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Cancer Center

Lu-177 PSMA617: A game changing therapy for prostate cancer treatment

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What is the field of theranostics?

- A field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests.

A *single* agent is used to:

- Image the presence of a target
- Deliver treatment to that target to destroy it

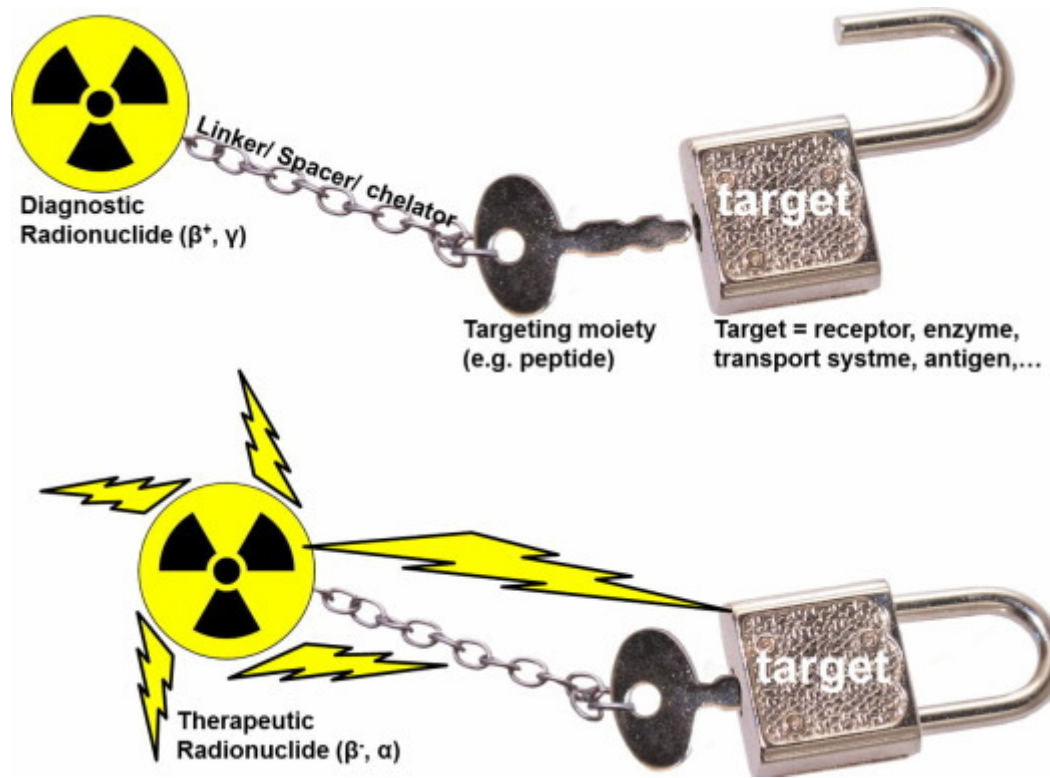
Theranostics are systems that are capable of *diagnosis, drug delivery and monitoring of therapeutic response*



What are the advantages of theranostics?

- You spare patients treatment who would otherwise not respond
 - (by identifying that they don't have the target)
- You can predict who will suffer side effects that are disproportionate to the anticipated benefit
 - (by seeing how normal tissues would be affected by the drug)
- You can determine how effective your treatment is, and then re-treat if necessary

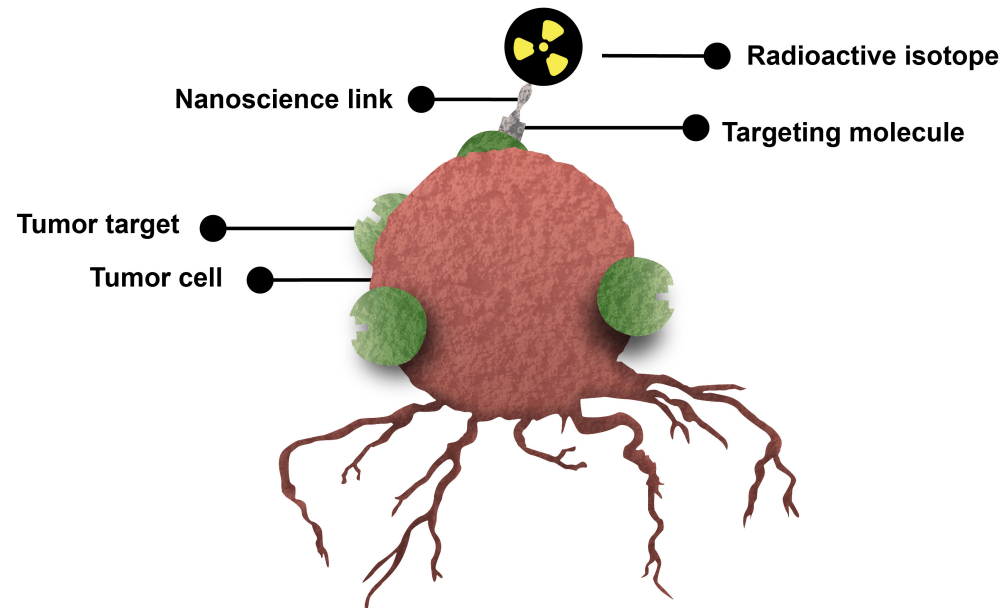
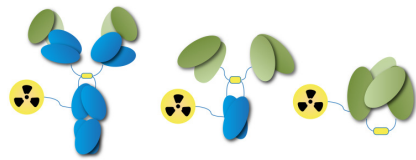
How does this work conceptually?



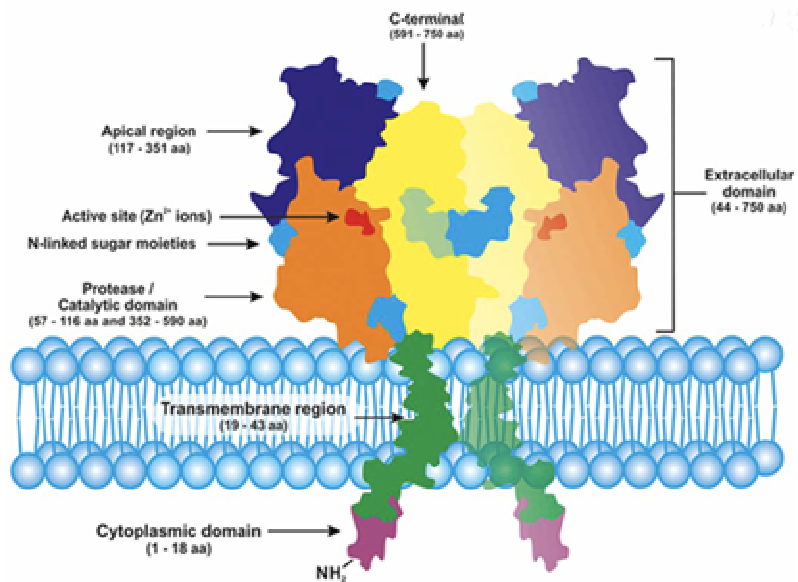
Radioligand Therapy: The elements of treatment

Imaging:
Ga-68
F-18

Therapy:
Lu-177
Ac-225
Th-227



PSMA



- An ideal target for both therapy and imaging
- High tumor specificity
- Regulated by AR (decreased signaling results in increased expression in mCRPC)

O'driscoll at al Br J Pharmacol, 2016



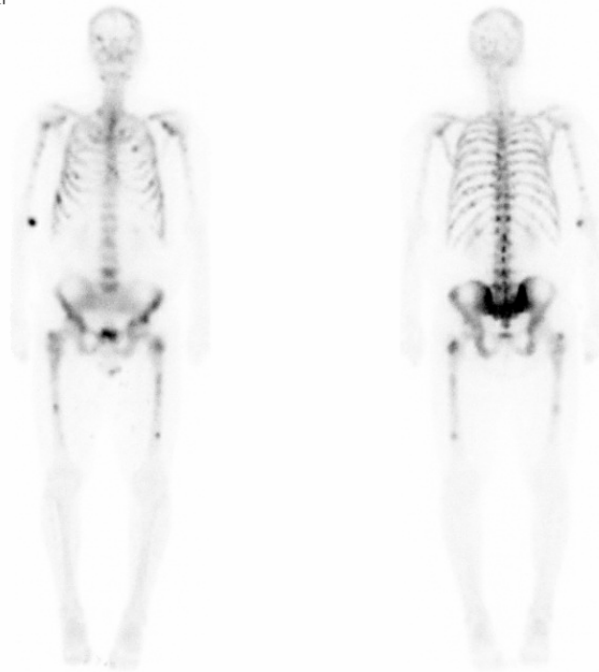
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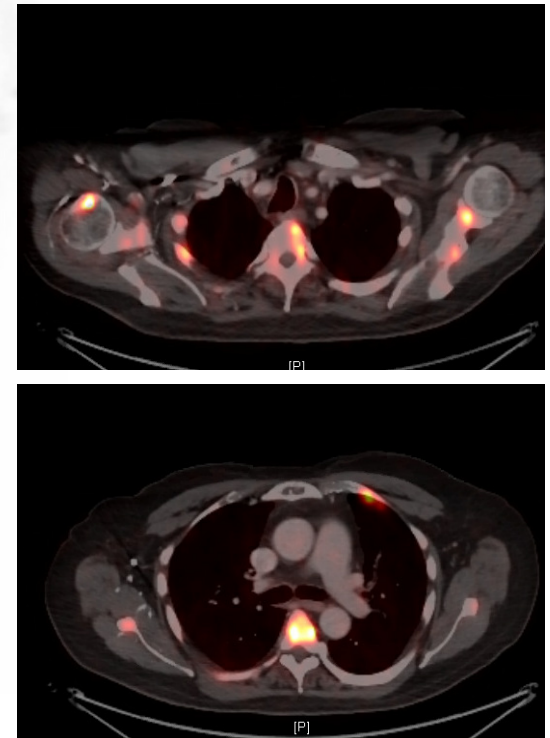
Where is PSMA?

- On normal prostate tissue
- On prostate cancer cells in the prostate
- On prostate cancer cells in the lymph nodes
- On prostate cancer cells in the bones
- On prostate cancer cells in other organs
- In very small amounts, in some rare normal tissues in the liver, kidney, gut, and nervous system

Bone scans vs. PET scans



Bone scan – images abnormal bone



PSMA PET – images cancer with PSMA



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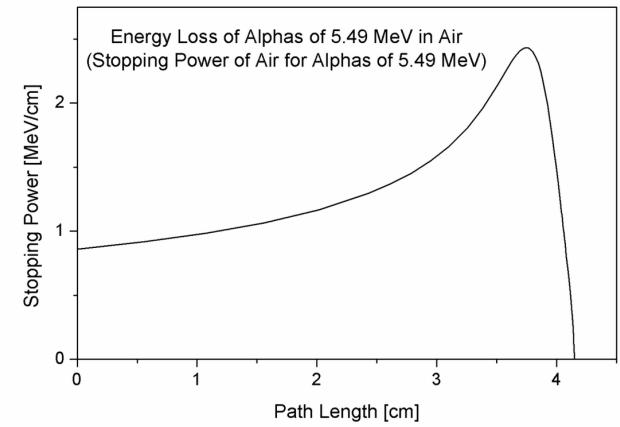
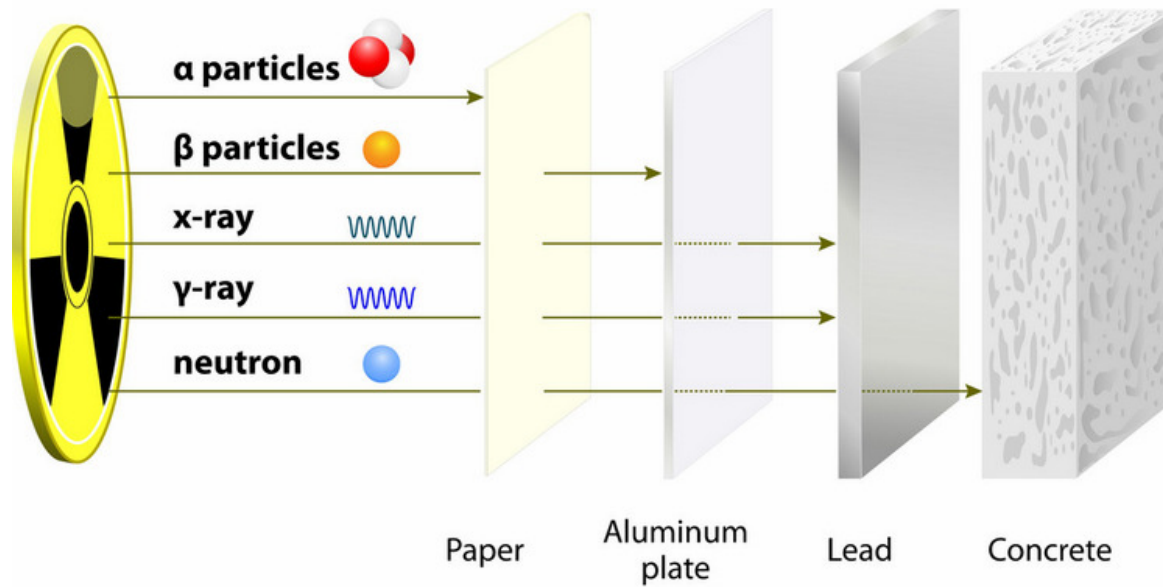
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**Now we can not only detect disease, but
treat it...**

How?

In real life...

TYPES OF RADIATION AND PENETRATION



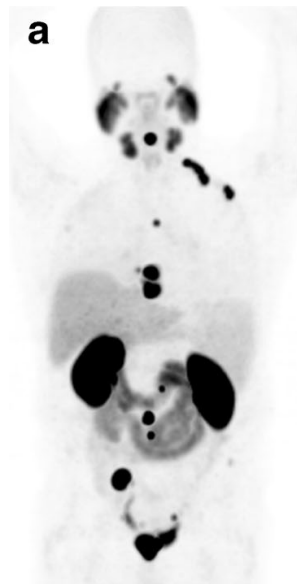
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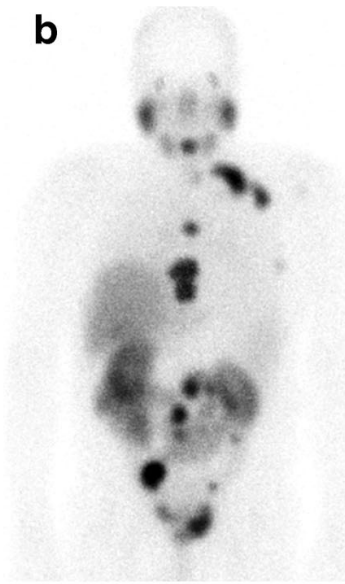
So...

- Alpha and betas are used as therapy
- They have very different properties
 - Side effects
 - Impact of tumor mass
- Pluses and minuses for each

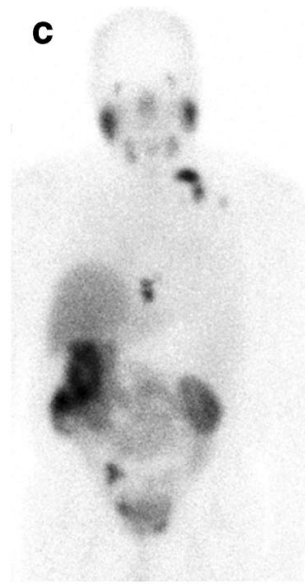
^{177}Lu -PSMA-617



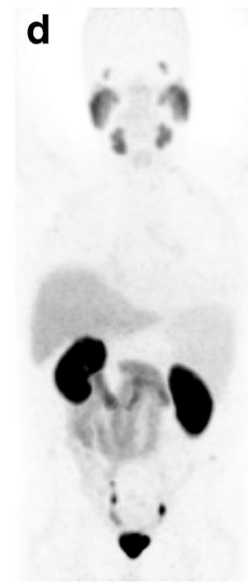
12/13
 ^{68}Ga -DKFZ-11
PSMA-PET/CT, MIP



02/14
 ^{177}Lu -DKFZ-617
Therapy, geometric mean



05/14
 ^{177}Lu -DKFZ-617
Therapy, geometric mean



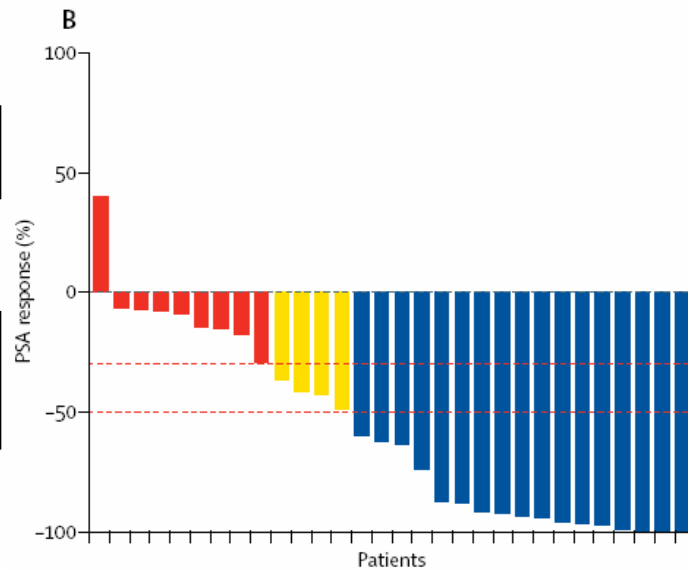
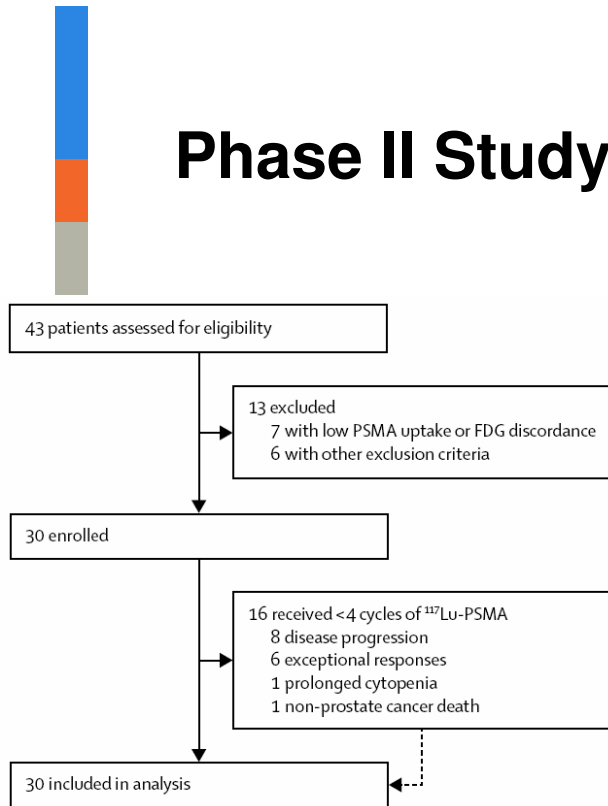
07/14
 ^{68}Ga -DKFZ-11
PSMA-PET/CT, MIP

U. Haberkorn

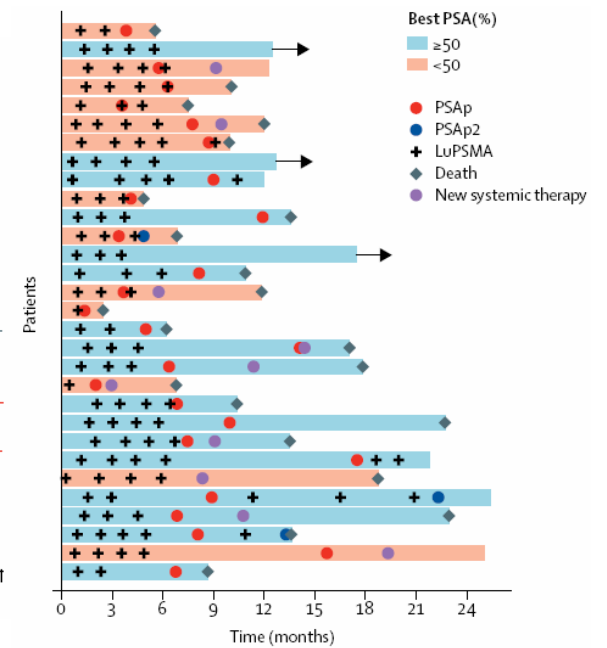


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Phase II Study on ¹⁷⁷Lu-PSMA-617



Best PSA Response



Phase II Study on ¹⁷⁷Lu-PSMA-617: Toxicity

	Grade 1-2	Grade 3	Grade 4	Grade 1-2, attributed to LuPSMA*	Grade 3 attributed to LuPSMA*	Grade 4 attributed to LuPSMA*
Dry mouth	26 (87%)	0	0	26 (87%)	0	0
Lymphocytopenia	12 (40%)	13 (43%)	0	11 (37%)	11 (37%)	0
Thrombocytopenia	12 (40%)	5 (17%)	3 (10%)	8 (27%)	3 (10%)	1 (3%)
Fatigue	16 (53%)	1 (3%)	0	15 (50%)	0	0
Nausea	15 (50%)	0	0	15 (50%)	0	0
Anaemia	7 (23%)	7 (23%)	0	4 (13%)	4 (13%)	0
Neutropenia	12 (40%)	2 (7%)	0	8 (27%)	2 (7%)	0
Pain	8 (27%)	3 (10%)	0	5 (17%)	1 (3%)	0
Vomiting	10 (33%)	0	0	10 (33%)	0	0
Anorexia	8 (27%)	0	0	7 (23%)	0	0
Dry eyes	5 (17%)	0	0	5 (17%)	0	0
Weight loss	3 (10%)	0	0	3 (10%)	0	0
Disseminated	0	1 (3%)	0	0	0	0

TheraP Study: Anticancer Activity of Lu-177 PSMA vs. Cabazitaxel

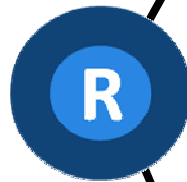
KEY ELIGIBILITY

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



⁶⁸Ga-PSMA + ¹⁸F-FDG PET/CT

- PSMA SUV_{max} >20 at any site
- Measurable sites SUV_{max} >10
- No FDG-positive/PSMA-negative sites of disease
- Centrally reviewed



¹⁷⁷Lu-PSMA-617

8.5 GBq IV q6 weekly
 ↓ 0.5 GBq each cycle
 Up to 6 cycles

200 men 1:1 randomization
 11 sites in Australia

Stratified by:

- Disease burden (>20 sites vs. ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

CABAZITAXEL

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

SPECT/CT @ 24 hours

Suspend R_x if exceptional response; recommence upon progression

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

Permission to present from Dr. M. Hofman.

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; F, fluorine; FDG, fluorodeoxyglucose; Ga, gallium; IV, intravenous;

Lu, lutetium; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; Rx, prescription. SPECT, single photon emission computed tomography; SUV, standardized uptake value.

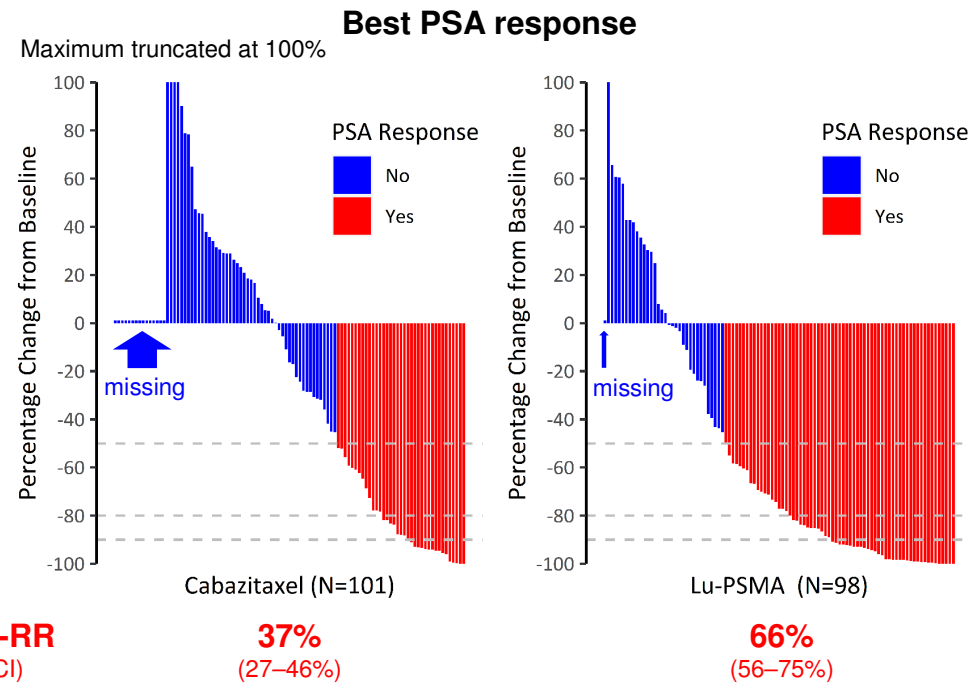
1. Hofman M, et al. Presentation at the 2020 ASCO Virtual Scientific Program; May 29–31, 2020; Abstract 5500.

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Primary Endpoint: PSA $\geq 50\%$ Response (PSA₅₀-RR)



Lu-PSMA: 29% absolute (95% CI 16–42%; p<0.0001) greater PSA₅₀-RR compared with cabazitaxel
 For sensitivity analysis per-protocol, the difference was 23% (95% CI 9–37%; p=0.0016)

Permission to present from Dr. M. Hofman.

CI, confidence interval; Lu, lutetium; PSA, prostate-specific antigen; PSA₅₀-RR, prostate-specific antigen ≥ 50 response rate; PSMA, prostate-specific membrane antigen.
 1. Hofman M, et al. Presentation at the 2020 ASCO Virtual Scientific Program; May 29–31, 2020; Abstract 5500.
 MED-ALL—2000001



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Safety: Selected Adverse Events by Worst Grade

Term	Cabazitaxel (N=85)		Lu-PSMA (N=98)	
	G1-2 %	G3-4 %	G1-2 %	G3-4 %
Neutropenia (+/- fever)	5	13	6	4
Thrombocytopenia	4	0	17	11
Dry mouth	21	0	59	0
Diarrhea	52	5	18	1
Dry eye	4	0	30	0
Dysgeusia	27	0	12	0
Neuropathy (motor or sensory)	26	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	39	1
Anemia	12	8	18	8
Vomiting	12	2	12	1
TOTAL (all AEs)	40	54	53	35

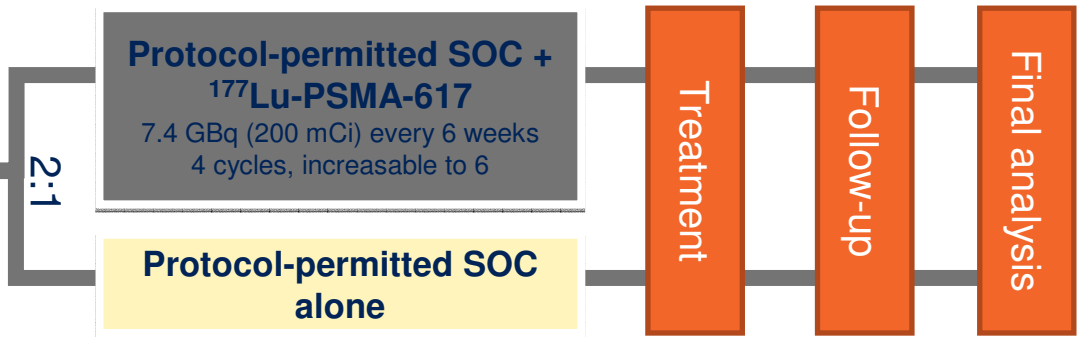
Discontinuations for toxicity occurred in 1/98 (1%) Lu-PSMA vs. 3/85 (4%) cabazitaxel-treated.
There were no Lu-PSMA-related deaths; 5 G5 AEs for cabazitaxel and 11 G5 AEs for Lu-PSMA.

Permission to present from Dr. M. Hofman.
AE, adverse event; G, grade; Lu, lutetium; PSMA, prostate-specific membrane antigen.
1. Hofman M, et al. Presentation at the 2020 ASCO Virtual Scientific Program; May 29–31, 2020; Abstract 5500.
MED-ALL—2000001

Open-label study of protocol-permitted standard of care ± ¹⁷⁷Lu-PSMA-617 in adults with PSMA-positive mCRPC

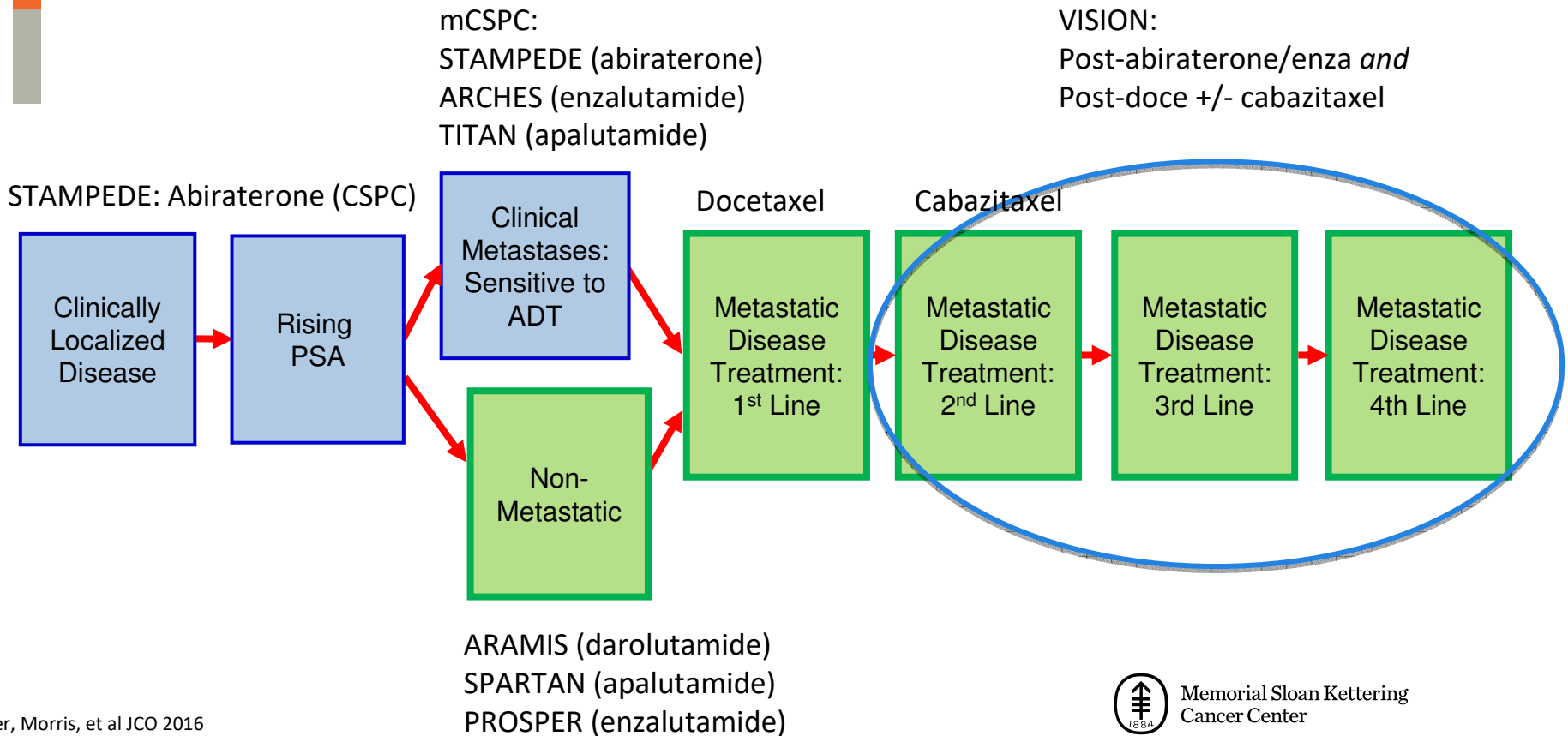
Eligible patients

- Previous treatment with both
 - ≥ 1 androgen receptor pathway inhibitor
 - 1 or 2 taxane regimens
- Protocol-permitted standard of care (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 ⁶⁸Ga-PSMA-11



- Randomization stratified by
 - ECOG 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

VISION population: At the end of the disease spectrum



Prespecified endpoints: alternate primary, key secondary and other secondary

Alternate primary endpoints

Radiographic progression-free survival (rPFS) per PCWG3

Overall survival (OS)

Key secondary endpoints

Time to first symptomatic skeletal event (SSE)

RECIST v1.1 overall response rate

RECIST v1.1 disease control rate

Other secondary endpoints

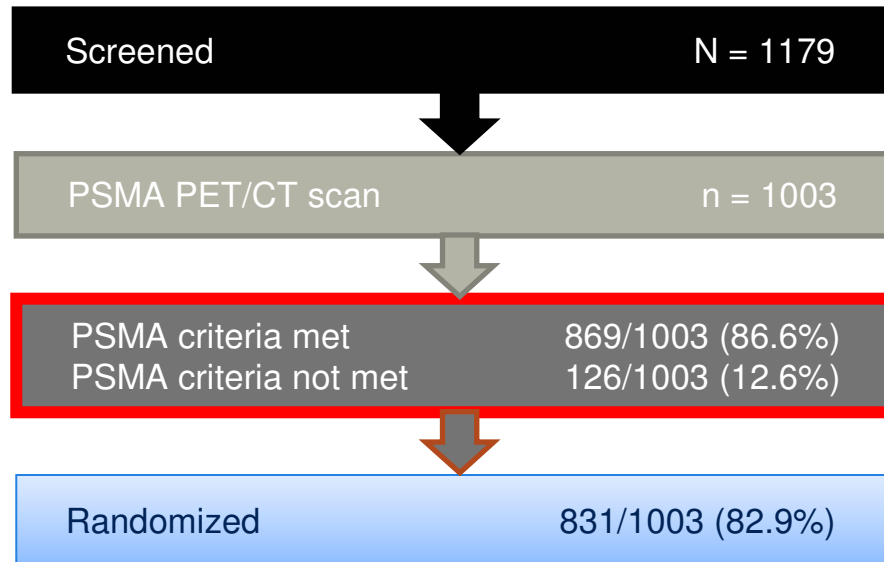
Safety and tolerability

Biomarkers including PSA

Health-related quality of life and pain

^{68}Ga -PSMA-11 PET/CT: ~87% of patients scanned met the VISION imaging criteria for PSMA-positive mCRPC

- Patient disposition in screening



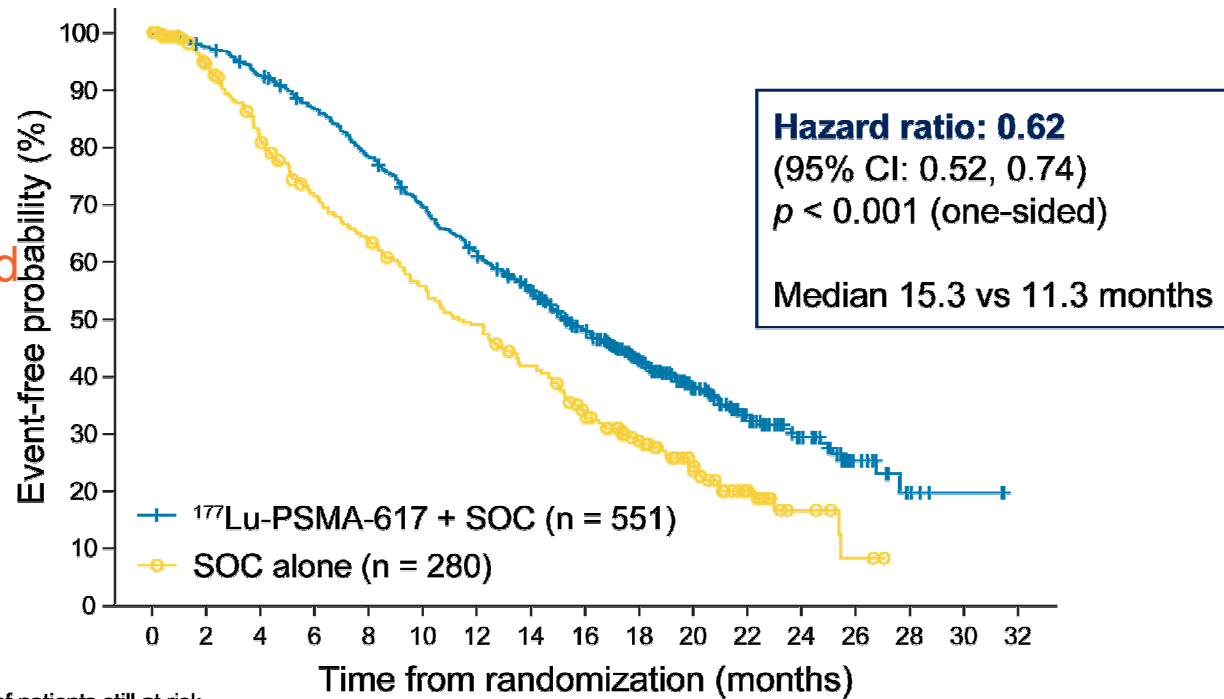
Previous cancer treatments were well balanced across treatment arms and the two analysis sets

	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (N=831)	
	¹⁷⁷ Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)	¹⁷⁷ Lu-PSMA-617 plus Standard Care (N=551)	Standard Care Alone (N=280)
Previous androgen-receptor–pathway inhibitor — no. (%)				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%) ^{**}				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)



Primary endpoints: ¹⁷⁷Lu-PSMA-617 prolonged OS

- Primary analysis
 - All randomized patients
 - (N = 831)

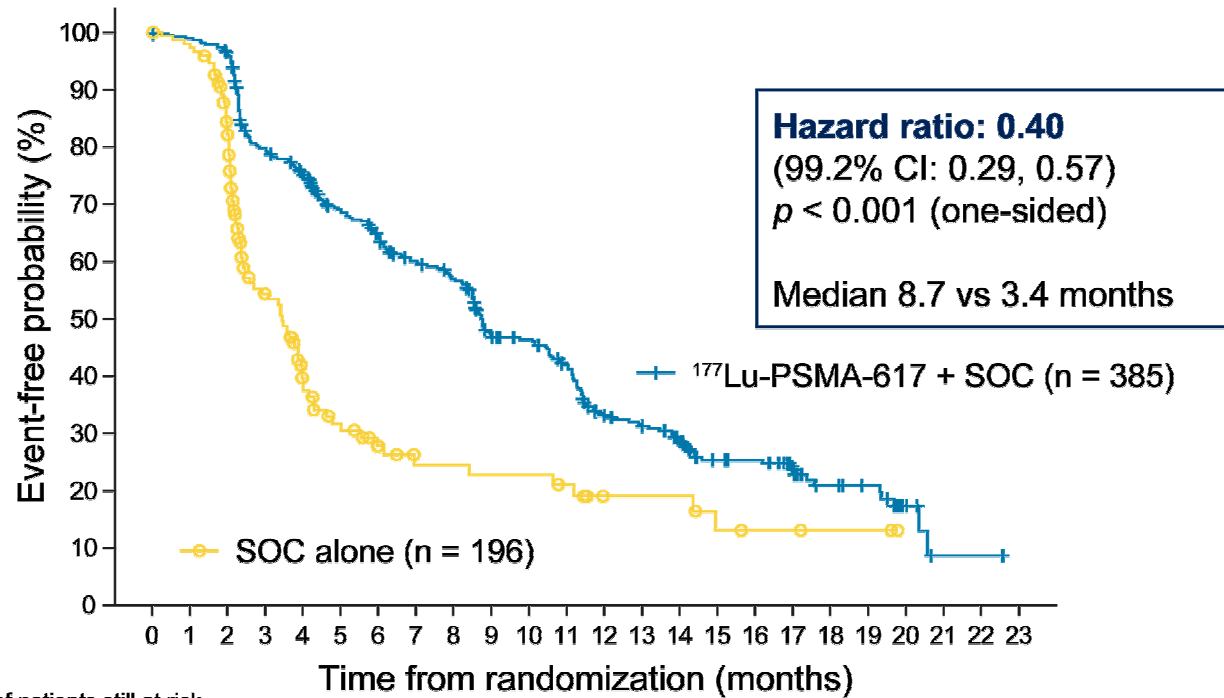


Number of patients still at risk

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

Primary endpoints: ¹⁷⁷Lu-PSMA-617 improved rPFS

- Primary analysis
- rPFS analysis set
- (n = 581)

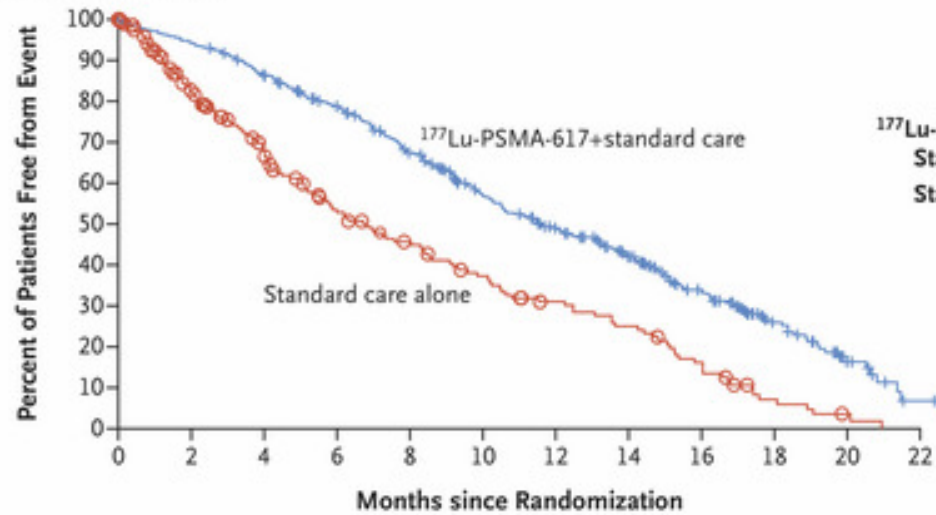


Number of patients still at risk

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

Time to first SSE

C Time to First Symptomatic Skeletal Event



	No. of Events/ No. of Patients	Median <i>mo</i>
¹⁷⁷ Lu-PSMA-617 + Standard Care	256/385	11.5
Standard Care Alone	137/196	6.8
Hazard ratio, 0.50 (95% CI, 0.40–0.62) P<0.001		

No. at Risk

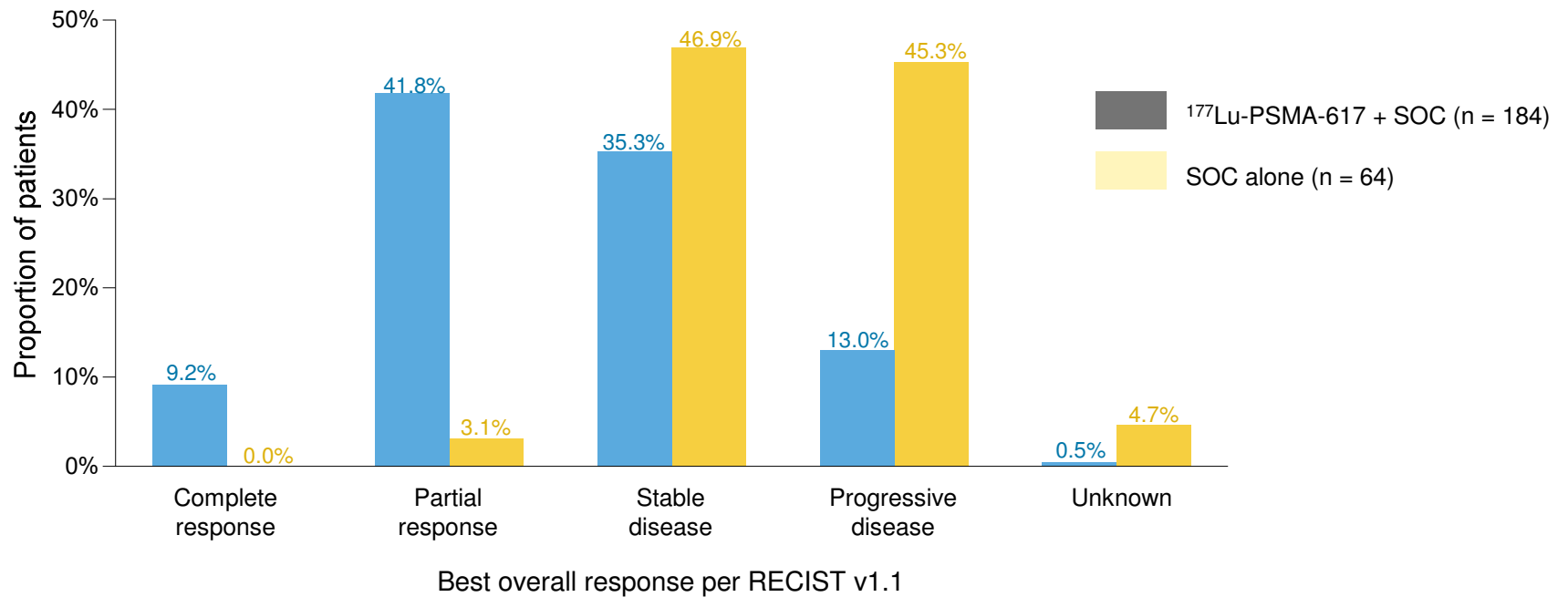
¹⁷⁷ Lu-PSMA-617+standard care	385	363	329	290	240	189	153	117	73	34	12	2
Standard care alone	196	141	104	75	61	48	36	29	15	6	2	0

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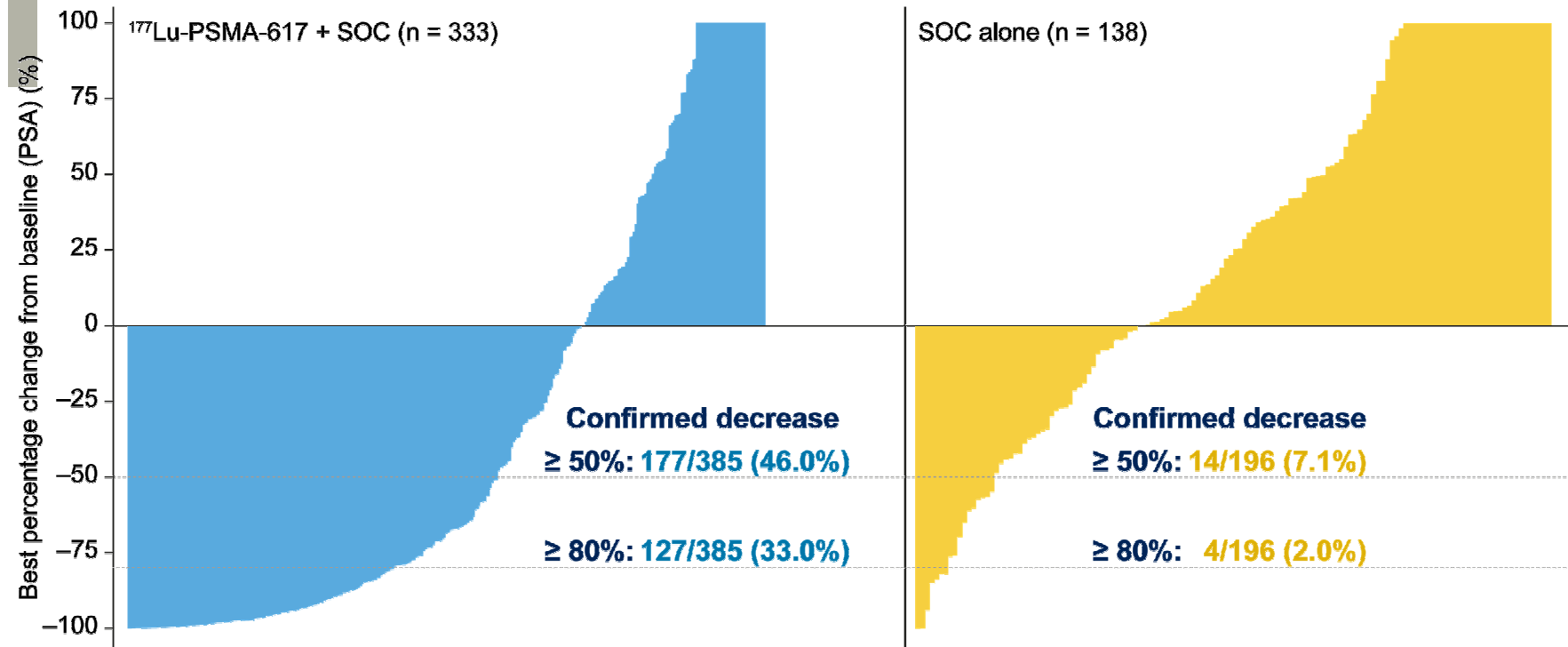
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Secondary endpoint: RECIST v1.1 responses favored the ¹⁷⁷Lu-PSMA-617 arm in patients with measurable disease



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Secondary endpoint: PSA responses favored the ^{177}Lu -PSMA-617 arm among evaluable patients



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Post-protocol therapies: slightly higher rates of chemotherapy and radiotherapy in the control arm

Received by > 5% of patients, n (%)	All randomized (N = 831)	
	¹⁷⁷ Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
Taxane	99 (18.0)	61 (21.8)
Cabazitaxel	82 (14.9)	53 (18.9)
Docetaxel	27 (4.9)	10 (3.6)
Paclitaxel	4 (0.7)	2 (0.7)
Platinum compound	40 (7.3)	27 (9.6)
Radiopharmaceutical	16 (2.9)	23 (8.2)
²²³ Ra	14 (2.5)	15 (5.4)
¹⁷⁷ Lu-PSMA-617	2 (0.4)	3 (1.1)
²²⁵ Ac-PSMA-617	1 (0.2)	0 (0.0)
Other/various	0 (0.0)	5 (1.8)
Immune checkpoint/VEGF mAb	16 (2.9)	22 (7.9)

Treatment-emergent adverse events

	¹⁷⁷ Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	→ 205 (38.8)	0	1 (0.5)	0
Nausea	→ 187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	→ 68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	→ 107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	→ 100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	→ 100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	→ 42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ¹⁷⁷ Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ¹⁷⁷ Lu-PSMA-617†	→ 85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ¹⁷⁷ Lu-PSMA-617†	→ 63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	→ 19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

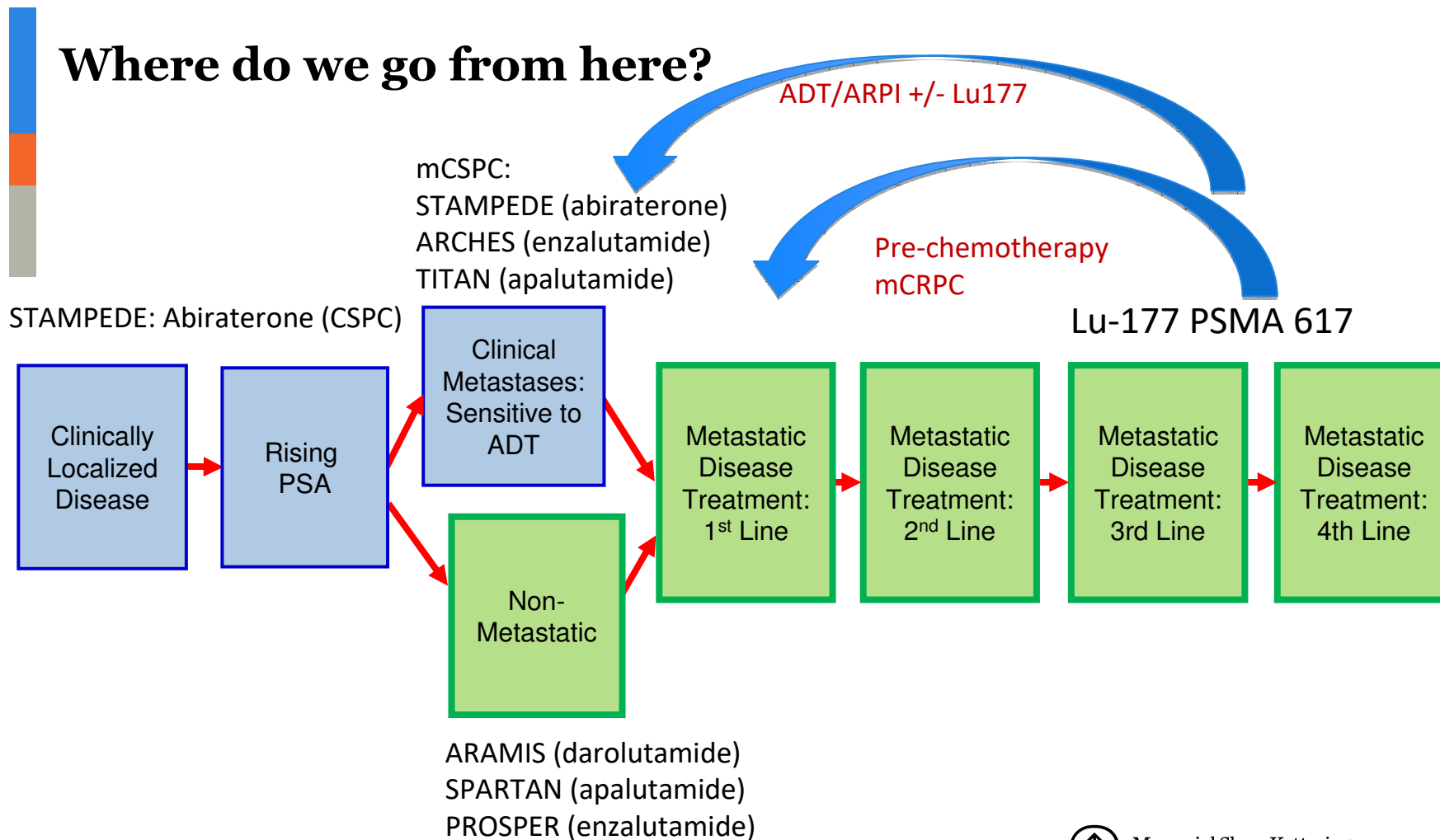
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VISION study conclusions

- Adding ^{177}Lu -PSMA-617 to safely combinable standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
 - Extended overall survival
 - Delayed radiographic disease progression
- ^{177}Lu -PSMA-617 was well tolerated
- These findings warrant adoption of ^{177}Lu -PSMA-617 as a new treatment option in patients with mCRPC, pending regulatory approval



Where do we go from here?





Where to go from here?

- Biomarker analyses from VISION
 - Role of imaging especially important to define
- Selected populations
 - DNA repair deficient populations
 - Specific ethnicities
- Combination strategies
 - Other drugs
 - Other modalities of treatment
- Sequencing of therapies
- Earlier disease than mCSPC
- As a field, new targets, targeting agents, and ligands

