

# Patient Selection and Follow up of PSMA-based RLT

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Location lorem ipsum

[bmuc.be/bmuc2024](https://bmuc.be/bmuc2024)



**11<sup>th</sup> Belgian Multidisciplinary  
Meeting on Urological Cancers**

# Conflicts of interest

- I have the following potential conflict(s) of interest to report

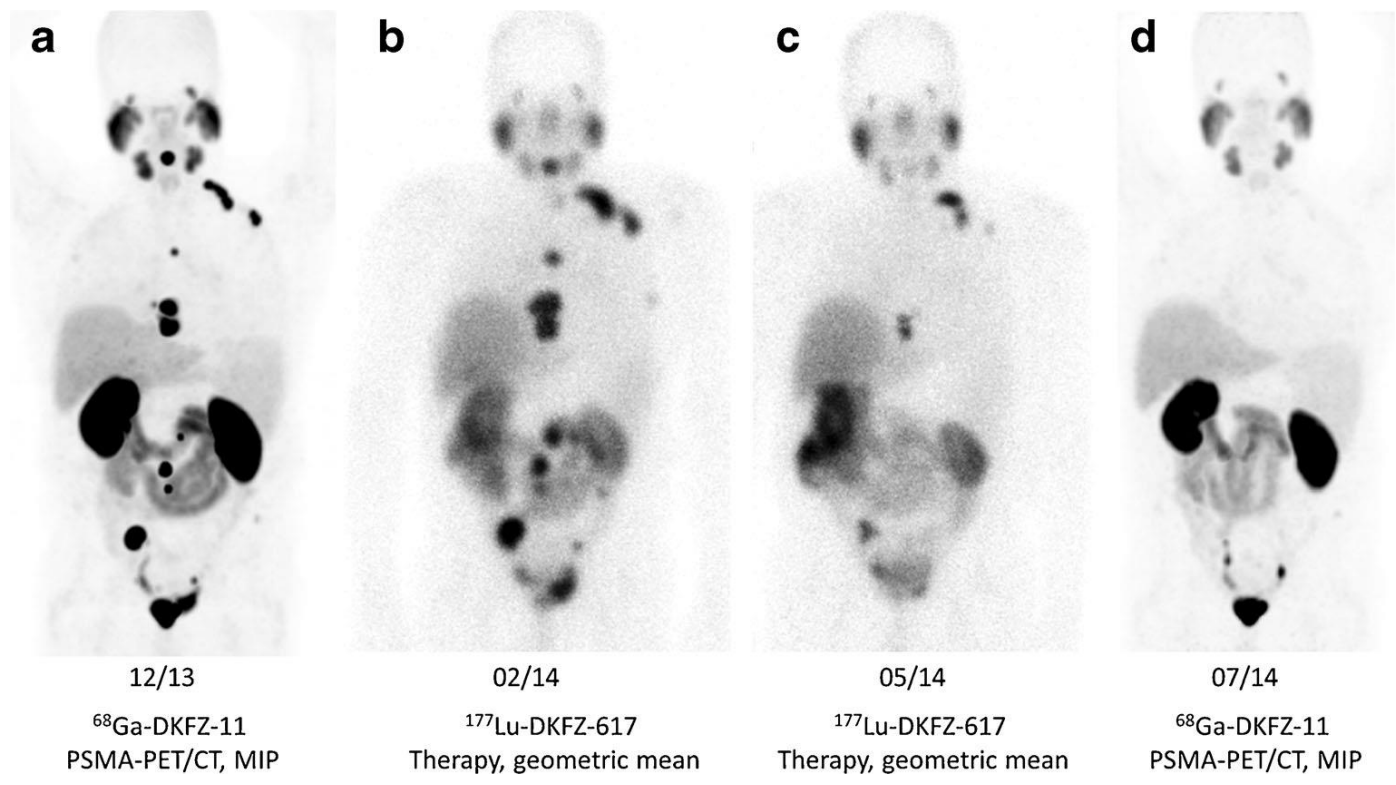
Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	-
Receipt of honoraria or consultation fees:	Bayer, Telix
Participation in a company sponsored speaker's bureau:	-
Stock shareholder:	-
Spouse/partner:	-
Other support (please specify):	-



# $^{177}\text{Lu}$ -PRLT: first cases

- $^{177}\text{Lu}$ -labelled PSMA ligand ( $^{177}\text{Lu}$ -PSMA DKFZ-617)
  - DOTA derivative of the Glu-urea-Lys motif.
  - Chelator improves tumour accumulation while **reducing kidney uptake**.

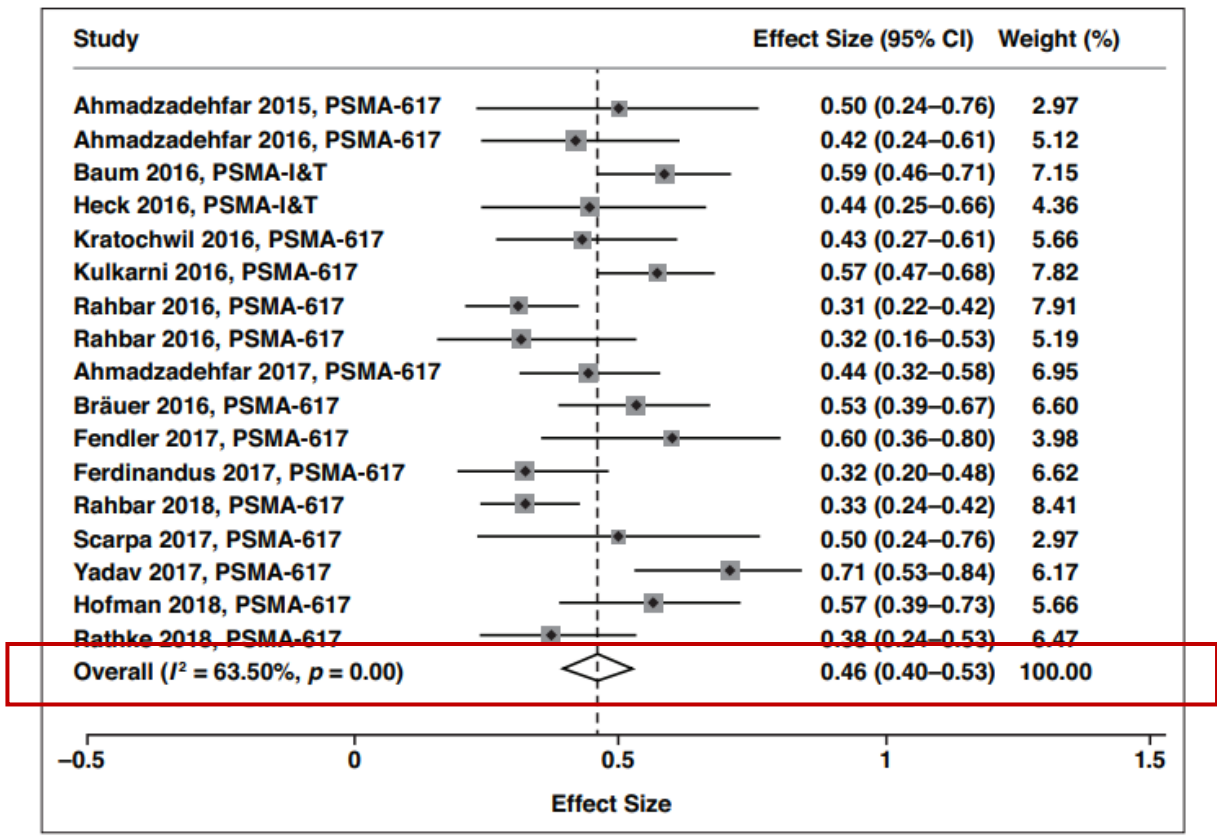
- mCRPC
- 7,4GBq  $^{177}\text{Lu}$ -DKFZ-617
- Complete PSMA response
- PSA decrease
  - 38ng/ml to 4,6ng/ml



# <sup>177</sup>Lu-PRLT: metanalysis

Metanalysis of <sup>177</sup>Lu-PRLT (16 studies)

Well tolerated  
 High efficacy



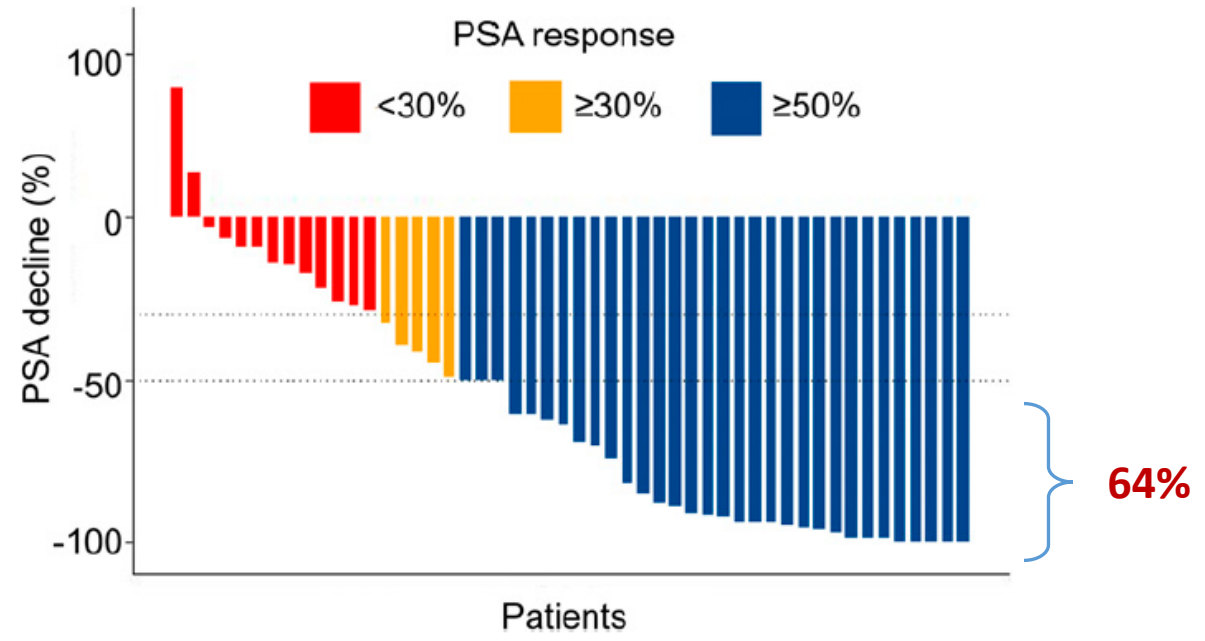
PSA<sub>50</sub> = 46%

**Fig. 6**—Forest plot shows greater than 50% decline in prostate-specific antigen level after <sup>177</sup>Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy. I&T = imaging and therapy.

## Efficacy results

- PSA decrease >50% in 64% (n=50)
- Objective Response (RECIST based) in 56%
- Decrease in pain scales

Remarquable responses in heavily pretreated patients



The NEW ENGLAND JOURNAL of MEDICINE

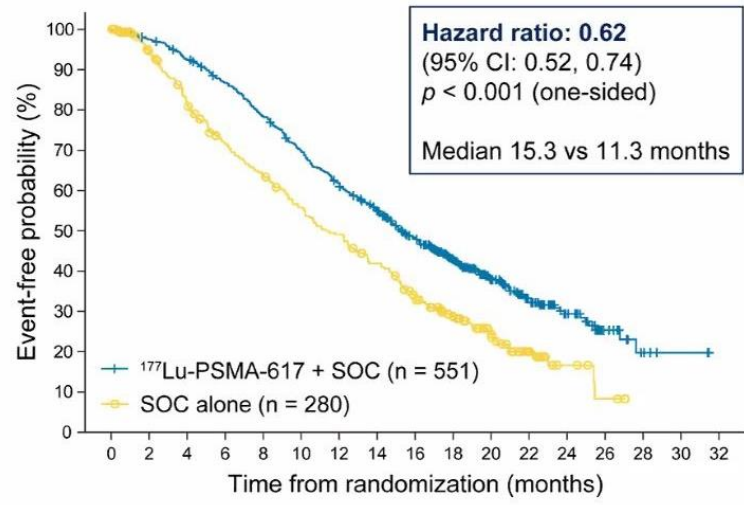
**ORIGINAL ARTICLE**

## Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

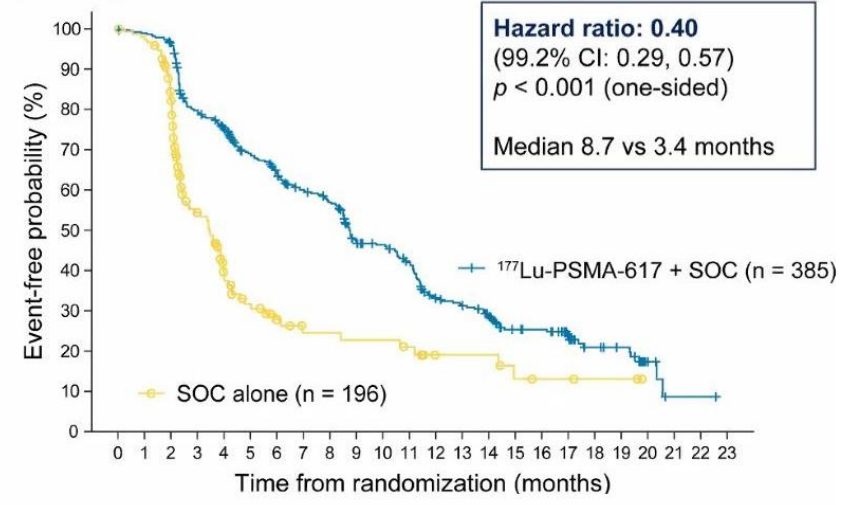
O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators\*

Primary endpoints:  
 -Overall Survival  
 -rPFS (PCWG3)

**38% reduced risk of death**

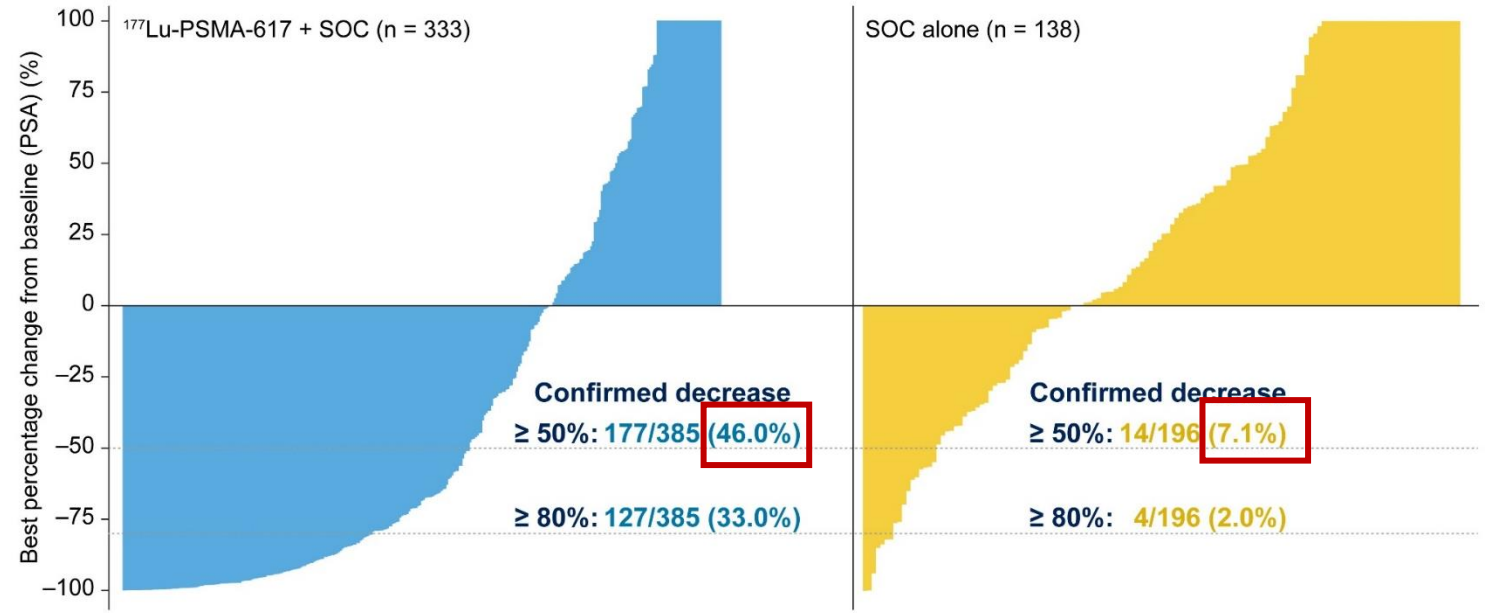


**60% reduced risk of progression**



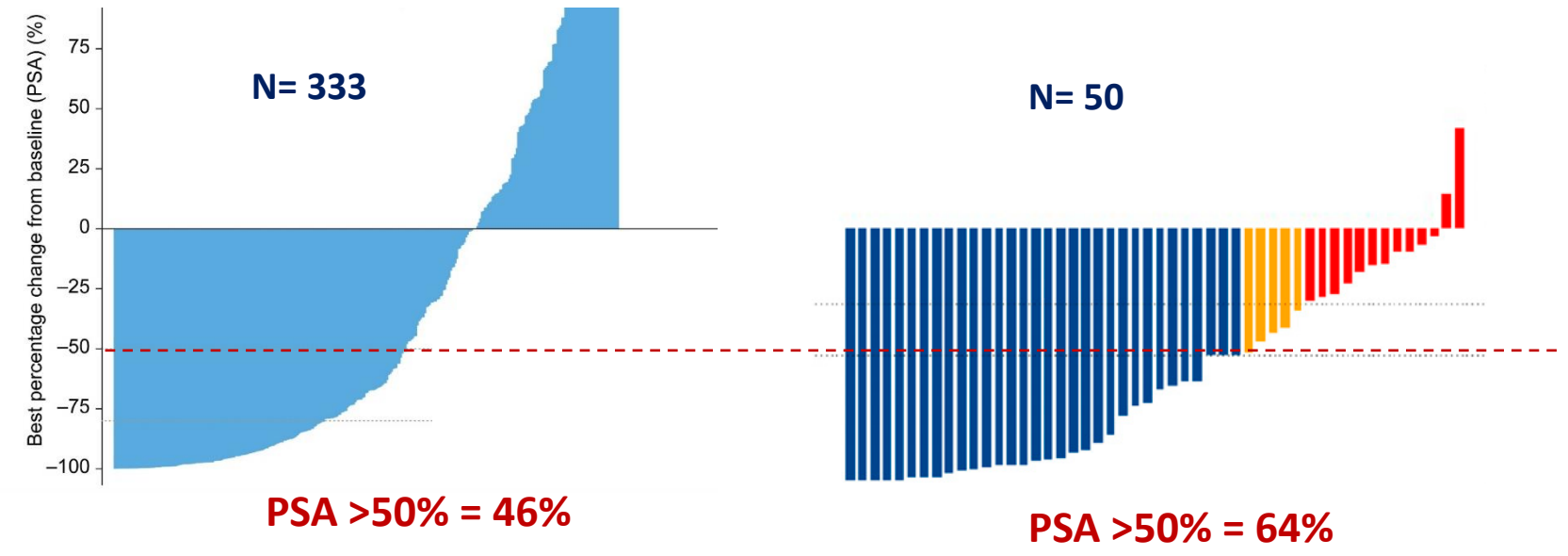
## 2ary endpoints

-PSA response with decrease >50%

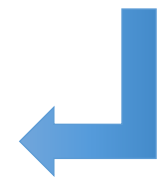




# $^{177}\text{Lu}$ -PRLT: efficacy



Patient selection difference



Morris et al. ASCO21

Violet et al. JNM 2020



## Progressive mCRPC

- Indication for Lu177-PSMA-RLT
  - mCRPC previously treated with at least 1 NAD and at least 1 taxane.
  - Only 1 taxane if patient is unsuitable or refuses to receive a 2nd taxane.

	rPFS analysis set (n = 581)		All randomized (N = 831)	
	<sup>177</sup> Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	<sup>177</sup> Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
<b>Number received, median (range)</b>				
Androgen receptor pathway inhibitor	1.0 (1–5)	1.5 (1–4)	1.0 (1–5)	2.0 (1–4)
Taxane regimen	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)
<b>Patients who received more than one, n (%)</b>				
Androgen receptor pathway inhibitor	172 (44.7)	98 (50.0)	253 (45.9)	152 (54.3)
Taxane regimen	178 (46.2)	94 (48.0)	226 (41.0)	124 (44.3)



# Pretherapeutic workout

## Blood test:

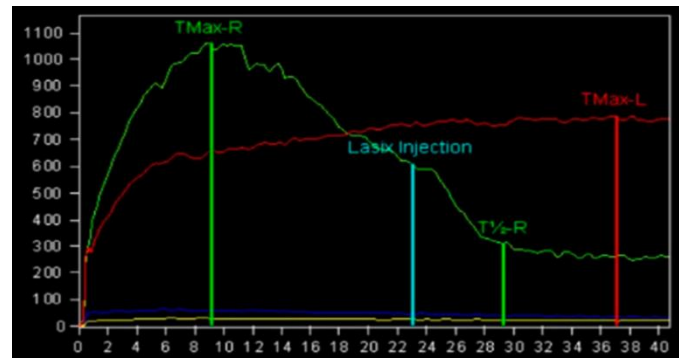
- White blood cell (WBC) count  $\geq 2.5 \times 10^9/L$
- Platelets  $\geq 100 \times 10^9/L$
- Hemoglobin  $\geq 9$  g/dL
- Normal liver function (ALT, AST  $< 3$  ULN)
- Creatinine clearance  $\geq 50$  mL/min

## Clinical conditions (consultation)

- Urinary status:
  - obstruction (MAG3)  $\rightarrow$  JJ stent
  - Incontinence  $\rightarrow$  urinary catheter during hospitalisation (avoid contamination)
- Expected survival  $> 6$  months and ECOG 2 or less.
- Ability to understand and follow radiation protection instructions
- Evaluation comorbidities (pain, mobility, nutrition, active infections, etc).

## PSMA expression in metastatic lesions

- Differences?



Slower blood clearance  $\rightarrow$  increase myelotoxicity  
Kidney retention  $\rightarrow$  increased abs dose (kidney function)



- Pre-therapeutic imaging PSMA PET/CT

- PSMA uptake > physiologic liver uptake
  - 1 lesion > liver SUV (VISION)
  - At least one lesion SUVmax > 20
  - Measurable disease SUVmax > 10
- Dual tracer imaging approach?
  - FDG/PSMA



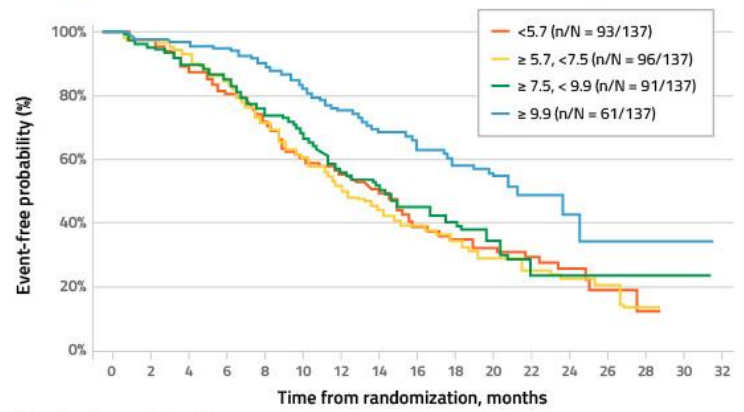
# Patient Selection for PRLT

Is this patient a good candidate for  $^{177}\text{Lu}$ -PSMA?



- PSMA uptake on PET/CT is a strong predictive biomarker for Lu177-PSMA RLT
  - Level of uptake is associated with patient outcome
    - Total Tumor SUVmean (takes into account heterogeneity).

Higher whole-body SUVmean was associated with improved OS

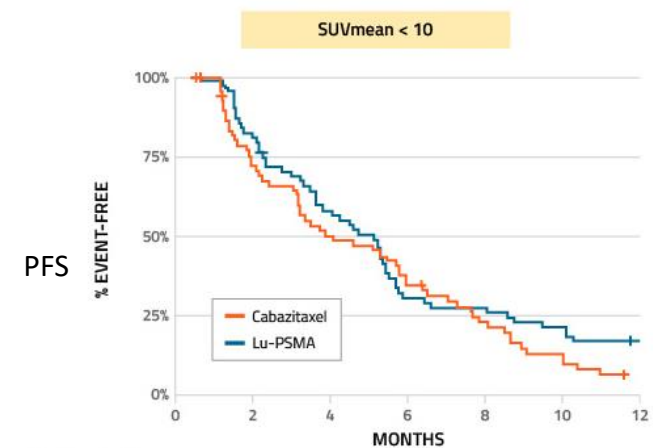


No. of patients still at risk

≥ 9.9 (highest)	137	135	132	130	124	116	104	91	79	56	37	17	6	2	1	1	0
≥7.5, <9.9	137	133	123	118	104	95	79	71	57	41	28	13	8	3	1	1	0
≥5.7, <7.5	137	134	128	112	97	82	71	61	50	34	20	15	10	5	1	0	0
<5.7 (lowest)	137	130	121	108	98	82	76	64	48	34	27	18	12	5	2	0	0

SUVmean quartile	Median rPFS (months)	SUVmean	OS HR (95% CI), p value
≥ 9.9 (highest)	21.4	Univariate analysis	0.92 (0.89, 0.95), <0.001
≥7.5, <9.9	14.6	Multivariate analysis	0.88 (0.84, 0.91), <0.001
≥5.7, <7.5	12.6		
<5.7 (lowest)	14.5		

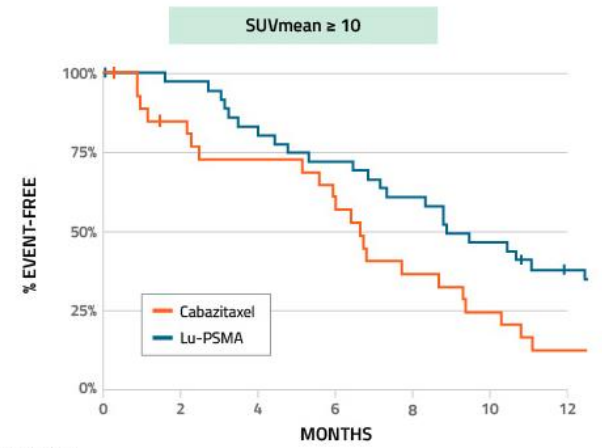
VISION substudy



Number at risk

	71	40	28	19	12	5	1
Cabazitaxel							
Lu-PSMA	64	46	34	17	15	11	8

LuPSMA vs. cabazitaxel HR, 0.77 (95% CI, 0.53-1.12)



Number at risk

	30	20	17	13	8	5	2
Cabazitaxel							
Lu-PSMA	35	33	28	24	20	15	10

LuPSMA vs. cabazitaxel HR, 0.45 (95% CI, 0.25-0.80)

TheraP trial



SUVmean >10

PSA 0,22

NEPC multiple treatments (pregression after Carboplatine)



SUVmean <10

PSA 2,000

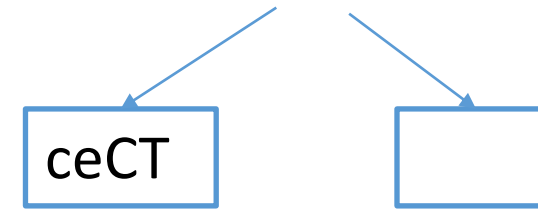
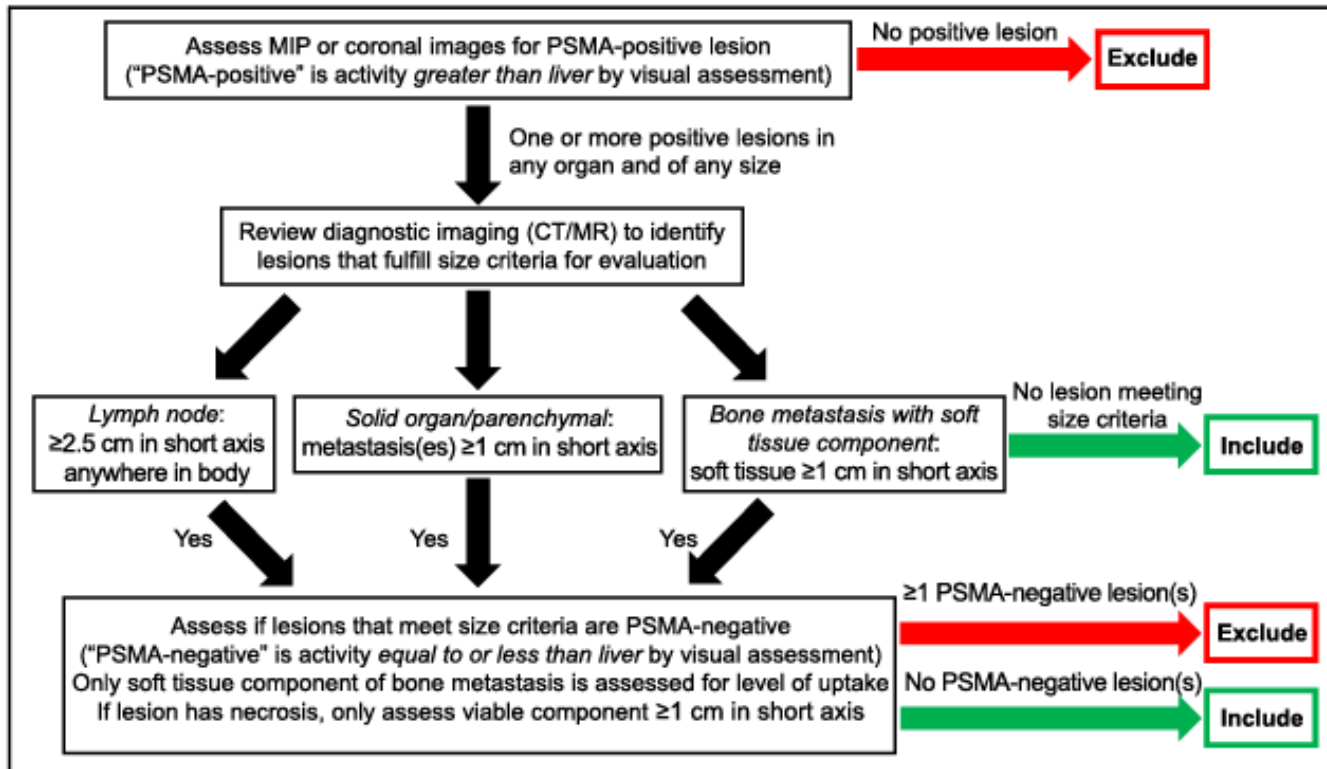
PSA >5,000

# Patient Selection for PRLT

Is PSMA uptake enough?



Are there any non-PSMA-expressing lesions?



VISION trial imaging  
exclusion 12%

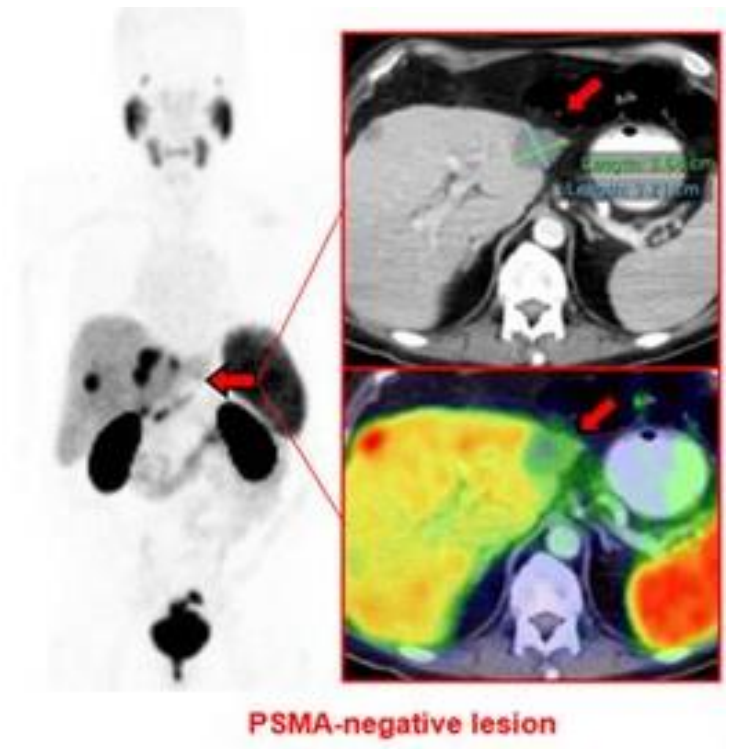


# Patient Selection for PRLT

Is PSMA uptake enough?



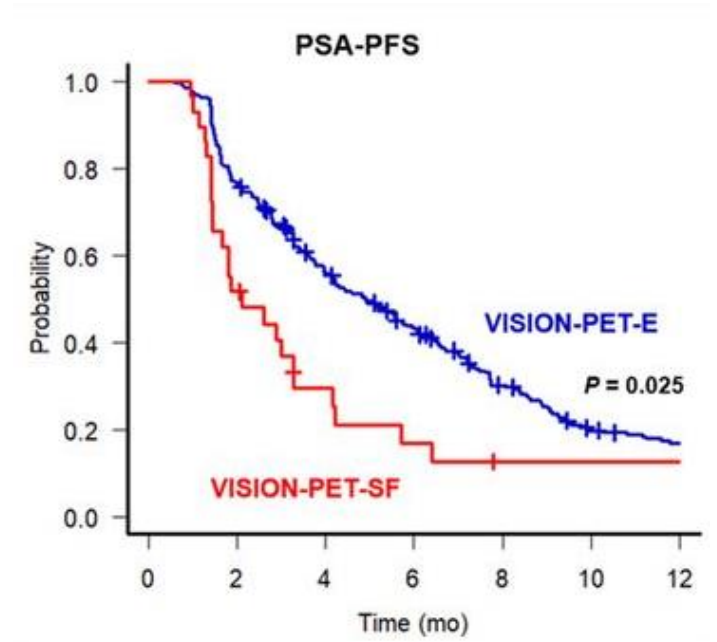
Are there any non-PSMA-expressing lesions?



Uptake > liver  
SUVmean >10

PSMA neg lesion

ceCT



# Patient Selection for PRLT

Is PSMA uptake enough?



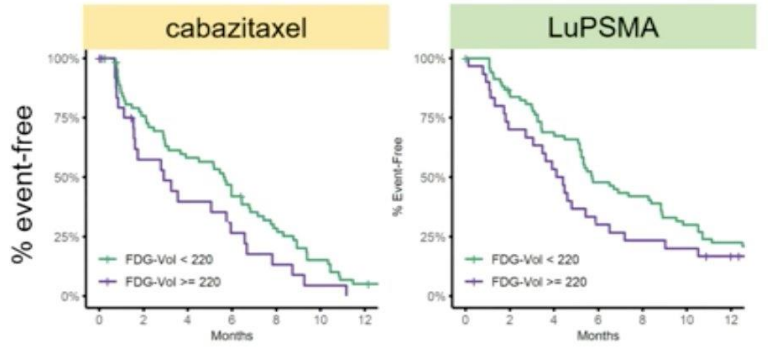
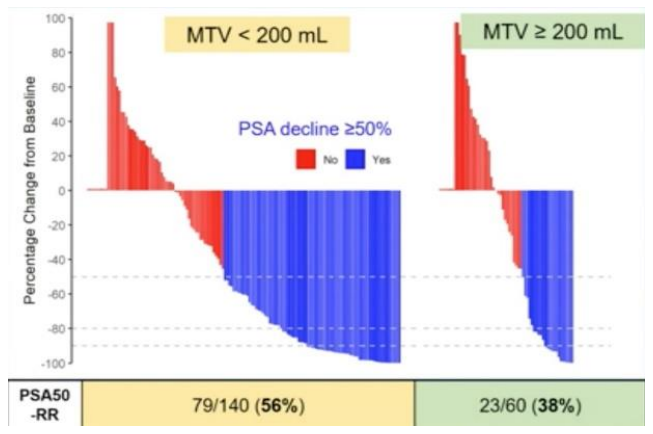
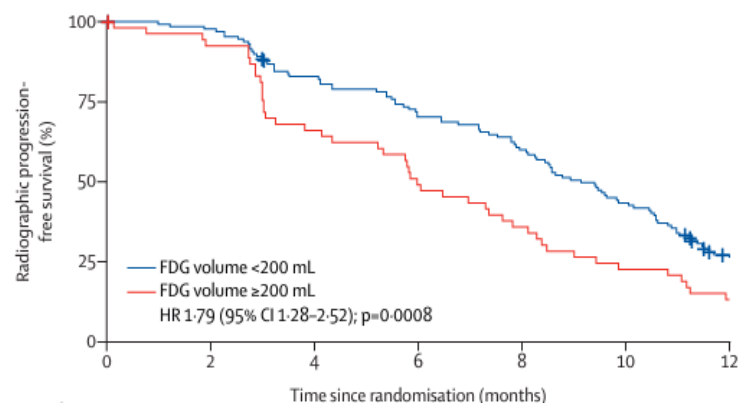
Are there any non-PSMA-expressing lesions?

**FDG PET/CT**

ceCT

**FDG**

Inspired in TNE.  
Prognostic value.  
Detecting aggressive/dedifferentiated disease.



lower responses in men with high metabolic tumour volumes regardless of treatment received.

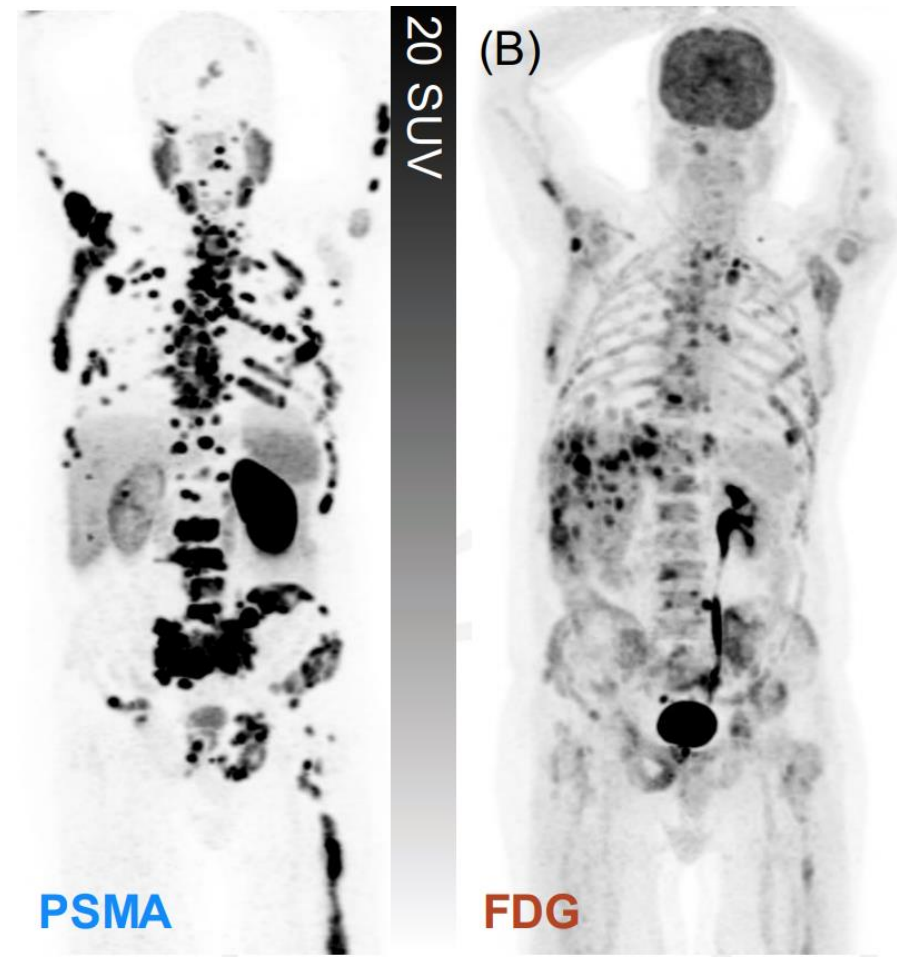
# Patient Selection for PRLT

Is this patient a good candidate for  $^{177}\text{Lu}$ -PSMA?



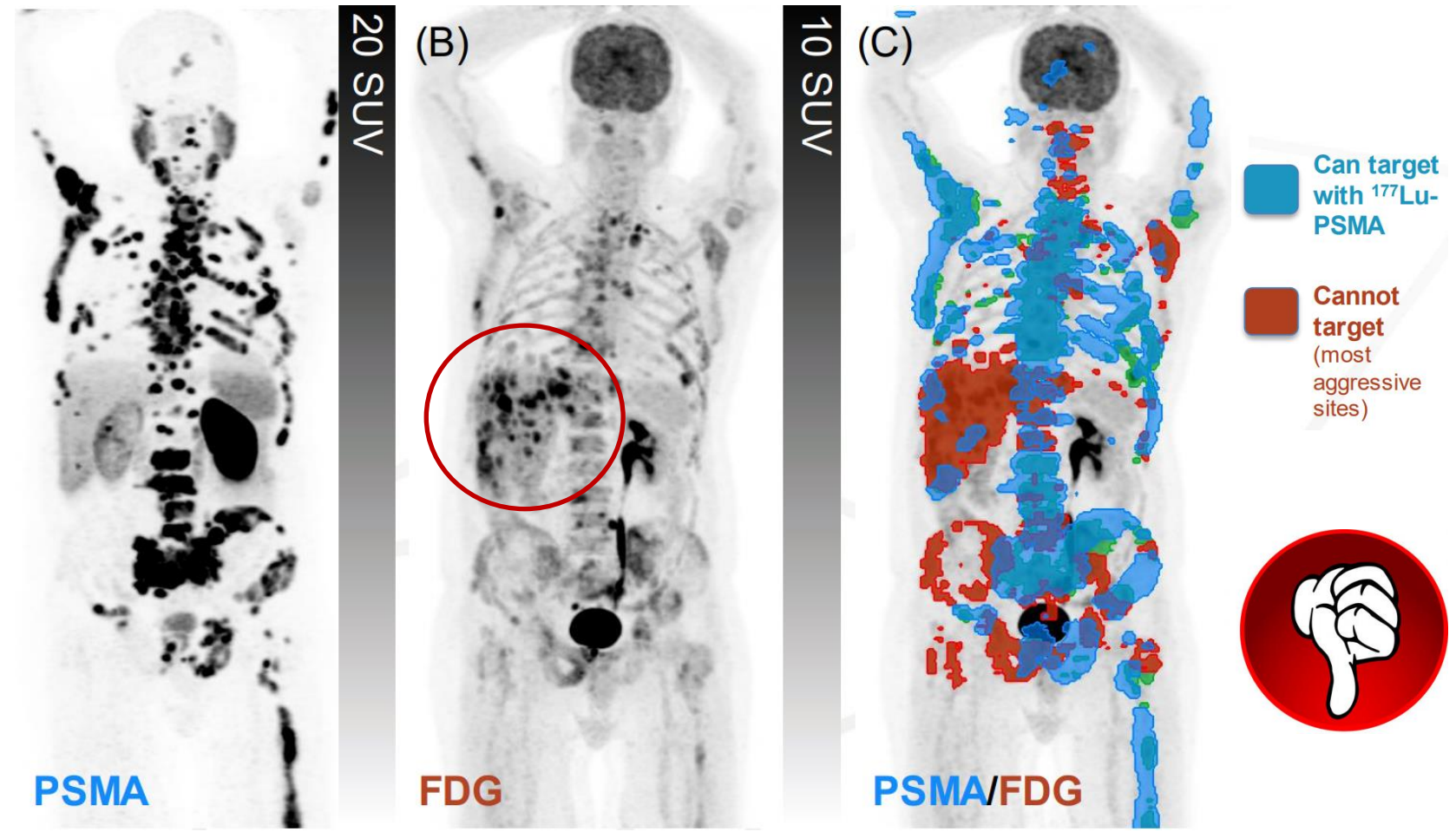
SUVmax 70

# Patient Selection for PRLT

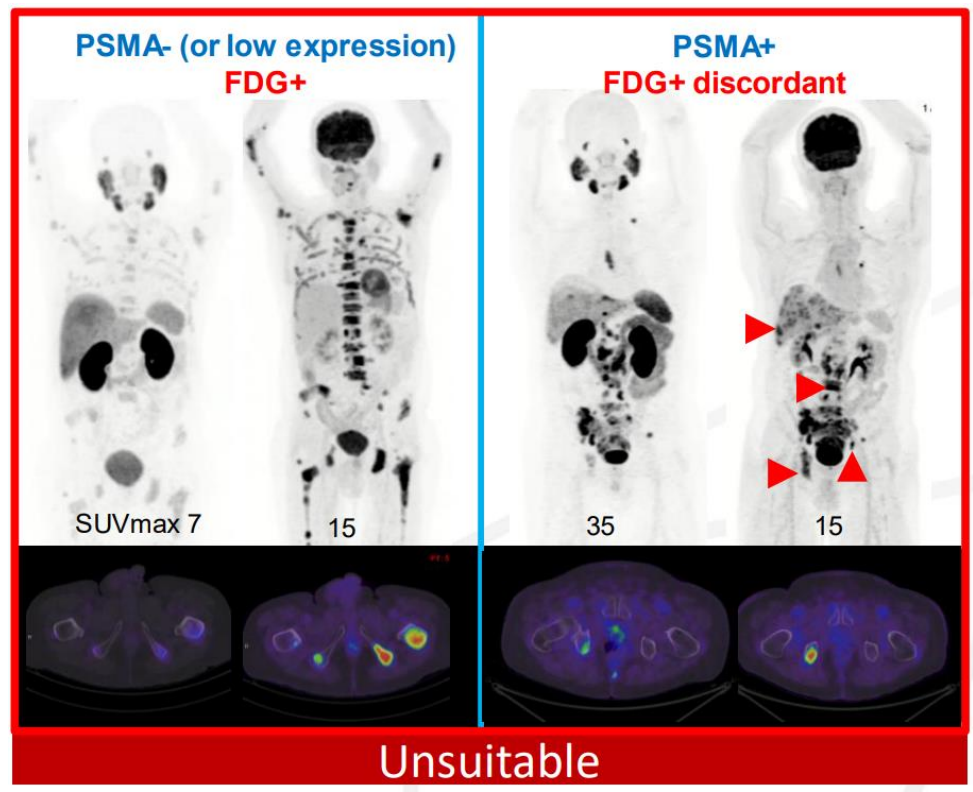


Is this patient a good candidate for  $^{177}\text{Lu}$ -PSMA?

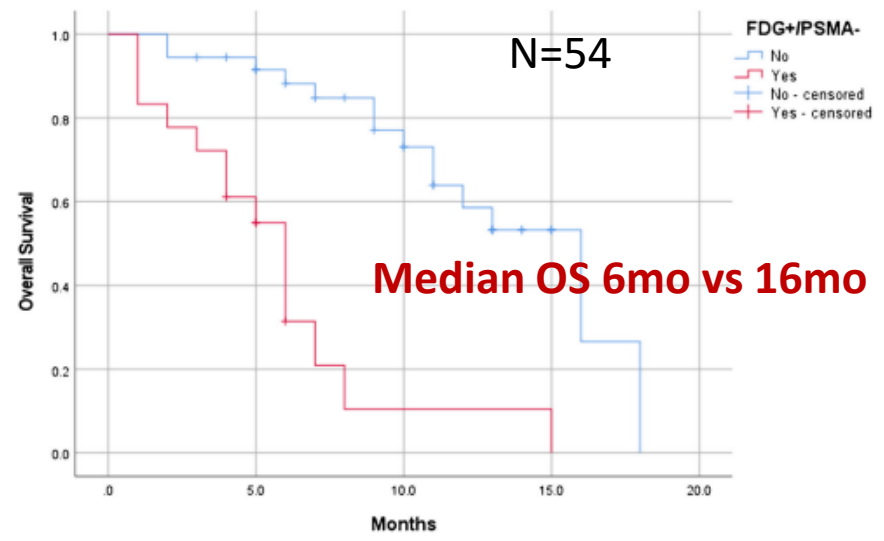
# Patient Selection for PRLT



# Patient Selection for PRLT



## Missmatch FDG+/PSMA-





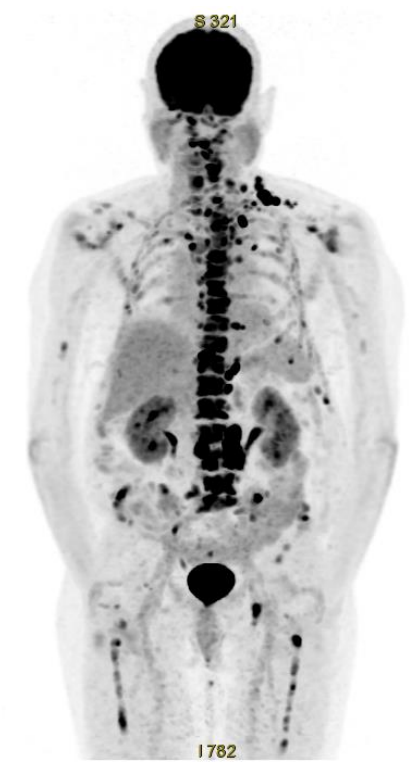
# Patient Selection Lu-PSMA RLT



Uptake > liver  
SUVmean>10



No CT scan  
mismatch



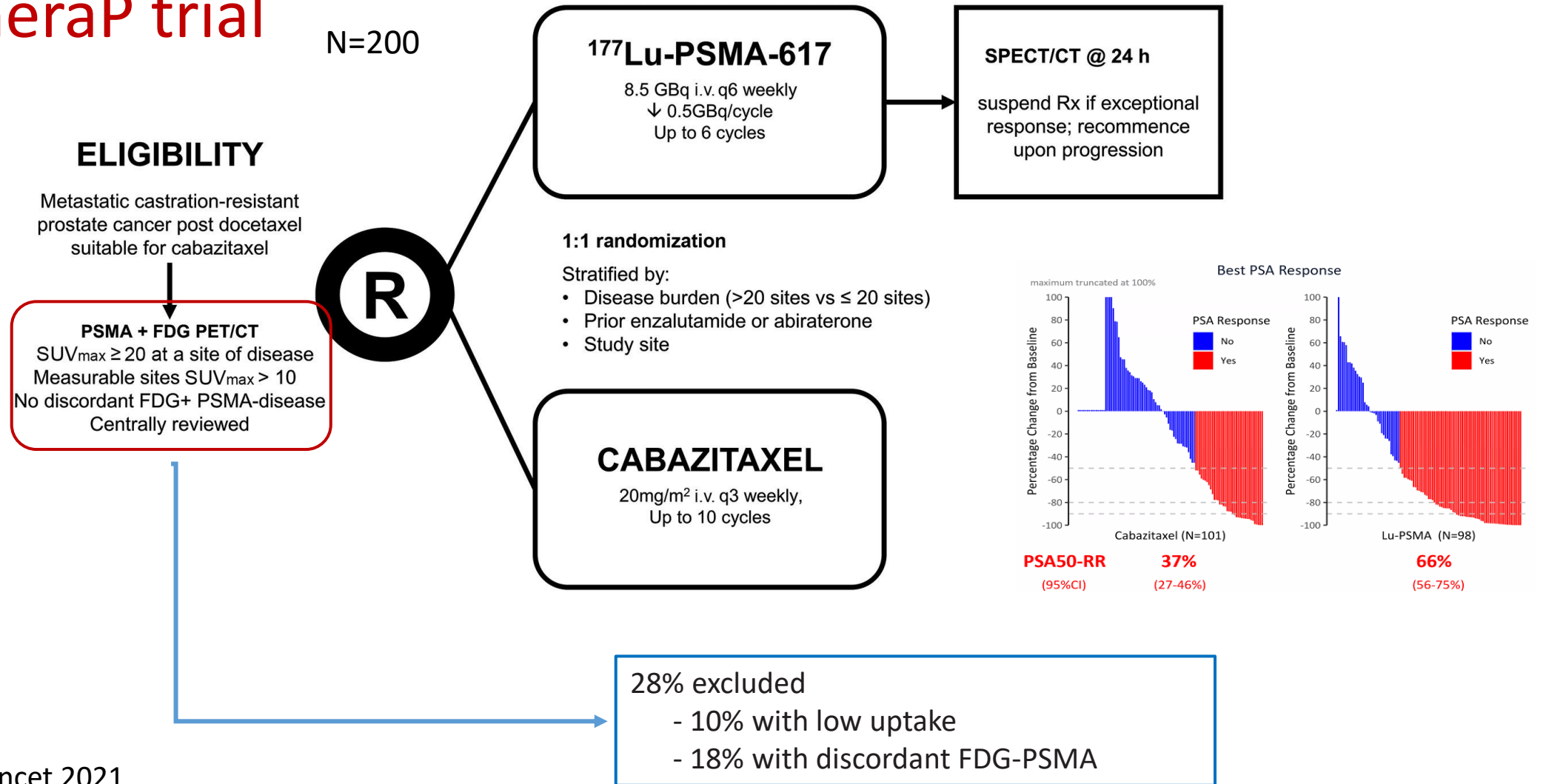
FDG mismatch  
FDGvol >200mL



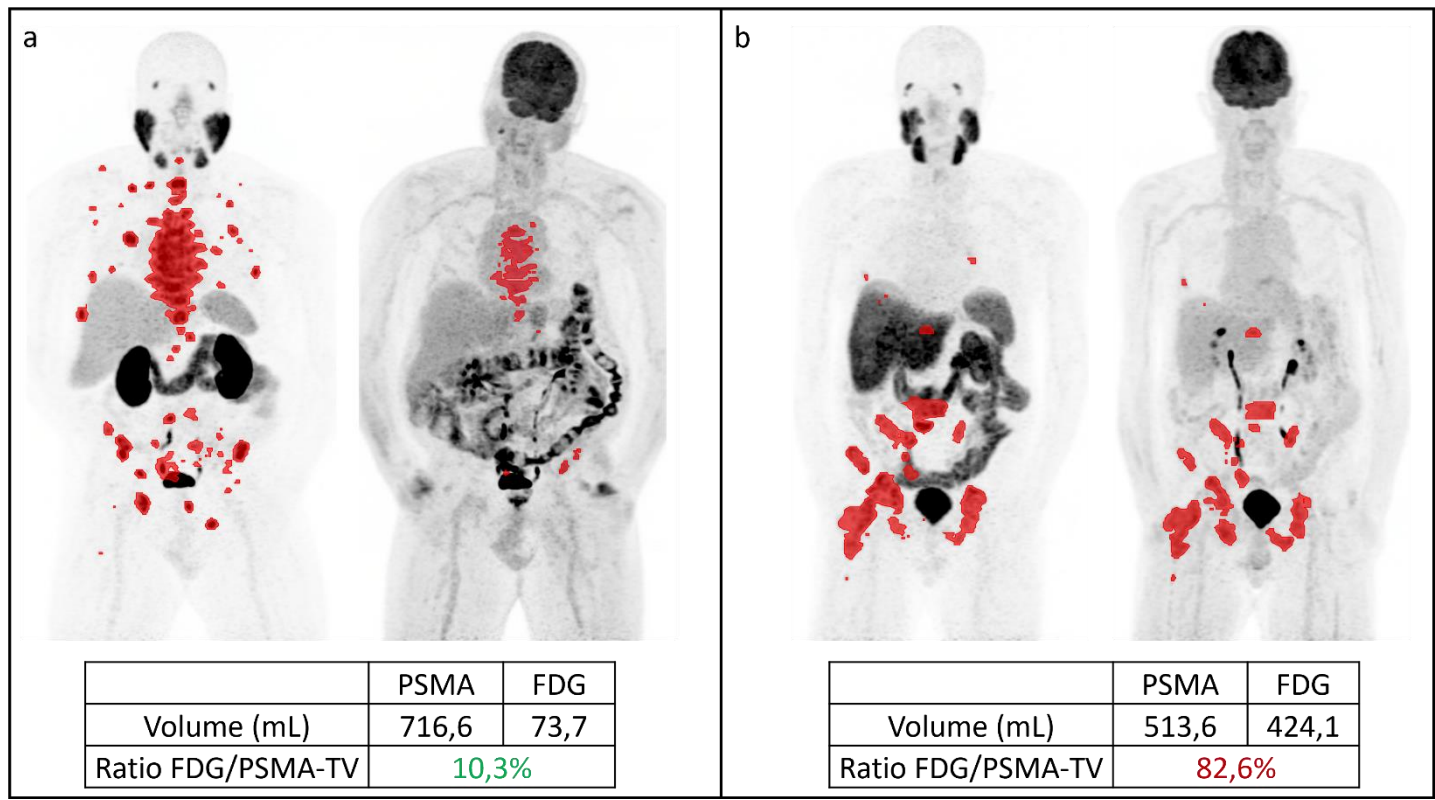




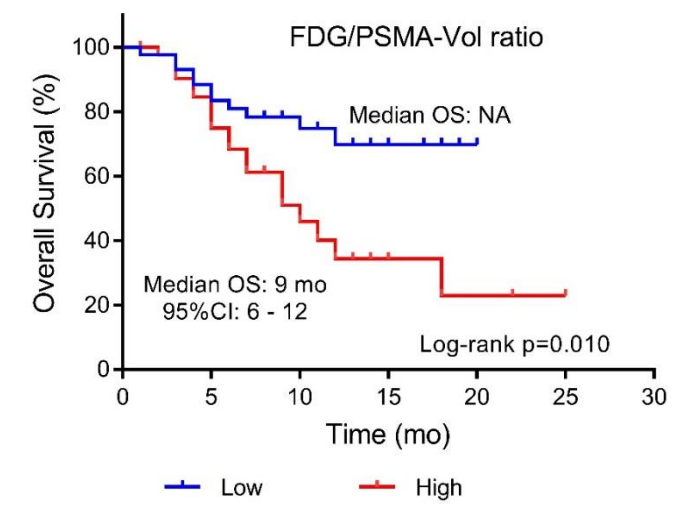
## TheraP trial

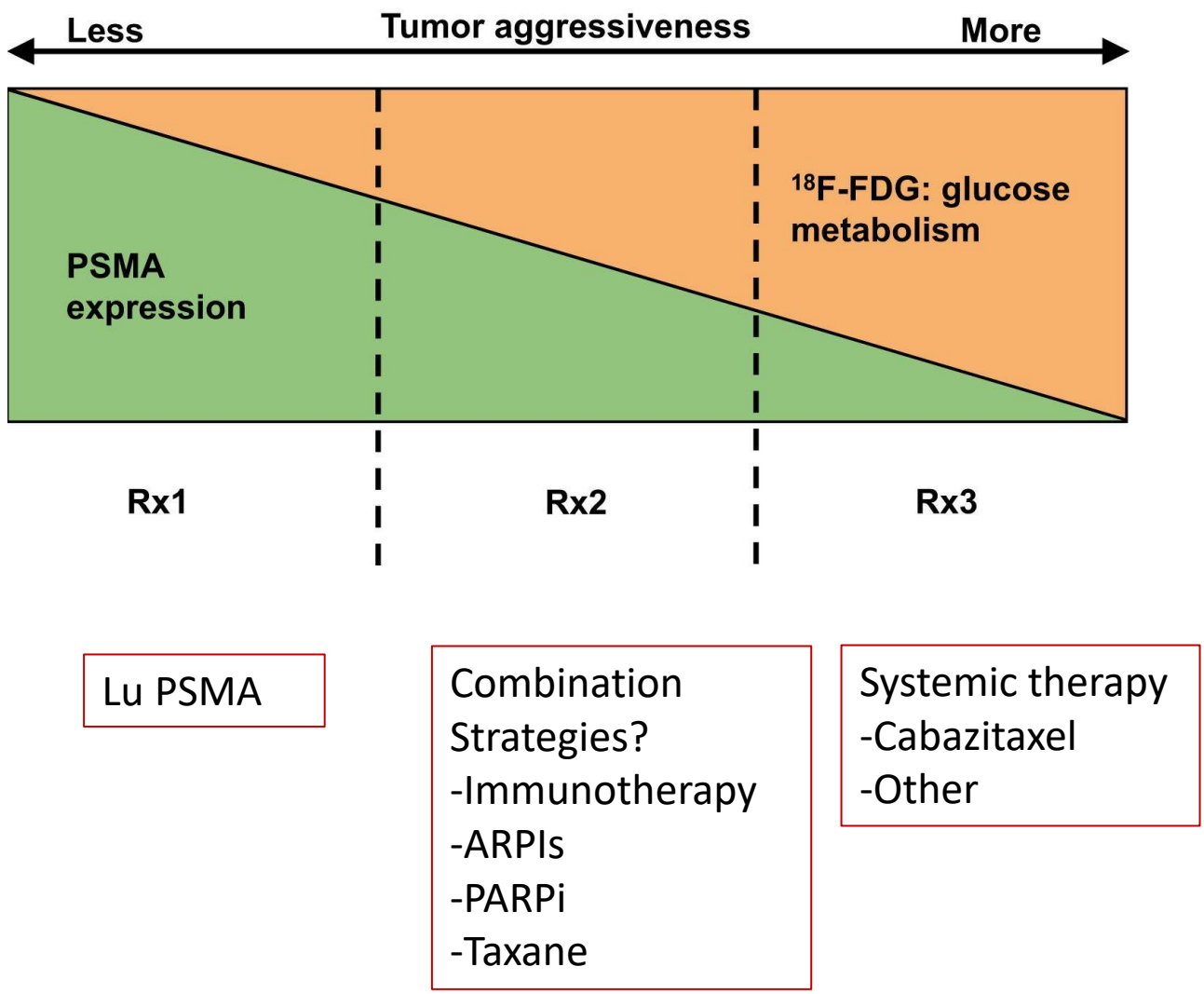


What in case of no mismatch but FDG positive disease?



**Median FDG/PSMA-Vol ratio: 30%**





## Biomarkers

### Nomograms to predict outcome after Lu-PSMA

N=270

-patients from previous phase II trials

-Define independent factors associated with

-OS

-PFS

-PSA response

-Internal and external validation

	Definition	Estimate HR or OR (95% CI)	p value
<b>Overall survival</b>			
Time since diagnosis	Continuous, years	0.92 (0.89-0.95)	<0.0001
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.53 (1.01-2.37)	0.044
Baseline haemoglobin	Continuous, g/dL	0.85 (0.77-0.95)	0.0035
Number of metastases	≥20 vs <20	1.66 (1.12-2.44)	0.0031
Tumour SUV <sub>mean</sub>	Continuous, no unit	0.94 (0.90-0.98)	0.0078
Bone involvement	M1b vs no M1b	1.10 (0.57-2.13)	0.77
Liver involvement	Liver metastases vs no liver metastases	2.11 (1.38-3.23)	<0.0001
<b>PSA-progression-free survival</b>			
Time since diagnosis	Continuous, years	0.94 (0.92-0.97)	0.00012
Chemotherapy status	Previous chemotherapy vs no chemotherapy	1.55 (1.03-2.34)	0.028
Tumour SUV <sub>mean</sub>	Continuous, no unit	0.92 (0.88-0.96)	0.00052
Pelvic nodal involvement	N1 vs N0	0.70 (0.51-0.97)	0.035
Bone involvement	M1b vs no M1b	1.93 (1.07-3.52)	0.032
Liver involvement	Liver metastases vs no liver metastases	2.59 (1.69-3.95)	<0.0001
<b>PSA decline ≥50%</b>			
Chemotherapy status	Previous chemotherapy vs no chemotherapy	0.32 (0.13-0.77)	0.012
Tumour SUV <sub>mean</sub>	Continuous, no unit	2.88 (1.80-4.62)	<0.0001
Pelvic nodal involvement	N1 vs N0	1.87 (0.96-3.62)	0.062
Liver involvement	Liver metastases vs no liver metastases	0.29 (0.11-0.81)	0.018

Estimates are hazard ratios for the overall survival and PSA-progression-free survival analyses, and odds ratios for the PSA decline of 50% or greater analysis. HR=hazard ratio. OR=odds ratio. SUV=standardised uptake value. PSA=prostate-specific antigen.

**Table 2: Multivariate analysis of predictors selected by LASSO regression procedure in the development cohort**

# Nomogram for <sup>177</sup>Lu-PSMA-RLT

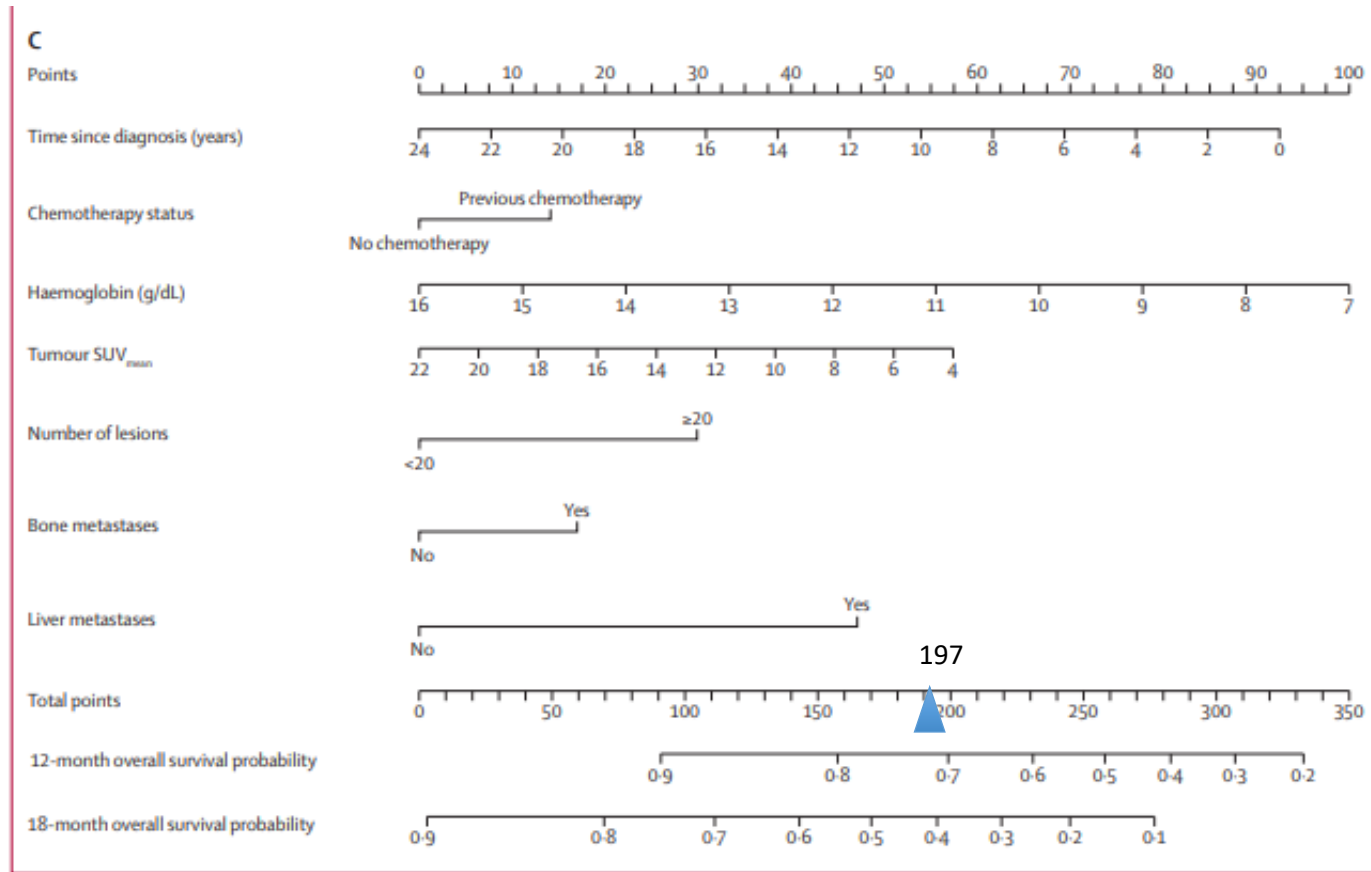


Figure 2: Overall survival probabilities

- Lu-PSMA Prognostic Model

### Risk Calculator

Medical History		PSMA PET/CT Parameters	
Time since diagnosis	<input type="text" value="0"/> years	Tumor SUVmean	<input type="text" value="0"/>
Previous chemotherapy	<input type="radio"/> Yes <input checked="" type="radio"/> No	Number of metastases	<input type="radio"/> $\geq 20$ <input checked="" type="radio"/> $< 20$
Laboratory Values		Pelvic lymph nodes	<input type="radio"/> Yes <input checked="" type="radio"/> No
Hemoglobin	<input type="text" value="0"/> g/dl	Bone metastases	<input type="radio"/> Yes <input checked="" type="radio"/> No
		Liver metastases	<input type="radio"/> Yes <input checked="" type="radio"/> No

Source: Gafita, Andrei, Jeremie Calais, Tristan R. Grogan, Boris Hadaschik, Hui Wang, Manuel Weber, Shahneen Sandhu et al. "Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study." *The Lancet Oncology* (2021).

<https://www.uclahealth.org/nuc/nomograms>



## Risk Calculator

### Medical History

Time since diagnosis  years

Previous chemotherapy

### Laboratory Values

Hemoglobin  g/dl

### PSMA PET/CT Parameters

Tumor SUVmean

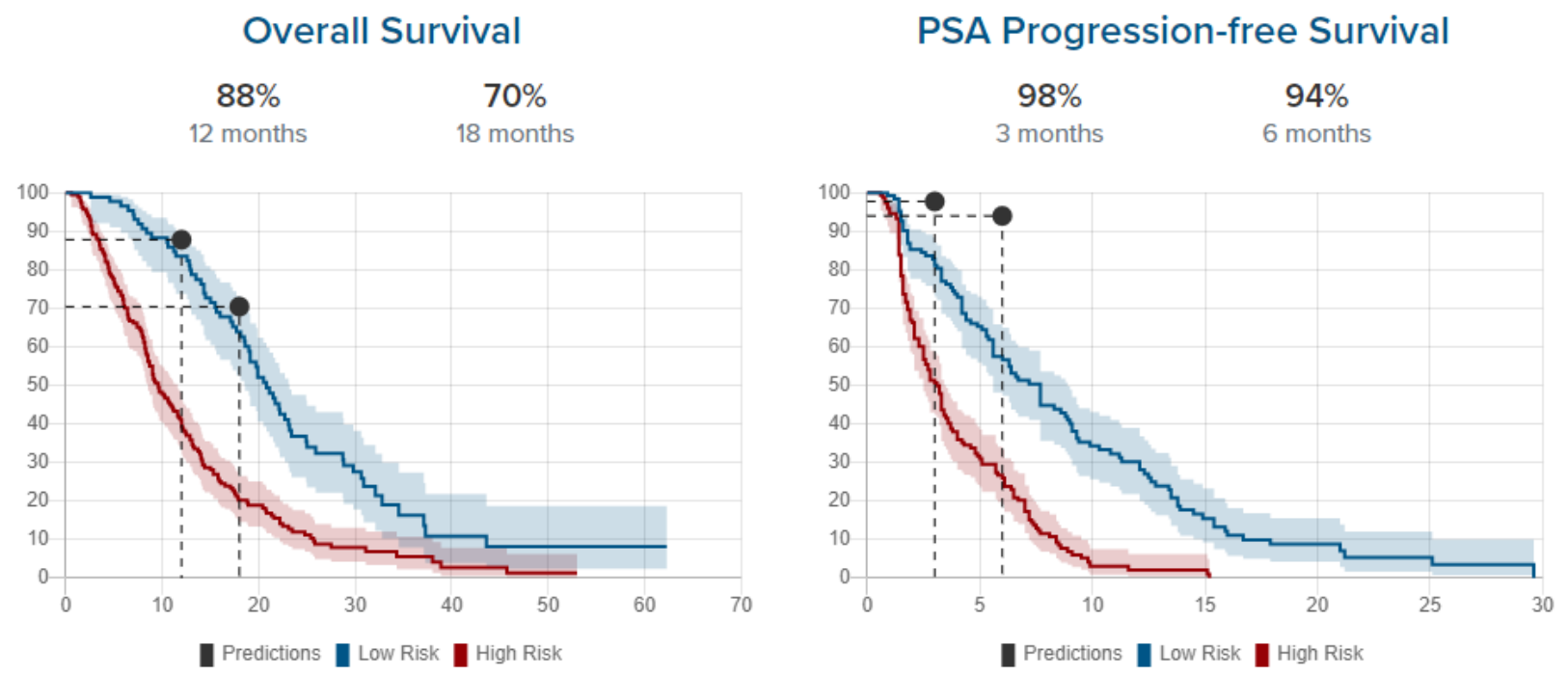
Number of metastases

Pelvic lymph nodes

Bone metastases

Liver metastases

# Patient Selection for PRLT



Probability of PSA Response 100%

<https://www.uclahealth.org/nuc/nomograms>

## Risk Calculator

### Medical History

Time since diagnosis  years

Previous chemotherapy

### Laboratory Values

Hemoglobin  g/dl

### PSMA PET/CT Parameters

Tumor SUVmean

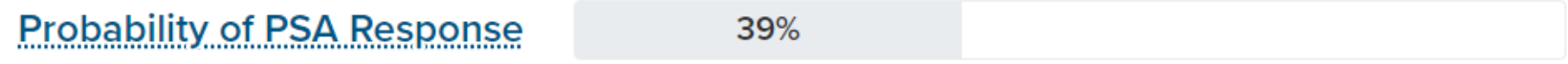
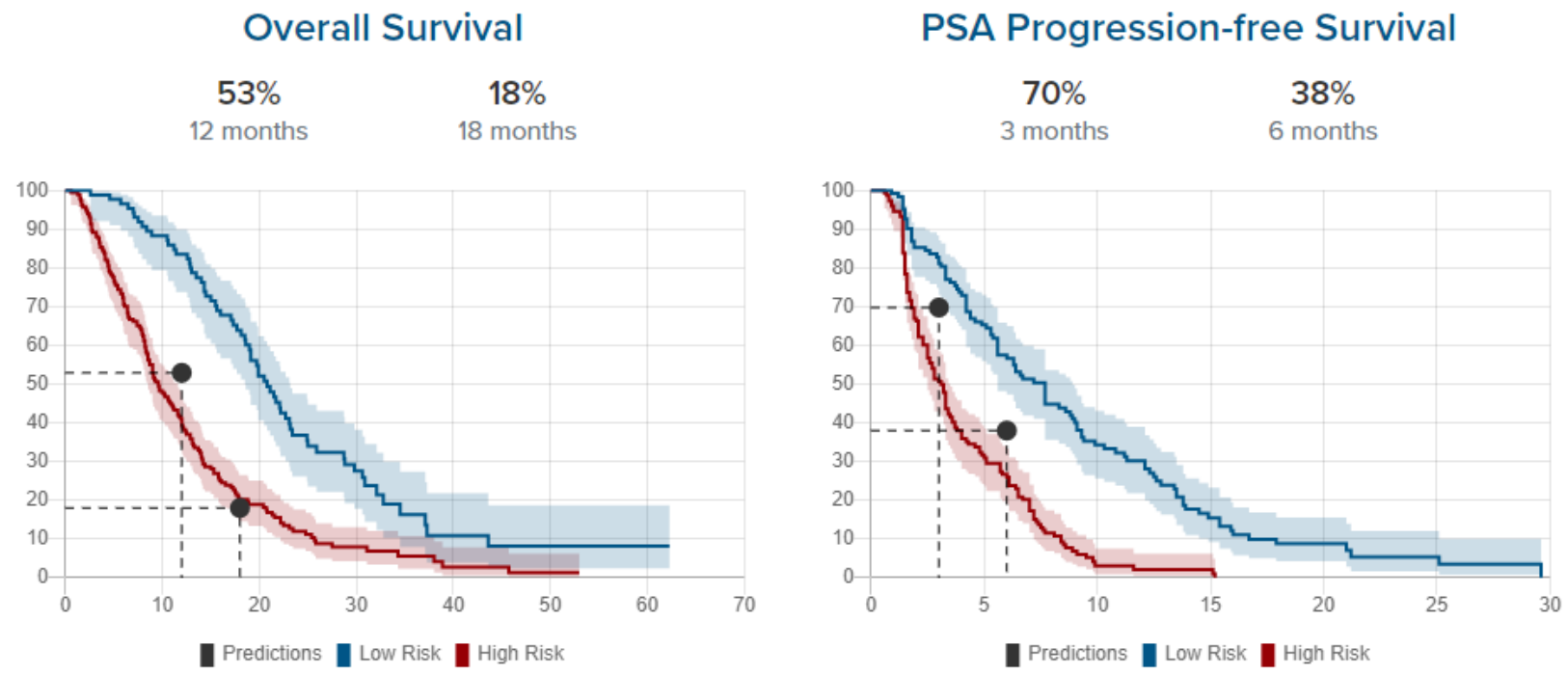
Number of metastases

Pelvic lymph nodes

Bone metastases

Liver metastases

# Patient Selection for PRLT



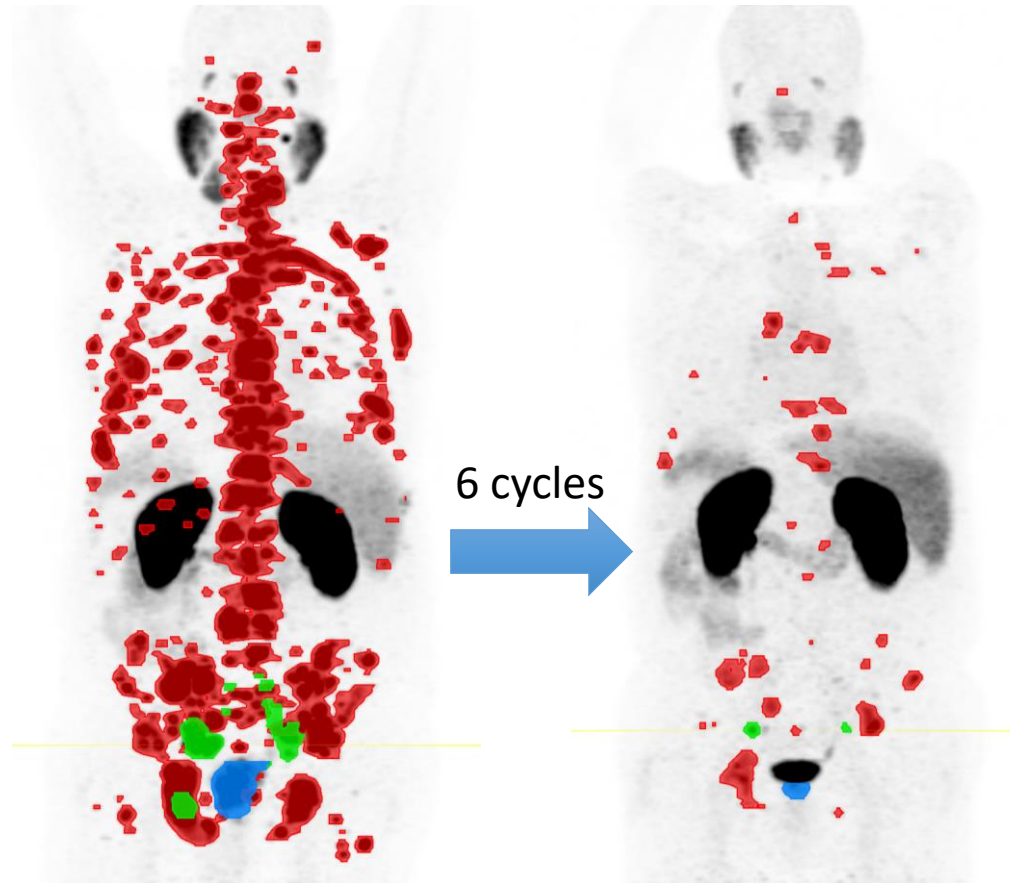
<https://www.uclahealth.org/nuc/nomograms>

- Before each cycles
  - Blood test
  - Consultation
- Every 12 weeks (2 cycles)
  - Response Assessment
  - Imaging (PSMA +/- FDG)
  - PSA values

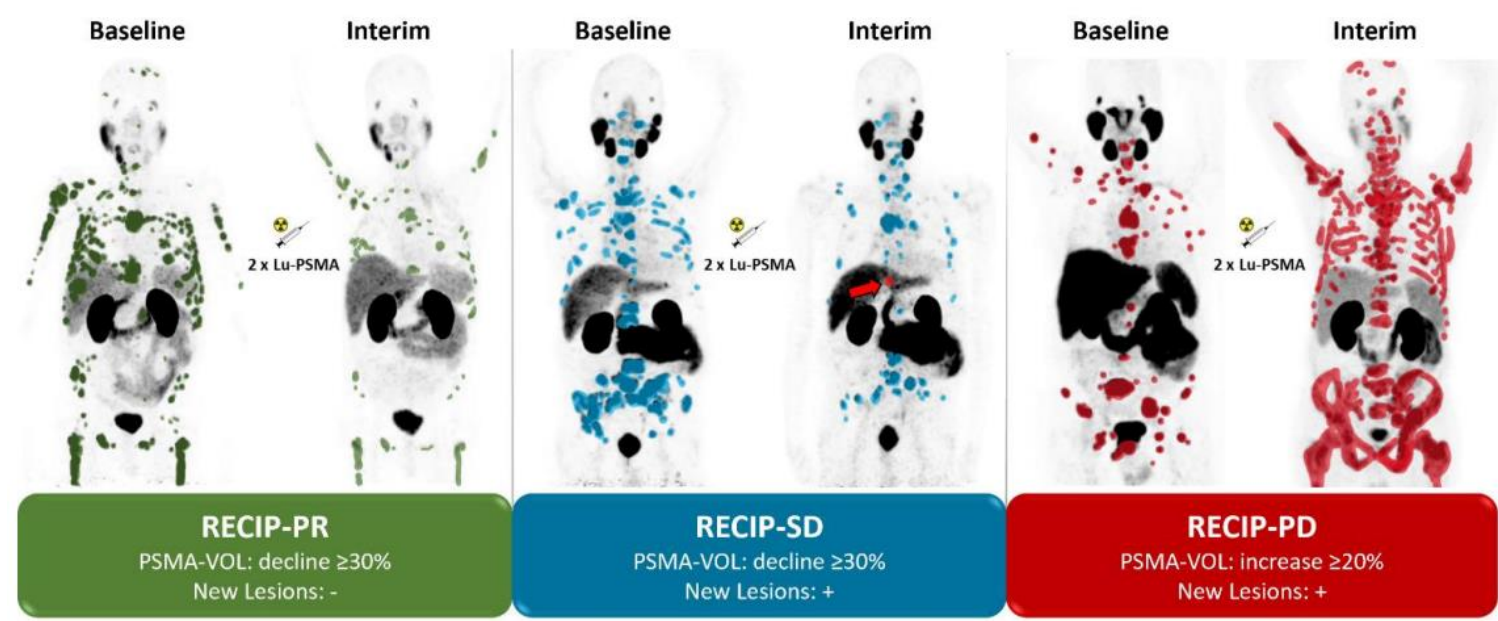


## PSMA Total Tumor Volume

- Counting lesions (difficult multiM1)
- Selection of target lesions (variability)
- Less variability between centers and different tracers
- **New software solutions** simplify implementation for clinical routine
- Excellent tool for **response assessment**

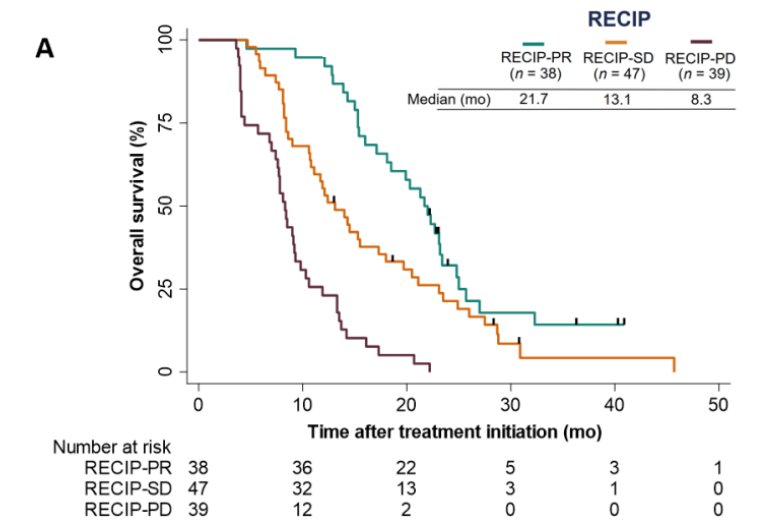


## Response Evaluation Criteria In PSMA-imaging v1.0 RECIP 1.0



**After 2 cycles of  $^{177}\text{Lu}$ -PSMA (OS predictive):**

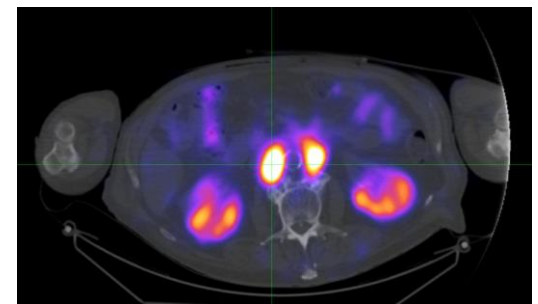
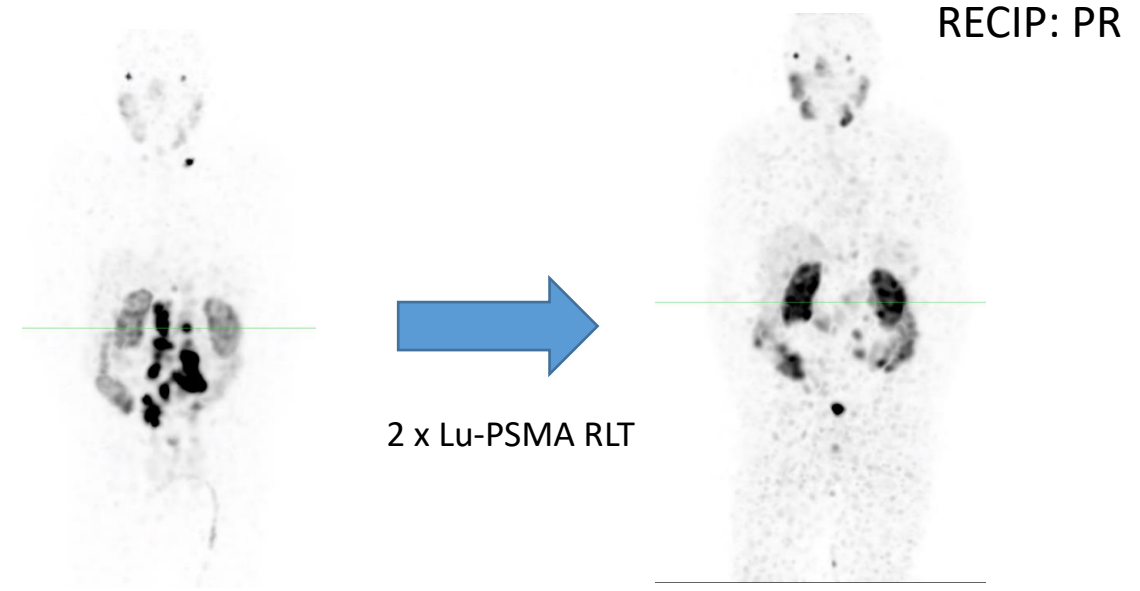
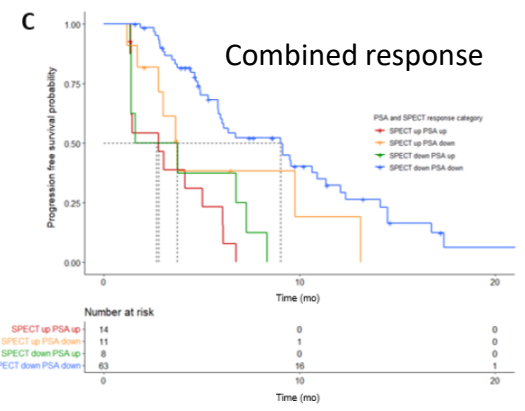
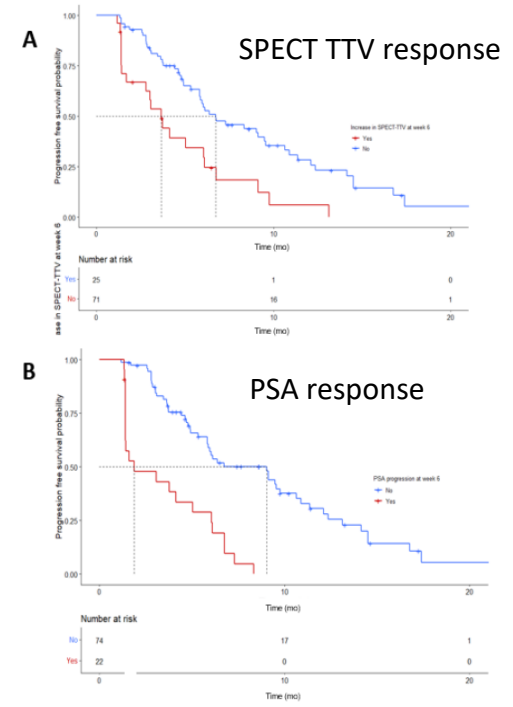
- Changes in PSMA-TV (30%)
- New lesions



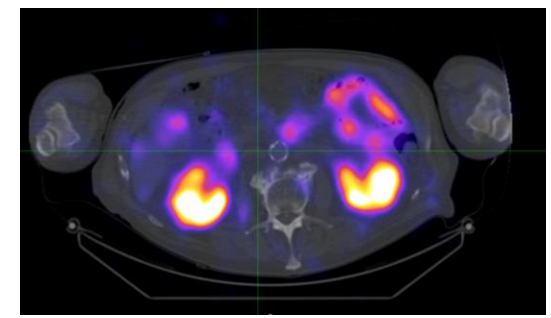


# Response Assessment (SPECT/CT)

- qSPECT used like PET: Baseline (C1) vs C2



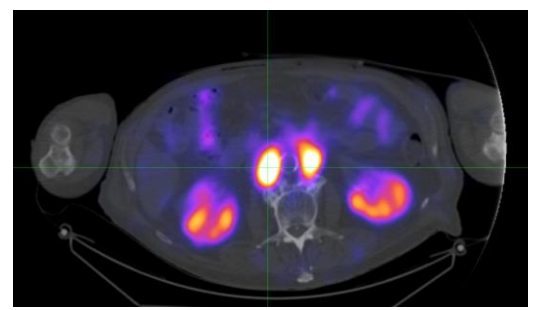
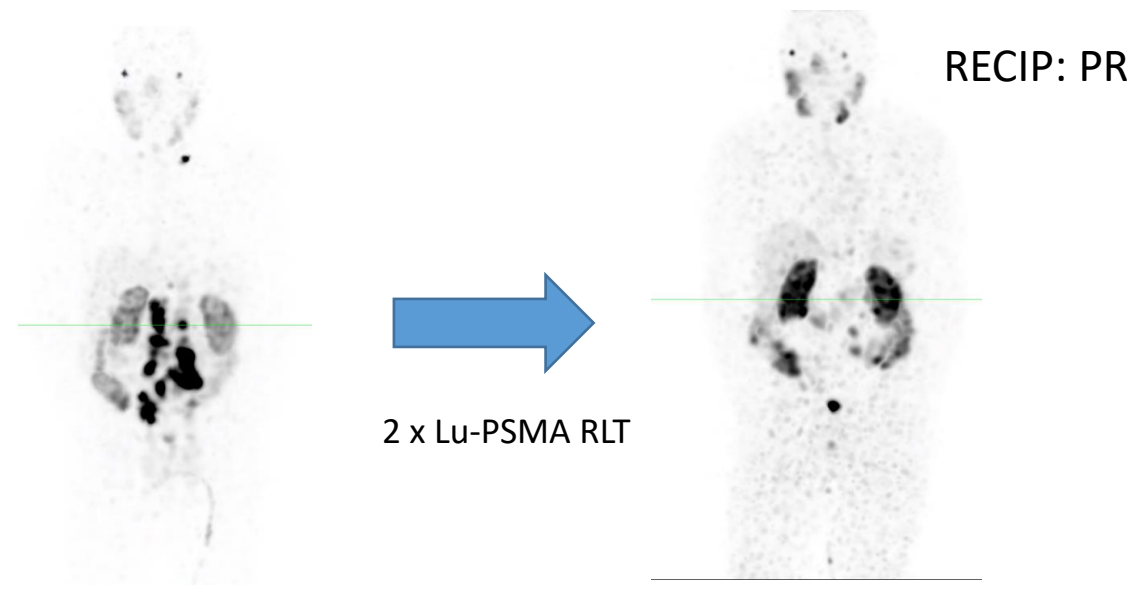
177Lu-PSMA SPECT/CT (C1)



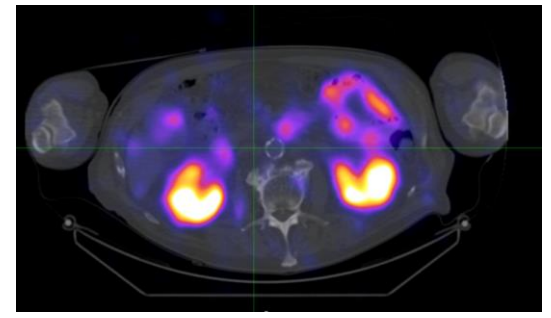
177Lu-PSMA SPECT/CT (C2)

# Response Assessment (SPECT/CT)

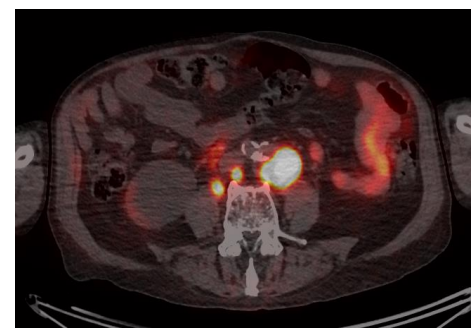
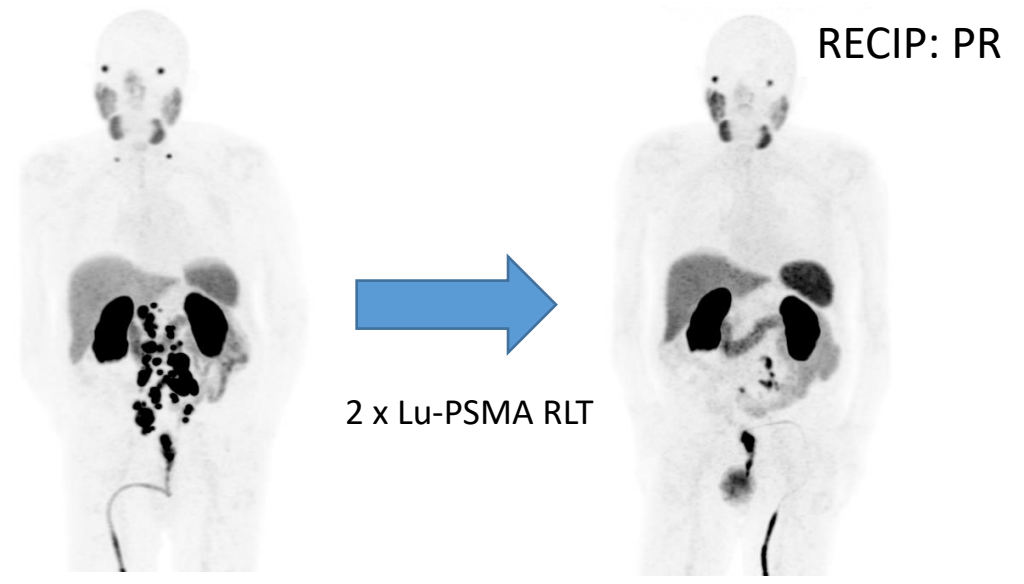
- qSPECT used like PET: Baseline (C1) vs C2



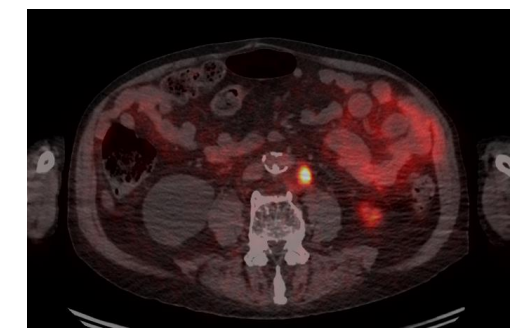
177Lu-PSMA SPECT/CT (C1)



177Lu-PSMA SPECT/CT (C2)

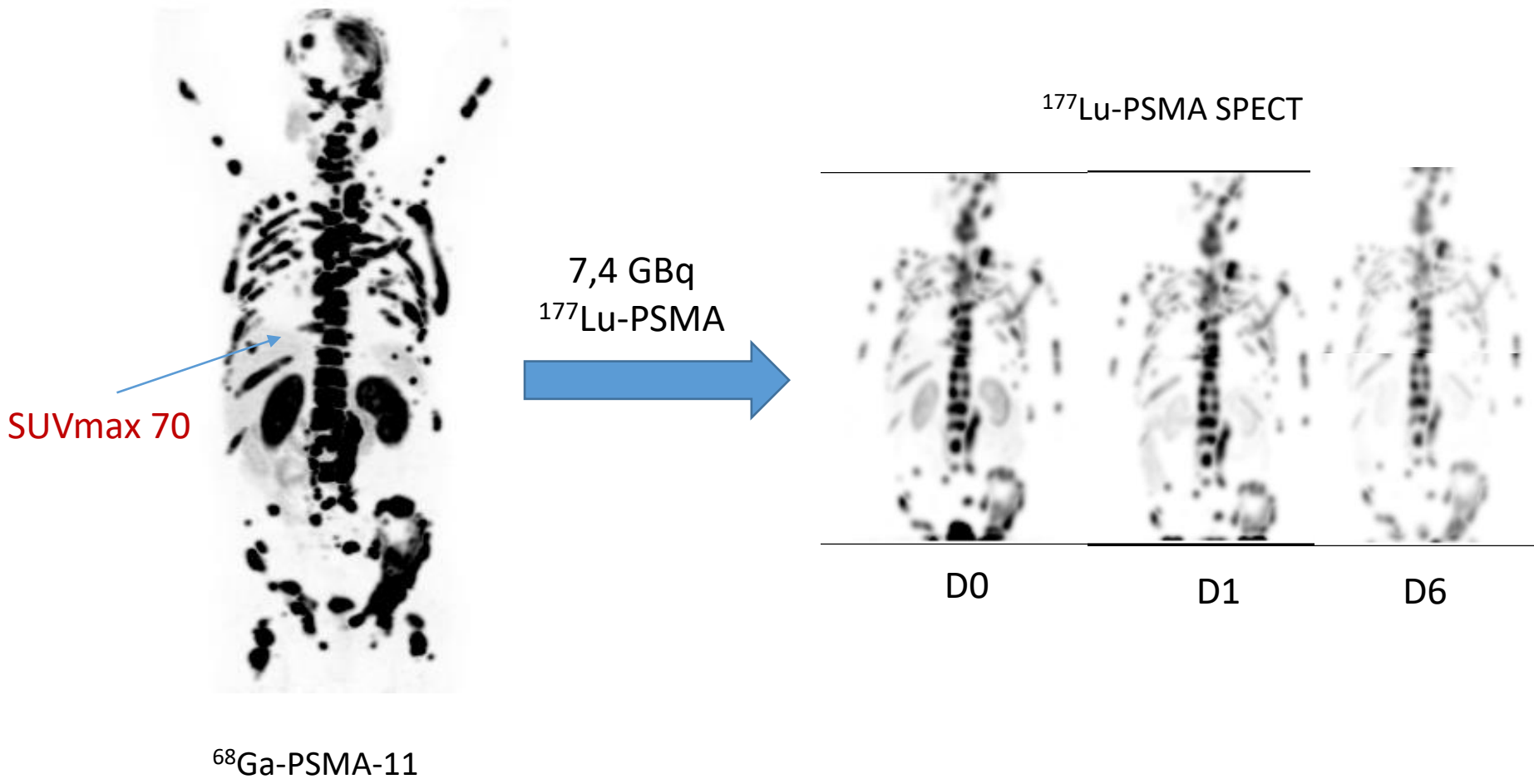


68Ga-PSMA PET/CT baseline



68Ga-PSMA PET/CT post C2

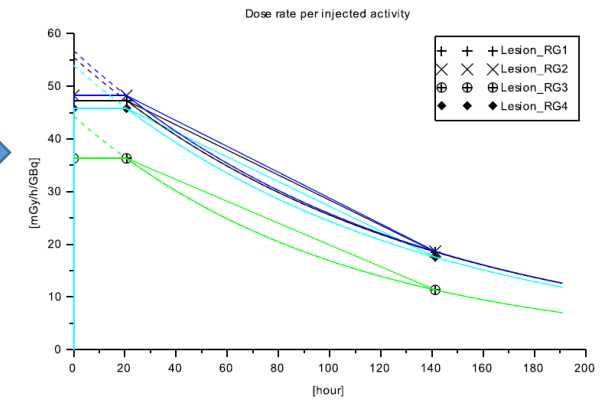
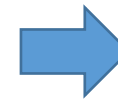
# Dosimetry with $^{177}\text{Lu}$ -PRLT



# Dosimetry with $^{177}\text{Lu}$ -PRLT

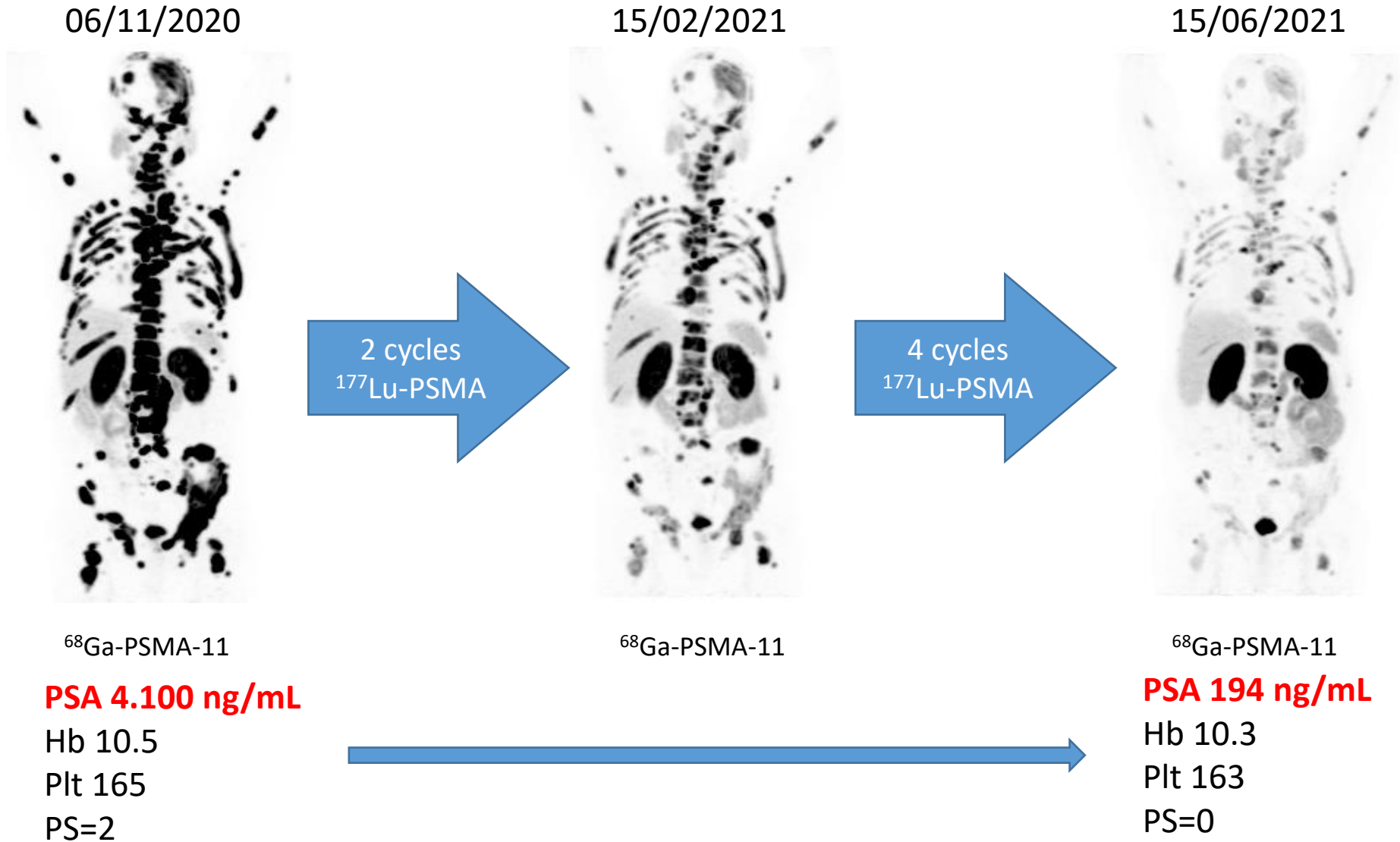


$^{68}\text{Ga}$ -PSMA-11

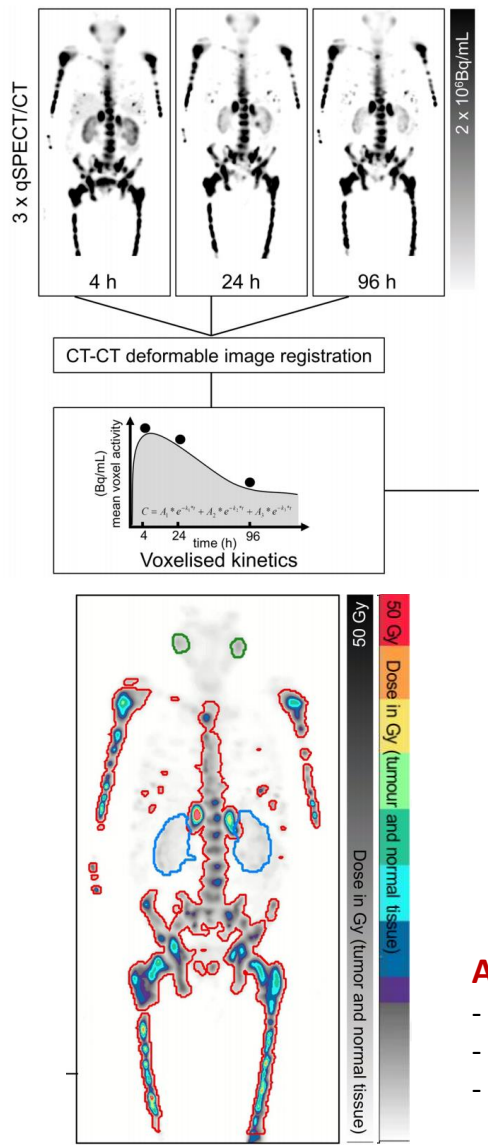


Name	Dose [Gy]
Lesion_RG1	53.56
Lesion_RG2	53.92
Lesion_RG3	34.18
Lesion_RG4	50.79

# Pre-therapeutic imaging

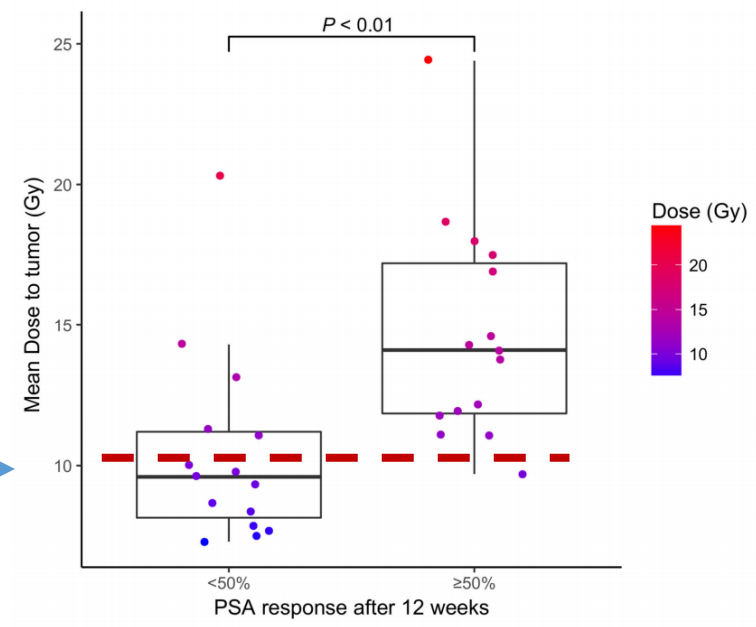


# Dosimetry with $^{177}\text{Lu}$ -PRLT



Whole Body tumor dose correlates with PSA response at 12 weeks

**Dose < 10Gy = Non-response**



**Dose treatment adaptation?  
 Predict toxicity in organs at risk?**

- Automatic segmentation** softwares
- qPSMA (siemens) Gafita et al. JNM 2019
  - MIM software solution (Remy et al. SNMMI'21)
  - METAVOL (open source)



## Conclusions

### Patient selection

- Vision Trial criteria
- Predictive Biomarkers
  - Total Tumor SUVmean
  - FDG PET mismatch (aggressive disease)

### Response:

- PSA and PSMA imaging at 2 cycles
- Need for better biomarkers
  - National Lu-PSMA Registry
  - Dosimetry Studies





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# Thank you very much

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11<sup>th</sup> Belgian Multidisciplinary  
Meeting on Urological Cancers