Optimal strategies for patients progressing on AR-pathway inhibitors

Radioligand Therapy

Ken Herrmann

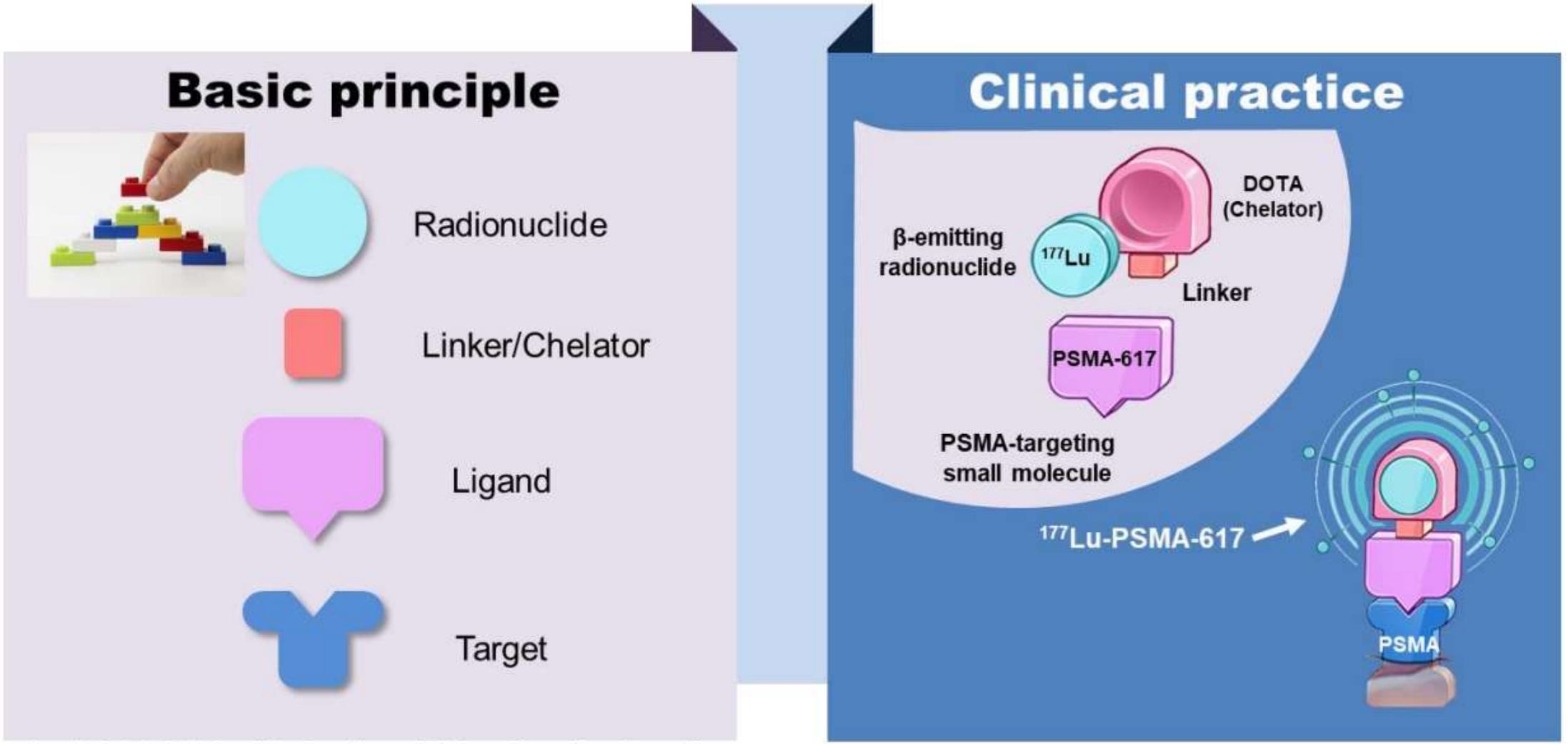
Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Boston Scientific, Sofie Biosciences, Novartis/Adacap
Receipt of honoraria or consultation fees	Bayer, Ipsen, Bain Capital, Sirtex, Curium, Boston Scientifics, Novartis/Adacap, Sofie Biosciences, ABX, Endocyte, Janssen, Amgen, GE, Siemens
Stock shareholder	Sofie Biosciences, Aktis Oncology, Theragnostics
Other support (please specify):	None.

Outline

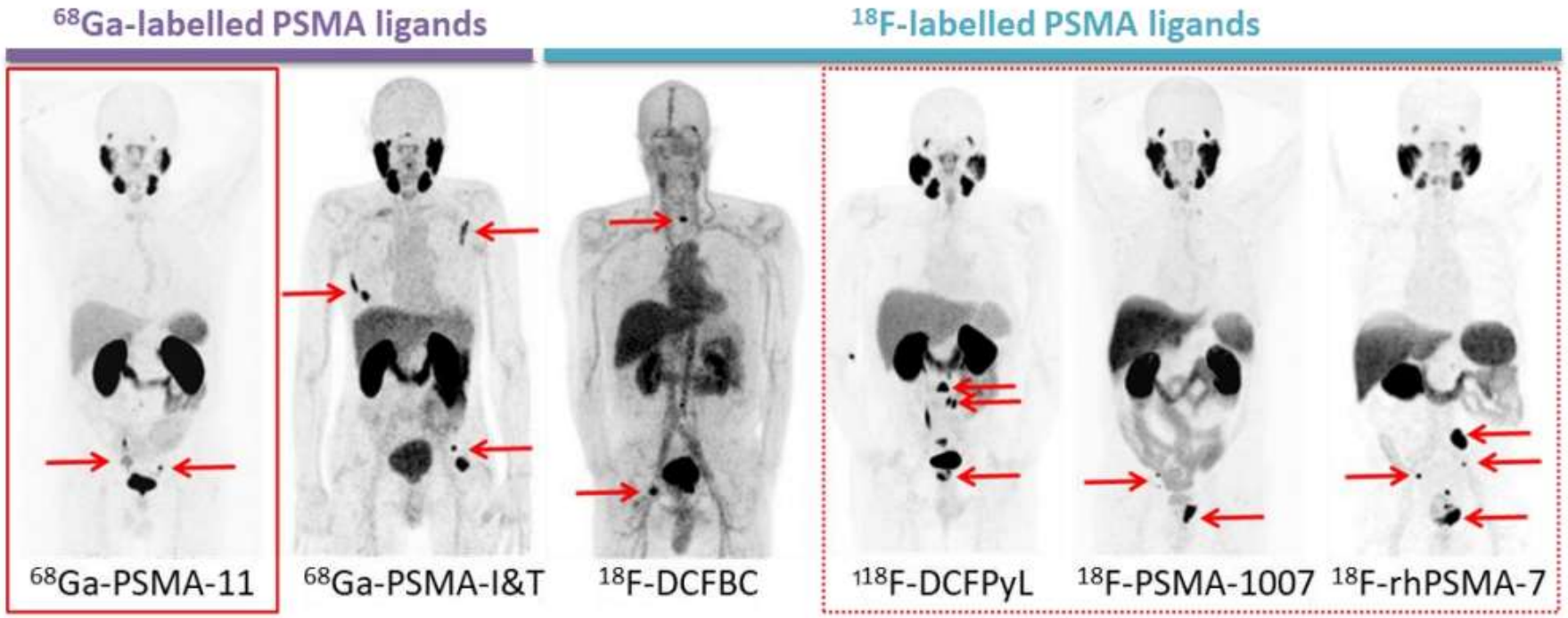
- Introduction Theranostic Principle
- Current State of PSMA RLT
- Next steps

Theranostic Principle



Lego blocks photo by Lim Seng Kui on dreamstime.com. PSMA, prostate-specific membrane antigen.
Eiber M, et al. J Nucl Med 2017;58(Suppl 2):67S-76S; Benešová M, et al. J Nucl Med 2015;56:914-20; Sartor O, et al. N Engl J Med 2021;385:1091-103.

“Seeing what you treat”



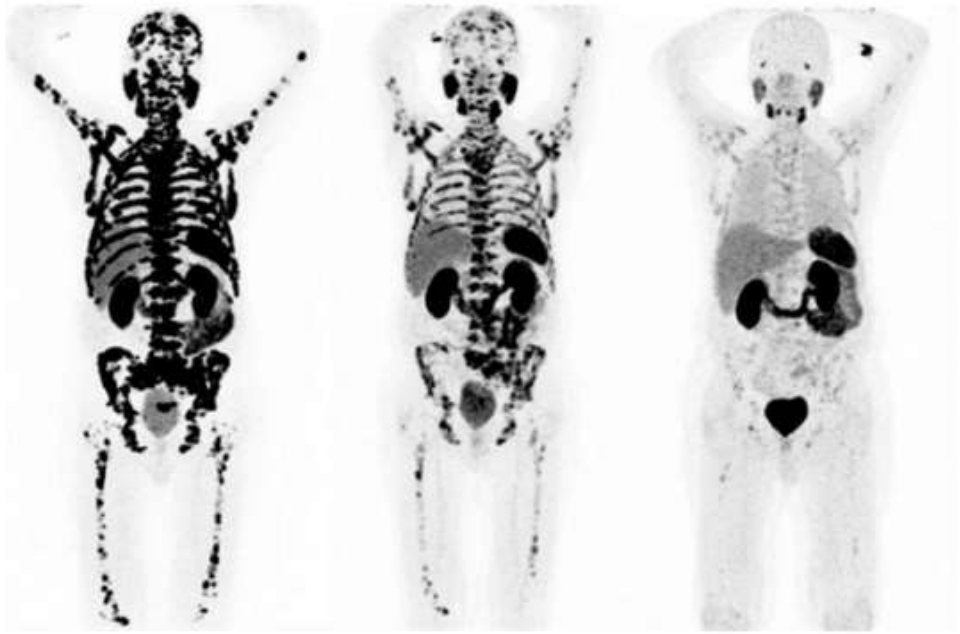
First report on human application:

^{68}Ga-PSMA-11 (Afshar-Oromieh A, et al. Eur J Nucl Med Mol Imaging 2012;39:1085-6); ^{68}Ga-PSMA-I&T (Weineisen M, et al. J Nucl Med 2015;56:1169-76); ^{18}F-DCFBC (Cho S, et al. J Nucl Med 2012;53:1883-91); ^{18}F-DCFPyL (Szabo Z, et al. Mol Imaging Biol 2015;17:565-74); ^{18}F-PSMA-1007 (Eur J Nucl Med Mol Imaging 2017;44:678-88); ^{18}F-rhPSMA-7 (Eiber M, et al. J Nucl Med 2020;61:696-701)

Images courtesy of Michael Eiber.
PSMA, prostate-specific membrane antigen.
Modified from Eiber M, et al. J Nucl Med 2017;58(Suppl 2):67S-76S.

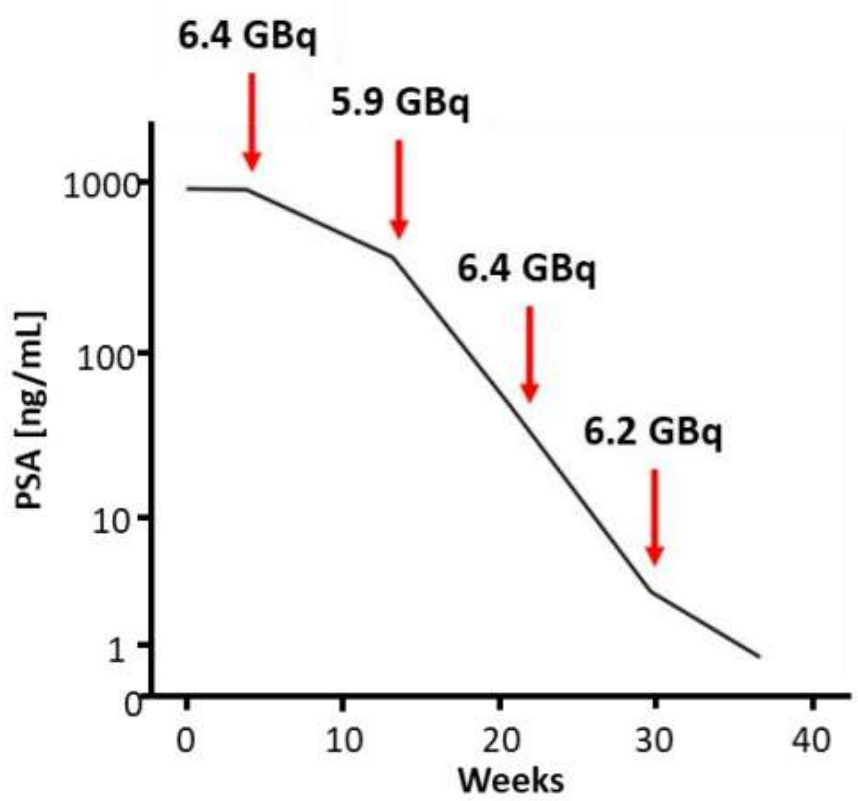
“Treating what you see”

PSMA PET CT scans: Target expression



Baseline After 2 cycles After 4 cycles

PSA levels



Images courtesy of Ken Herrmann.
CT, computed tomography; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
Rahbar K, et al. Eur J Nucl Med Mol Imaging 2018;45:2055-61; Fendler WP, et al. JAMA Oncol 2019;5:856-63.

Current State of PSMA Tracers

	Probe	IP protected	Company Europe	Company US	Status
	^{68}Ga-PSMA-11	No	Telix, Isotopia, academic centers	**Telix, AAA, academic centers**	**FDA approved**
	^{18}F-DCFPyL	Yes	Curium	**Progenics**	**FDA approved**
	^{18}F-PSMA-1007	Yes	ABX	ABX	**Phase 3; Marketing authorisation in France**
^{68}Ga	^{68}Ga-PSMA-I&T	No	N/A	N/A	N/A
	^{68}Ga-THP-PSMA	Yes	Theragnostics, GE	Theragnostics, GE	Phase 3 planned
^{18}F	^{18}F-rh-PSMA-7.3	Yes	BlueEarth Diagnostics	BlueEarth Diagnostics	Phase 3 ongoing
	^{18}F-CTT1057	Yes	AAA	AAA	Phase 3 ongoing
Other	^{99}Tc-MIP1404	Yes	ROTOP	Progenics	Phase 3 planned
	^{64}Cu-PSMA I&T	Yes	Curium	Curium	Phase 3 planned

PSMA, prostate-specific membrane antigen.
https://www.clinicaltrials.gov/ct2/results?cond=prostate+cancer&term=PSMA+PET&cntry=&state=&city=&dist=; https://www.has-sante.fr/jcms/p_3337468/en/radelumin-18f-psma-1007 (last accessed 15 July 2022).

Current State of PSMA RLT

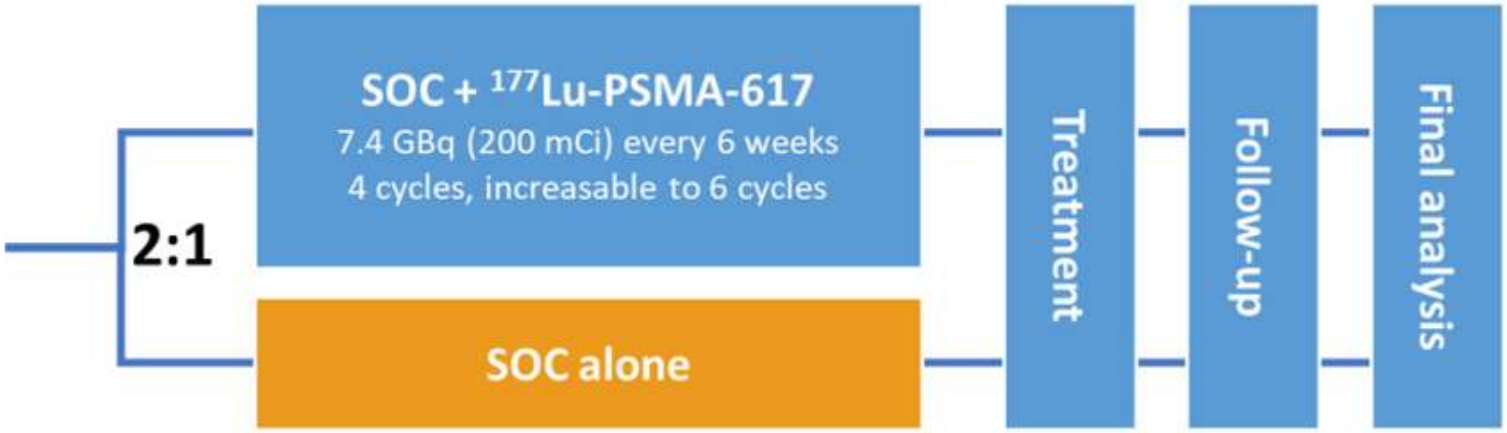
	Probe	Ligand type	Company	Status
	^{177}Lu-PSMA-617	Small molecule	AAA, academic centers	**FDA approved**
^{177}Lu	^{177}Lu-PSMA-I&T / ^{177}Lu-PSMA-PNT2002	Small molecule	Curium Pharma / Point Biopharma	Phase 3 ongoing
	^{177}Lu-DOTA-rosopatamab	Antibody (human)	Telix Pharmaceuticals Ltd	Phase 3 ongoing
	^{177}Lu-J591	Antibody (murine; deimmunised)	Academic centers (Weill Cornell)	Phase 2 ongoing
	^{177}Lu-EB-PSMA-617	Small molecule	Academic centers	Phase 1
^{225}Ac	^{225}Ac-PSMA-617	Small molecule	AAA	Phase 2 ongoing
	^{225}Ac-J591	Antibody (murine)	Academic centers (Weill Cornell)	Phase 2 ongoing
Other	^{131}I-PSMA-1095	Small molecule	Progenics Pharmaceuticals	Phase 2 ongoing
	^{227}Th-PSMA-TTC	Antibody (human)	Bayer	Phase 1

mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.
https://www.clinicaltrials.gov/ct2/results?cond=prostate+cancer&term=radioligand+therapy+&cntry=&state=&city=&dist= (last accessed 15 July 2022).

VISION Study (Design)

Eligibility

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- SOC planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11



Randomization stratified by

- ECOG performance status (0–1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- Androgen receptor pathway inhibitors in SOC (yes or no)

CT/MRI/bone scans

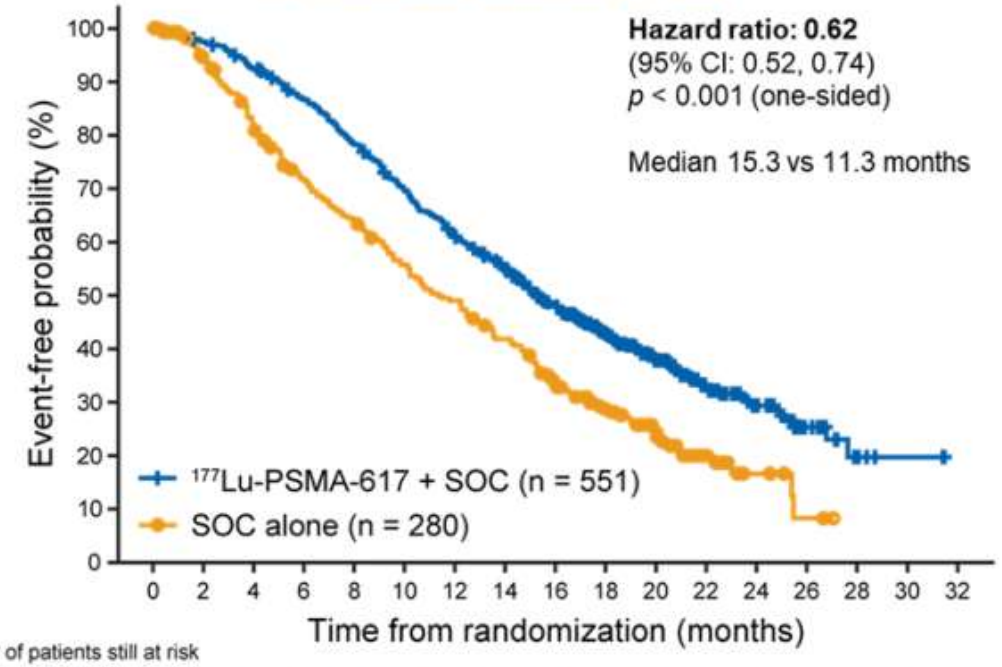
- Every 8 weeks (treatment)
- Every 12 weeks (follow-up)
- Blinded independent central review

Sartor et al., NEJM 2021

VISION Study (OS and rPFS)

^{177}Lu-PSMA-617 prolonged overall survival

All randomized patients (N = 831)

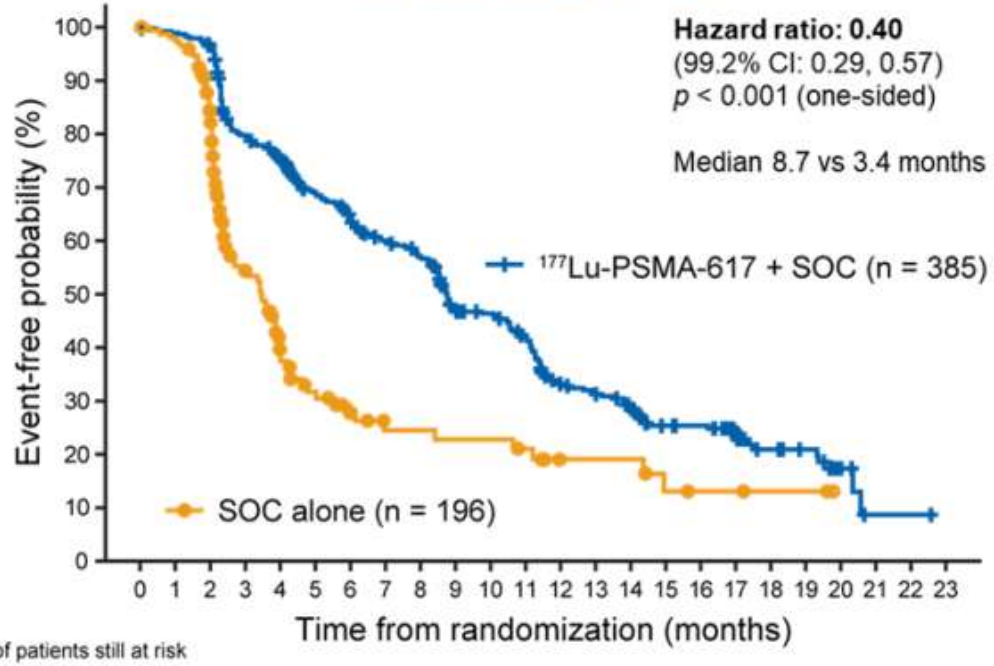


Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

^{177}Lu-PSMA-617 improved rPFS

rPFS analysis set (n = 581)



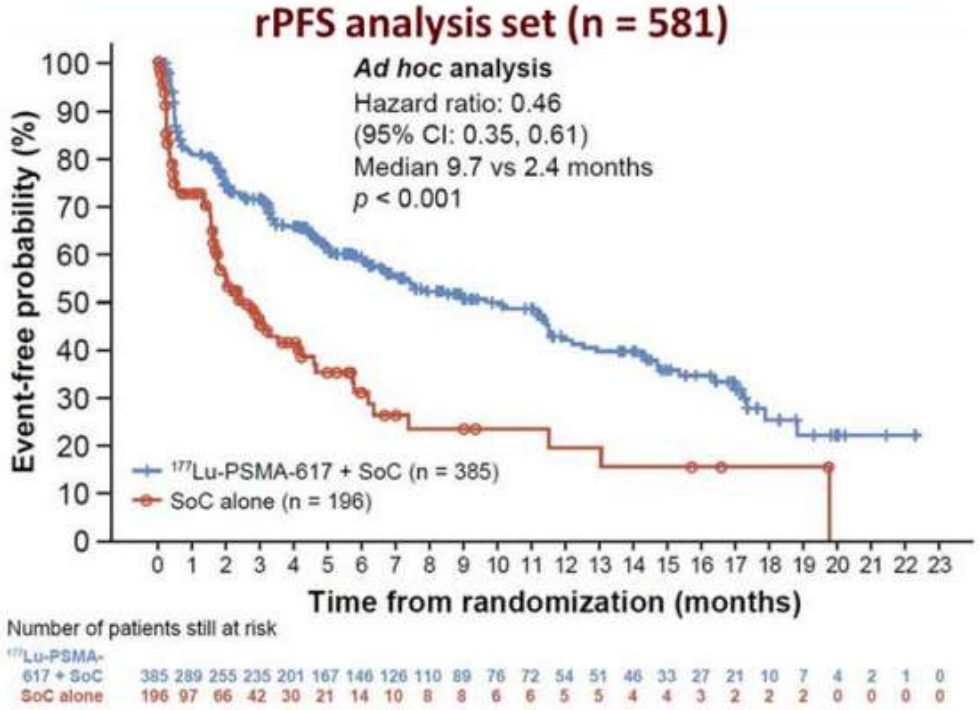
Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SOC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

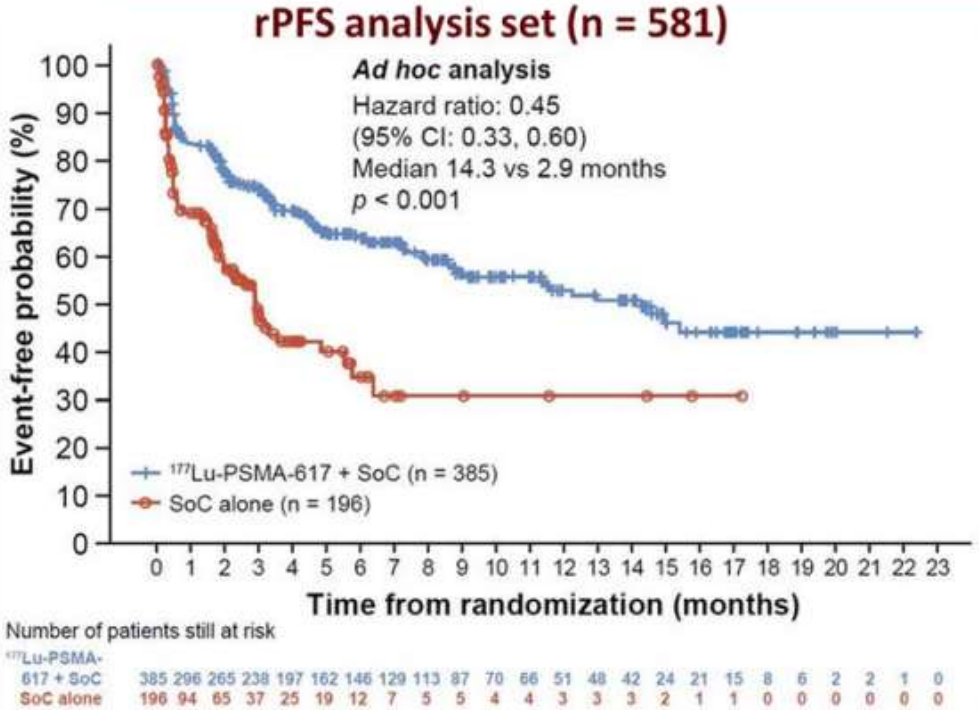
Sartor et al., NEJM 2021

VISION Study

Time to worsening in FACT-P total score favoured the ^{177}Lu-PSMA-617 arm



Time to worsening in BPI-SF pain intensity favoured the ^{177}Lu-PSMA-617 arm



BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy – Prostate; HRQoL, health-related quality of life; PSMA, prostate-specific membrane antigen; SOC, protocol-permitted standard of care.

Time to worsening was defined as the time from randomization to ≥ 10 points decrease from baseline in FACT-P total score, and to ≥ 30% or ≥ 2 points increase from baseline in BPI-SF pain intensity. Testing was two-sided using the Cox model (Wald Chi-square test). All *p* values are nominal, descriptive, and non-inferential. Analyses in the 581 patients randomized after measures were implemented on or after 5 March 2019.

Fizazi et al., ESMO 2021

FDA Approval (UK, CAN)

NOVARTIS

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Novartis Pluvicto™ approved by FDA as first targeted radioligand therapy for treatment of progressive, PSMA positive metastatic castration-resistant prostate cancer

Mar 23, 2022

Ad hoc announcement pursuant to Art. 53 LR

- *FDA also approved complementary diagnostic imaging agent, Locametz®, after radiolabeling with gallium-68 for the identification of PSMA-positive lesions[2]*
- *Metastatic prostate cancer has a 5-year survival rate of less than 30%[3]; mCRPC patients who progress on multiple lines of therapy have limited treatment options*
- *FDA approval was based on pivotal Phase III VISION trial, where patients with pre-treated PSMA-positive mCRPC who received Pluvicto plus standard of care had a statistically significant reduction in risk of death[1]; both alternate primary endpoints of overall survival and radiographic*

TheraP

Aim: to determine the activity and safety of Lu-PSMA vs cabazitaxel

ANZUP

KEY ELIGIBILITY

- mCRPC post docetaxel suitable for cabazitaxel
- Progressive disease with rising PSA and PSA ≥ 20 ng/mL
- Adequate renal, haematologic and liver function
- ECOG performance status 0-2

↓

^{68}Ga-PSMA + ^{18}F-FDG PET/CT

- PSMA SUVmax > 20 at any site
- Measurable sites SUVmax > 10
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

R

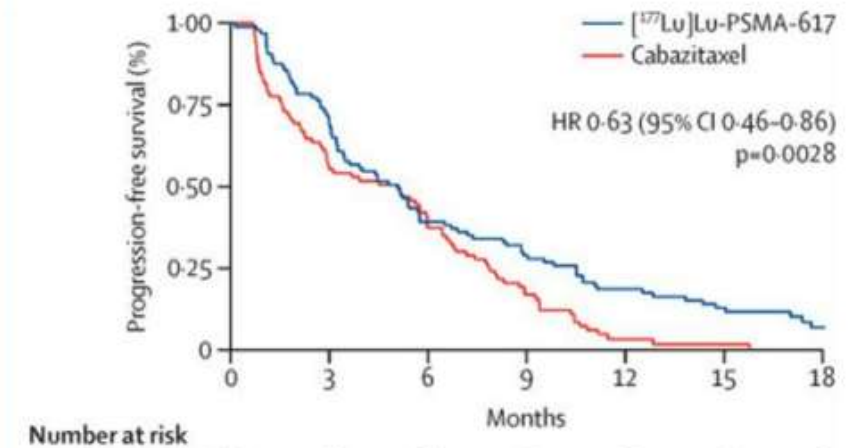
^{177}Lu-PSMA-617
8.5 GBq IV q6 weekly
↓ 0.5GBq each cycle
Up to 6 cycles

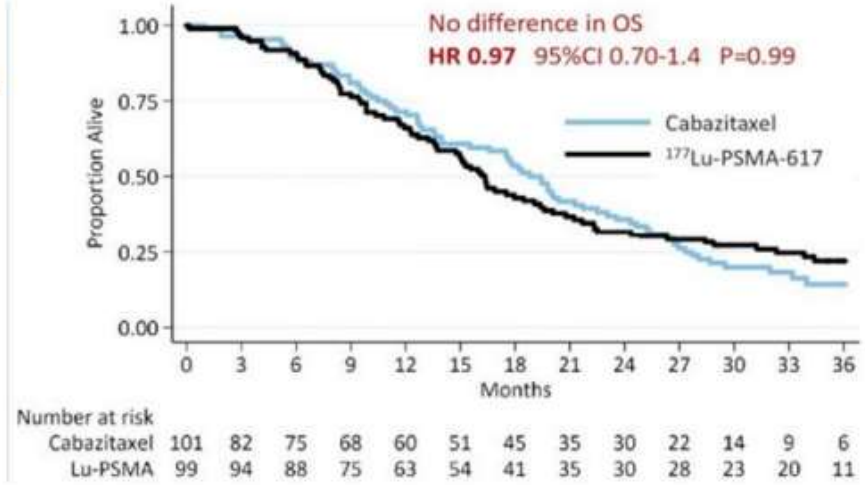
SPECT/CT @ 24 hours
suspend Rx if exceptional response; recommence upon progression

200 men 1:1 randomisation
11 sites in Australia
Stratified by:
- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

CABAZITAXEL
20mg/m^2 IV q3 weekly,
Up to 10 cycles

80% power to detect a true absolute difference of 20% in the PSA response rate (from 40% to 60%), with a 2-sided type 1 error of 5% and allowance of 3% for missing data.





Hofman et al., Lancet Oncol 2020; Hofman et al., ASCO 2022

PSMA RLT according to Guidelines (EAU and ASCO)

Recommendations	Strength rating
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

1.1 The panel recommends the use of ^{177}Lu-PSMA-617 intravenously once every 6 weeks for 4–6 cycles as a treatment option in patients with PSMA PET/CT positive mCRPC who have progressed on one prior line of androgen receptor pathway inhibitor and at least one line of prior chemotherapy.

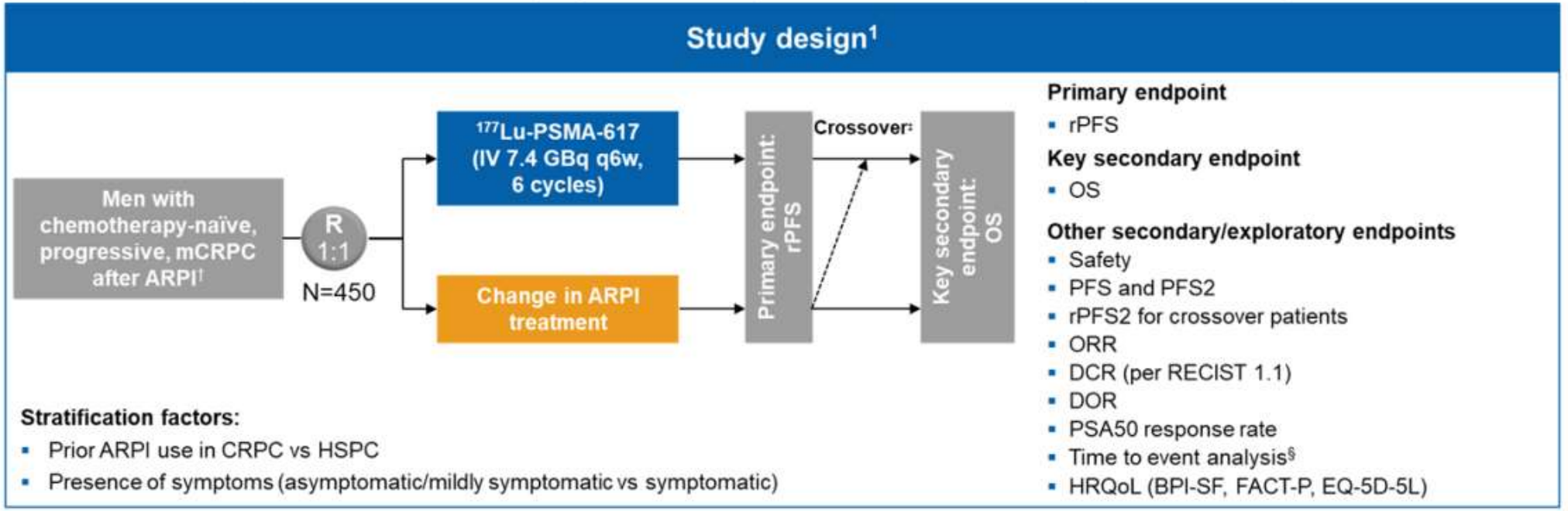
1.2.1 The panel recommends that patients should be selected using PSMA PET.

1.2.2 The panel recommends that either Ga-68 PSMA-11 or F-18 piflufolastat be used as radiotracers to determine eligibility currently

Next Steps: PSMAfore

PSMAfore: a prospective, open-label, randomized, phase 3 study of ^{177}Lu-PSMA-617 vs change of ARPI in patients with chemotherapy-naïve mCRPC

- PSMAfore aims to assess the efficacy and safety of ^{177}Lu-PSMA-617 RLT vs a change of ARPI in chemotherapy-naïve men with PSMA-positive* mCRPC, and progression after prior treatment with ARPI (NCT04689828)[1]

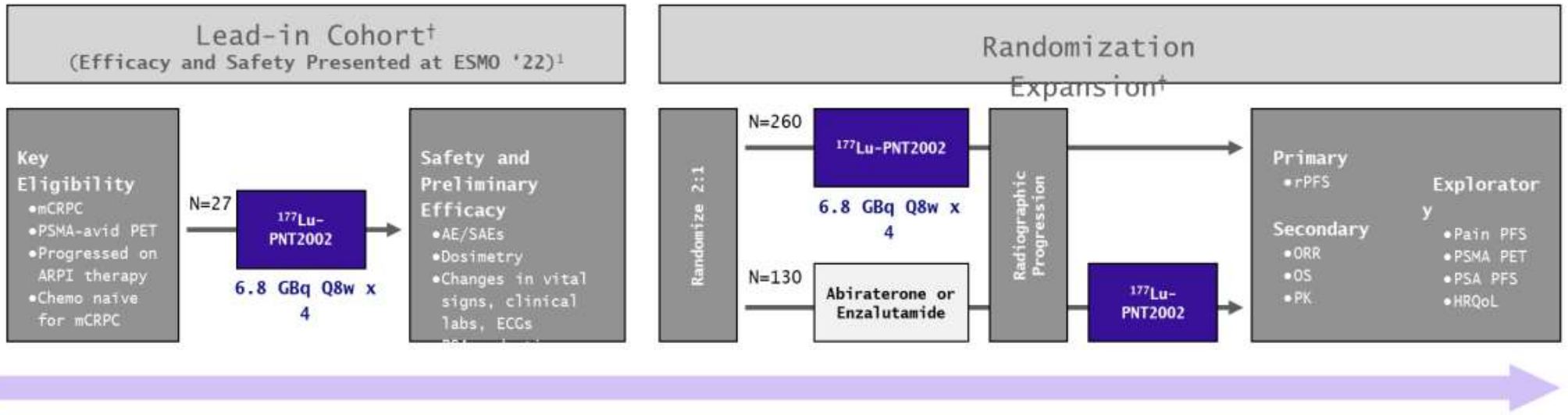


Novartis (NCT04689828)

Next Steps: SPLASH

SPLASH (**S**tudy Evaluating Metastatic Castrate Resistant **P**rostate Cancer Using ^{177}**L**u-PNT2002 PSMA Therapy versus Abiraterone or Enzalutamide **A**fter **S**econd-Line **H**ormonal Treatment*, a multi-center, open label, randomized study)

SPLASH is designed to evaluate ^{177}Lu-PNT2002 earlier in the treatment pathway and using fewer and lower doses, as compared to the currently approved indication for radioligand treatment in prostate cancer



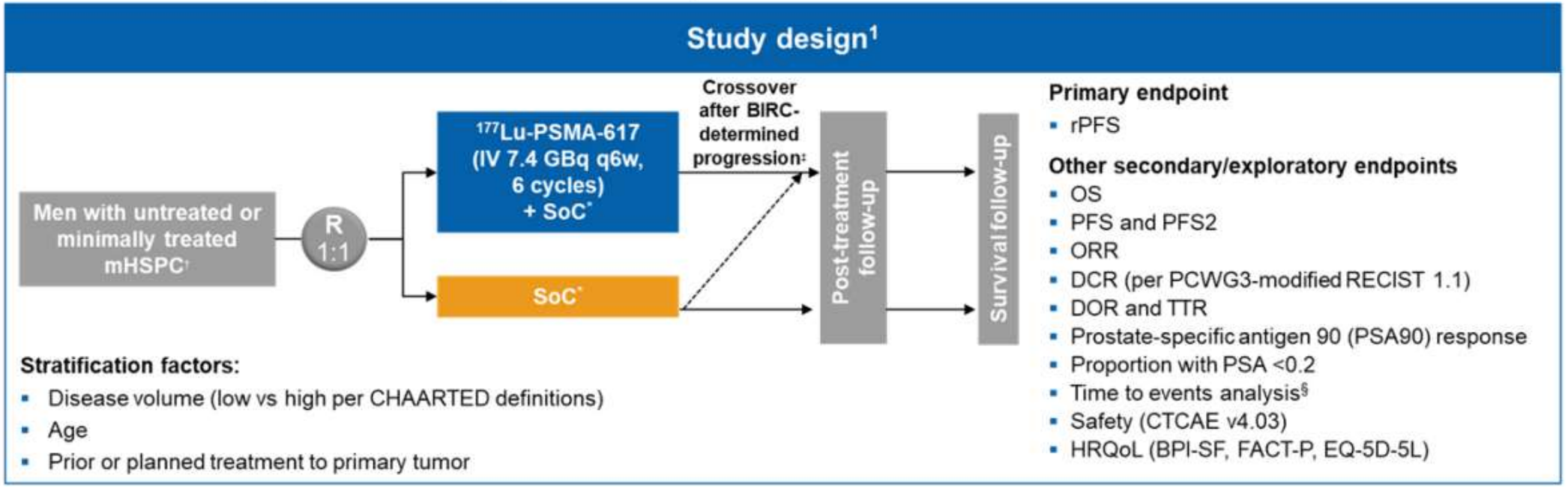
*NCT04647526; †Screening 6 weeks; [1]e-Poster presentation #1400P, ESMO 2022, Paris, France. AE, adverse event; ARPI, androgen receptor pathway inhibitor; ECG, electrocardiogram; HRQoL, health-related quality of life; mCRPC, metastatic castrate-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetic; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SAE, serious adverse event.

Point Biopharma (NCT04647526)

Next Steps: PSMAddition

PSMAddition: a randomized, phase 3 study of ^{177}Lu-PSMA-617 in patients with untreated or minimally treated mHSPC

- PSMAddition aims to assess the efficacy and safety of ^{177}Lu-PSMA-617 RLT plus SoC* vs SoC in men with untreated/minimally treated mHSPC (NCT04720157)[1]



Novartis (NCT04720157)

Summary

- ^{177}Lu-PSMA 617 RLT is FDA approved (VISION setting)
- Need to perform PSMA PET for selection of patients
- Next Steps: moving to earlier lines (PSMAfore, SPLASH, PSMAddition)
- New radionuclides (e.g. ^{212}Pb, ^{225}Ac), new ligands (e.g. J591) and new targets (e.g. GRP, HK2) in clinical translation

Theranostics: Field of Growth

Thank you very much for your attention!

#ProfKHerrmann

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