City of Hope®

Southeastern Multidisciplinary Approaches to Cancer Symposium

Updates in Systemic Therapies for Prostate Cancer

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Disclosures

- Consultant for Eisai, Exelixis & Pfizer.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Actinium-225, Capivasertib & Ipatasertib will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

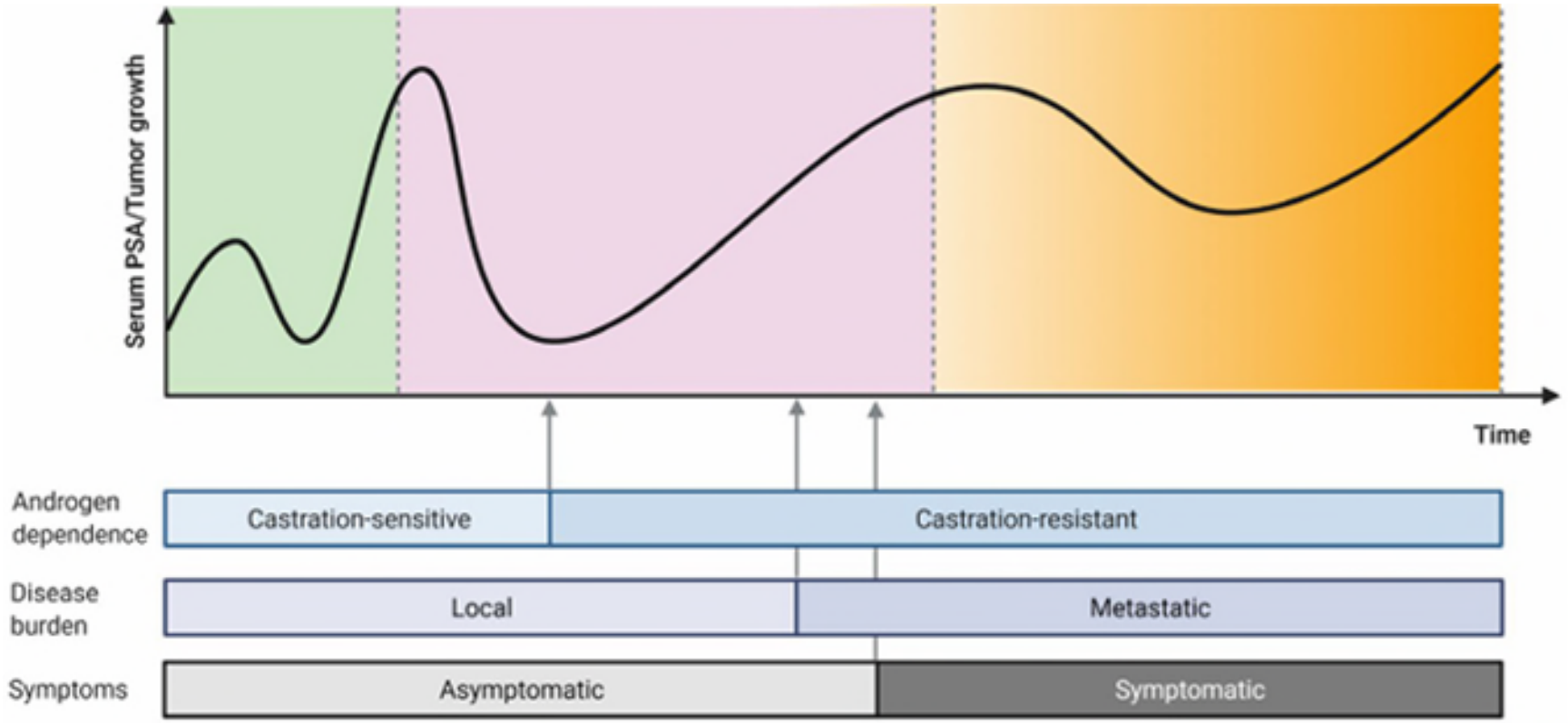
This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Learning Objectives

By the end of this session, participants should be able to:

- Review the systemic therapy landscape for prostate cancer
- Discuss emerging treatment modality in localized prostate cancer
- Summarize key updates in metastatic hormone-sensitive prostate cancer (mHSPC)
- Discuss advances in metastatic castration-resistant prostate cancer (mCRPC)
- Apply evidence-based sequencing strategies

Disease States in Prostate Cancer



Tianyan Wang 2022

Localized Prostate Cancer

NCCN Risk Groups

Risk Group	Clinical/Pathologic Features (Staging, ST-1)		
Low[j]	Has all of the following: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[j]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[k]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (eg, ≥6 of 12 cores)[k]
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL		
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL		

Current Management

Active surveillance, radiotherapy, prostatectomy

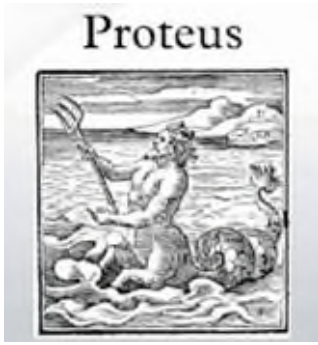
Active surveillance, radiotherapy, prostatectomy

RT + ADT (4-6 months)
Prostatectomy

RT + ADT (12-36 months)
Prostatectomy

RT + ADT (24 months) + Abiraterone
Prostatectomy

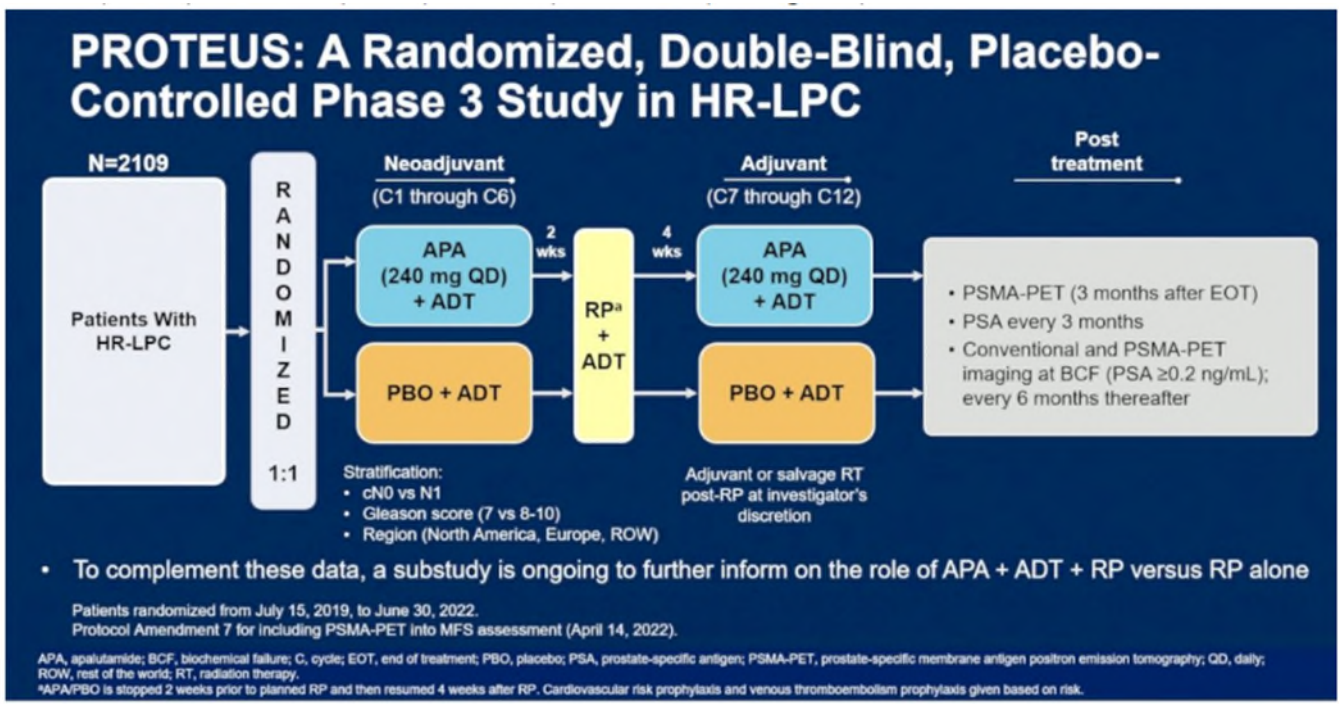
Locally advanced (N1)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Apalutamide in High-Risk Localized Prostate Cancer



Dual Primary Endpoint
- pCR – no identifiable tumor (ypT0)
- MRD - ≤ 5 mm residual tumor (ypT2 or lower)

NEJM. 2026 May 31

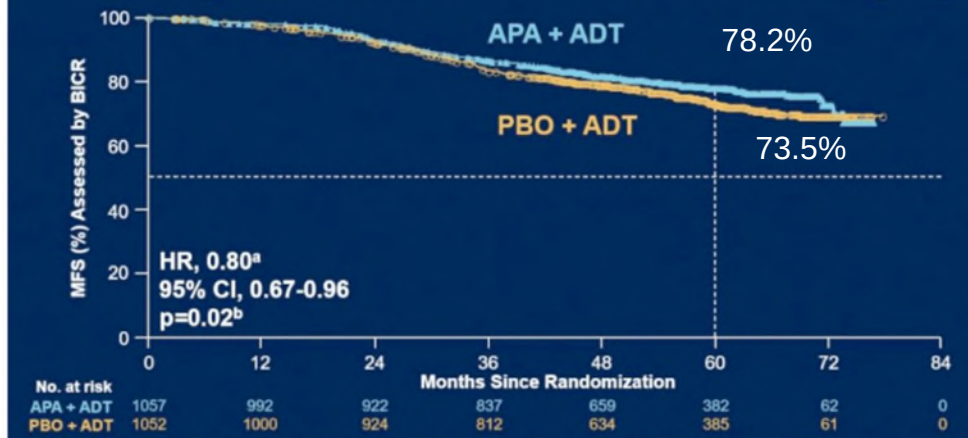
Baseline Characteristics

		APA + ADT (n=1057)	PBO + ADT (n=1052)
Median age (IQR), years		66.0 (62-71)	66.0 (61-70)
≥75, n (%)		106 (10.0)	94 (8.9)
Gleason score at initial diagnosis, n (%)	7	45 (4.3)	44 (4.2)
	≥8	1012 (95.7)	1008 (95.8)
Baseline PSA[a]	Median (IQR), ng/mL	14.4 (8.3-29.2)[b]	15.1 (8.1-33.7)[c]
	<20, n (%)	630 (61.5)	604 (58.5)
	≥20, n (%)	395 (38.5)	429 (41.5)
Tumor stage at diagnosis, n (%)[d]	≤T2	684 (64.7)	667 (63.4)
	≥T3	371 (35.1)	377 (35.8)
Regional lymph node stage at diagnosis, n (%)	N0	928 (87.8)	922 (87.6)
	N1	129 (12.2)	130 (12.4)

- **Median follow-up**: 61.7 months at clinical cutoff: (February 2, 2026); 85.1% (APA + ADT, n=899) and 87.6% (PBO + ADT, n=922) were still on the study

PRIMARY END POINT

Dual Primary End Point Met: MFS by Conventional or PSMA-PET Imaging



20% reduction in the risk of metastasis or death after 1 year of perioperative APA + ADT with RP by BICR

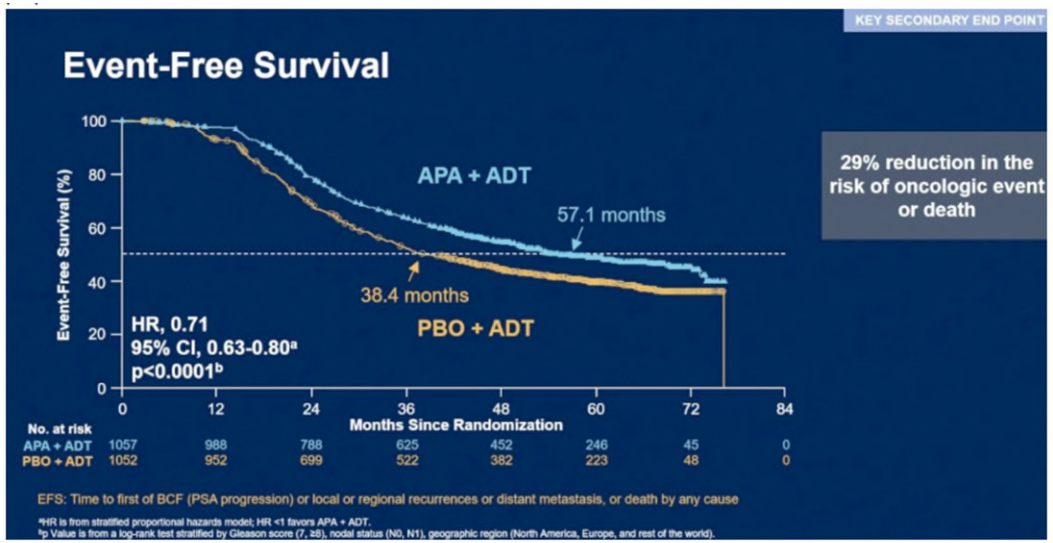
Investigator-assessed MFS was consistent:

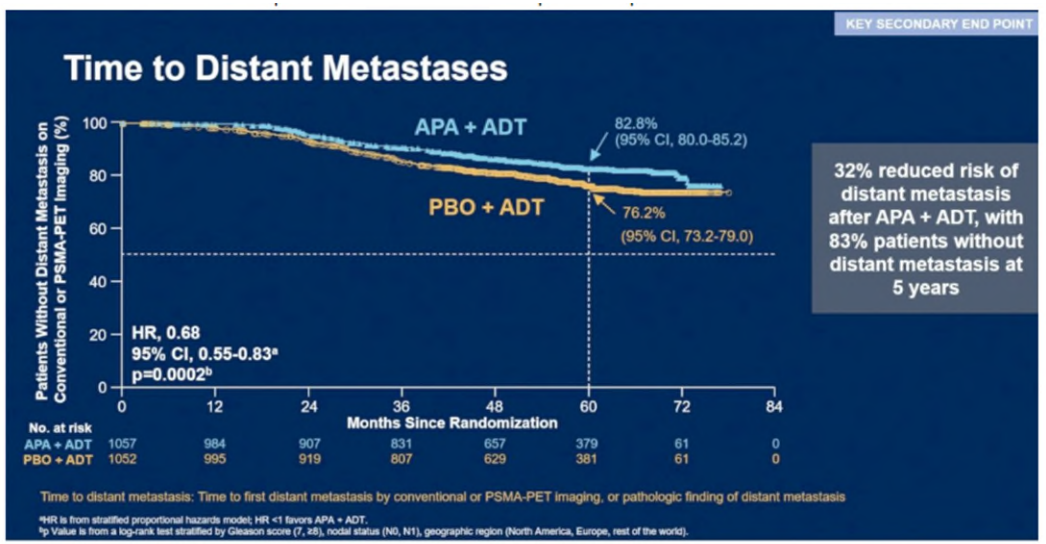
- HR, 0.74; 95% CI, 0.62-0.87; p=0.0004

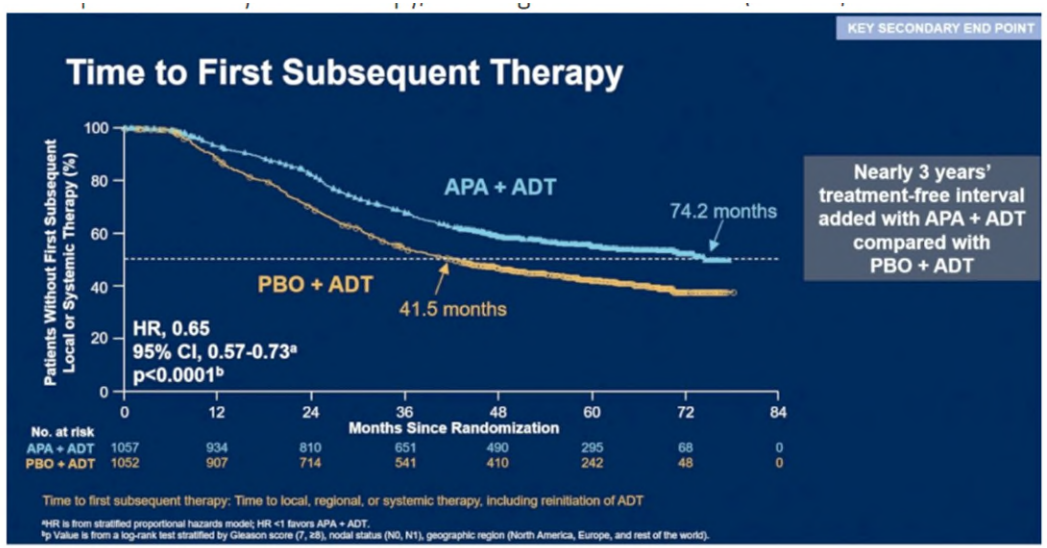
MFS: Time to first occurrence of radiographic distant metastasis based on conventional imaging or PSMA-PET imaging, pathologic finding of distant metastasis, or death from any cause

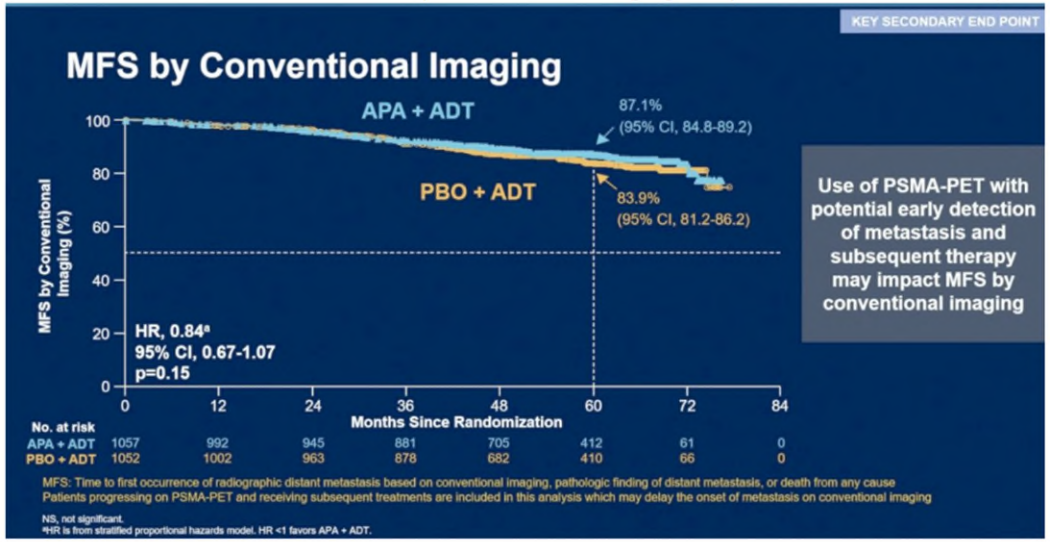
[a]Hazard ratio (HR) is from stratified proportional hazards model. HR <1 favors APA + ADT.
[b]p Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

Key Secondary Endpoints









Back to The Future: 2004

In the News

USRF
Urological Sciences Research Foundation

Taxotere, First Drug That Prolongs Life in Hormone Refractory Prostate Cancer, Approved by FDA

Abstracted from FDA News and other sources

May 19, 2004

Chemotherapy Drug Taxotere Extends Life of Prostate Cancer Patients

Study Led by NewYork-Presbyterian/Columbia Finds 20 Percent Longer Survival Compared with Standard Therapy

Jun 7, 2004

New York, NY

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Breast Cancer Drug Approved for Prostates

L.A. Times Archives

May 22, 2004 12 AM PT

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NEWS RELEASE 7-JUN-2004

Docetaxel extends life in advanced prostate cancer patients

Should be 'standard of care,' researchers say

Peer-Reviewed Publication

JOHNS HOPKINS MEDICINE

Docetaxel: The first effective chemotherapy
2004

$C_{43}H_{53}NO_{14}$

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Evolution of Treatment Paradigm

Past
- ADT
- Chemotherapy

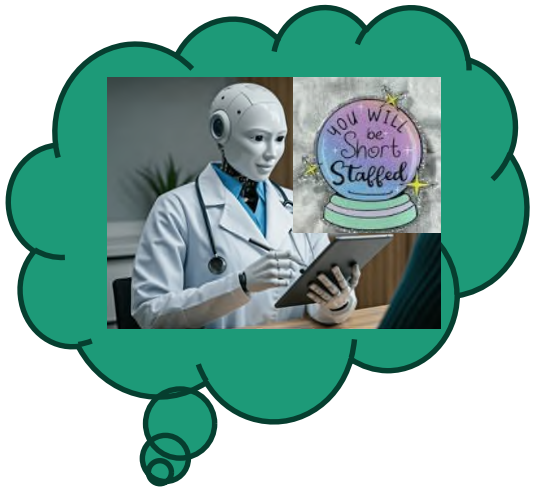
Present
- ARPi
- Chemohormonal
- Triple therapy
- PARPi
- Radioligands
- Immunotherapies

(nearest) Future
- Bispecifics
- CAR-T therapy
- AKT inhibitors
- AI-guided oncology

Early treatment intensification

Precision medicine

The (other) Future



mHSPC: Intensification is Standard

*ADT alone no longer adequate for most patients

Standard Approaches

ADT + ARPI
ADT + docetaxel
ADT + PARP inhibitor

Triple Therapy

ADT + docetaxel + abiraterone
ADT + docetaxel + darolutamide

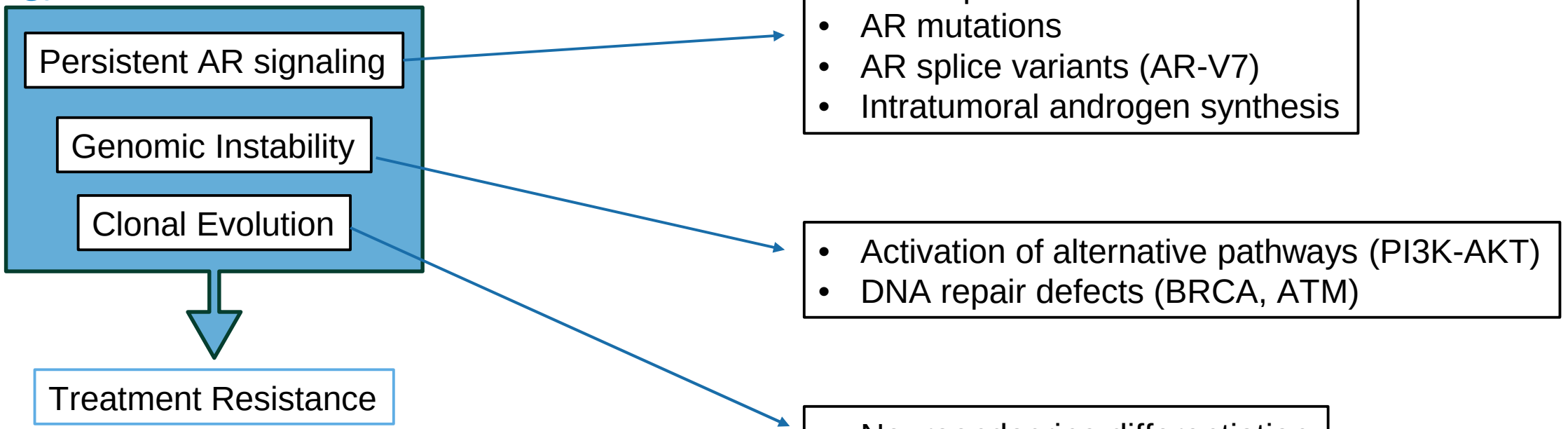
Outcomes

Improve overall survival
Delay progression
Better symptom control

Agent	Trial	Key Benefits
Docetaxel	CHAARTED	OS
Abiraterone	LATITUDE	OS
Enzalutamide	ENZAMET	OS
Apalutamide	TITAN	rPFS/OS
Darolutamide	ARANOTE	rPFS
Niraparib + Abiraterone (mBRCA)	AMPLITUDE	rPFS
TRIPLE THERAPY (HIGH-VOLUME)		
Docetaxel + abiraterone	PEACE-1	rPFS/OS
Docetaxel + darolutamide	ARASENS	OS

Metastatic CRPC

Biology of Castration Resistance



Treatment Categories

- ARPIs
- Taxanes
- PARP inhibitors
- Radioligands
- Immunotherapy

PARP Inhibition

	TALAPRO-2 (Talazoparib/enzalutamide)	PROpel (Olaparib/abiraterone)	MAGNITUDE (Niraparib/abiraterone)
Setting	HRR alteration (prospective)	HRR (unselected)	HRR alteration (prospective)
N	399 (BRCA 158)	796	423 (BRCA 225)
Randomization	1:1	1:1	1:1
Comparator	Enzalutamide	Abiraterone	Abiraterone
Primary endpoint	rPFS	rPFS	rPFS
Median rPFS, months	30.7 vs 12.3 (HR 0.47)	24.8 vs 16.6 (HR 0.66)	16.5 vs 13.7 (HR 0.73)
Median OS, months	45.1 vs 31.1 (HR 0.62)	42.1 vs 34.7 (HR 0.81)	No benefit (HR 0.94)
	Trial showed both **rPFS** and **OS** benefits	**rPFS** benefit irrespective of HRR **Numerical OS** benefit - Strong rPFS and OS in BRCA	Only **rPFS** benefit

Lancet. 2023;402:291,Lancet Oncol. 2023;24:1094, JCO. 2023;41:3339

Immunotherapies

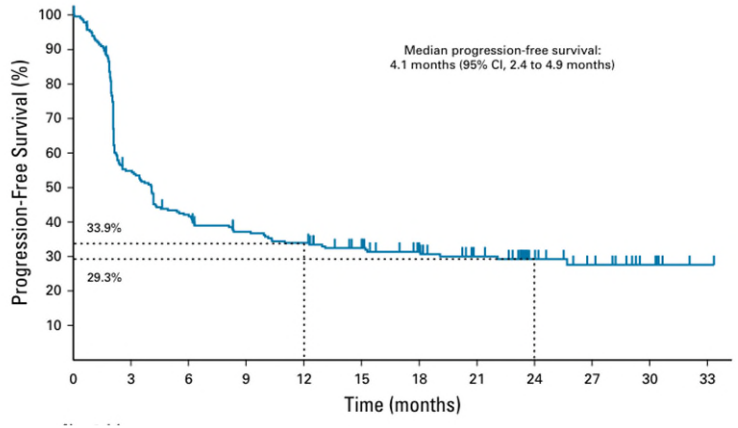
	Sipuleucel-T	Pembrolizumab
Relevant trial	IMPACT	KEYNOTE 16/158
Biomarker	-	MSH-H/dMMR, TMB-high
	Autologous cellular immunotherapy	Anti-PD-1

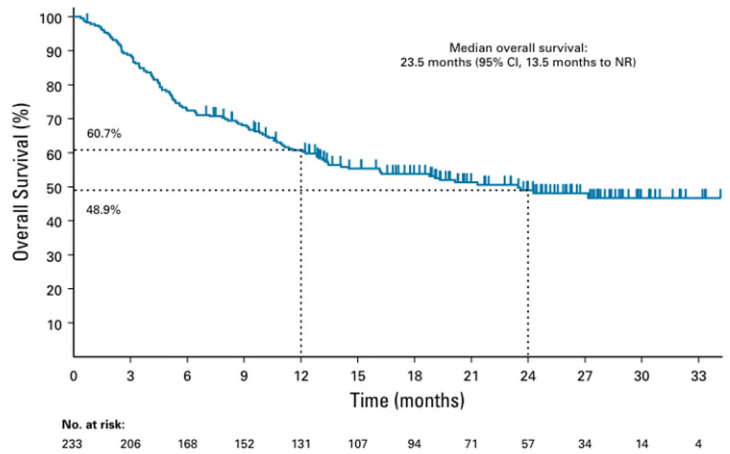
Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Open label single arm phase II
- Pembrolizumab 200 mg IV Q3W for 2ys/progression
- Primary Endpoint - ORR

233 patients
- Advanced non-colorectal cancer
- MSI-H/dMMR by IHC or PCR
- 6 (2.6%) prostate

Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable disease	42 (18.0)
Progressive disease	92 (39.5)
Nonevaluable	2 (0.9)
No assessment‡	17 (7.3)





JCO. 2020;38:1

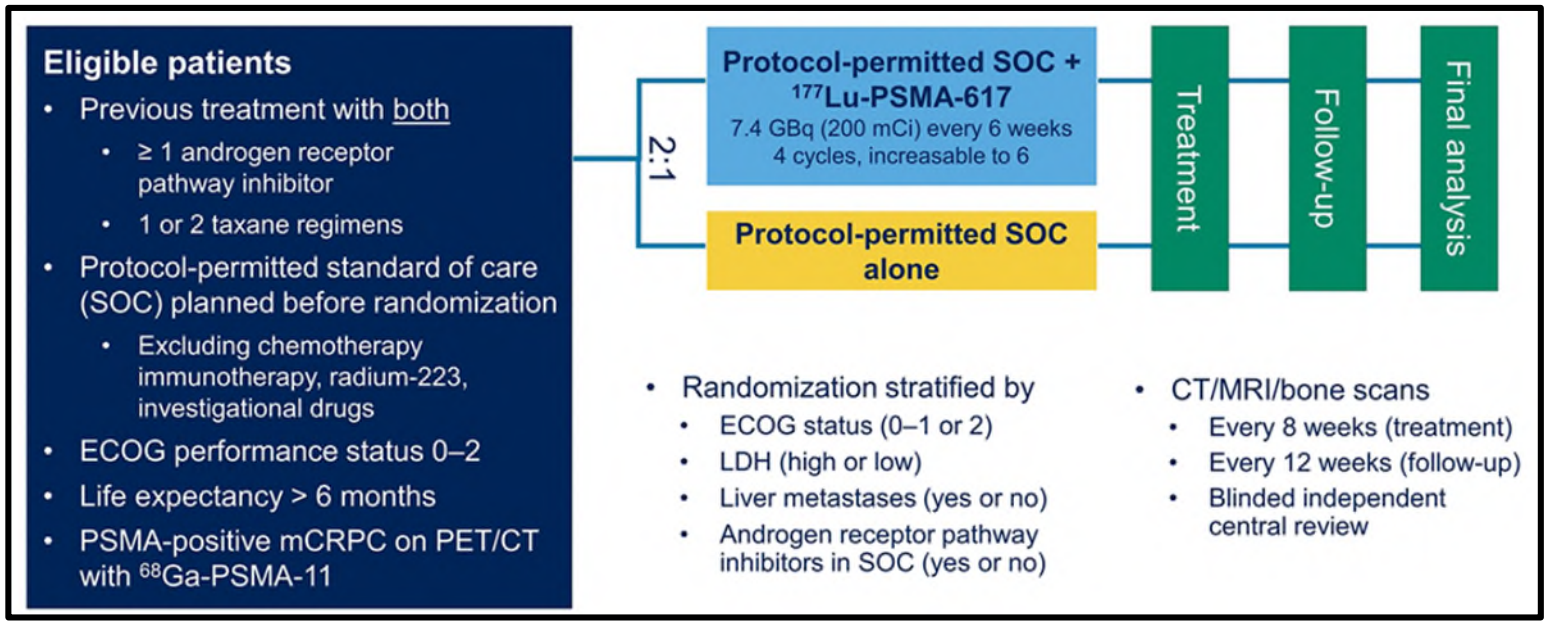
PSMA Radioligand Therapy

	Beta	Alpha
LET	Low (0.1-1 KeV/µm)	High (100-200 KeV/µm)
Path length	Long (0.5-2mm)	Short (50-100 µm)
DNA damage	Single stranded DNA breaks	Double stranded DNA breaks
Crossfire effect	Yes	Minimal
Distribution	Wider area	Focused, high intensity hits
Ideal tumor	Bulky/heterogenous	Micrometastasis/ uniform

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

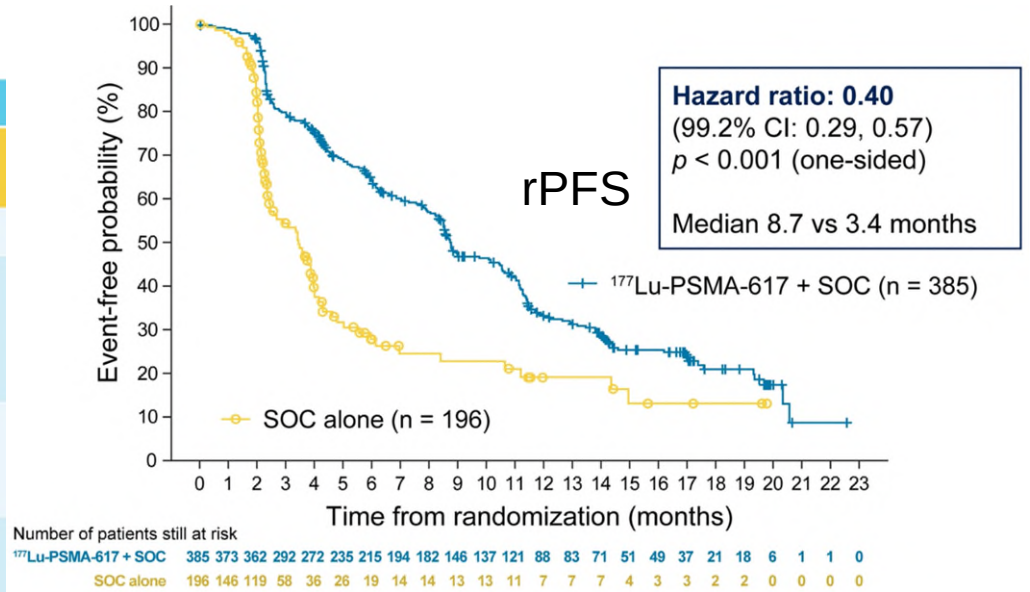


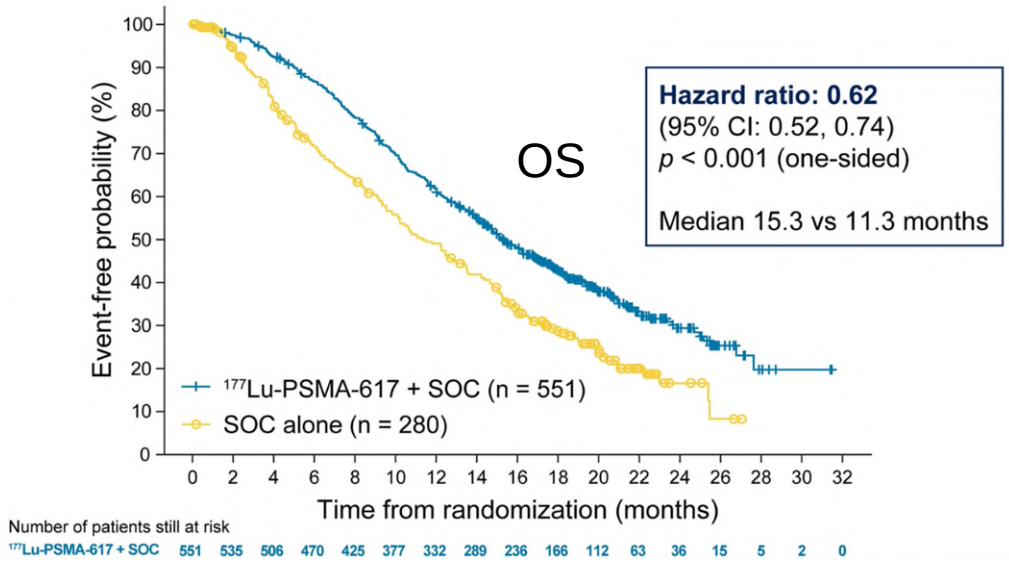
Alternate primary endpoints

- Radiographic progression-free survival (rPFS) per PCWG3
- Overall survival (OS)

NEJM. 2021;385:1091

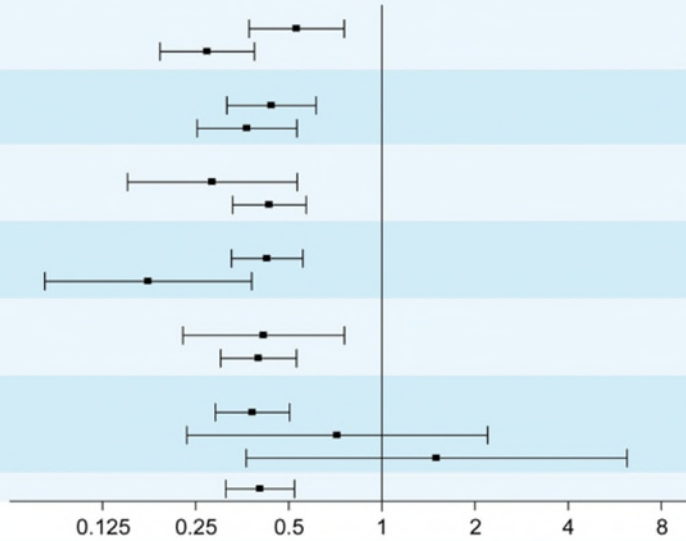
	rPFS analysis set (n = 581)		All randomized (N = 831)	
	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
Age, median (range)	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
Race, n (%)				
White	336 (87.3)	166 (84.7)	486 (88.2)	235 (83.9)
Black/African-American	29 (7.5)	14 (7.1)	34 (6.2)	21 (7.5)
Asian	6 (1.6)	9 (4.6)	9 (1.6)	11 (3.9)
ECOG status, n (%)				
0 or 1	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
2	33 (8.6)	17 (8.7)	41 (7.4)	22 (7.9)
Site of disease, n (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Number received, median (range)				
Androgen receptor pathway inhibitor	1.0 (1–5)	1.5 (1–4)	1.0 (1–5)	2.0 (1–4)
Taxane regimen	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)
Patients who received more than one, n (%)				
Androgen receptor pathway inhibitor	172 (44.7)	98 (50.0)	253 (45.9)	152 (54.3)
Taxane regimen	178 (46.2)	94 (48.0)	226 (41.0)	124 (44.3)





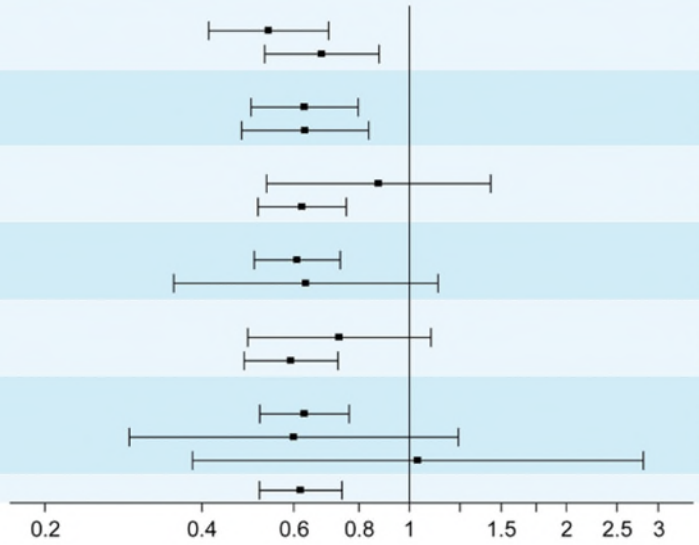
rPFS

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	170	107	0.53 (0.37, 0.76)
No	215	89	0.27 (0.19, 0.39)
LDH			
≤ 260 IU/L	244	120	0.44 (0.32, 0.61)
> 260 IU/L	140	75	0.37 (0.25, 0.53)
Liver metastases			
Yes	37	22	0.28 (0.15, 0.53)
No	348	174	0.43 (0.33, 0.57)
ECOG score			
0 or 1	352	179	0.43 (0.33, 0.56)
2	33	17	0.18 (0.08, 0.38)
Age			
< 65 years	96	39	0.42 (0.23, 0.76)
≥ 65 years	289	157	0.40 (0.30, 0.53)
Race			
White	336	166	0.38 (0.29, 0.50)
African American or Black	29	14	0.72 (0.23, 2.20)
Asian	6	9	1.50 (0.36, 6.19)
All patients	385	196	0.40 (0.31, 0.52)



OS

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	243	146	0.54 (0.41, 0.70)
No	308	134	0.68 (0.53, 0.87)
LDH			
≤ 260 IU/L	368	182	0.63 (0.50, 0.80)
> 260 IU/L	182	97	0.63 (0.48, 0.84)
Liver metastases			
Yes	48	34	0.87 (0.53, 1.43)
No	503	246	0.62 (0.51, 0.76)
ECOG score			
0 or 1	510	258	0.61 (0.50, 0.74)
2	41	22	0.63 (0.35, 1.13)
Age			
< 65 years	145	60	0.73 (0.49, 1.10)
≥ 65 years	406	220	0.59 (0.48, 0.73)
Race			
White	486	235	0.63 (0.52, 0.77)
African American or Black	34	21	0.60 (0.29, 1.24)
Asian	9	11	1.04 (0.38, 2.81)
All patients	551	280	0.62 (0.52, 0.74)



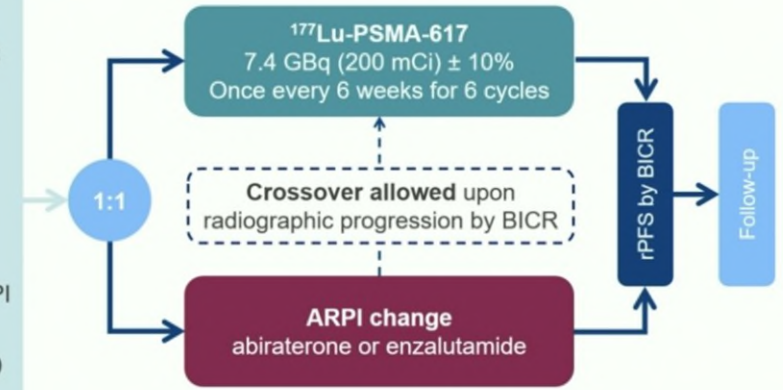
^{177}Lu-PSMA-617 pre-chemotherapy

^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

PSMAfore: a phase 3, randomized, open-label study

Eligible adults

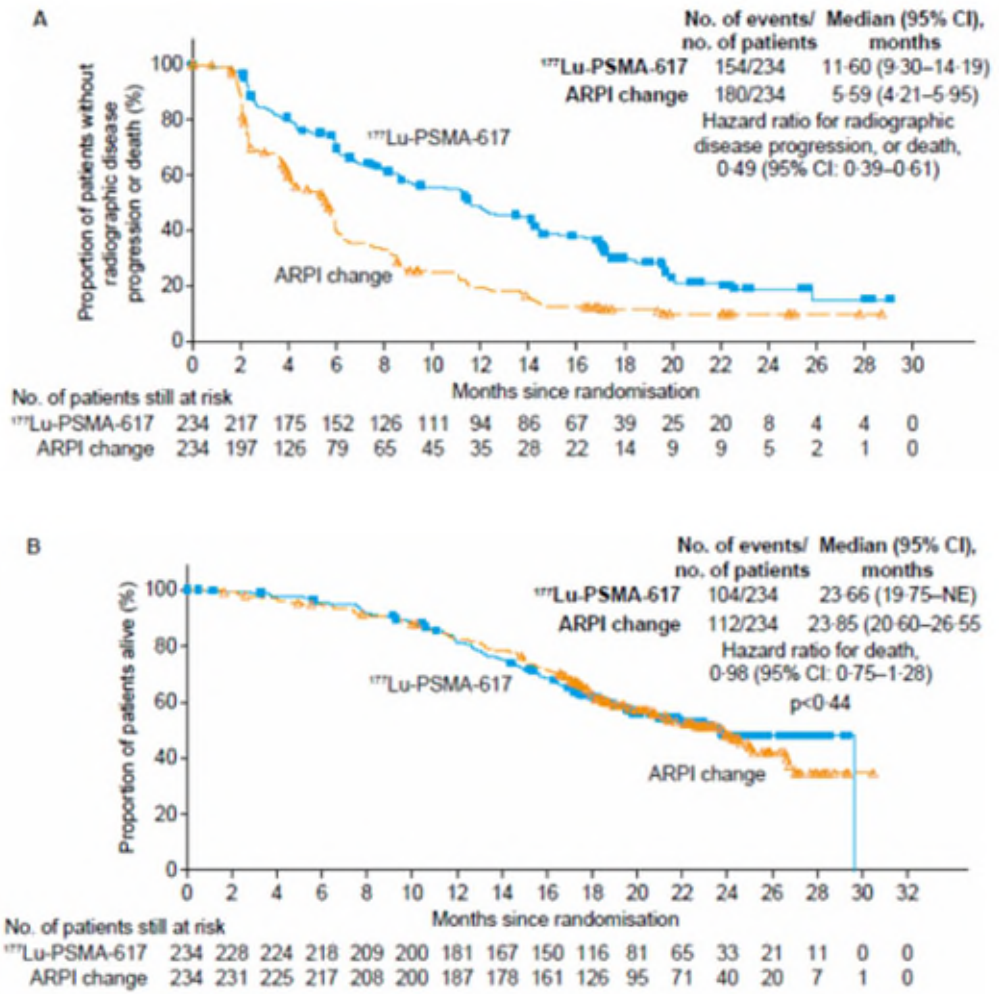
- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



Stratification factors

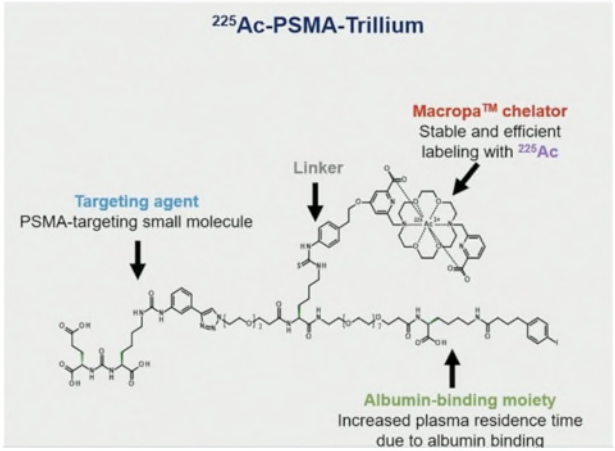
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

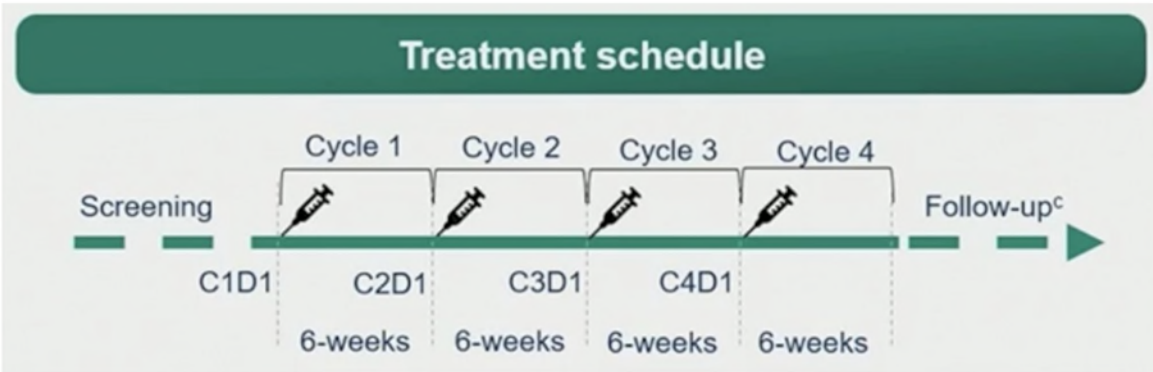
ITT Population



Lancet. 2024;404:1227

First-in-human assessment of actinium-225-prostate-specific membrane antigen (^{225}Ac-PSMA)-Trillium (BAY 3563254) in mCRPC: Dose-escalation results of the phase 1 PAnTHa study.

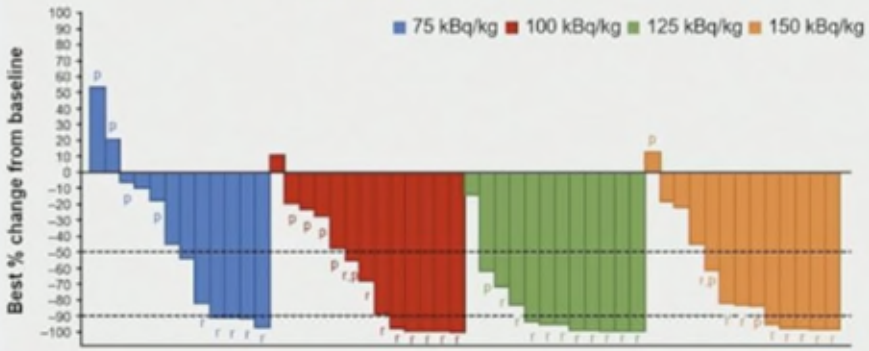




Baseline characteristics	75 kBq/kg (N=12)	100 kBq/kg (N=13)	125 kBq/kg (N=12)	150 kBq/kg (N=13)	Total (N=50)
Median age, years (range)	65 (56–84)	71 (57–80)	73 (60–85)	69 (46–85)	70.5 (46–85)
RECIST soft tissue lesions, n (%)					
Target only	1 (8)	1 (8)	2 (17)	1 (8)	5 (10)
Non-target only	2 (17)	2 (15)	2 (17)	2 (15)	8 (16)
Target and non-target	2 (17)	7 (54)	5 (42)	5 (38)	9 (38)
None	7 (58)	3 (23)	3 (25)	5 (38)	18 (36)
Bone metastases , n (%)	11 (92)	10 (77)	12 (100)	12 (92)	45 (90)
ECOG PS, n (%)					
0	5 (42)	5 (38)	7 (58)	5 (38)	22 (44)
1	7 (58)	8 (62)	6 (50)	8 (62)	29 (58.0)
Median PSA, µg/L (range)	22 (0.1–345)	103 (1.3–5,500)	73 (4–845)	21 (8–316)	43 (0.1–5,500)
Prior taxanes, n (%)					
1	4 (33)	7 (54)	4 (33)	9 (69)	24 (48)
≥2	3 (25)	6 (46)	4 (33)	2 (15)	15 (30)
No prior taxane reported	5 (42)	0 (0)	4 (33)	2 (15)	11 (22)
Prior ARPIs, n (%)					
1	11 (92)	10 (77)	10 (83)	12 (92)	43 (86)
2	1 (8)	3 (23)	2 (17)	1 (8)	7 (14)

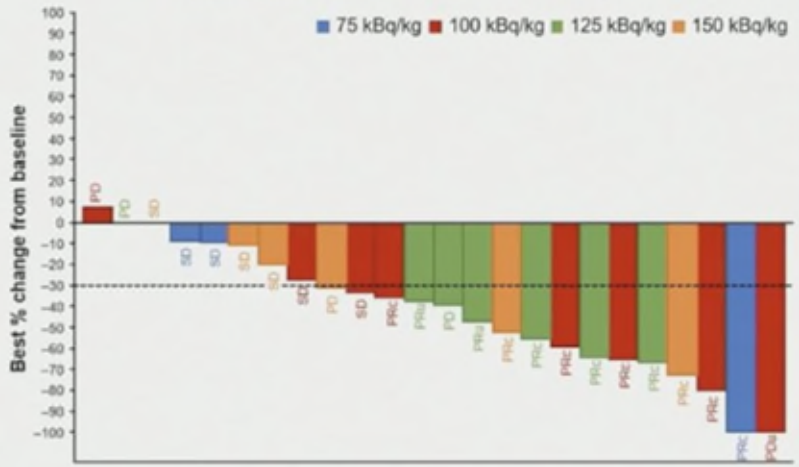
Follow-up and doses received	
Median follow-up time, months (range)	7.2 (2.5–18.2)
Patients completing 4 cycles	80%
Median cycles received	4

PSA response (N=50)



	All patients (N=50)	125 kBq/kg dose (N=12)
PSA50 response rate, %	62	83
PSA90 response rate, %	40	67
Overall response rate[a,c], %		
Confirmed responses only	42	43
Confirmed and unconfirmed	50	71
Disease control rate[a,c], %	79	71

Radiographic response (N=24)[a,b]



Based on the observed efficacy and safety data, the recommended dose for expansion was established as 125 kBq/kg

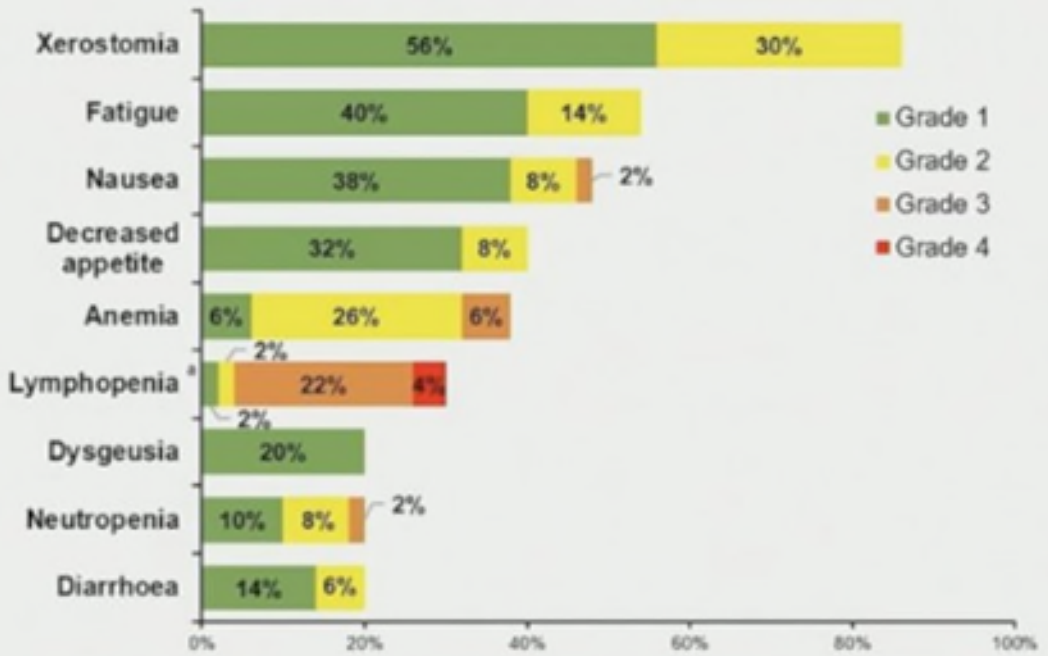
Dose	N at C2D1	ctDNA clearance at C2D1	Median decline	IQR
75 kBq/kg	9	1 (11%)	57	267
100 kBq/kg	11	3 (27%)	67	71
125 kBq/kg	11	4 (36%)	89	44
150 kBq/kg	8	1 (13%)	73	38

Treatment-emergent adverse events (TEAEs)	75 kBq/kg (N=12)	100 kBq/kg (N=13)	125 kBq/kg (N=12)	150 kBq/kg (N=13)	Total (N=50)
Any TEAE, n (%)	12 (100)	13 (100)	12 (100)	13 (100)	50 (100)
Grade 3-4	5 (42)	2 (15)	6 (50)	9 (69)	22 (44)
Leading to dose modification	0 (0)	1 (8)	1 (8)	3 (23)	5 (10)
Leading to permanent discontinuation	1 (8)	1 (8)	1 (8)	0 (0)	3 (6)
Leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DLTs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TEAEs leading to permanent discontinuation were:

- Grade 3 lymphopenia (worsened from Grade 2; related to study drug)
- Grade 3 glomerular filtration rate decreased (unrelated to study drug)
- Grade 2 renal impairment (related to study drug)

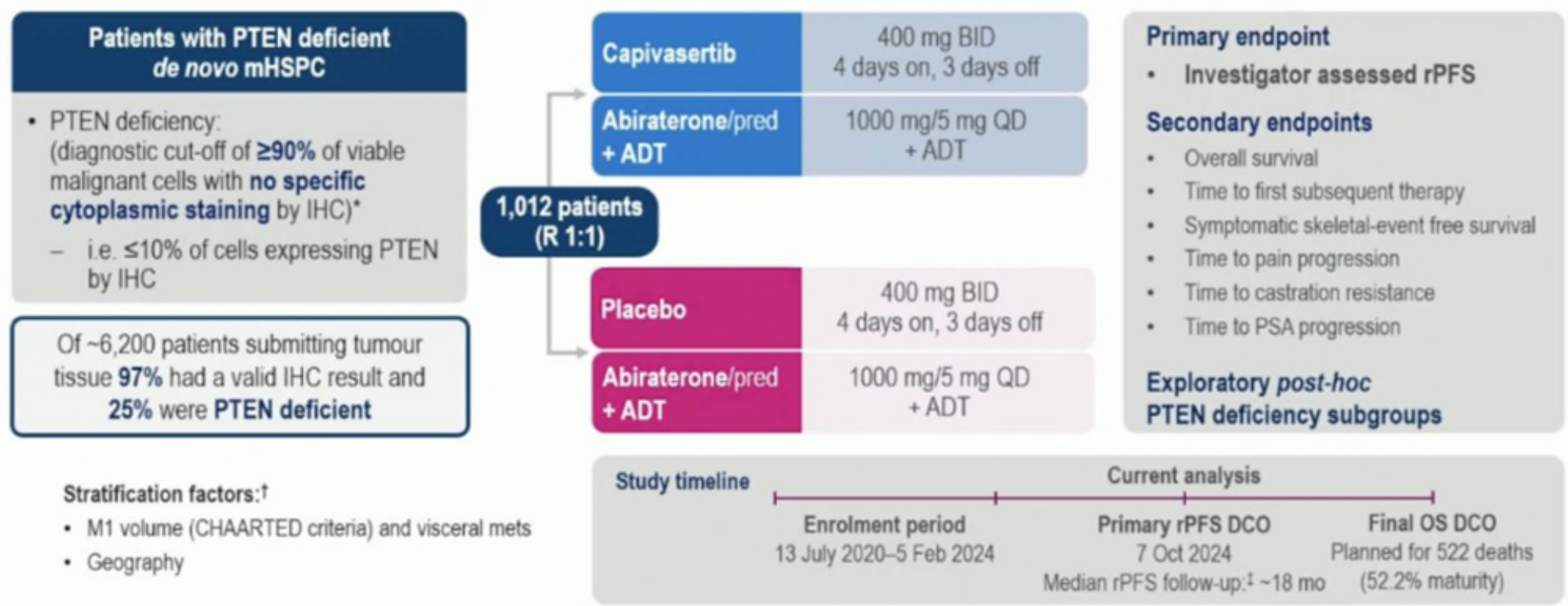
Most common TEAEs (≥20% of patients)



Lymphopenia and anemia were the only Grade ≥3 TEAEs occurring in more than 2% of patients

AKT Inhibition (PTEN Loss)

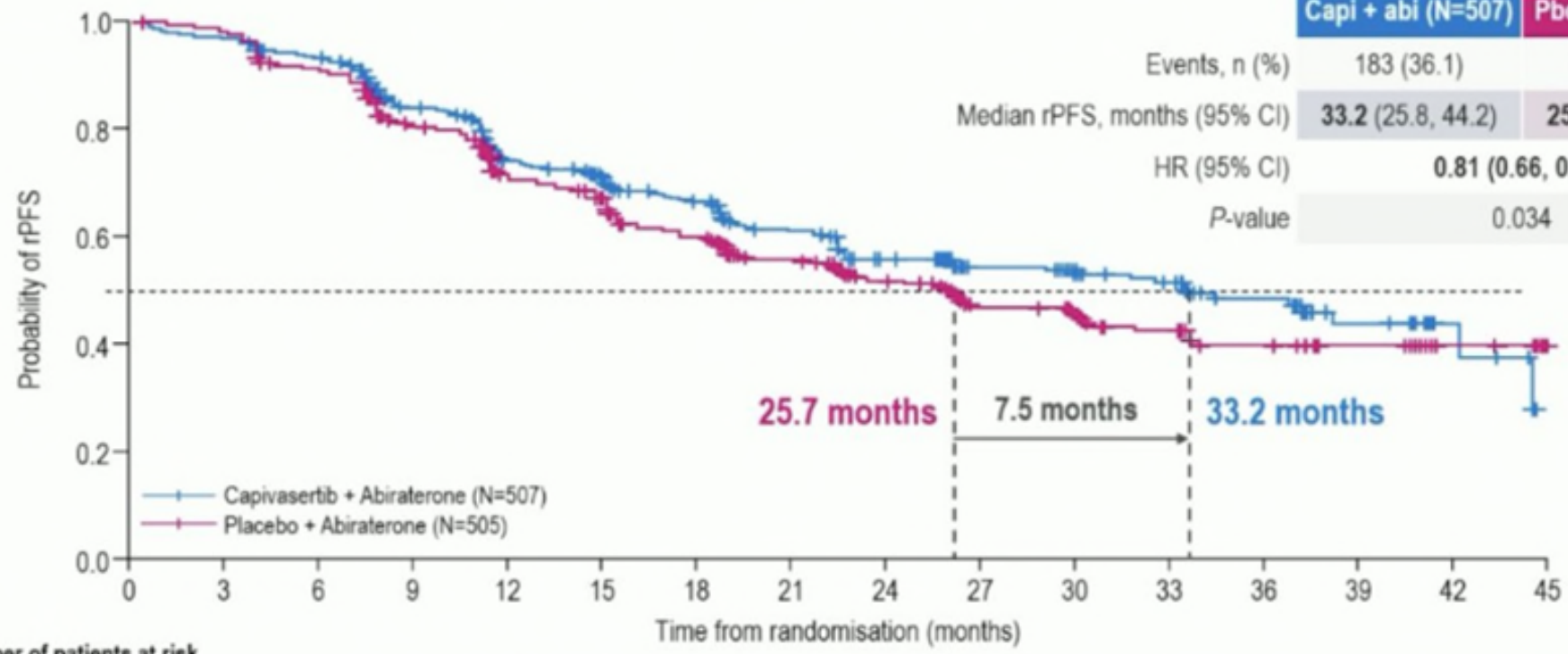
Capivasertib plus abiraterone in PTEN-deficient metastatic hormone-sensitive prostate cancer: CAPItello-281 phase III study☆



Ann Oncol. 2026;37:574

		Capi + abi (N=507)	Pbo + abi (N=505)
Median age, years (range)		67.0 (42–87)	68.0 (43–88)
'Race', n (%)*	White	266 (52.5)	259 (51.3)
	Asian	186 (36.7)	189 (37.4)
	Black or African American	6 (1.2)	6 (1.2)
ECOG PS, n (%)	(0) Normal activity	329 (64.9)	320 (63.4)
	(1) Restricted activity	178 (35.1)	185 (36.6)
Metastases, n (%)	Bone	462 (91.1)	467 (92.5)
	Liver	30 (5.9)	25 (5.0)
	Lung	69 (13.6)	72 (14.3)
	Non-regional lymph node	217 (42.8)	214 (42.4)
Median time from diagnosis to randomization, months (range)		2.46 (0.3–12.8)	2.45 (0.6–27.4)
Total Gleason score at diagnosis, n (%)*	<8	94 (18.5)	95 (18.8)
	≥8	398 (78.5)	399 (79.0)
Disease risk, n (%)*	High	311 (61.3)	333 (65.9)
	Low	184 (36.3)	164 (32.5)
M1 volume/visceral metastases, n (%)*	High vol. disease with visceral mets	98 (19.3)	95 (18.8)
	High vol. disease without visceral mets	276 (54.4)	283 (56.0)
	Low vol. disease	131 (25.8)	126 (25.0)

CAPItello-281 Primary endpoint: investigator-assessed rPFS



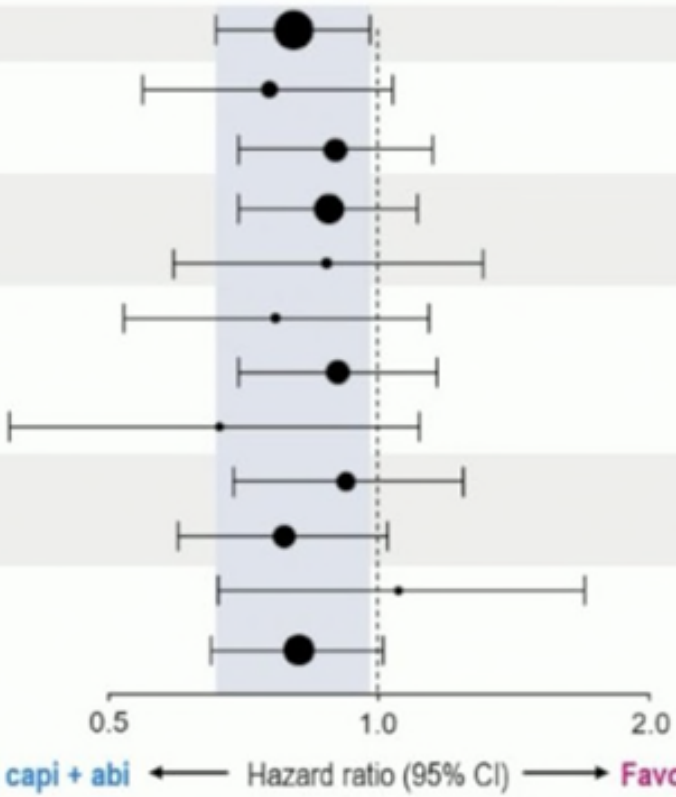
	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	183 (36.1)	215 (42.6)
Median rPFS, months (95% CI)	**33.2** (25.8, 44.2)	**25.7** (22.0, 29.9)
HR (95% CI)	**0.81 (0.66, 0.98)**	
P-value	0.034	

Number of patients at risk

Capi + abi	507	460	435	353	282	233	217	165	123	93	69	62	41	21	6	0
Pbo + abi	505	479	440	359	276	215	198	154	113	83	59	51	37	23	8	0

CAPItello-281: Investigator-assessed rPFS by prespecified subgroups

		Events/Patients, n (%)		
		Capi + abi	Pbo + abi	HR (95% CI)
All randomised patients		**183/507 (36.1)**	**215/505 (42.6)**	**0.81 (0.66, 0.98)**
Age	<65 years	65/174 (37.4)	89/190 (46.8)	0.75 (0.55, 1.04)
	≥65 years	118/333 (35.4)	126/315 (40.0)	0.90 (0.70, 1.15)
Disease risk	High	132/311 (42.4)	160/333 (48.0)	0.88 (0.70, 1.11)
	Low	49/184 (26.6)	50/164 (30.5)	0.88 (0.59, 1.31)
M1 volume/visceral mets	High with visceral mets	49/98 (50.0)	52/95 (54.7)	0.77 (0.52, 1.14)
	High without visceral mets	110/276 (39.9)	129/283 (45.6)	0.91 (0.70, 1.17)
	Low	24/131 (18.3)	34/126 (27.0)	0.67 (0.39, 1.12)
Baseline PSA*	≤Median (6.415 ng/mL)	86/260 (33.1)	92/242 (38.0)	0.93 (0.69, 1.24)
	>Median (6.415 ng/mL)	97/245 (39.6)	119/256 (46.5)	0.79 (0.60, 1.03)
Gleason score	<8	38/94 (40.4)	34/95 (35.8)	1.06 (0.66, 1.69)
	≥8	141/398 (35.4)	175/399 (43.9)	0.82 (0.65, 1.02)

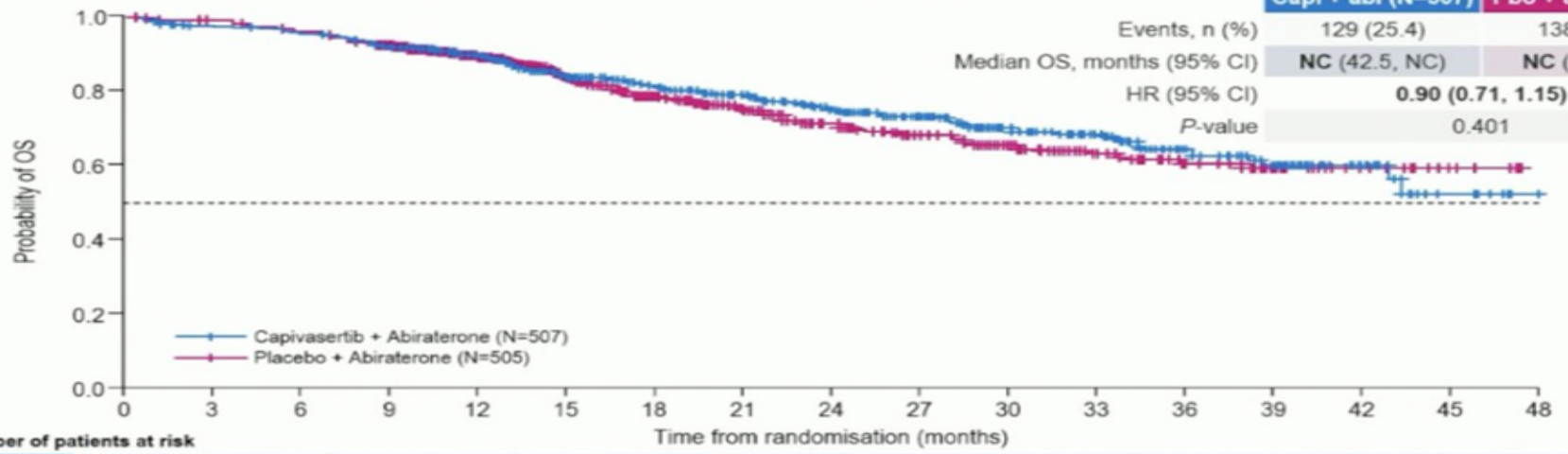


Key secondary endpoints were tested according to the hierarchical testing procedure

		Events, n (%)	Median, months: Capi + abi	Median, months: Pbo + abi	HR (95% CI)	
	Overall survival	267 (26.4)	NC	NC	0.90 (0.71, 1.15)	Interim
	Time to	Formal testing was halted following OS analysis				
Key Secondary Endpoints	Next treatment	398 (39.3)	37.0	28.5	0.91 (0.75, 1.11)	Final
	SSE-FS	326 (32.2)	42.5	37.3	0.82 (0.66, 1.02)	Interim
	Pain progression	87 (8.6)	NC	NC	1.14 (0.75, 1.75)	Interim
Other Secondary Endpoints	CRPC	416 (41.1)	29.5	22.0	0.77 (0.63, 0.94)	Interim
	PSA progression	142 (14.0)	NC	NC	0.73 (0.52, 1.01)	Interim

CAPItello-281: Interim OS

OS analysis was conducted at 26% maturity, further follow-up is planned



	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	129 (25.4)	138 (27.3)
Median OS, months (95% CI)	**NC** (42.5, NC)	**NC** (NC, NC)
HR (95% CI)	**0.90 (0.71, 1.15)**	
P-value	0.401	

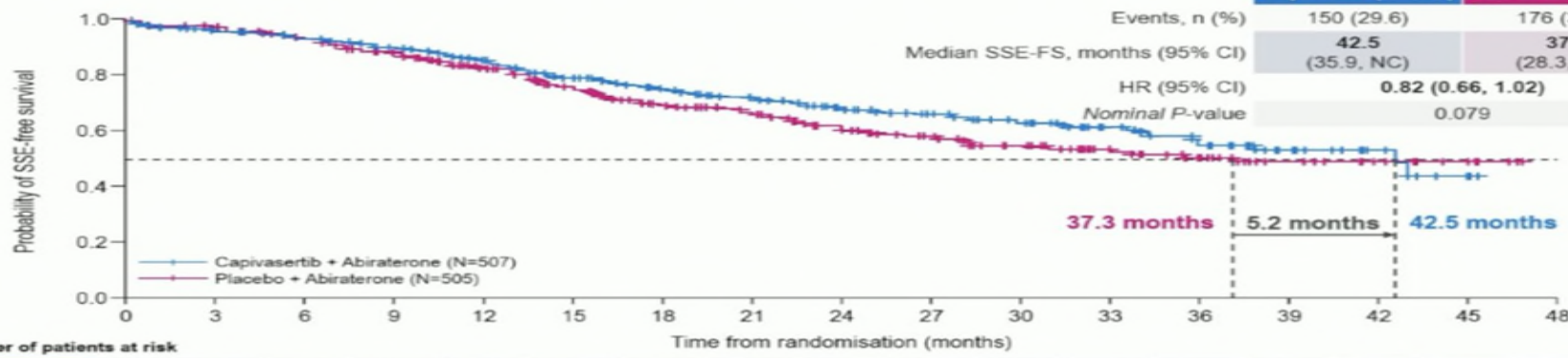
Number of patients at risk

Capi + abi	507	487	476	447	400	335	286	242	199	164	128	96	60	42	22	7	0
Pbo + abi	505	494	479	449	388	330	273	227	188	153	113	88	56	33	19	7	0

A stratified log-rank test was used to calculate two-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model.
CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; pbo, placebo

CAPItello-281: Symptomatic skeletal event-free survival

Composite endpoint of pathological fracture, spinal cord compression, use of radiation, surgical intervention, and death



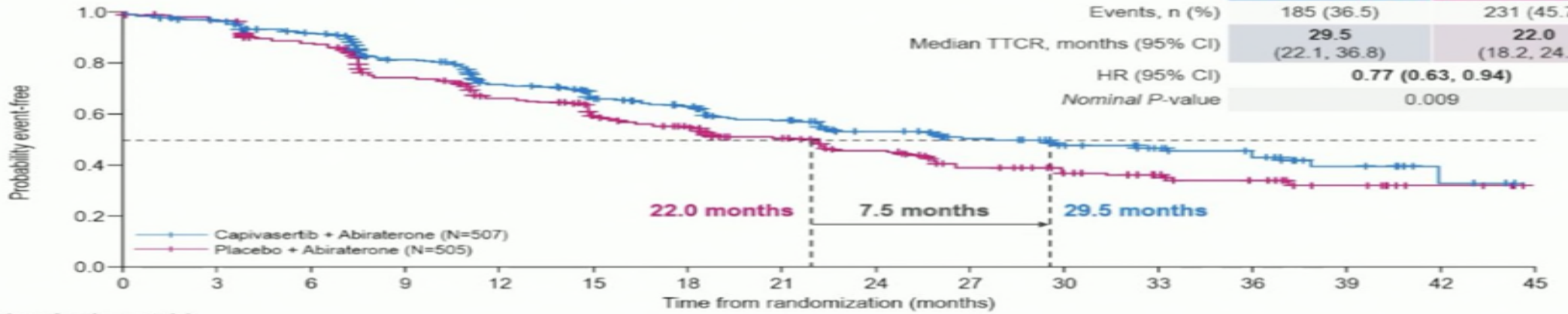
	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	150 (29.6)	176 (34.9)
Median SSE-FS, months (95% CI)	**42.5** (35.9, NC)	**37.3** (28.3, NC)
HR (95% CI)	**0.82 (0.66, 1.02)**	
Nominal P-value	0.079	

Number of patients at risk

Capi + abi	507	458	439	408	346	292	245	206	162	129	104	67	46	26	13	5	0
Pbo + abi	505	479	455	412	336	285	223	190	142	113	85	59	38	26	13	6	0

CAPItello-281: Time to castration resistance

Composite endpoint of radiographic disease progression, PSA progression, and symptomatic skeletal events



	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	185 (36.5)	231 (45.7)
Median TTCR, months (95% CI)	**29.5** (22.1, 36.8)	**22.0** (18.2, 24.9)
HR (95% CI)	**0.77 (0.63, 0.94)**	
Nominal P-value	0.009	

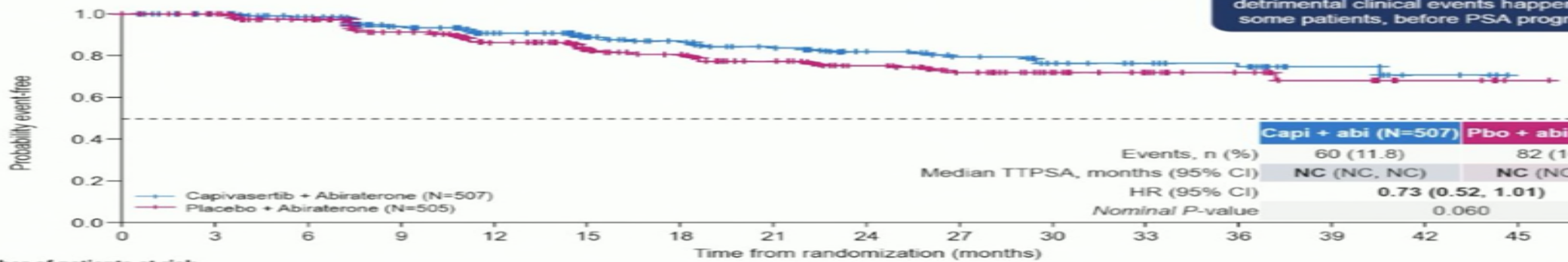
Number of patients at risk

Capi + abi	507	440	404	323	251	205	184	144	112	82	57	45	35	18	5	0
Pbo + abi	505	468	412	319	249	192	166	128	92	66	48	39	26	16	6	0

CAPItello-281: Time to PSA progression

PSA progression, defined per the PCWG3 definition[1], required confirmation

In this PTEN-deficient population detrimental clinical events happened, for some patients, before PSA progression

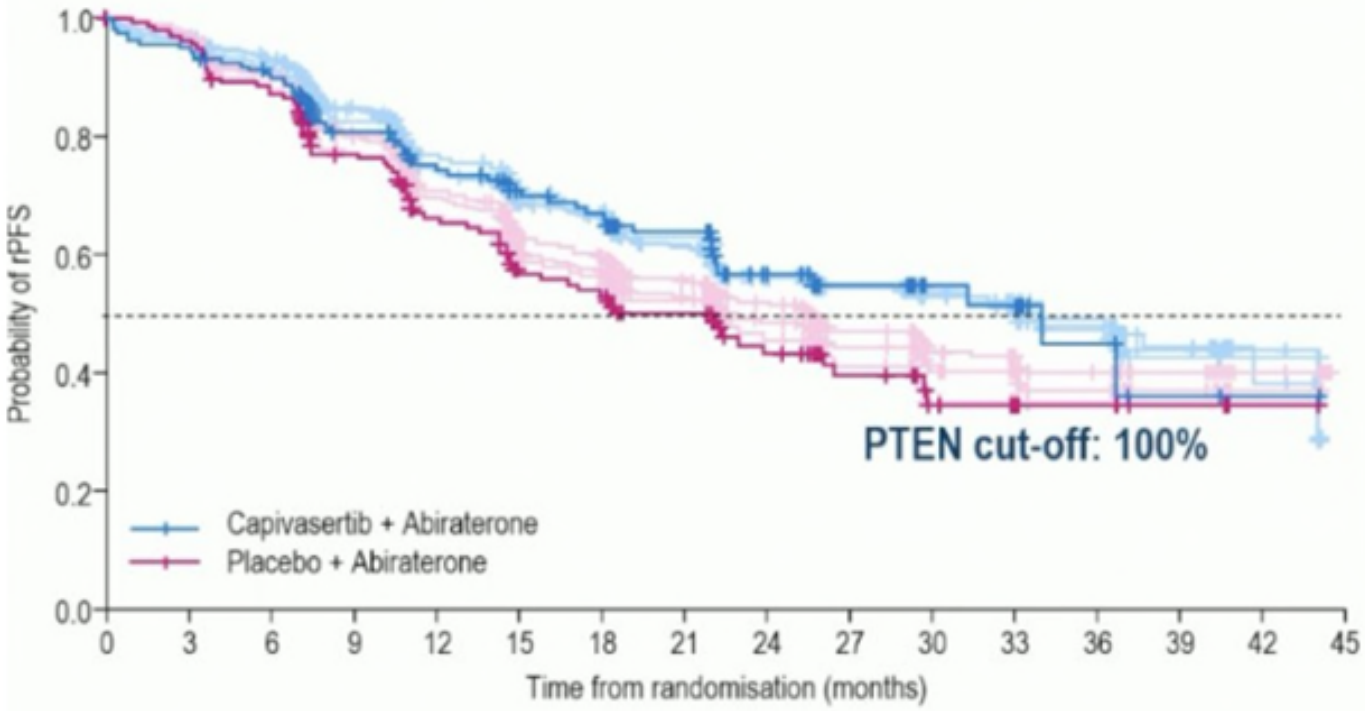


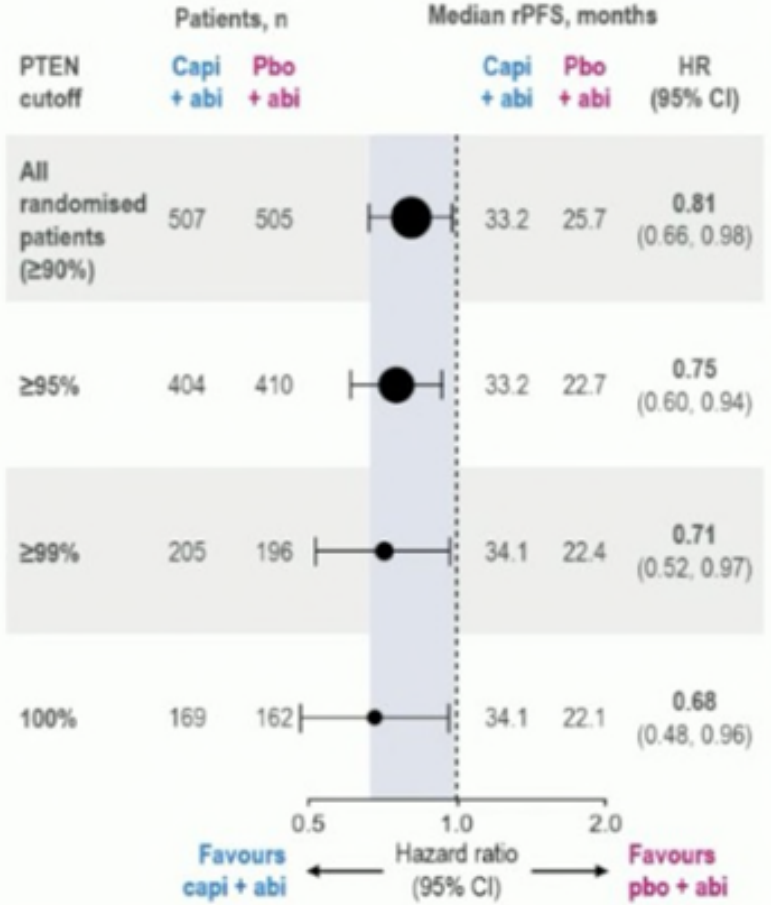
	Capi + abi (N=507)	Pbo + abi (N=505)
Events, n (%)	60 (11.8)	82 (16.2)
Median TTPSA, months (95% CI)	**NC** (NC, NC)	**NC** (NC, NC)
HR (95% CI)	**0.73 (0.52, 1.01)**	
Nominal P-value	0.060	

Number of patients at risk

Capi + abi	507	443	403	325	256	218	200	150	117	86	62	56	40	20	6	0	0
Pbo + abi	505	469	420	337	261	208	182	134	99	76	57	48	31	17	6	1	0

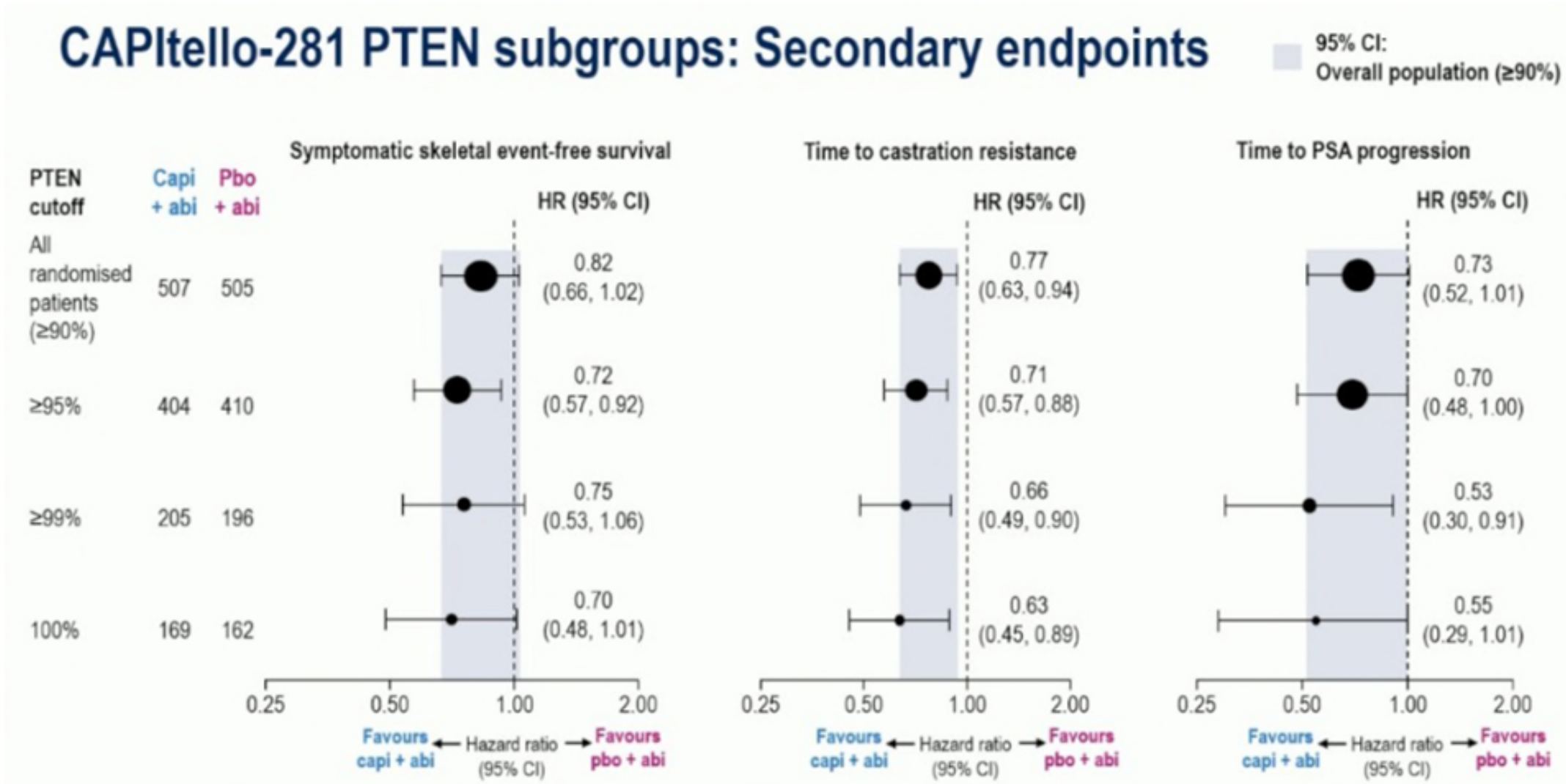
CAPItello-281 PTEN subgroups: investigator-assessed rPFS





rPFS maturity in PTEN subgroups was consistent with the overall population

CAPItello-281 PTEN subgroups: Secondary endpoints



Sequencing Challenges

Common Questions

- ARPI after ARPI?
- When to use chemotherapy?
- Earlier radioligand therapy?
- Best timing for PARPi combination?

Emerging Therapies

PSMA-directed
- Alpha emitters
- Combination radioligand approach

Bispecific antibodies
- PSMA x CD3

Cellular therapy
- CAR-T

Androgen receptor degraders

Key Take-Home Messages

ADT monotherapy is no longer standard of care for most mHSPC

Triplet therapy improves outcomes in selected patients

Genomic testing is increasingly required

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Thank you!