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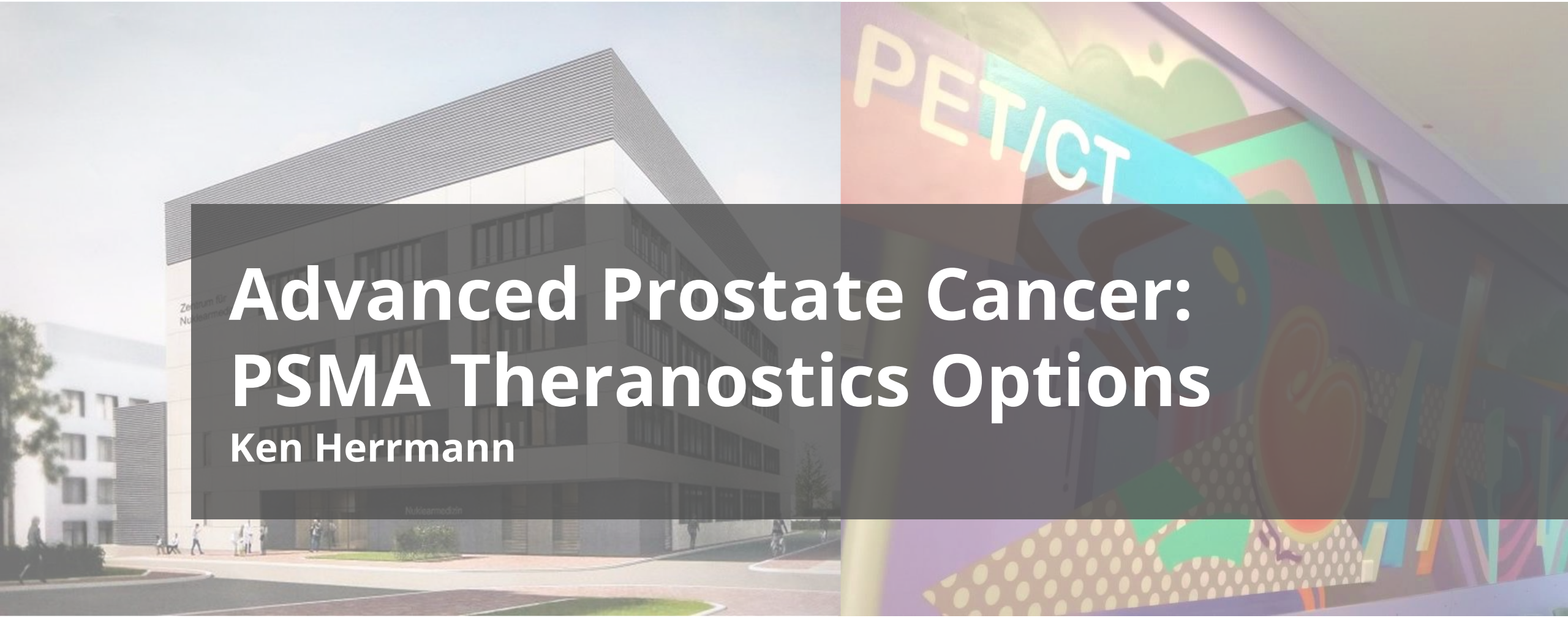

Advanced Prostate Cancer: PSMA Theranostics Options

Ken Herrmann

DISCLOSURES (ACCORDING TO EANM)

1) I or one of my co-authors hold a position as an employee, consultant, assessor or advisor for a pharmaceutical, device or biotechnology company. **Consultant/Advisor of Bayer, IPSEN, Sofie Biosciences, Aktis Oncology, MPM Capital, Bain Capital, SIRTEX, Curium, ABX, BTG/BSC, Adacap/Novartis, Endocyte, Janssen, Amgen, Theragnostics, GE and Siemens.**

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4) I or one of my co-authors have written articles for (radio)pharmaceutical, medical device, biotechnology or consulting companies during the last 5 years. **None.**

5) Great collaboration with Johannes Czernin, Matthias Eiber, Wolfgang Fendler, Jeremie Calais, Matthew Rettig, Rob Reiter, Boris Hadaschik, Martin Schuler, Michael Forsting, Michael Lassmann, Andreas K. Buck, Constantin Lapa, Ulrich Dührsen, Lale Umutlu, Samuel Samnick, Hans-Jürgen Wester, Uwe Haberkorn and many others…..

Structure

1. Background
2. Approved PSMA Theranostic
3. Moving forward PSMA Theranostic
4. Opportunities (and Challenges)

VERY TIMELY TOPIC

NEWS FEATURE | FOCUS

Check for updates

Theranostics could be big business in precision oncology

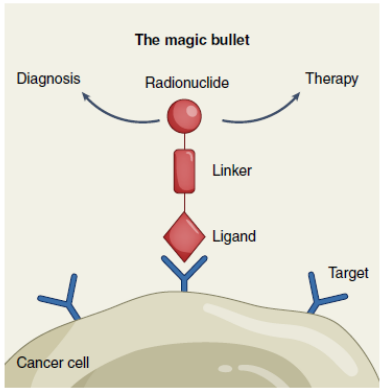
Theranostics aim to both diagnose and treat cancer. Although few such drugs are on the market, many are being tested in clinical trials, with early results showing promise.

Carrie Arnold

The right therapy depends on the right diagnosis. Hippocrates wrote as much more than 2,000 years ago, and physicians have honed their diagnostic ability over the years. In an era of personalized medicine, when treatments can vary based on molecular markers, getting a precise diagnosis is even more crucial. Nowhere in medicine has this become more apparent than in oncology.

Radioactive results

In the past few years, interest in combining therapies and diagnostics has boomed and turned into a field of its own: theranostics. Major cancer centers across the United States, Europe and around the world have all opened dedicated theranostics centers in



The magic bullet. Theranostics target unique

by developing the right chemical. Just two years later, Ehrlich's lab at the Institute of Experimental Therapy in Frankfurt developed the first magic bullet in arsphenamine (Salvarsan), the first effective drug for syphilis. The idea spread outside microbiology, and cancer researchers took up the banner. Their task was more difficult because, biologically speaking, a tumor cell is nearly identical to the surrounding tissue. Early developers of cancer therapies began to take advantage of the vagaries of the body itself: bone disproportionately snatches up calcium and phosphorus, and the butterfly-shaped thyroid gland hogs the body's iodine intake.

For scientists studying bone cancer and metastases, as well as thyroid cancer and

NATURE MEDICINE | VOL 28 | APRIL 2022 | 606–608 | www.nature.com/naturemedicine

March 2022: FDA approval

d Databases / Resources for Information | Approved Drugs / FDA approves Pluvicto for metastatic castration-resistant prostate cancer

FDA approves Pluvicto for metastatic castration-resistant prostate cancer

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On March 23, 2022, the Food and Drug Administration approved Pluvicto (lutetium Lu 177 vipivotide tetraxetan, Advanced Accelerator Applications USA, Inc., a Novartis company) for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

On the same day, the FDA approved Locametz (gallium Ga 68 gozetotide), a radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Locametz is the first radioactive diagnostic agent approved for patient selection in the use of a radioligand therapeutic agent.

Patients with previously treated mCRPC should be selected for treatment with Pluvicto using Locametz or another approved PSMA-11 imaging agent based on PSMA expression in tumors. PSMA-positive mCRPC was defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded from enrollment if any lesions exceeding certain size criteria in the short axis had uptake less than or equal to uptake in normal liver (See full prescribing information, section 14).

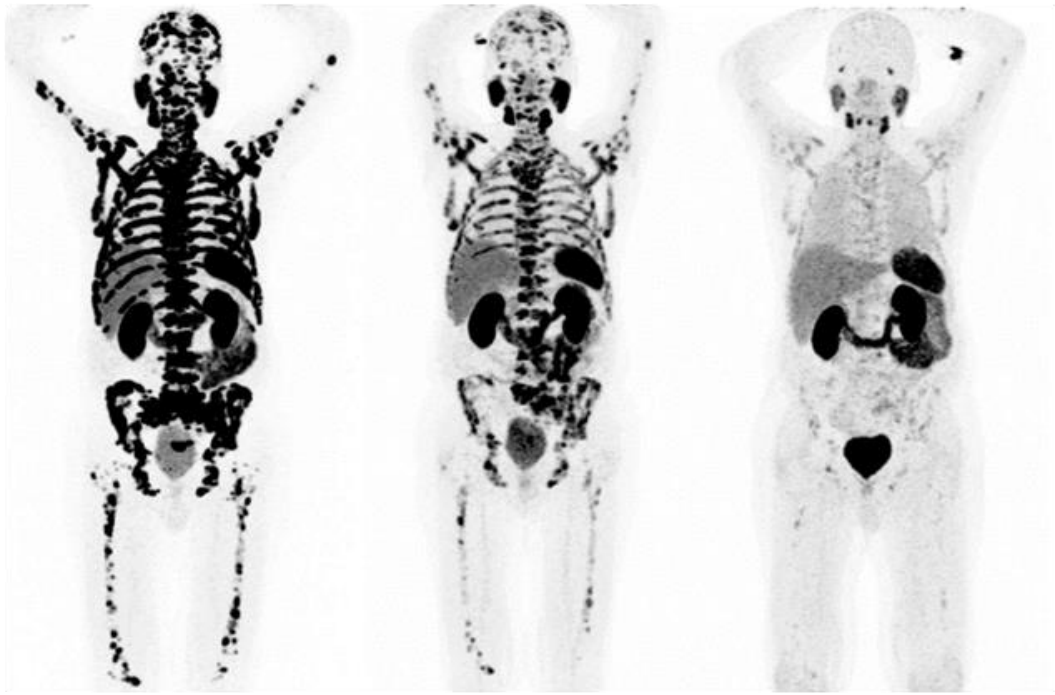
Novartis receives European Commission approval for Pluvicto® as the first targeted radioligand therapy for treatment of progressive PSMA–positive metastatic castration-resistant prostate cancer

Dec 13, 2022

- *EC approval based on results from pivotal Phase III VISION trial, in which Pluvicto® plus best standard of care (BSoC) significantly improved overall survival and radiographic progression-free survival in patients with pre-treated PSMA–positive mCRPC[1]*

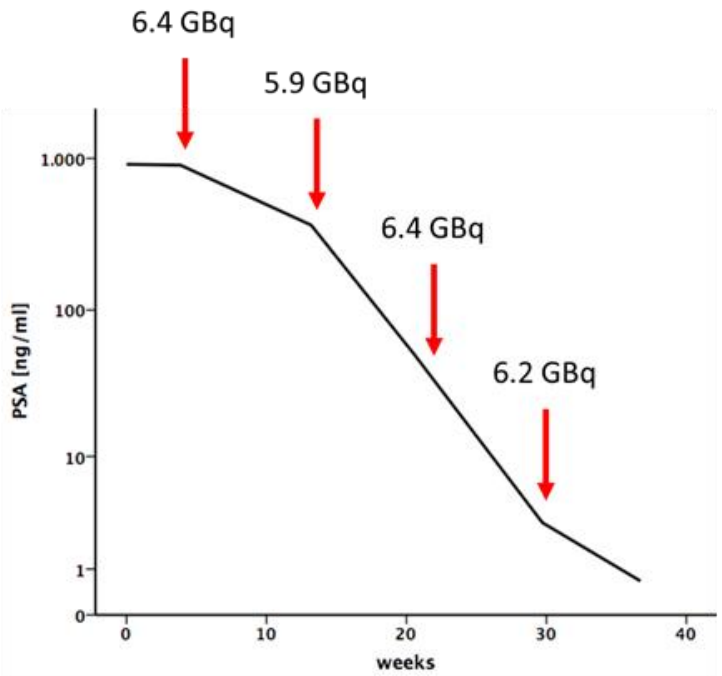
„SEEING WHAT YOU TREAT“ AND „TREATING WHAT YOU SEE“

PSMA PET/CT Scans: Target Expression



Baseline after 2 cycles after 4 cycles

PSA Levels



Rahbar et al. EJNMMI 2018; Fendler et al. JAMA Oncol 2019;

Structure

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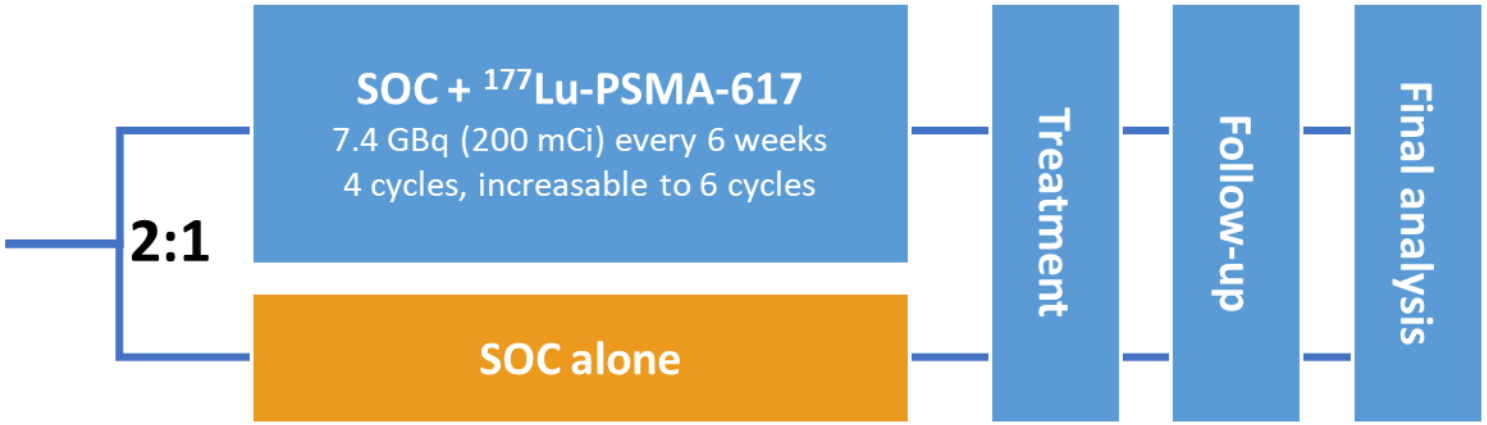
VISION Study Design

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

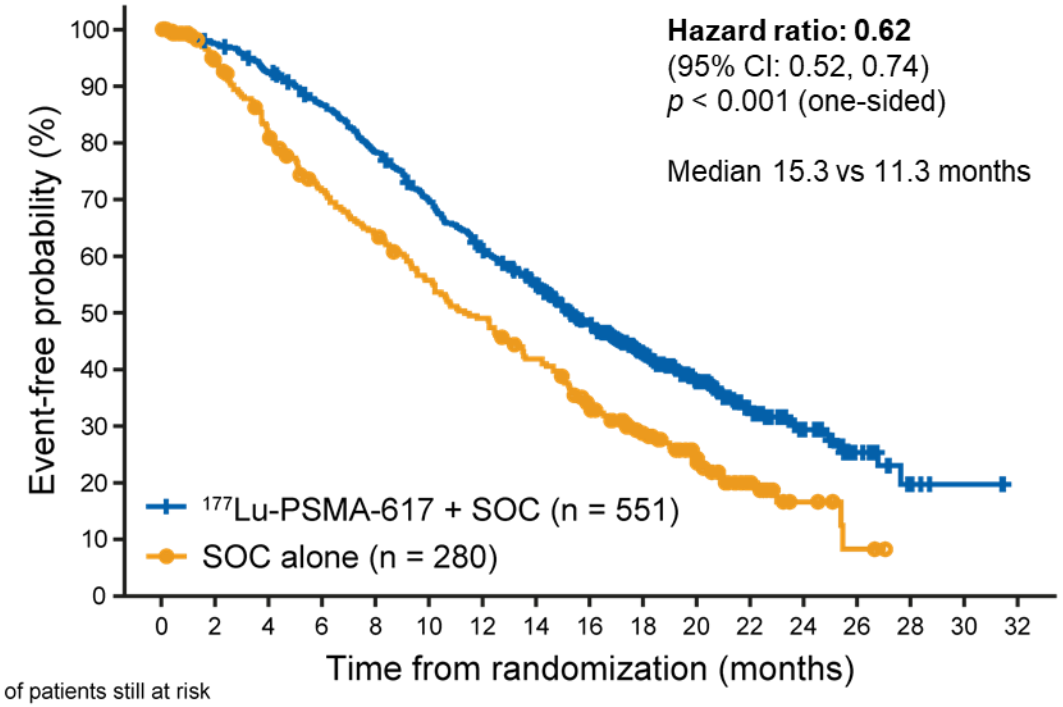
- Every 8 weeks (treatment)
- Every 12 weeks (follow-up)
- Blinded independent central review

Sartor et al., NEJM 2021

VISION RESULTS

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

All randomized patients (N = 831)

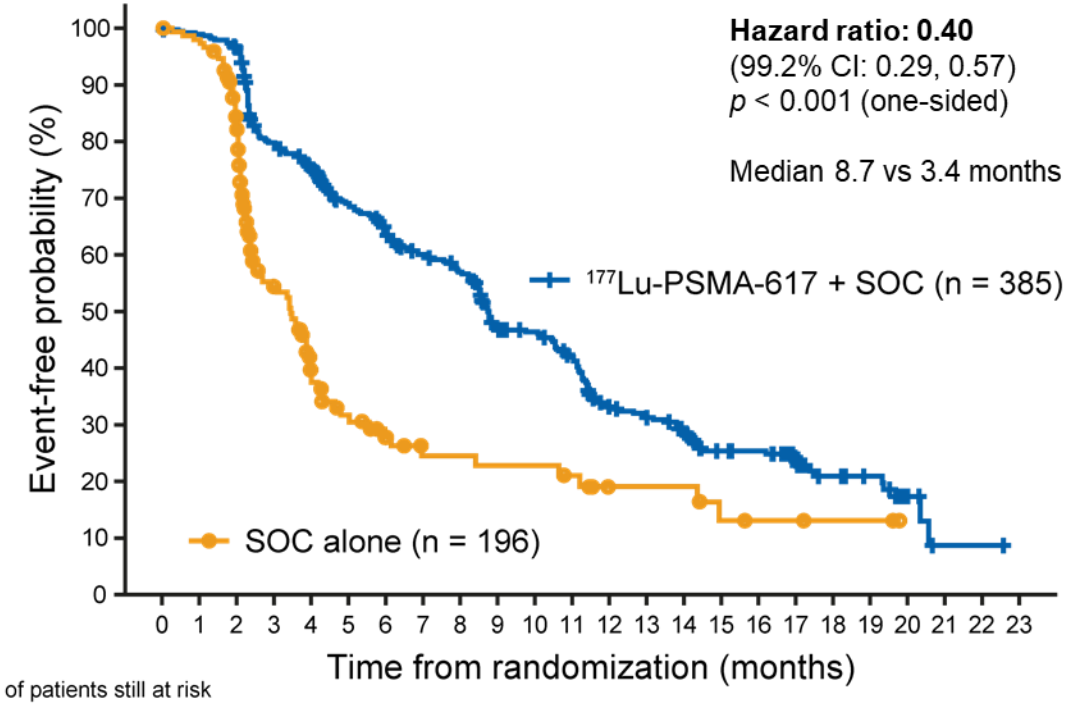


Number of patients still at risk

^{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

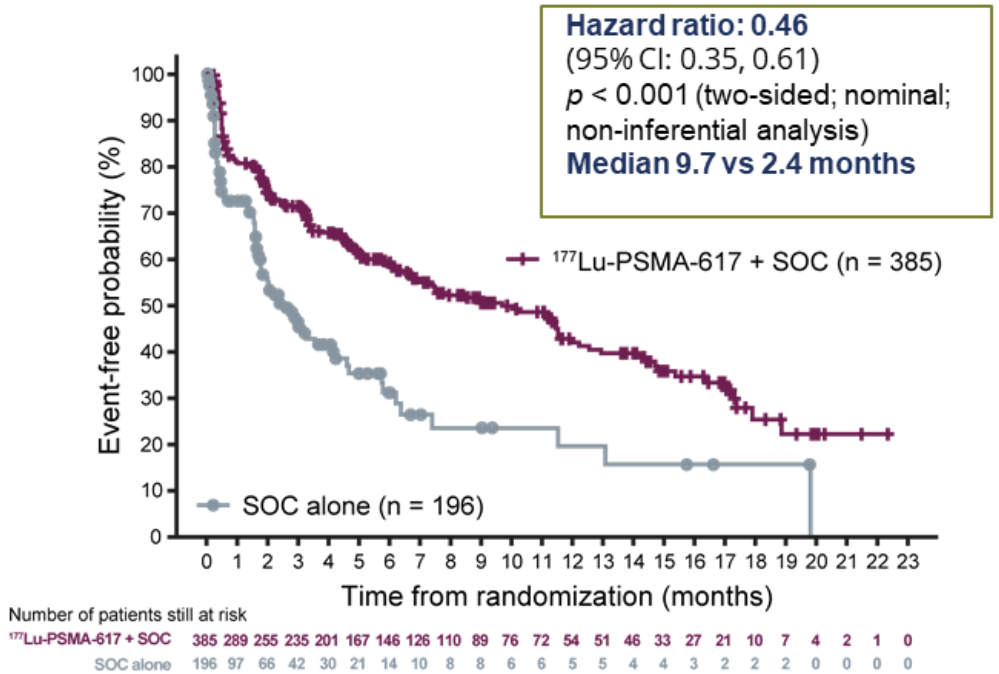
Sartor et al., NEJM 2021

VISION RESULTS

***Ad hoc* analyses**

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

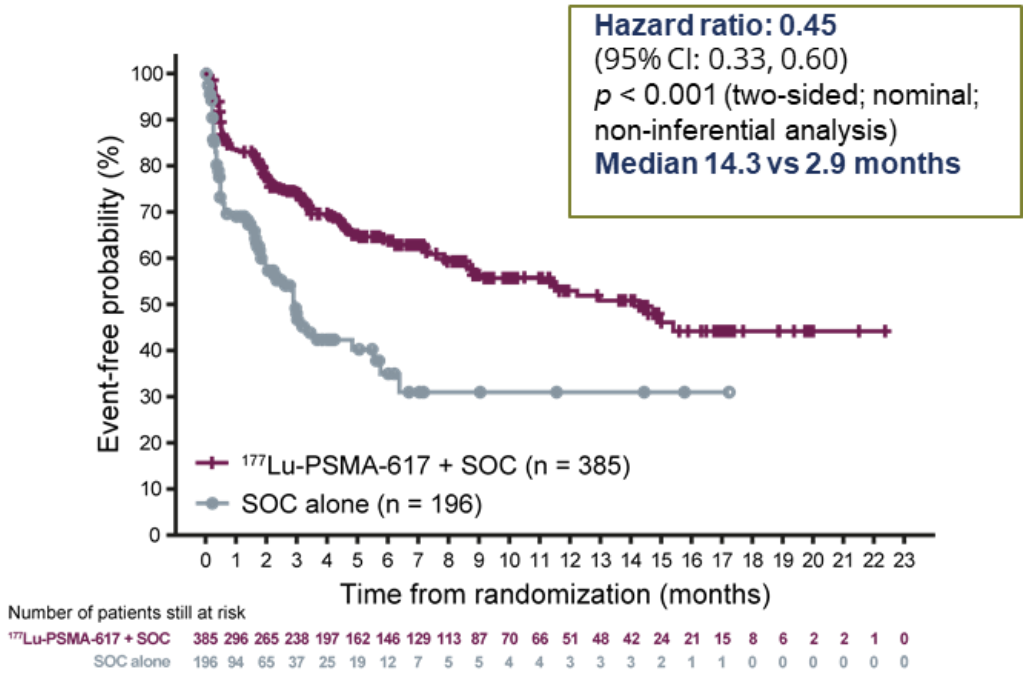
rPFS analysis set (n = 581)



Time to the first occurrence of ≥ 10-point decrease in FACT-P total from baseline

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

rPFS analysis set (n = 581)



Time to the first occurrence of ≥ 30% or ≥ 2-point increase in BPI-SF pain intensity from baseline

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

Fizazi et al. ESMO 2021: 576MO

VISION Toxicity

Patients, n (%)	^{177}Lu-PSMA-617 + SOC (n = 529)		SOC alone (n = 205)	
	All grades	Grade 3–5	All grades	Grade 3–5
Any drug-related TEAE	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
Serious	49 (9.3)	43 (8.1)	5 (2.4)	5 (2.4)
Grade 5[a]	5 (0.9)	5 (0.9)	0 (0.0)	0 (0.0)
TEAEs grouped by topics of interest				
Fatigue	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Bone marrow suppression	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Anaemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Dry mouth	208 (39.3)	0 (0.0)	2 (1.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Renal effects	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
Second primary malignancies	11 (2.1)	4 (0.8)	2 (1.0)	1 (0.5)
Intracranial haemorrhage	7 (1.3)	5 (0.9)	3 (1.5)	2 (1.0)

Fizazi et al. ESMO 2021: 576MO

THERAP TRIAL

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

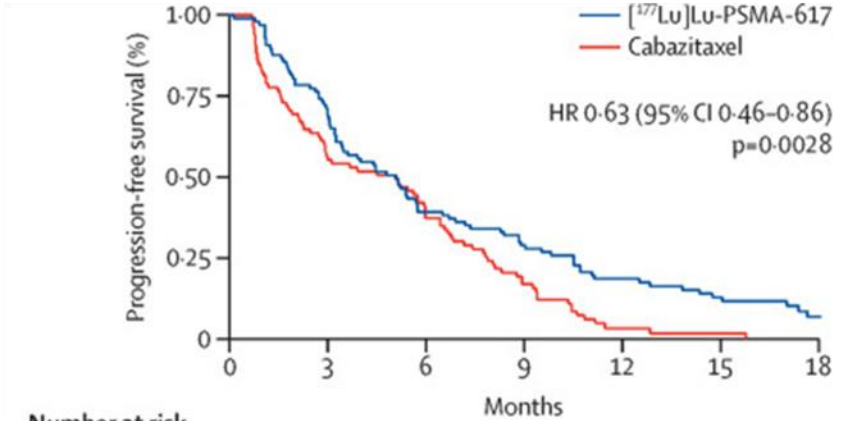
^{177}Lu-PSMA-617
8.5 GBq IV q6 weekly
↓ 0.5GBq each cycle
Up to 6 cycles

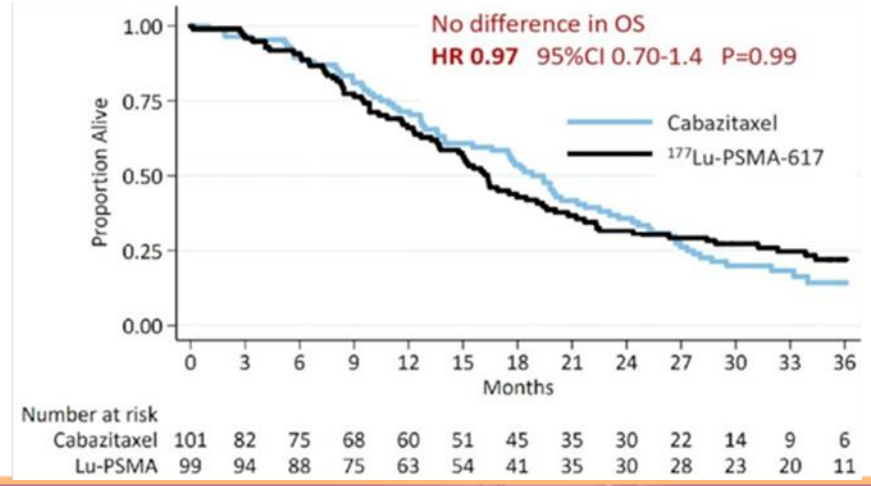
→ **SPECT/CT @ 24 hours**
suspend Rx if exceptional response; recommence upon progression

CABAZITAXEL
20mg/m² IV q3 weekly,
Up to 10 cycles

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

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

RLT FOR mCRPC APPROVED AND IN DEVELOPMENT

	Probe	Ligand type	Company	Status
	^{177}Lu-PSMA-617	Small molecule	AAA, academic centers	**FDA and EMA 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

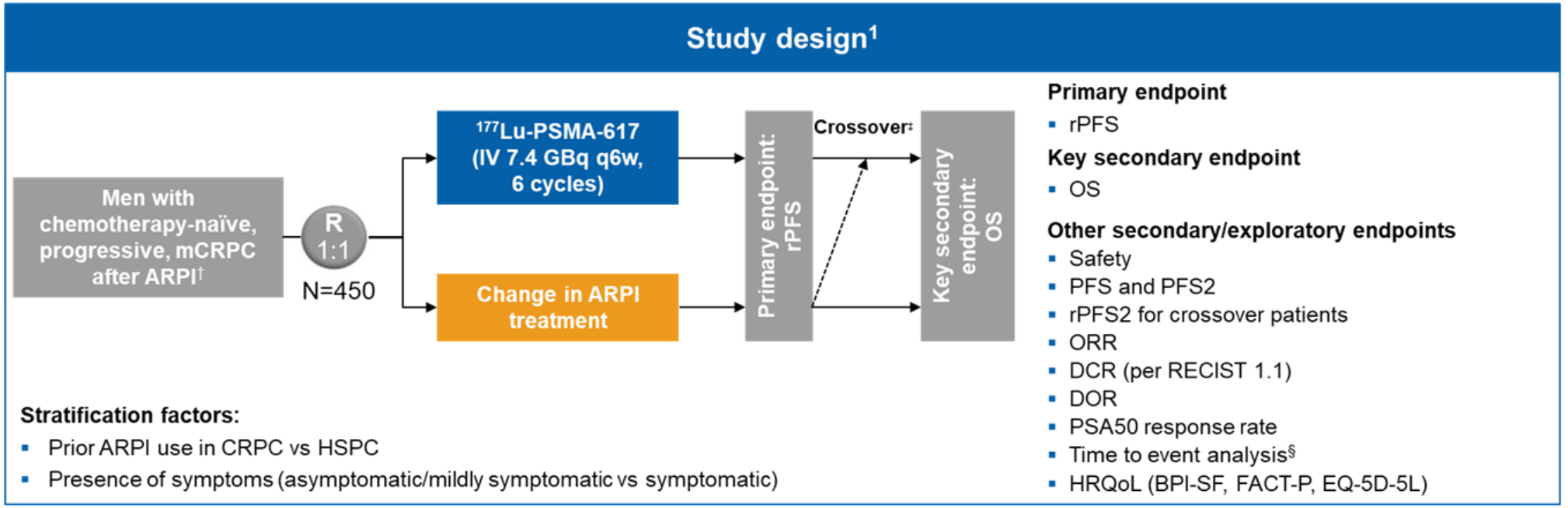
mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.
https://www.clinicaltrials.gov/ct2/results?cond=prostate+cancer&term=radioligand+therapy+&cntry=&state=&city=&dist= (last accessed 15 July 2022).

Structure

1. Background
2. Approved PSMA Theranostic
3. Moving forward PSMA Theranostic
4. Opportunities (and Challenges)

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)

EARLIER LINES mCRPC (PRE-CHEMO)

NOVARTIS

Search Global | en Menu

Home > News > Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA–positive metastatic c ...

Novartis Pluvicto™ shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA–positive metastatic castration-resistant prostate cancer

Dec 05, 2022

Ad hoc announcement pursuant to Art. 53 LR

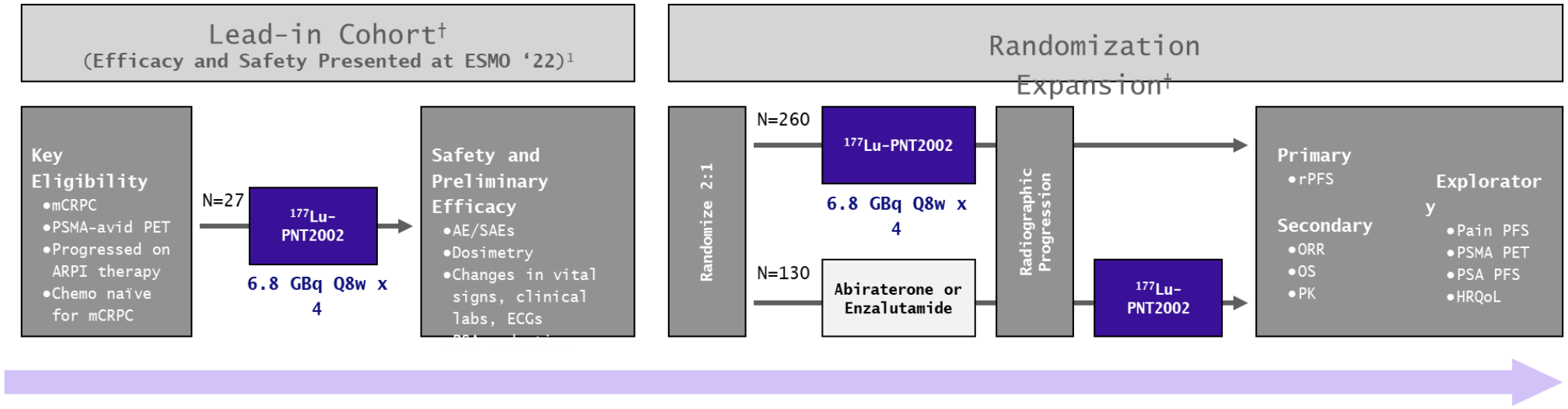
- *Phase III PSMAfore trial with Pluvicto™ met the primary endpoint of radiographic progression-free survival (rPFS) in PSMA–positive mCRPC who have been treated with androgen-receptor pathway inhibitor (ARPI) therapy[1]*
- *Pluvicto becomes the first PSMA-targeted radioligand therapy to demonstrate clinical benefit in mCRPC patients before receiving taxane-based chemotherapy[1], addressing a significant unmet need[2]*
- *Findings to be presented at an upcoming medical meeting and submitted to regulatory authorities for approval in 2023*
- *Novartis is advancing a broad portfolio of radioligand therapies to treat cancer and is investing in manufacturing capacity to meet the growing global demand for treatment*

Novartis (NCT04689828)

EARLIER LINES MCRPC (PRE-CHEMO)

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

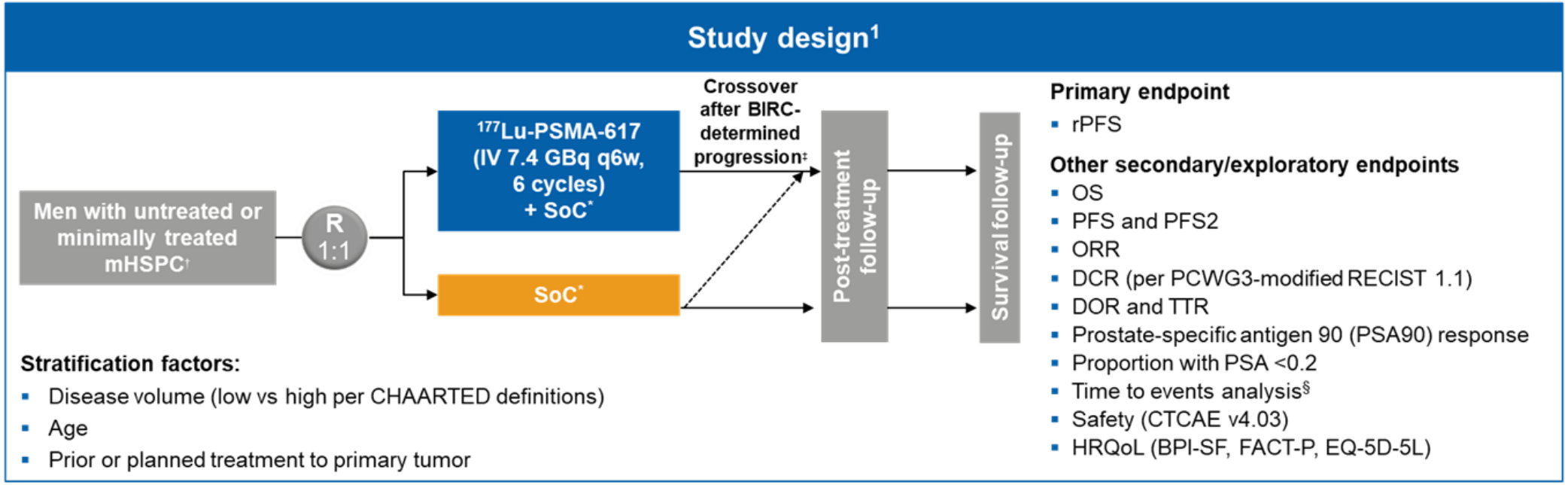


*NCT04647526; † Screening 6 weeks; [1]e-Poster presentation #1400P, ESMO 2022, Paris, France. AE, adverse event; ARPI, androgen receptor pathway inhibitor; ECG, electrocardiogram; HRQoL, health-related quality of life; mCRPC, metastatic castrate-resistant prostate cancer; ORR, objective response rate; 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)

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)

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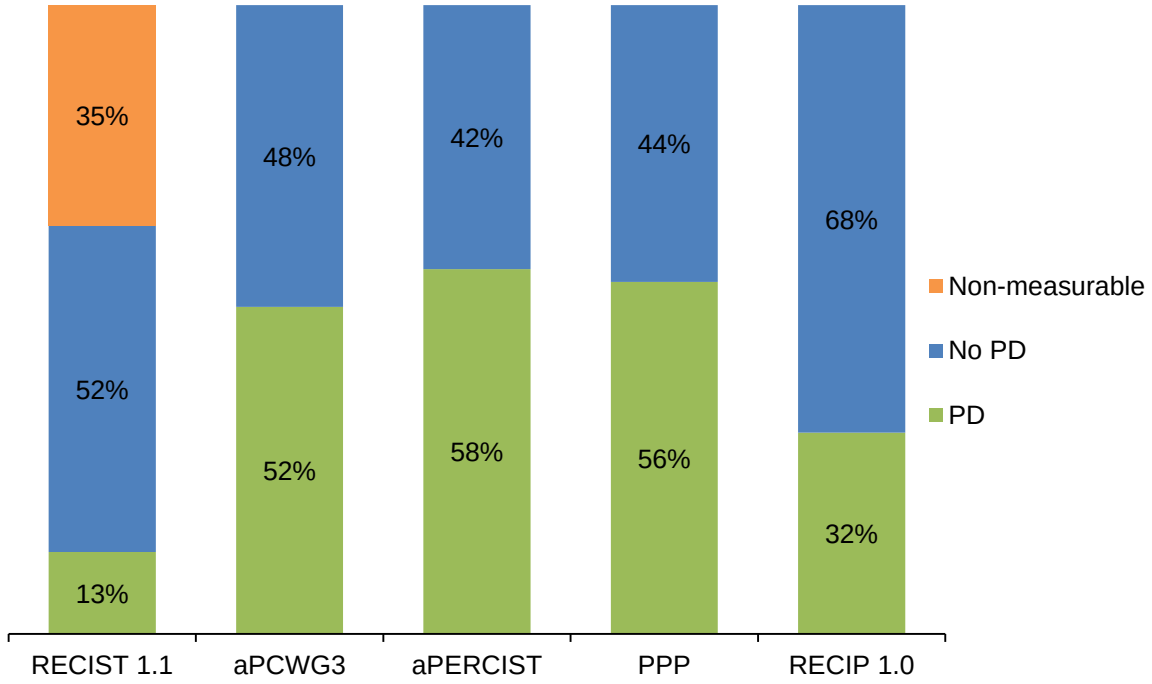
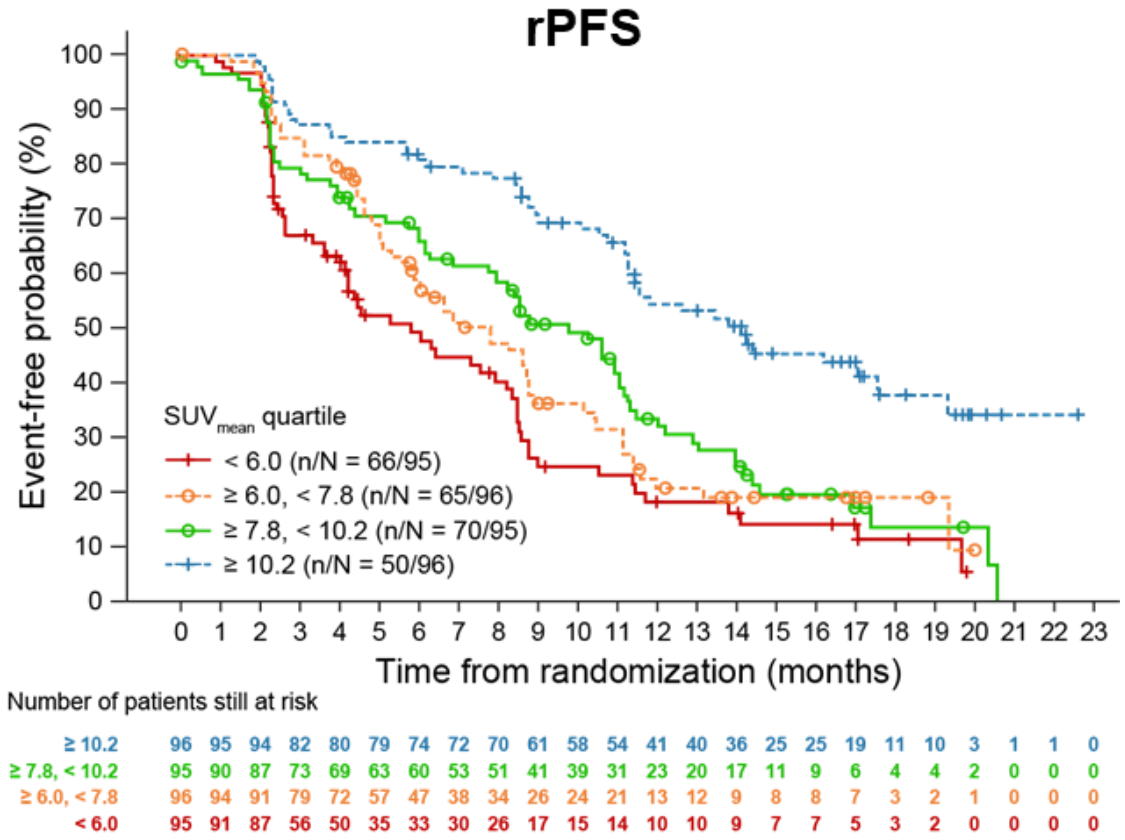
Establishing PSMA PET for Patient Selection and Response Monitoring

Interpretation of response among criteria for response evaluation at 12 weeks after ^{177}Lu-PSMA radioligand therapy[1]



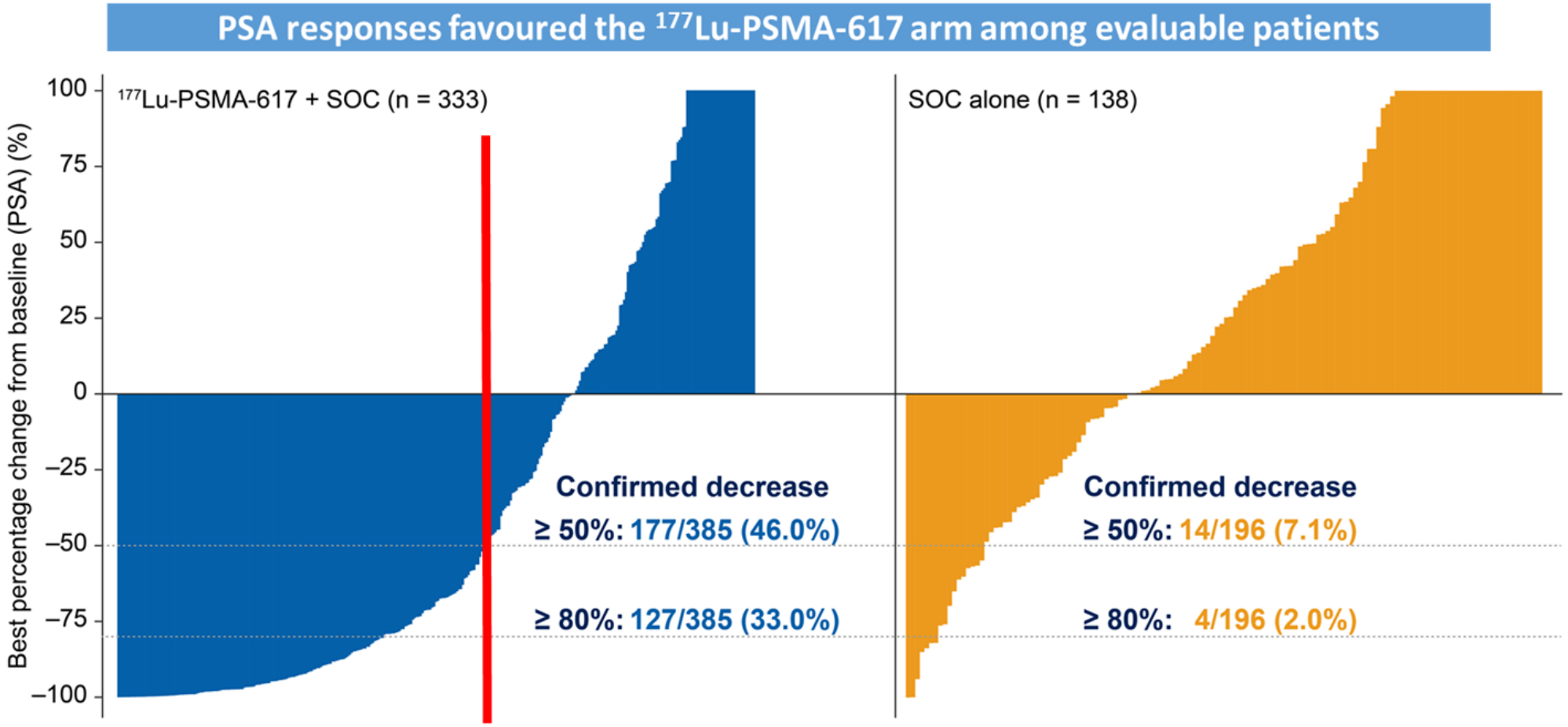
PSMA PET SUV_{mean} at baseline as a predictor of response to ^{177}Lu-PSMA-617 radioligand therapy[2]



aPERCIST, adapted Positron Emission Tomography Response Criteria in Solid Tumors; aPCWG3, adapted Prostate Cancer Working Group Criteria; PD, progressive disease; PET, positron emission tomography; PPP, PSMA PET progression; PSMA, prostate-specific membrane antigen; RECIP, Response Evaluation Criteria In PSMA-Imaging; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival; SUV, standardized uptake value.

1. Gafita A, et al. Eur J Nucl Med Mol Imaging 2022;doi:10.1007/s00259-022-05882-x; 2. Kuo P, et al. J Clin Oncol 2022;40(no. 16_suppl):5002.

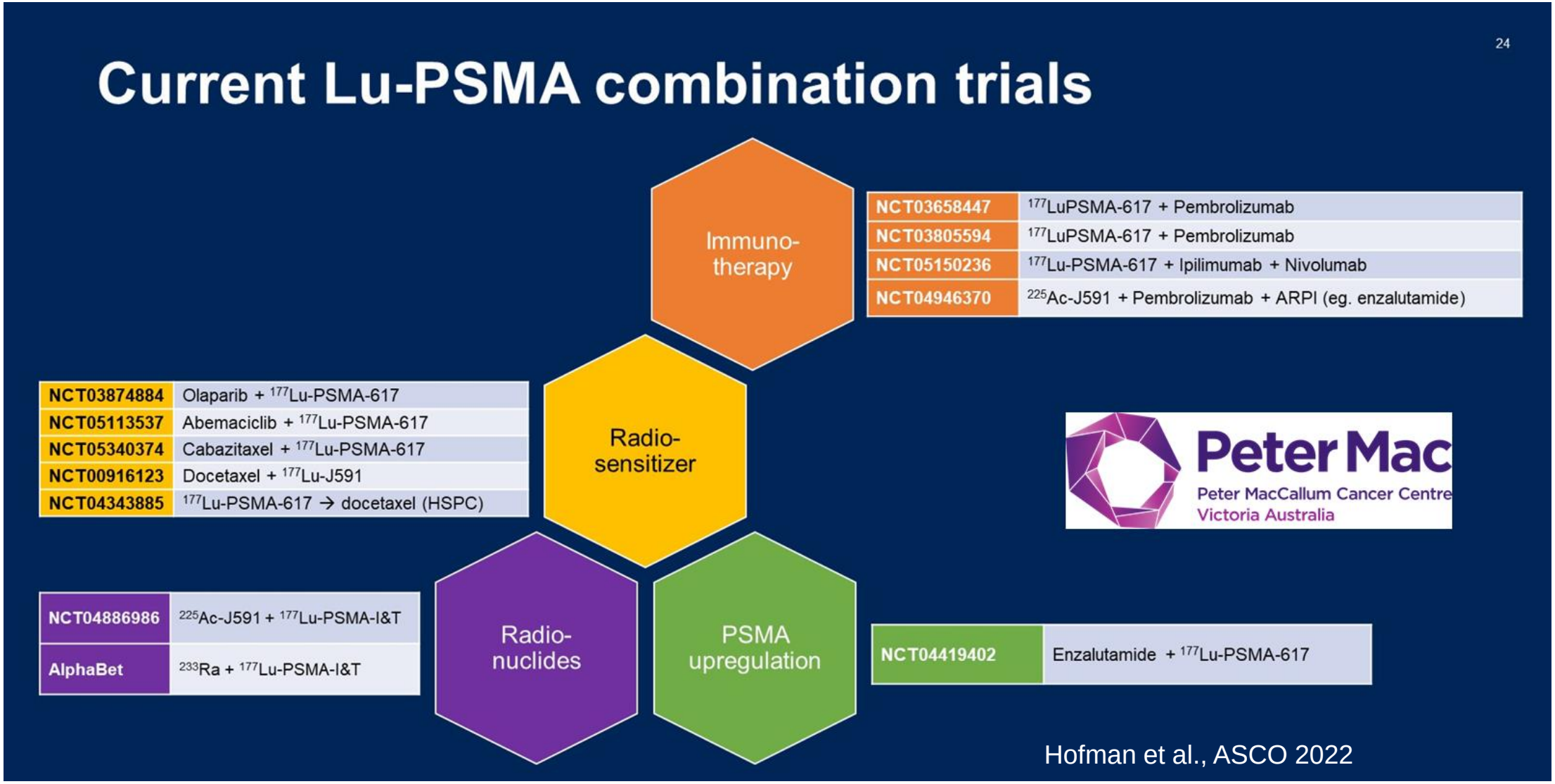
VISION: Room For Improvement



More than 50% of patients do NOT respond (PSA decrease >50%).

Sartor et al., NEJM 2021

COMBINATION TREATMENT



Different Targets and Radionuclides

Clinicaltrials.gov Search:

LRRC15-binders

GRPR-peptide binders

hK2-mab (JNJ-69086420)

H5A10-mab

Neurotensine-peptide binders

https://www.nicepng.com/maxp/u2w7u2a9i1w7q8u2/

New Radionuclides such as ^{212}Pb, ^{64}Cu, ^{161}Tb etc.

MAJOR CHALLENGES

1. Lack of Professionals
2. Patient Referral
3. Economics

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-022-05785-x

GUIDELINES

Joint EANM, SNMMI and IAEA enabling guide: how to set up a theranostics centre

Ken Herrmann[1,2] · Luca Giovanella[3] · Andrea Santos[4] · Jonathan Gear[5] · Pinar Ozgen Kiratli[6] · Jens Kurth[7] · Ana M. Denis-Bacelar[8] · Roland Hustinx[9,10] · Marianne Patt[11] · Richard L. Wahl[12] · Diana Paez[13] · Francesco Giammarile[13] · Hossein Jadvar[14] · Neeta Pandit-Taskar[15] · Munir Ghesani[16] · Jolanta Kunikowska[17]

Received: 15 March 2022 / Accepted: 25 March 2022

Journal of Nuclear Medicine, published on April 21, 2022 as doi:10.2967/jnumed.122.264321

Joint EANM, SNMMI and IAEA Enabling Guide: How to Set Up a Theranostics Centre

Ken Herrmann[1], Luca Giovanella[2], Andrea Santos[3], Jonathan Gear[4], Pinar Ozgen Kiratli[5], Jens Kurth[6], Ana M Denis-Bacelar[7], Roland Hustinx[8], Marianne Patt[9], Richard L. Wahl[10], Diana Paez[11], Francesco Giammarile[11], Hossein Jadvar[12], Neeta Pandit-Taskar[13], Munir Ghesani[14] and Jolanta Kunikowska[15]

Summary

- PSMA Theranostics ready for prime time: FDA and EMA approval
- VISION paved the way to establish PSMA Theranostics as „volume“ indication
- Next steps: moving PSMA RLT into earlier lines
- Major opportunities/challenges need to be addressed (Scale Up, Logistics, Combination Treatment, Costs)
- Most important need: To „oncologize“ nuclear medicine
- Opportunity to establish a „new platform technology“

Theranostics: Field of Growth

Thank you very much for your attention!

Twitter: #ProfKHerrmann

Universitätsmedizin Essen
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Klinik für Nuklearmedizin