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PSMA targeted therapy in cRMPC

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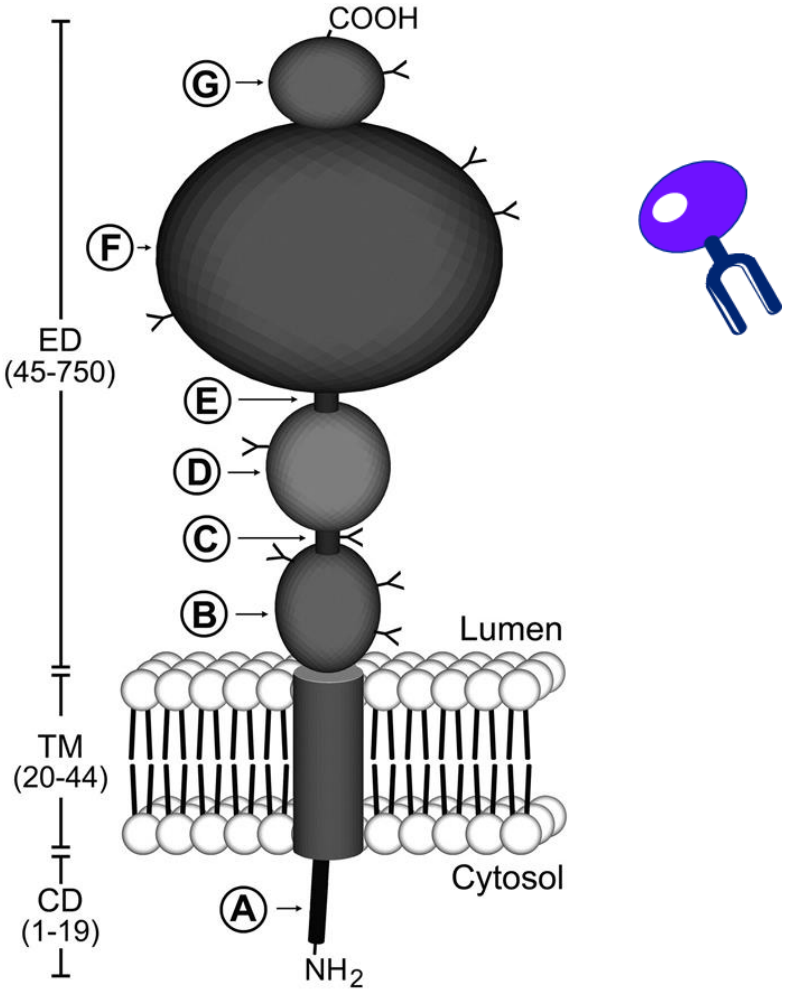
PSMA as a potential tumor-associated target

Prostate specific membrane antigen (PSMA)



expression

- Membrane bound glykoprotein
- Detectable on normal prostate cells
- Significantly increased (100x) expression on prostate cancer cells
- Expression rate increases with grade of differentiation and progression (aggressiveness)

enzymatic activity

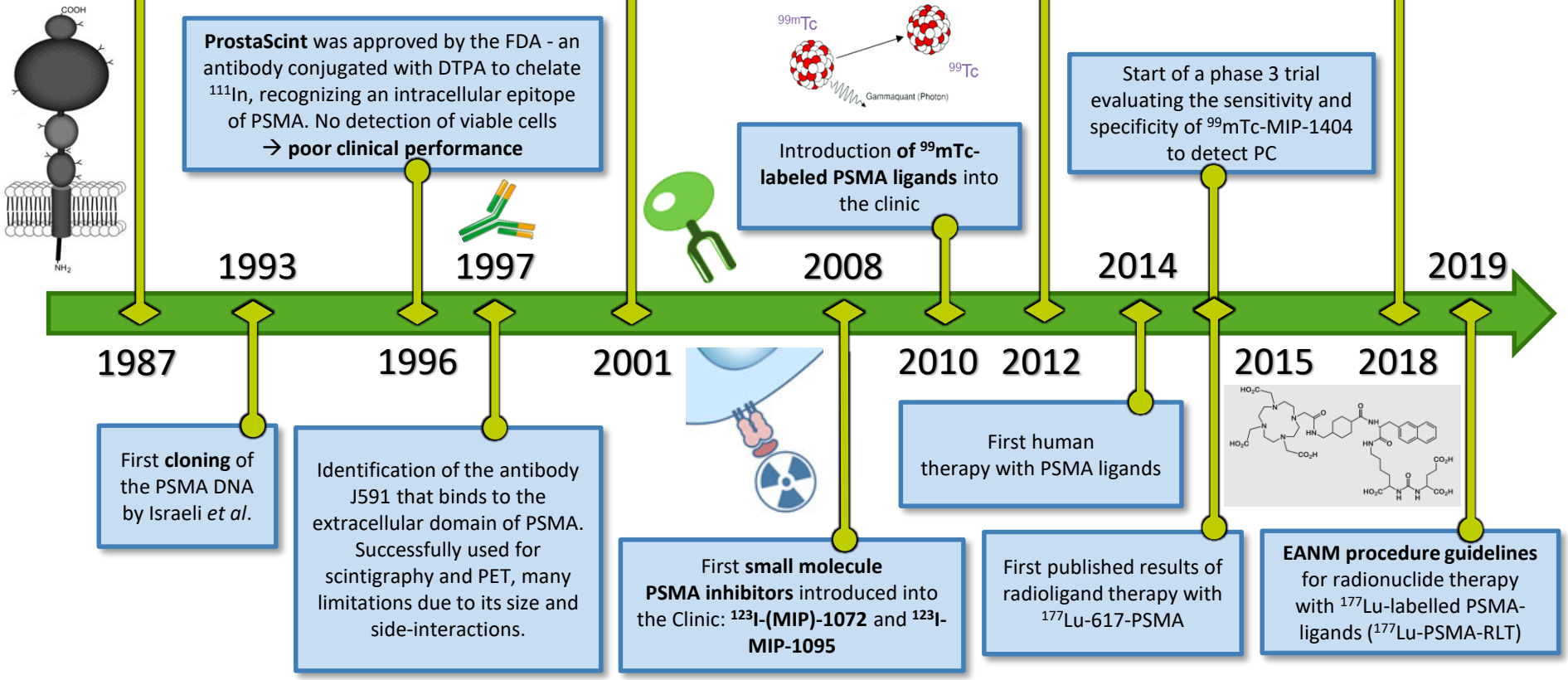
PSMA has a c-terminal glutamate Carboxypeptidase II and folate hydrolase I activity; it catalyses hydrolysis of N-acetylaspartylglutamat to glutamate and N-acetylaspartate.

function

-Maintenance of cellular homeostasis
- Migration of cells

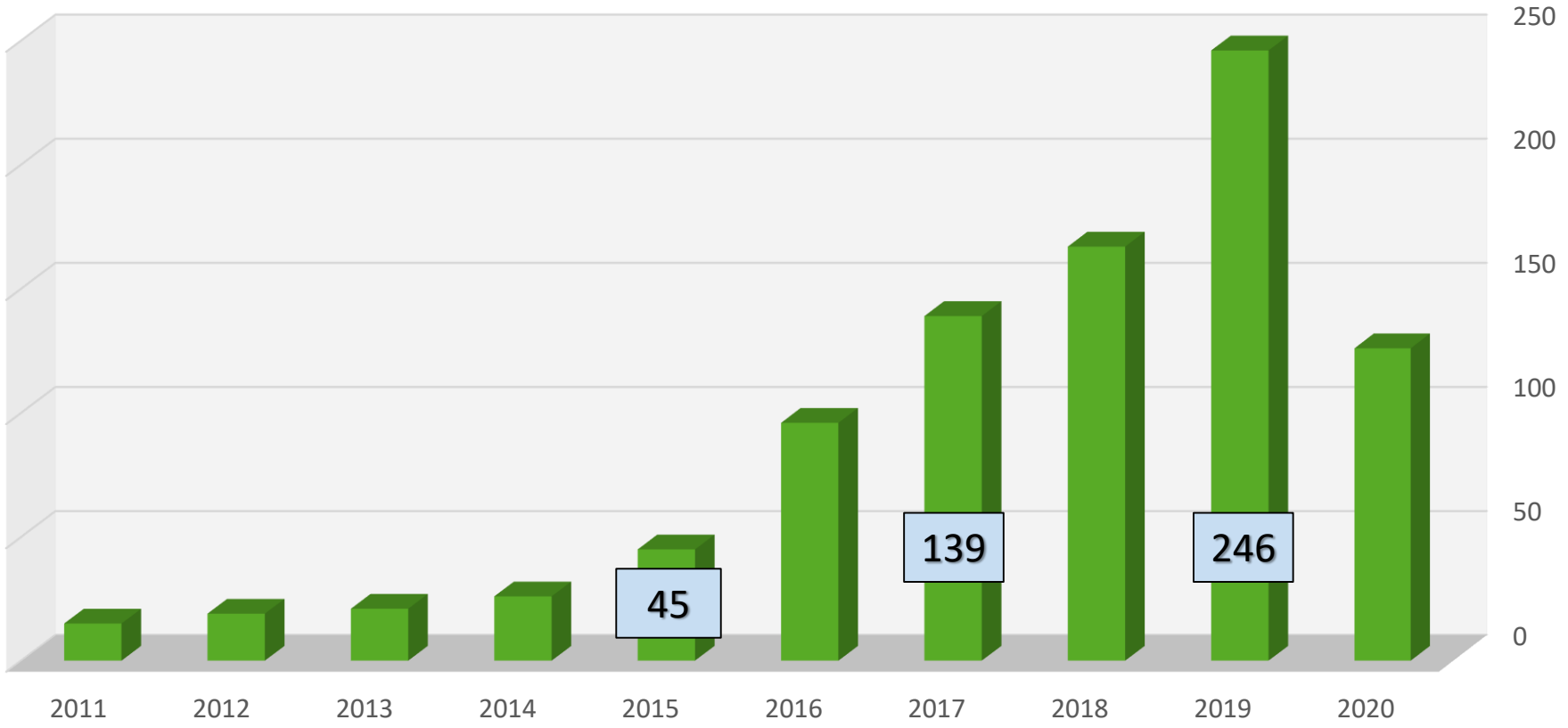
Rajasekaran et al. *Am J Physiol Cell Physiol* (2005)

Historical overview – targeting PSMA for diagnostics and therapy in nuclear medicine



compiled according to Rahbar et al., Mol Imaging., 2018 & Wüstemann *et al*., Med Res Rev., 2019

Frequency of articles covering PSMA and therapy (keywords) referenced in PubMed as of 01.05.2020



Clinical trials started with ^{177}Lu-PSMA according to clinicaltrials.gov as of 01.05.2020

Title	Status	Sponsor/Collaborators	Phase	Start Date
In Men With Metastatic Prostate Cancer, What is the Safety and Benefit of ^{177}Lu-PSMA Radionuclide Treatment in Addition to Chemotherapy	Not yet recruiting	Peter Mac, Australia | Movember Foundation | PCRA| USDOD | AAA | ANSTO | ANZUP | ARTnet | BaCT	2	23.04.2020
^{177}Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease	Recruiting	Rabin Medical Center	N/A	20.11.2019
PRINCE (PSMA-lutetium Radionuclide Therapy and ImmuNotherapy in Prostate CancEr)	Recruiting	Peter Mac, Australia	1| 2	12.07.2019
^{177}Lu-PSMA-617 Therapy and Olaparib in Patients With Metastatic CRPC	Recruiting	Peter Mac, Australia	1	09.07.2019
^{177}Lu-PSMA-617 and Pembrolizumab in Treating Patients With Metastatic CRPC	Recruiting	UCSF|PCF| NCI	1	10.05.2019
^{177}Lu-PSMA-I&T PSMA Radioligand Therapy in Metastatic CCRPC	Recruiting	Nanjing First Hospital, Nanjing Medical University	2	01.01.2019
Lutetium-177-PSMA-617 in Low Volume Metastatic Prostate Cancer	Completed	Radboud University	1| 2	01.07.2018
^{177}Lu-PSMA-R2 in Patients With PSMA Positive Progressive, Metastatic, CRPC	Recruiting	Advanced Accelerator Applications	1| 2	24.05.2018
Study of ^{177}Lu-PSMA-617 In Metastatic CRPC	Active, not recruiting	Endocyte	3	23.05.2018
^{177}Lu-J591 and ^{177}Lu-PSMA-617 Combination for mCRPC	Recruiting	Weill Medical College of Cornell University	1| 2	18.04.2018
^{177}Lu-EB-PSMA617 Radionuclide Treatment in Patients With Metastatic CRPC	Recruiting	Peking Union Medical College Hospital| NIBIB	1	15.04.2018
A Trial of ^{177}Lu-PSMA617 Theranostic Versus Cabazitaxel in Progressive Metastatic Castration Resistant Prostate Cancer	Active, not recruiting	ANZUP| ANSTO | Endocyte| PCFA | ARTnet | Movember Foundation	2	29.01.2018
^{177}Lu-EB-PSMA617 in Patients With Metastatic Castration-resistant Prostate Cancer	Unknown status	Peking Union Medical College Hospital|NIBIB	1	01.12.2017
Lutetium-177 (Lu177) Prostate-Specific Antigen (PSMA)-Directed EndoRadiotherapy	Active, not recruiting	Endocyte	2	12.07.2017
Radiometabolic Therapy (RMT) With ^{177}Lu PSMA 617 in Advanced CRPC	Recruiting	IRST	2	19.04.2017
Phase I Dose-escalation Study of Fractionated ^{177}Lu-PSMA-617 for Progressive Metastatic CRPC	Recruiting	Weill Medical College of Cornell University	1	01.12.2016

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:2536–2544
https://doi.org/10.1007/s00259-019-04485-3

GUIDELINES

Check for updates

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

Clemens Kratochwil[1] · Wolfgang Peter Fendler[2] · Matthias Eiber[3] · Richard Baum[4] · Murat Fani Bozkurt[5] · Johannes Czernin[6] · Roberto C. Delgado Bolton[7] · Samer Ezziddin[8] · Flavio Forrer[9] · Rodney J. Hicks[10] · Thomas A. Hope[11] · Levant Kabasakal[12] · Mark Konijnenberg[13] · Klaus Kopka[1] · Michael Lassmann[14] · Felix M. Mottaghy[15] · Wim Oyen[16,17,18] · Kambiz Rahbar[19] · Heiko Schöder[20] · Irene Virgolini[21] · Hans-Jürgen Wester[22] · Lisa Bodei[20] · Stefano Fanti[23] · Uwe Haberkorn[1] · Ken Herrmann[2]

- Life expectancy < 6 months
- Unacceptable medical or radiation safety risk
- Unmanageable urinary tract obstruction or hydronephrosis
- Progressive deterioration of organ function (kidney or liver)
- Myelosuppression (white cell count<2.5x10^9/L; platelet count<75x10^9/L)
- Conditions which require timely interventions

Kratochwil *et al*., Eur J Nucl Med Mol Imaging., 2019

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

- **Radiopharmaceutical:** QC < 2% radiochemical impurities due to free ^{177}Lu
- No clinical **interaction studies** have been performed.
- **Dosimetry:**
  - exposures of target volumes are to be individually planned and verified
  - involvement of a medical physics expert
  - sequential imaging over several time points should be performed, the minimal standard would be dosimetry based on a single imaging time point
  - individual tumor/normal-organ dosimetry should be reported
  - In cases where no dosimetry is performed, mean values available from recent studies as a rough estimate
- **Radiation protection:** more data and dose assessments are needed, minimum hospitalisation of 48 h post-application (Germany)
- **Treatment regimens for the non-compromised patient:**
  - administered activity per treatment: 3.7 - 9.3 GBq (Based on observational data)
  - 2 to 6 cycles with a time interval of 6 - 8 weeks
  - A cumulative kidney absorbed dose of 40 Gy per patient should generally not be exceeded in patients with a life expectancy > 1 year
  - Response assessment: PSA, emission scans, staging exams every 2 cycles

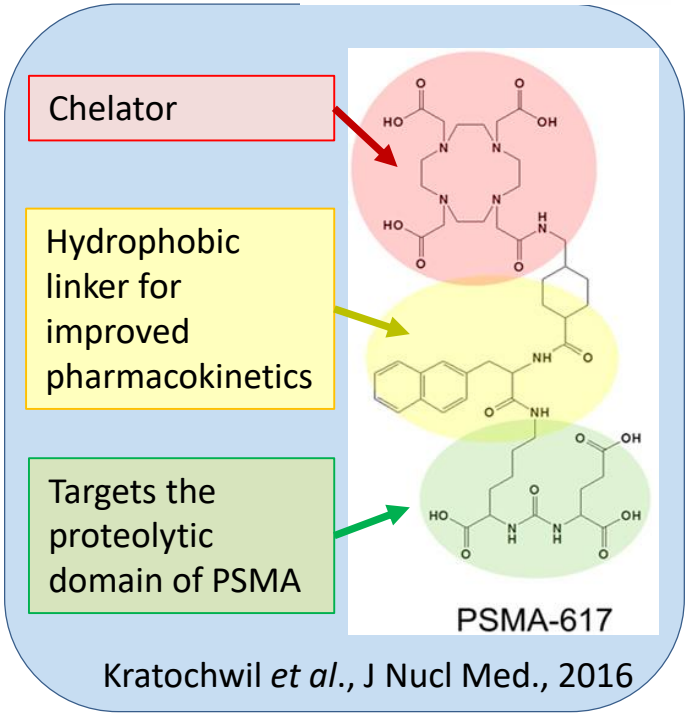
Kratochwil *et al*., Eur J Nucl Med Mol Imaging., 2019

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

- **^{177}Lu-PSMA administration:**
  - RLT is administered by slow I.V. injection of ^{177}Lu-PSMA
  - I.V. or oral hydration as per individual cardiovascular and voiding conditions should be initiated before
- **Follow-up:**
  - Follow-up examinations every 2 - 3 weeks (PSA, blood cell count)
  - Basic liver and kidney profile every 6 - 8 weeks
  - Physical exam before each treatment
  - After later cycles: Imaging-based restaging with PET/diagnostic CT every 2 – 3 cycles
- **Repeat therapy**: Blood count, overall medical condition and other criteria should be reevaluated prior to any repeat treatment
- **Safety:** serious haematotoxicity in less than 10% of patients in several observational trials
- **Efficacy**:
  - Biochemical response after repeated RLT is expected in **more than half of patients**, and partial response by imaging is expected in more than one-third of patients.
  - Pain and quality of life improved significantly in **more than one half of patients** within smaller observational trials

Kratochwil *et al*., Eur J Nucl Med Mol Imaging., 2019

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



Kratochwil *et al.*, J Nucl Med., 2016

- Between August 2015 and December 2016
- 30 men with mCRPC and progressive disease after standard treatments
- The patients received up to four cycles of intravenous [^{177}Lu]-PSMA-617, at six weekly intervals, mean administered radioactivity 7.5 GBq per cycle
- Aim: Investigation of the safety, efficacy, and effect on quality of life of [^{177}Lu]-PSMA-617 in men with metastatic castration-resistant prostate cancer who progressed after standard treatments

Hofman *et al.*, Lancet Oncol., 2018

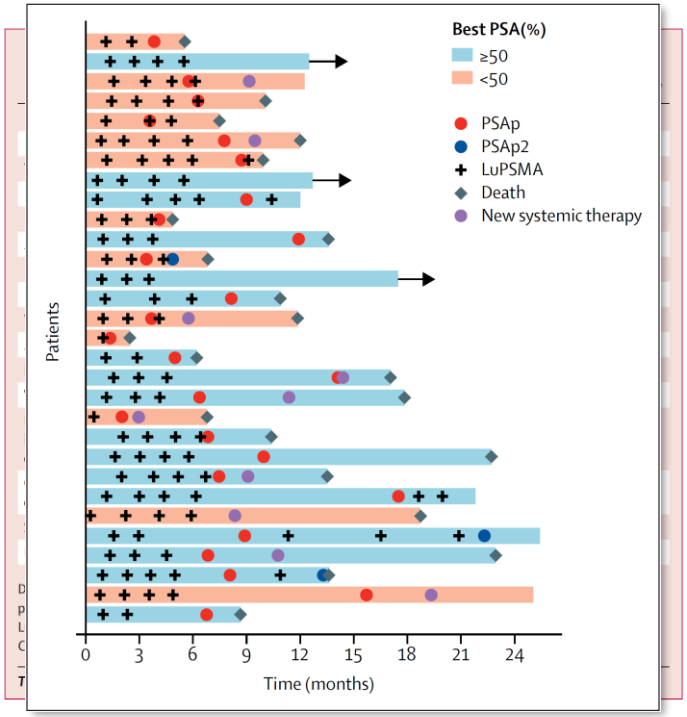
Response to the treatment

- 17 (57%) of 30 patients (95% CI 37–75) achieved a PSA decline of 50% or more
- 11 (37%) patients experienced a ten point or more improvement in global health score by the second cycle of treatment

	All patients (n=30)
Age (years)	71 (67–75)
Time since diagnosis of prostate cancer (years)	9 (5–13)
Gleason score at diagnosis	8 (7–9)
Alkaline phosphatase (U/L)	117·5 (80·8–184·5)
Haemoglobin (g/L)	118 (103–127)
Lactate dehydrogenase (U/L)*	247 (209–304)
PSA (µg/L)	189·8 (80·1–372·0)
PSA doubling time (µg/L per month)	2·4 (1·4–3·5)
ECOG performance status	
0	11 (37%)
1	14 (47%)
2	5 (17%)
Number of previous chemotherapy regimens	
1	12 (40%)
2	12 (40%)
≥3	2 (7%)
Previous treatments	
Abiraterone or enzalutamide or both	25 (83%)
Docetaxel	24 (80%)
Cabazitaxel	14 (47%)
Palliative-intent radiotherapy	14 (47%)
Bisphosphonate or denosumab	22 (73%)
Sites of disease on PSMA-PET	
Bone	29 (97%)
Nodal	24 (80%)
Visceral†	4 (13%)
Extent of disease on PSMA-PET	
≤20 metastases	2 (7%)
>20 metastases	28 (93%)
On opiate analgesia for pain	15 (50%)
Pain at baseline (BPI score‡)	
No pain (<1)	5 (17%)
Mild (1–4)	18 (60%)
Moderate to severe (5–10)	7 (23%)

Data are median (IQR) or n (%). PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. PSMA=prostate-specific membrane antigen. BPI=Brief Pain Inventory. *Data missing for four patients. †Visceral includes adrenal, lung, liver, and spleen. ‡As per Chow et al.[27]

Table 1: **Baseline characteristics**



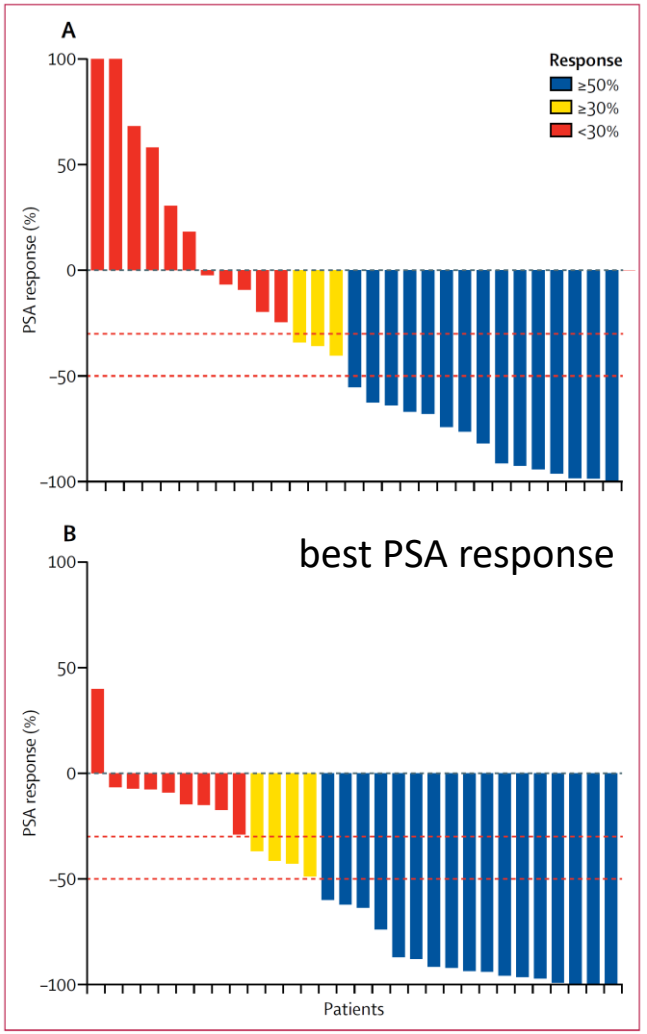


Figure 3: **(A) PSA response after 12 weeks* and (B) best PSA response from baseline**
Two dashed lines represent PSA response greater than 30 and 50%. PSA=prostate-specific antigen. *One patient deceased by 12 weeks (non-prostate related).

Hofman *et al.*, Lancet Oncol., 2018

Response to the treatment

Findings show that radionuclide treatment with [^{177}Lu]-PSMA-617 has **high response rates, low toxic effects, and reduction of pain** in *men* with metastatic castration-resistant prostate cancer **who have progressed after conventional treatments**. This evidence supports the **need for randomised controlled trials** to further assess efficacy compared with current standards of care.

Hofman *et al*., Lancet Oncol., 2018

Long term follow-up and outcomes of re-treatment in an expanded 50 patient single-center phase II prospective trial of Lutetium-177 (^{177}Lu) PSMA-617 theranostics in metastatic castrate-resistant prostate cancer.

Imaging response at 3 months after the last cycle of induction LuPSMA

	Bone scintigraphy	Soft-tissue lesions on CT (nodal and &/or visceral) (n=27)	PSMA PET	FDG PET
CR	16 (32%)	5 (19%)	6 (12%)	7 (14%)
PR		10 (37%)	15 (30%)	8 (18%)
SD		0	0	3 (6%)
PD	12 (24%)	9 (33%)	14 (28%)	15 (30%)
Not performed	22 (44%)	3 (11%)	15 (30%)	17 (34%)

CR: complete response.
PR: partial response.
SD: stable disease.
PD: progressive disease.
Not performed: due to clinical progression or death.

This expanded 50 patient cohort of men with extensive prior therapy confirms our earlier report of **high response rates, low toxicity and improved QoL** with LuPSMA radioligand therapy. Upon progression, re-challenge LuPSMA demonstrated **higher response rates than other systemic therapies**.

Violet *et al*., J Nucl Med., 2019

Results of a prospective phase 2 pilot trial of 177-PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression

- 14 men with mCRPC - previously unsuccessfully treated with abiraterone/enzalutamide or taxane-based chemotherapy
- They first underwent ^{68}Ga-HBEDD PSMA-11 PET screening
- They received up to 4 cycles of ^{177}Lu-PSMA at 6 weekly intervals for treatment
- Goal: Evaluation whether the use of these **paired theranostic agents** allows to **predict the treatment response** based on parameters from the PET screening scans, specifically the PSMA PET standardized uptake value (SUV)



Emmet *et al*., Clin Genitourin Cancer, 2019

Table 1 Baseline Characteristics

Characteristic	Value
Age (y)	69.5 (56-81)
Serum testosterone (nmol/L)	NA (undetectable-0.4)
Baseline PSA (ng/mL)	88 (7-2950)
Gleason score (n = 10)	9 (8-9)
Time From Diagnosis, y	
≤2	3 (22)
>2 and ≤5	2 (14)
>5	9 (64)
Extent at Diagnosis	
Localized	8 (57)
De novo metastatic	6 (43)
Prior Androgen-Directed Therapy	
LHRH agent	14 (100)
Bicalutamide	10 (71)
Abiraterone or enzalutamide	14 (100)
Abiraterone and enzalutamide	7 (50)
Prior chemotherapy	10 (71)
Docetaxel	9 (64)
Cabazitaxel	6 (43)
Prior palliative radiotherapy	8 (57)
Prior bisphosphonates/denosumab	7 (50)
ECOG PS at Study Entry	
0	5 (36)
1	9 (64)
Opiate use at study entry	7 (50)
Site of Metastases at Study Entry	
Nodal	8 (57)
Bone	14 (100)
Visceral	4 (28)
Ongoing Treatments	
LHRH agent	14 (100)
Denosumab/bisphosphonate	6 (43)

Data are presented as n (%) or median (range).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LHRH = luteinizing hormone releasing hormone; PSA = prostate-specific antigen.

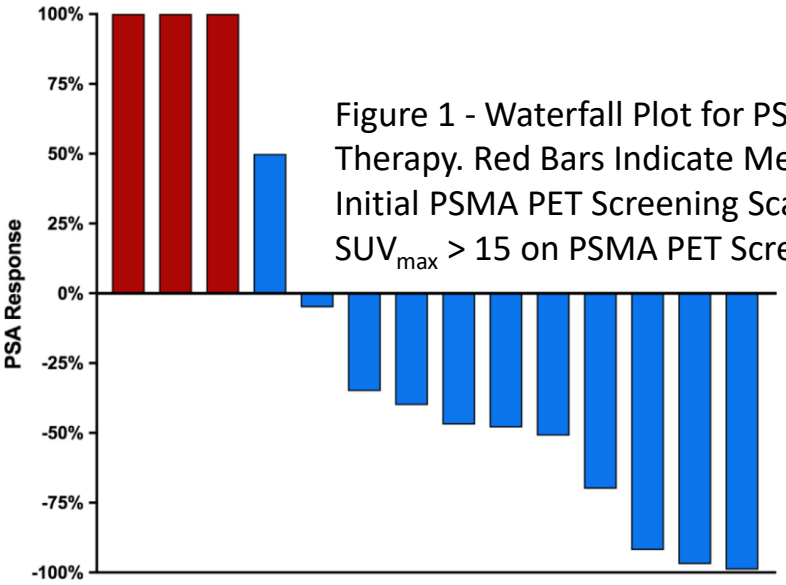


Figure 1 - Waterfall Plot for PSA Responses to Lu-PSMA Therapy. Red Bars Indicate Men With SUV_{max} < 15 on Initial PSMA PET Screening Scans; Blue, All Men With SUV_{max} > 15 on PSMA PET Screening

- ≥ 50% reduction in PSA in 36% of men treated, with 64% experiencing a ≥ 30% reduction in PSA
- Both PSMA SUV_{max} and SUV_{mean} at screening were predictive of a ≥ 30% reduction in PSA with Lu-PSMA therapy

Table 2 Toxicity

Toxicity	All Grades	Grade 1	Grade 2	Grade 3/4
Nausea	10/14 (71%)	8/14 (57%)	2/14 (14%)	—
Dry mouth	11/14 (78%)	11/14 (78%)	—	—
Fatigue	7/14 (50%)	6/14 (43%)	1/14 (7%)	
Anemia	2/14 (14%)	1/14 (7%)	1/14 (7%)	
Thrombocytopenia	1/14 (7%)	1/14 (7%)		—
Abnormal LFT	3/14 (21%)	3/14 (21%)	—	—
Diarrhea	2/11 (14%)	2/11 (14%)	—	—

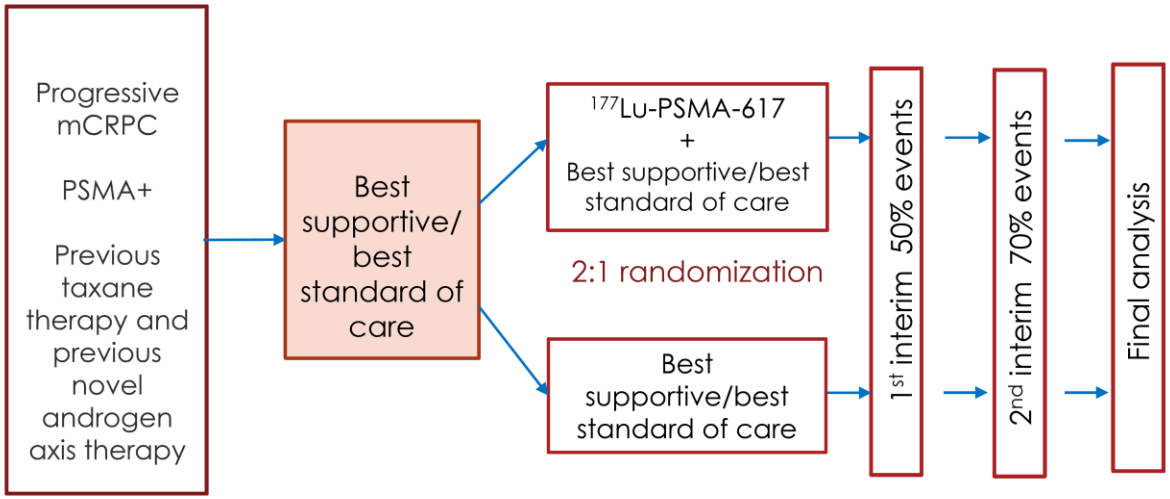
Abbreviation: LFT = liver function test.

Emmet *et al*., Clin Genitourin Cancer, 2019

VISION: A phase 3 Study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive mCRPC

- Currently ongoing (estimated completion date May 2021)
- 750 patients (inclusion closed!)
- Primary Objective: evaluate the effects of ^{177}Lu-PSMA-617 in combination with best supportive/best standard of care compared to best supportive/standard of care alone

VISION: Clinical Trial Procedure/Design



Additional Secondary Endpoints
- Safety and tolerability
- Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form [BPI-SF])
- Health economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphatase levels and lactate dehydrogenase levels

Stratification Factors
- Serum lactate dehydrogenase (LDH) (≤260 IU/L vs. >260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

Primary Endpoint
- Overall survival

Key Secondary Endpoints (with α control)
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

Therapy Paradigm for castrate-resistant prostate cancer (crPCa)

Line	Therapy	Survival benefit
Line 1	Chemotherapy - Docetaxel Hormone therapy - Abiraterone Hormone therapy - Enzalutamide	~ 2.5 month ~ 4 month ~ 2 month
Line 2	Chemotherapy - Cabazitaxel after Docetaxel Hormone therapy - Abiteraterone after Docetaxel Hormone therapy - Enzalutamide after Docetaxel	~ 2.5 month ~ 4.5 month ~ 4.5 month
Line 3	The choice of further treatment is open Endogeneous Radiotherapy - Radium-223 (XOFIGO®) Chemotherapy - Cabazitaxel after Docetaxel and hormonal treatment Targeted therapy - Olaparip (PARP inhibitor)	 ~ 3.5 month less beneficial than earlier use To be determined
Line 4	Best supportive/best standard of care	

uroweb.org/guideline/prostate-cancer

Therapy Paradigm for castrate-resistant prostate cancer (crPCa)

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Line 1	Chemotherapy - Docetaxel Hormone therapy - Abiraterone Hormone therapy – Enzalutamide	~ 2.5 month ~ 4 month ~ 2 month
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Line 3	The choice of further treatment is open Endogeneous Radiotherapy - Radium-223 (XOFIGO®) Chemotherapy - Cabazitaxel after Docetaxel and hormonal treatment Targeted therapy - Olaparip (PARP inhibitor)	 ~ 3.5 month less beneficial than earlier use To be determined
Line 4	Endogeneous Radiotherapy - ^{177}Lu-PSMA-617	4 – 18 month (first experience from phase 2 studies)

uroweb.org/guideline/prostate-cancer

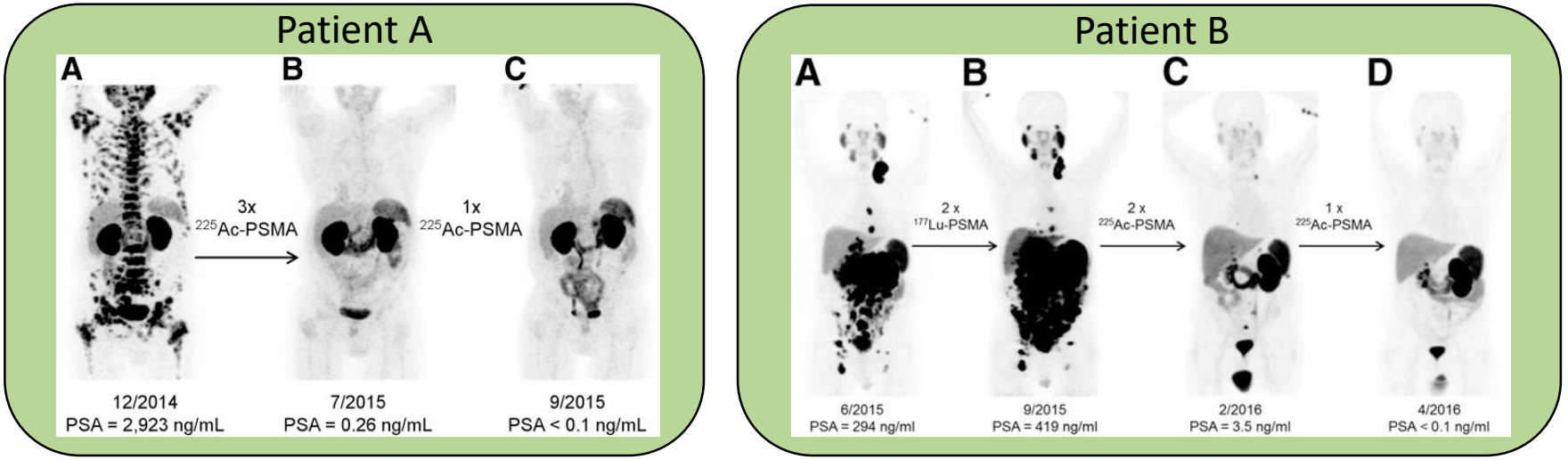
Possible integration into the clinical treatment of mCRPC

- Palliative situation
- Visceral metastases
- Further progress/therapy resistance to "conventional" methods
- Contraindication for Alpharadin (XOFIGO®)

➔Treatment with radioactively labelled PSMA ligands

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

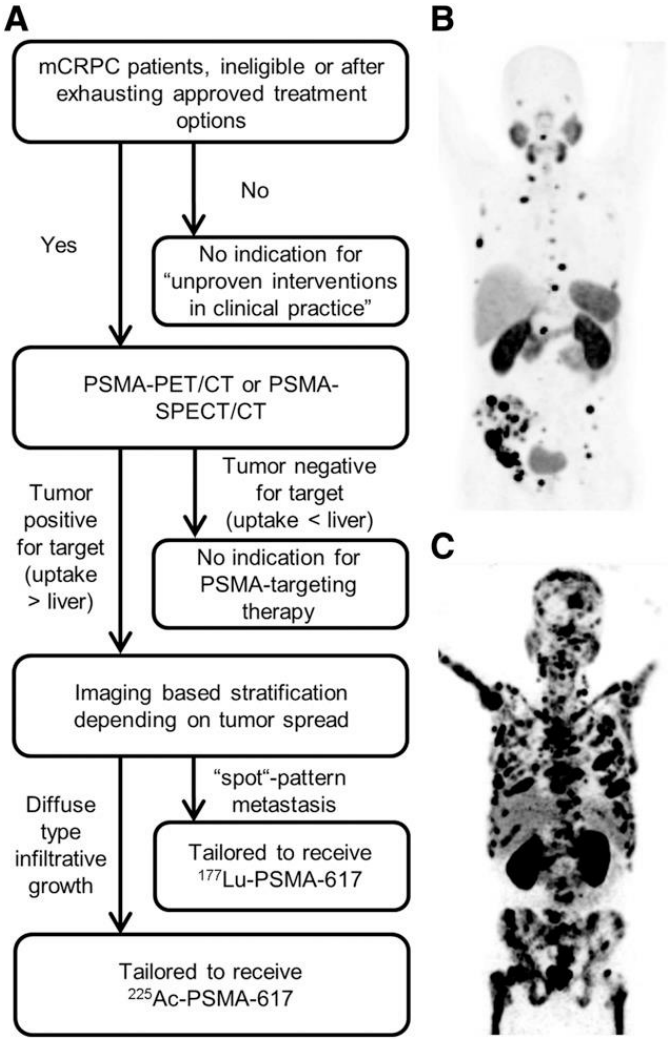
- ^{225}Ac-PSMA-617 α-therapy in one patient in whom treatment with β-emitters was contraindicated (patient A) and one patient resistant to ^{177}Lu-PSMA-617 (patient B)
- Initial treatment of 3 cycles of ^{225}Ac-PSMA-617 (100 kBq per kilogram of body weight) at bimonthly intervals



Clinical Course illustrated with ^{68}Ga-PSMA-11 PET/CT scans

Kratochwil *et al.*, J Nucl Med., 2016

Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac-PSMA-617: Swimmer-Plot Analysis



- Salvage therapy for 40 patients
- 100 kBq/kg of body weight were administered every 2 month
- Aim: identification of the first indicators of efficacy for ^{225}Ac-labeled prostate-specific membrane antigen (PSMA)–617 therapy in a retrospectively analyzed group of patients
- Elaborate selection process/criteria
  - Patients with oligometastatic, hot-spot pattern of tumor spread were preferably stratified to receive ^{177}Lu-PSMA-617
  - Patients with diffuse pattern of bone marrow infiltration were stratified for ^{225}Ac-PSMA-617

Kratochwil *et al.*, J Nucl Med., 2018

Summary: Endogeneous radiotherapie with radiolabelled PSMA ligands

- A new "arrow in the quiver" against metastatic castration-resistant prostate cancer?
- First approaches with monoclonal antibodies were promising, approaches with "small molecules" (MIP1095 or DKFZ-617) show a better biodistribution.
- Minor side effects (bone marrow suppression, salivary glands)
- So far only evidence in Phase II that endogenous anti-PSMA radiotherapy has a significant impact on progression-free survival (PFS) and potential overall survival (OS).
- Casuistics/case series using Ac-PSMA very promising, selection of patients seems important (splice variants of PSMA: data Heidelberg)

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Thank you