

#APCCC2019



**ADVANCED PROSTATE CANCER
CONSENSUS CONFERENCE: APCCC 2019**
29-31 August 2019, Basel/Switzerland

PSMA Targeted Therapies

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Peter MacCallum Cancer Centre / The University of Melbourne



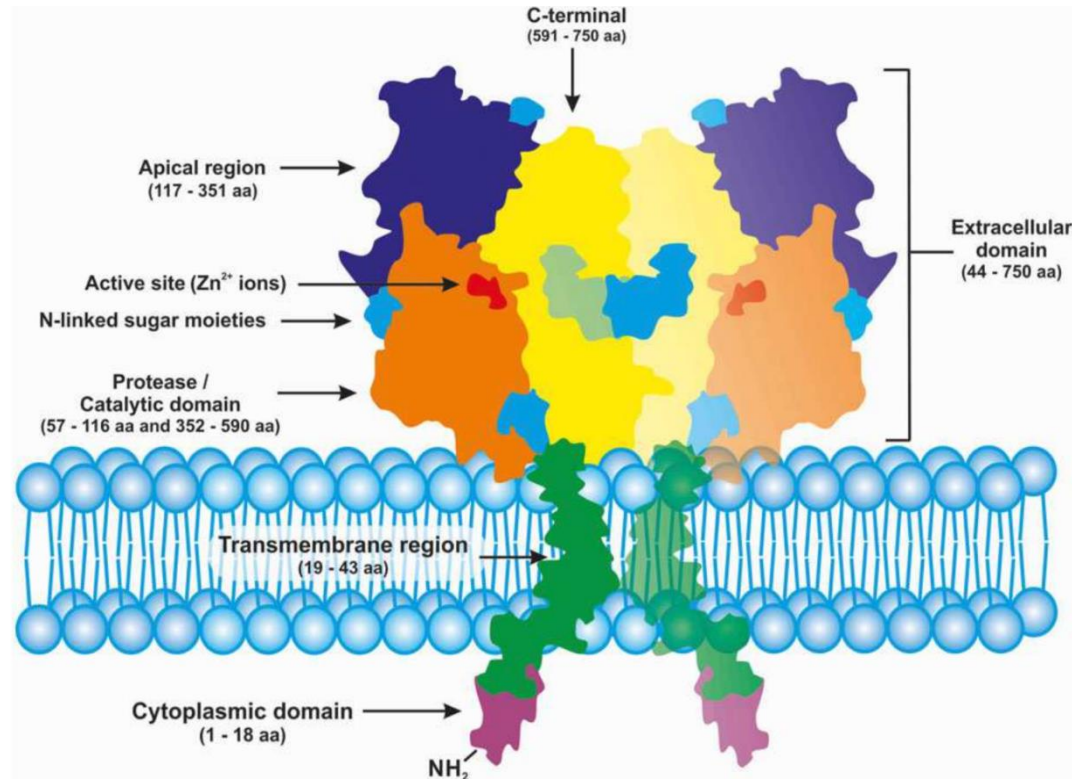
@DrMHofman

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Disclosures

Research Support	Endocyte (a Novartis company)
Consulting	none
Honoraria/travel support	Janssen, Sanofi Genzyme, Ipsen
Stock ownership	None
Study Chair	TheraP

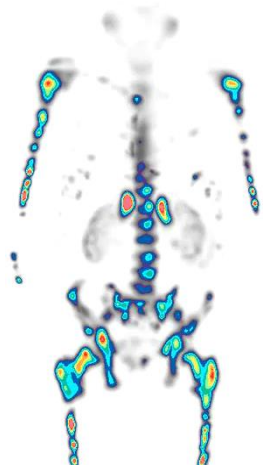
Prostate Specific Membrane Antigen (PSMA)



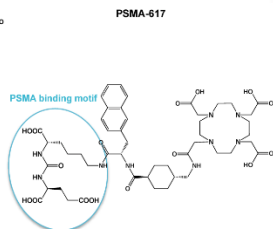
THERANOSTICS

TARGETED THERAPEUTIC + DIAGNOSTIC COMPANION

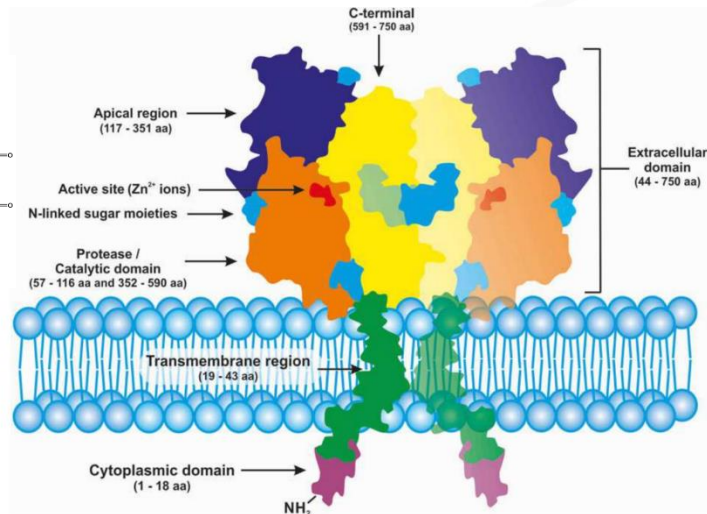
^{177}Lu -PSMA-617 SPECT



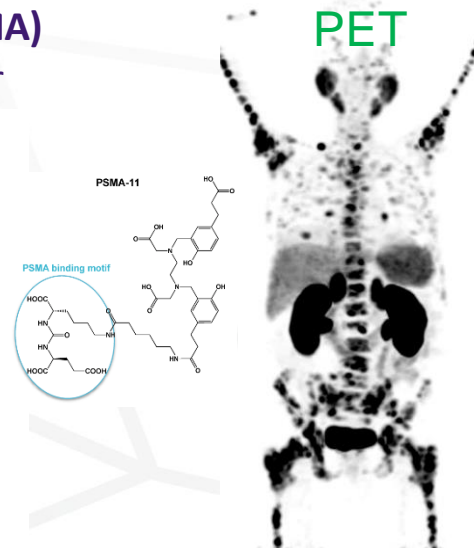
Post-therapy SPECT/CT



radioactive small molecule targeting
prostate specific membrane antigen (PSMA)
highly over-expressed in prostate cancer



⁶⁸Ga-PSMA-11
PET

Pre-therapy
PET/CT

Lutetium-177 (^{177}Lu): short path-length beta emitter

mean path length 1mm, average penetration 0.3mm, 6.7 day half-life



targeted drug: “too smart”

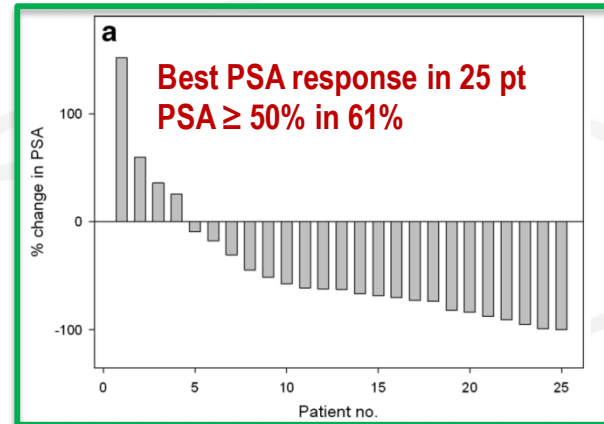
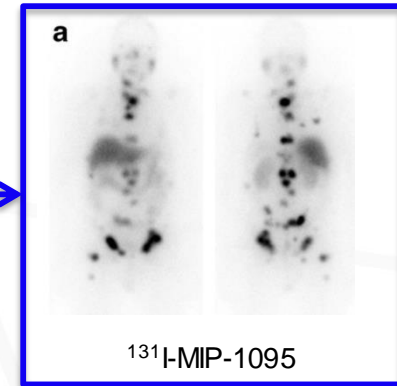
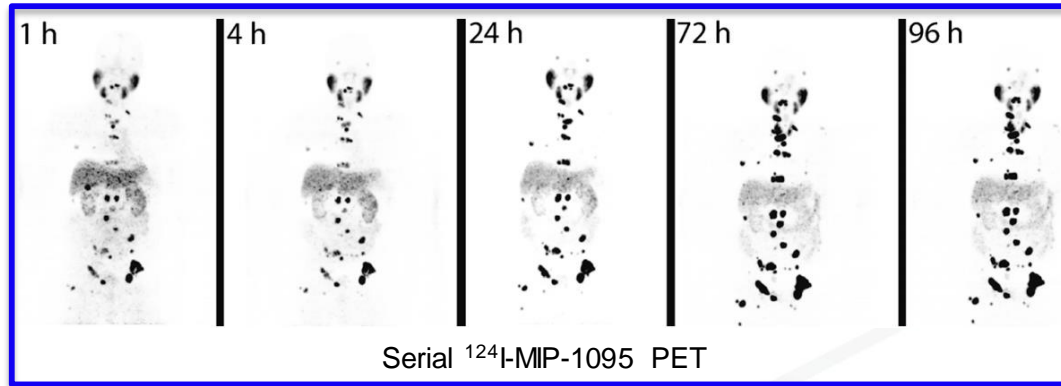
nearby cells not expressing target
develop resistance



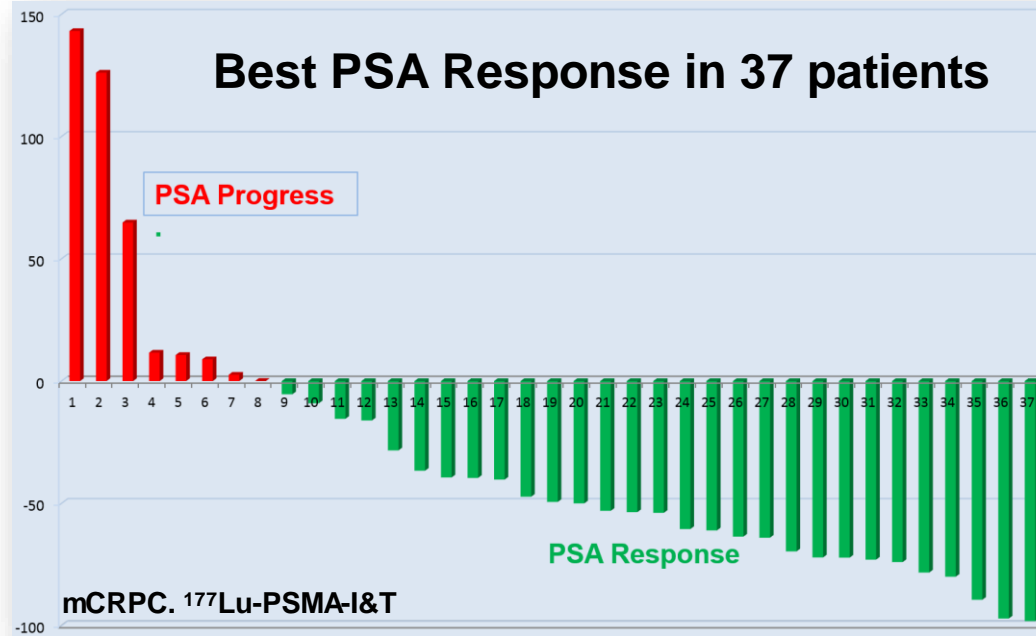
1mm path-length: cross-fire effect

all cells in 1mm radius targeted

2014: high activity of small molecule (not Ab) targeting PSMA

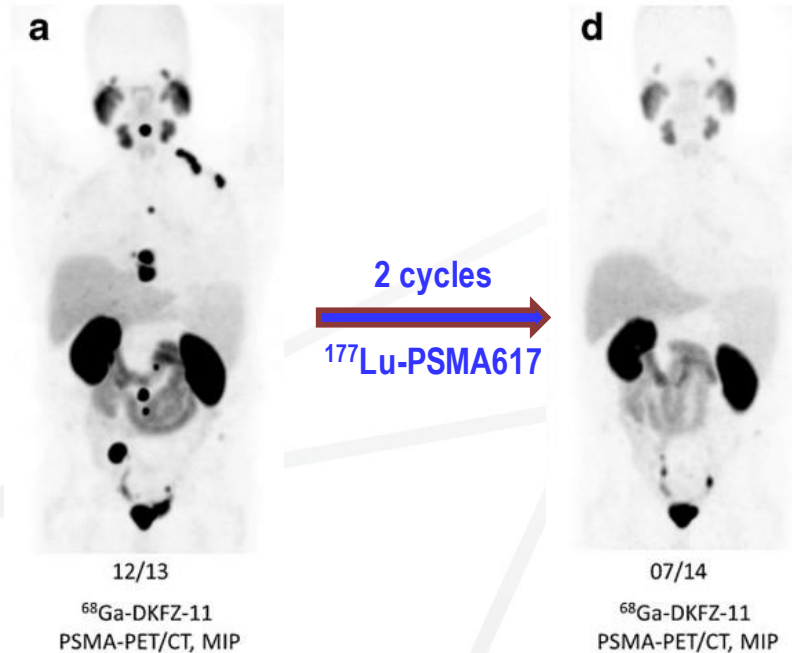


2015: retrospective data suggests high activity of ^{177}Lu



Baum R et al, 3rd World Congress in Theranostics,
John Hopkins Medical Centre, USA, **March 2015**

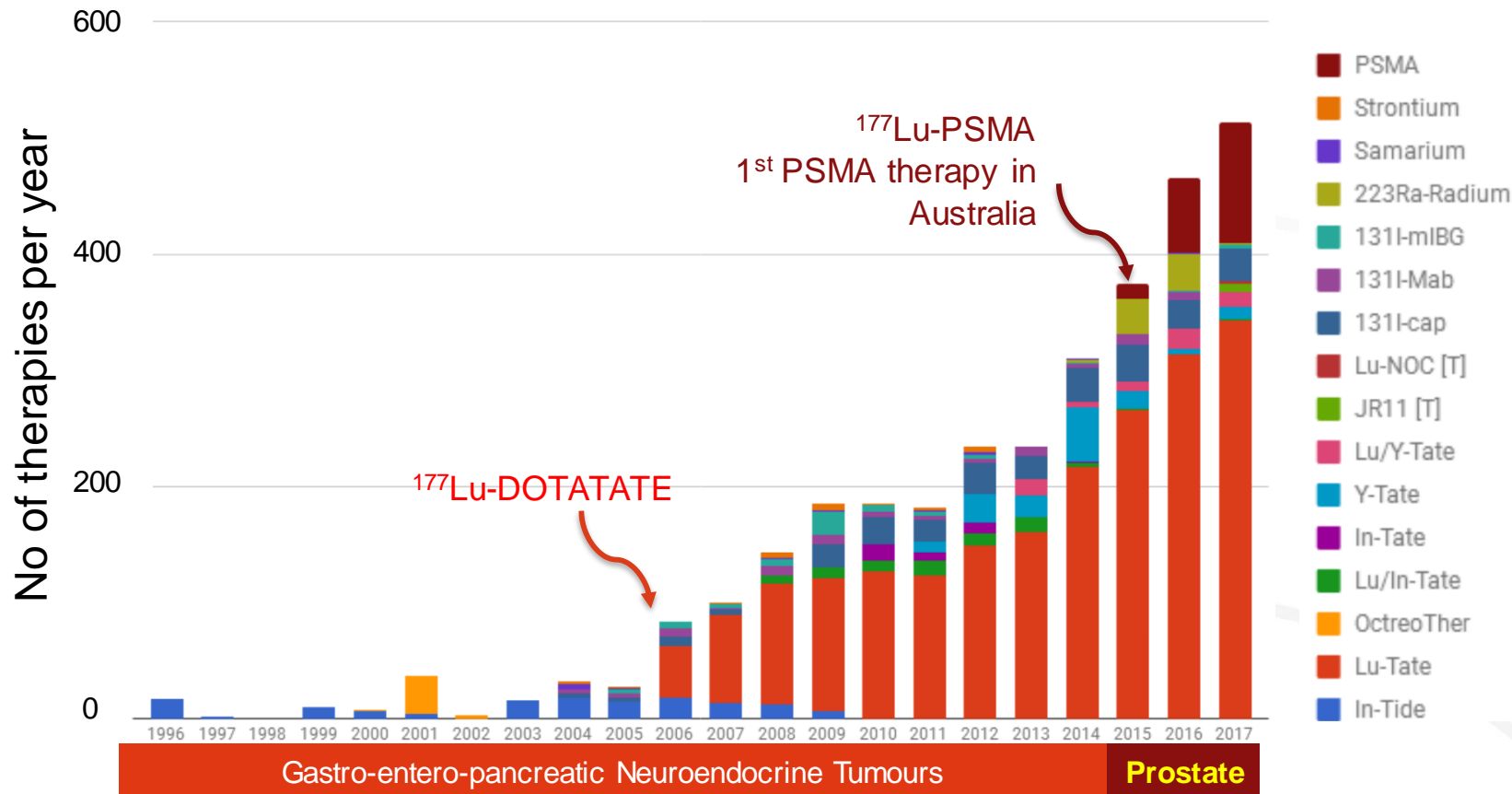
2015: 1st published report of ^{177}Lu -PSMA617



Kratochwil et al, *Eur J Nucl Med Mol Imaging* **2015**. May;42(6):987-8

DOI 10.1007/s00259-014-2978-1

Theranostics @ Peter Mac



2015-8: 1st *prospective* phase II study @ Peter Mac

Articles

www.thelancet.com/oncology Published online May 8, 2018 [http://dx.doi.org/10.1016/S1470-2045\(18\)30198-0](http://dx.doi.org/10.1016/S1470-2045(18)30198-0)

[¹⁷⁷Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

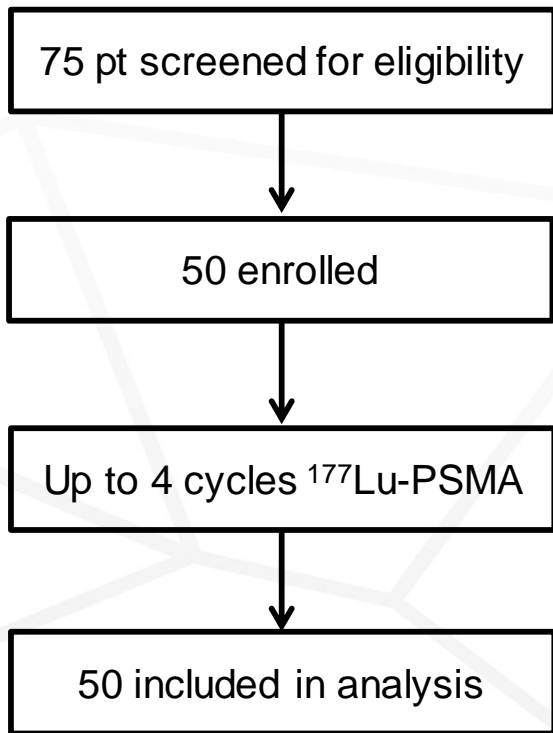


Michael S Hofman*, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu

Remarkable responses in patients who *progressed* after conventional therapies

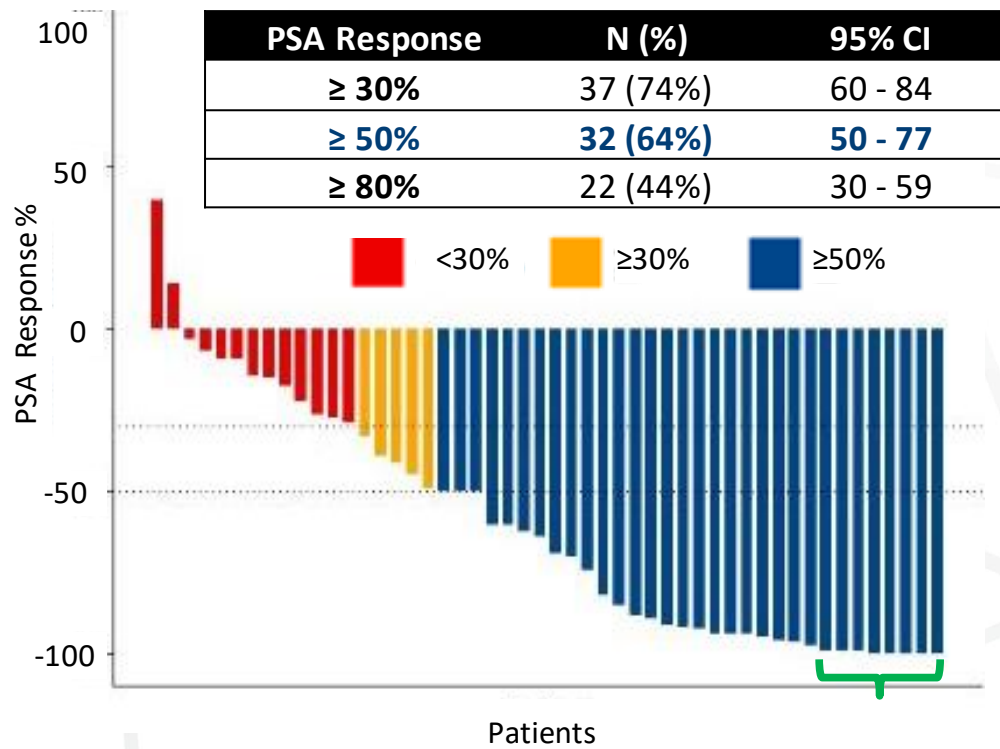
Peter Mac Phase II Baseline characteristics & schema

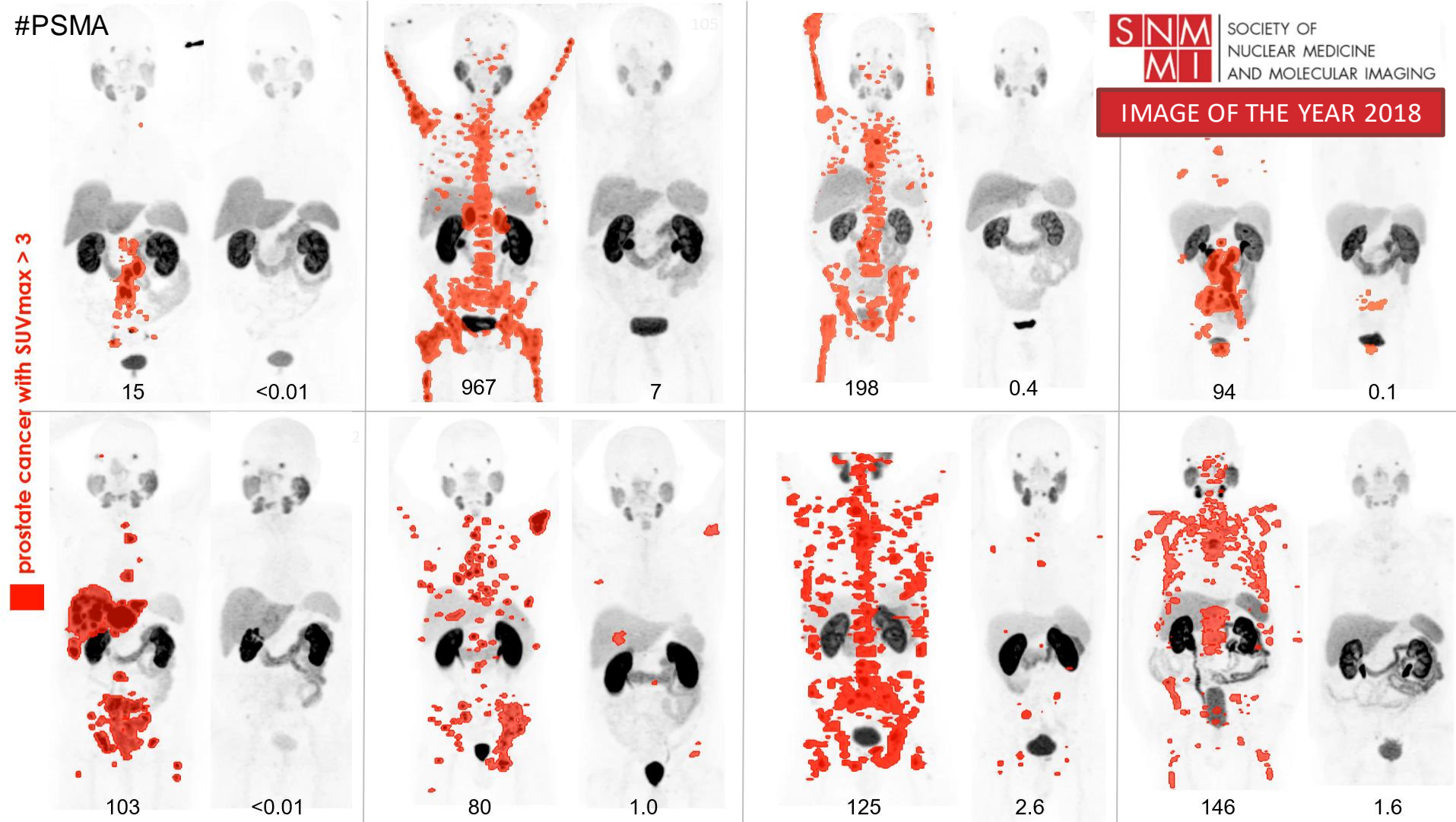
Characteristic	Median or N (%)
Age (years)	71
Alkaline phosphatase (U/L)	131
PSA (ng/mL)	189.8
PSA doubling time (ng/mL/month)	2.6
ECOG performance status	
0	20 (40%)
1	22 (44%)
2	8 (16%)
Prior treatments	
Abiraterone or enzalutamide or both	45 (90%)
Docetaxel	42 (84%)
Cabazitaxel	24 (48%)
Docetaxel + abi / enza ± Cabazitaxel	39 (78%)



median follow-up: 31.4 months

Best PSA Response (N=50)





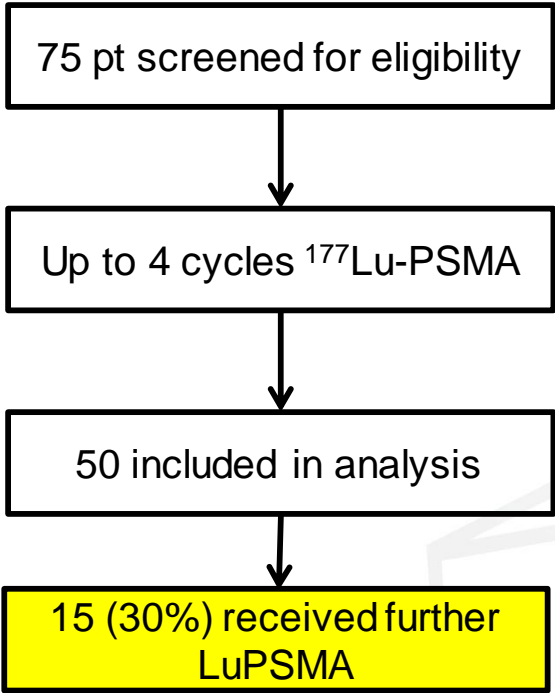
Treatment-emergent adverse events

attributable to Lu-PSMA

	1	2	3	4
Dry mouth	29 (58%)	4 (8%)	0 (0%)	0 (0%)
Lymphocytopenia	7 (14%)	13 (26%)	16 (32%)	0 (0%)
Thrombocytopenia	11 (22%)	3 (6%)	4 (8%)	1 (2%)
Fatigue	15 (30%)	3 (6%)	1 (2%)	0 (0%)
Nausea	20 (40%)	4 (8%)	0 (0%)	0 (0%)
Anaemia	3 (6%)	6 (12%)	5 (10%)	0 (0%)
Neutropenia	6 (12%)	6 (12%)	3 (6%)	0 (0%)
Bone Pain	5 (10%)	4 (8%)	0 (0%)	0 (0%)
Vomiting	11 (22%)	2 (4%)	0 (0%)	0 (0%)
Anorexia	8 (16%)	0 (0%)	0 (0%)	0 (0%)
Dry eyes	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Renal injury*	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Weight loss	3 (6%)	1 (2%)	0 (0%)	0 (0%)

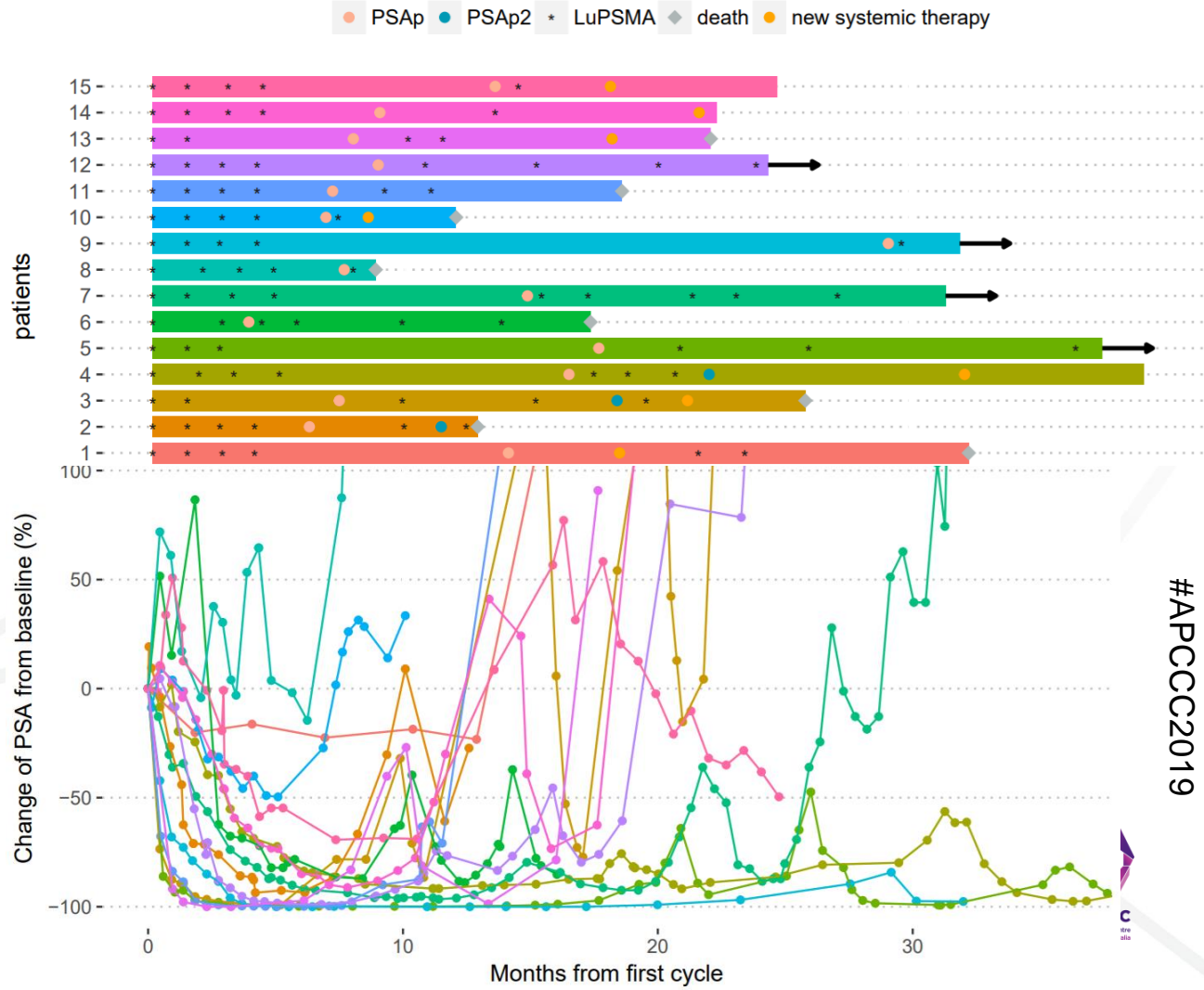
*⁵¹Cr-EDTA GFR measured 3 months after completion of ¹⁷⁷Lu-PSMA-617
in 28 pt demonstrated mean decline of -11.7 mL/min (95% CI -19 to -4)

Lu-PSMA re-treatment

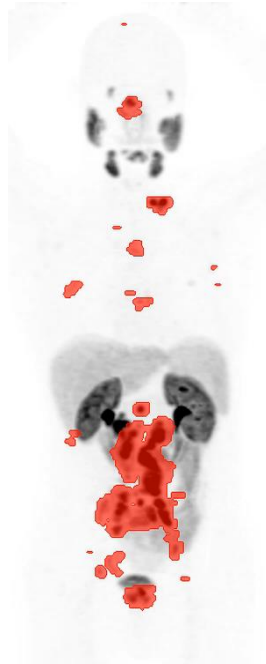


PSA ≥50% response: 73%

Hofman MS et al (unpublished)

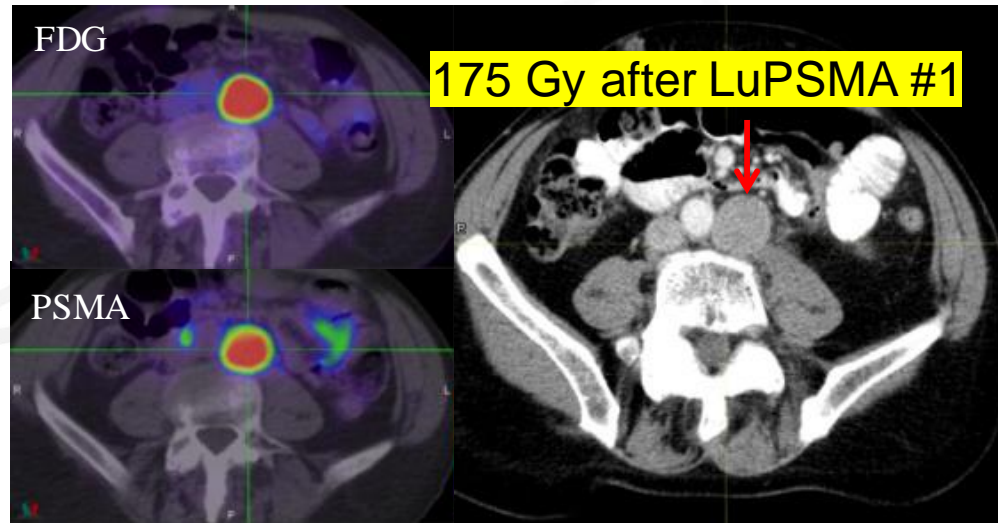


69yo progressed after docetaxel, enzalutamide, abiraterone & cabazitaxel

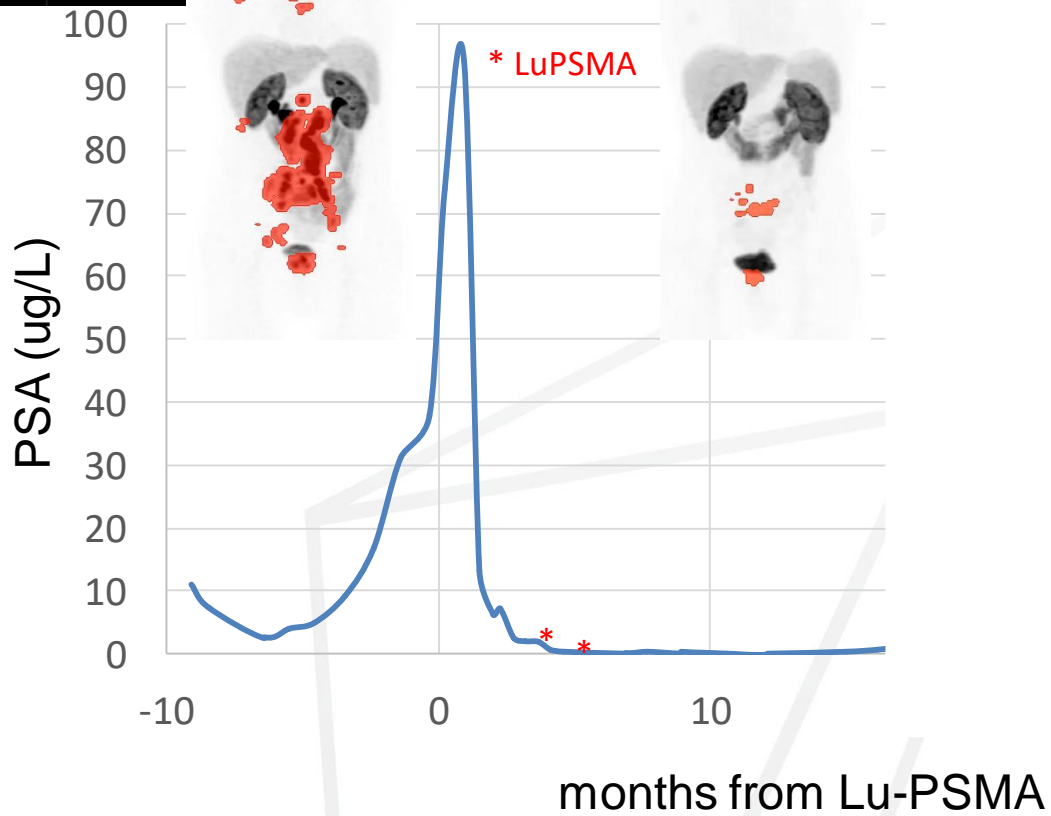
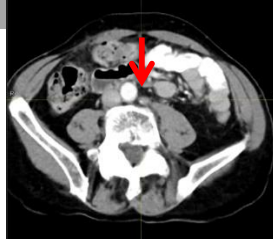
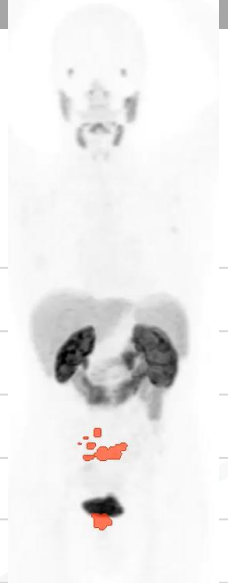


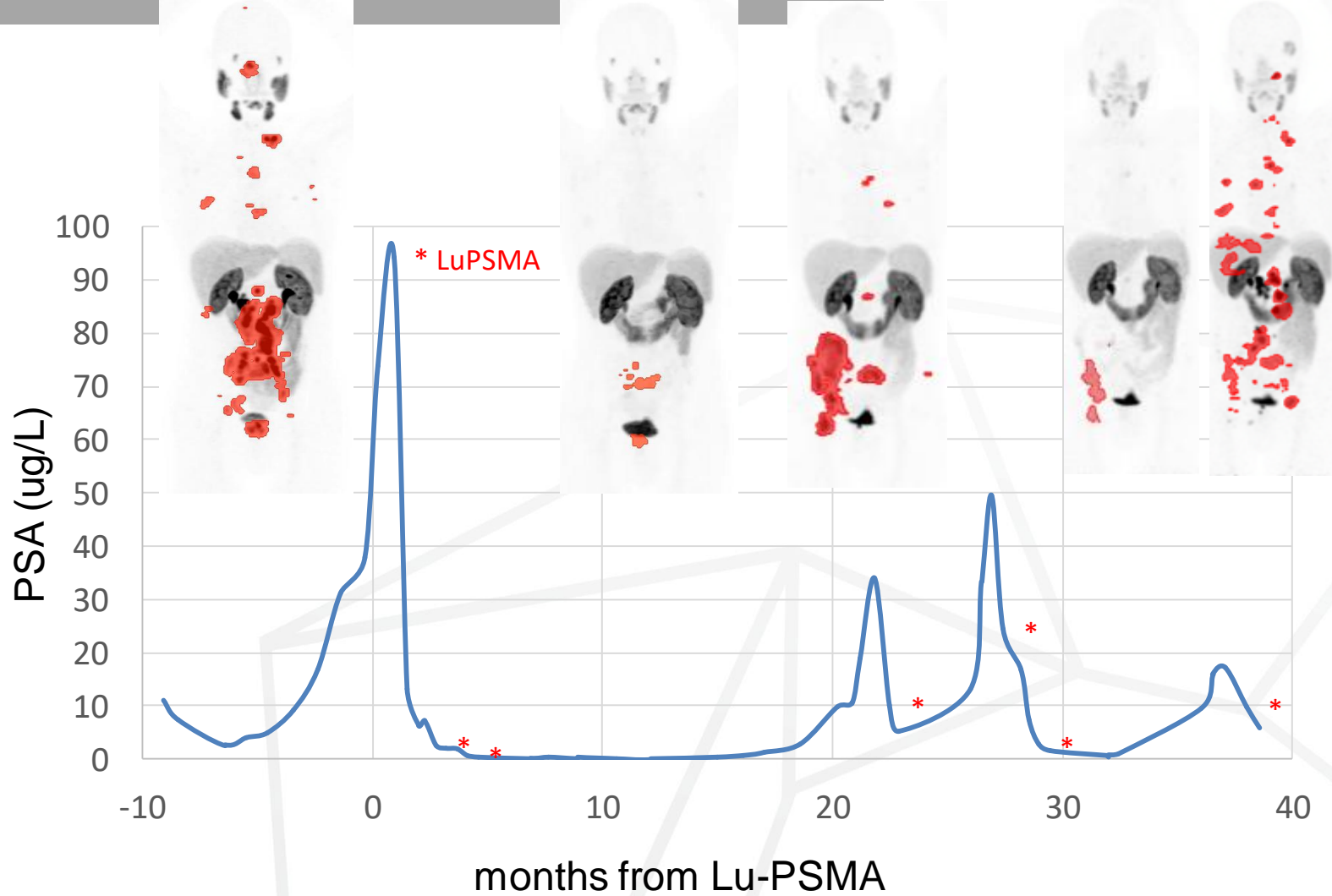
PSMA PET
baseline

baseline

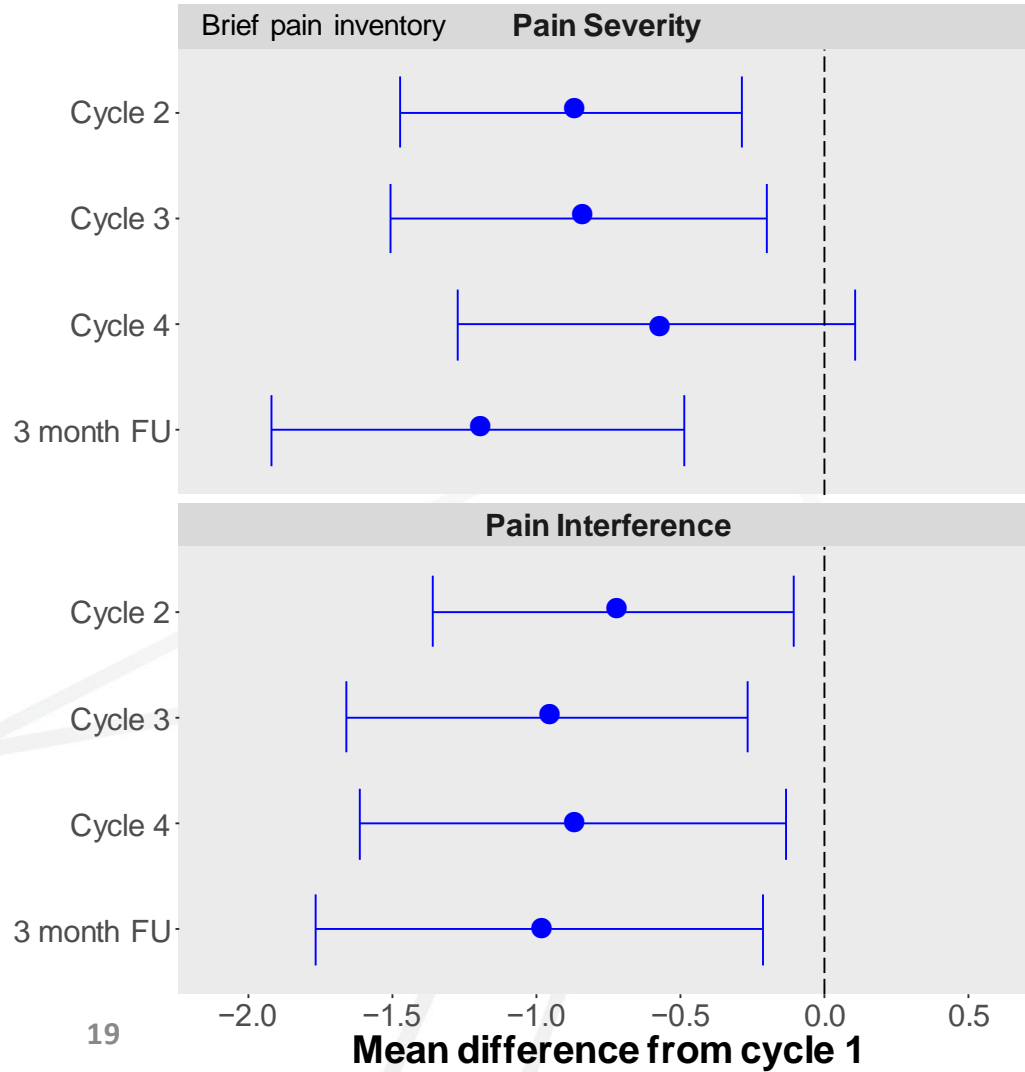


175 Gy after LuPSMA #1

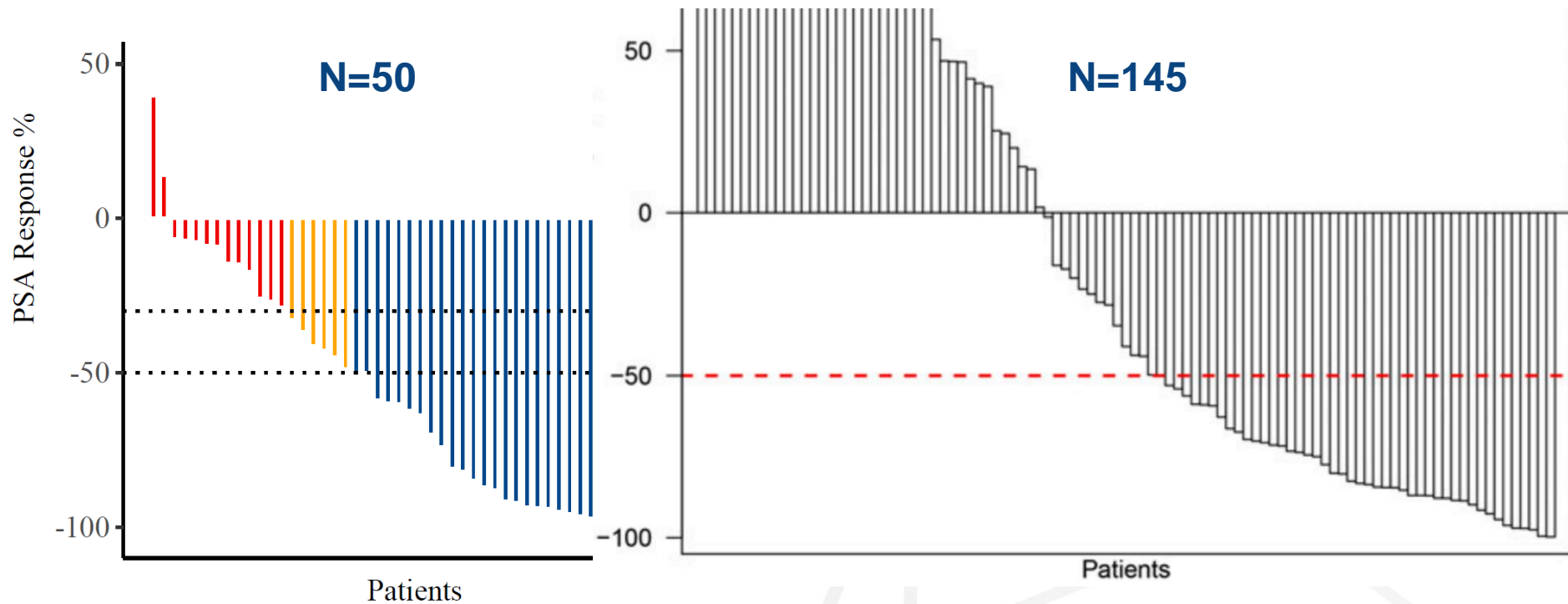




↑QoL



How do our results compare to others?



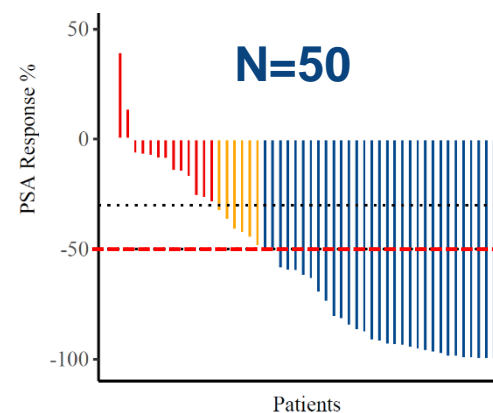
PSA $\geq 50\%$ in 64%

Hofman MS et al

PSA $\geq 50\%$ in 45%**

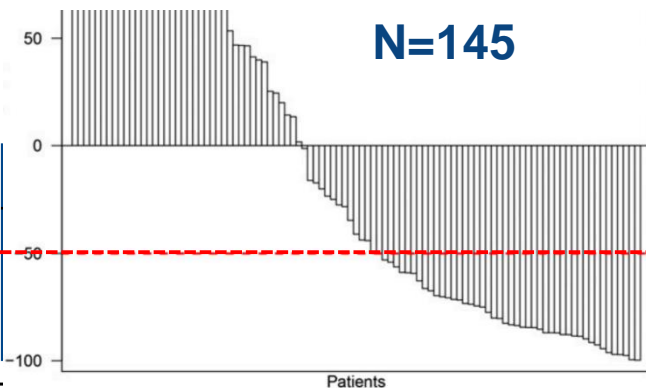
Rahbar K et al

46 pt had PSA follow-up less than 8 wk



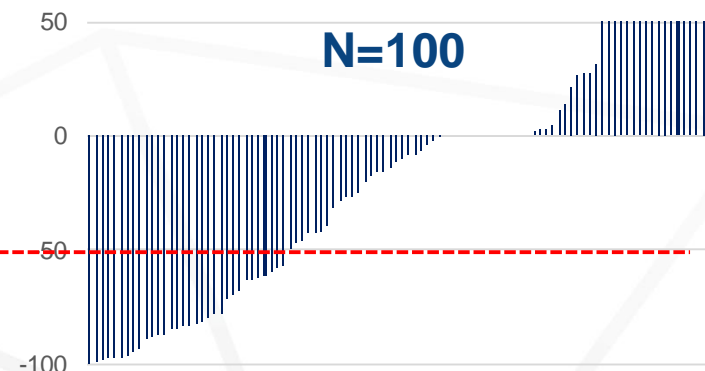
PSA $\geq 50\%$ in 64%

Hofman MS et al



PSA $\geq 50\%$ in 45%

Rahbar K et al

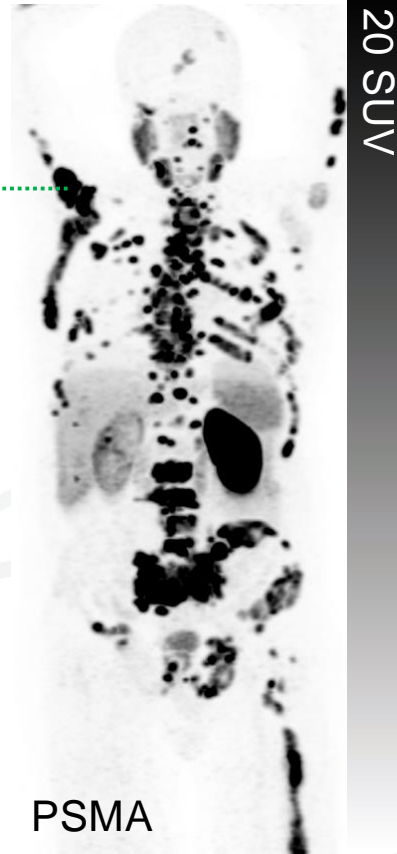


PSA $\geq 50\%$ in 32%

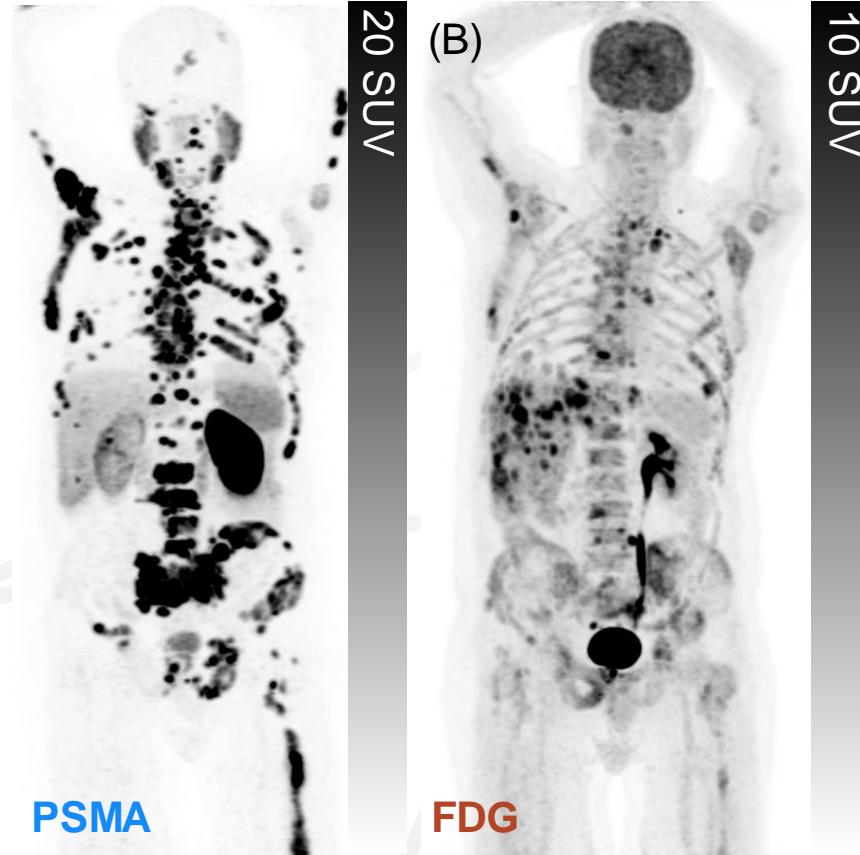
Heck et al

Is this patient suitable?

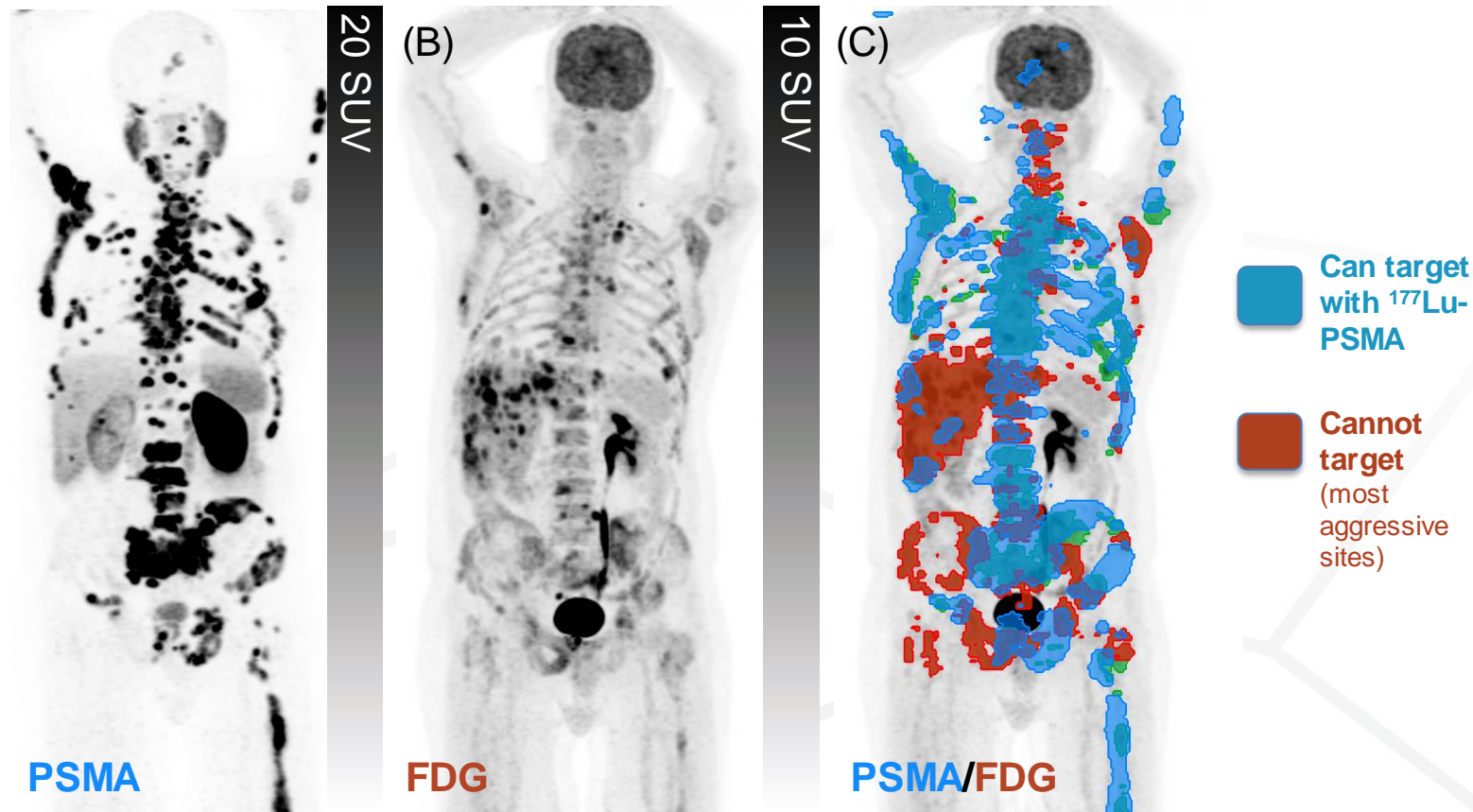
SUVmax 70



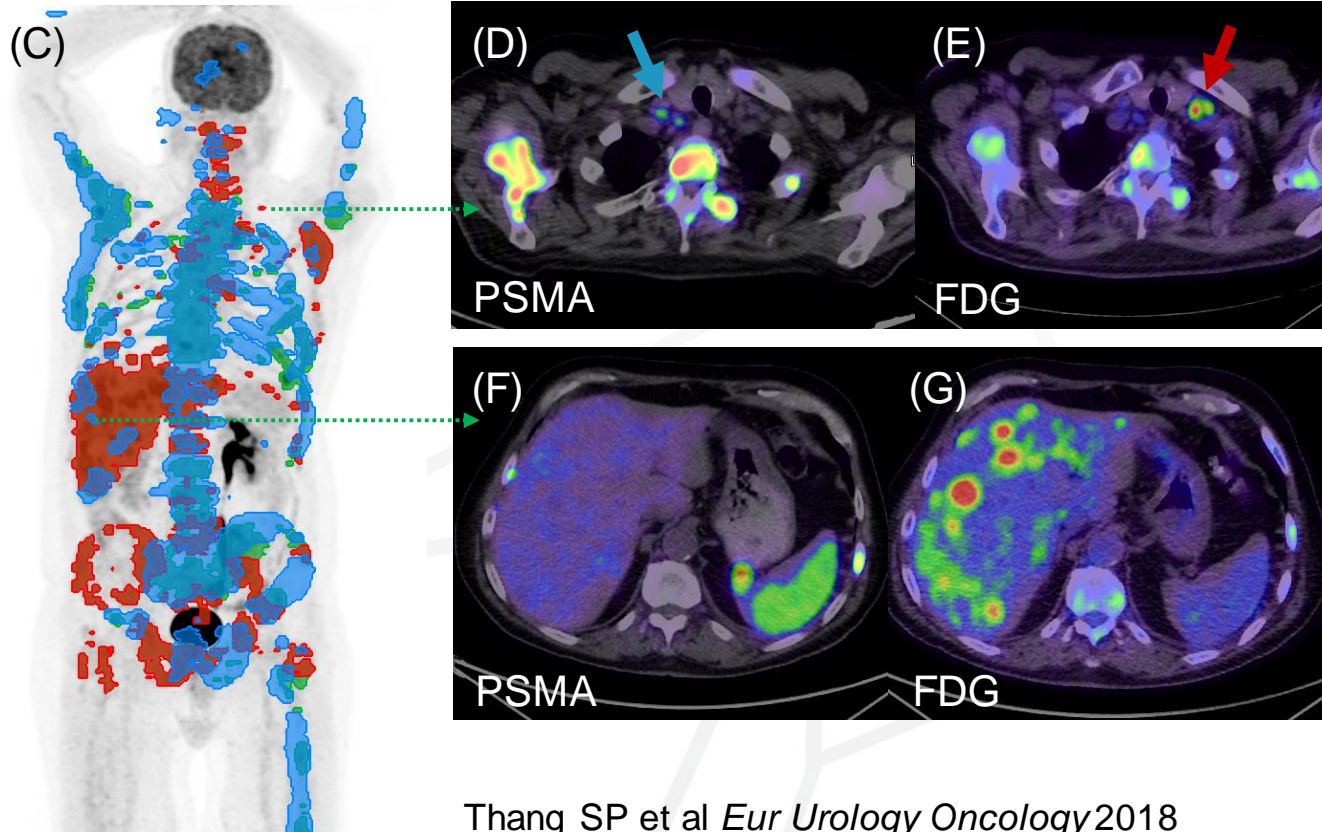
FDG PET: see something different



FDG+ PSMA- disease in liver (& bone)

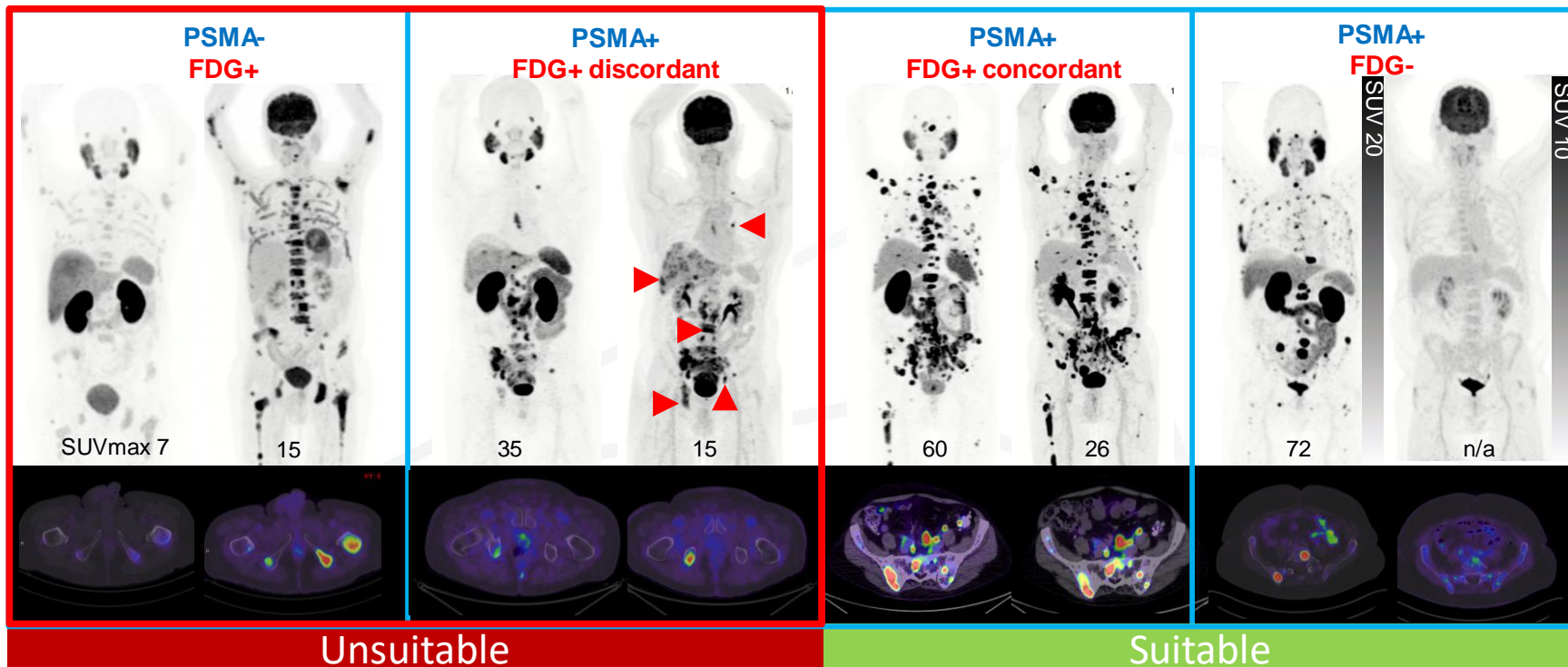


Disease heterogeneity: what does it mean?



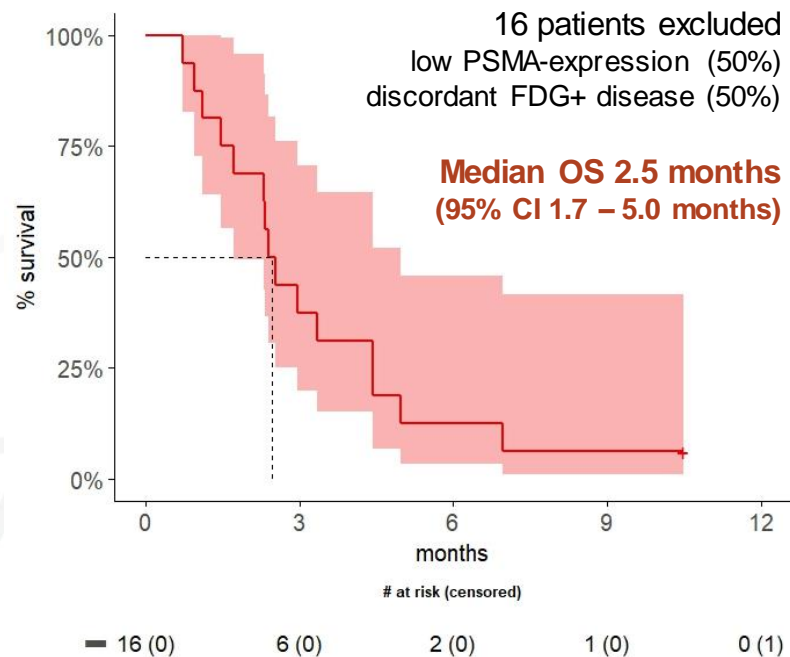
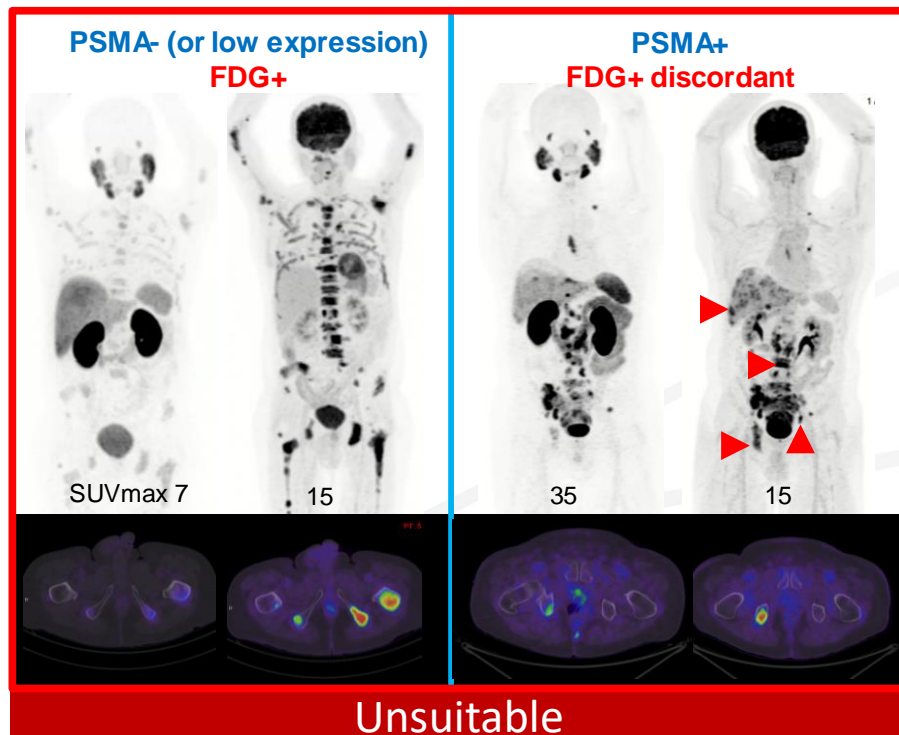
Thang SP et al *Eur Urology Oncology* 2018

PSMA/FDG phenotypes



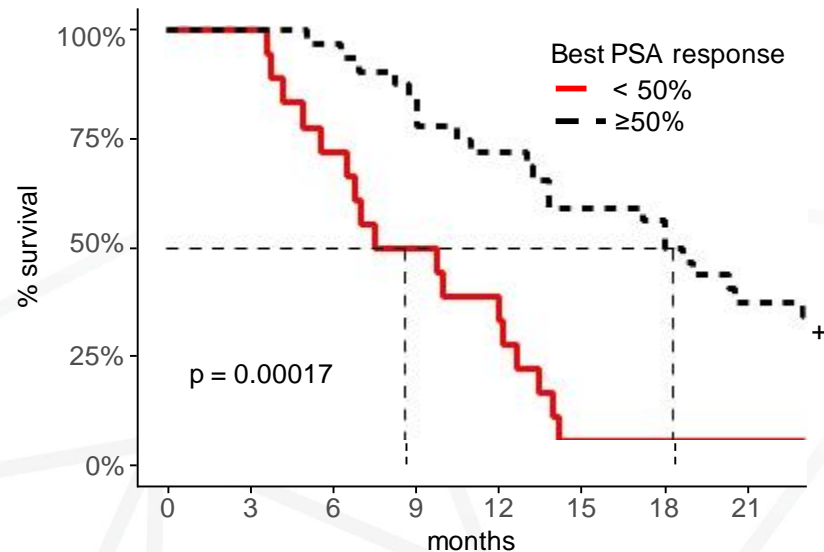
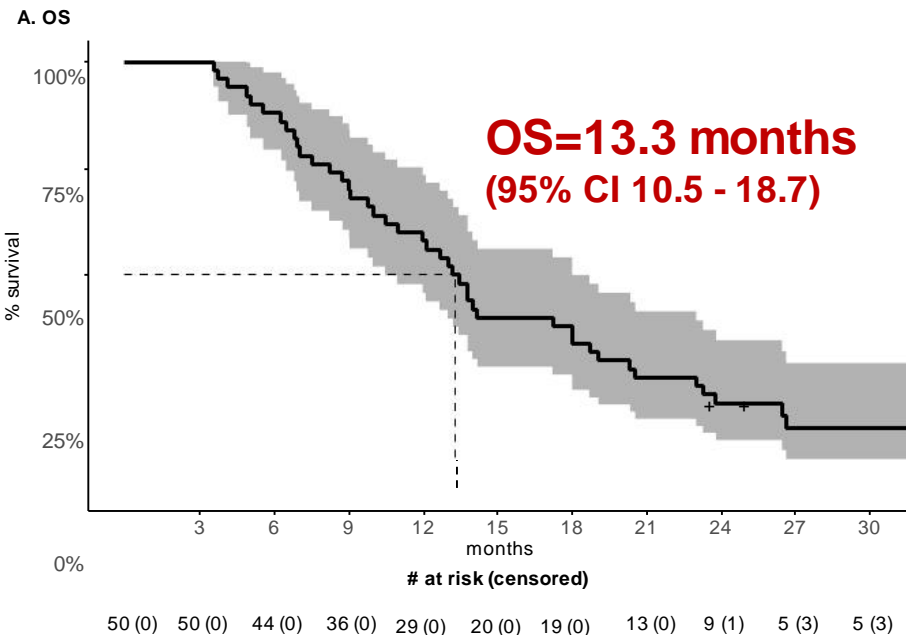
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What happened to the patients *we didn't treat*?



Thang SP et al *Eur Urology Oncology* 2018

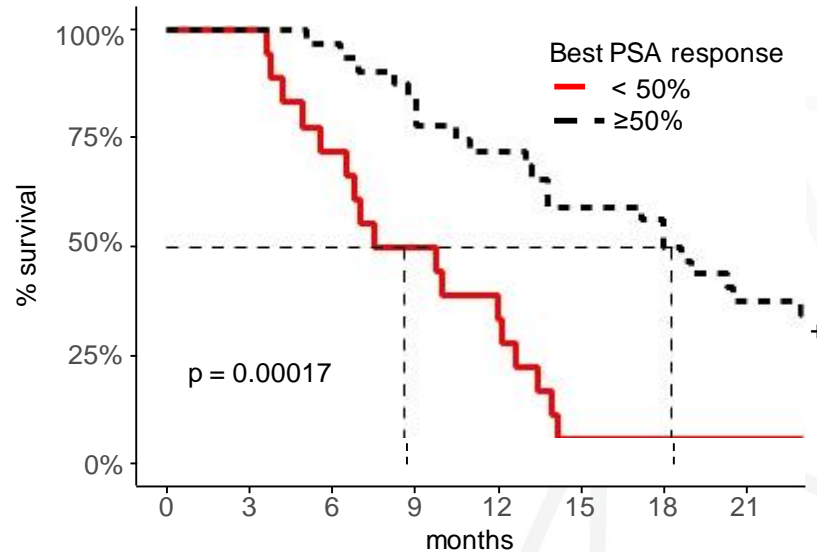
Overall survival (n=50)



PSA ≥ 50%: 18.4 months (95% CI 13.8 – 23.8)

PSA < 50%: 8.7 months (95% CI 6.5 to 13.4)

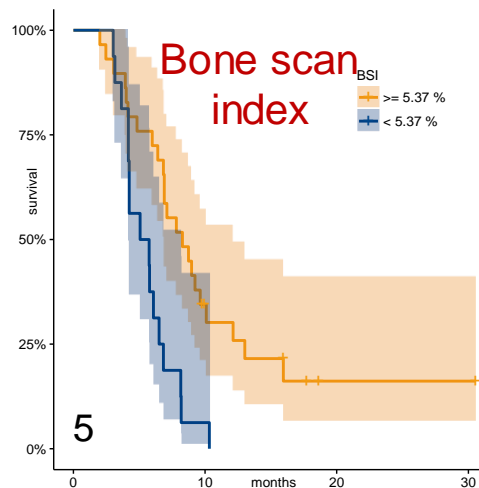
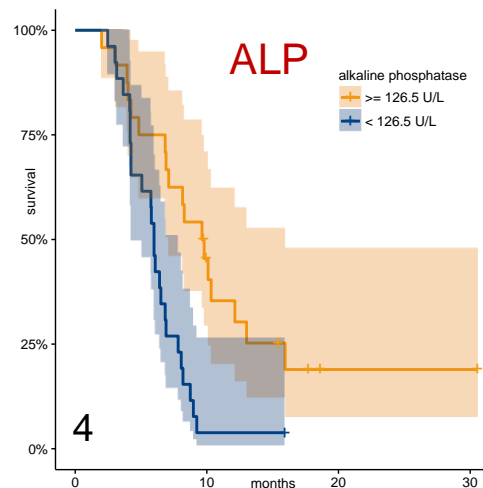
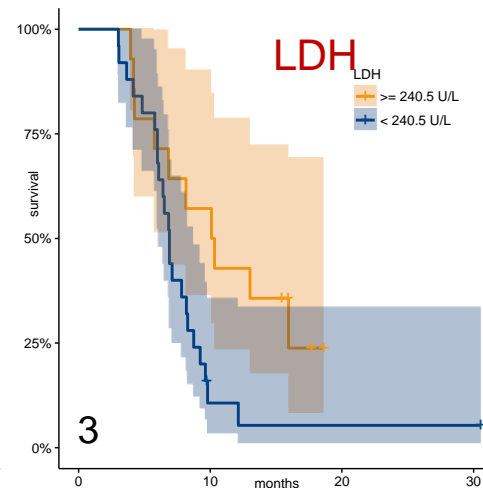
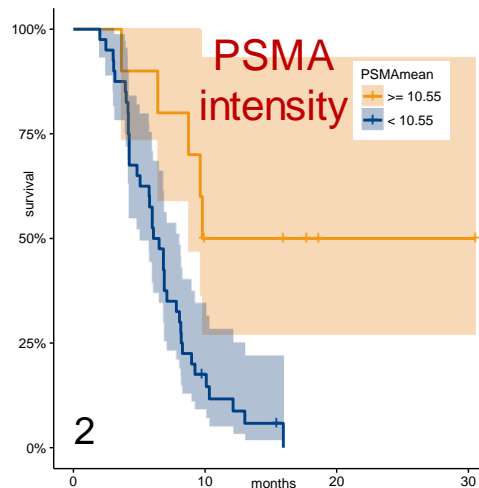
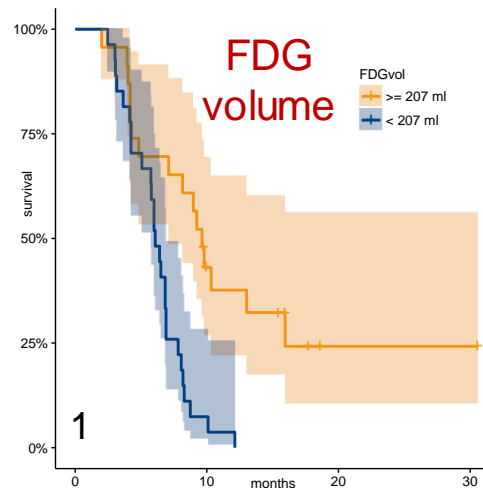
PSA \geq 50%: significantly longer overall survival



PSA \geq 50%: 18.4 months (95% CI 13.8 – 23.8)

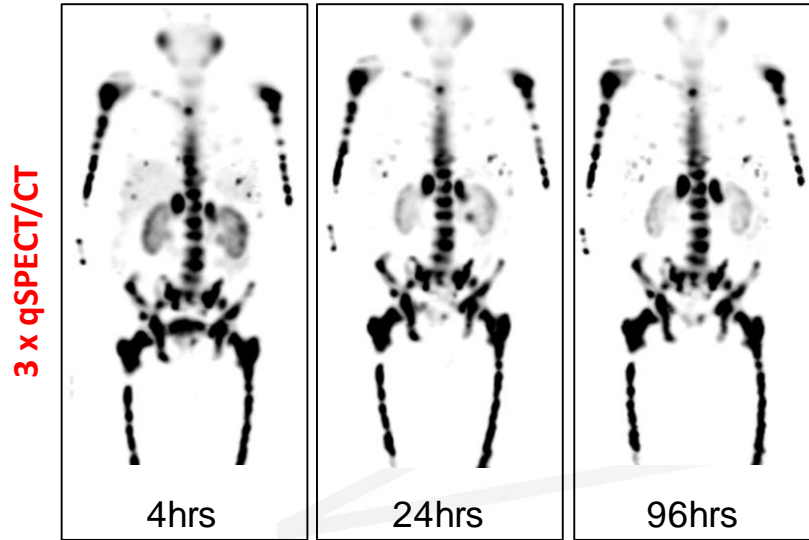
PSA<50%: 8.7 months (95% CI 6.5 to 13.4)

Prognostic markers with Lu-PSMA



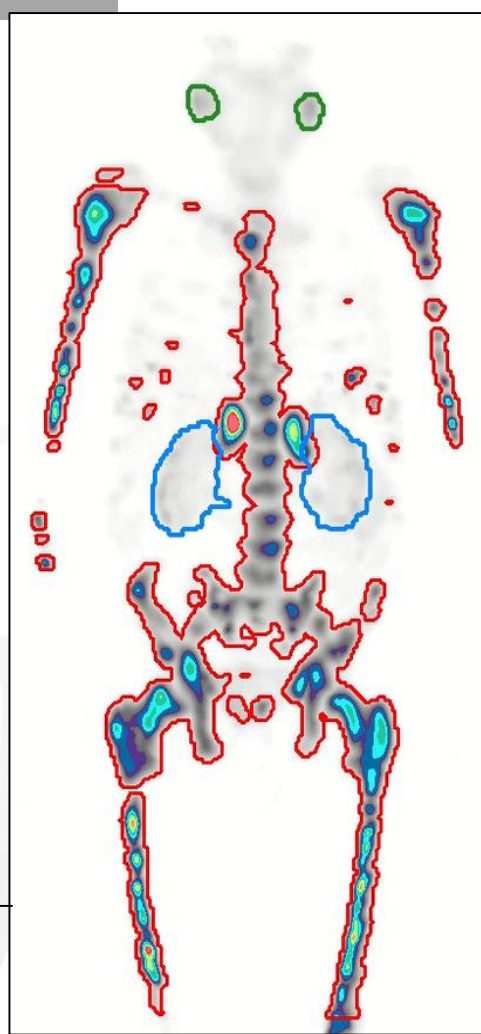
- 1: Whole-body FDG volume**
 Cut-off : 207 ml
 Median OS: 6.1 vs 9.6 months ($p < 0.001$)
- 2: Whole-body PSMA SUVmean**
 Cut-off : 10.3
 Median OS: 9.8 vs 6.3 months ($p = 0.002$)
- 3: Lactate dehydrogenase**
 Cut-off : 240.5 U/L
 Median OS: 6.9 vs 10.2 months ($p = 0.03$)
- 4: Alkaline phosphatase**
 Cut-off : 126.5 U/L
 Median OS: 6.0 vs 9.7 months ($p < 0.001$)
- 5: EXINI Bone Scan Index (%)**
 Cut-off : 5.37 %
 Median OS: 5.4 vs 8.3 months ($p = 0.002$)

Theranostics: we can quantify radiation dose (“dosimetry”)

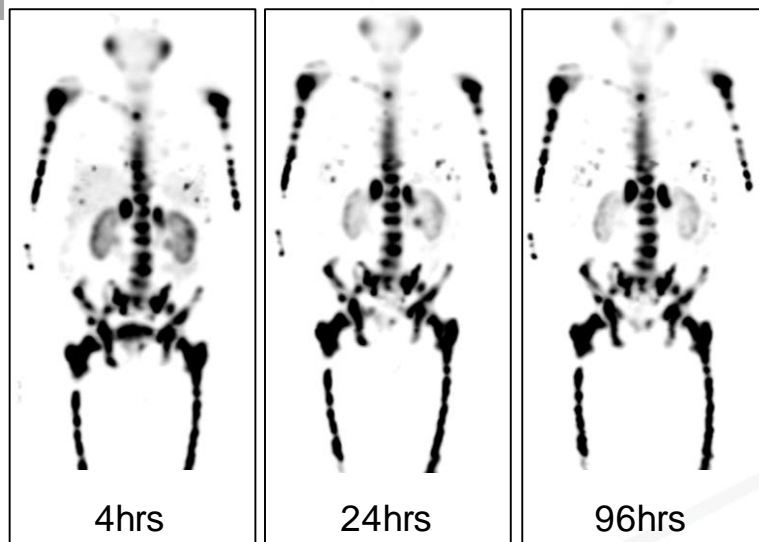


Violet J ... Hofman MS, JNM 2019

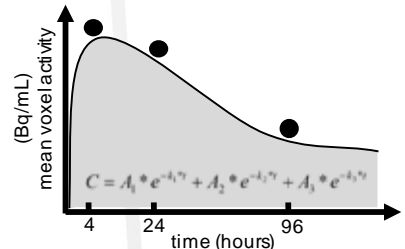
50 Gy Dose in Gy (tumour and normal tissue)



$2 \times 10^6 \text{Bq/mL}$



CT-CT deformable image registration

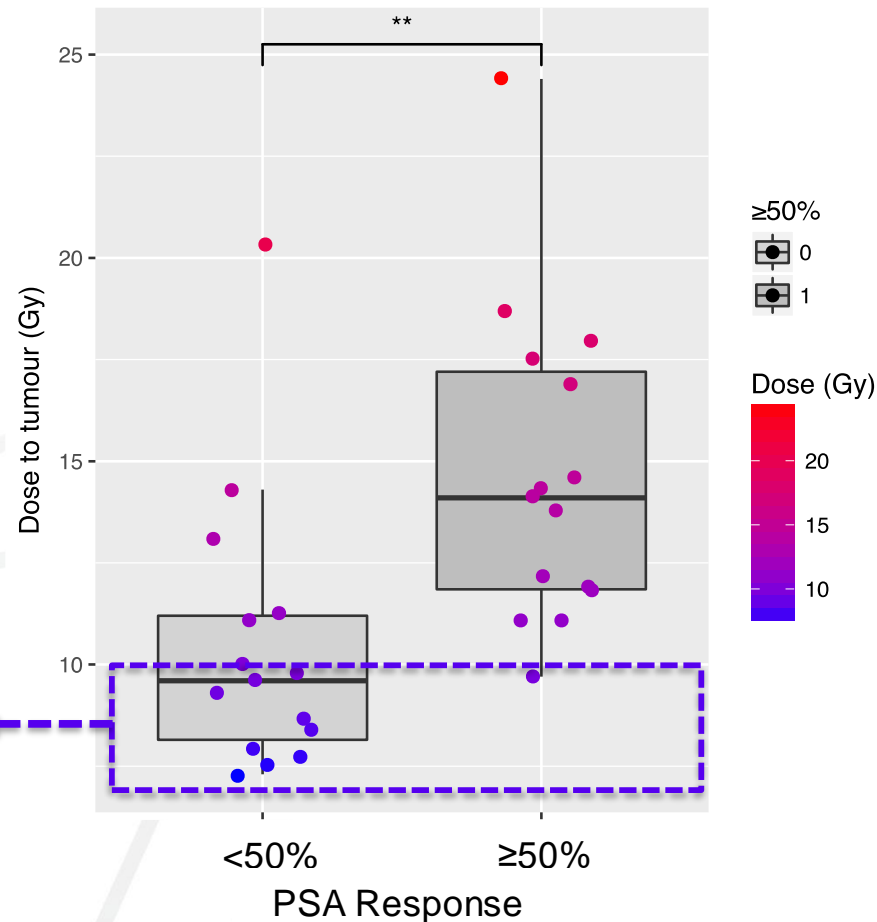


voxelised kinetics

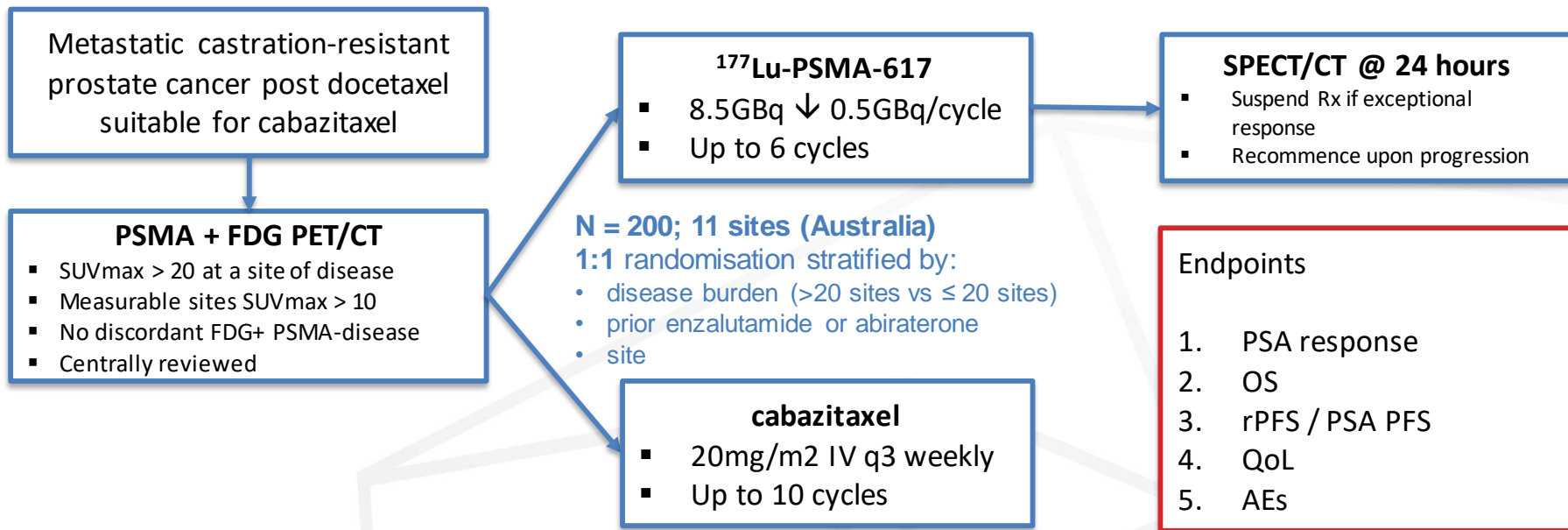
3 x qSPECT/CT

“Whole body” tumour dose correlates with PSA response @ 12 weeks

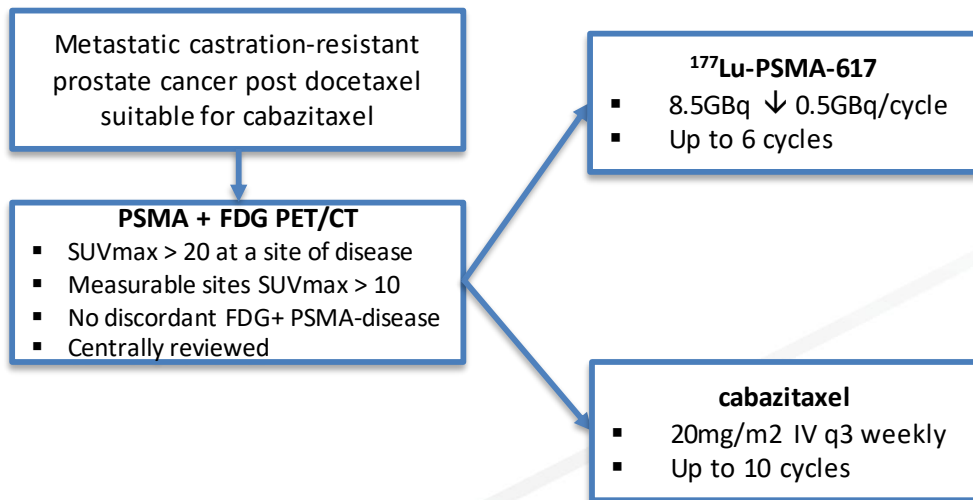
<10 Gy:
10 non-responders
1 responder



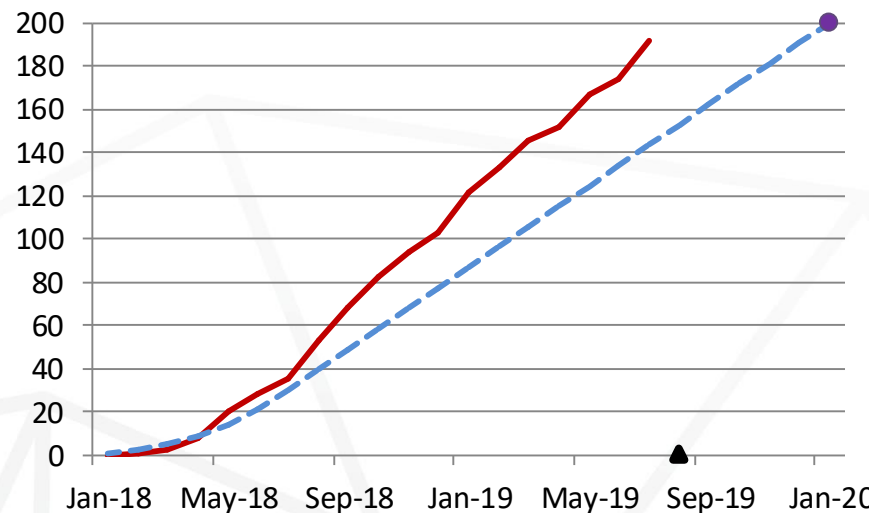
TheraP Trial: ^{177}Lu -PSMA-617 vs. cabazitaxel



TheraP Trial: ^{177}Lu -PSMA-617 vs. cabazitaxel



Patients randomised



1 more patient to recruit !

<https://clinicaltrials.gov/ct2/show/NCT03392428>

Australian Sponsor: ANZUP

Study Chair: Prof Michael Hofman

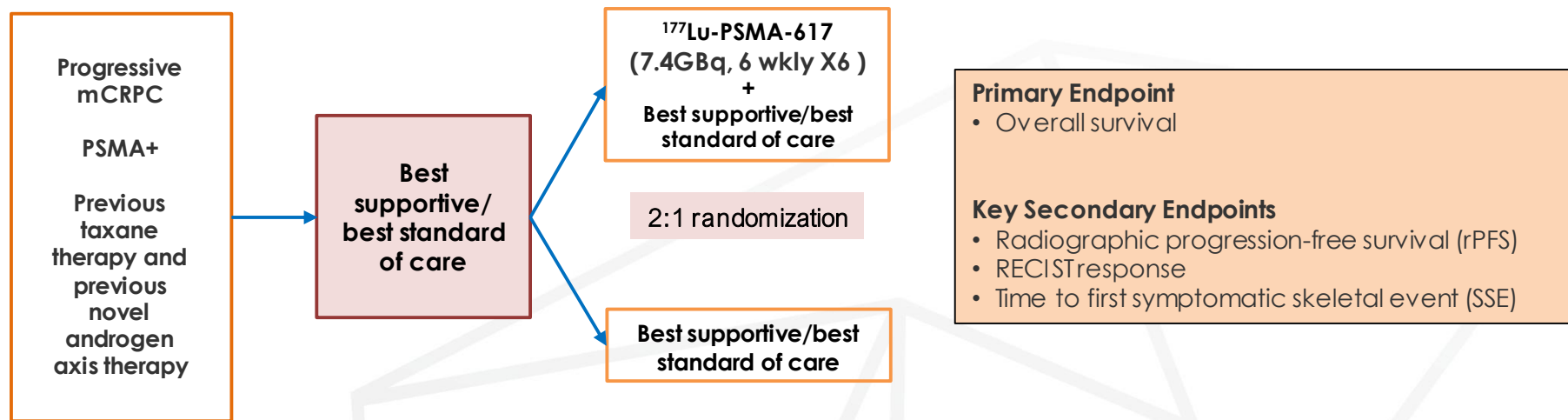
Co-ordinating Centre: NHMRC Clinical Trials Centre

Collaborative Group Chair: Prof Ian Davis

Funding: Prostate Cancer Foundation of Australia (PCFA), Endocyte, ANSTO, Movember

Senior Statistician: Dr Andrew Martin | CTC Clinical Lead: Prof Martin Stockler

VISION Trial: ^{177}Lu -PSMA versus best supportive care



- 9 Countries (NA and EU)
- >750 patients recruited
- 12-14 months FU min 15 month

PRINCE Trial

PSMA-lutetium Radionuclide therapy and ImmuNotherapy in prostate CancEr

@UCSFImaging
NCT03805594
Dr Rahul Aggarwal
Dr Tom Hope

- Metastatic CRPC
- Progressed after enzalutamide, abiraterone or apalutamide

PSMA + FDG PET/CT

Pembroluzimab 200mg
3 weekly

+

^{177}Lu -PSMA-617
6 weekly, 4 cycles
Day 4 \pm 2 days
8.5 GBq, \downarrow 0.5 GBq/cycle

BaCT
Prostate Cancer Therapeutics and Clinical Trials



ANSTO

MERCK
INVENTING FOR LIFE

ENDOCYTE
A Novartis Company

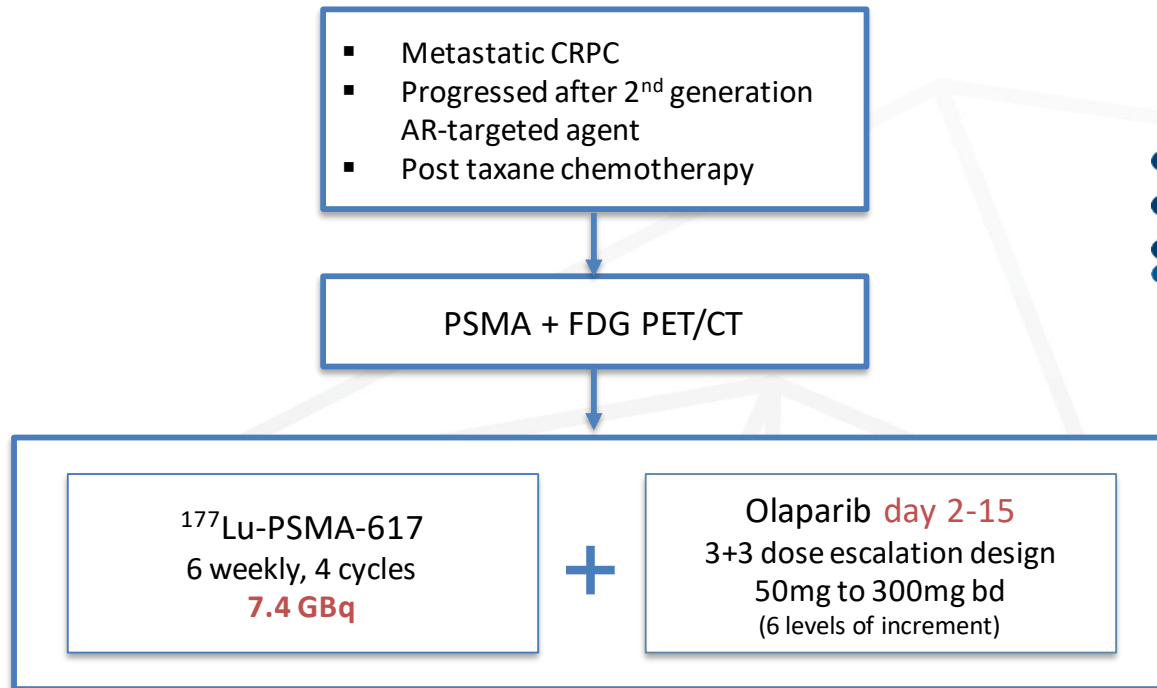
Victorian
Cancer
Agency
Linking research and patient care



clinicaltrials.gov: NCT03658447
PI: A/Prof Shahneen Sandhu

LuPARP Trial

Phase 1 trial of ^{177}Lu -PSMA-617 therapy and Olaparib (PARPi)



Prostate Cancer
Foundation
Curing Together.



ENDOCYTE
A Novartis Company



AstraZeneca



ANSTO



BaCT
Centre for Biostatistics and Clinical Trials



clinicaltrials.gov: NCT03874884
PI: A/Prof Shahneen Sandhu

#UpFrontPSMA: high-volume metastatic hormone naïve PC

ARM A (n = 70)
Upfront Lu-PSMA x 2-3 + ADT
followed by Docetaxel x 6

De novo High-Volume mHNPc

- ≥ 4 bone mets with ≥ 1 extra-axial AND/OR
- Visceral mets

ARM B (n = 70)
ADT + Docetaxel x 6



Primary endpoint: undetectable PSA at 12 months



PI: A/Prof Arun Azad



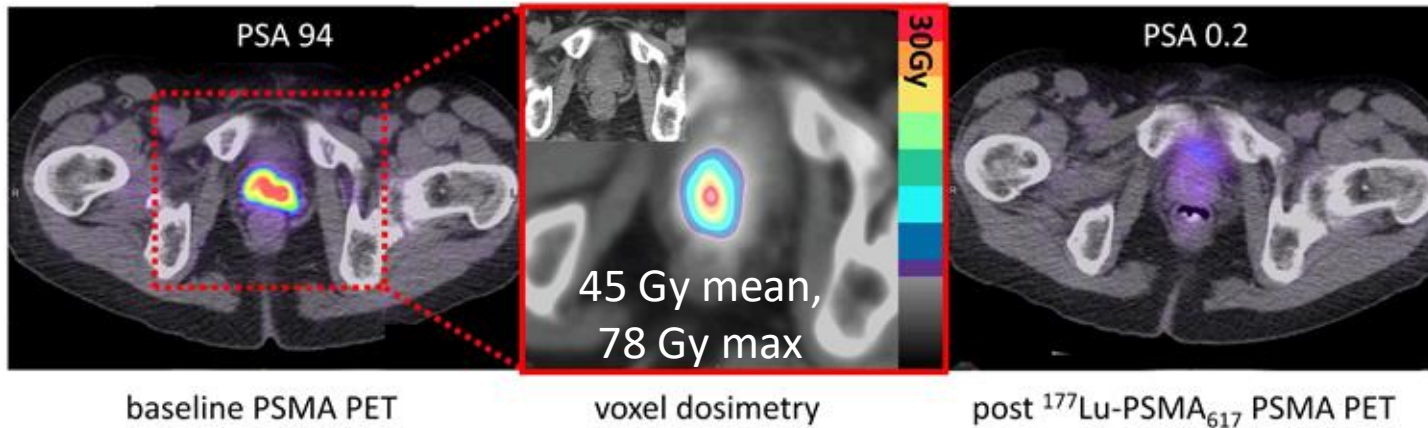
Statistical assumptions

- P1 0.5, P2 0.25
- 2-sided $\alpha=0.05$, $\beta=0.8$

#LuTectomy: ^{177}Lu -PSMA prior to surgery

Hofman et al [unpublished]

GG9 post docet, abi,
enza & cabazitaxel



**High-risk localised
prostate cancer ± N1**

High PSMA Expression

^{177}Lu -PSMA
x 1-2 cycles

At 6-8 weeks:

- Prostatectomy +
pelvic LN dissection

Correlative samples

- Tumour tissue
- PBMCs
- ctDNA, serum

Primary endpoints:

- Dosimetry

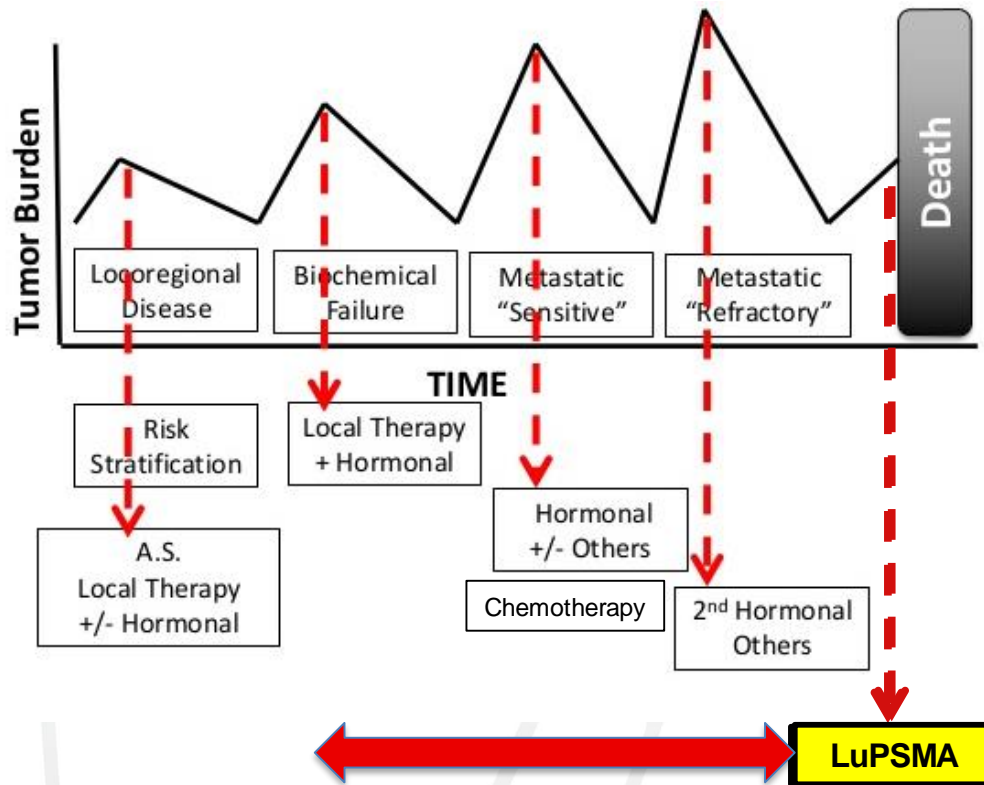
Key Secondary endpoints

- Safety
- PSMA PET Response



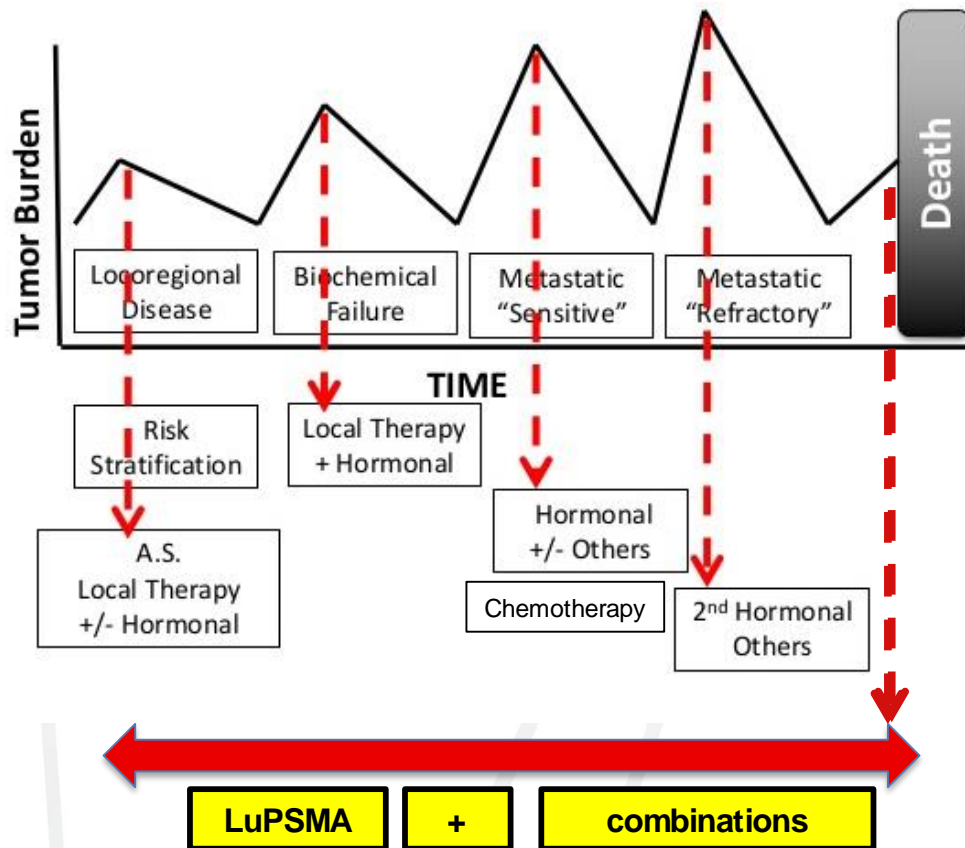
PI: Prof Declan Murphy

^{177}Lu -PSMA shows promise: can it be used earlier?



^{177}Lu -PSMA shows promise: can it be used earlier?

+/- combined with other therapies?





Thank-you #GoNuclear



Molecular Imaging | Nuclear Medicine

- Rod Hicks (Director)
- Amir Iravani, Aravind Ravi Kumar, Grace Kong, Tim Akhurst, Ramin Alipour (Nuc Med “Dream Team”)
- A/Prof Louise Emmett (St Vs, Sydney)
- Peter Eu (Radiopharmacist)
- Mark Scalzo (Lead Technologist)
- Price Jackson (Medical Physicist)

Uro-oncology Multi-Disciplinary Team

- Scott Williams, John Violet, Shankar Siva (Rad Onc)
- Shahneen Sandhu, Arun Azad, Ben Tran (Med Onc)
- Declan Murphy, Nathan Lawrentschuk (Urology)
- Gail Risbringer (Laboratory Research)



Funding partners (alphabetical order)

- ANSTO (^{177}Lu)
- Cancer Australia
- Endocyte / AAA (Novartis)
- Movember
- Peter MacCallum Foundation
- Prostate Cancer Foundation (PCF)
- Prostate Cancer Foundation of Australia (PCFA)
- Victorian Cancer Agency (VCA)

Collaborative partners

- ANZUP Prof Ian Davis | Margaret McJannett
- ARTnet A/Prof Ros Francis
- BaCT
- NHMRC CTC
- PropPSMA & TheraP investigators

