Whats new with Metastatic Prostate Cancer?

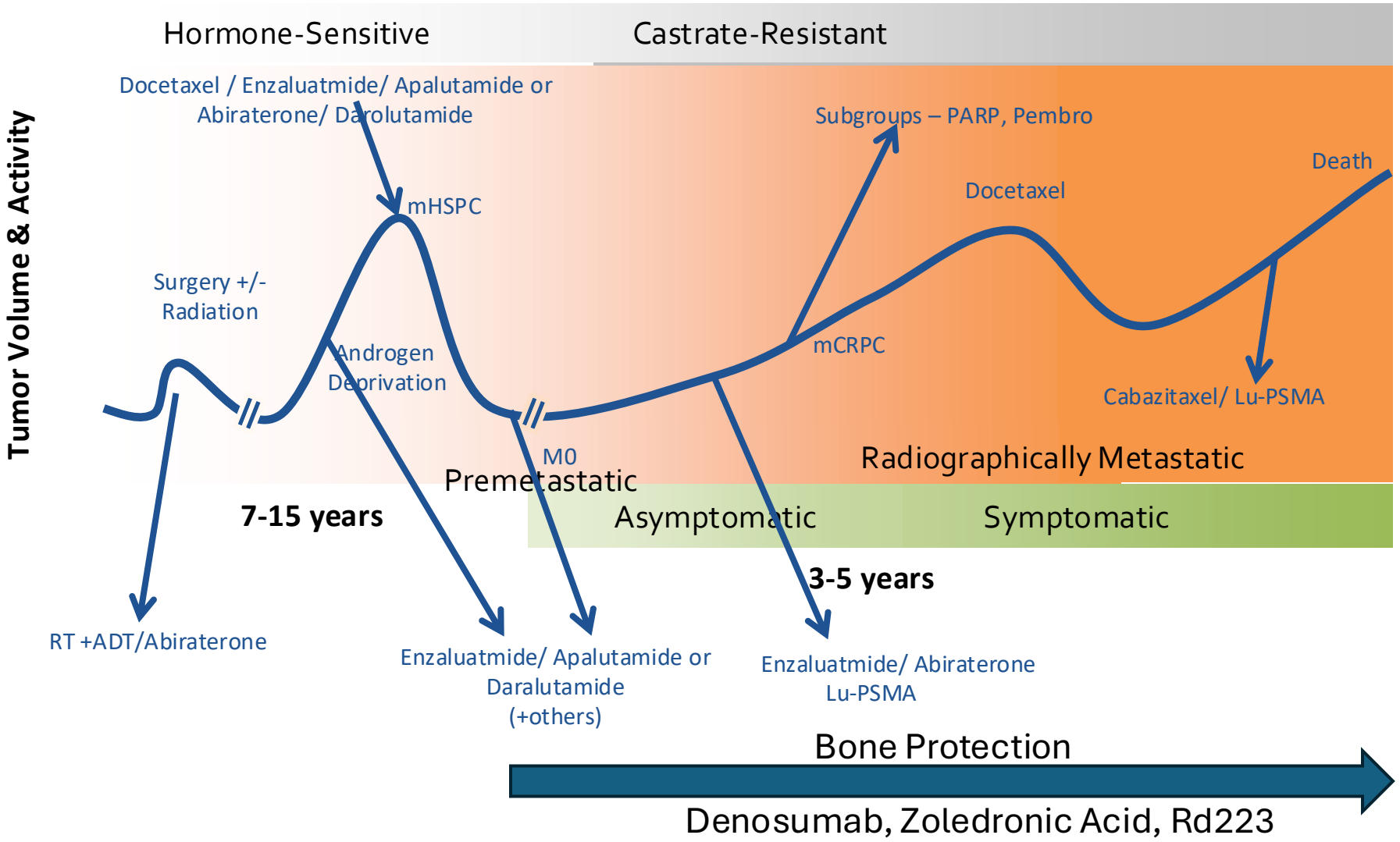
Professor Anthony Joshua

BSc(Med) MBBS PhD FRACP

Head, Department of Medical Oncology

Kinghorn Cancer Centre, St Vincents Hospital, Sydney

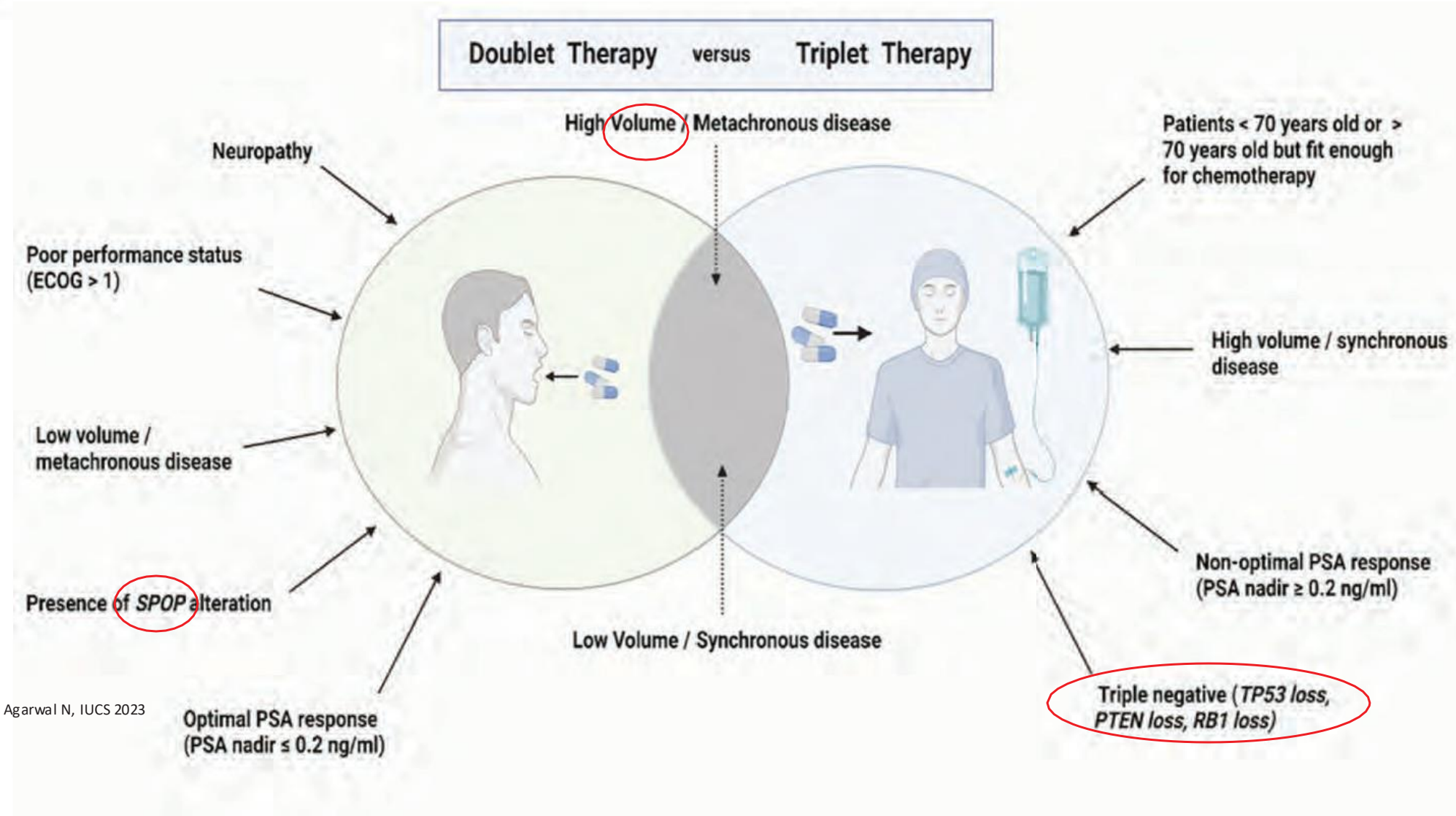
Natural History of Prostate Cancer



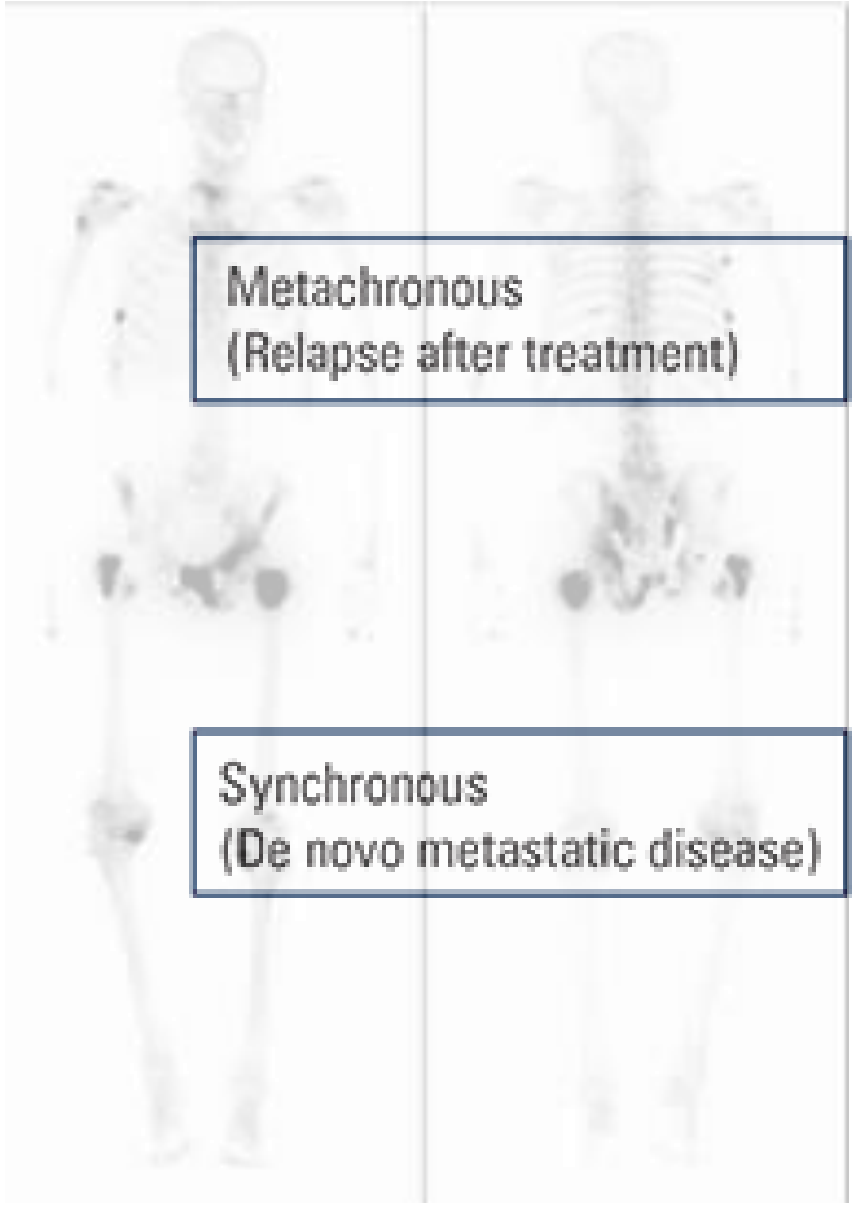
Outline

mHSPC	• Doublets • Triplets
mCRPC	• Lutetium
Supportive Care	• Hot Flushes

	ARANOTE*		ENZAMET		ARCHES*		TITAN		LATITUDE		STAMPEDE-G	
Characteristics	A+daro	A	A+enz	A+nad	A+abi	A	A+apa	A	A+abi	A	A+abi	A
No. of patients	446	223	563	562	574	576	525	527	597	602	957	960
% concurrent docetaxel	0	0	45	44	18	18	10	10	0	0	0	0
Age, years	70	70	69	69	70	70	69	68	67	67	67	67
High-volume, %	71	70	52	53	62	65	62	64	82	78	NR	NR
PFS, overall	NR	25	81	25	NR	19	NR	22.1	33	14.8	NR	13.9
HR (95%CI)	0.54 (0.41-0.71)		0.41 (0.39-0.53)		0.39 (0.30-0.50)		0.48 (0.39-0.60)		0.47 (0.39-0.55)		0.29 (0.25-0.34)	
OS, overall												
HR (95% CI)	0.81 (0.59-1.12)		0.67 (0.52-0.86)		0.66 (0.53-0.81)		0.67 (0.51-0.89)		0.66 (0.56-0.78)		0.63 (0.52-0.76)	
OS, HR (95% CI)												
HV	NR		0.80 (0.59-1.07)		0.66 (0.52-0.83)		0.68 (0.50-0.92)		0.62 (0.52-0.74)		0.60 (0.46-0.78)	
LV	NR		0.43 (0.26-0.72)		0.66 (0.43-1.03)		0.67 (0.34-1.32)		0.72 (0.47-1.10)		0.64 (0.49-0.79)	



Agarwal N, IUCS 2023



Metachronous
(Relapse after treatment)

Synchronous
(De novo metastatic disease)

Low volume

High volume

Low volume

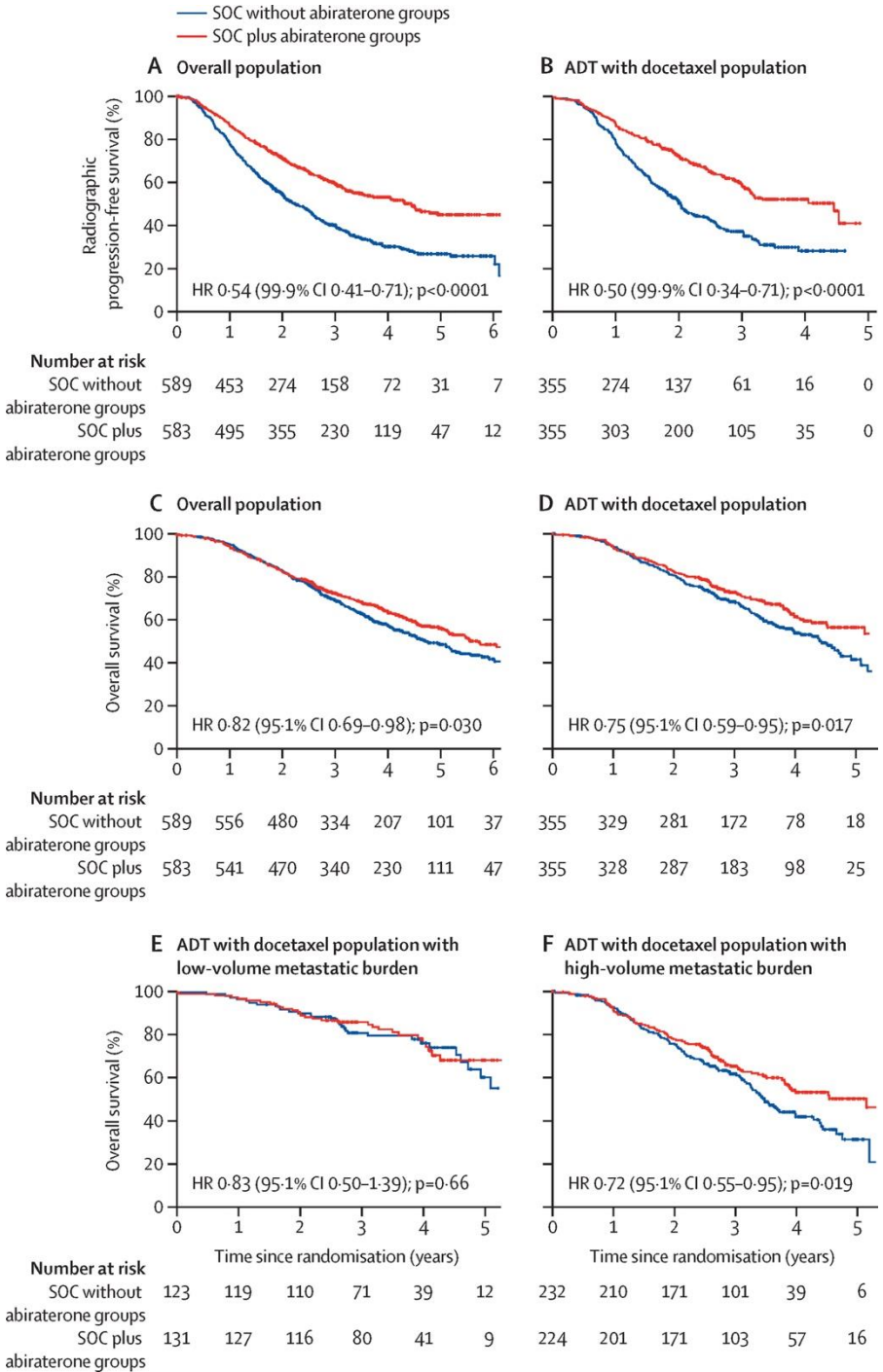
High volume

Doublet (ADT + abi/enza/apa)

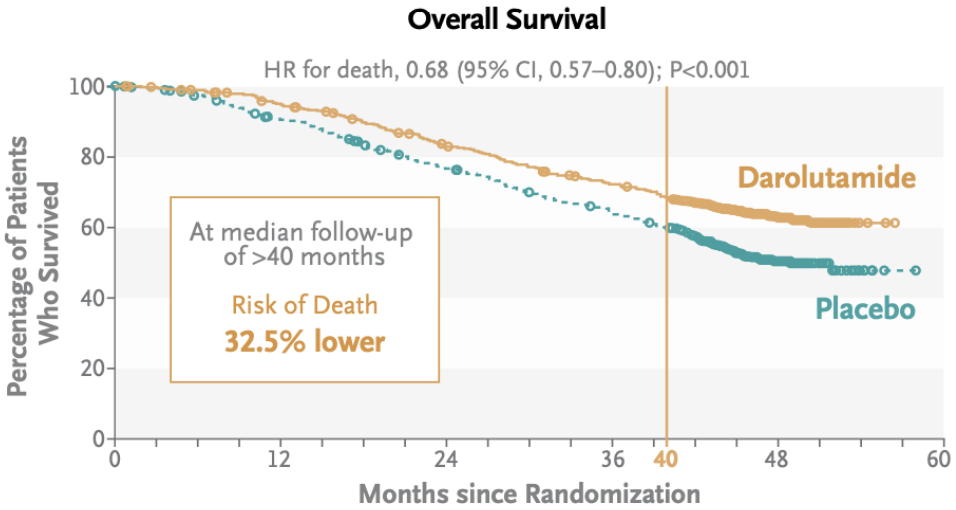
Doublet (ADT + abi/enza/apa
or docetaxel) or
triplet (ADT + abi/enza/daro)

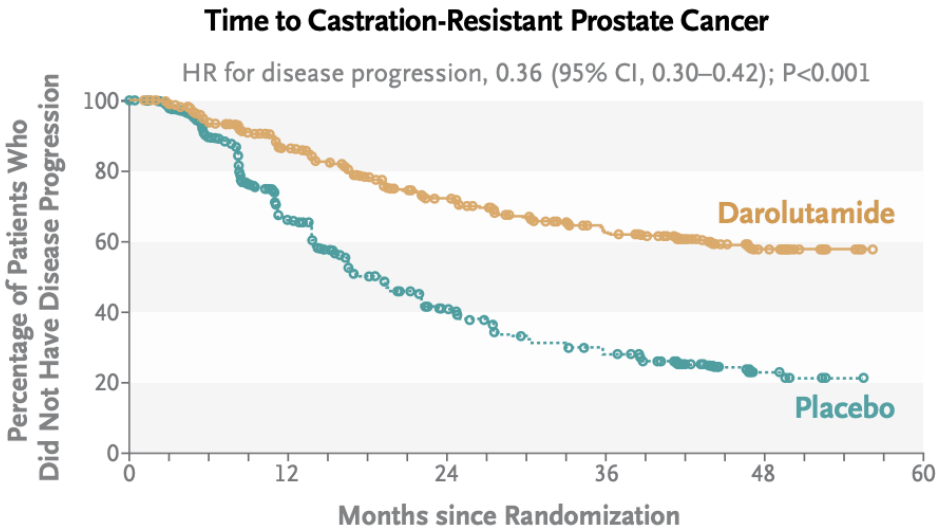
Doublet (ADT + abi/enza/apa)
radiotherapy to primary

Doublet (ADT + abi/enza/apa
or docetaxel) or
triplet (ADT + abi/enza/daro)


SOC without abiraterone groups
SOC plus abiraterone groups
A Overall population
B ADT with docetaxel population
Radiographic progression-free survival (%)
HR 0·54 (99·9% CI 0·41–0·71); p<0·0001
HR 0·50 (99·9% CI 0·34–0·71); p<0·0001
Number at risk
SOC without abiraterone groups 589 453 274 158 72 31 7 355 274 137 61 16 0
SOC plus abiraterone groups 583 495 355 230 119 47 12 355 303 200 105 35 0
C Overall population
D ADT with docetaxel population
Overall survival (%)
HR 0·82 (95·1% CI 0·69–0·98); p=0·030
HR 0·75 (95·1% CI 0·59–0·95); p=0·017
Number at risk
SOC without abiraterone groups 589 556 480 334 207 101 37 355 329 281 172 78 18
SOC plus abiraterone groups 583 541 470 340 230 111 47 355 328 287 183 98 25
E ADT with docetaxel population with low-volume metastatic burden
F ADT with docetaxel population with high-volume metastatic burden
Overall survival (%)
HR 0·83 (95·1% CI 0·50–1·39); p=0·66
HR 0·72 (95·1% CI 0·55–0·95); p=0·019
Time since randomisation (years)
Time since randomisation (years)
Number at risk
SOC without abiraterone groups 123 119 110 71 39 12 232 210 171 101 39 6
SOC plus abiraterone groups 131 127 116 80 41 9 224 201 171 103 57 16

Triplets


Overall Survival
HR for death, 0.68 (95% CI, 0.57–0.80); P<0.001
Percentage of Patients Who Survived
At median follow-up of >40 months
Risk of Death
32.5% lower
Darolutamide
Placebo
Months since Randomization


Time to Castration-Resistant Prostate Cancer
HR for disease progression, 0.36 (95% CI, 0.30–0.42); P<0.001
Percentage of Patients Who Did Not Have Disease Progression
Darolutamide
Placebo
Months since Randomization

Outline

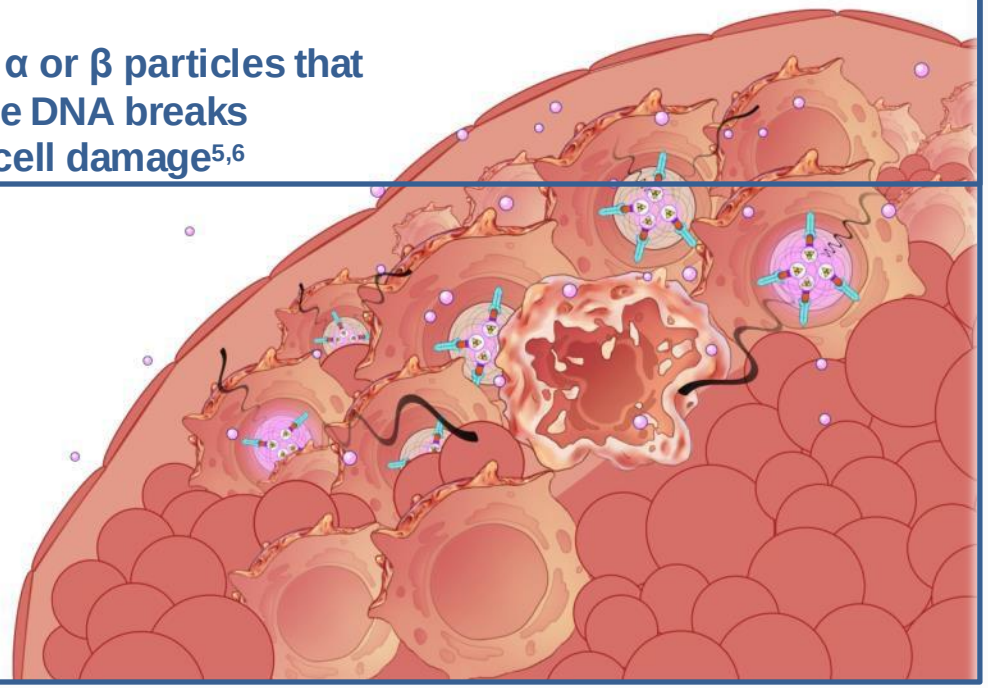
mHSPC	• Doublets • Triplets
mCRPC	• Lutetium
Supportive Care	• Hot Flushes

Theranostics: Therapy + Diagnostics

Use of the same/similar targeting compound labeled with either diagnostic or therapeutic radionuclides[1]

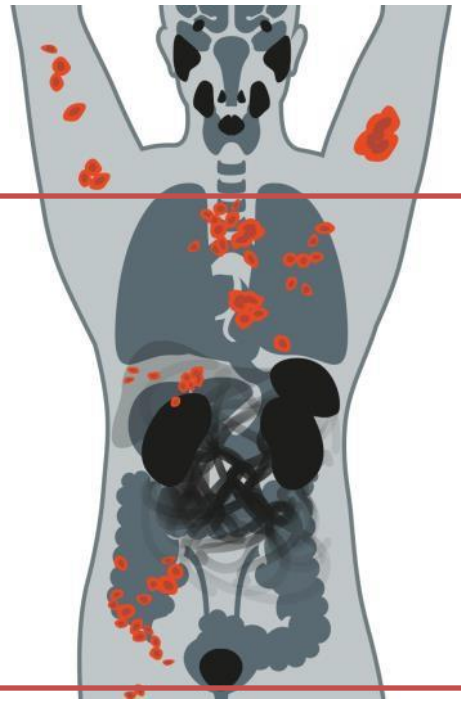
Therapeutic radionuclides (RLT)

Emit α or β particles that cause DNA breaks and cell damage[5,6]



Diagnostic radionuclides (Diagnostic Imaging)

Emit β^+ or ɣ energy that can be read by PET/SPECT machines[2–4]



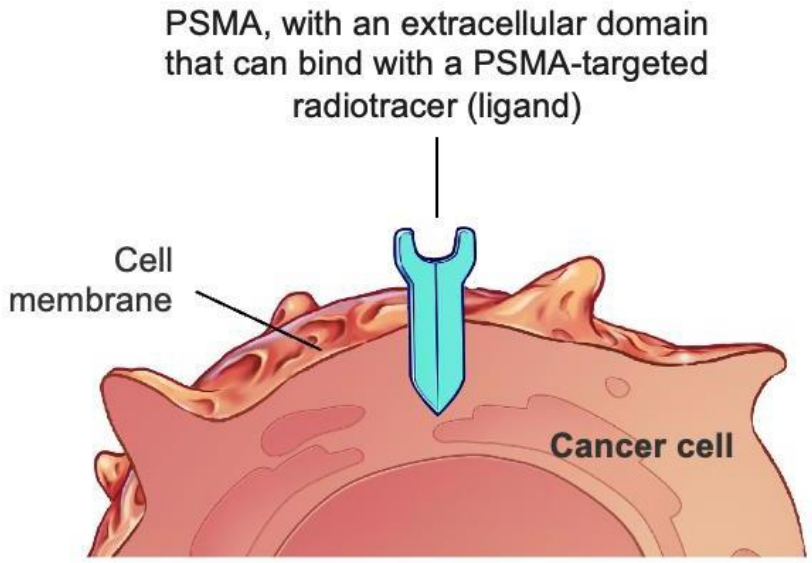
PET, positron emission tomography; RLT, radioligand therapy; SPECT, single-photon emission computed tomography.

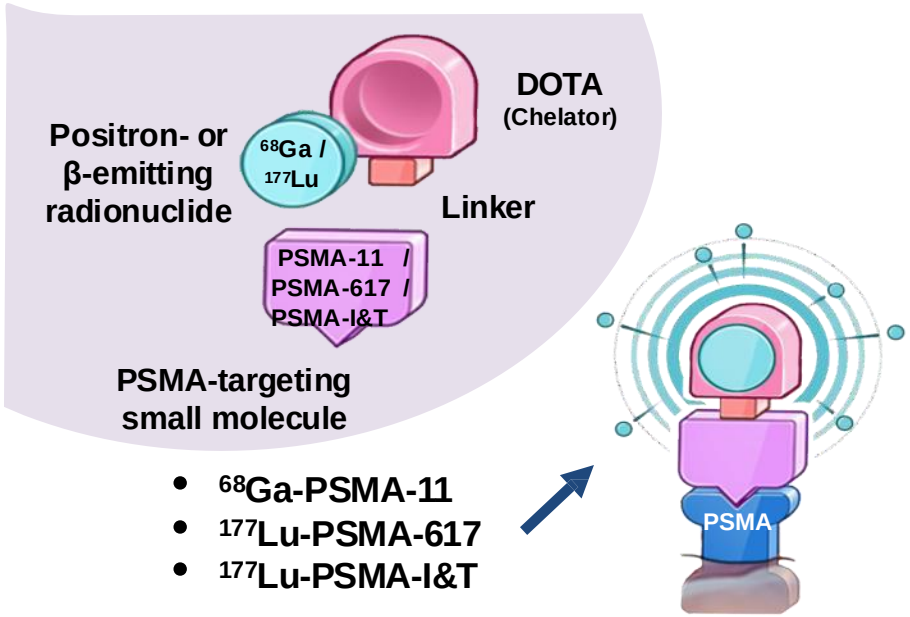
1. Emmett L, et al. Clin Genitourin Cancer. 2019;17(1):15–22; 2. Jones W, et al. Cancers (Basel). 2020;12(6):1367; 3. Wallitt KL, et al. Radiographics. 2017;37:1512–1536; 4. Li Z, Conti PS. Adv Drug Deliv Rev. 2010;62(11):1031–1051; 5. Ruigrok EAM, et al. Eur J Nucl Med Mol Imaging. 2021;48(5):1339-1350; 6. Scheinberg DA, McDevitt MR. Curr Radiopharm. 2011;4(4):306–320.

Courtesy K. Herrmann, adapted

Prostate Specific Membrane Antigen (PSMA) as target

- PSMA is highly expressed on the surface fo prostate cancer cells
- Limited physiological expression outside of the prostate
  - Kidney (proximal renal tubules), salivary & lacrimal glands and proximal small intestine





Morris MJ et al. Clin Cancer Res 2005;11(20):7454–7461; Barrett JA et al. J Nucl Med 2013;54(3):380–387; Mesters JR et al. EMBO J 2006;25(6):1375–1384; Troyer JK et al. Int J Cancer 1995;62:552–558; Hope TA et al. J Nucl Med 2017;58(12):1956–1961; Hupe MC et al. Front Oncol 2018;8:623; Pomykala KL, et al. J Nucl Med. 2020;61(3):405–411; Minner S, et al. Prostate. 2011;71(3):281–288; Bostwick DG, et al. Cancer. 1998;82(11):2256–2261; Silver DA, et al. Clin Cancer Res. 1997;3(1):81–85; Wright GL, et al. Urol Oncol. 1995;1(1):18–28

Courtesy K. Herrmann, adapted

Current role: Based on VISION Trial

Design: Randomised, multicenter, Phase 3

mCRPC: 3rd or later lines

Prior treatment with:
- AR pathway inhibitor (2 or more: 49%)
- 1 or 2 lines of taxanes (41% two taxanes)

Selection:
- **68Ga PSMA PET positivity**
- **"No" PSMA negative lesions**
  - LN ≥2.5cm
  - Visceral ≥1cm
  - Bone with soft tissue ≥1cm

n=831

1:2
Randomisation

Protocol permitted SOC*

177Lu-PSMA-617
- 7.4 GBq every 6 weeks
- 4x with option to increase to 6x

+

Protocol permitted SOC*

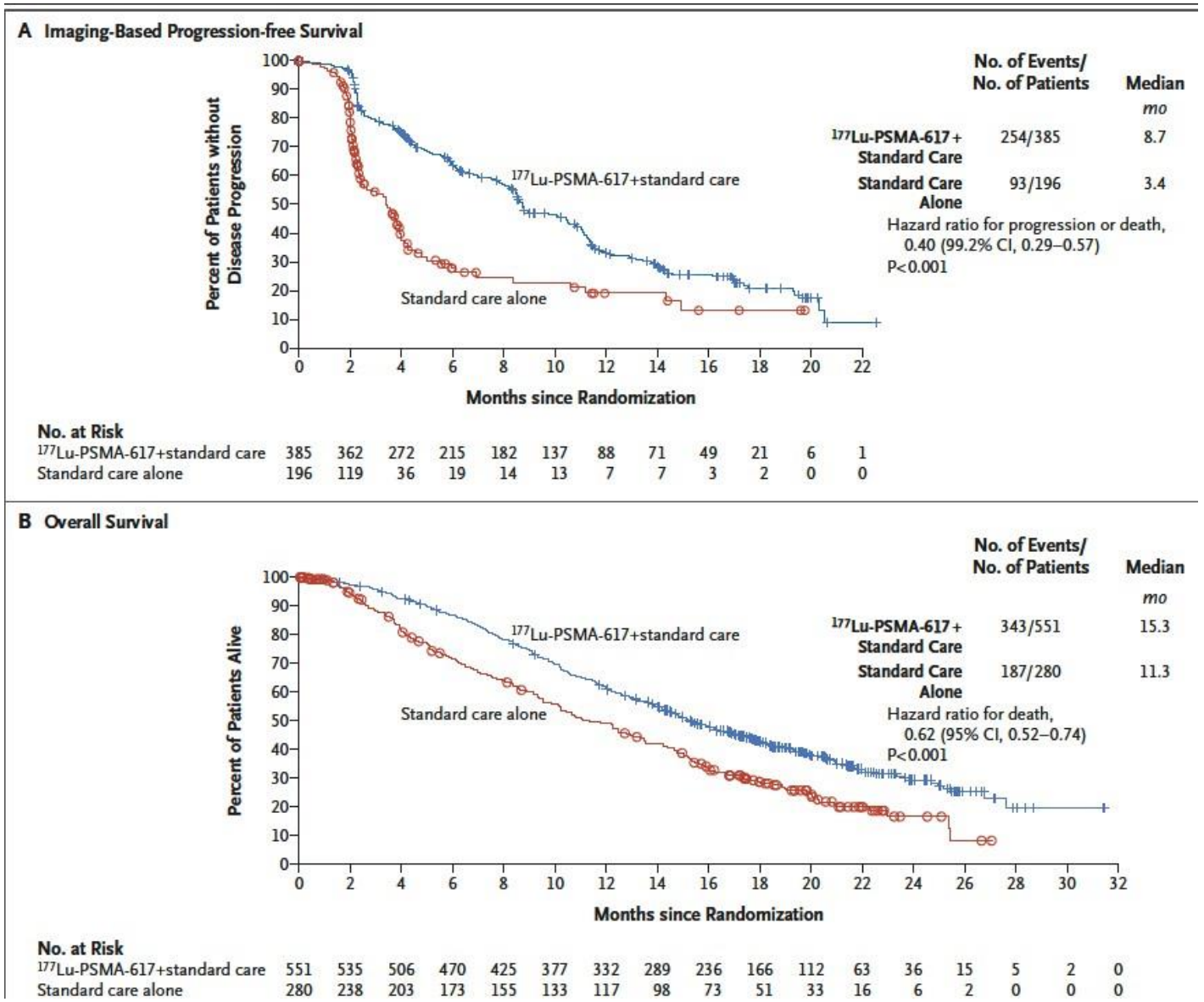
Accrual: 06/2018 – 10/2019

***Protocol permitted SOC:** AR pathway inhibitors, steroids, radiation therapy.
NOT: Chemotherapy or Radium-223 or clinical trial

Alternate Primary Endpoints
- rPFS
- OS

Morris M et al. ASCO 2021; Sartor O et al. NEJM 2021

VISION: Positive for primary endpoints



rPFS

HR: 0.4 (95% CI 0.29-0.57)

OS

HR: 0.62 (95% CI 0.52-0.74)

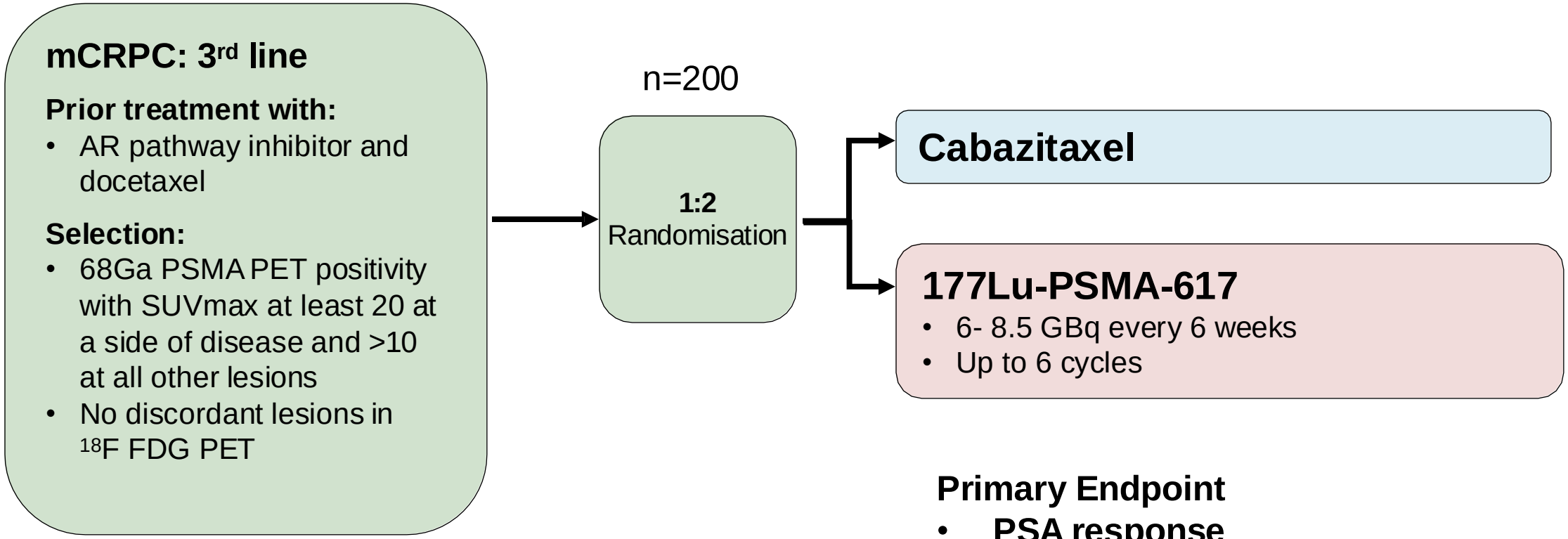
ORR: 9% CR and 42% PR

PSA ≥50%: 46%

Sartor O et al. NEJM 2021

TheraP Trial

Design: Randomised, multicenter, unblinded Phase 2 trial



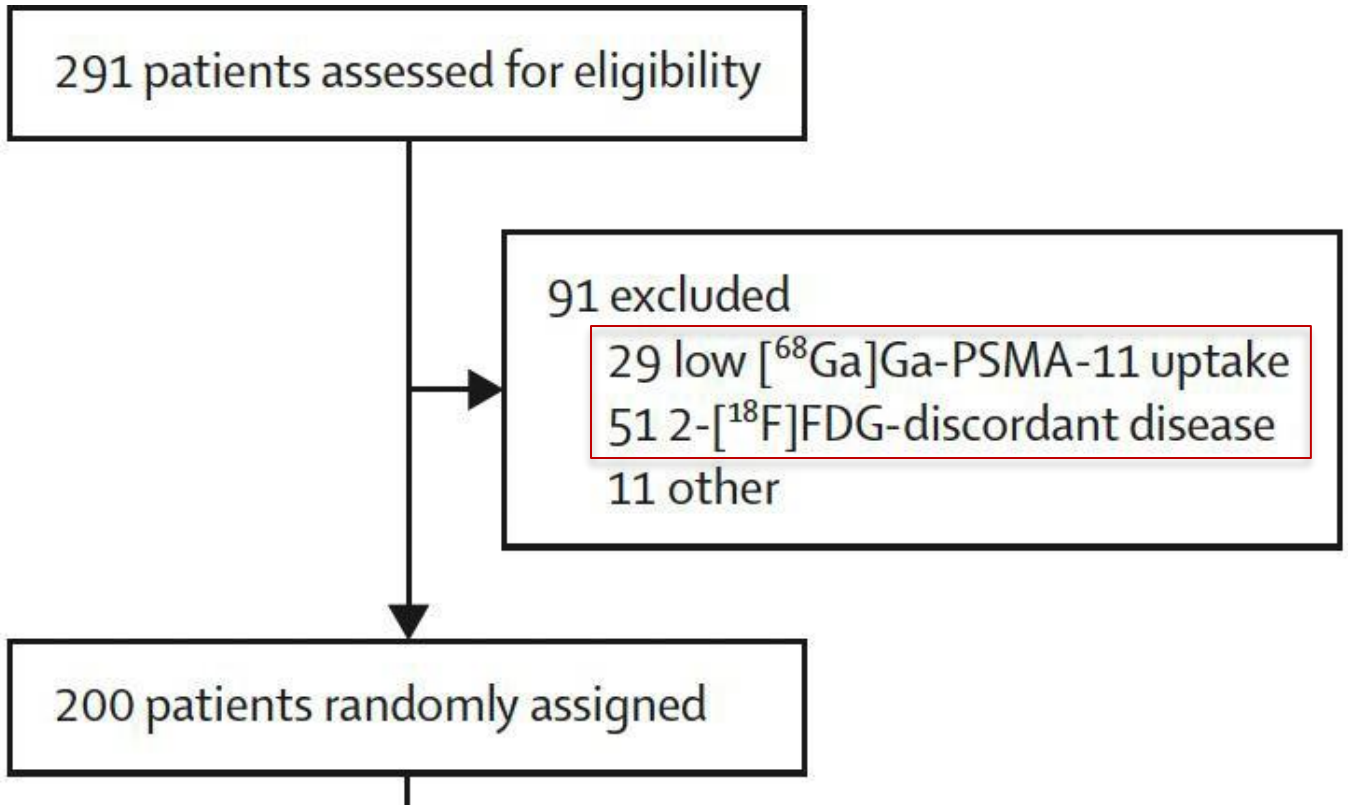
Primary Endpoint

- **PSA response**

Accrual: 02/2018 – 09/2019

Hofman M et al. Lancet 2021

TheraP Trial: Inclusion per PET-scans



- ^{68}Ga-PSMA PET positivity with SUVmax at least 20 at a side of disease and >10 at all other lesions
- No discordant lesions in ^{18}F FDG PET

Centrally reviewed

10% excluded based on ^{68}Ga-PSMA PET

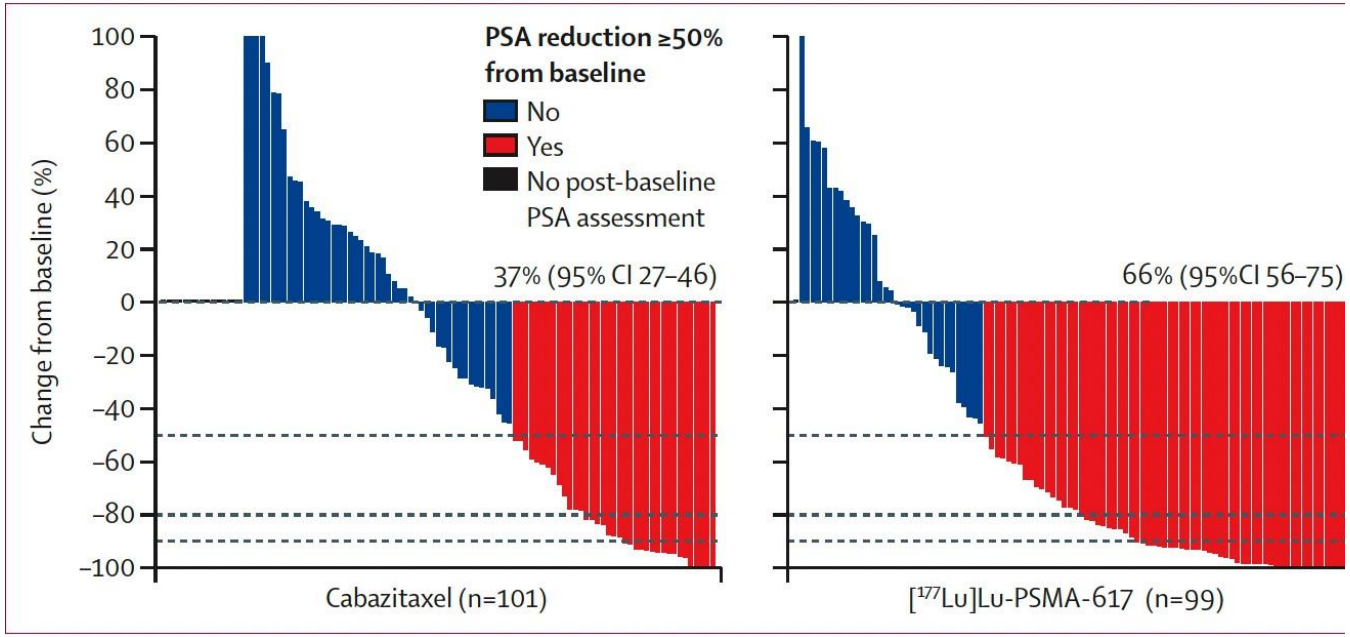
17.5% excluded due to FDG-PET discordant disease

27.5% excluded in total based on PET scans

Hofman M et al. Lancet 2021

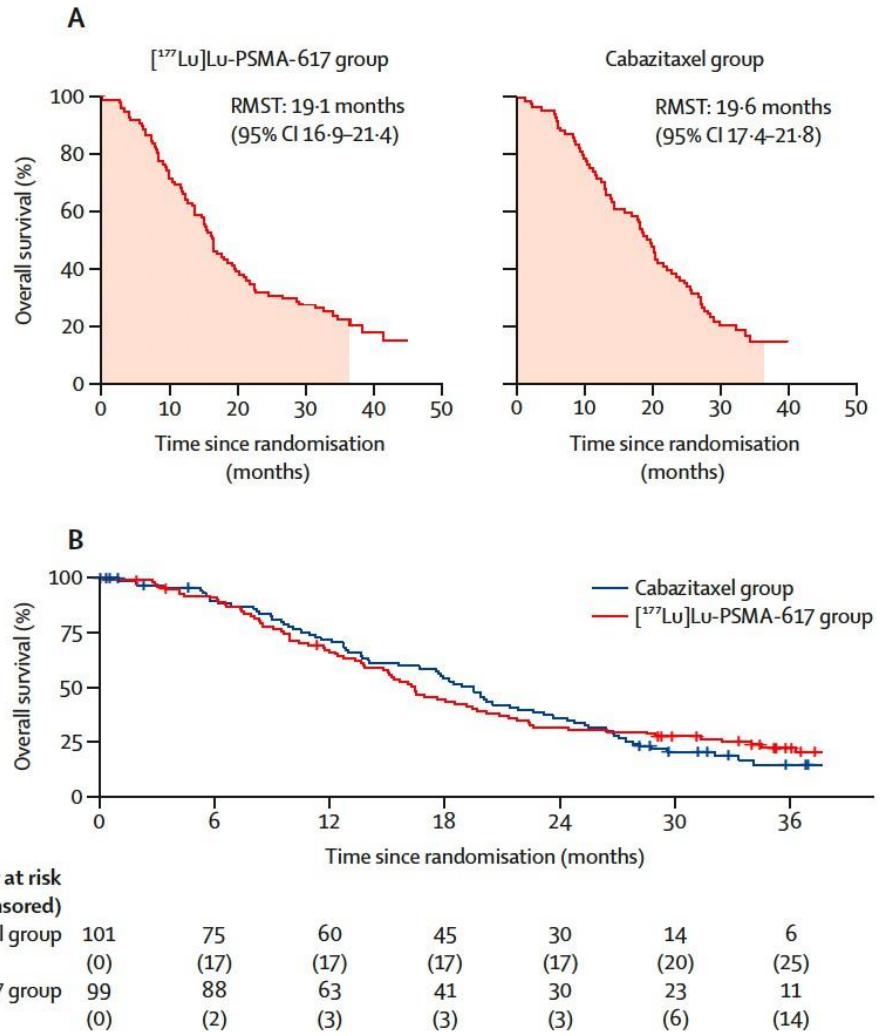
TheraP: Results

Primary endpoint (PSA response) postitive



Less G3/4 adverse events!

No difference in OS



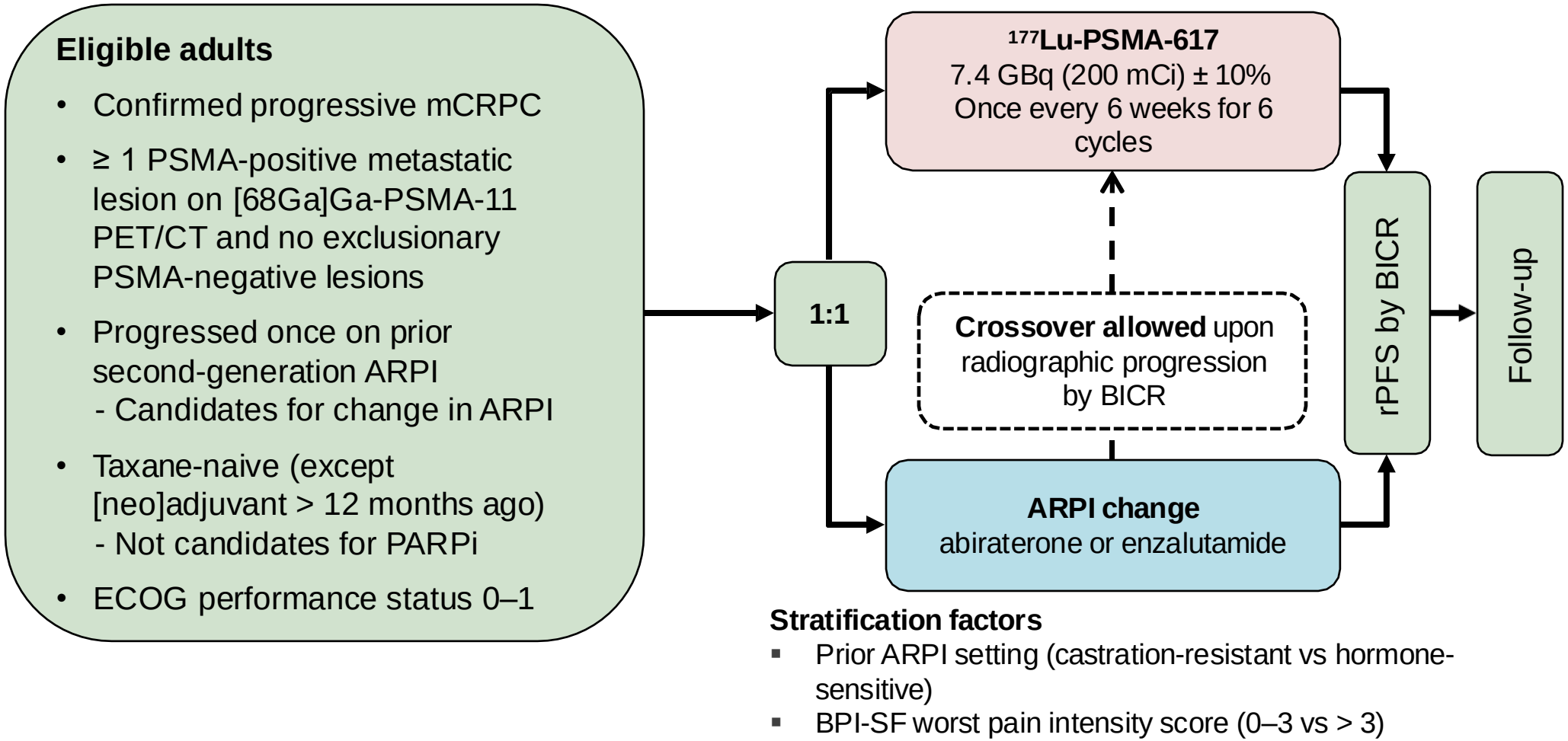
Hofman M et al. Lancet 2021 and Lancet Oncol 2023

TheraP and VISION

	TheraP: Phase 2 N=200 Cabazitaxel +	**VISION: Phase 3** N= 831
Control arm		Protocol permitted standard care (no chemotherapy, no radium-223) Many dropouts
Pretreatments	All Docetaxel 15% Abi **and** Enza	41% **two** taxanes 49% Abi **and** Enza
PET selection criteria (% excluded pts)	More stringent, including also FDG PET/CT: **28%**	PSMA negative metastases identified in CT: **12%**
Dose/Schedule	Start: 8.5GBq, reduced by 0.5 per cycle, every 6 weeks Max. 6 cycles, based on SPECT CT	7.4GBq per cycle, every 6 weeks 4 cycles + 2 cycles if evidence of response
Primary endpoint(s)	**PSA RR**	**rPFS** and **OS** +
PSA decline ≧ 50%	**66%**	**46%**
ORR (RECIST)	**49%**	**51%**

PSMAfore

Design: Phase 3, randomized, open-label study



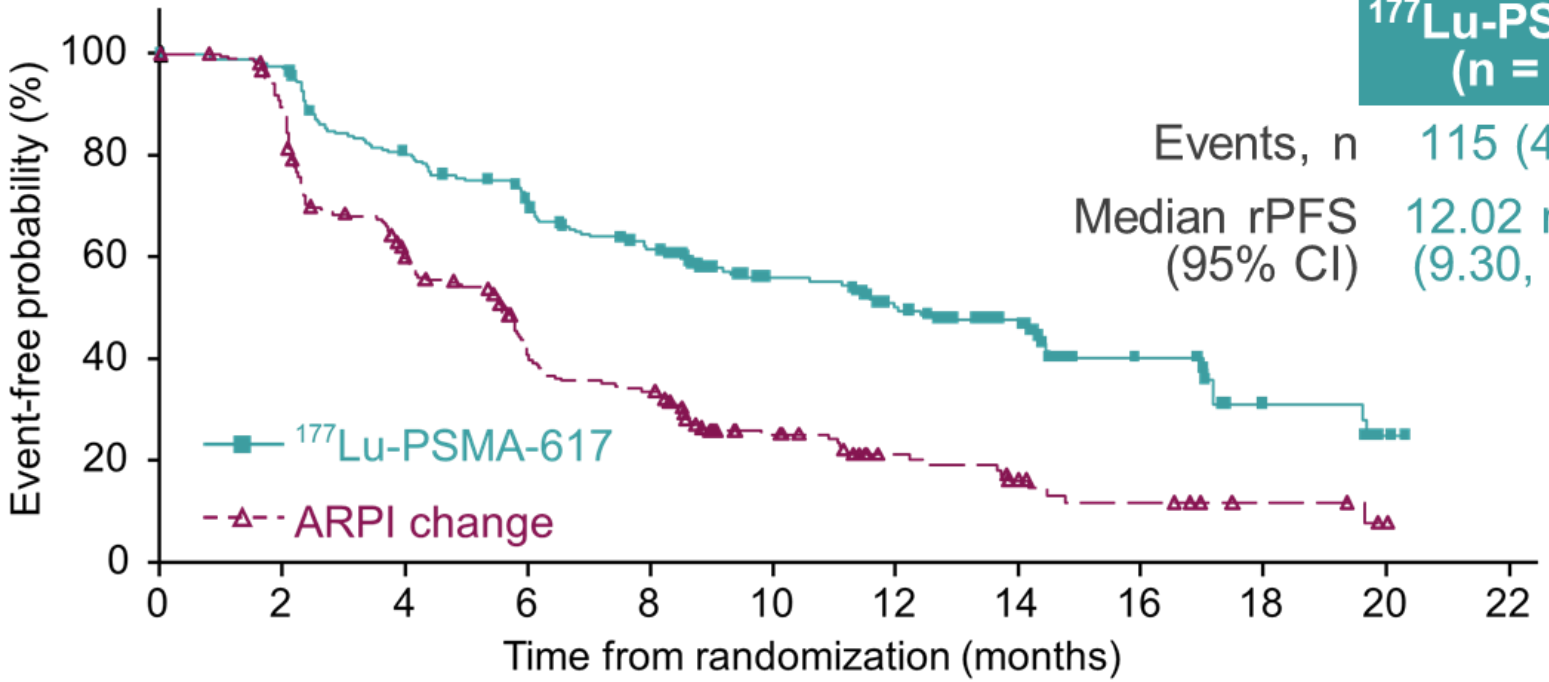
Sartor O et al. ESMO 2023

PSMAfore: Results

rPFS: primary endpoint was met

Primary HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Updated HR: 0.43 (95% CI: 0.33, 0.54)



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

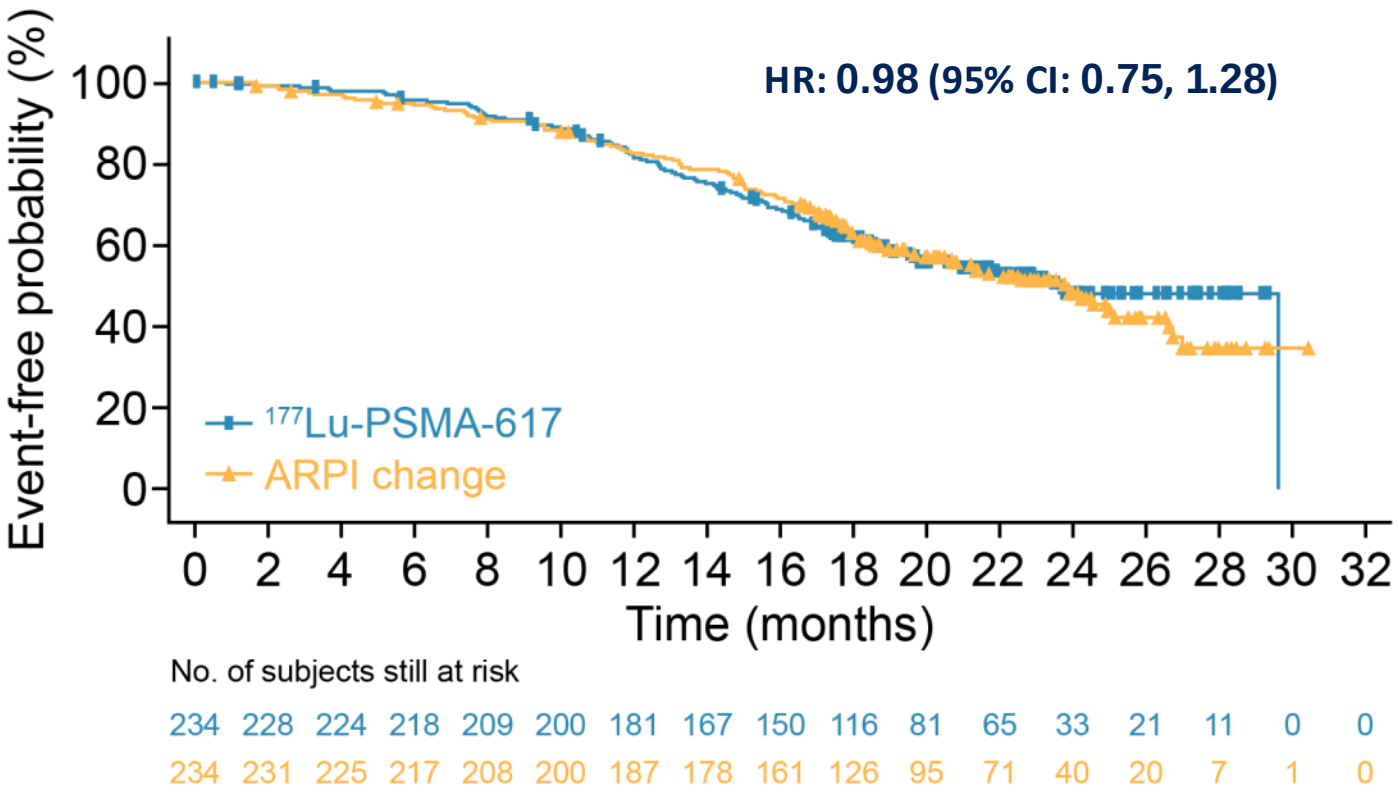
Number of patients still at risk

234	216	174	150	125	82	64	45	20	10	2	0
234	197	126	79	65	36	21	12	8	4	1	0

Courtesy: Ken Herrmann

Sartor O et al. ESMO 2023

PSMAfore: Updated OS



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	104 (44.4%)	112 (47.9%)
Median, months (95% CI)	23.66 (19.75, NE)	23.85 (20.6, 26.55)

Crossover:

134/234 (57.3%) in ARPI change group
134/173 (77.5%) eligible patients

RPSFT crossover-adjusted OS analysis

- HR: 0.98 (95% CI: 0.76, 1.27)
- No difference versus the ITT analysis because RPSFT cannot adjust for crossover confounding in the context of overlapping ITT curves

ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; IF, information fraction; ITT, intent-to-treat ; NE, not evaluable; OS, overall survival; PSMA, prostate-specific membrane antigen; RPFST, rank-preserving structural failure time

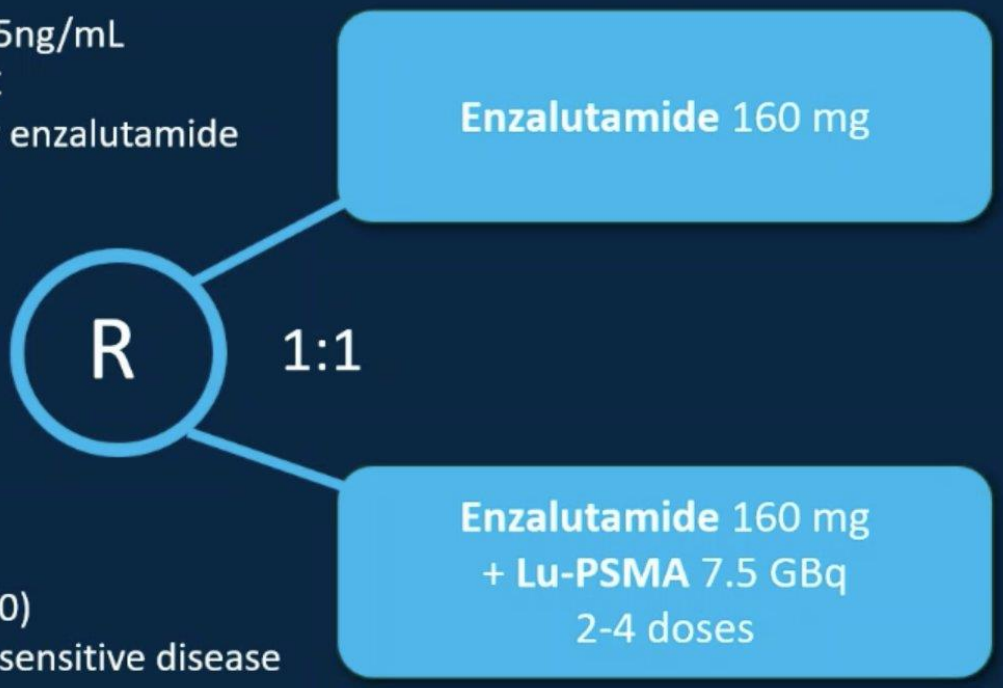
Courtesy: Karim Fizazi

Fizazi K et al., ASCO 2024

ENZA-p schema

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 high risk features for early enzalutamide failure
Positive ^{68}Ga PSMA PET/CT



Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Objectives

PSA-PFS (primary endpoint)
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
HRQOL
Adverse events
Overall survival
Health economic analyses
Translational/correlative

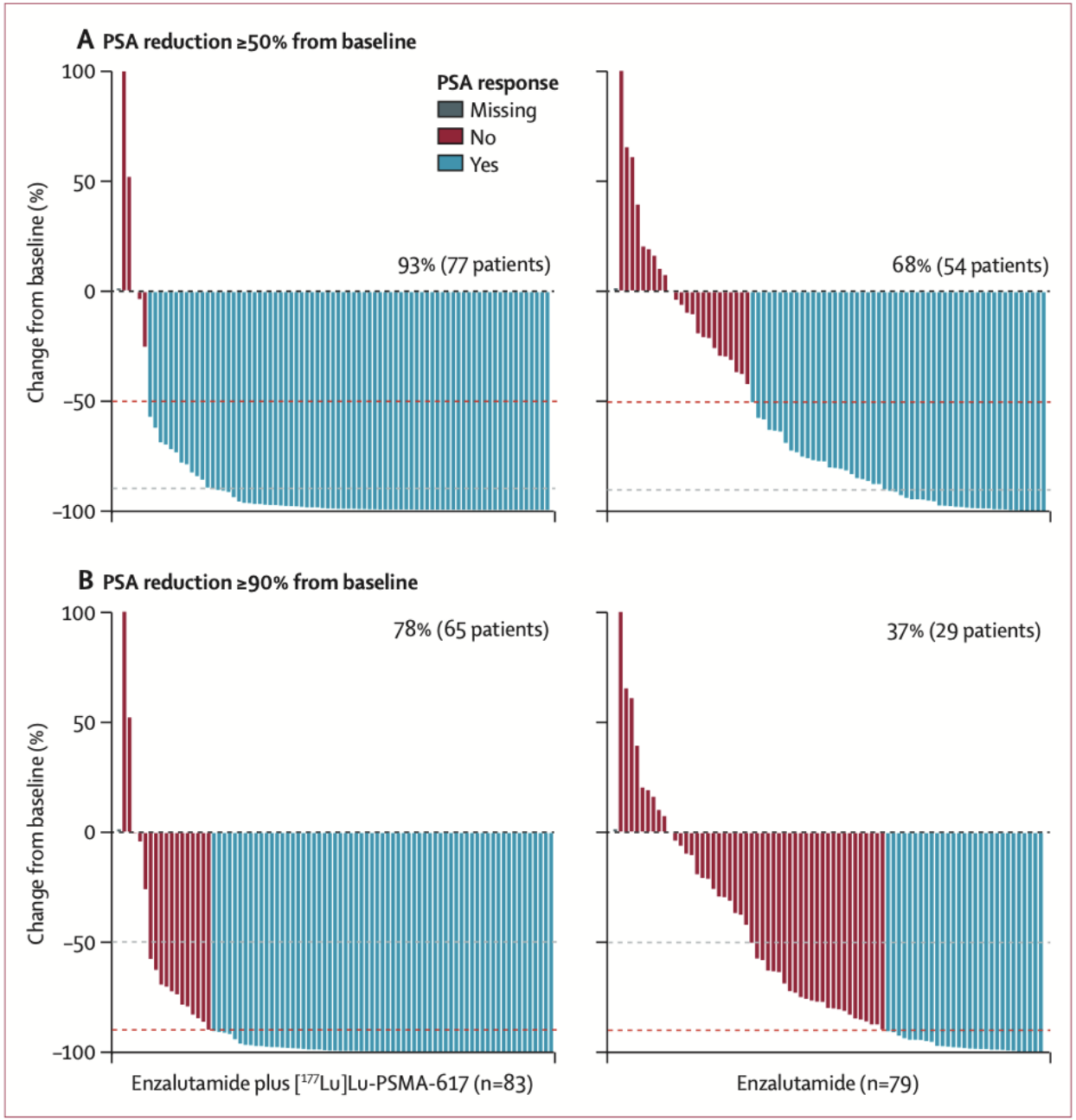
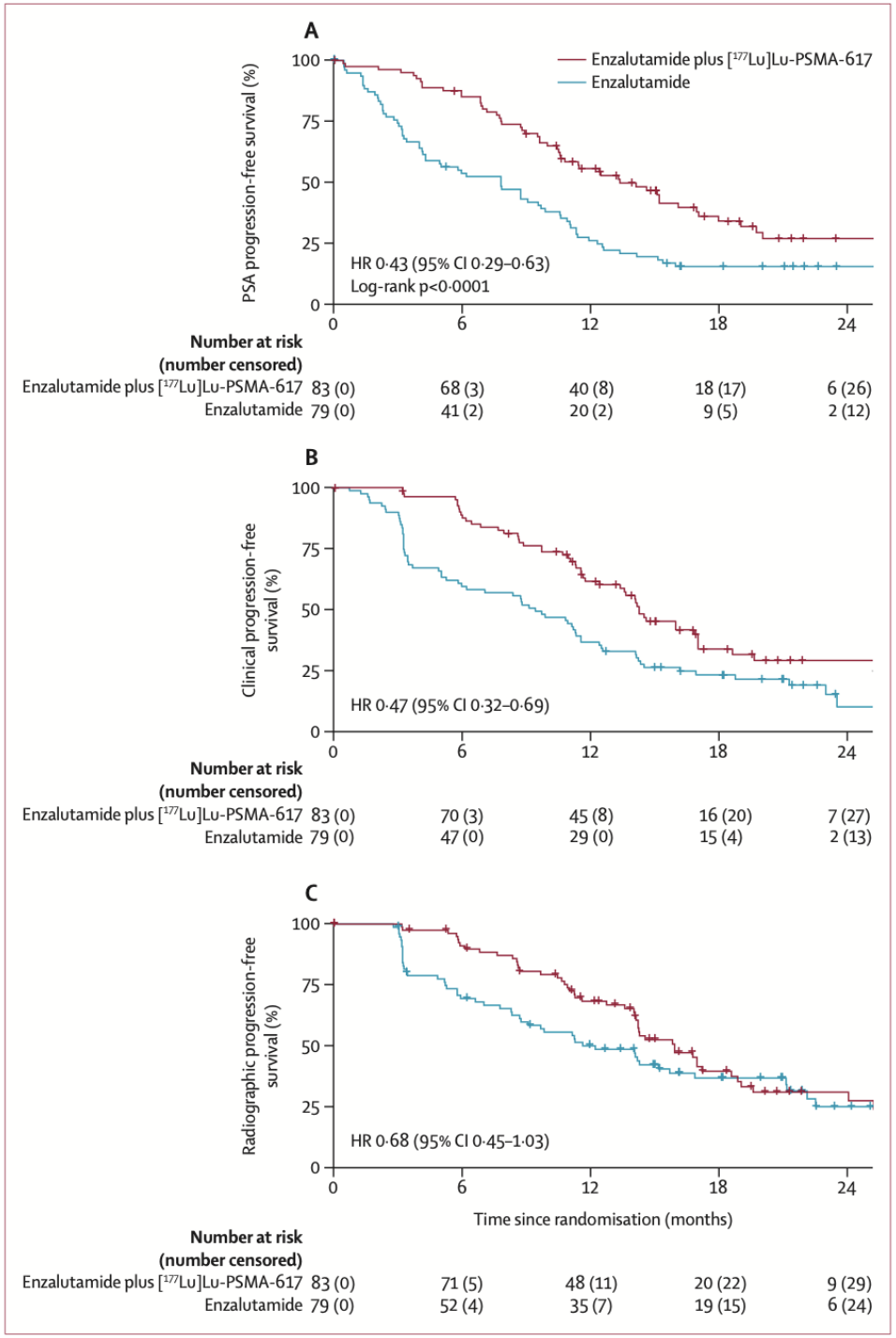


Figure 3: **PSA response**

Waterfall plots depicting the proportion of participants who had reduction in PSA of 50% (A) and 90% (B). ^{177}Lu=lutetium-177. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.



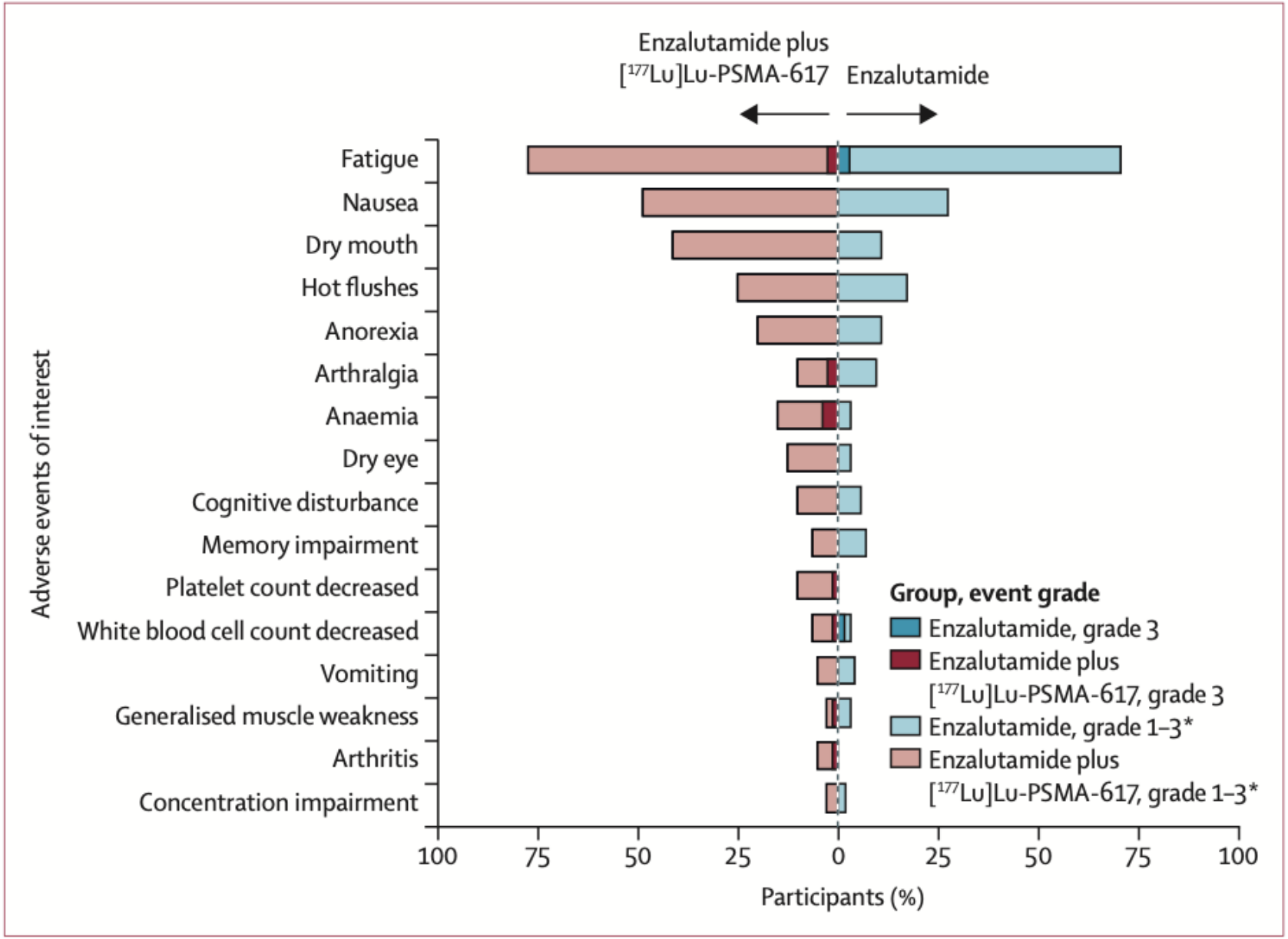


Figure 4: **Adverse events of interest**

Outline

mHSPC	• Doublets • Triplets
mCRPC	• Lutetium
Supportive Care	• Hot Flushes

Pathophysiology

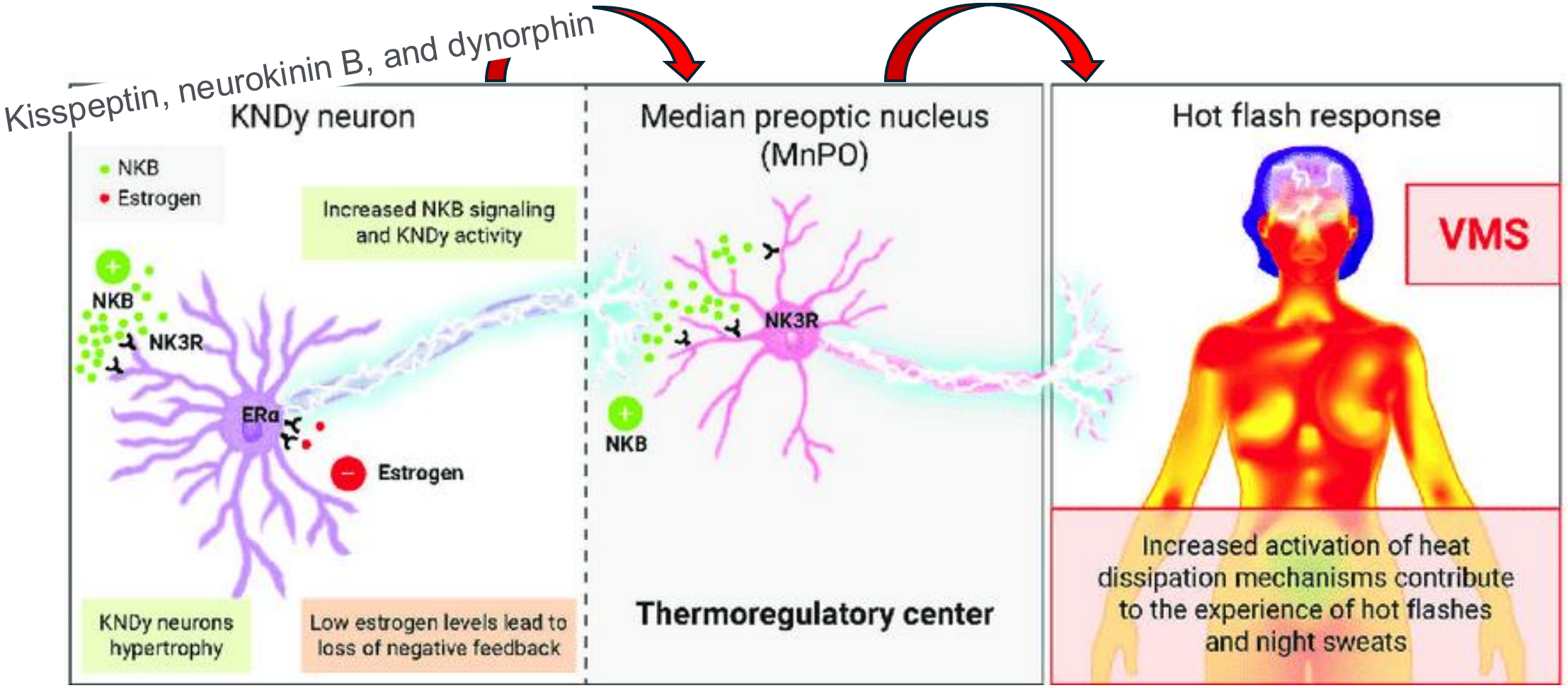
LHRHa → Suppression of testosterone → Suppression of endogenous oestradiol
(80% synthesised from aromatised testosterone)

- Erectile dysfunction
- Loss of muscle mass
- Loss of muscle strength

- Osteoporosis and increased fracture risk
- Lipid changes
- Increased fat deposition
- Increased insulin resistance
- Memory loss
- Hot flushes

1. Gilbert et al., Clinical Oncology, 2024

Pathophysiology



1. Depypere et al., Exp Opinion on Investigational Drugs, 2021

Incidence

44-80% of men undergoing ADT[1,2]

4m

Peak after LHRH[3], with no useful predictors[4,5,6]

12m

Median time to cessation is 7.6m/ T 5.7[7]

5 years to 8 years

70% to 40%[8]

1. Charig et al., Urology 33:157-178 2. Spetz et al., J Urol 166:517-520 3.Dosani et al., Clinical Oncology, 29 (2017), 696-701 4. Hunter et al., Climateric 19:1, 91-97, 2016 5. Iversen et al., PCPD 2011;14;184-190 6. Gonzalez et al., J urol 2015 7. Dosani et al., Clinical Oncology, 29 (2017), 696-701 8. Karling et al., J Urol 152:1170-1173

Impact

- ~30% report HF as most troublesome effect of therapy[1,2]
- Sleep disturbance, diminished cognition, lower QOL[3,4]
- Up to 55% of patients report distress and 11% severe distress[5]
- Can lead to treatment discontinuation/ abbreviation [6,7]

1. Desai, K, et al., Endocr Rev 2021:42:254-73 2. . Frodin et al., Prostate 7:203-208 3. Gonzalez et al., Cancer 2018: 124; 499-506 4. Engstrom et al., Am J Mens Health 2008:2:122-132 4. Guise et al., Rev Urol 2007:9:163-180 5. Spetz et al., J Urol 2001:166:517-20 6Freedland et al., Prostate Cancer Prostatic Disease 2009:12:333-8 7 7 Molhile et al., 2009

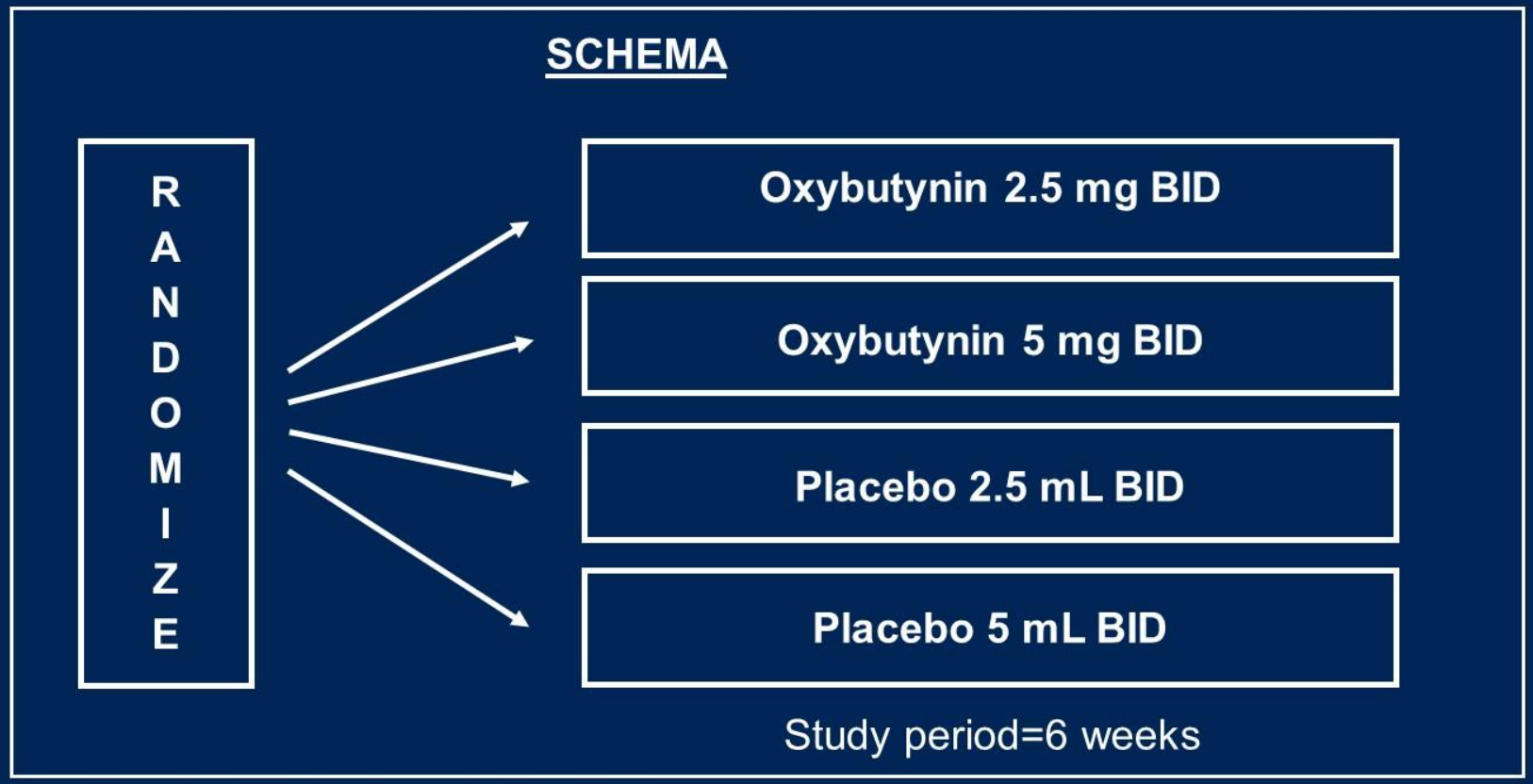
Management – Hormonal (Non-castrate Estrogenic)

Agent	Trial	Results	Other
Oestradiol gel (0.9mg of 0.1%) vs placebo[1] for 6m	78 randomized 1:1	Mean adjusted difference (MAD) of -1.6 HF/day (95% CI: -2.7 to -0.5; P = 0.04). The effect on weekly hot flush score was non-significant, with a MAD -19.6 (95% CI: -35.5 to -3.8; P = 0.11).	No effect on QOL; G/mastia 44% vs 21%; NippleT 28% vs 3%
Estetrol vs placebo[2]	62 randomized 2:1	At 24 wk, HFs was significantly lower in the HDE4 group than in the placebo group (14.3% vs 60.0%; $p < 0.001$). Daily HF score 3.7 vs 0.1*	Some effect on QOL, G/mastia 82% vs 25%; NippleT 88% vs 0%
Oestradiol gel (0.9mg, 1.8mg) vs placebo[3] for 28d	37 patients randomized 1:1:1	Decline in E2 groups (MAD -2.2/day, P=0.02).	No effect on QOL; Nipple tenderness (~10-20%)

1. Russell et al., 2022 2. Zimmerman et al., 2022 3.Russell et al., 2018

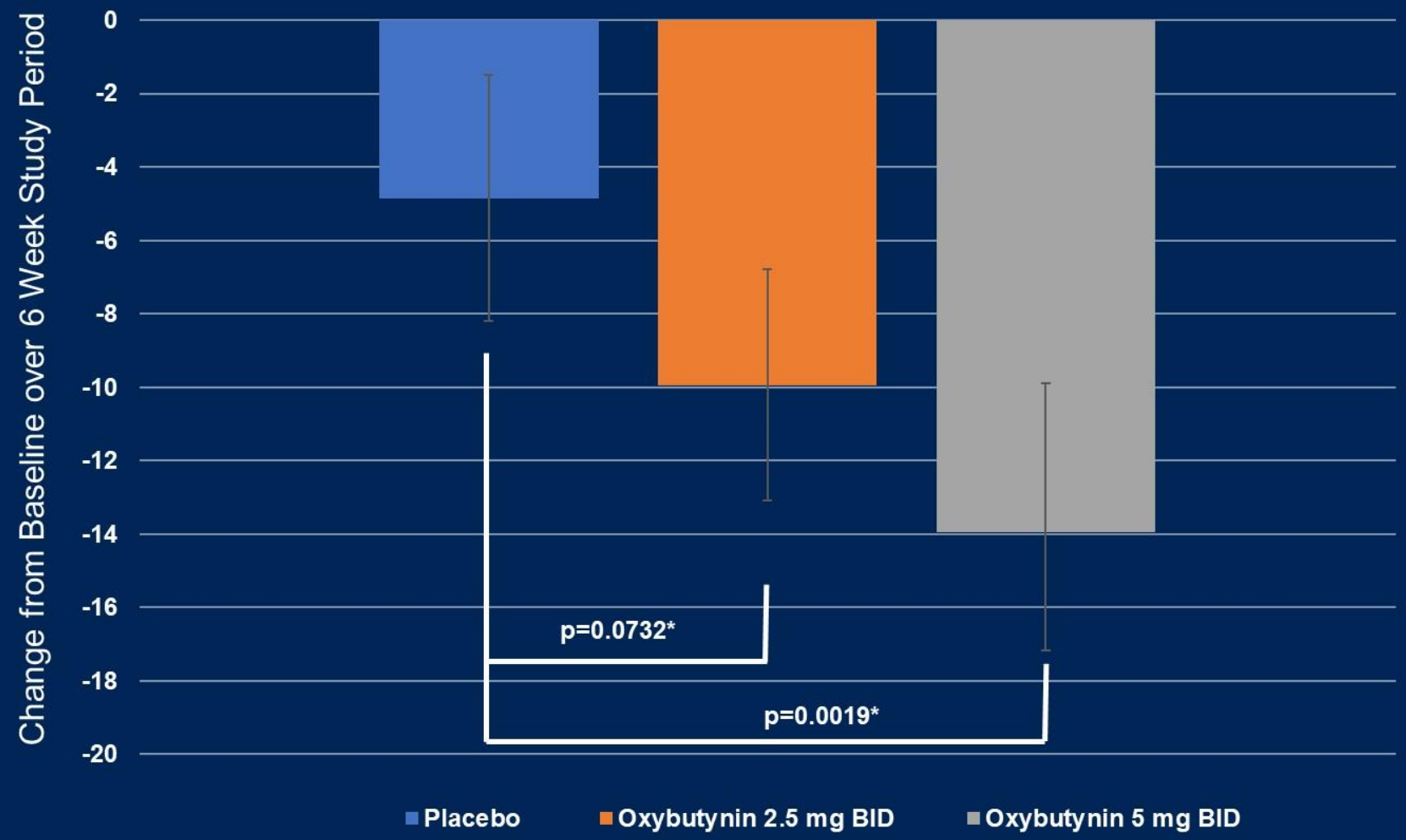
* number of HFs multiplied by their mean severity per day measured over 7 d

Methods



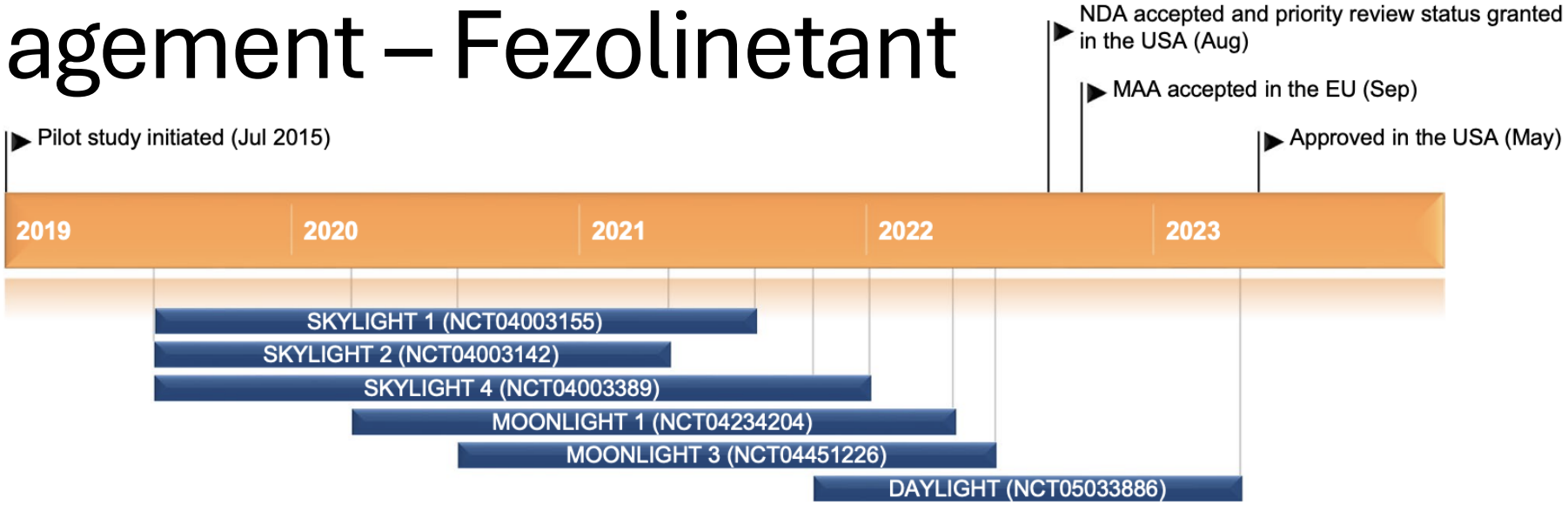
*Oxybutynin syrup concentration=1 mg/mL
*2:1 randomization for oxybutynin: placebo
*Placebo arms pooled for analysis
*Stratification factors: hot flash frequency at baseline, hot flashes duration, prior hot flash therapy, and planned RT during study

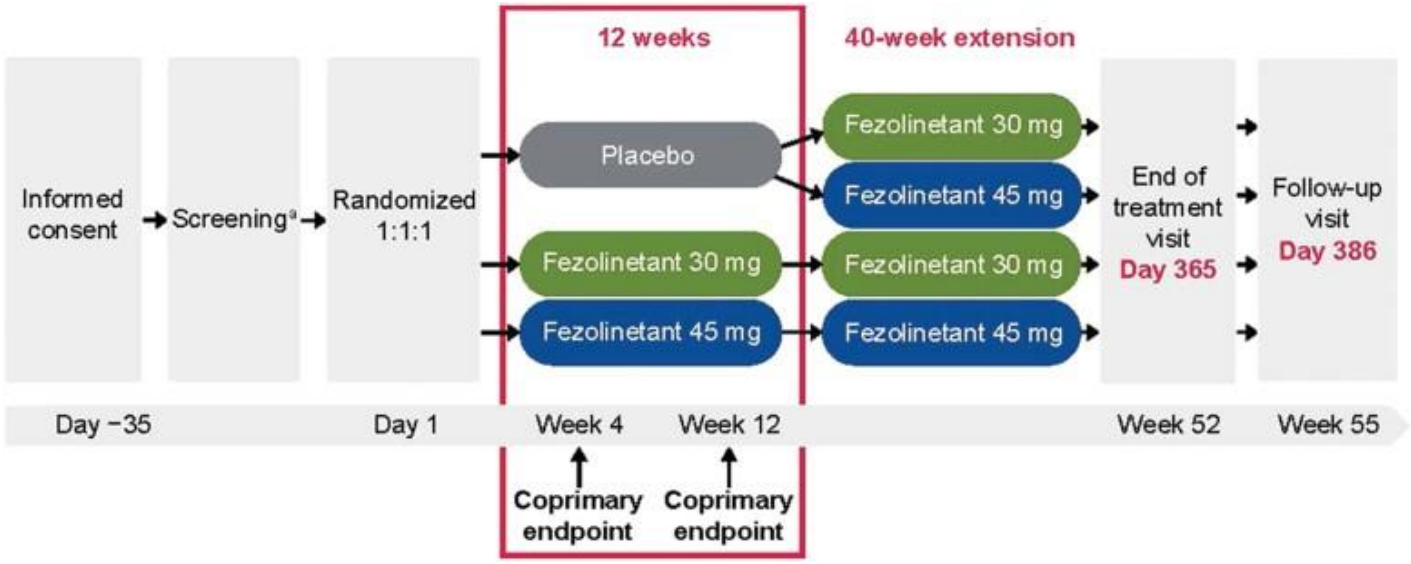
Primary Endpoint: Change from Baseline in Hot Flash Score



*Repeated measures mixed model adjusting for age and stratification factors

Management – Fezolinetant





Both at week 4 and week 12;

↓ Hot Flush Severity
~0.2; P<0.01

↓ Hot Flush Frequency
~-2.3; P< 0.01

↑ QOL indices eg HFRDIS, GCS, MENQOL

Rahman et al., 2023

Conclusions

mHSPC	• Doublets • Triplets	INDIVIDUALISE
mCRPC	• Lutetium	INDIVIDUALISE
Supportive Care	• Hot Flushes	INDIVIDUALISE