591



$^{99\text{m}}\text{Tc}$ Bone scan



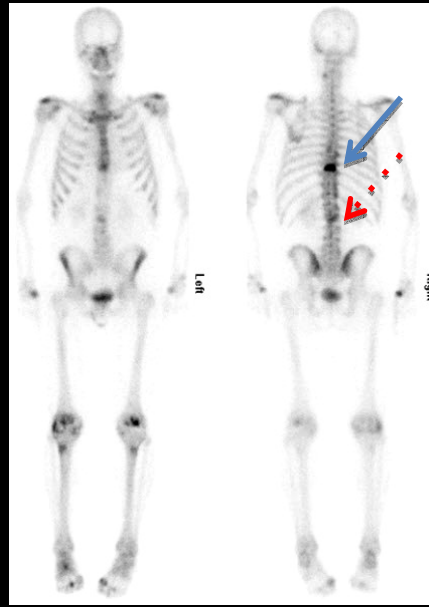
J591 PET



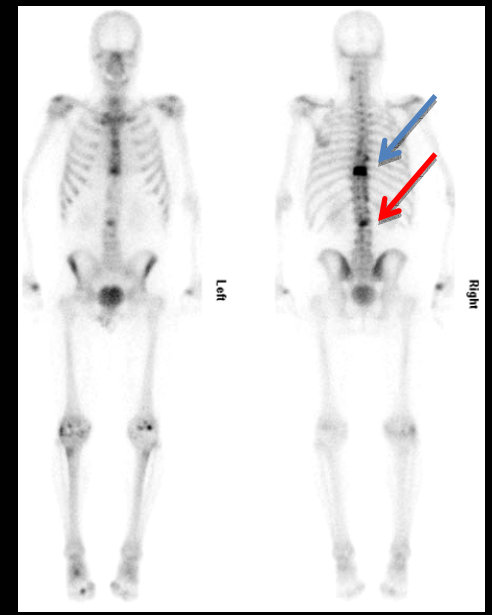
^{89}Zr -J591
Scan



Baseline Bone Scan

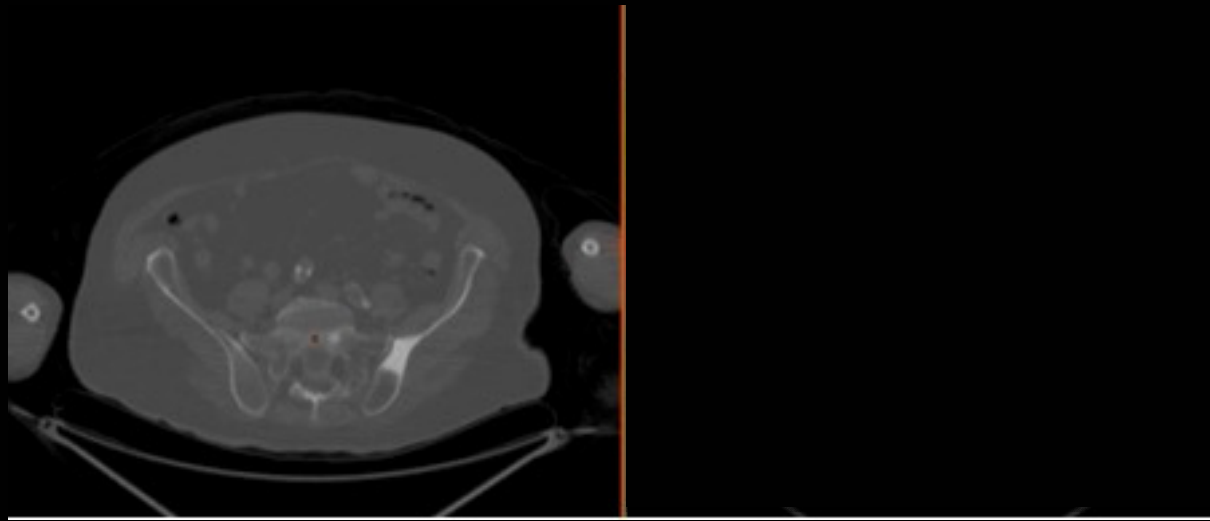


Bone scan 2 mo
later



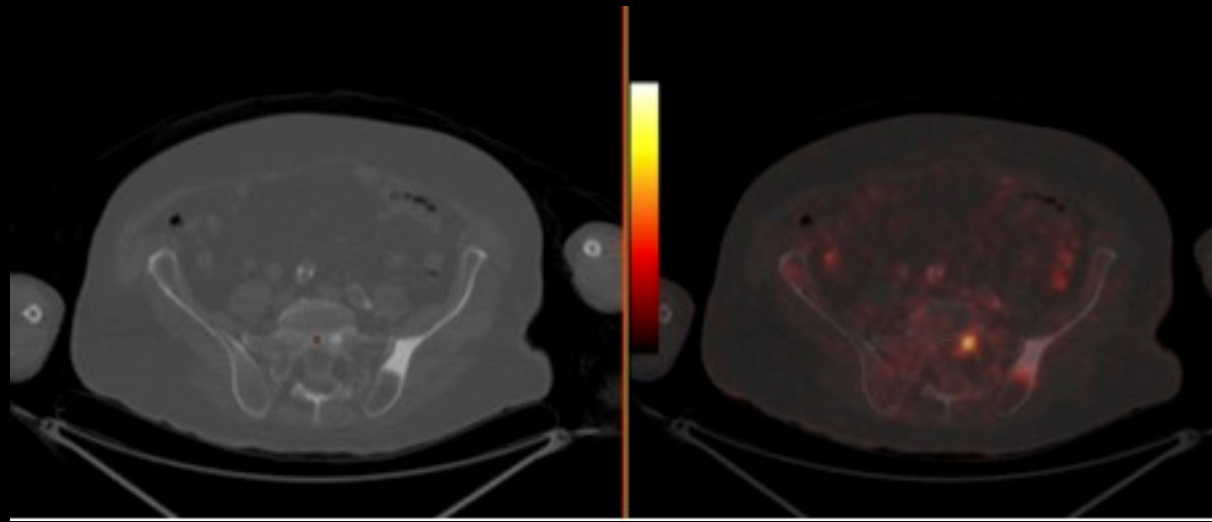
Bone scan 5 mo
after baseline

J591 PET Imaging



CT

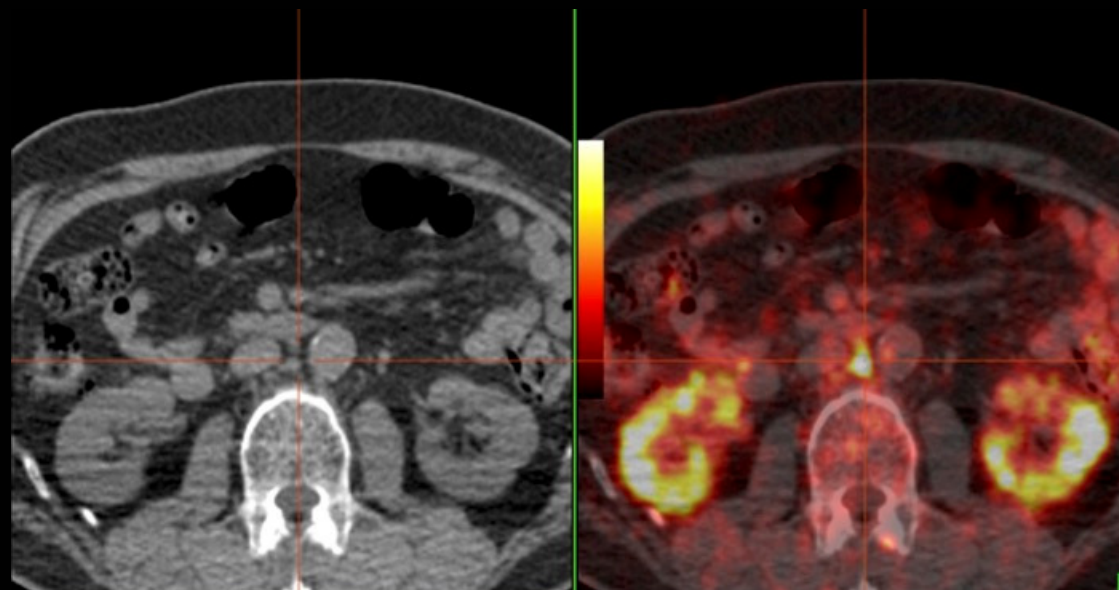
J591 PET Imaging



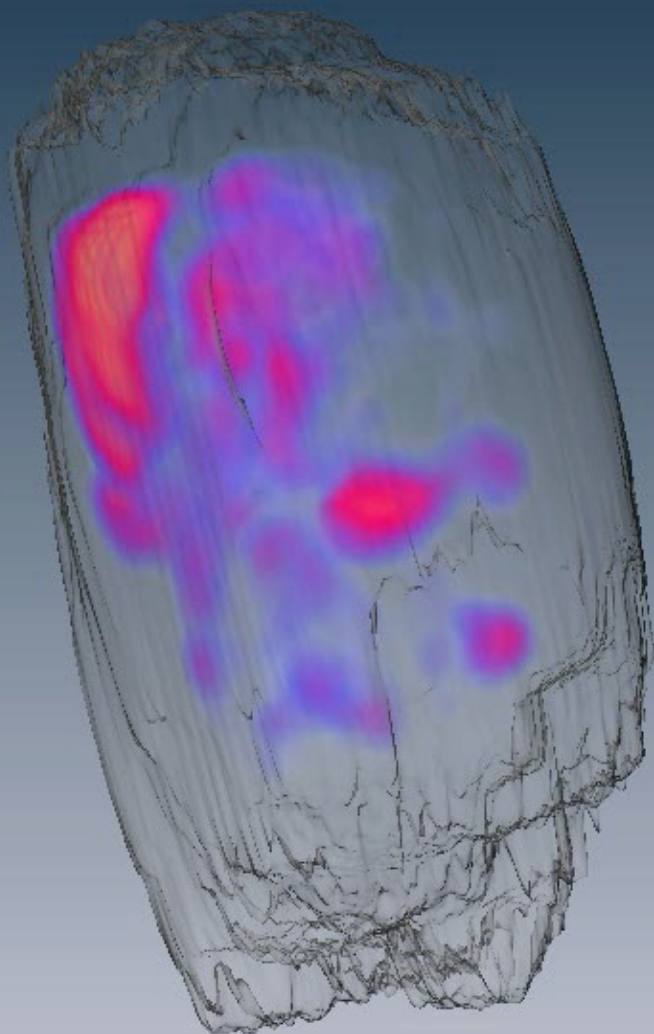
CT

CT/J591 PET

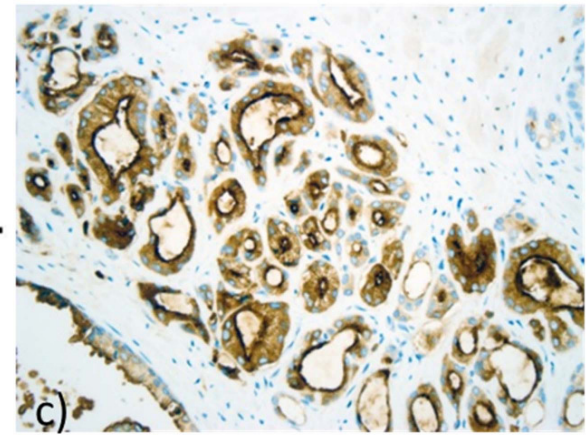
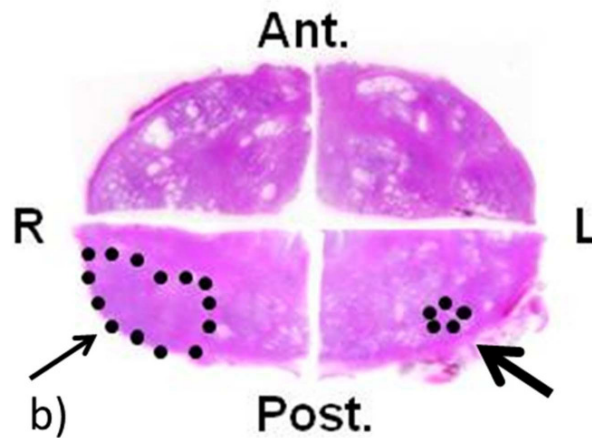
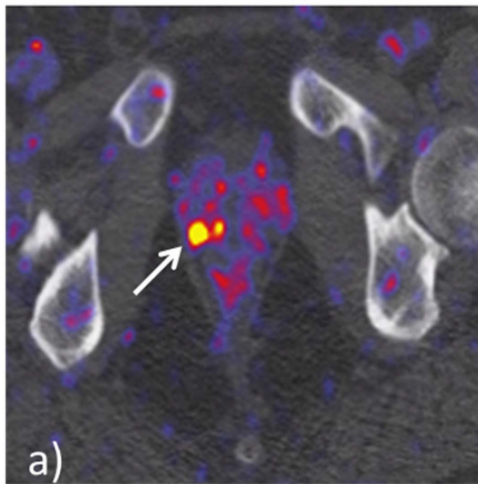




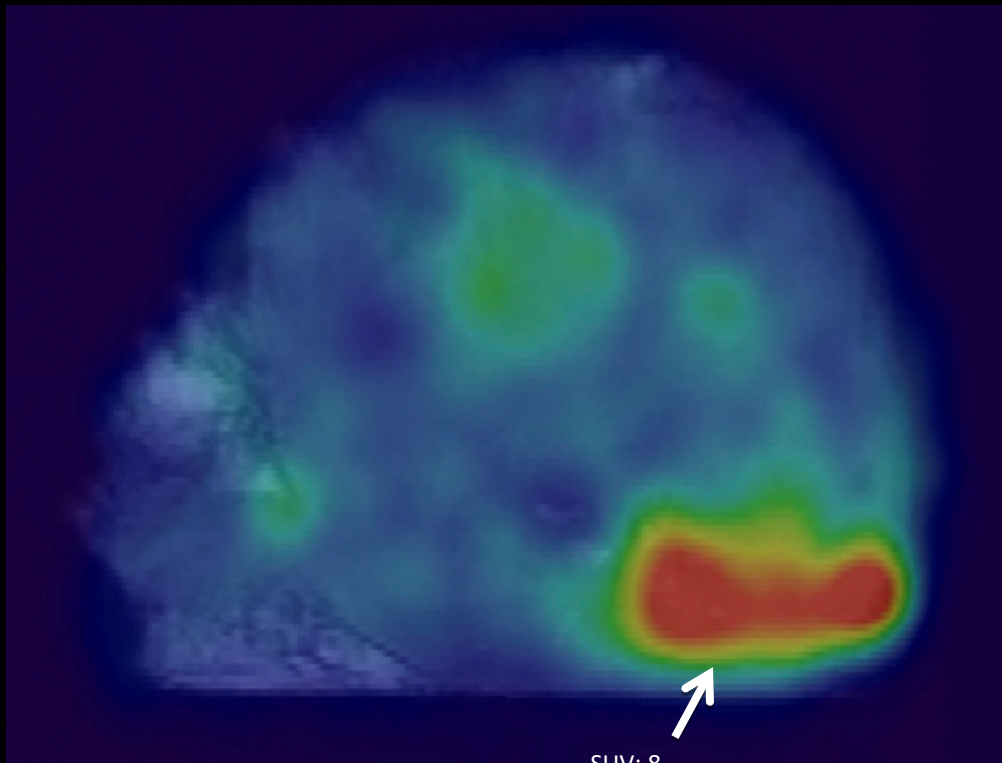
Study of ^{89}Zr J591 in localized PC



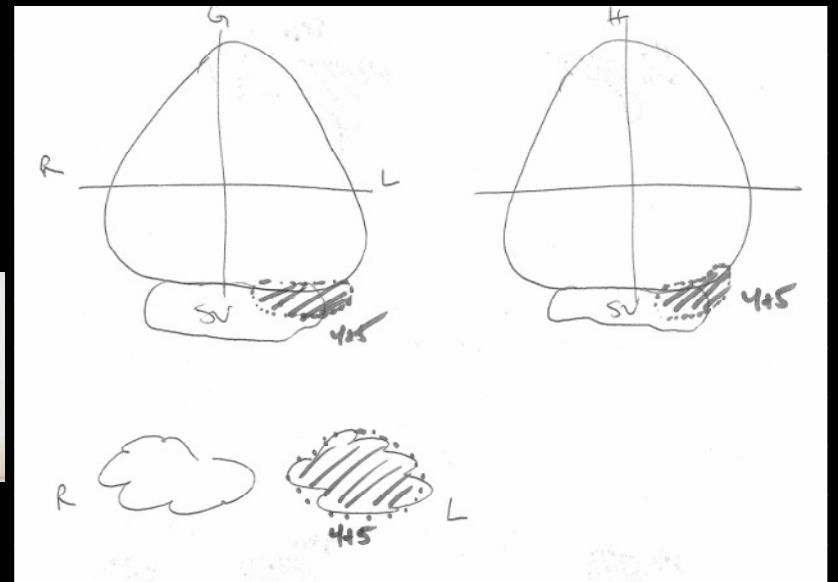
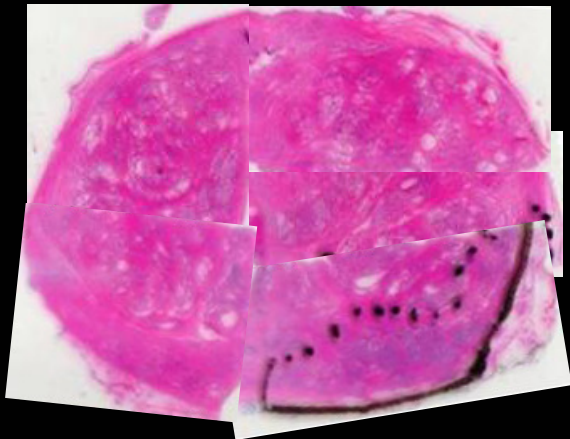
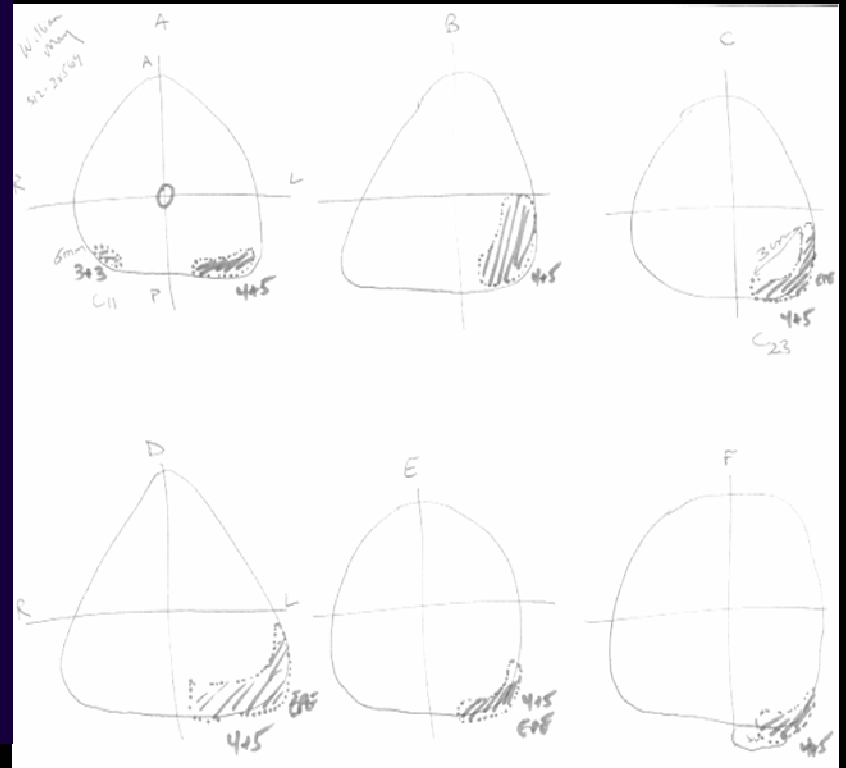
PSMA PET Imaging: Early PCa



- a) Zr89-J591 pre-surgical PET with high-intensity focal uptake in right apex (white arrow)
- b) H&E stained specimen showing Gleason 7 PCa lesion in right apex (thin arrow) corresponding to Figure 1a focus (white arrow); Small focus of Gleason 6 (thick arrow) was not seen on PET study
- c) High-magnification image of right-sided lesion in b) demonstrating PSMA-positivity



SUV: 8



Potential Impact of Improved Imaging

- Earlier, more accurate detection of recurrent or metastatic disease
 - => Earlier treatment => better outcomes
- Improved monitoring of response to Rx
 - => Improved Rx tailoring=> better outcomes
- Improved assessment of new, experimental therapies
 - => Faster drug approvals by FDA => better outcomes
- Improved imaging of disease within prostate
 - => Identify who needs biopsy
 - => Where in prostate to biopsy
 - => Ability to monitor patients on active surveillance
 - => Enable focal therapy

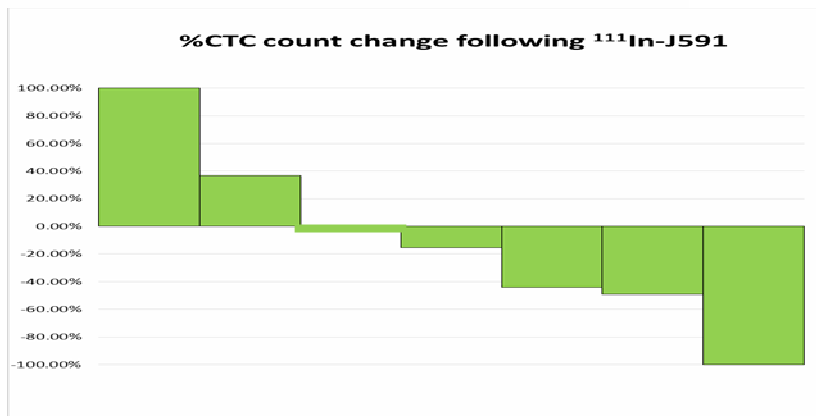
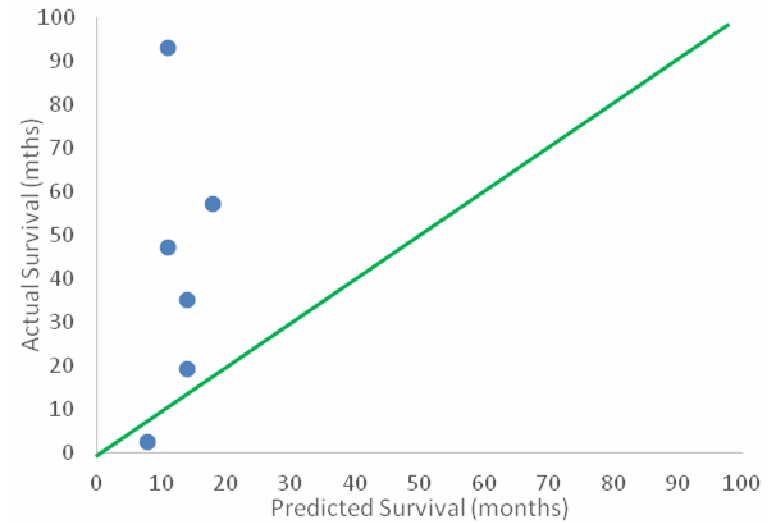
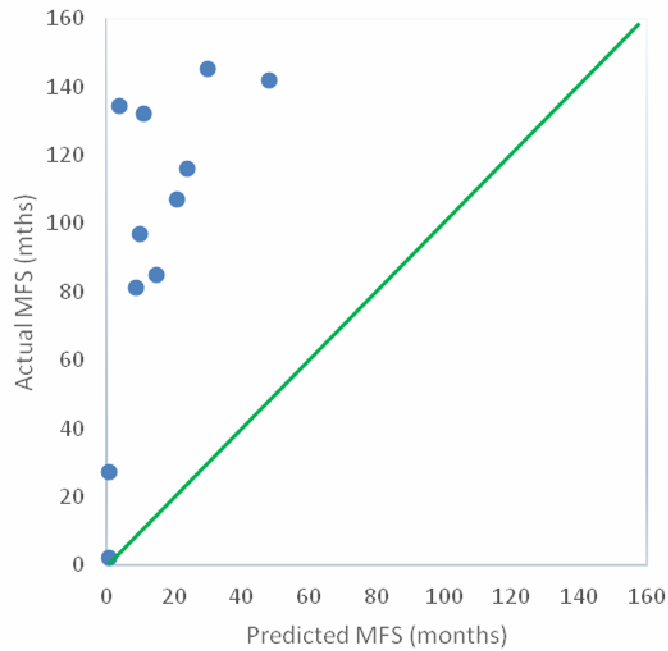
Therapeutic advances

- Antibody (“naked” or unmodified)
- Radiolabeled antibody
- Antibody-drug conjugate

Naked Antibody

- Naked antibodies are effective in other tumors
 - Non-Hodgkins Lymphoma
 - Breast cancer
 - Colon
 - Renal cancers
 - Head & neck cancers

J591 anti-PSMA in PCa



Naked J591 Ab Trials

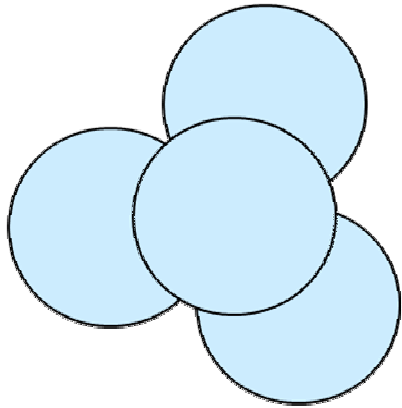
1. mAb J591 in Patients with Advanced PCa and Unfavorable Circulating Tumor Cell Counts (CTCs) [NCT02552394]
 - For patients with CTCs ≥ 5 per 7.5ml of blood
 - Primary Endpoint: Decline in CTCs from unfavorable (≥ 5) to favorable (< 5)
2. Pre-operative mAb J591 for high and/or intermediate-risk PCa [NCT02693860]
 - Intermediate or high risk prostate cancer defined as:
 - Gleason grade ≥ 7
 - PSA > 10
 - Plan for radical prostatectomy
 - Primary Endpoint
 - Assess whether J591 induces an inflammatory and/or apoptotic response of PCa cells

Favorable data would lead to phase 3 trial for FDA approval

Radiolabeled anti-PSMA

- PCa is a radio-sensitive tumor
 - External beam radiation
 - Radioactive implants
 - Painful metastasis
- Xofigo ($^{223}\text{Radium}$)

Alpha- vs. Beta-Particles



Alpha

Beta



	α	β
Relative particle mass	7300	1
Initial energy (MeV) per particle	3-8	0.01-2.5
Range in tissue (μm)	40-100	50-5000
LET (KeV/μm)	60-230	0.015-0.4
DNA hits to kill cells	1-10	≥ 1000 's

LET = linear energy transfer.

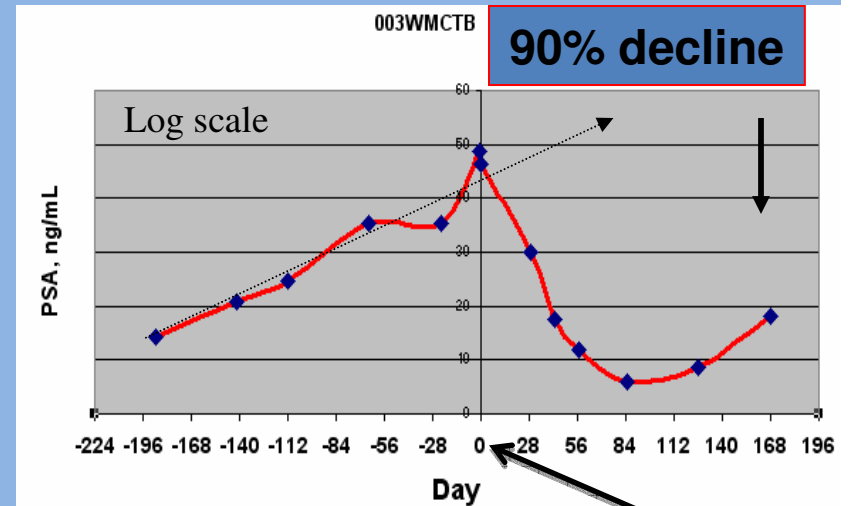
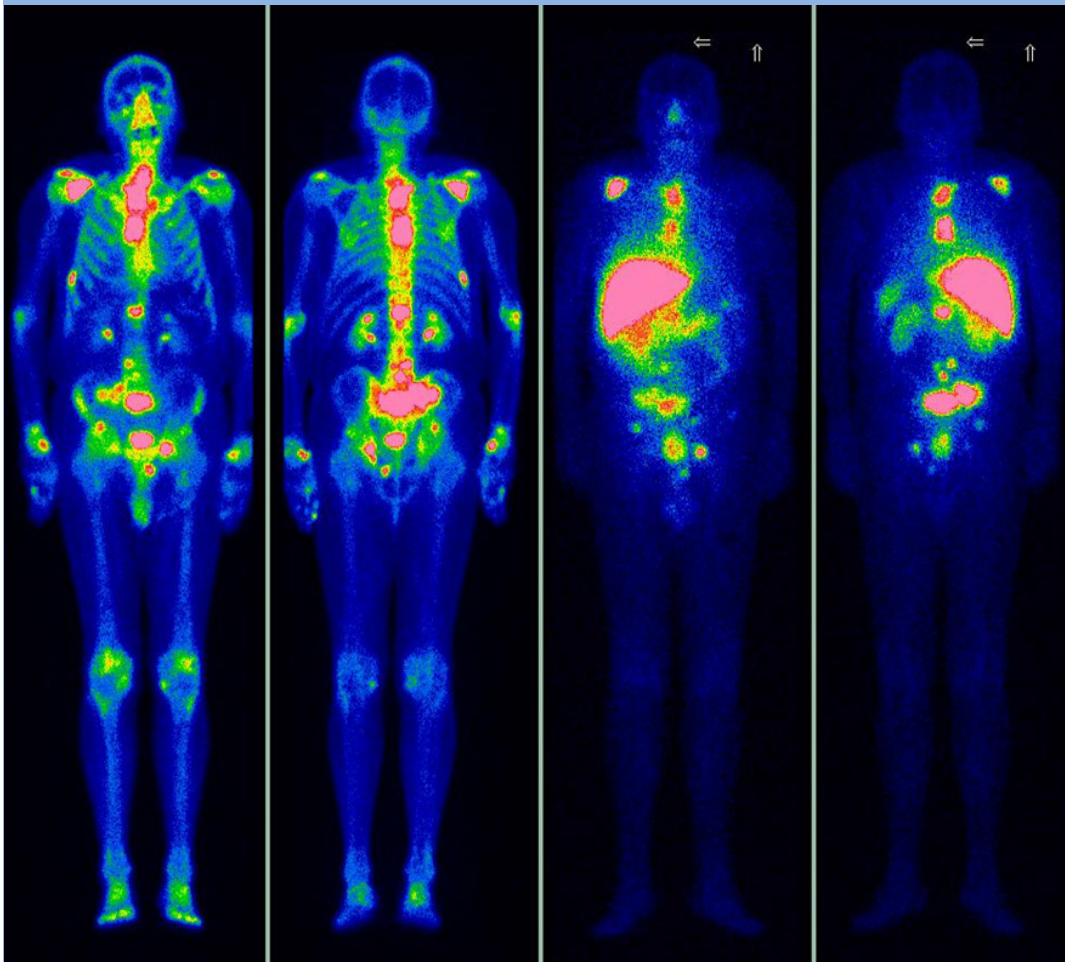
Henriksen et al. *J Nucl Med.* 2003;44:252-259

^{177}Lu -J591 Rx: Excellent Targeting & PSA Response

44/47 (93.6%) with accurate targeting of known sites of disease

$^{99\text{m}}\text{Tc}$ -MDP bone scan

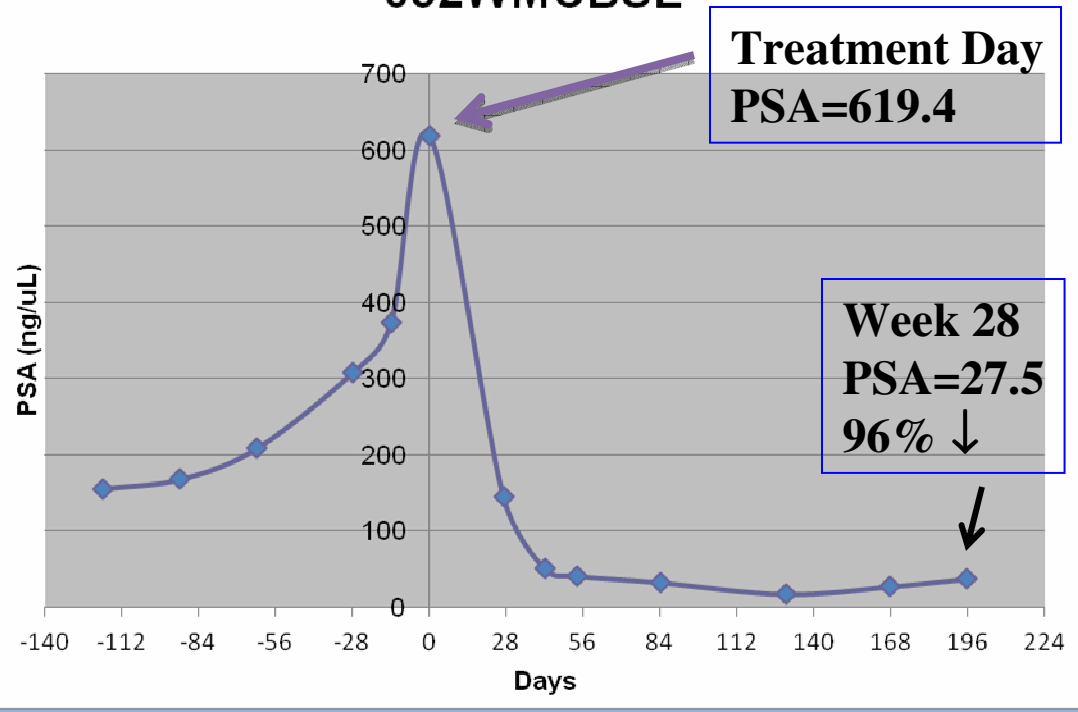
^{177}Lu -J591 mAb



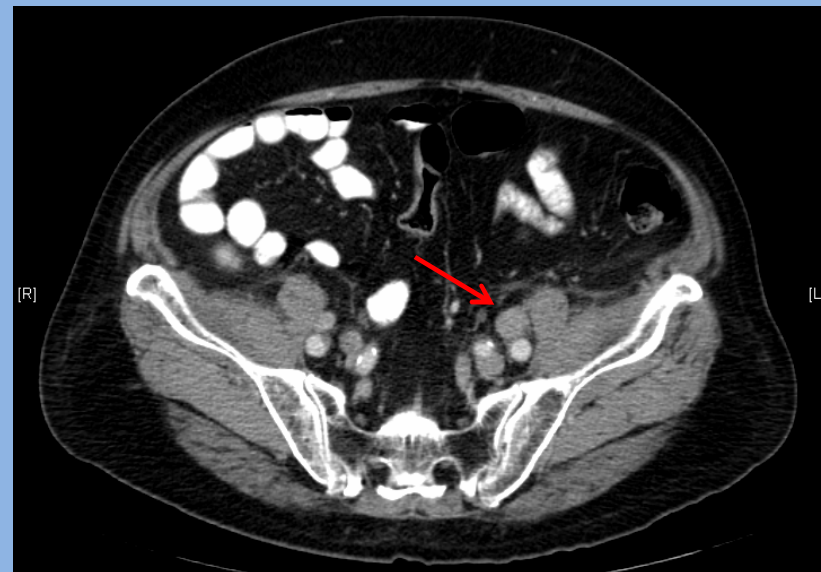
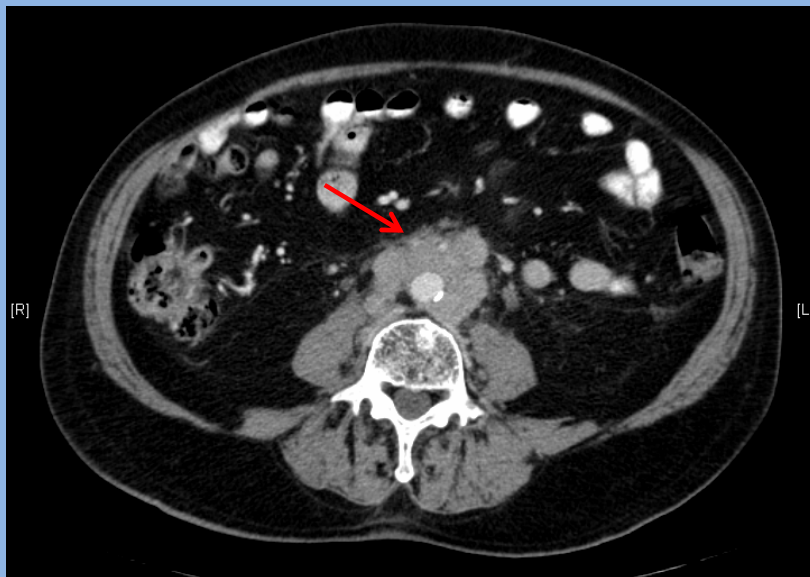
Pre-Rx PSADT=3.9 mo Day of Rx

**66% experienced PSA decline after a single infusion,
47% had major decline**

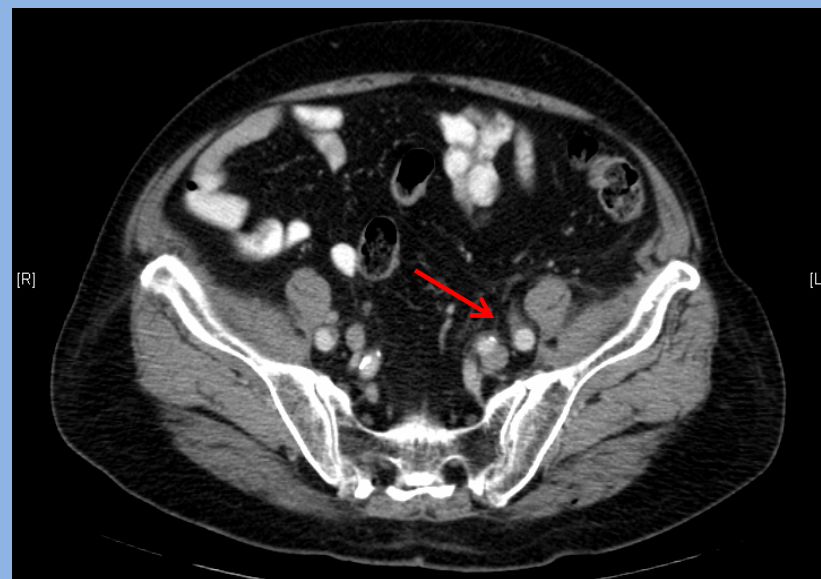
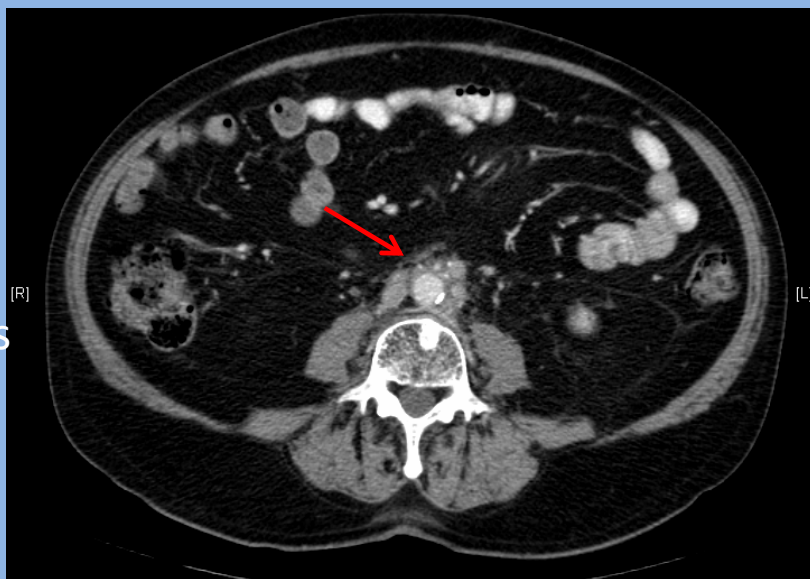
052WMCBSL



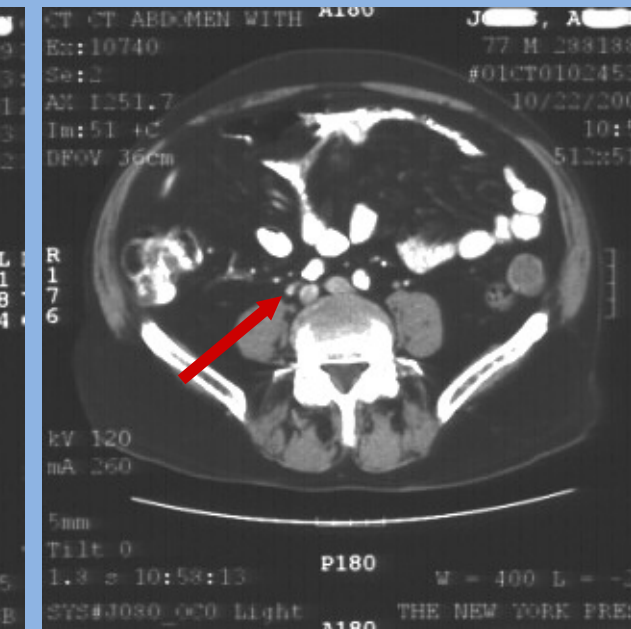
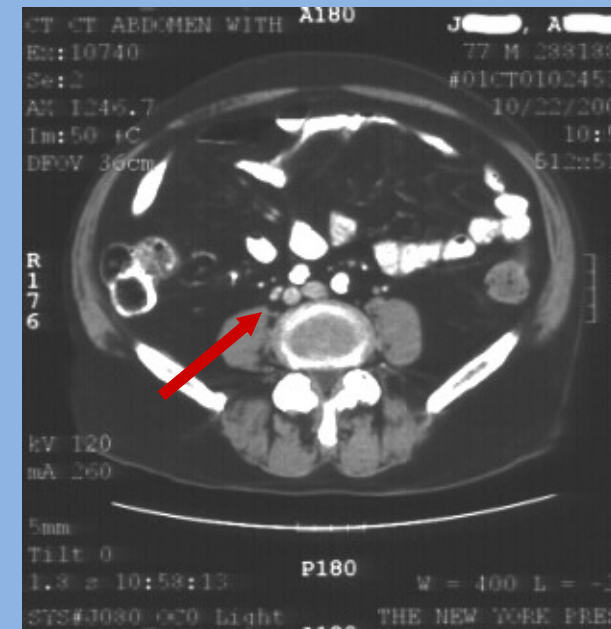
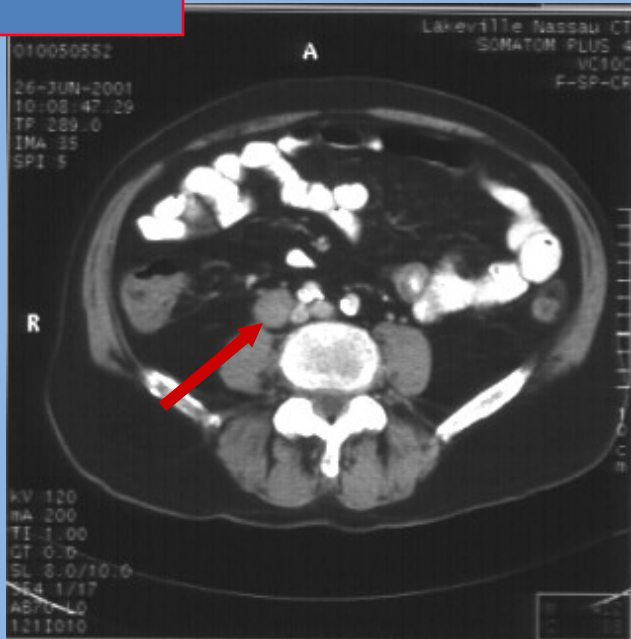
Baseline
pre-Rx



3 months



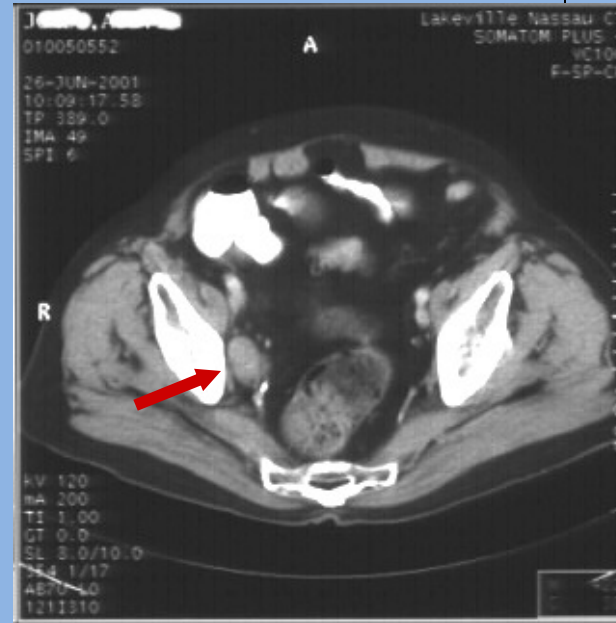
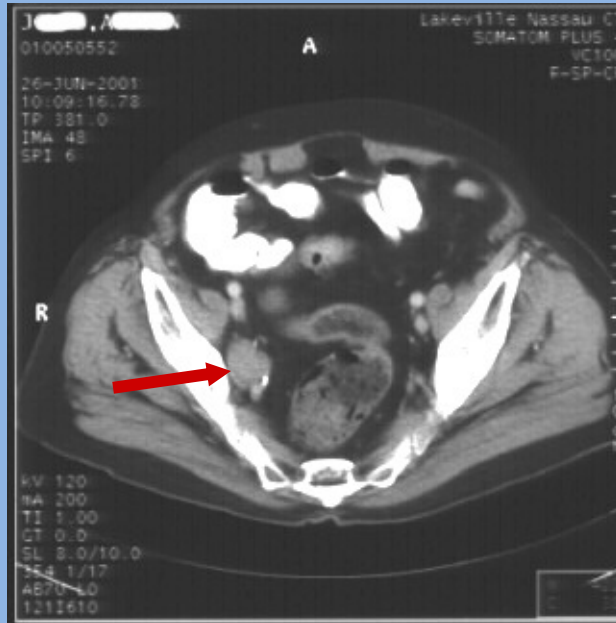
Pre-Rx



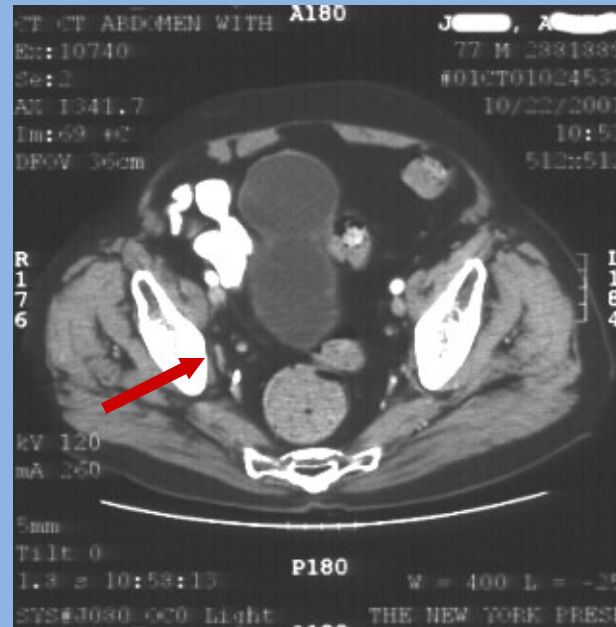
9 wks Post-Rx



Pre-Rx

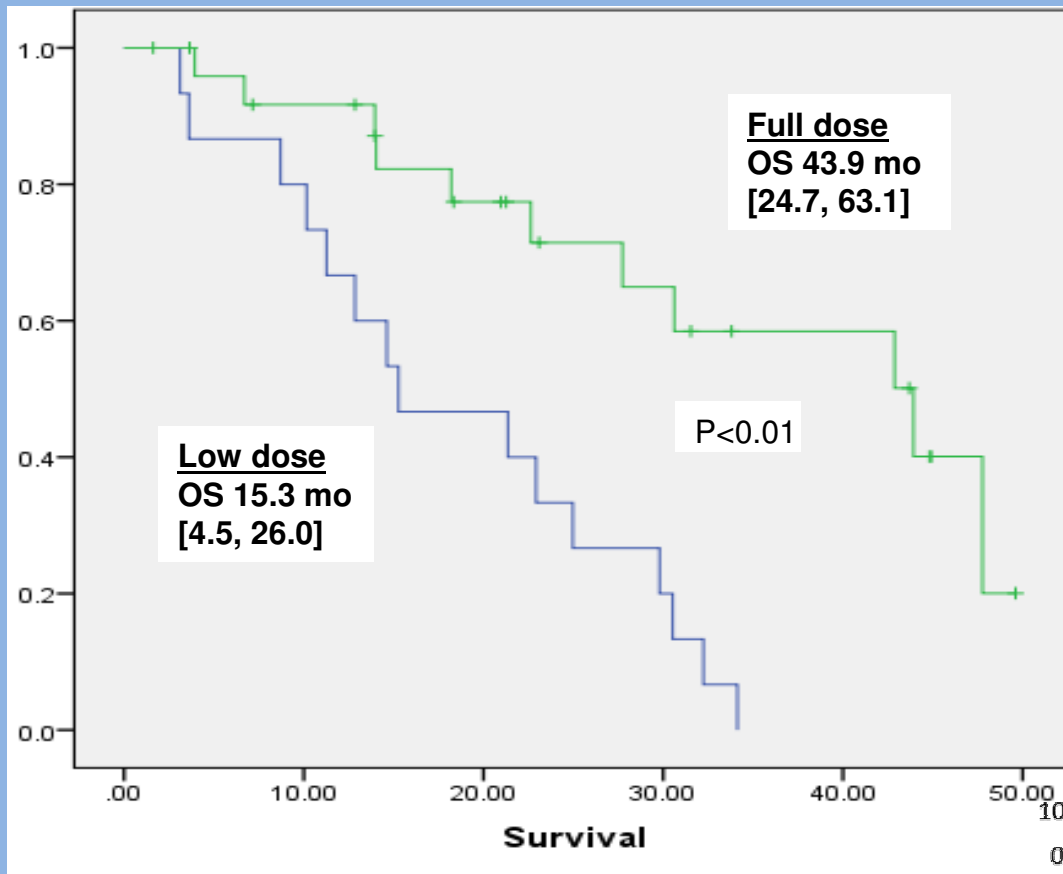


9 wks Post-Rx



Phase I Fractionated Dose ^{177}Lu -J591

“Split dose” ^{177}Lu -J591 is able to be delivered at higher total doses safely



Full dose patients (n=26*)

Any PSA decline: 57%

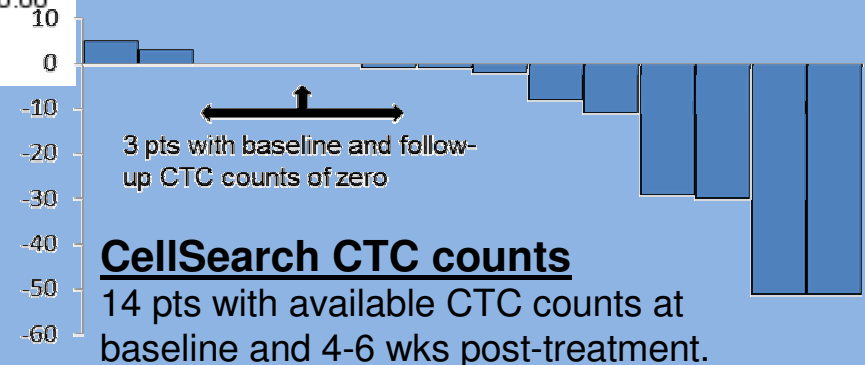
>30% PSA decline: 38%

>50% PSA decline: 27%

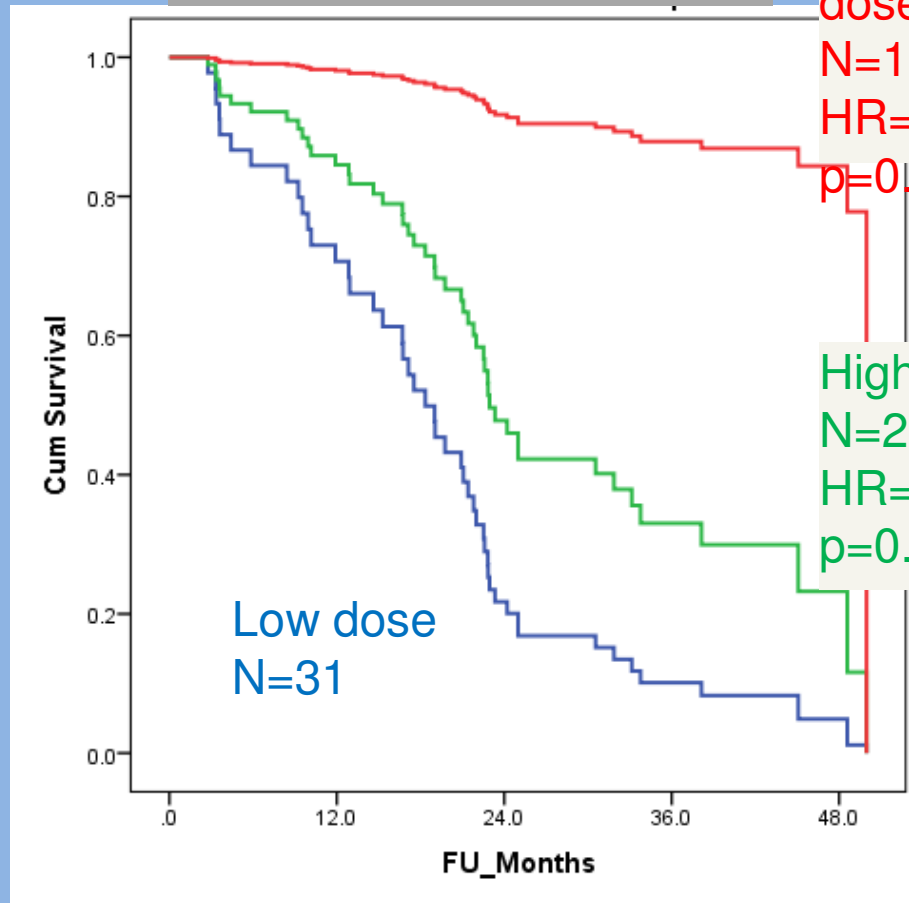
* 1 addl pt on study with 29% PSA decline

Overall Survival

Median OS for the entire study is 27.7 mo [95%CI 18.4, 37.1]



Cox model



High fractionated dose

N=16

HR=0.06 [0.01-0.41]

p=0.005

High single dose

N=26

HR=0.48 [0.26-0.91]

p=0.023

Low dose

N=31

As seen in the animal models, higher fractionated dosing improves response and survival.

²²⁵Ac-PSMA

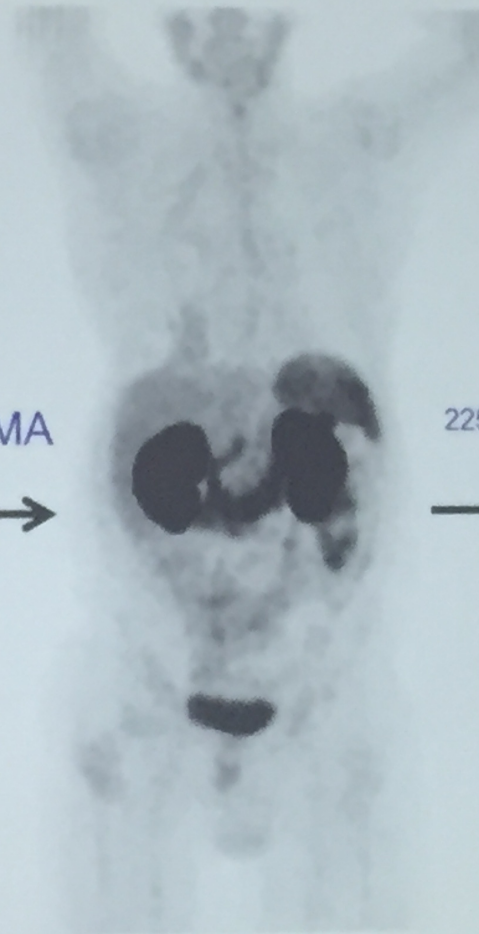
Patient-A
LHRH (urupetyl, leuprorelin)
zoledronate
Docetaxel (50 cycles)
Carmustin/Epirubicin in hyperthermia
Arbiterone
Enzalutamide
Ra-223 (6 cycles)
Arbiterone re-exposition
Estramustine



12/2014
PSA = 2923 ng/ml

3 x
²²⁵Ac-PSMA

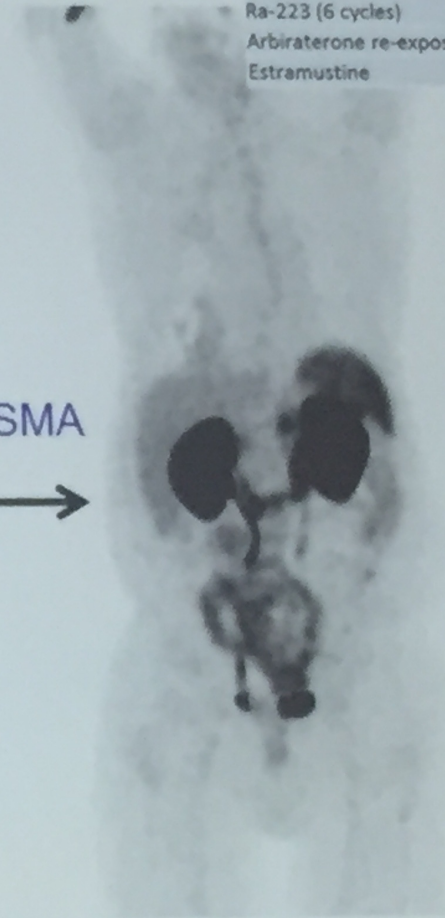
→



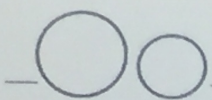
7/2015
PSA = 0.26 ng/ml

1 x
²²⁵Ac-PSMA

→

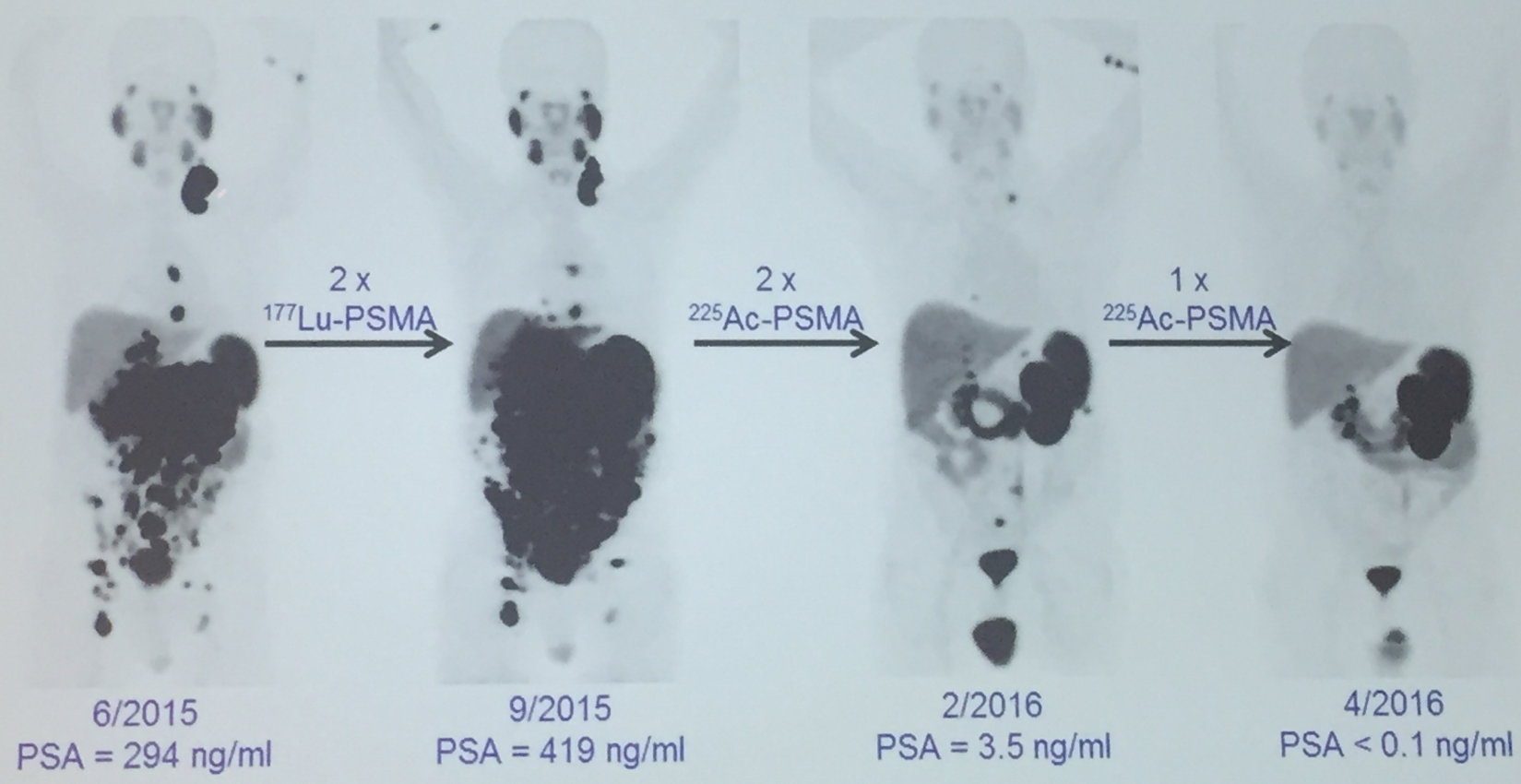


9/2015
PSA < 0.1 ng/ml



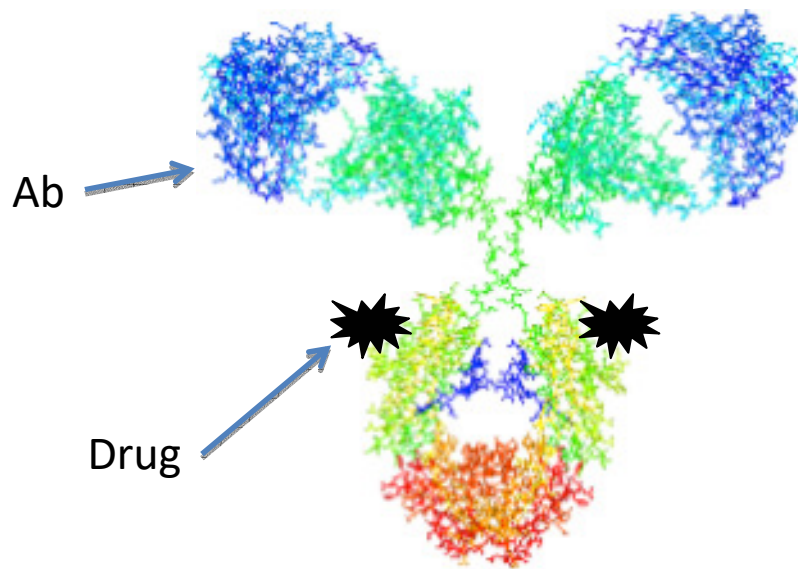
²²⁵Ac-PSMA

Patient-B
radical prostatectomy
radiotherapy of lymphnode metastasis
LHRH (leuprorelin)
LHRH (leuprorelin) + Bicalutamide 150mg/die
Docetaxel (11 cycles)
Cabazitaxel (10 cycles)
Arbiterone
Enzalutamide - NOT TOLERATED



Ab-Drug Conjugate

Linking a drug to an Ab =>
a drug that can discriminate cancer
from normal cells



Active clinical trials

- J591 imaging pre-radical prostatectomy
- J591 neo-adjuvant trial (pre- prostatectomy)
- ^{177}Lu J591 + hormonal Rx in PSA relapse
- J591 in mCRPC with elevated CTC
- RL-anti-PSMA in mCRPC (multiple trials)

Conclusions

- PSMA is an ideal PC-specific molecular target
- PSMA imaging is under active study in US & Europe
 - Better than conventional technologies
- Potential to transform diagnosis, staging, monitoring and treatment of PC
- Multiple ways to therapeutically target PSMA in patients with PCa
 - All promising and all under active study