Imaging and Theranostics in early phase trials

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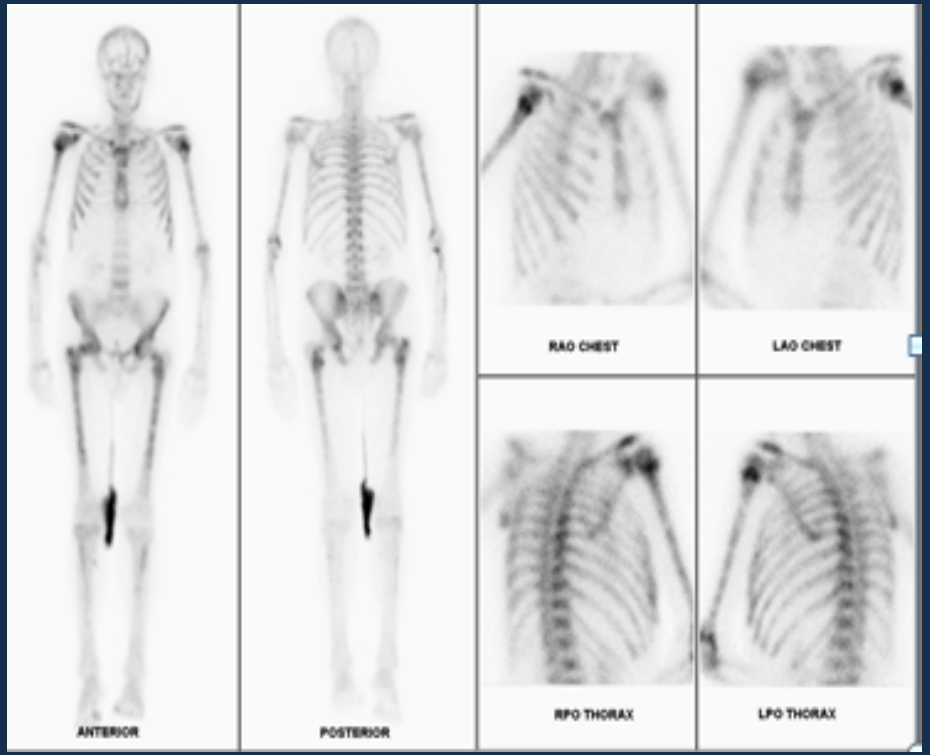
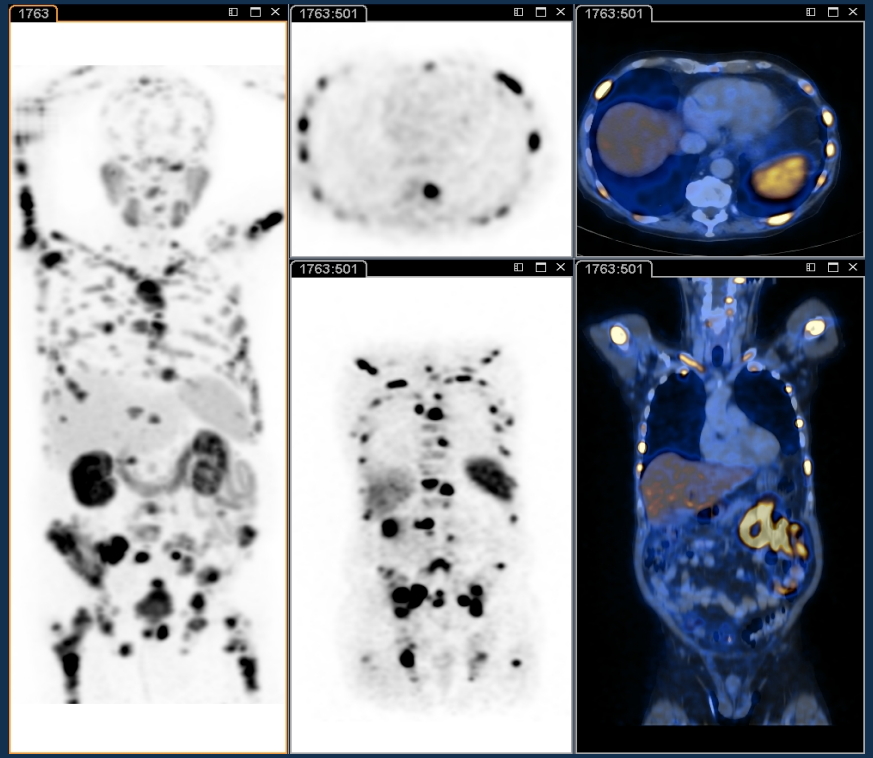
OLD TECHNOLOGY



BONE scan

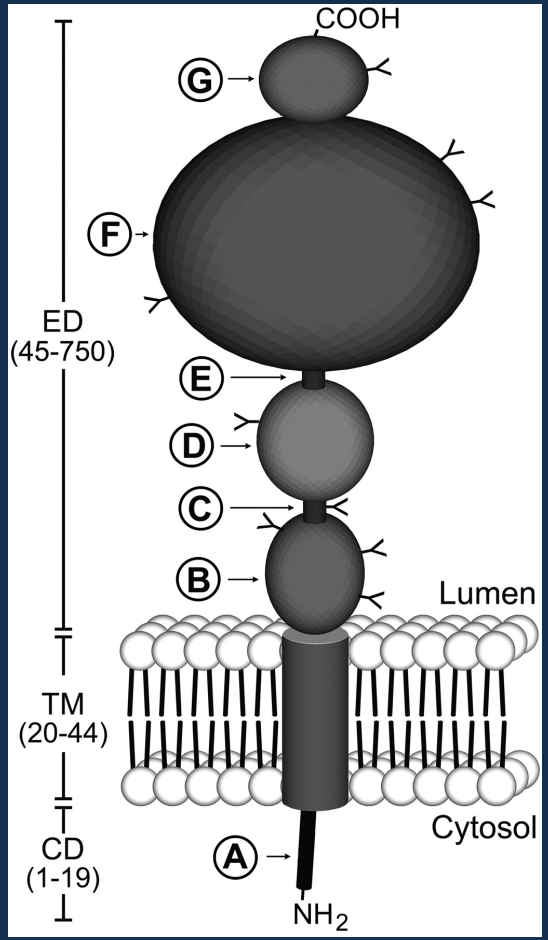
NEW TECHNOLOGY



PSMA PET CT scan

Imaging biomarkers

- Predictors of response (important for eligibility for treatment)
- Ligands for delivering therapeutic payload
- Quantify dose delivered to tumour cell.
- Measure treatment response
- Determine best next treatment options



PERFECT TARGET- PSMA

Cell surface enzyme –folate hydrolase

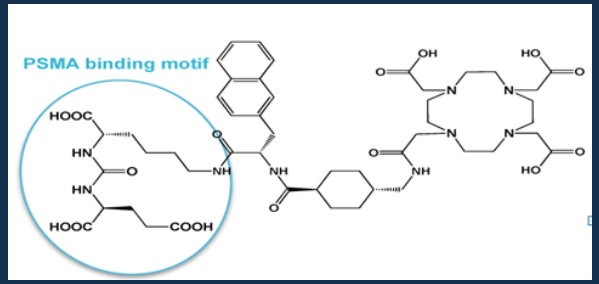
750-amino acid type II transmembrane glycoprotein expressed in normal human prostate epithelium.

Over-expressed (1000 x) in virtually all prostate cancers (95%). Expression increased in poorly differentiated, metastatic and castration-resistant carcinomas.

Rapid cellular internalisation via clarithrymycin coated pits following ligand-receptor binding.

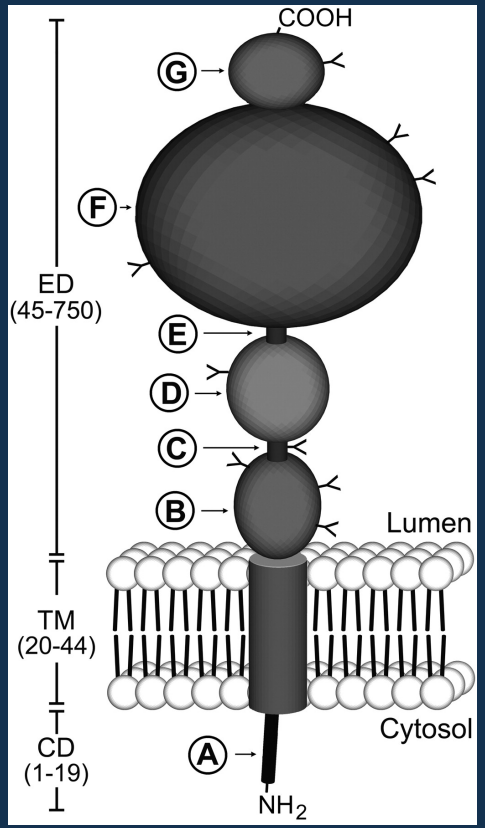
THERANOSTICS

THERAPY

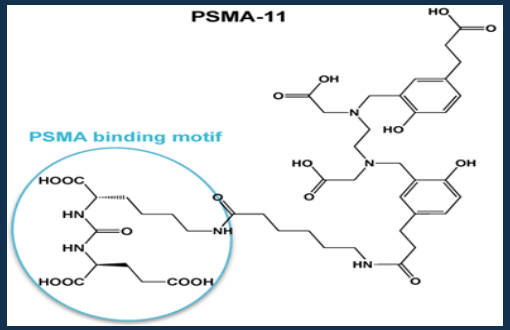


Lu ^{177} DKFZ – 617 PSMA

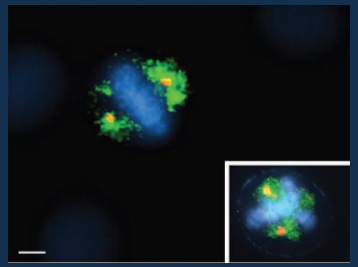
Small molecule peptides and Radionuclides used for both Therapy and diagnosis ‘Theranostics’



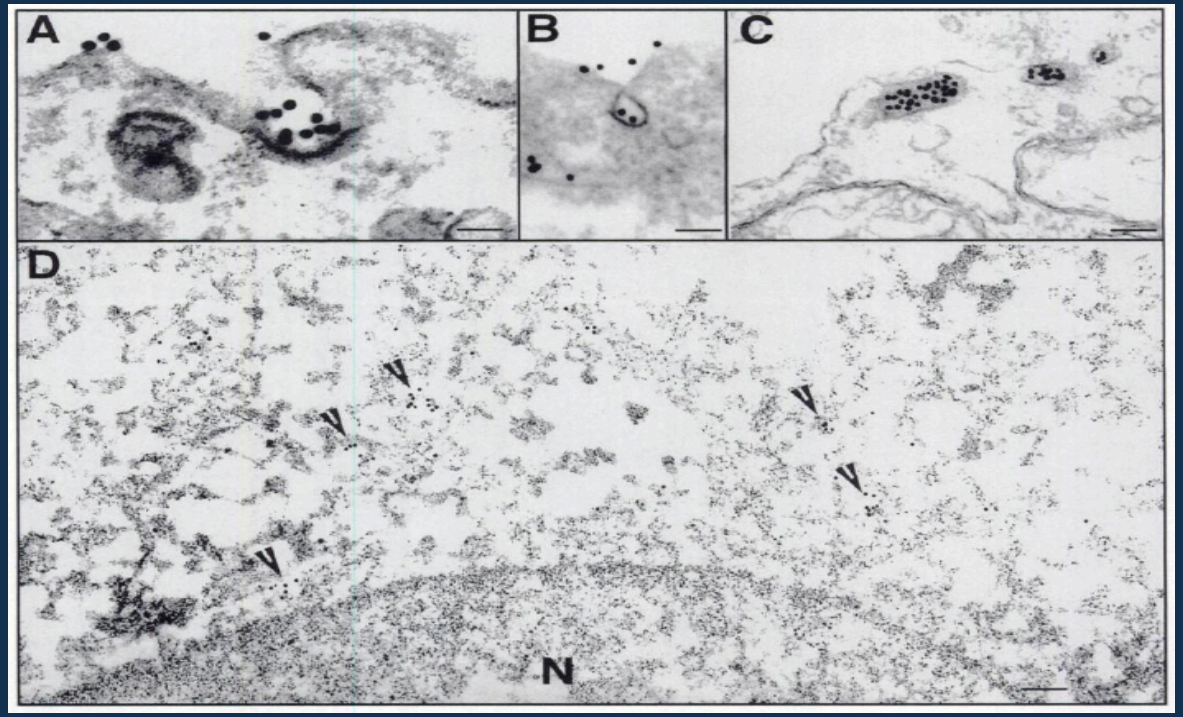
DIAGNOSIS



Ga^{68} PSMA -11



Immuno-electron microscopy revealing endocytosis of PSMA binding antibody in prostate cancer cells



Antibody location revealed using gold bead labelled goat anti-mouse antibody

Liu et al. *Cancer Res* 1998; 58(18): 4055-60.

PSMA as imaging biomarker

- Highly specific for prostate cancer
- Volume of active disease on PSMA reflective of disease burden in most patients
- Not all prostate cancers express PSMA
- Significant heterogeneity in end stage patients

Lutetium 177

- Radioactive element
- $T^{1/2}$ 6.7 days
- 90% decay as Beta emission
- 10% Gamma and X-ray.
- Outpatient treatment possible with careful management of radiation safety.
- Rapid renal excretion
- Good physical characteristics for radionuclide therapy
- Able to chemically label to PSMA (stable)

Prospective Observational Trial of Lu^{177} PSMA in men with symptomatic progressive mCRPC: Toxicity, safety, dosimetry and biochemical response.

Louise Emmett, Anthony Joshua, Richard Epstein, Bao Ho, Quoc Nguyen, Robert Kent, Jane Shin, Jenny Hvalica, Ashley Blanksby, Lalith Ratnayake, Lisa Horvath, Phillip Stricker.

Partner trial with Peter Macallum Cancer Institute

Lu PSMA – St Vincent's

- Prospectively accrued trial in men with mCRPC (n=15).
- Must have failed ADT, Androgen blockade therapy and either failed, refused or not eligible for Chemotherapy
- Rising PSA and imaging failure.
- Symptomatic disease.

- Study Aims
  - Assess biochemical response to therapy and measure treatment response with both RECIST and PERCIST measures
  - Assess safety and toxicity profile
  - QOL and pain assessments

Enrolment

- Must meet clinical criteria (mCRPC) and symptomatic rising PSA
- eGFR >40mls/min, HB>90, platelets >70.
- Must have imaging compatible with likely response
    - Ga PSMA and F18 FDG PET CT as screening
    - Require disease > 90% PSMA avid and intensity 2 x liver on PSMA PET CT imaging.

Screening

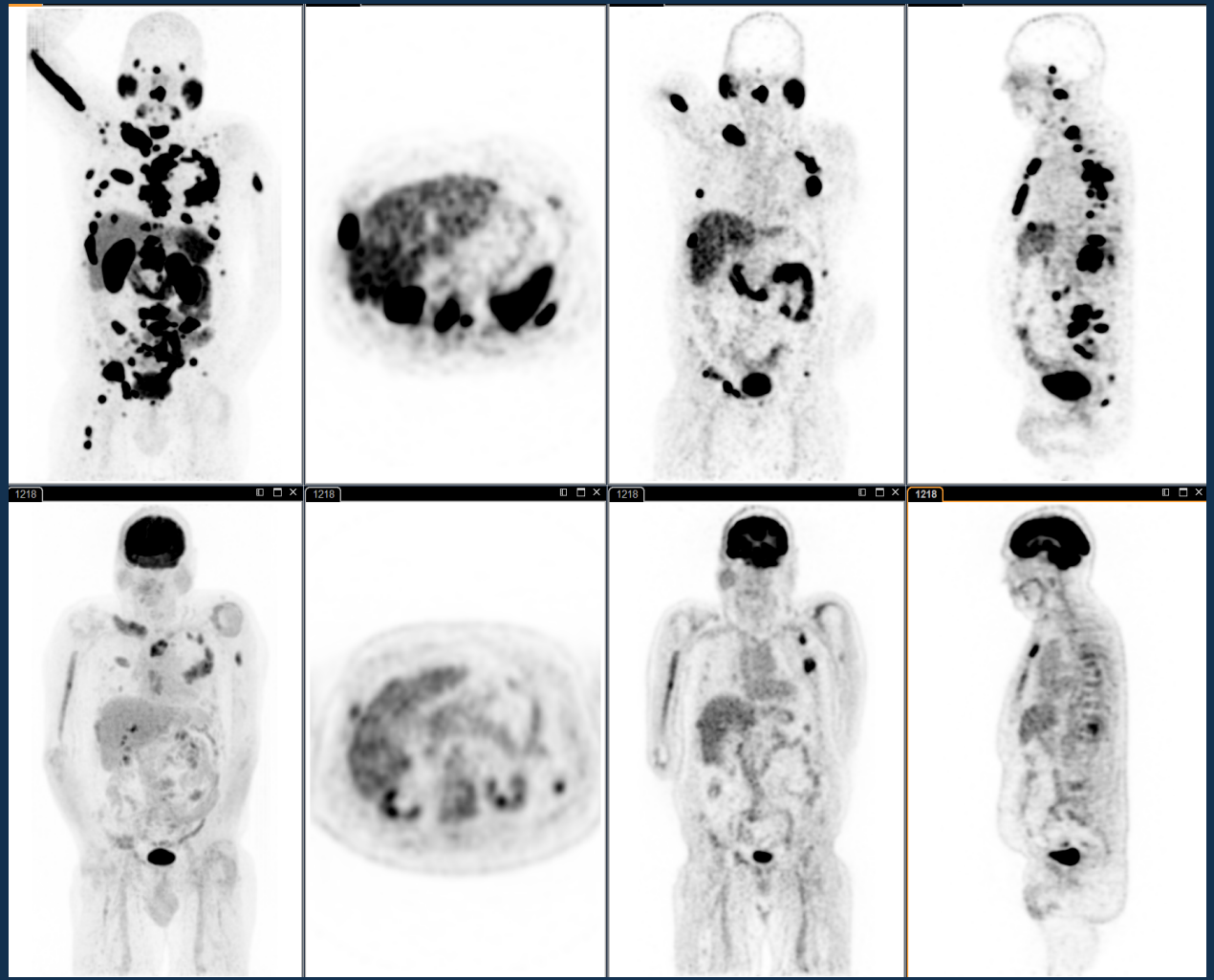
- 20 men screened for trial with GaPSMA PET CT and F18 FDG
- 14/20 Eligible on trial criteria and enrolled.
- 6/20 Ineligible
  - 2/20 insignificant PSMA expression
  - 4/20 PSA stable (1/20)/ marrow failure prior to injection of Lu PSMA (3/20).

Screen Failures

F18FDG

Ga PSMA

- 5-10% Prostate cancers do not express PSMA
- PSMA -/FDG +
- 2/20 Screens in mCRPC cohort



SCREEN SUCCESS

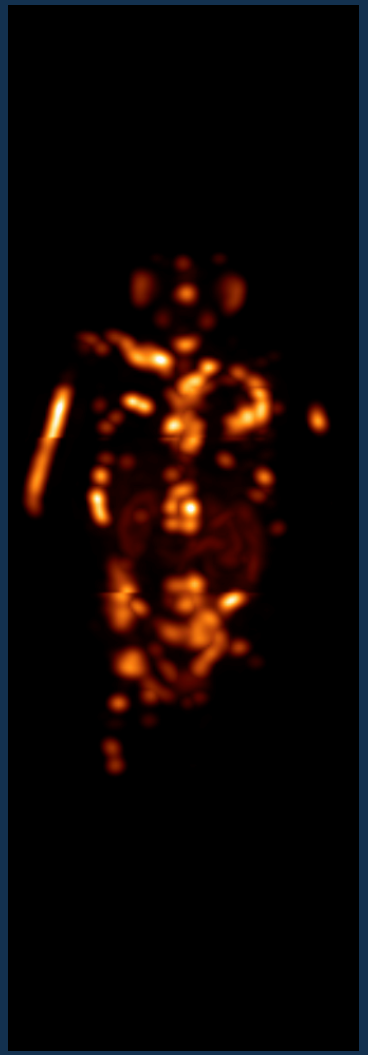
GaPSMA

Median SUV max 40

F18 FDG

Therapy Schedule

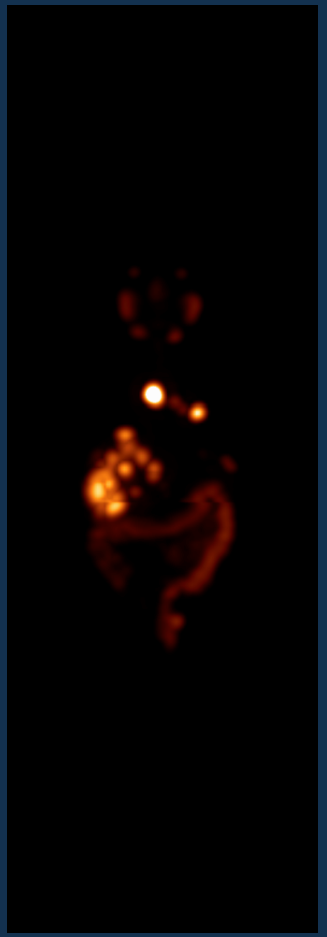
- Lu PSMA dose determined on GFR, number of sites and patient weight – 6.5-8.0Gbq.
- 4 doses of Lu PSMA at 6 weekly intervals
- 2nd weekly bloods
  - PSA
  - Hb, platelets, wcc, UEC, LFT.

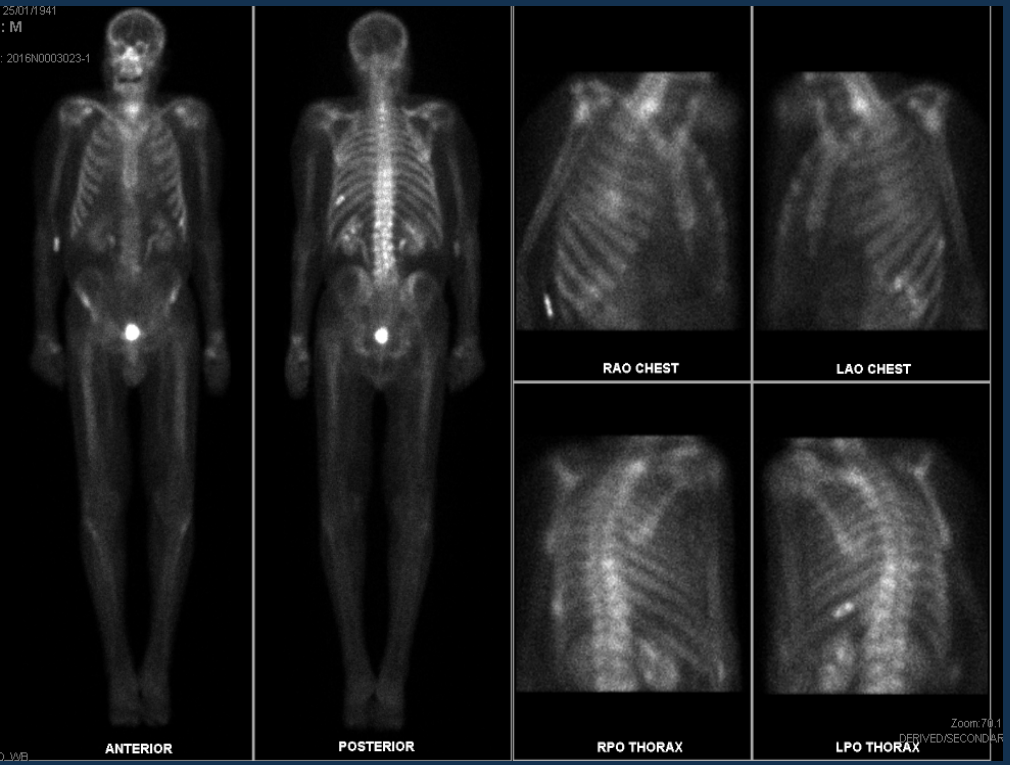


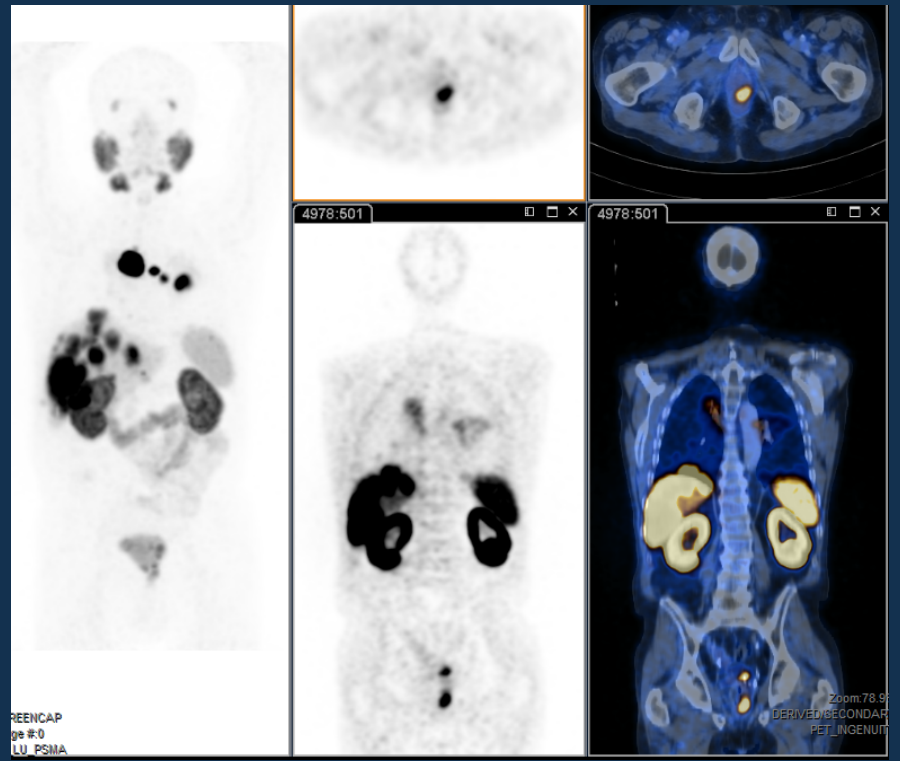
LU PSMA Scan Dose 1

- 75 yo mCRPC
- Visceral and LN mets
- RTX hilar mets 2015
- Failed ENZA/ DOCE/ CAB
- PSA 340 ng/ml
- PSA 15 ng/ml post dose 2 Lu PSMA

LU PSMA Scan Dose 2




ANTERIOR
POSTERIOR
RAO CHEST
LAO CHEST
RPO THORAX
LPO THORAX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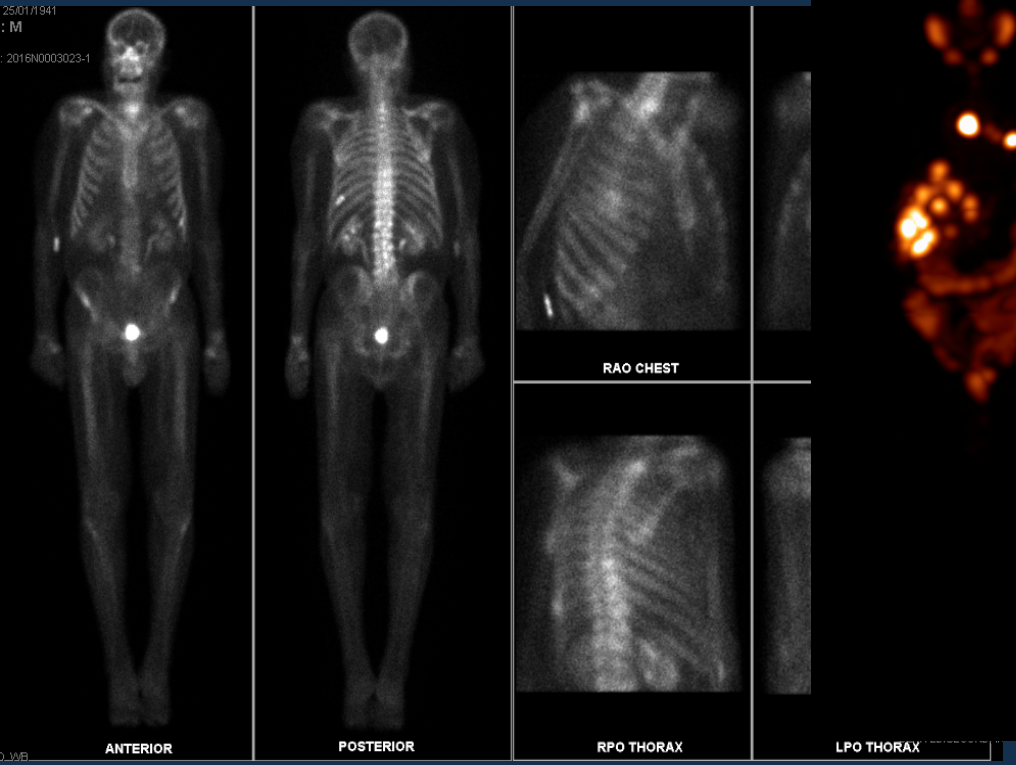
25/01/1941
: M
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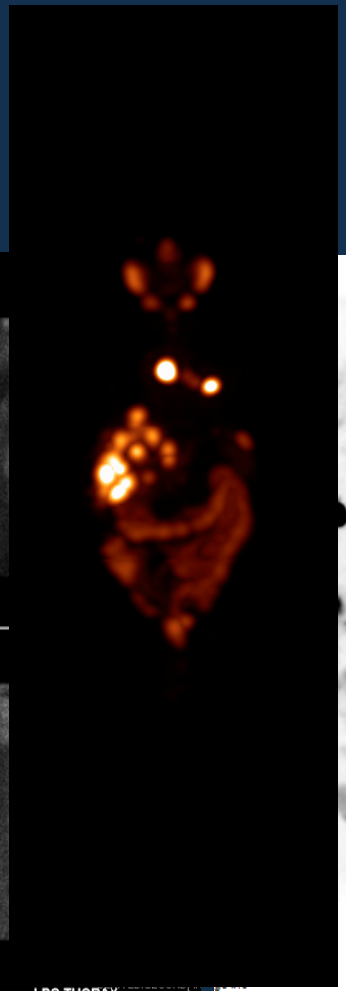
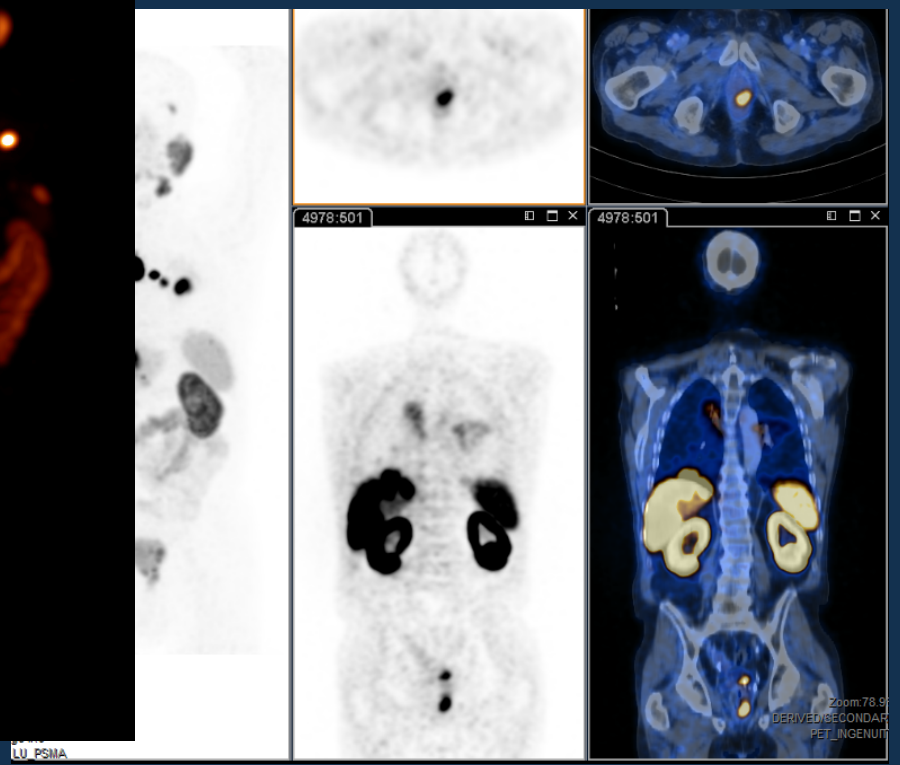
ANTERIOR
POSTERIOR
RAO CHEST
RPO THORAX
LPO THORAX

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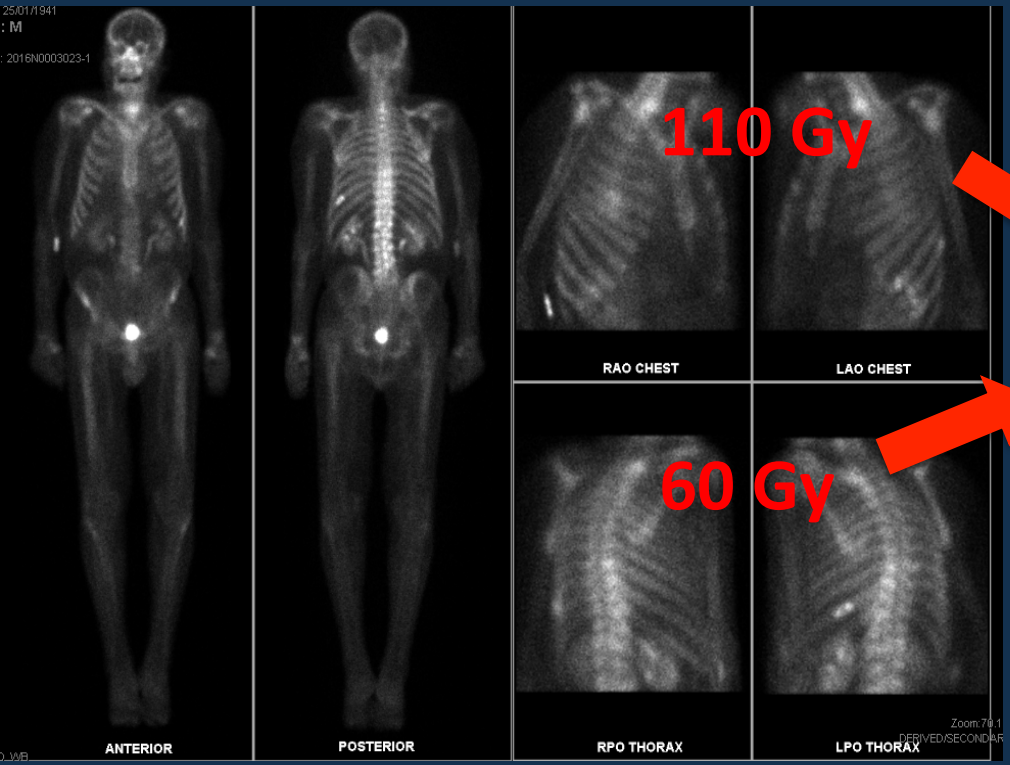
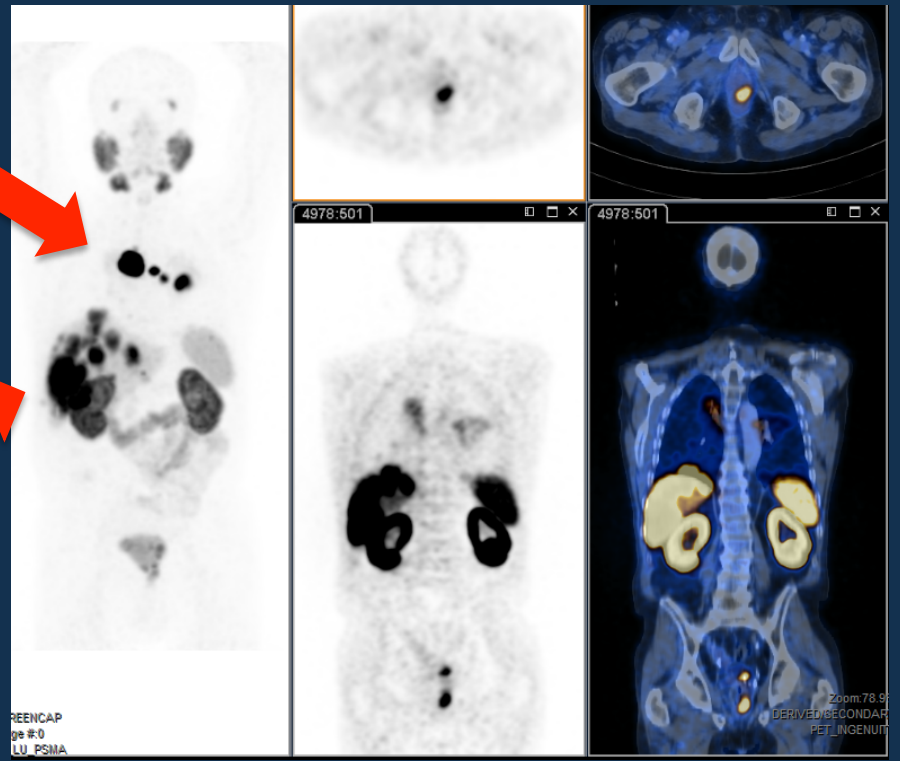
LU_PSMA


110 Gy
60 Gy
RAO CHEST
LAO CHEST
RPO THORAX
LPO THORAX
ANTERIOR
POSTERIOR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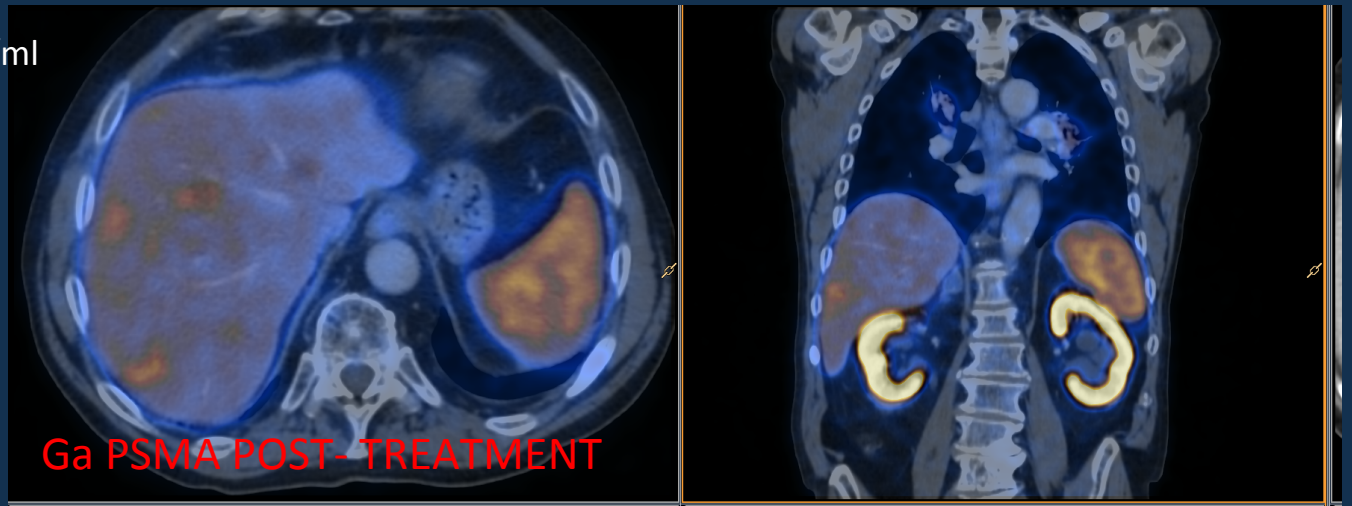
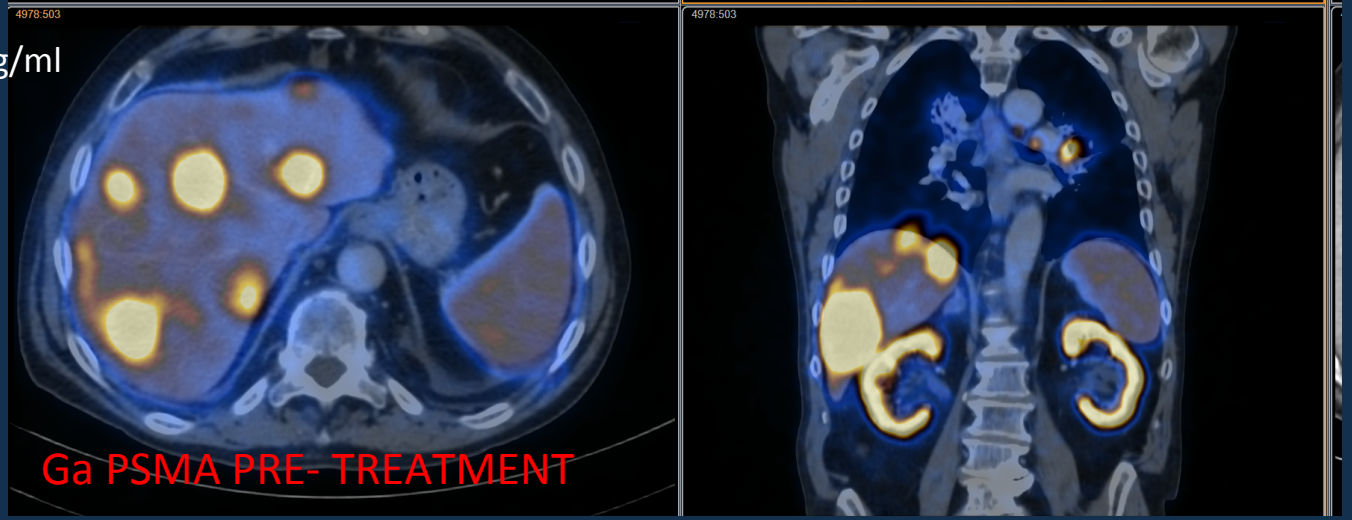
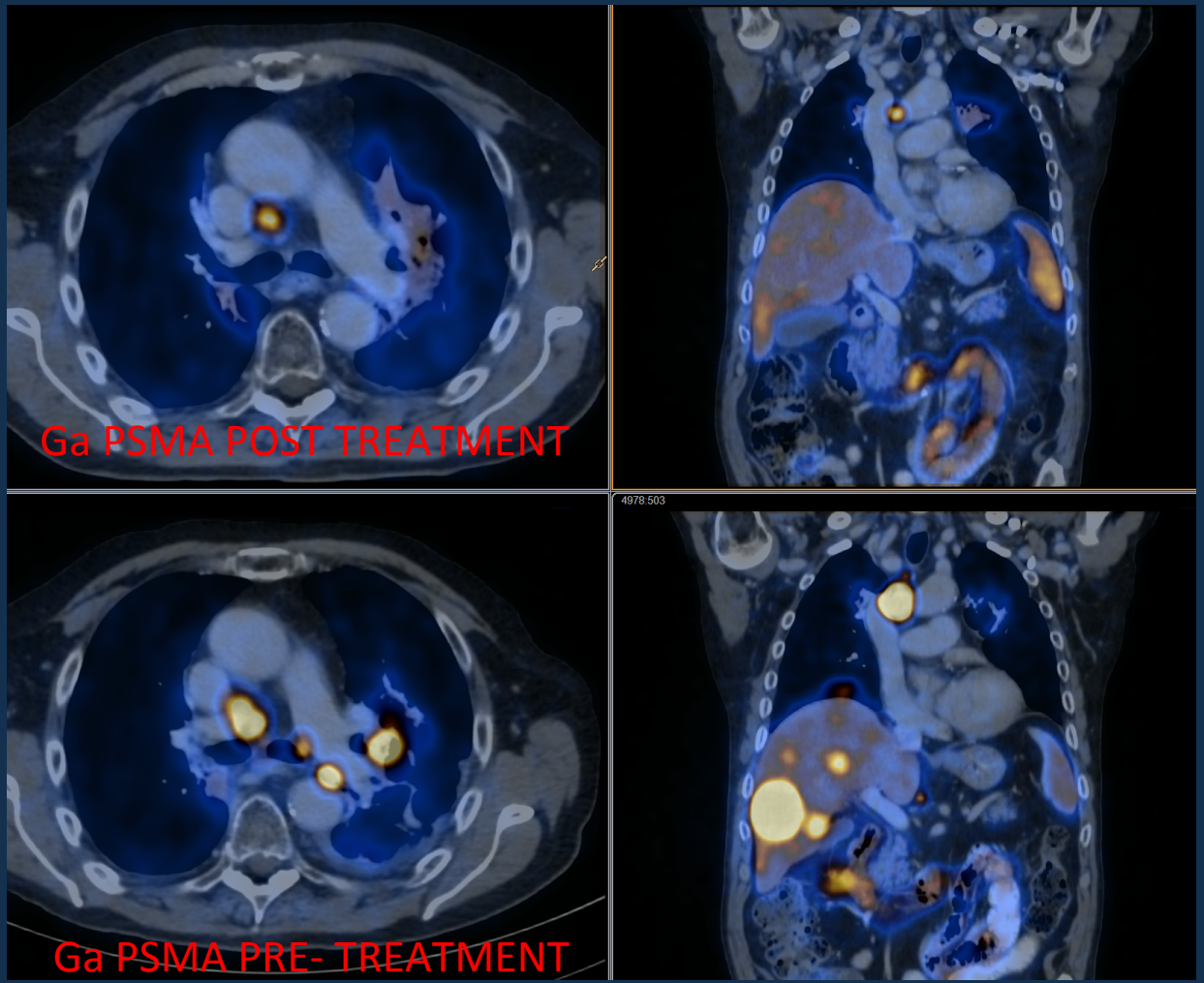
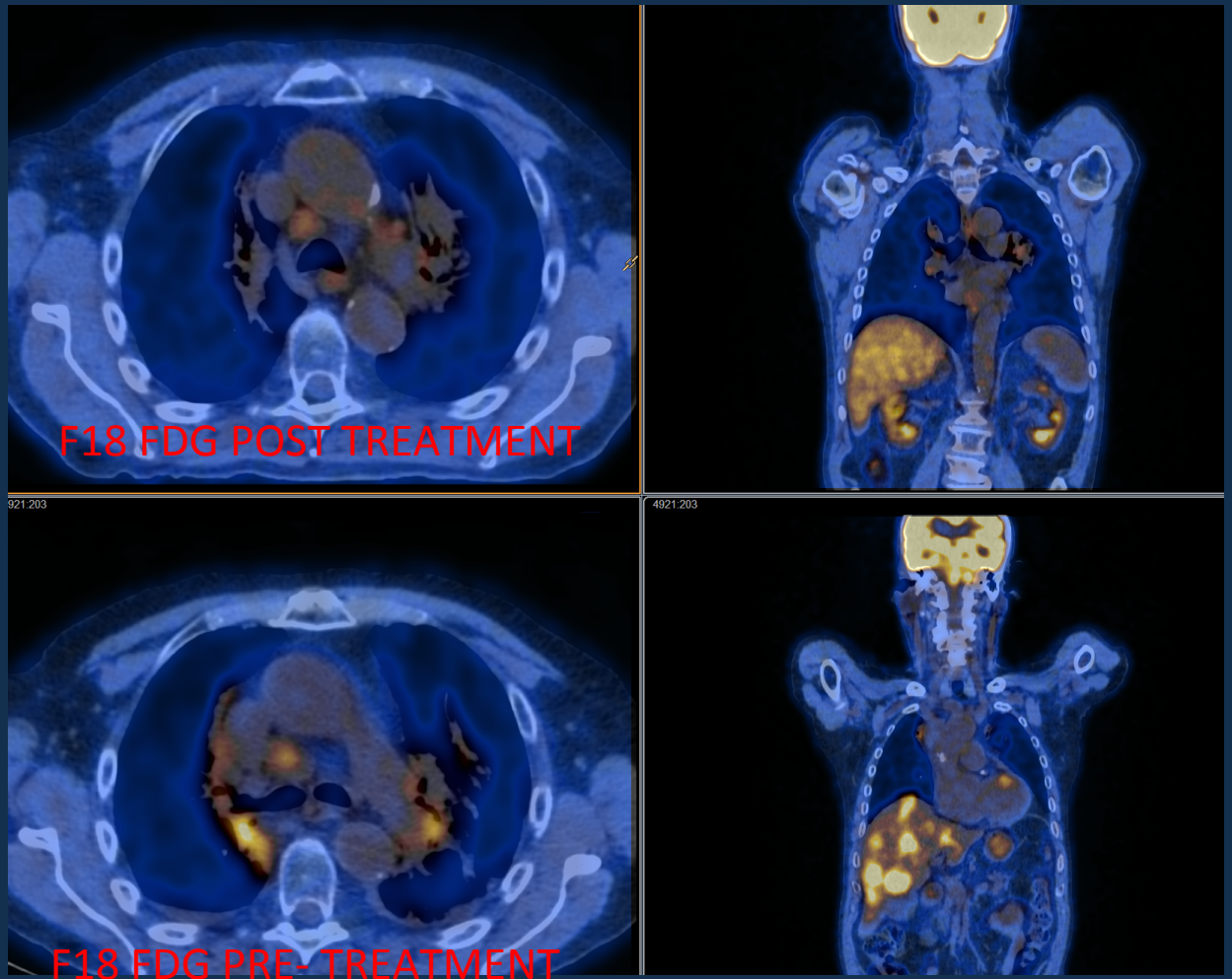
PSA Jan 17 = 1.5 ng/ml



PSA April 16 = 340ng/ml




Ga PSMA POST TREATMENT
4978:503
Ga PSMA PRE- TREATMENT


F18 FDG POST TREATMENT
921:203
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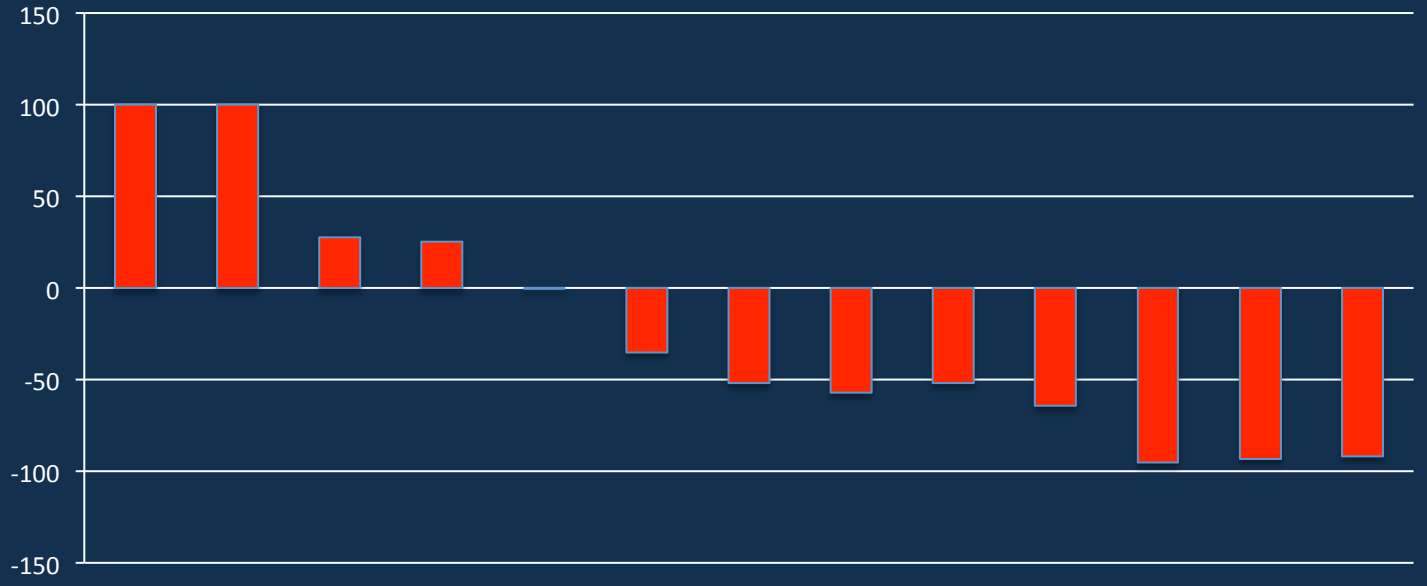
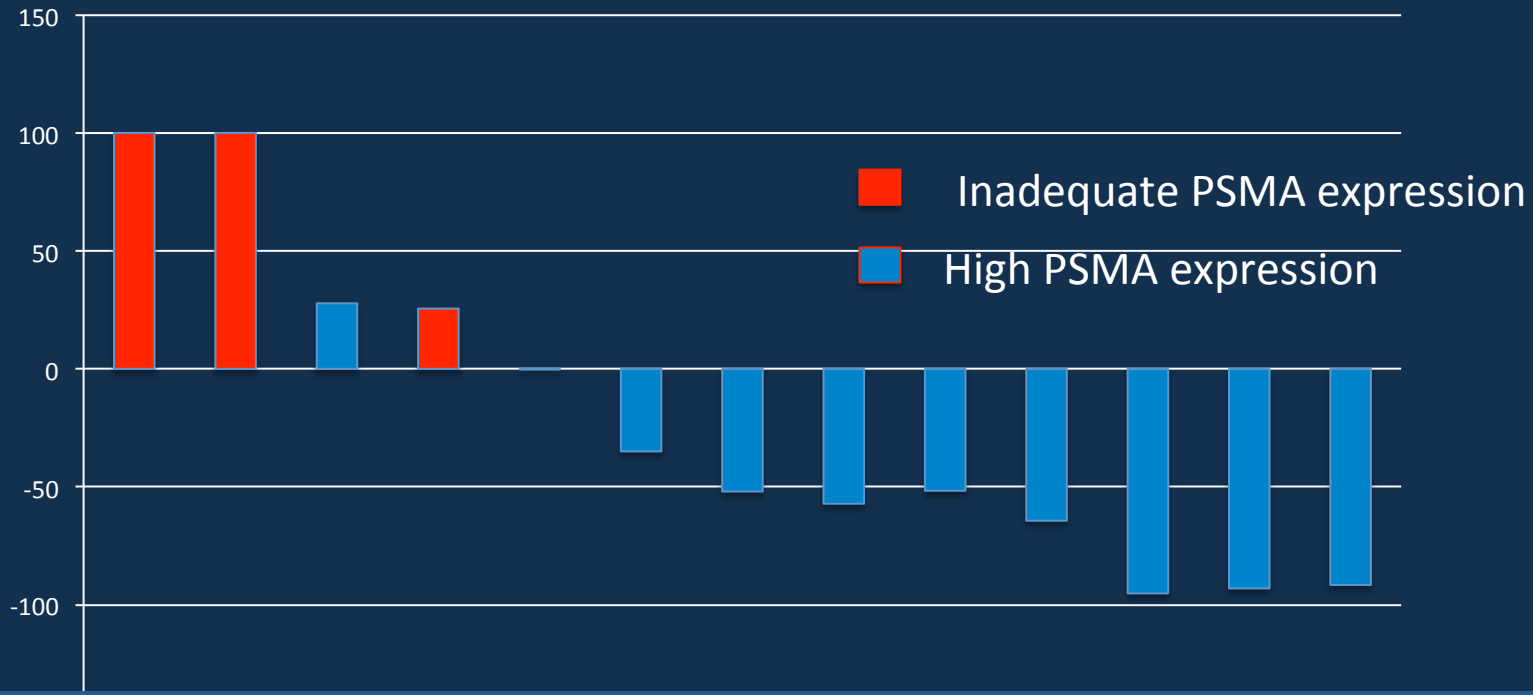
F18 FDG PRE- TREATMENT

PSA Response



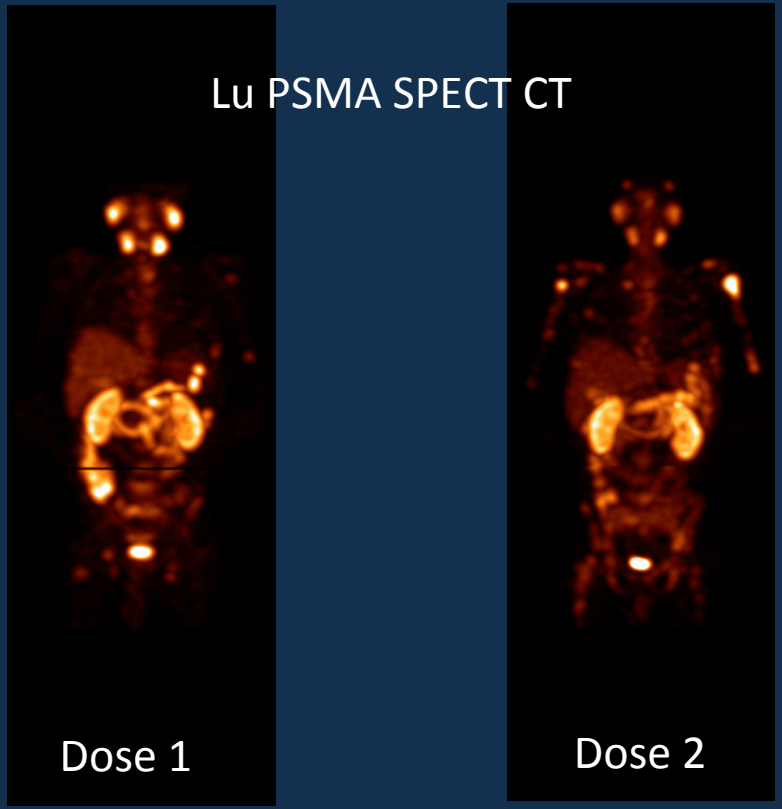
Any PSA response 10/14 patients 71% (mean 59% reduction in PSA)
> 50% reduction in 5/14 (36%) (4/5 >70% reduction)
> 30% reduction in 9/14 (64%)

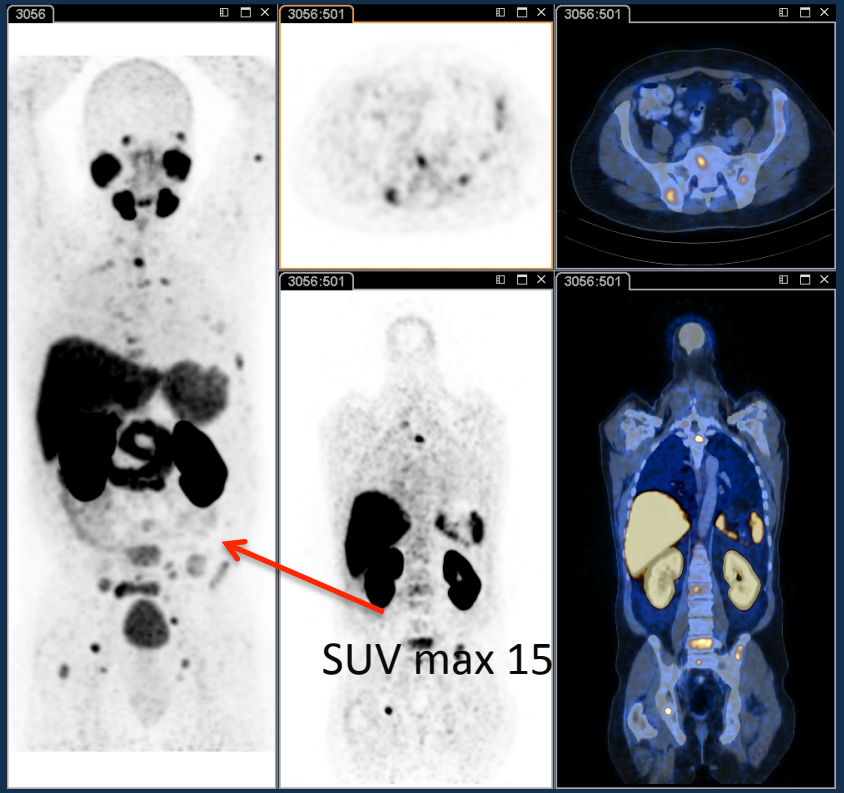
PSA Response



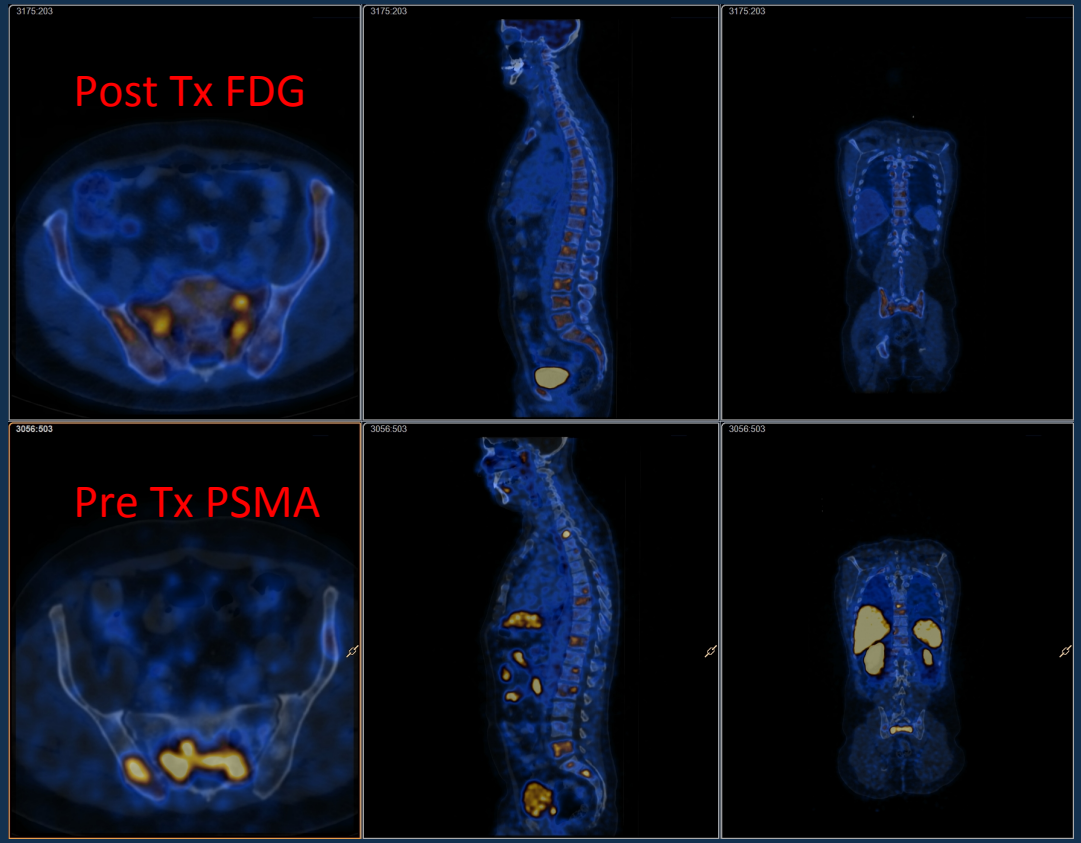
Non Responders: 3/4 men borderline / markedly heterogenous PSMA expression on screening images.

No PSA response to therapy

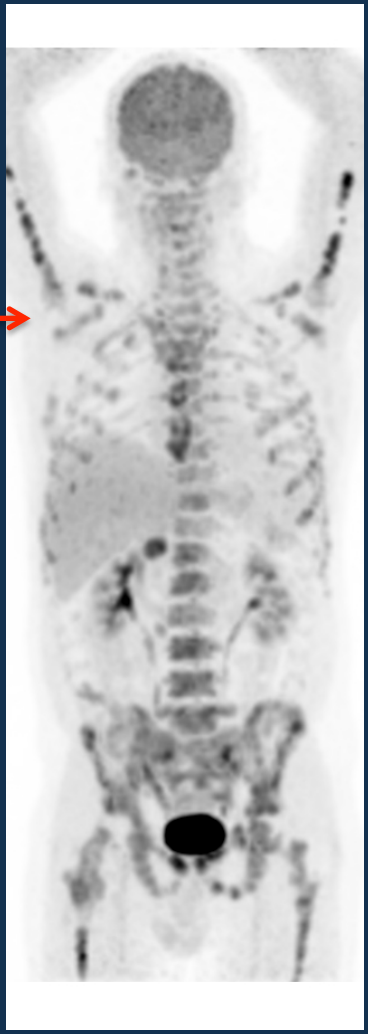




Inadequate PSMA intensity



Post Tx FDG diffuse marrow activity



Marrow trephine: Poorly Diff adeno ca.

Patterns of Response

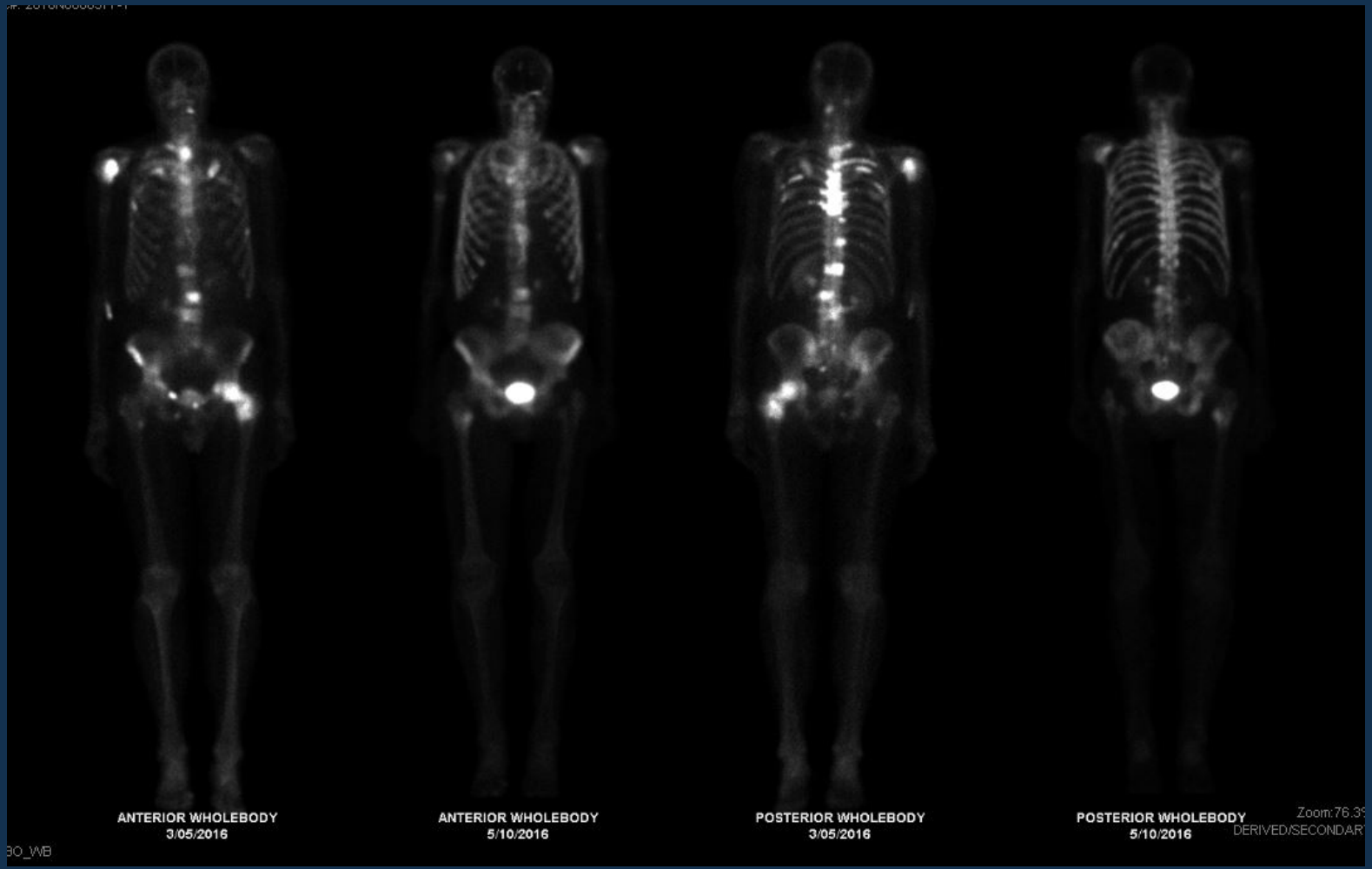
	FINDING	SIGNIFICANCE FOR MANAGEMENT
Pattern 1	Progression with diffuse, widespread low PSMA avid disease (SUV max 2-7 all sites)	Progressive non PSMA avid phenotype. change tx
Pattern 2	Marked tx response at all initial sites. Solitary PSMA -/FDG+ lesion	Treat solitary site of PSMA – disease with focal tx. Continue treating PSMA avid sites with Lu PSMA
Pattern 3	Marked reduction in PSMA + sites, but persistent PSMA activity (SUV max >10) + new PSMA avid lesions	Disease amenable to tx with LuPSMA. Consider continuing beyond 4 doses of Lu PSMA.
Pattern 4	Marked reduction in PSMA /FDG at all sites (>75%). Low volume residual activity only	Cease tx with Lu PSMA until PSA rise / repeat PSMA shows progression, then retreat with Lu PSMA.

Response Type 1

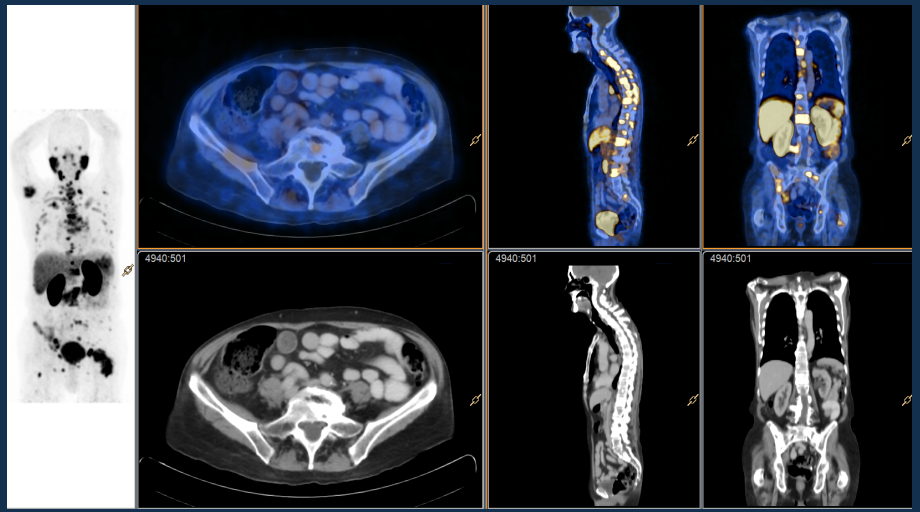
Treatment Response 1

- 75 yo male CRPC
- Failed ADT, ENZA, DOCE, CABAZITAXEL
- Lu PSMA 2 doses

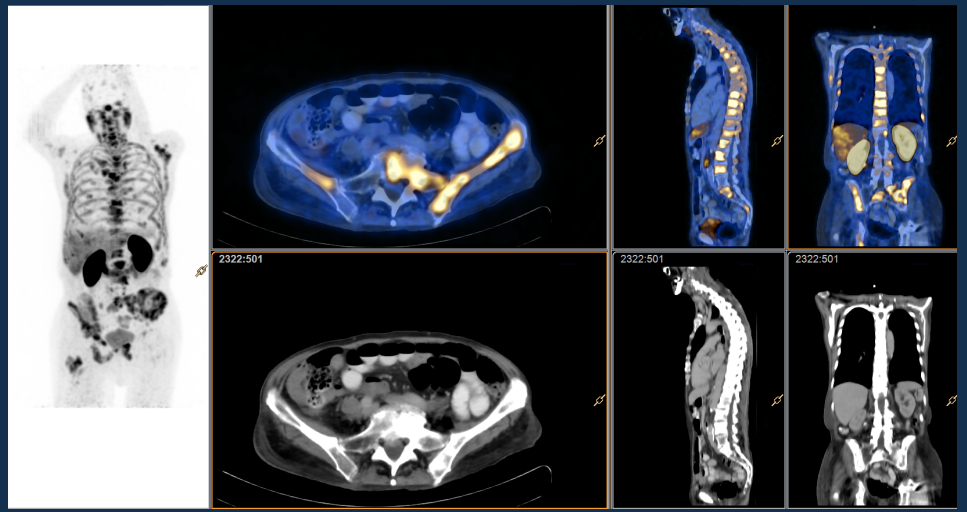
- PSA 1580 → 1520ng/ml → 1680ng/ml


ANTERIOR WHOLEBODY
3/05/2016
ANTERIOR WHOLEBODY
5/10/2016
POSTERIOR WHOLEBODY
3/05/2016
POSTERIOR WHOLEBODY
5/10/2016
Zoom:76.3
DERIVED/SECONDAR

Treatment Response

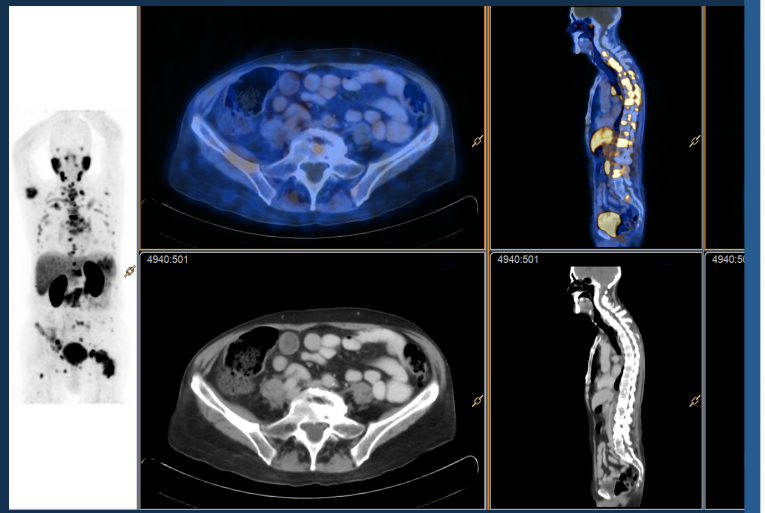


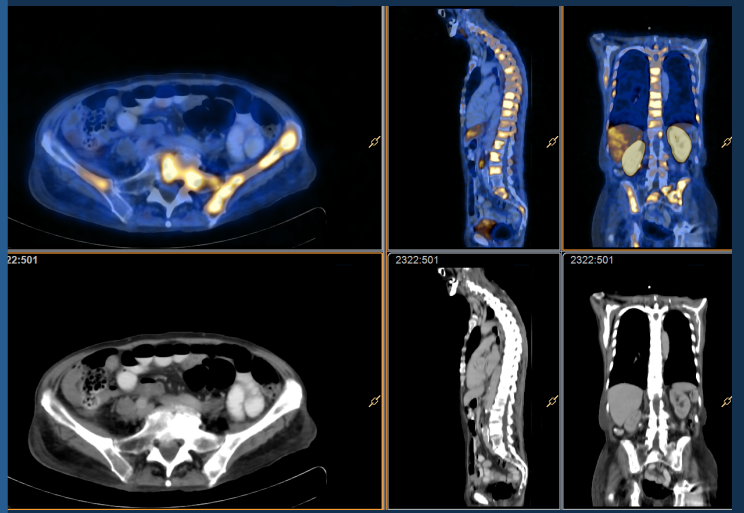
Mean SUV max 15- 25



Mean SUV max 9

Treat[illegible]ponse



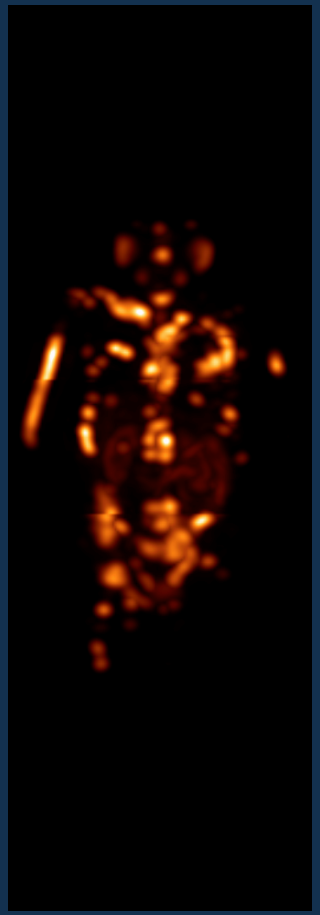


Mean SUV max 15-

Mean SUV max 9

Response Type II

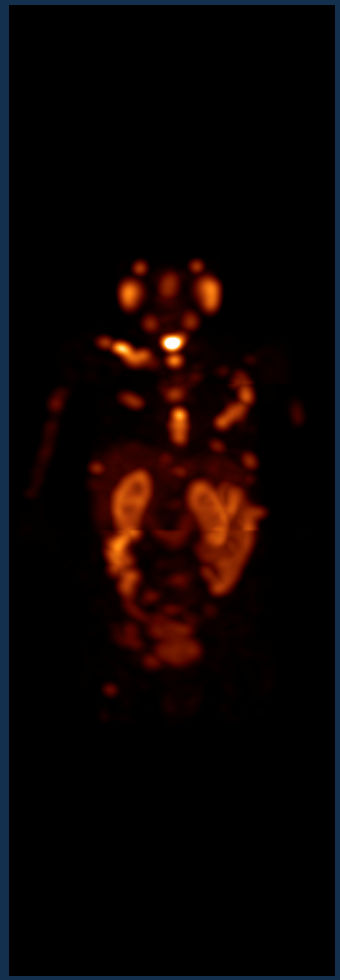
LU PSMA Scan Dose 1



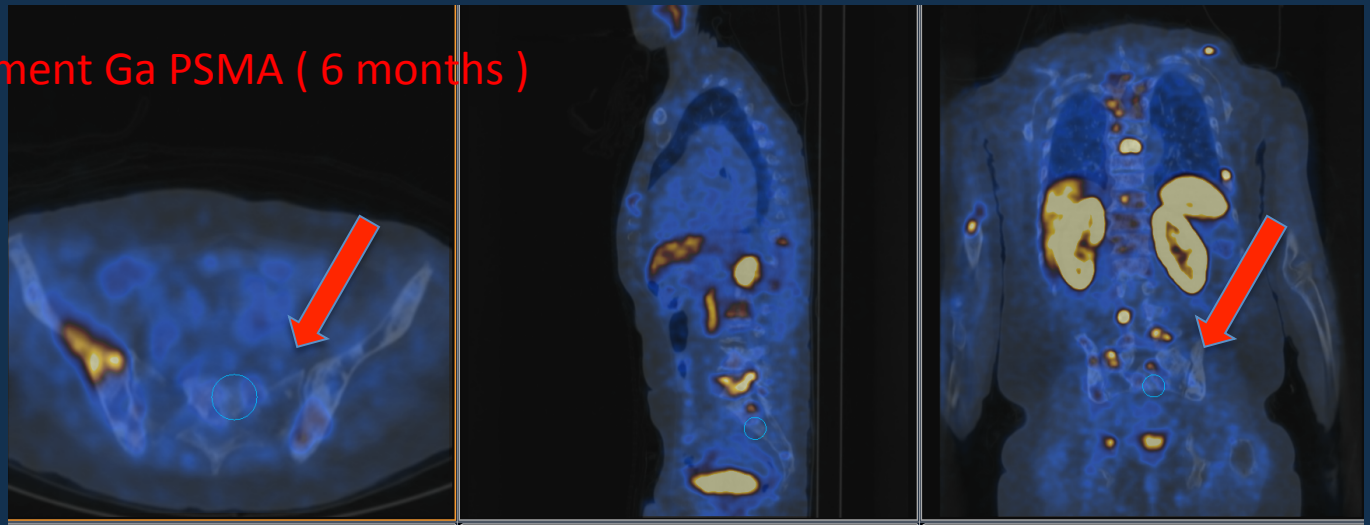
- CRPC – extensive bone metastases
- Failed ADT,Enza,Doce Cabazi
- PSA 95 ng/ml at enrolment
- PSA 8 ng/ml at 6 weeks
- Single injection

Reduced sites of activity →

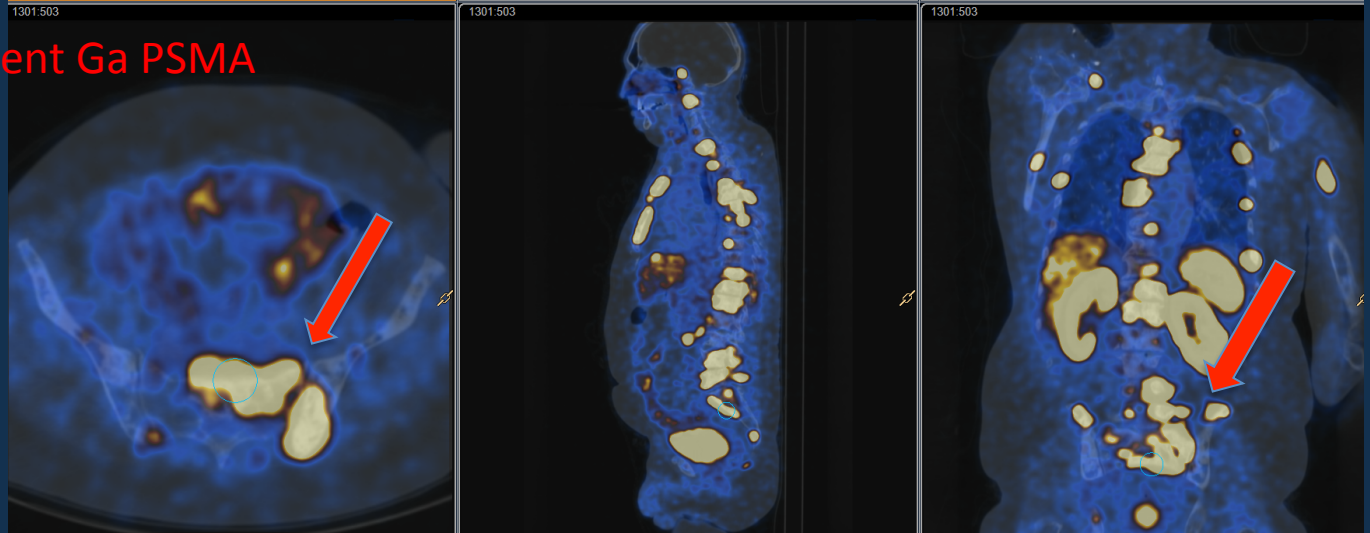
LU PSMA Scan Dose 2



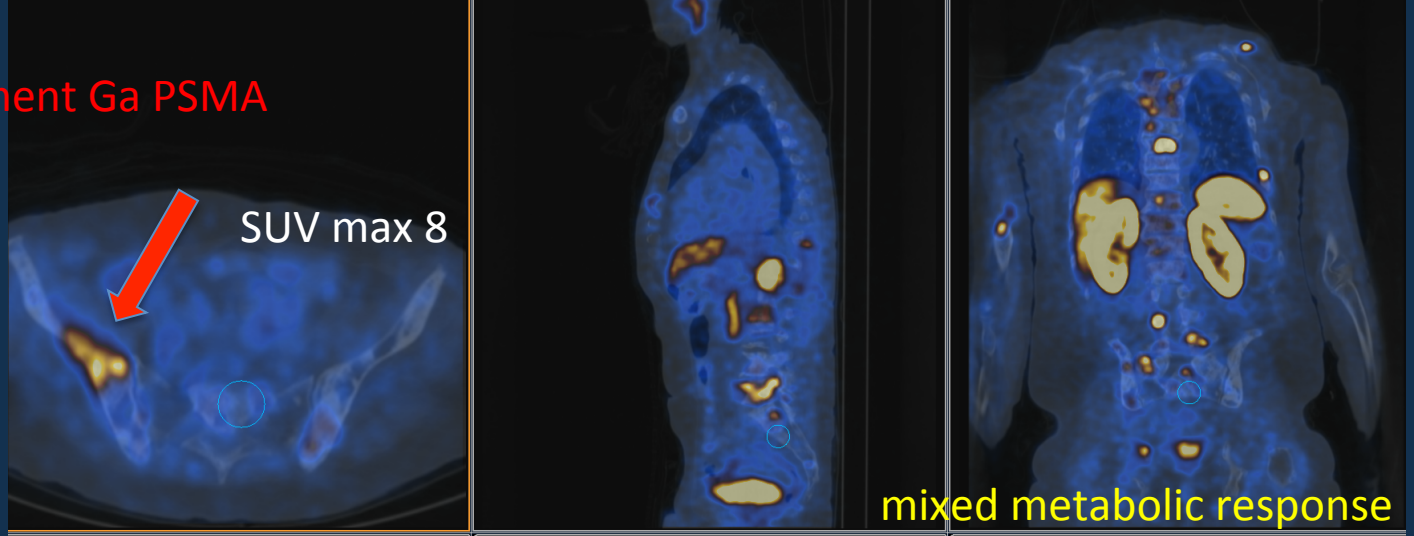
Post treatment Ga PSMA (6 months)



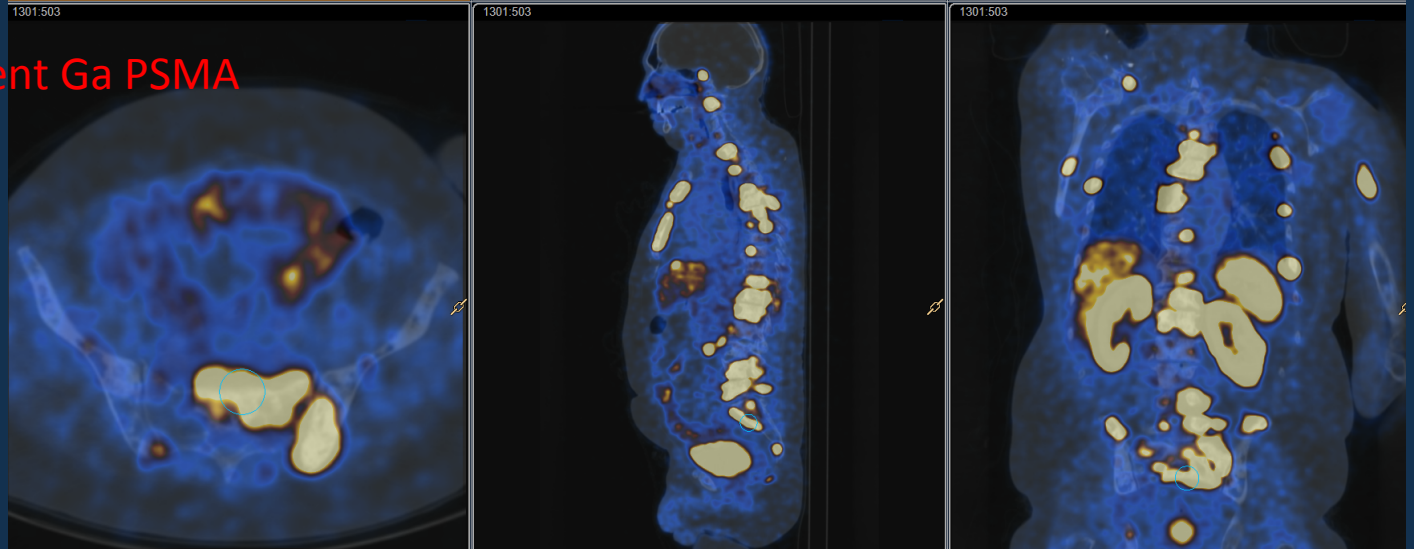
Pre treatment Ga PSMA



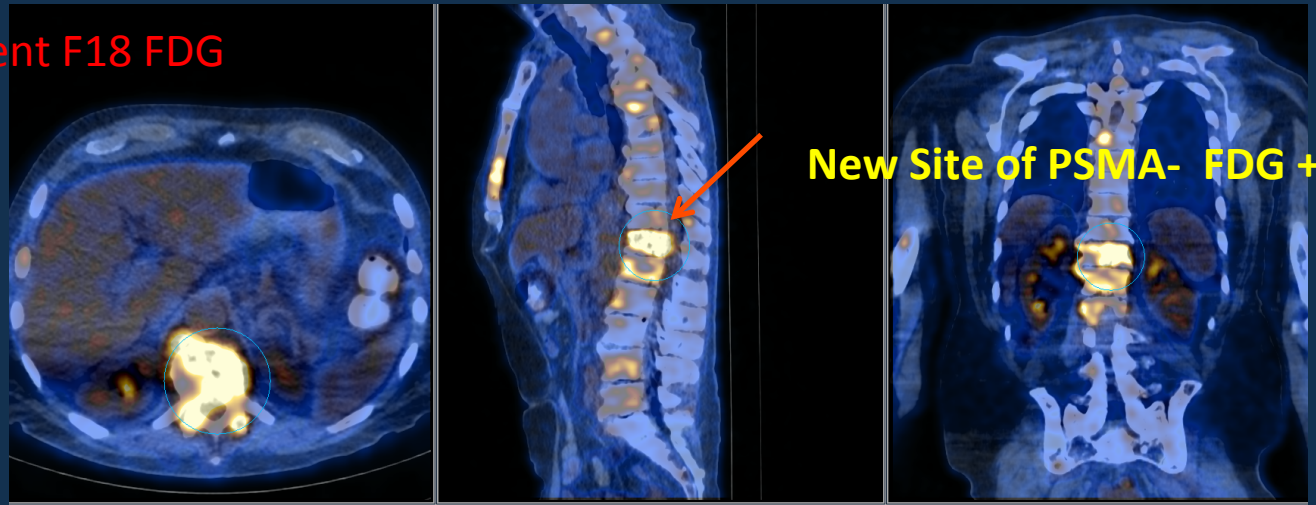
Post treatment Ga PSMA



Pre treatment Ga PSMA

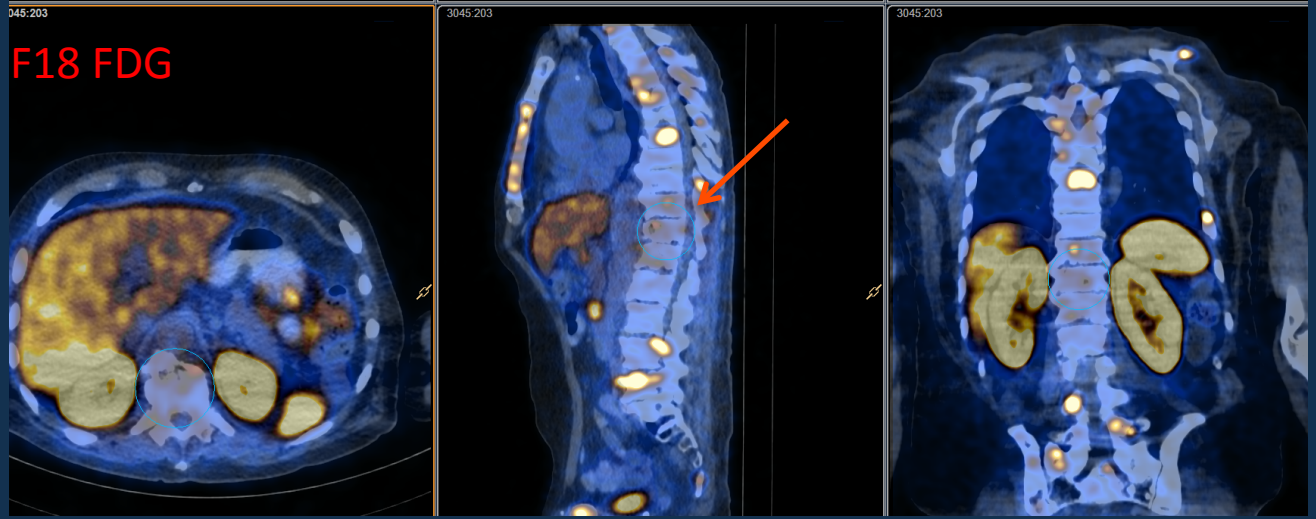


Post treatment F18 FDG

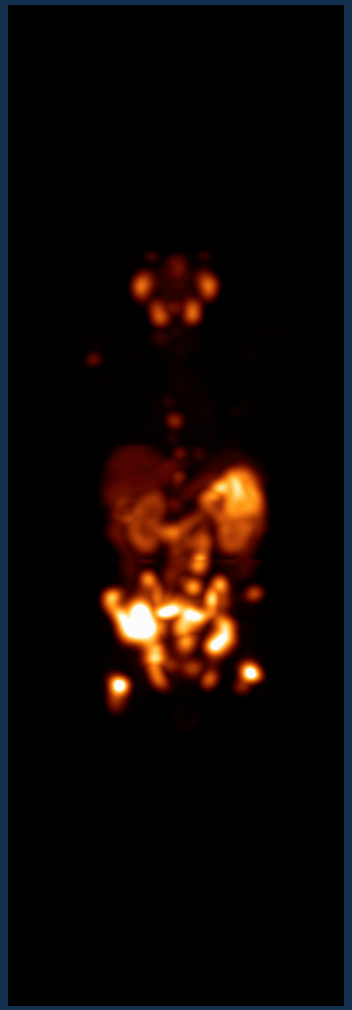


New Site of PSMA- FDG + disease

Pre treatment F18 FDG

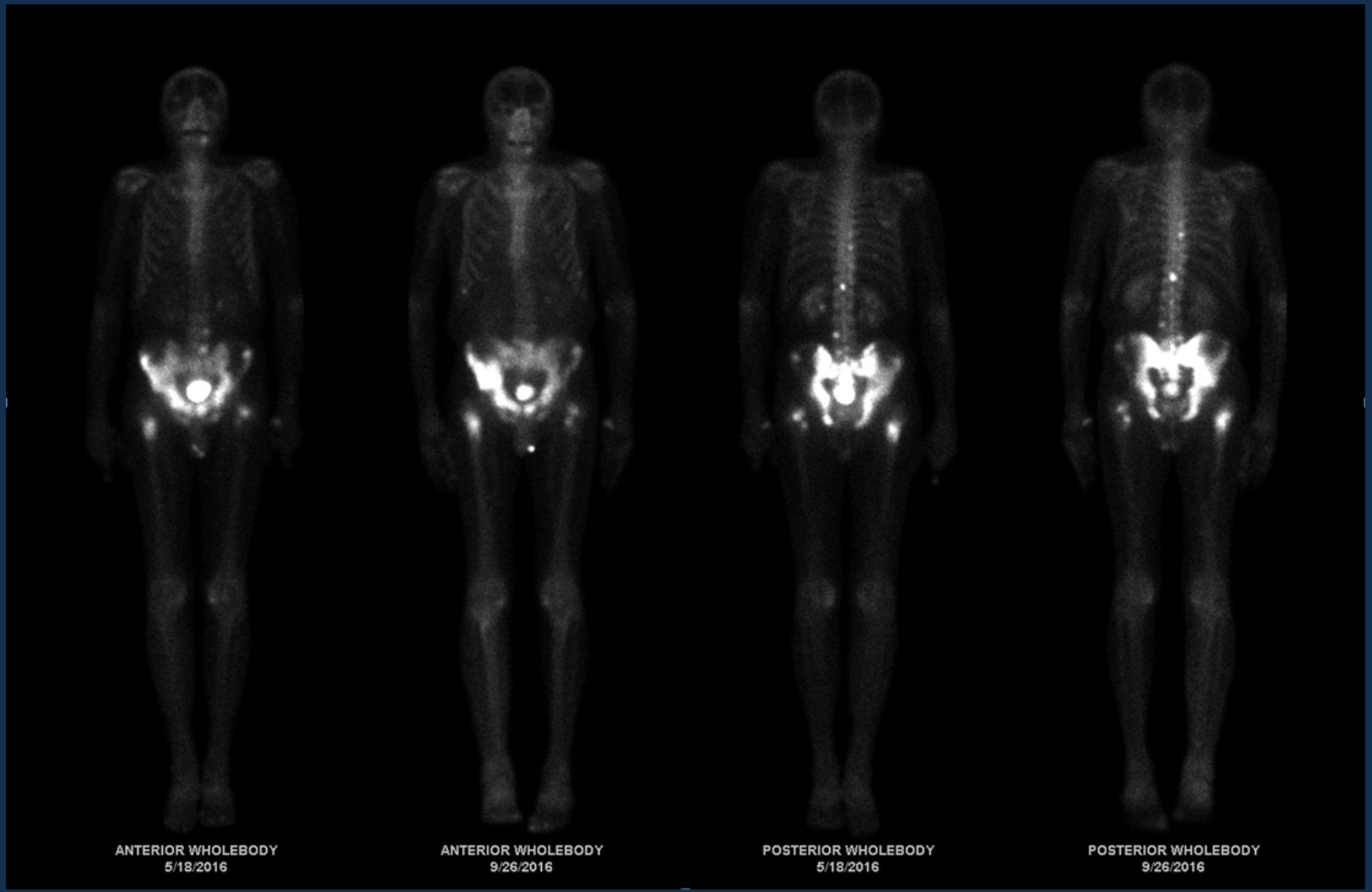


Response Type III



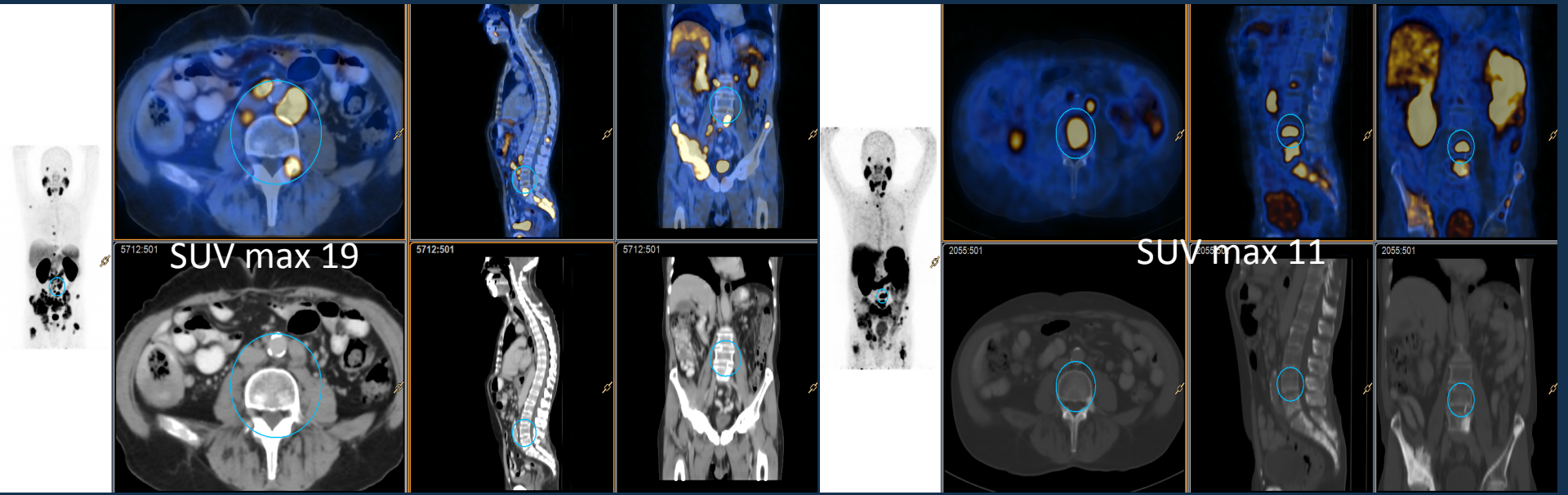
- 67 y o
- mCRPC failed ADT, Abi, docetaxel
- PSA 87 → 16ng/ml → 29ng/ml
- Rise in PSA post dose 3

? Should we continue with treatment


ANTERIOR WHOLEBODY
5/18/2016
ANTERIOR WHOLEBODY
9/26/2016
POSTERIOR WHOLEBODY
5/18/2016
POSTERIOR WHOLEBODY
9/26/2016

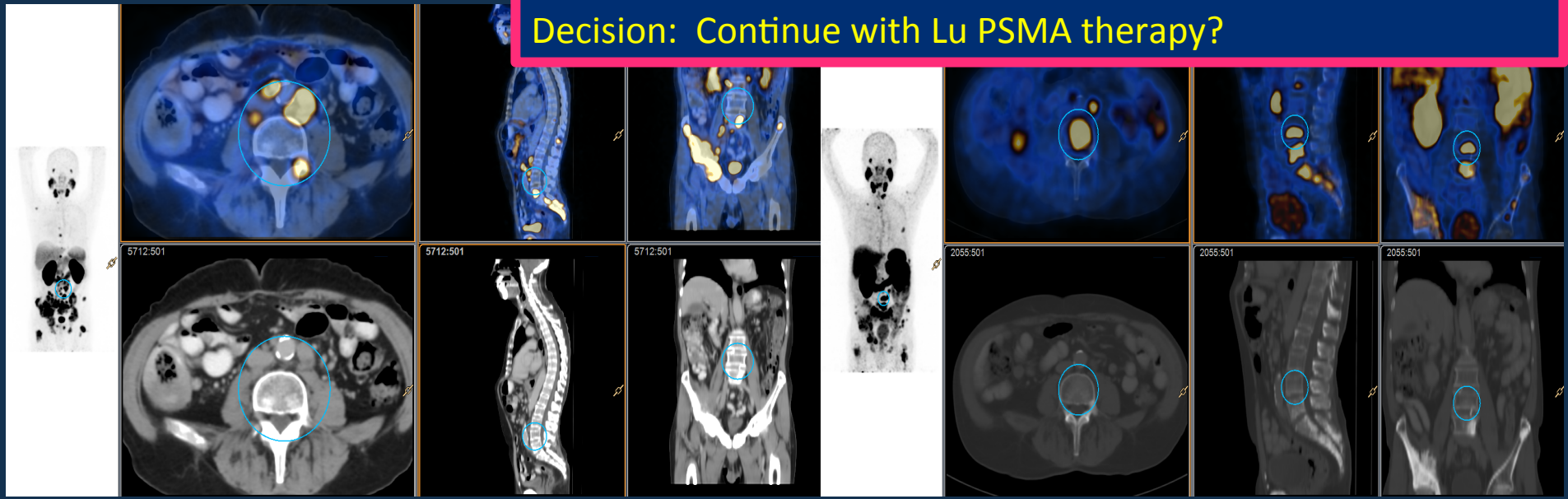
Pre treatment Ga PSMA

Post treatment Ga PSMA

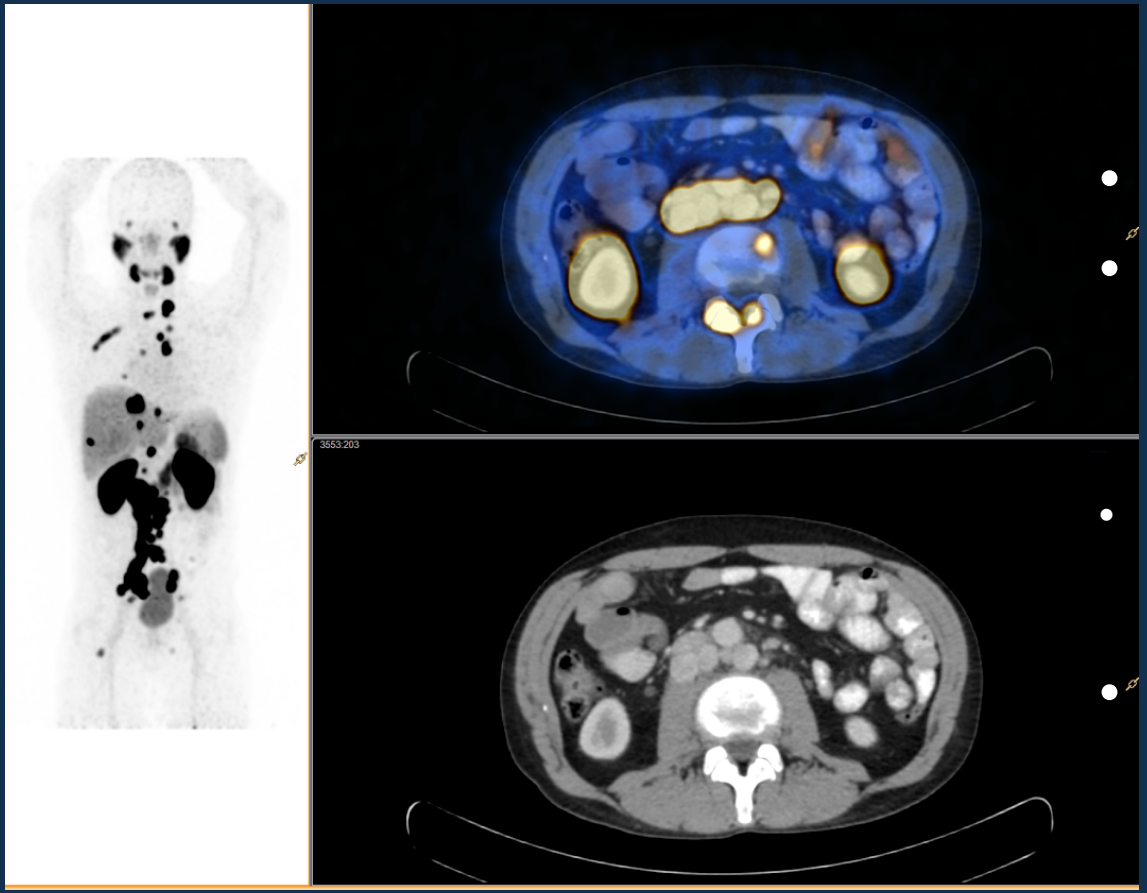


Significant partial metabolic response to therapy
at all nodal sites.
2 new sites of metastatic bone disease – still PSMA avid

Decision: Continue with Lu PSMA therapy?

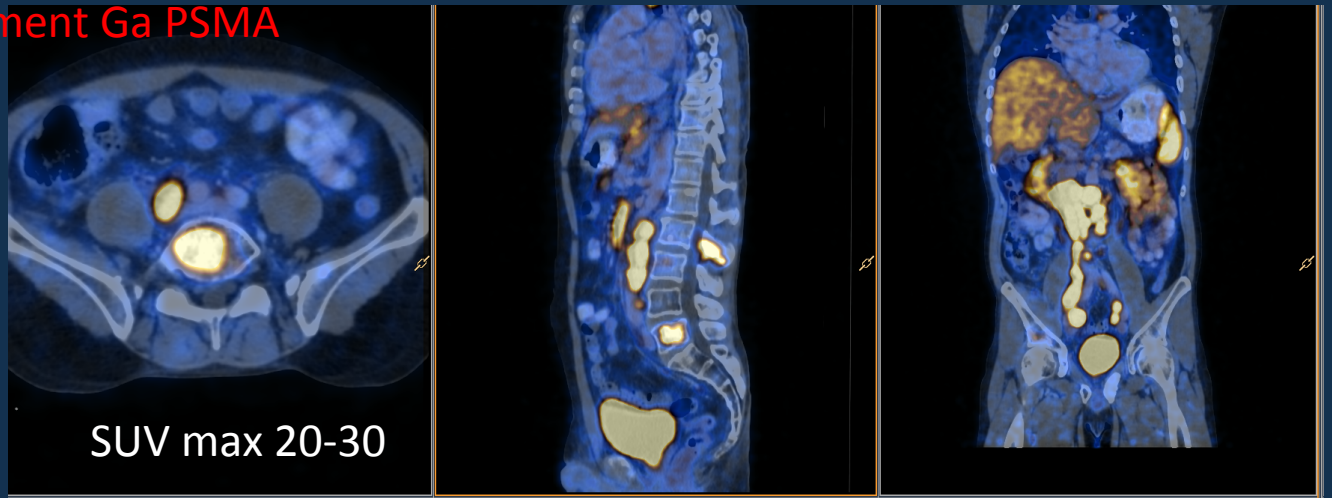


Response Type IV

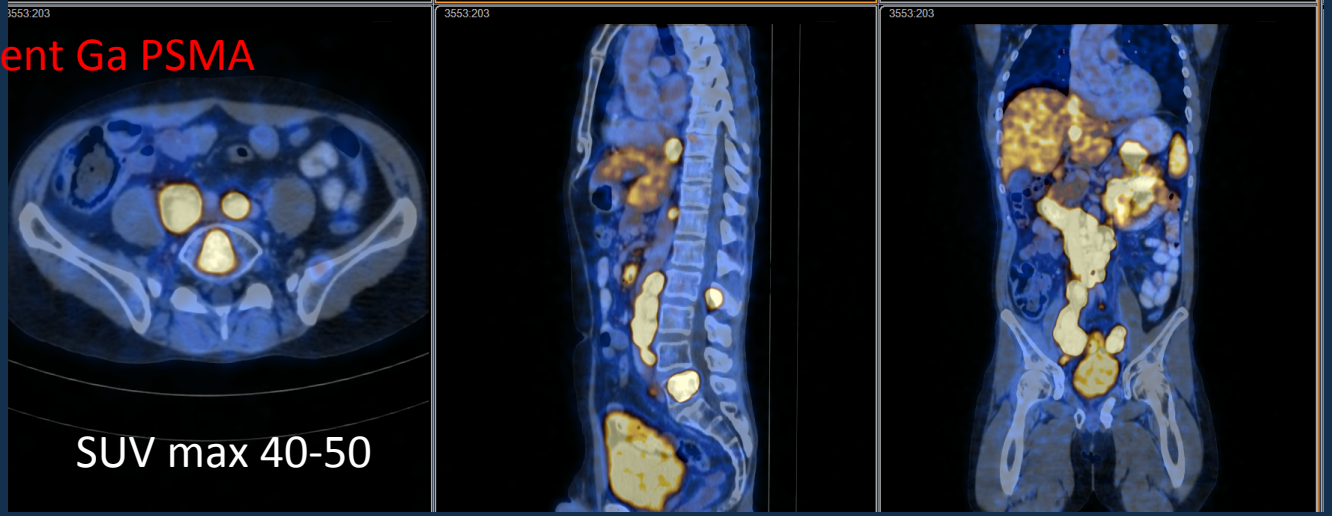


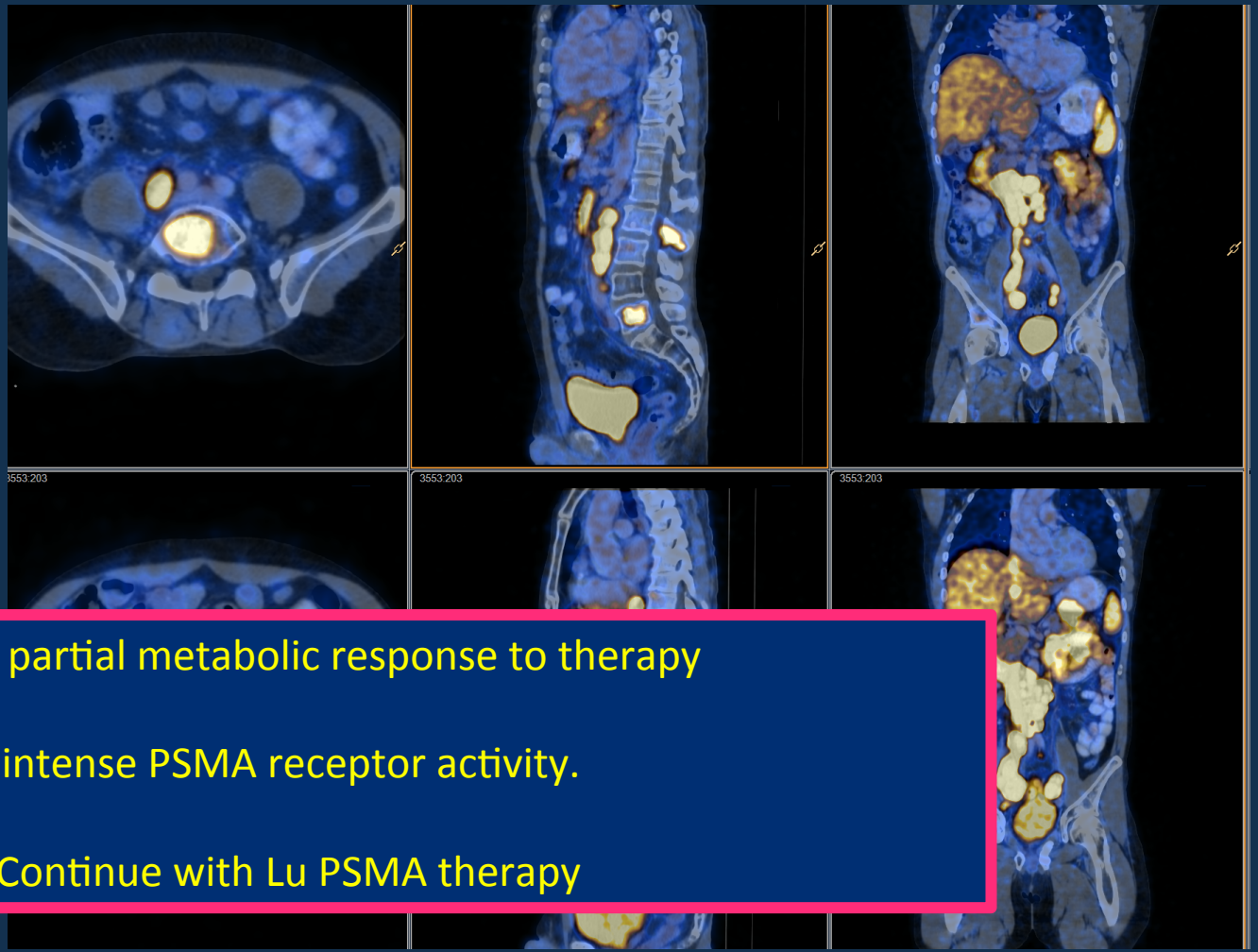
- 58 y.o
- mCRPC failed ADT, Abi, Docetaxel , Cabazitaxel
- PSA 11 → 5.6 → 9.0ng/ml
- ? Continue dose 4

Post treatment Ga PSMA



Pre treatment Ga PSMA

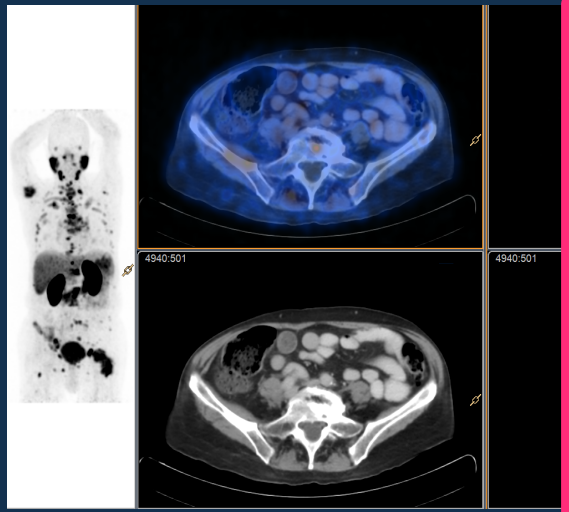




Significant partial metabolic response to therapy
at all sites.
Persistent intense PSMA receptor activity.

Decision: Continue with Lu PSMA therapy

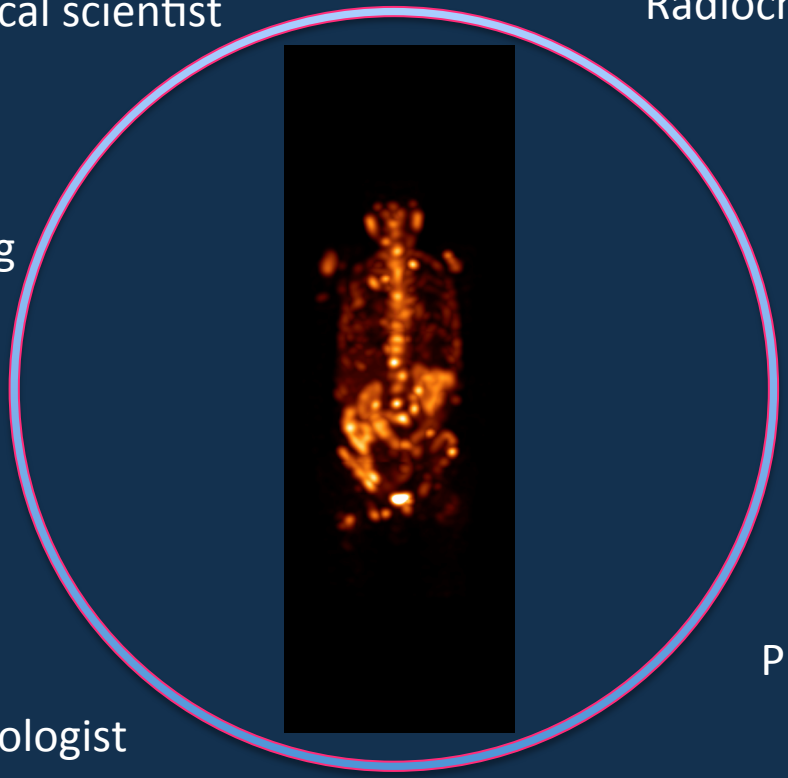
Treatment Response



SUV max 15-

PSMA PET CT response imaging may allow:

- Delineation of pattern of failure
- Identifying selected genetic subtypes.
- Gives direction to next best treatment options


Preclinical scientist
Radiochemist
Industry funding
Oncologist
Nuclear medicine specialist
Radiation oncologist
Physicist
Urologist
Radiologist