GONORTE
Grupo Oncológico

REUNIÓN POST CONGRESO DE LA
SOCIEDAD EUROPEA DE ONCOLOGÍA MÉDICA 2025

Presentaciones más destacadas en cáncer de próstata

Dr. Urbano Anido

Hospital Clínico Universitario de Santiago de Compostela

Conflicts of interest

Stocks Novavax, Biomea Fusion, Candel Therapeutics

Consultant or Advisory board: Novartis, Ipsen, Astra-Zeneca, Merck, Pfizer, Astellas, Bayer, Janssen

Travel Support: Ipsen, Bayer, Merck, Pfizer

Honoraria: Novartis, Ipsen, Astellas, Bayer, BMS, Pfizer, Roche, Astra-Zeneca, Merck, Eisai, BMS, Rovi, Priothera (an inmediate family member)

Participation in clinical trials|| Institutional: Pfizer, Astra-Zeneca, Janssen, BMS, Roche, Ipsen, Bayer, Novartis, MSD, Astellas, ITM, Gilead, Bicycle

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Schedule

High risk PC	BCR	mHSPC	mCRPC
• ENZARAD	• Presto • EMBARK	• AMPLITUDE • CAPItello-281 • PSMAddition • ARASAFE	• PR21

ENZARAD

ENZARAD schema

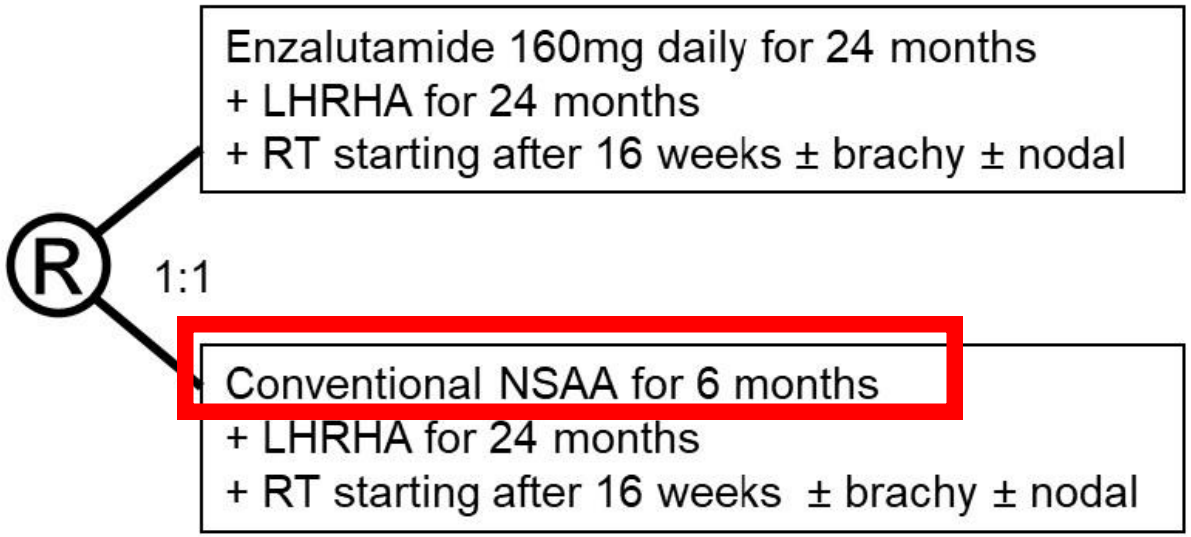
Eligibility

Localised prostate cancer
High risk of recurrence
Suitable for EBRT

Stratification

Gleason score 8-10
T3-4 disease
N1 disease
PSA ≥20 ng/mL
Brachytherapy boost
Pelvic nodal RT
Study Site

N=800



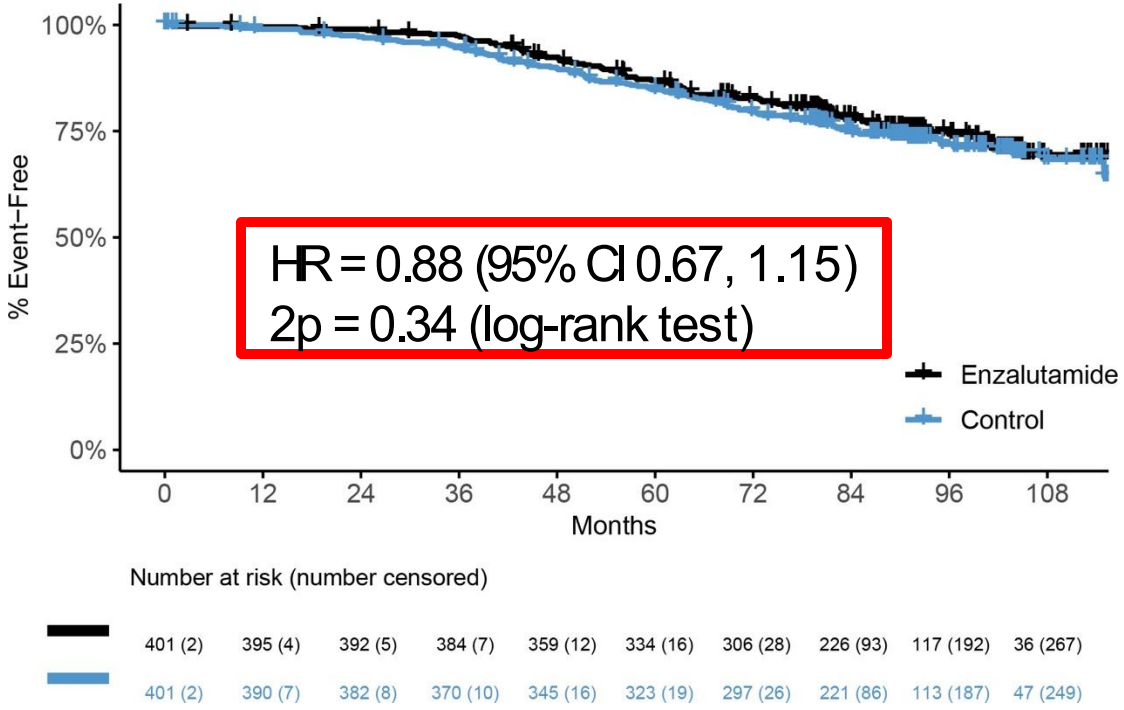
Endpoints

Metastasis-free survival (primary)
Overall survival
Cause specific survival
PSA progression free survival
Clinical progression free survival
Castration-resistance
Health related quality of life
Adverse events
Incremental cost-effectiveness

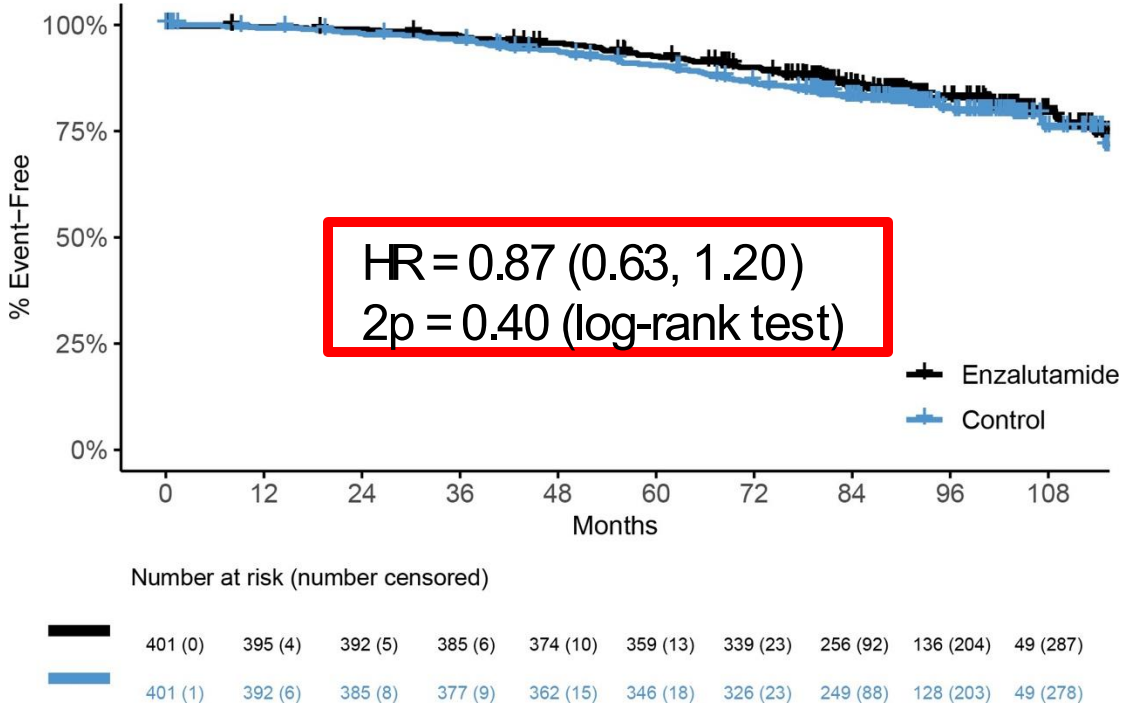
Primary Endpoint:
MFS based on conventional imaging (CT or MRI or bone scan, per ICECAP)
Lesions on PSMA-PET alone insufficient
Event = metastasis or death from any cause before m

ENZARAD	STAMPEDE
cT3 (45%), cT2 (42%)	cT3-4 (90%)
cN1 (11%)	cN1 (40%)

MFS by conventional imaging

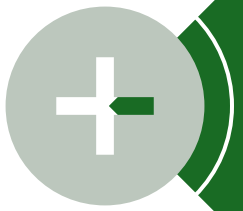


Overall Survival

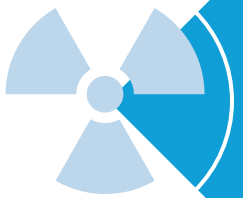


ENZARAD

ENZARAD is negative



The addition of Enzalutamide to ADT – Radiotherapy in unslected high-risk prostate cancer didn’t improve MFS or OS



Abiraterone is the only ARPI recommended in combination with Radiotherapy + ADT in very high-risk prostate cancer

Ongoing trials in high-risk localized PCa

	ATLAS	DASL-HiCaP	ALADDIN
ARPI	Apalutamide	Darolutamide	Darolutamide
Treatment duration	2 years	2 years	2 years
Primary outcome	MFS	MFS	FFS
Inclusion criteria	**Charlson ≤ 3** **1 of the following characteristics at baseline**: 1) Gleason score ≥ 8 and ≥ cT2c 2) Gleason score ≥ 7, PSA ≥ 20 ng/mL and ≥ cT2c	**cN1** or **ISUP 5** or **ISUP4** and **1 of the following criteria**: ≥ T2b, PSA ≥ 20 ng/ml, VS+	**cN1 (PET-CT)**
Primary Completion Date	06/2026	01/2028	02/2026

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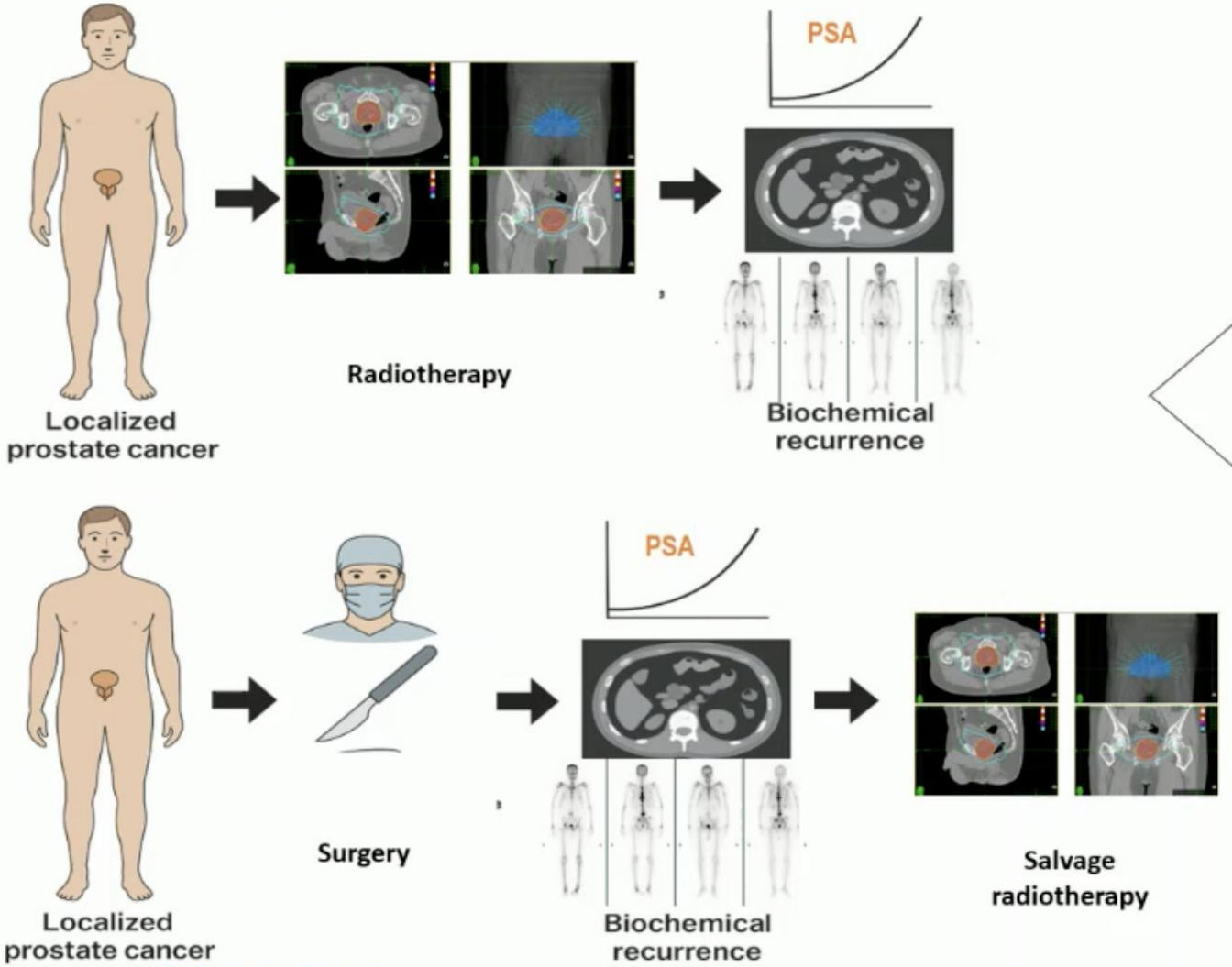
PRESTO

Standard of Care until 2024



Low risk BCR (EAU)
(PSA DT ≥ 1 year, ISUP Grade <4)

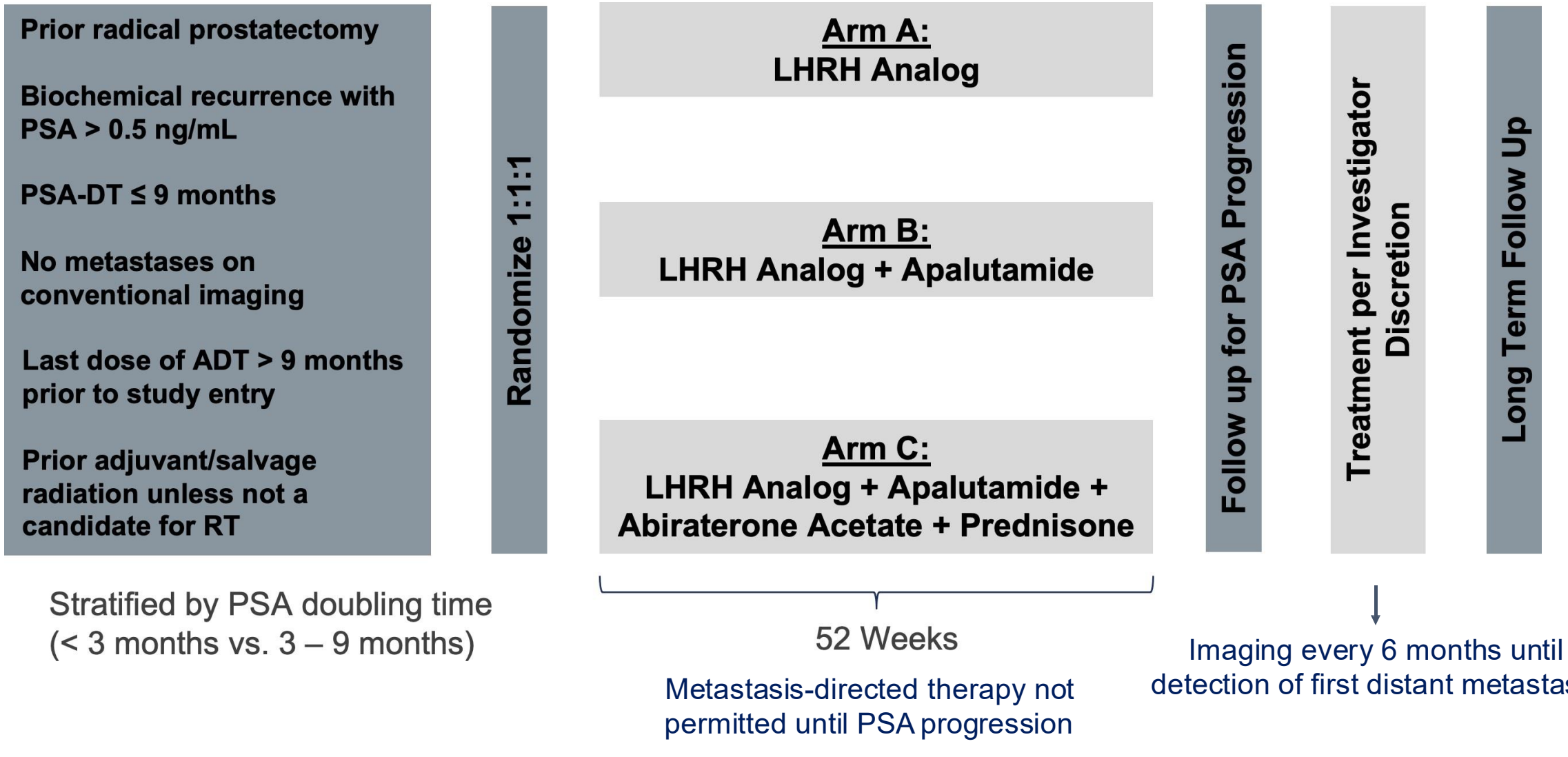
Offer monitoring

High risk BCR (EAU)
(PSA DT < 1 year, ISUP Grade 4-5)

Intermittent ADT

Dr Constance Thibault

Study Schema PRESTO study



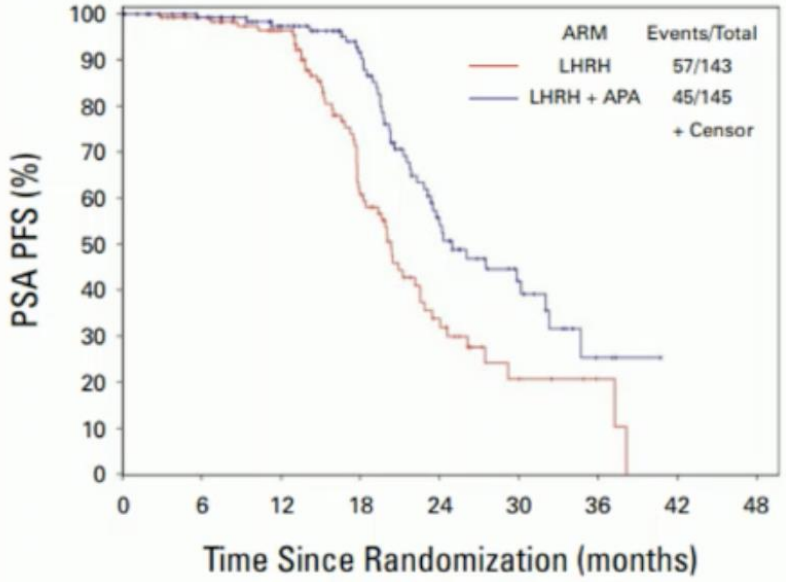
PRESTO study

PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19)

Rahul Aggarwal, MD[1]; Glenn Heller, PhD[2]; David W. Hillman, MS[3]; Han Xiao, MD[2]; Joel Picus, MD[4]; Mary-Ellen Taplin, MD[5]; Tanya Dorff, MD[6]; Leonard Appleman, MD[7]; Douglas Weckstein, MD[8]; Akash Patnaik, MD[9]; Alan Bryce, MD[10]; Daniel Shevrin, MD[11]; James Mohler, MD[12]; Daniel Anderson, MD[13]; Arpit Rao, MD[14]; Scott Tagawa, MD[15]; Alan Tan, MD[16]; Susan Halabi, PhD[17]; Katharine Dooley, MPH[3]; Patrick O'Brien, BS[3]; Ronald Chen, MD, MPH[18]; Charles J. Ryan, MD[19]; Scott E. Eggener, MD[9] and Michael J. Morris, MD[2]; on behalf of the PRESTO Study Investigators

DOI https://doi.org/10.1200/JCO.23.01157

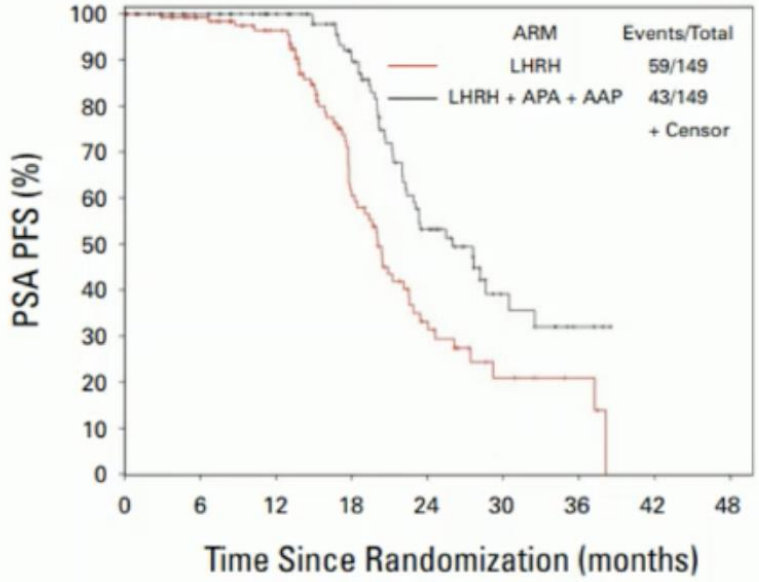
A



No. at risk:

LHRH	143	94	18	2	0
LHRH + APA	145	101	32	3	0

B



No. at risk:

LHRH	149	97	18	3	0
LHRH + APA + AAP	149	103	35	3	0

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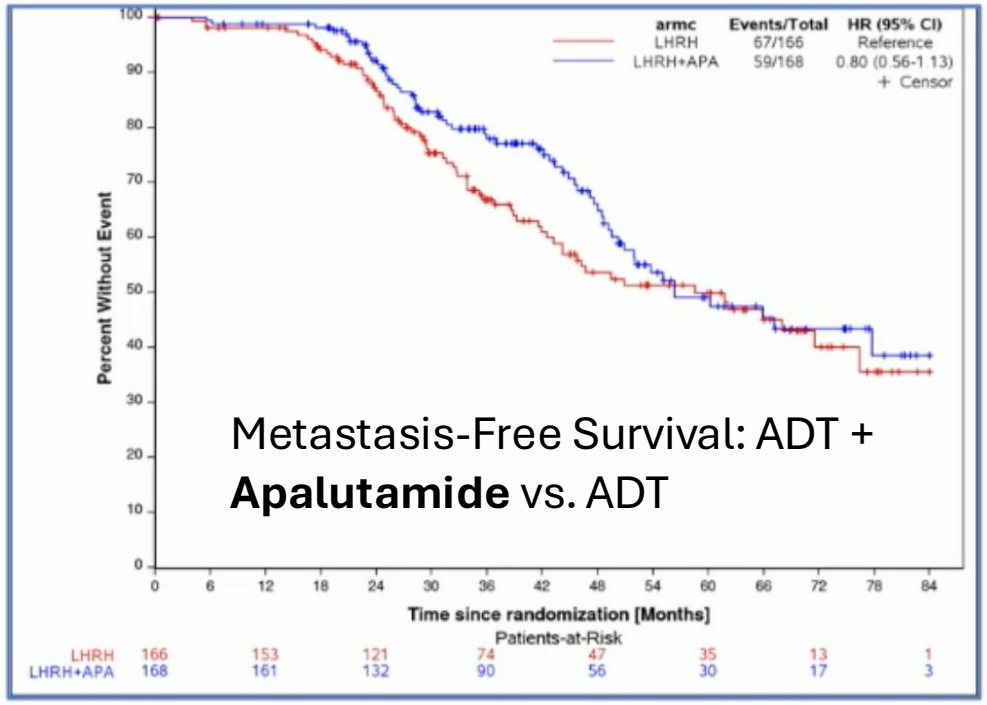
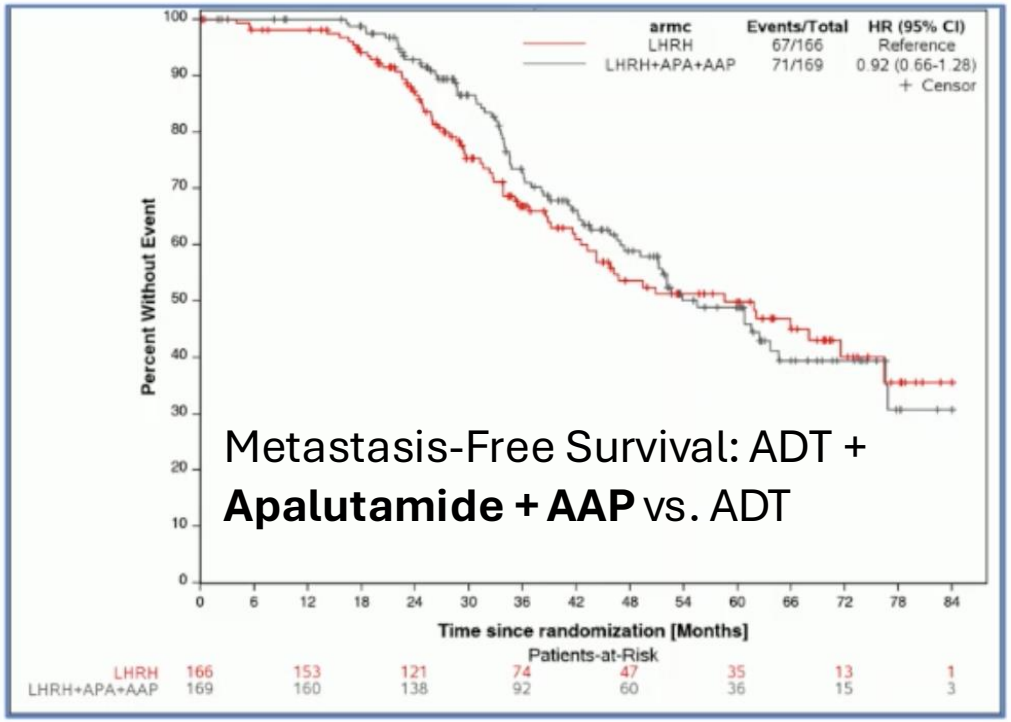
PRESTO study: secondary endpoints



Metastasis-Free Survival: ADT + **Apalutamide** vs. ADT

- MFS events: 38% of patients randomized
- HR = **0.80 (95% CI: 0.56 – 1.13)**



Metastasis-Free Survival: ADT + **Apalutamide + AAP** vs. ADT

- MFS events: 41% of patients randomized
- HR = **0.92 (95% CI: 0.56 – 1.13)**

Not practice changing

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EMBARK

EMBARK study

PARIS 2022 ESMO congress

PARIS FRANCE
9-13 SEPTEMBER 2022

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2023 VOL. 389 NO. 16

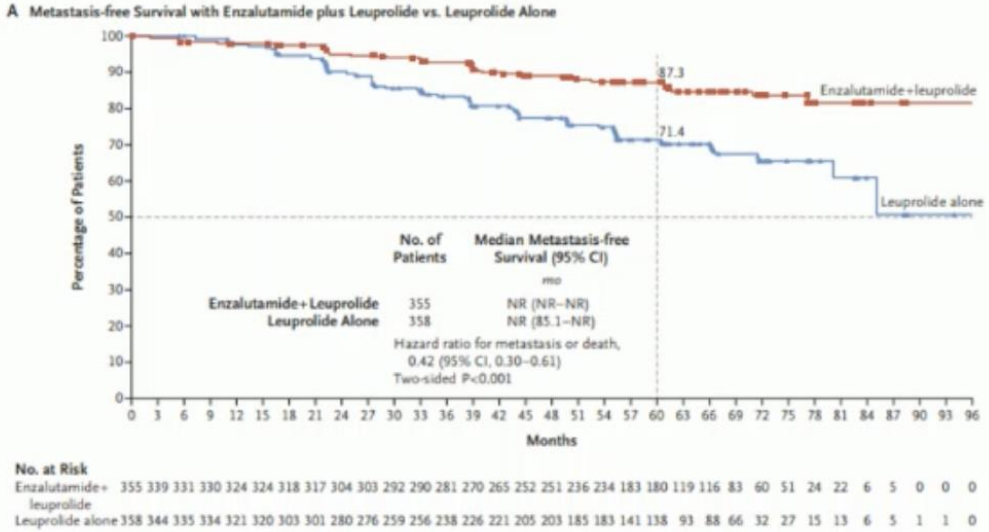
Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

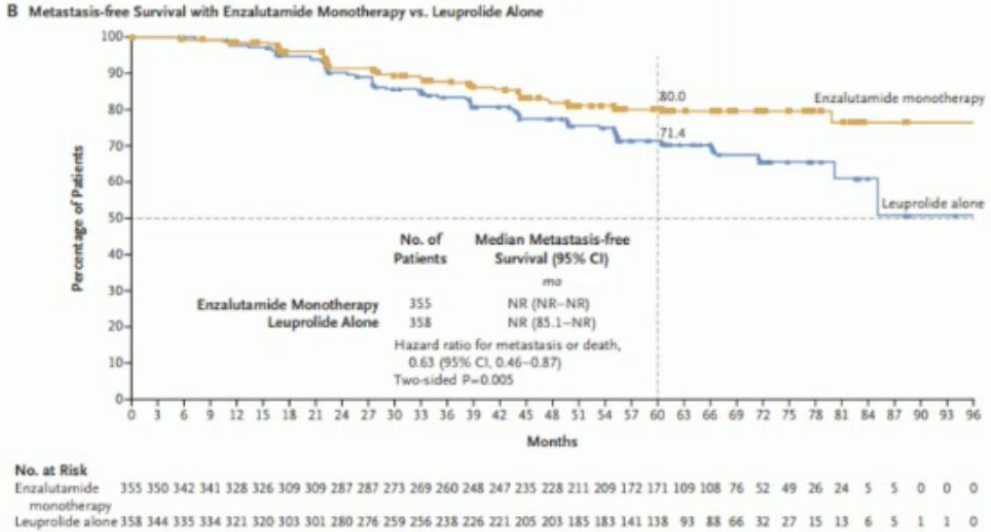
S.J. Freedland, M. de Almeida Luz, U. De Giorgi, M. Gleave, G.T. Gotto, C.M. Pieczonka, G.P. Haas, C.-S. Kim, M. Ramirez-Backhaus, A. Rannikko, J. Tarazi, S. Sridharan, J. Sugg, Y. Tang, R.F. Tutrone, Jr., B. Venugopal, A. Villers, H.H. Woo, F. Zohren, and N.D. Shore

Primary Endpoint:
ADT + placebo vs ADT + Enza

Secondary Endpoint:
ADT + placebo vs Enza

Metastasis-free survival (MFS)





Presenter: Dr. Constance Thibault

BERLIN 2025 ESMO congress

EMBARK study

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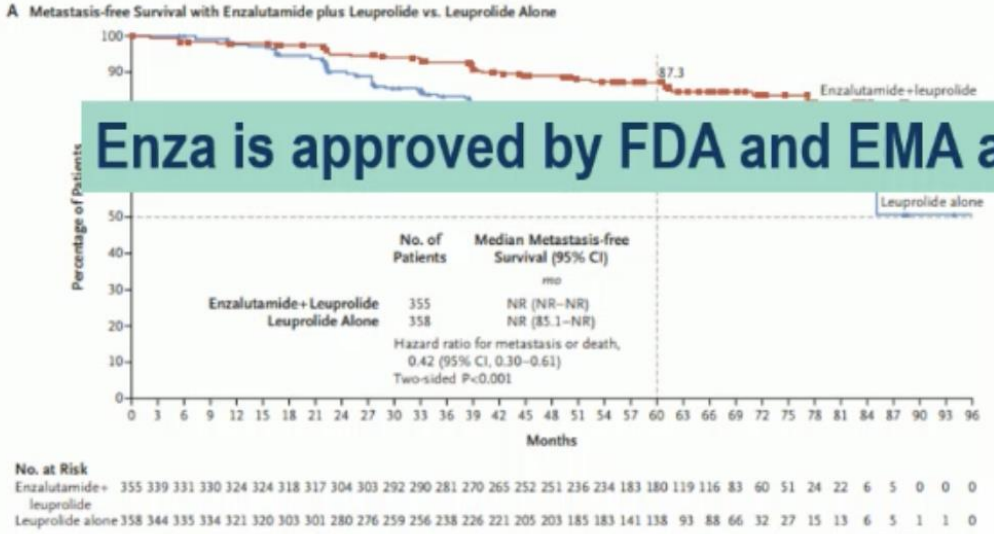
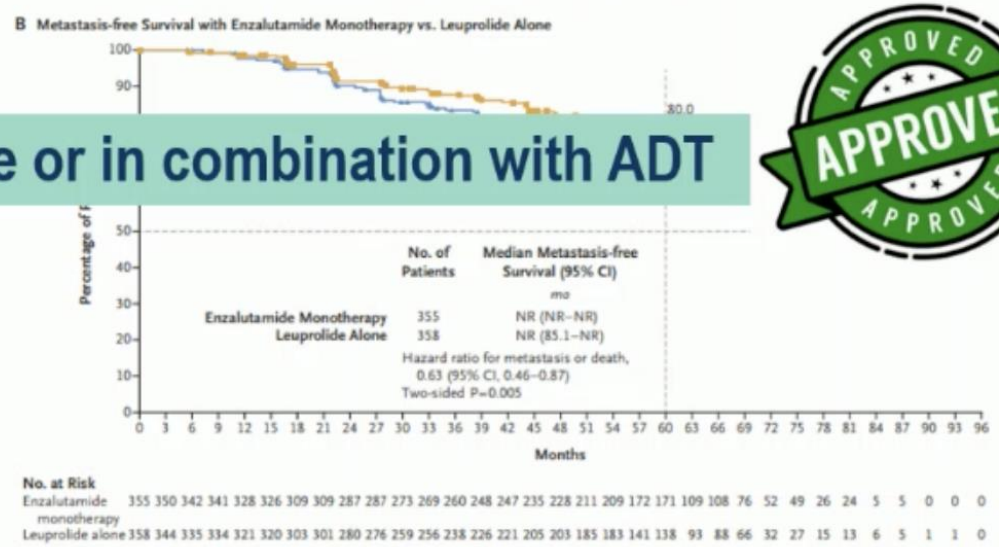
Primary Endpoint:
ADT + placebo vs ADT + Enza

Secondary Endpoint:
ADT + placebo vs Enza

Metastasis-free survival (MFS)





Enza is approved by FDA and EMA alone or in combination with ADT

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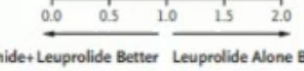
Secondary Endpoints:
ADT + placebo vs ADT + Enza

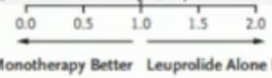
Only 12% of deaths

End Point	Enzalutamide+ Leuprolide (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide+ Leuprolide (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival (primary end point)	355	358	45	92	0.42 (0.30–0.61)	<0.001
Overall survival	355	358	33	55	0.59 (0.38–0.91)	0.02
PSA progression	355	358	8	93	0.07 (0.03–0.14)	<0.001
First use of new antineoplastic therapy	355	358	58	140	0.36 (0.26–0.49)	<0.001
Distant metastasis	355	358	30	59	0.44 (0.28–0.69)	
Resumption of any hormonal therapy	321	240	256	217	0.69 (0.58–0.83)	
Castration resistance	355	358	14	120	0.09 (0.05–0.16)	
Symptomatic progression	355	358	104	169	0.55 (0.43–0.70)	
First symptomatic skeletal event	355	358	9	32	0.26 (0.13–0.55)	
First deterioration in FACT-P total score	355	358	257	248	1.14 (0.95–1.36)	



Secondary Endpoints:
ADT + placebo vs Enza

End Point	Enzalutamide Monotherapy (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide Monotherapy (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival	355	358	63	92	0.63 (0.46–0.87)	0.005
Overall survival	355	358	42	55	0.78 (0.52–1.17)	0.23
PSA progression	355	358	37	93	0.33 (0.23–0.49)	<0.001
First use of new antineoplastic therapy	355	358	84	140	0.54 (0.41–0.71)	<0.001
Distant metastasis	355	358	40	59	0.61 (0.41–0.92)	
Resumption of any hormonal therapy	304	240	279	217	1.66 (1.38–1.98)	
Symptomatic progression	355	358	117	169	0.62 (0.49–0.79)	
First symptomatic skeletal event	355	358	14	32	0.42 (0.23–0.79)	
First deterioration in FACT-P total score	355	358	263	248	1.17 (0.98–1.39)	



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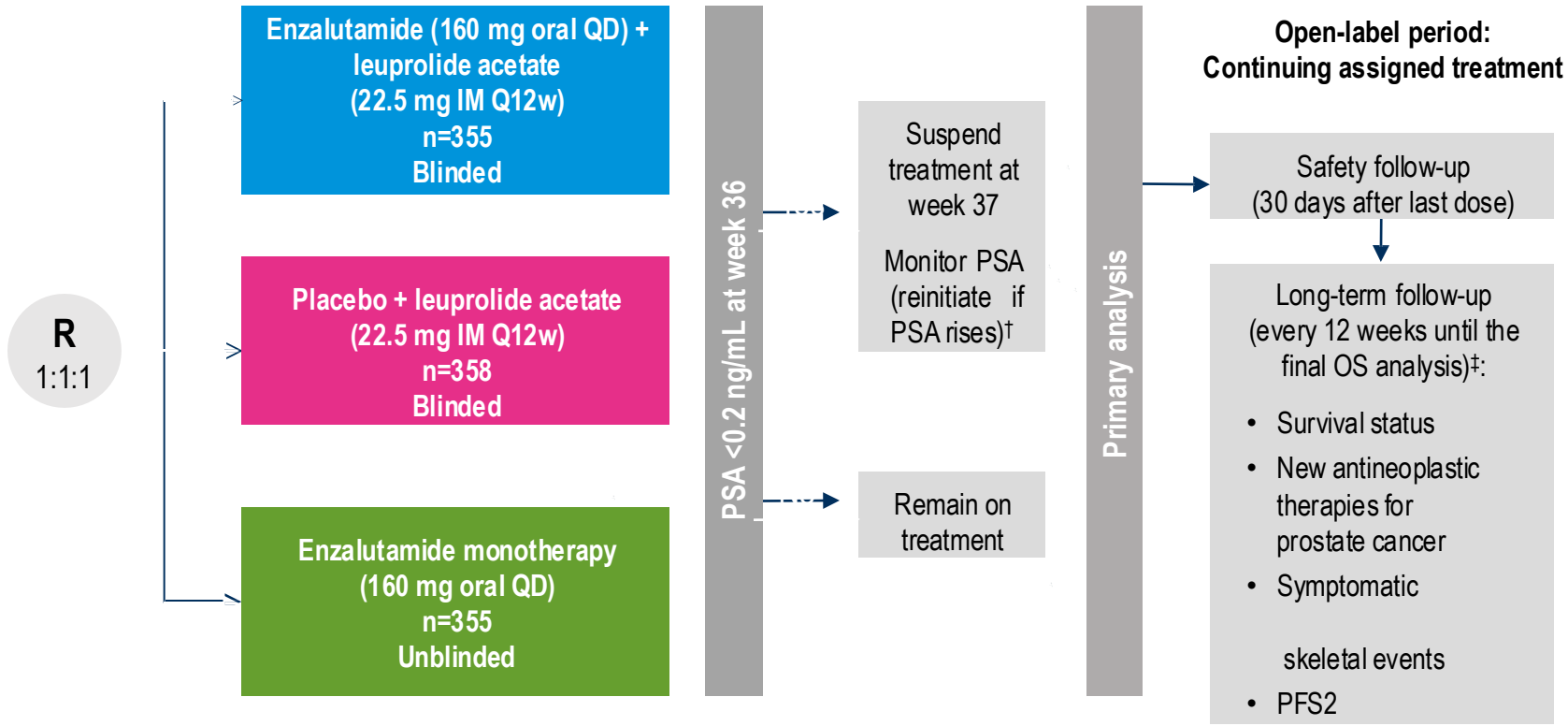
EMBARK study

Patient population:

- Screening PSA ≥1 ng/mL after RP or ≥2 ng/mL above the nadir after primary EBRT
- PSADT ≤9 mo
- No metastases on bone scan and CT/MRI per central read – conventional imaging-negative
- T ≥150 ng/dL
- Prior hormonal therapy ≥9 mo prior to R (neoadjuvant/adjuvant for ≤36 mo or ≤6 mo for rising PSA) allowed

Stratification factors:

- Screening PSA (≤10 ng/mL vs >10 ng/mL)
- PSADT (≤3 mo vs >3 to ≤9 mo)
- Prior hormonal therapy (yes vs no)



Primary endpoint: MFS by BICR for enzalutamide + leuprolide vs leuprolide alone

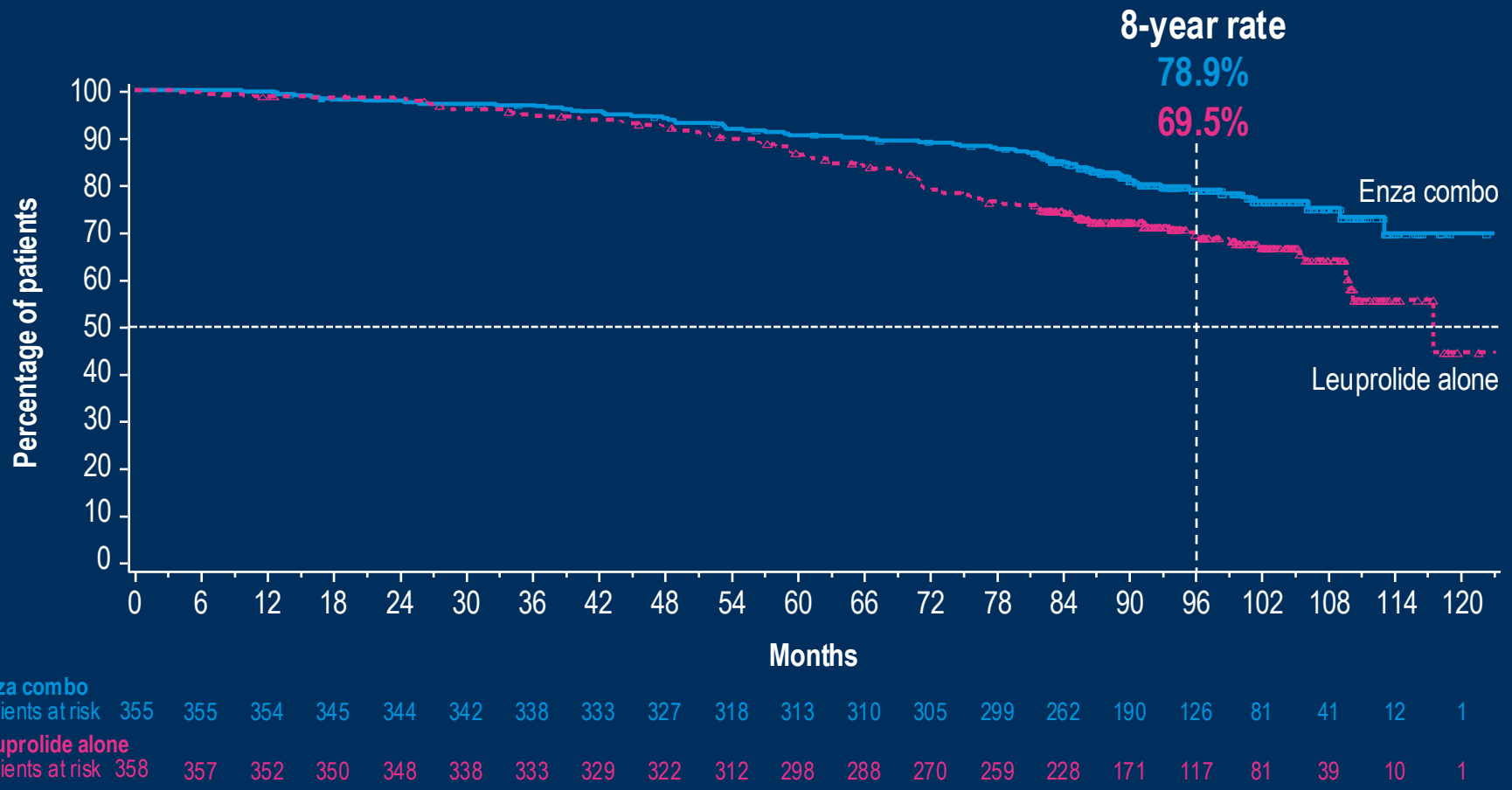
Key secondary endpoints: MFS by BICR for enzalutamide monotherapy vs leuprolide alone, time to PSA progression, time to first use of new antineoplastic therapy, OS

Other secondary endpoints included: Time to first symptomatic skeletal event, safety

Exploratory endpoint: PFS2

†Study treatment was suspended once at week 37 if PSA was <0.2 ng/mL and restarted when PSA was ≥5.0 ng/mL without prior RP or ≥2 ng/mL with prior RP.
‡OS was a key alpha-protected secondary endpoint. Updated results from the following endpoints were not alpha-protected and are thus considered nominal: time to first use of new antineoplastic therapy, time to first symptomatic skeletal event, and PFS2.
BICR, blinded independent central review; CT, computed tomography; D, day; EBRT, external beam radiation therapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; PSADT, PSA doubling time; Q, every; R, randomization; RP, radical prostatectomy; T, testosterone; w, weeks.
Freedland SJ, et al. *New Engl J Med*. 2023;389(16):1453–1465.

Overall survival: Enza combo



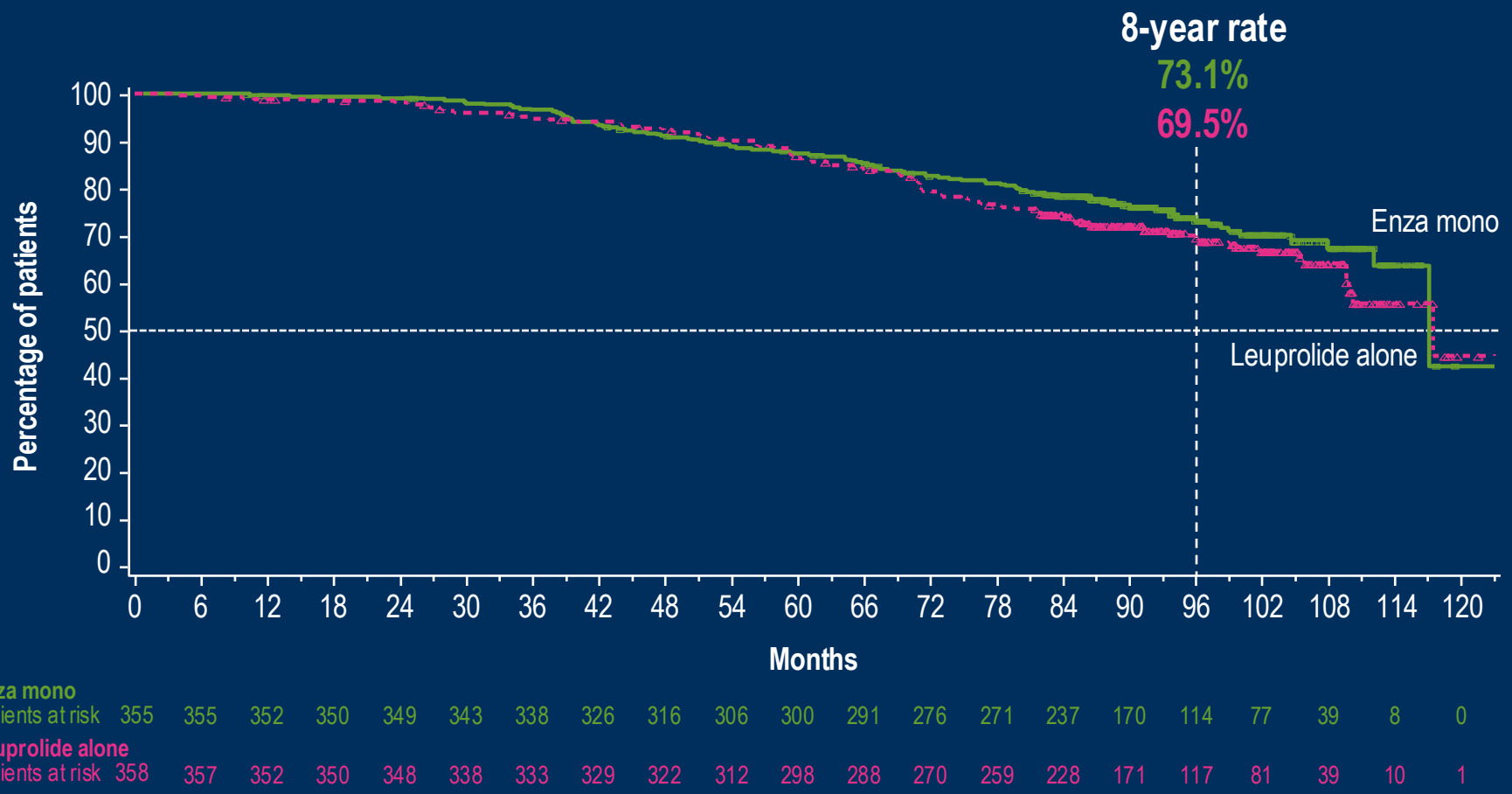
	Enza combo (n=35)	Leuprolide alone (n=358)
Events	73	111
8-year OS (95% CI), %	78.9 (73.9, 83.1)	69.5 (64.0, 74.3)

HR (95% CI): 0.597 (0.444, 0.804); *P*=0.0006

The risk of death was 40.3% lower for enza combo compared with leuprolide alone

Intent-to-treat population. The median follow-up was 94.2 months in the enza combo group and 94.0 months in the leuprolide-alone group. OS was defined as the time between randomization and death due to any cause. HRs were calculated using a Cox regression model with treatment as the only covariate, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza combo, enzalutamide plus leuprolide; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Overall survival: Enza mono



	Enza mono (n=35)	Leuprolide alone (n=358)
Events	93	111
8-year OS (95% CI), %	73.1 (67.6, 77.9)	69.5 (64.0, 74.3)

HR (95% CI): 0.830 (0.630, 1.095); *P*=0.1867

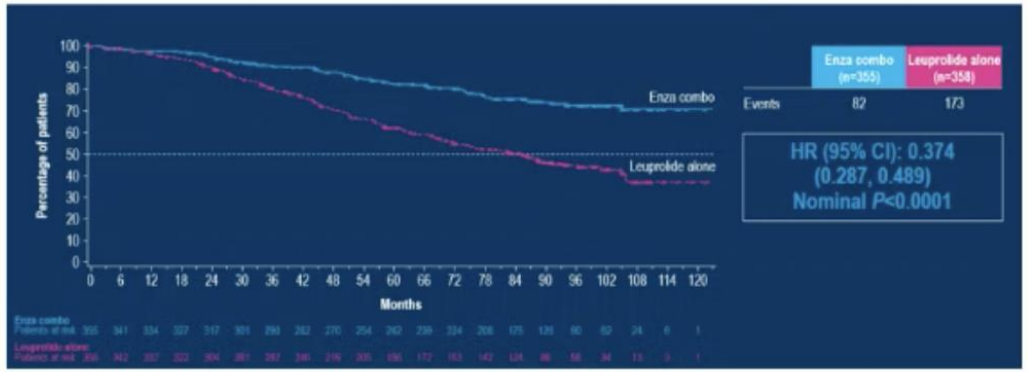
The risk of death was 17.0% lower for enza mono compared with leuprolide alone, which did not reach statistical significance

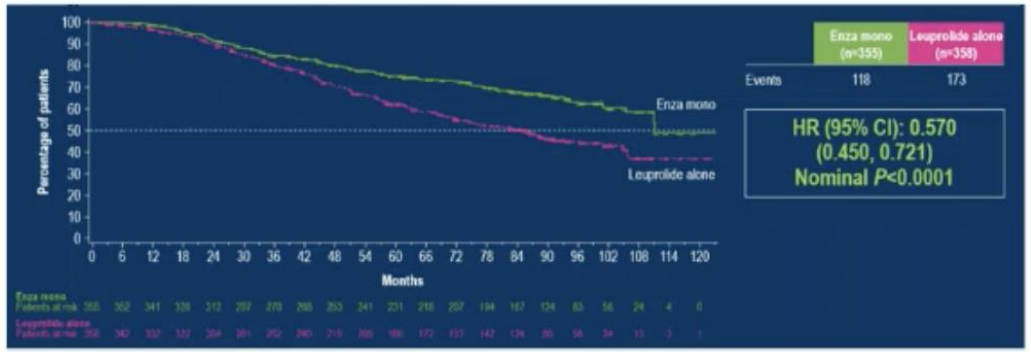
Intent-to-treat population. The median follow-up was 93.8 months in the enza mono group and 94.0 months in the leuprolide-alone group. OS was defined as the time between randomization and death due to any cause. HRs were calculated using a Cox regression model with treatment as the only covariate, with stratification according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The two-sided *P*-values were determined on the basis of a log-rank test, stratified according to PSA level at screening, PSADT, and previous hormonal therapy, as reported in the interactive Web-response system. The data cutoff date was May 27, 2025. The squares and triangles indicate censored data.
CI, confidence interval; enza mono; enzalutamide monotherapy; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time.

EMBARK study

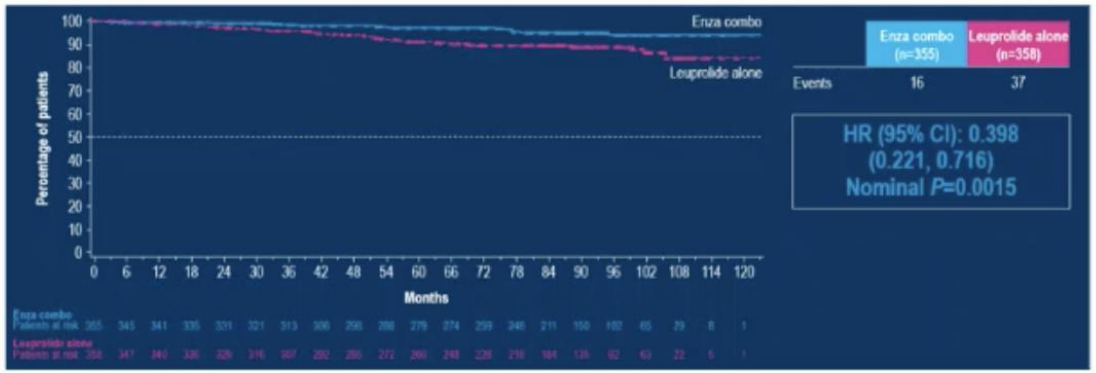
Other secondary endpoints

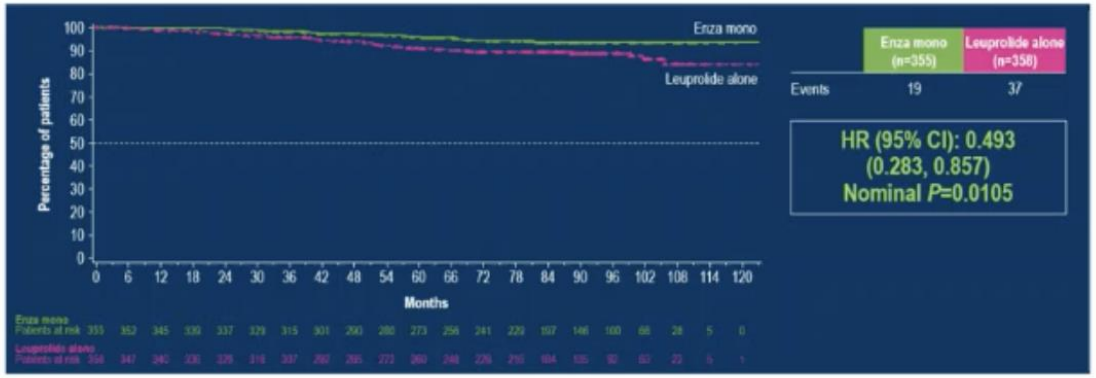
Time to first use of new antineoplastic therapy





Time to first SRE





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EMBARK conclusions

- **Adding Enzalutamide to ADT improves significantly MFS and OS**
- Enzalutamide + ADT is the new standard of care in selected patients:
  - M0 on conventional imaging
  - PSA DT <9 months
  - PSA >1 after RP or >2 after EBRT
  - Duration at least 36 weeks
  - Suspended if PSA <0.2 ng/mL after 26 weeks

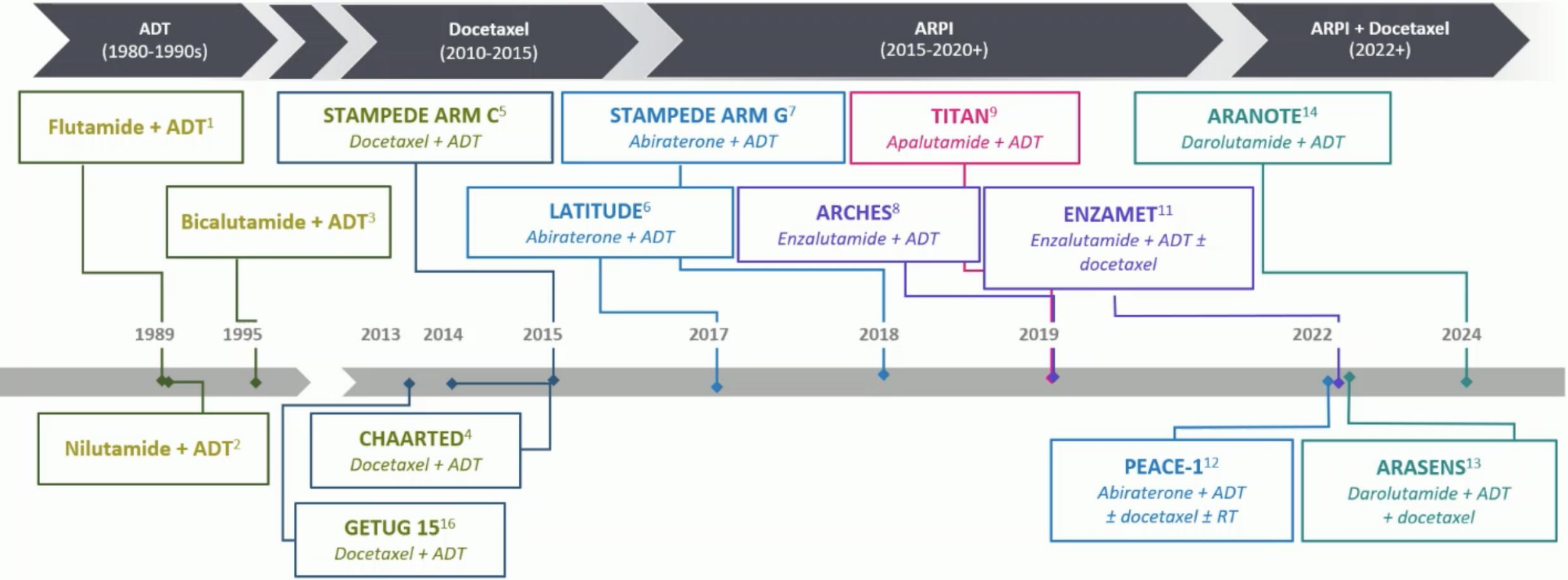
- **Enzalutamide alone improves significantly MFS and trends to improve OS**
  - Enzalutamide alone may be an option for selected patients refusing ADT or with many CV comorbidities

Ongoing trials

	EMBARK (n=1068)	PRESTO / AFT-19 (n=504)	CARLHA-2 (n=490)	ARASTEP (n=750)
Randomization	Double blind	Open	Open	Double blind
Experimental arm	ADT + enzalutamide Enzalutamide mono	ADT + apalutamide ADT + apalutamide + ABI	ADT + SRT + apalutamide	ADT + darolutamide
Control arm	ADT + PBO	ADT	ADT + SBRT	ADT + PBO
Duration of treatment	36 weeks	52 weeks	24 weeks	104 weeks
Intermittent	YES	NO	NO	NO
PSA at inclusion	≥ 1 ng/mL after RP Nadir + ≥ 2 ng/mL post SBRT	> 0,5 ng/mL	≥ 0,2 ng/mL	≥ 0,2 ng/mL post RP Nadir + ≥ 2 ng/mL post SBRT
Inclusion criteria	PSA at inclusion PSA-DT ≤ 9 months	PSA at inclusion PSADT ≤ 9 months	1 of the following: PSA at relapse > 0,5 ng/mL, Gleason > 6, pT3b, R0 ou PSADT ≤ 6 months	PSA at inclusion PSADT ≤ 12 months
Imaging	CT and bone scann	CT and bone scann	PSMA/Choline PET	PSMA-PET
Lymph node	Pelvic if < 2 cm	Abdominal and/or pelvic If ≤ 2 cm	N0 or Nx	If above the bifurcation of the iliac artery
Primary endpoint	MFS (ADT + enza vs ADT + PBO)	PSA-PFS	PFS	rPFS according to PSMA-PET
Results	ESMO 2022, ESMO 2025	ESMO 2022, ESMO 2025	September 2028	January 2027

Presenter: Dr. Constance Thibault

Therapeutic landscape evolution of mHSPC



ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; NSAA, nonsteroidal anti-androgens. 1. Crawford ED, et al. New Engl J Med. 1989;321:419-424; 2. Kuhn JM, et al. New Engl J Med. 1989;321:413-418; 3. Soloway MS, et al. J Urol. 1995;154(6):2110–4; 4. Sweeney C, et al. J Clin Oncol. 2014;32(suppl; abstract LBA2); 5. James ND, et al. J Clin Oncol. 2015;33(suppl 15):5001; 6. Fizazi K, et al. J Clin Oncol. 2017;35(suppl; abstract LBA3); 7. Hoyle A, et al. Ann Oncol. 2018;29(suppl 8; abstract 3982); 8. Armstrong AJ, et al. J Clin Oncol. 2019;37(7 suppl; abstract 687); 9. Chi KN, et al. J Clin Oncol. 2019;37(suppl 15; abstract 5006); 11. Sweeney C, et al. J Clin Oncol. 2019;37(18 suppl; abstract LBA2); 12. Fizazi K, et al. Lancet. 2022;399:1695-1707; 13. Smith M, et al. N Engl J Med. 2022;386:1132-1142; 14. ClinicalTrials.gov identifier: NCT04736199. Accessed October 11, 2024. https://clinicaltrials.gov/ct2/show/NCT04736199; 15. ClinicalTrials.gov identifier: NCT05059236. Accessed August 22, 2024. https://clinicaltrials.gov/ct2/show/NCT05059236. 16. Gravis G, et al. Lancet Oncol. 2013 Feb;14(2):149-58

Presenter: Dr. Constance Thibault

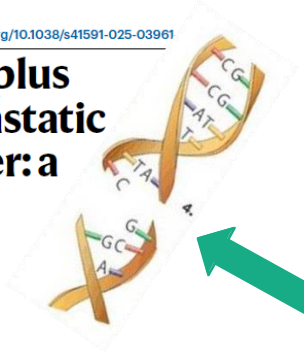
ASCO Genitourinary Cancers Symposium #GU25

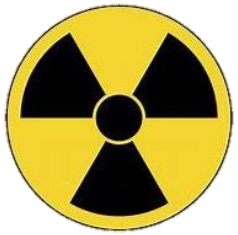
nature medicine

Article https://doi.org/10.1038/s41591-025-03961

AMPLITUDE

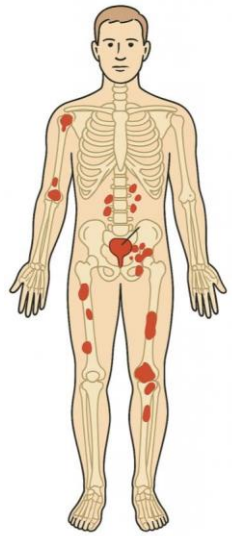
Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: a randomized phase 3 trial





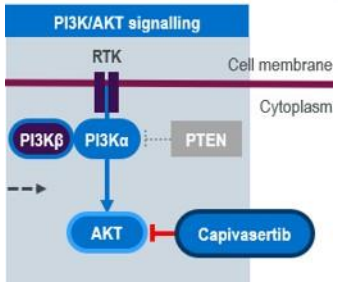
BERLIN 2025 ESMO congress

Phase 3 trial of [^{177}Lu]Lu-PSMA-617 combined with ADT + ARPI in patients with PSMA-positive metastatic hormone-sensitive prostate cancer (PSMAddition)



BERLIN 2025 ESMO congress

A Phase 3 study of capivasertib plus abiraterone versus placebo plus abiraterone in patients with PTEN deficient *de novo* metastatic hormone-sensitive prostate cancer: CAPItello-281



ADT + ARPI
or
ADT + ARPI + docetaxel Q3W

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3-Weekly Docetaxel 75 mg/m^2 vs. 2-Weekly Docetaxel 50 mg/m^2 in Combination with Darolutamide + ADT in Patients with mHSPC

Results from the Randomised, Phase 3 ARASAFE Trial

ARASAFE

50 YEARS ESMO

AMPLITUDE

AMPLITUDE: Randomized, Double-Blind, Placebo- Controlled Trial in HRRm mHSPC

Key inclusion criteria:
mHSPC[a] , alteration in ≥1 HRR-eligible gene[b] , ECOG PS 0-2

Key exclusion criteria:
Any prior PARPi or ARPI other than AA + P

Prior allowed treatments in mHSPC:
ADT ≤6 months, docetaxel ≤6 cycles[c], AA + P ≤45 days, palliative radiotherapy

R 1:1
N=696

Niraparib (200 mg QD) + AA (1000 mg QD) + P (5 mg QD) + ADT (n=348)

PBO + AA (1000 mg QD) **+ P** (5 mg QD) **+ ADT (n=348)**

Assessed PRO instruments and subscales

- FACT-G
  - Single item GP5 side-effect bother
- FACT-P
  - FACT-P physical well-being subscale
- EQ-5D-5L VAS

- **PRO e-questionnaires were completed at screening, cycles 1-25, then every 4 months up to end of treatment**
- **PROs were analyzed as least-squares mean change from BL by mixed-effects repeated-measures model[f]**
- **The overall questionnaire completion compliance was ≥94.3%[g]**

Stratifications:
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Clinical data cutoff: January 7, 2025
Median follow-up: 30.8 months
Median number of cycles: 25 in both arms

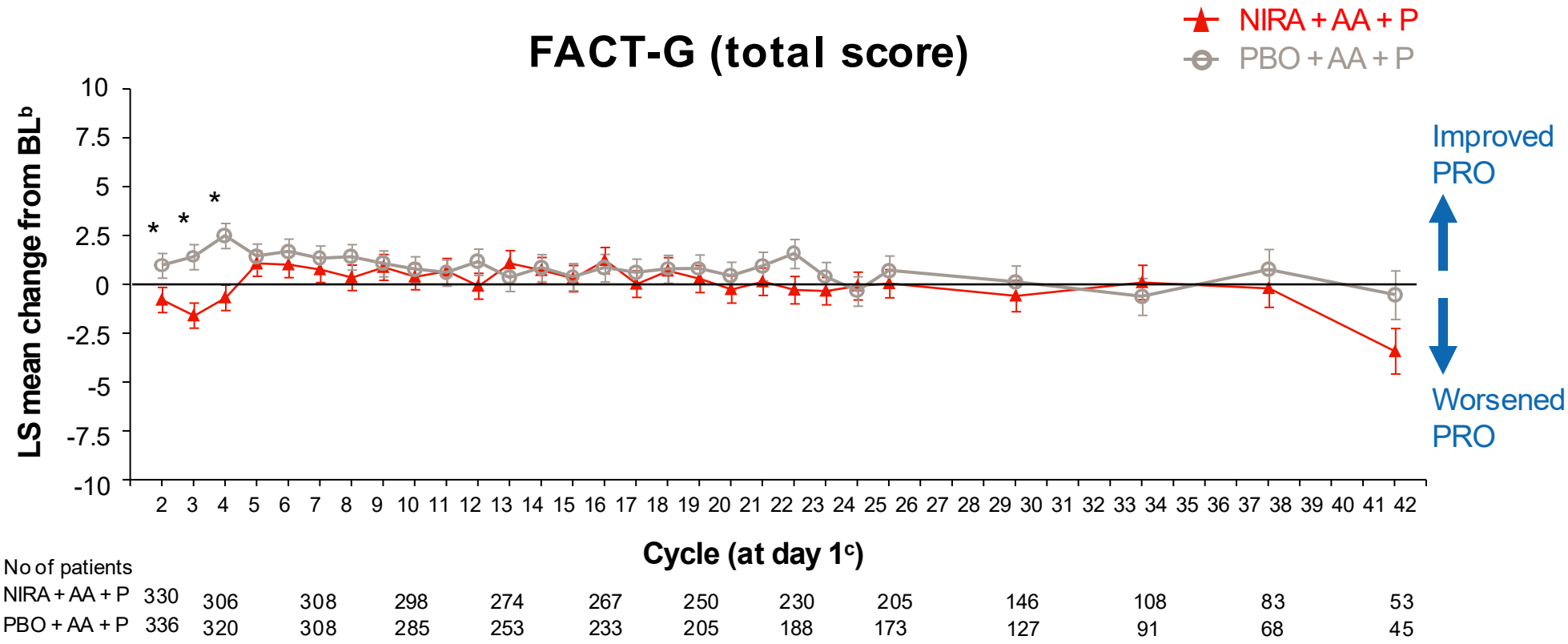
AA, abiraterone acetate; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D-5L VAS, Euro-Quality of Life Questionnaire visual analog scale; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PARPi, poly ADP-ribose polymerase inhibitor; PBO, placebo; P, prednisone; PRO, patient-reported outcome; QD, once daily. [a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. HRR eligible genes: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*. [c]Last dose ≤3 months prior to randomization. [d]Final analysis for rPFS. [e]First interim analysis. [f]No imputation for missing data. [g]Overall over treatment phase includes all values from BL to end of treatment.
1. Fizazi, et al. *N Engl J Med.* 2017;377:352-360. 2. James, et al. *N Engl J Med.* 2017;377:338-351. 3. Fizazi , et al. *Lancet*. 2022;399:1695-1707. 4. Smith, et al. *N Engl J Med*. 2022;386:1132-1142. 5. Lowrance et al. *J Urol.* 2023; 209:1082-90. 6. EAU - EANM - ESTRO - ESUR - ISUP - SIOG guidelines on prostate cancer. Accessed: Sept 9, 2025. 7. Olmos, et al. Presented at ASCO 2025. Abstract 5094. 8. Chi, *J Clin Oncol.* 2023;41:3339-3351. 9. Chi, et al. *Ann Oncol.* 2023;34:772-782. 10. AKEEGA. PI. 8/2023. 11. Attard et al. Presented at ASCO 2025. Abstract LBA5006.

HRQoL FACT-G Was Maintained and Comparable Between Arms After Differences in Initial Cycles

FACT-G score:
0 to 108 points

Mean BL FACT-G (SD)
NIRA + AA + P: 79.7 (14.9)
AA + P: 79.3 (15.2)

Overall LS mean change from BL (SE)
NIRA + AA + P: 0.02 (0.50)
AA + P: 0.77 (0.50)
p=0.289[a]



No of patients													
NIRA + AA + P	330	306	308	298	274	267	250	230	205	146	108	83	53
PBO + AA + P	336	320	308	285	253	233	205	188	173	127	91	68	45

- **Initial reduction in HRQoL may be explained by onset of the most frequently observed AEs, hypertension and anemia, within the first 4 cycles**

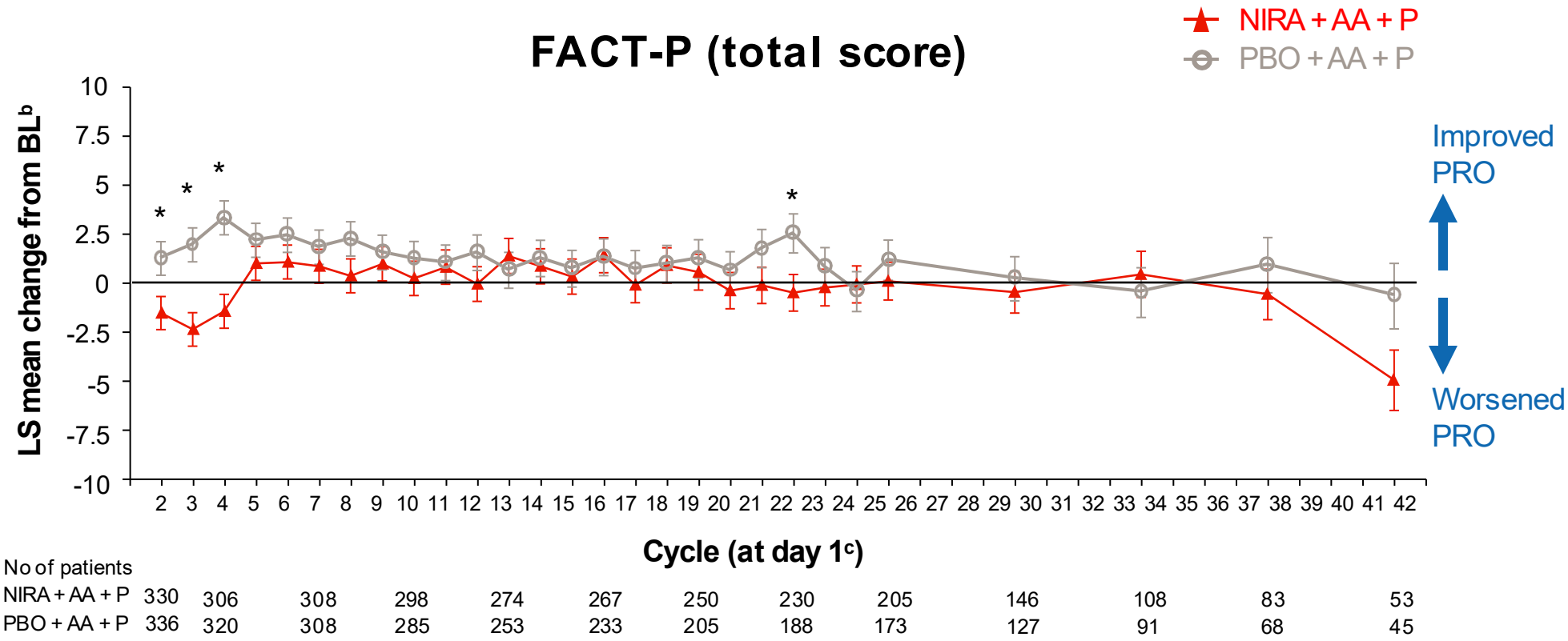
Error bars are SE estimates. Truncation was applied across arms for all subsequent visits at the first visit where ≥90% of patients were missing for each end point and from either arm. FACT-G includes physical well-being, social/family well-being, emotional well-being and functional well-being subscales. Responses: 0 "not at all" to 4 "very much". FACT-G total score: A decrease of 9 points or more from baseline in an individual patient's score is considered clinically meaningful deterioration (a decrease in score is worsening in HRQoL). [a]F-test comparing niraparib + AA + P vs AA + P. [b]LS means are derived based on the mixed effects model with baseline, visit, treatment, visit by treatment interactions as fixed effect and individual patients as random effect. [c]Completed on day 1 of cycle. *p<0.05.

HRQoL FACT-P Was Maintained and Comparable Between Arms After Differences in Initial Cycles

FACT-P score:
0 to 156 points

Mean BL FACT-P (SD)
NIRA + AA + P: 113.3 (20.2)
AA + P: 112.7 (20.4)

Overall LS mean change from BL (SE)
NIRA + AA + P: -0.05 (0.67)
AA + P: 1.22 (0.67)
p=0.181[a]



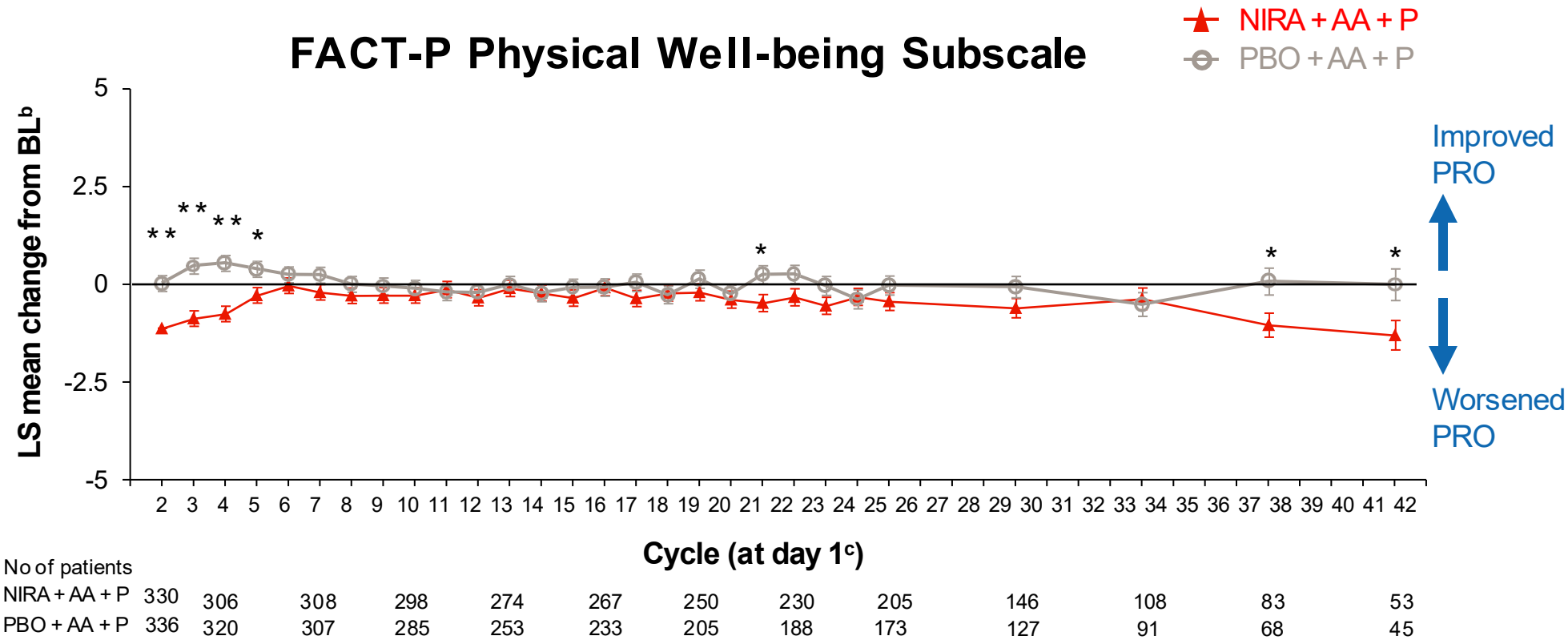
Error bars are SE estimates. Truncation was applied across arms for all subsequent visits at the first visit where ≥90% of patients were missing for each end point and from either arm. FACT-P includes FACT-G (physical well-being, social/family well-being, emotional well-being and functional well-being subscales) plus a prostate cancer–specific subscale. Responses: 0 "not at all" to 4 "very much." FACT-P total score: A decrease of 10 points or more from baseline in an individual patient's score is considered clinically meaningful deterioration (a decrease in score is worsening in HRQoL). [a]F-test comparing niraparib + AA + P vs AA + P. [b]LS means are derived based on the mixed effects model with baseline, visit,

FACT-P PWB Subscale Was Maintained and Comparable Between Arms After Initial Cycles

FACT-P PWB score:
0 to 28 points

Mean BL FACT-P PWB (SD)
NIRA + AA + P: 23.5 (4.6)
AA + P: 23.6 (4.4)

Overall LS mean change from BL (SE)
NIRA + AA + P: -0.43 (0.15)
AA + P: -0.01 (0.15)
p=0.0467[a]



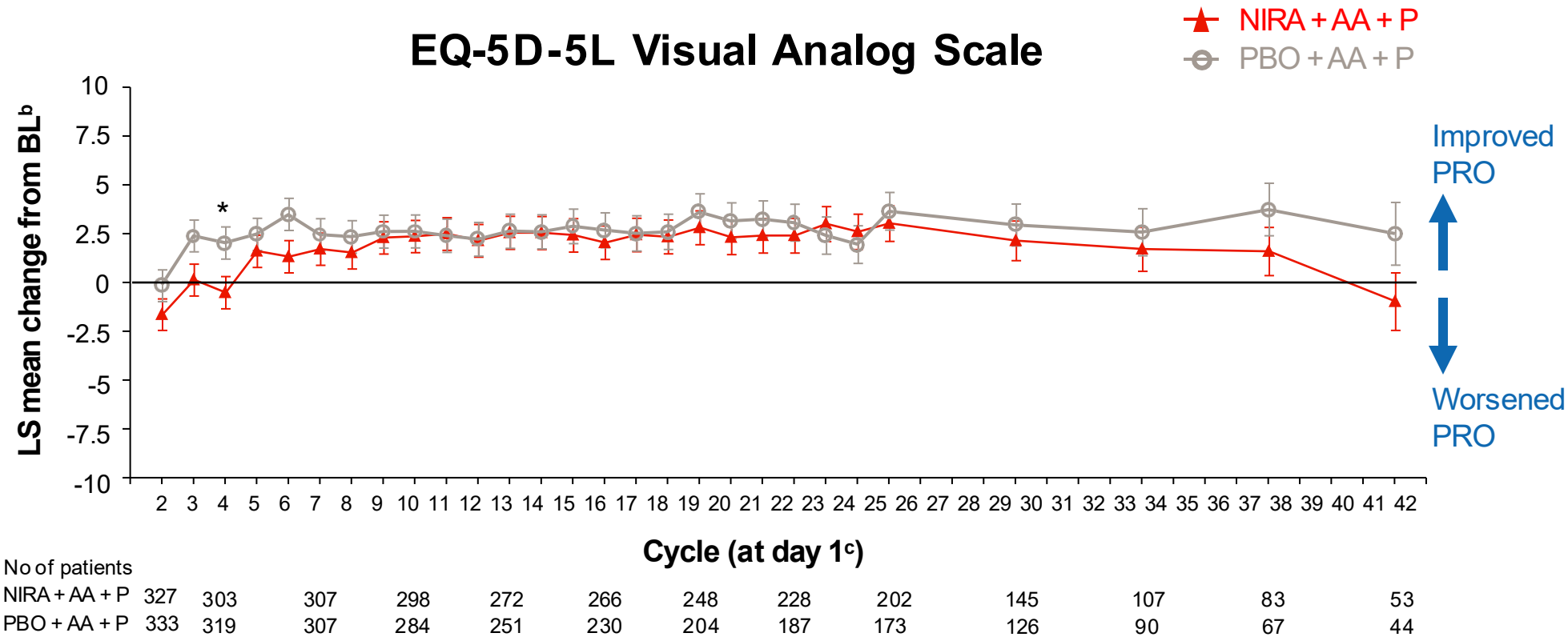
Error bars are SE estimates. Truncation was applied across arms for all subsequent visits at the first visit where ≥90% of patients were missing for each end point and from either arm. The FACT-P PWB is one of the 4 subscales that make up FACT-G and FACT-P. Responses: 0 "not at all" to 4 "very much." FACT-P PWB subscale: A decrease of 3 points or more from baseline in an individual patient's score is considered clinically meaningful deterioration (a decrease in score is worsening in health state). [a]F-test comparing niraparib + AA + P vs AA + P. [b]LS means are derived based on the mixed effects model with baseline, visit, treatment, visit by treatment interactions as fixed effect and individual patients as random effect. [c]Completed on day 1 of cycle. **p<0.0001; *p<0.05.

EQ-5D-5L Visual Analog Scale Was Comparable Between Arms

EQ-5D-5L VAS score:
0 to 100 points

Mean BL EQ-5D-5L VAS (SD)
NIRA + AA + P: 74.9 (17.4)
AA + P: 73.9 (18.6)

Overall LS mean change from BL (SE)
NIRA + AA + P: 1.82 (0.63)
AA + P: 2.59 (0.63)
p=0.390[a]



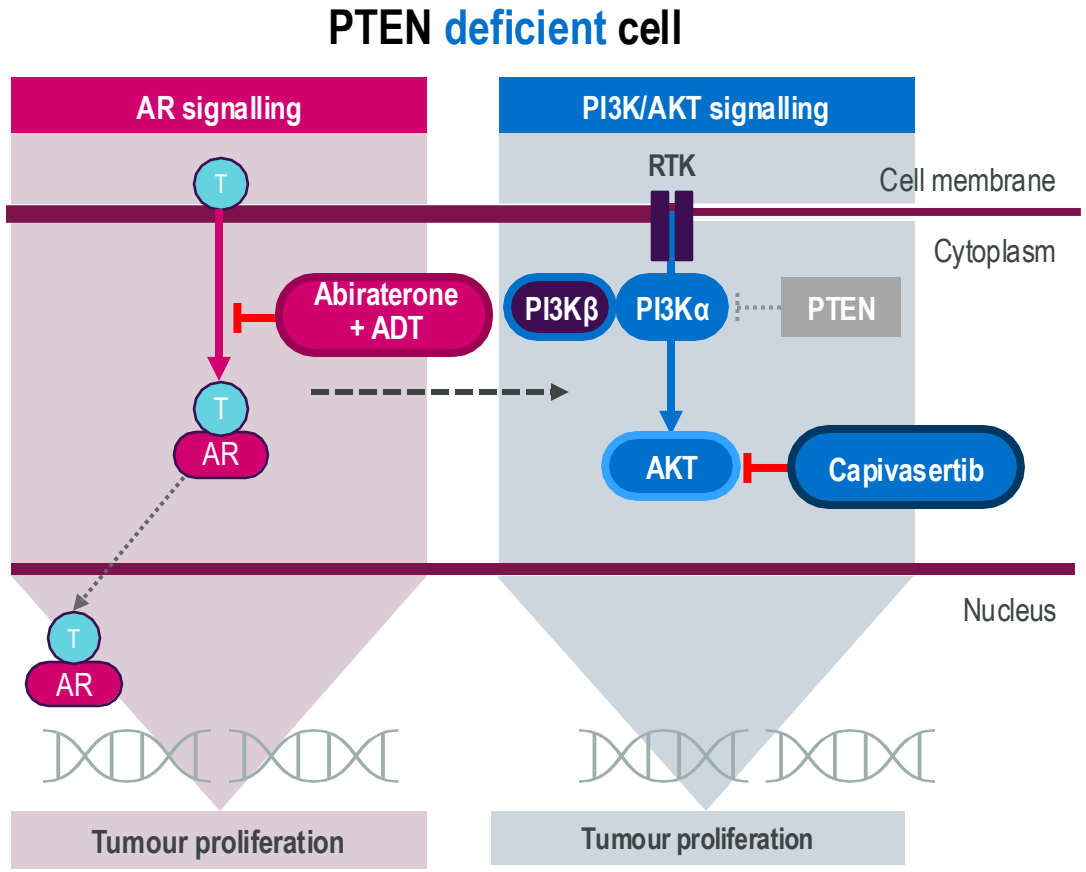
No of patients													
NIRA + AA + P	327	303	307	298	272	266	248	228	202	145	107	83	53
PBO + AA + P	333	319	307	284	251	230	204	187	173	126	90	67	44

Error bars are SE estimates. Truncation was applied across arms for all subsequent visits at the first visit where ≥90% of patients were missing for each end point and from either arm. The EQ-5D-5L VAS is a self-administered, standardized measure of health status; score range: 0 (worst imaginable health state) to 100 (best imaginable health state). EQ-5D-5L VAS score: A decrease of 10 points or more from baseline in an individual patient's score is considered clinically meaningful deterioration. [a]F-test comparing niraparib + AA + P vs AA + P. [b]LS means are derived based on the mixed effects model with baseline, visit, treatment, visit by treatment interactions as fixed effect and individual patients as random effect. [c]Completed on day 1 of cycle. *p<0.05.

CAPItello-281

PTEN deficiency in prostate cancer

- In **PTEN-proficient** hormone-sensitive tumour cells, **AR signalling** is the key driver of proliferation[1]
- In PTEN-deficient tumour cells, there is an **additional proliferative drive** from upregulation of the PI3K/AKT pathway, that **complements** and provides an alternative survival mechanism to AR signalling[2]
- **PTEN deficiency** is associated with poor prognosis[2–4]
- **Capivasertib** is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- **Phase 2/3 evidence** showed benefits with ipatasertib (AKTi) plus abiraterone in **PTEN deficient mCRPC**[2,3]



AR, androgen receptor; mHSPC, metastatic hormone-sensitive prostate cancer; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; T, testosterone

1. Quistini A, *et al*. *Res Rep Urol.* 2025;17:211-223; 2. De Bono JS, *et al*. *Clin Cancer Res* 2019;25:928–936; 3. Sweeney C, *et al*. *Lancet* 2021;398:131–42; 4. Rathkopf D, *et al*. *J Clin Oncol* 2025;43:abst 5096. .

CAPItello-281 Study Design

A global, multicentre, randomized, double-blind, Phase 3 study

Patients with PTEN deficient *de novo* mHSPC

- PTEN deficiency: (diagnostic cut-off of **≥90%** of viable malignant cells with **no specific cytoplasmic staining** by IHC)*
  - i.e. ≤10% of cells expressing PTEN by IHC

Of ~6,200 patients submitting tumour tissue **97%** had a valid IHC result and **25%** were **PTEN deficient**

1,012 patients (R 1:1)

Capivasertib	400 mg BID 4 days on, 3 days off
Abiraterone/pred **+ ADT**	1000 mg/5 mg QD + ADT
Placebo	400 mg BID 4 days on, 3 days off
Abiraterone/pred **+ ADT**	1000 mg/5 mg QD + ADT

Primary endpoint

- **Investigator assessed rPFS**

Secondary endpoints

- Overall survival
- Time to first subsequent therapy
- Symptomatic skeletal-event free survival
- Time to pain progression
- Time to castration resistance
- Time to PSA progression

Exploratory *post-hoc* PTEN deficiency subgroups

Stratification factors:†

- M1 volume (CHAARTED criteria) and visceral mets
- Geography

Study timeline

Enrolment period
13 July 2020–5 Feb 2024

Primary rPFS DCO
7 Oct 2024
Median rPFS follow-up:‡ ~18 mo

Final OS DCO
Planned for 522 deaths (52.2% maturity)

NCT04493853. Full eligibility criteria available in the online article. *Determined using investigational antibody for PTEN (SP218) (Roche Diagnostics).
†High-vol. disease with visceral mets, high-vol disease without visceral mets, low-vol. disease; North America; Western Europe and Australia; Latin America and Eastern Europe; Asia. ‡In censored patients.
ADT, androgen deprivation therapy; BID, twice daily; IHC, immunohistochemistry; mHSPC, metastatic hormone-sensitive prostate cancer; pred, prednisone/prednisolone; QD, once daily; rPFS, radiographic progression-free survival

CAPItello-281: Baseline characteristics

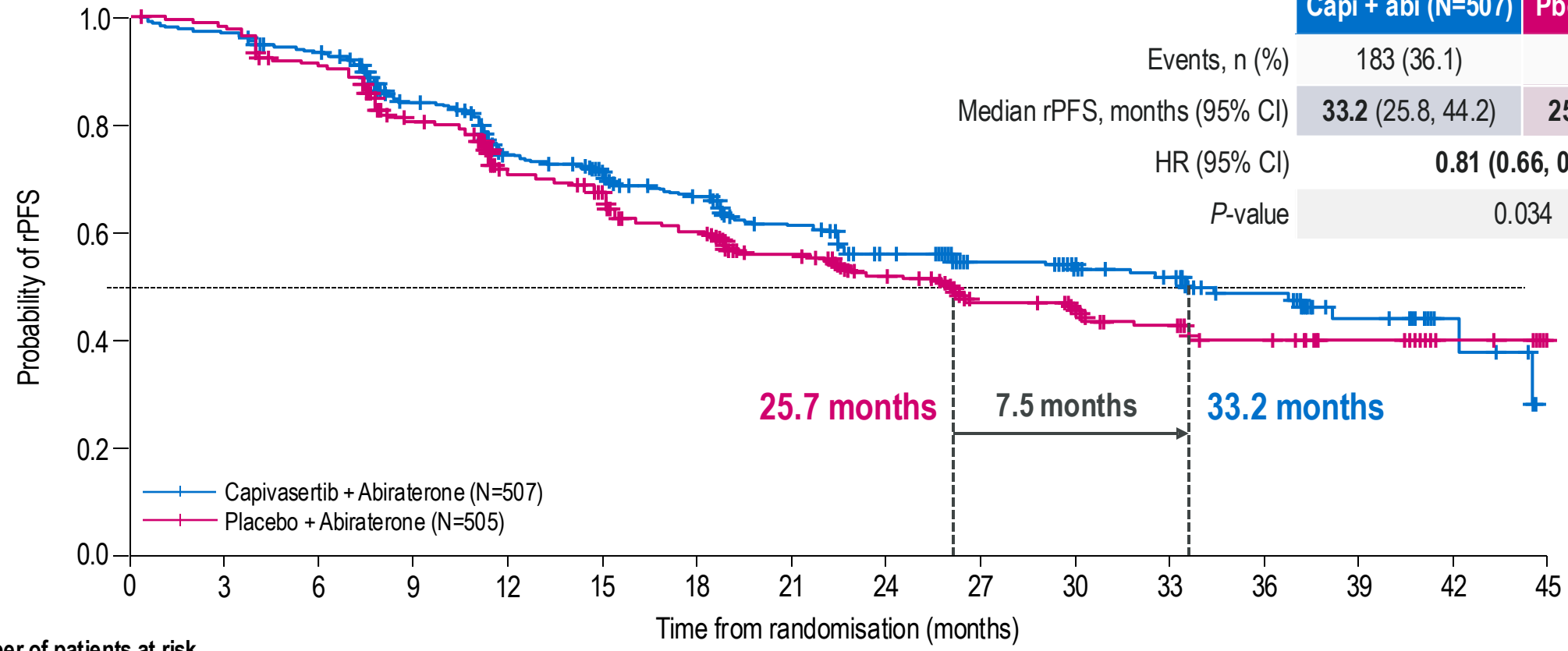
		Capi + abi (N=507)	Pbo + abi (N=505)
Median age, years (range)		67.0 (42–87)	68.0 (43–88)
'Race', n (%)*	White	266 (52.5)	259 (51.3)
	Asian	186 (36.7)	189 (37.4)
	Black or African American	6 (1.2)	6 (1.2)
ECOG PS, n (%)	(1) Normal activity	329 (64.9)	320 (63.4)
	(2) Restricted activity	178 (35.1)	185 (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)

*Percentage values do not sum to 100% due to data categorised as Missing/Other/Not Reported. Baseline characteristics in post-hoc PTEN subgroups are available in the article.
abi, abiraterone; capi, capivasertib; ECOG PS, Eastern Cooperative Oncology Group Performance Status; pbo, placebo

SoC: triplete

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

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. Median follow-up: 18.4 months (capi + abi), 18.5 months (pbo + abi)
abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; pbo, placebo; rPFS, radiographic progression-free survival

CAPItello-281: Secondary endpoints

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

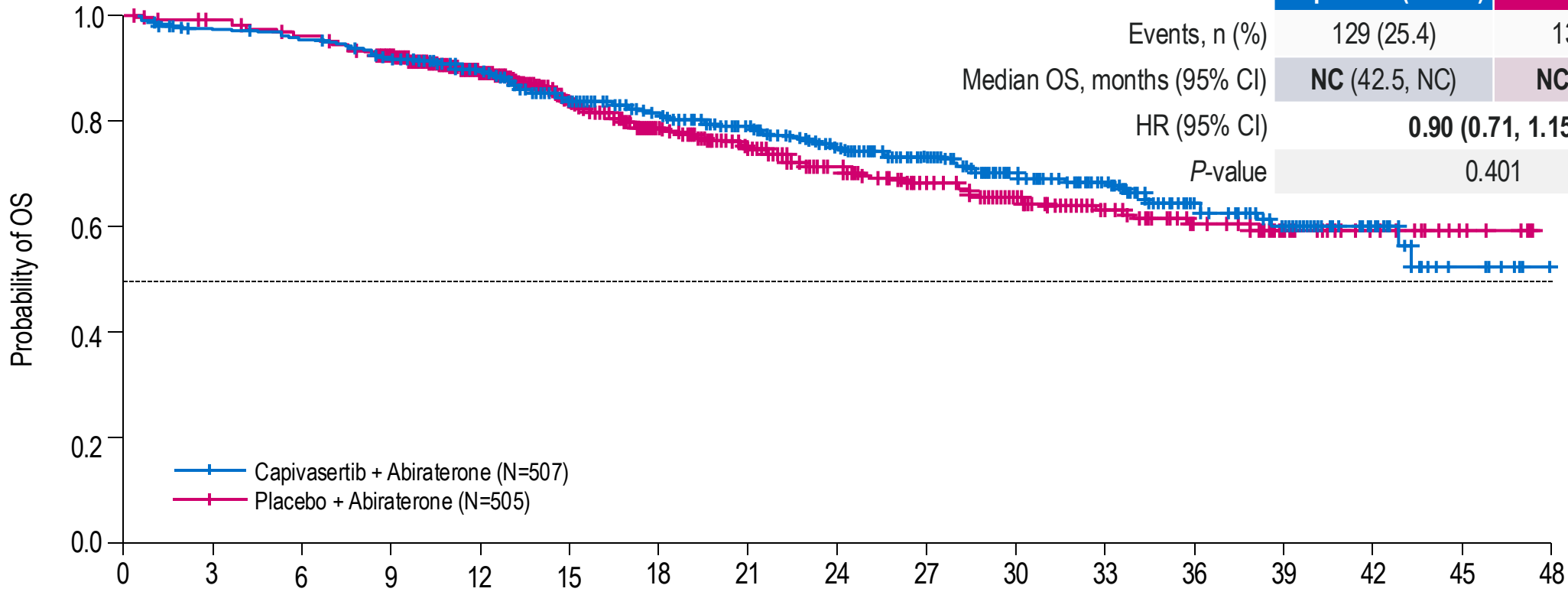
At low maturity (9%), time to pain progression data were difficult to interpret due to the small number of events (46/507 capi + abi; 41/505 pbo + abi)

DCO, data cut-off; HR, hazard ratio; OS, overall survival; SSE-FS, symptomatic skeletal event-free survival; time to next treatment = time to first subsequent therapy or death

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

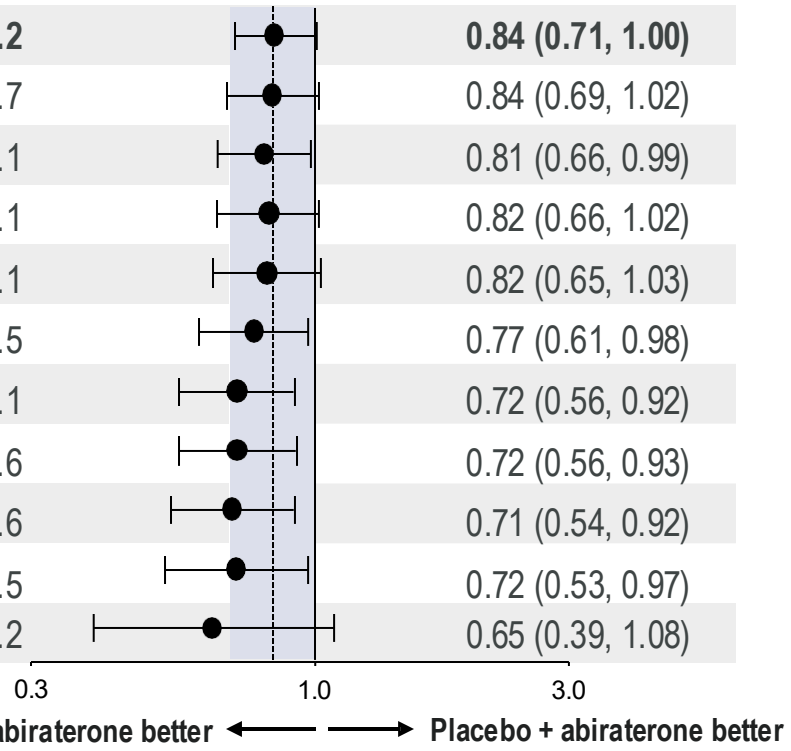
Capi + abi	507	487	476	447	400	335	286	242	199	164	128	96	60	42	22	7	0
Pbo + abi	505	494	479	449	388	330	273	227	188	153	113	88	56	33	19	7	0

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

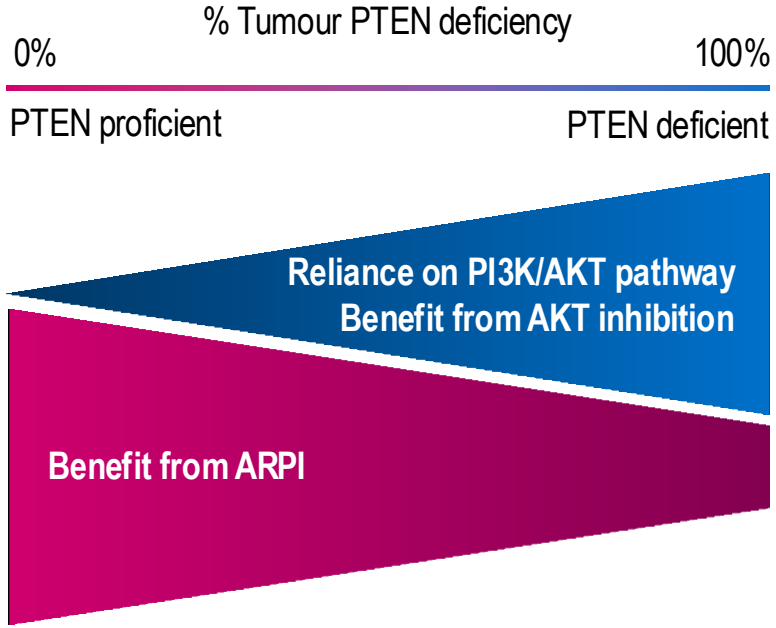
Exploratory data from the IPATential-150 study in mCRPC led to hypothesis of increasing AKTi treatment effect with increasing PTEN deficiency

rPFS by tumour PTEN deficiency in IPATential-150[1]

PTEN deficiency	No. of patients	Median rPFS, mo: Placebo + abiraterone	Median rPFS, mo: Ipatasertib + abiraterone	HR for Progression or Death (95% CI)
All patients	**1101**	**16.6**	**19.2**	**0.84 (0.71, 1.00)**
≥10%	771	16.6	17.7	0.84 (0.69, 1.02)
≥20%	684	16.5	17.1	0.81 (0.66, 0.99)
≥30%	618	16.5	17.1	0.82 (0.66, 1.02)
≥40%	575	16.5	17.1	0.82 (0.65, 1.03)
≥50%	523	16.5	18.5	0.77 (0.61, 0.98)
≥60%	489	15.1	19.1	0.72 (0.56, 0.92)
≥70%	462	15.0	18.6	0.72 (0.56, 0.93)
≥80%	424	14.8	18.6	0.71 (0.54, 0.92)
≥90%	335	14.7	18.5	0.72 (0.53, 0.97)
100%	123	16.5	19.2	0.65 (0.39, 1.08)



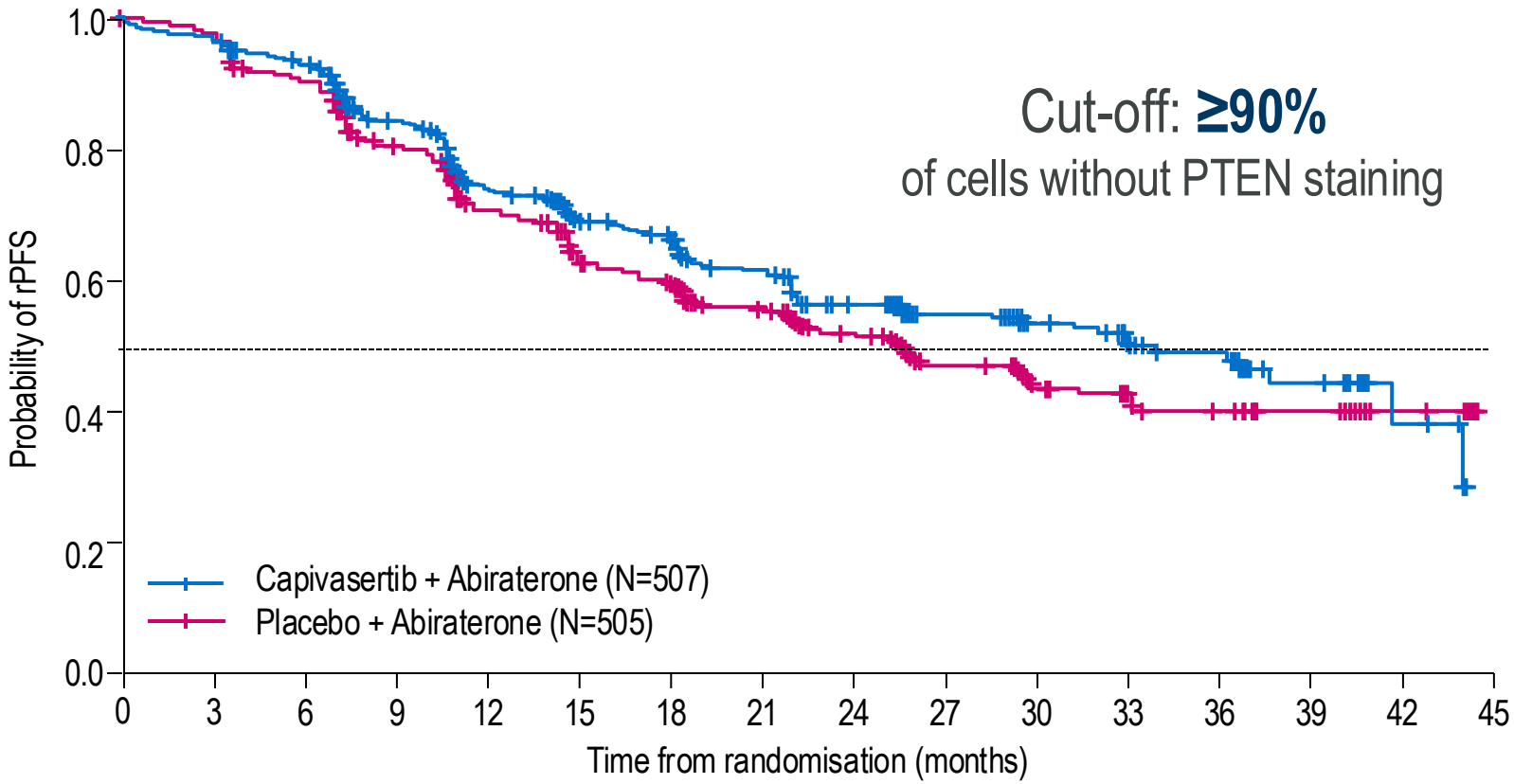
This gradient effect is supported by biologic rationale[2]



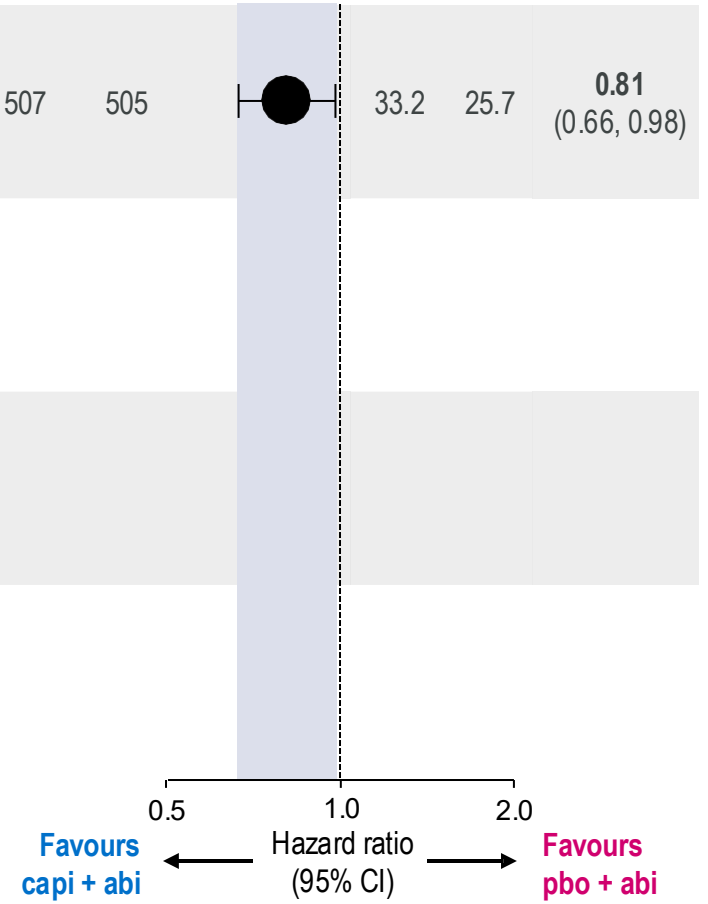
AKTi, AKT inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PTEN, phosphatase and tensin homolog

1. Sweeney C, *et al*. *Lancet* 2021;398:131–42 (reproduced with permission); 2. Marques RB, *et al*. *Eur Urol*. 2015;67:1177–1185

CAPItello-281 PTEN subgroups: investigator-assessed rPFS



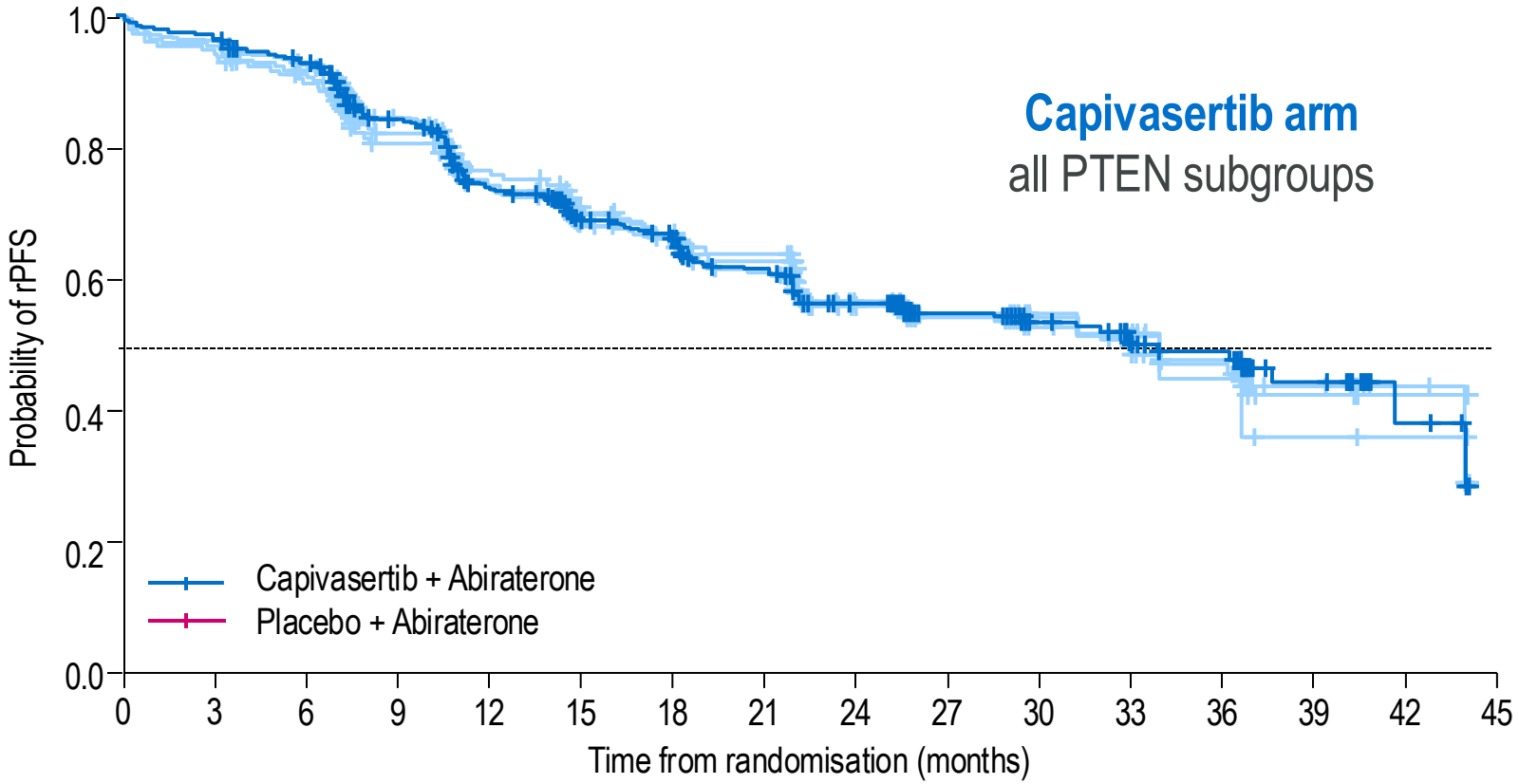
PTEN cutoff	Patients, n Capi + abi	Patients, n Pbo + abi	Median rPFS, months Capi + abi	Median rPFS, months Pbo + abi	HR (95% CI)
All randomised patients (≥90%)	507	505	33.2	25.7	**0.81** (0.66, 0.98)



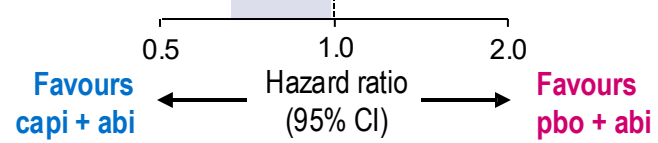
rPFS maturity in PTEN subgroups was consistent with the overall population

abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; pbo, placebo; rPFS, radiographic progression-free survival

CAPItello-281 PTEN subgroups: investigator-assessed rPFS



PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median rPFS, months: Capi + abi	Median rPFS, months: Pbo + abi	HR (95% CI)
All randomised patients (≥90%)	507	505	33.2	25.7	**0.81** (0.66, 0.98)
≥95%	404	410	33.2	22.7	**0.75** (0.60, 0.94)
≥99%	205	196	34.1	22.4	**0.71** (0.52, 0.97)
100%	169	162	34.1	22.1	**0.68** (0.48, 0.96)



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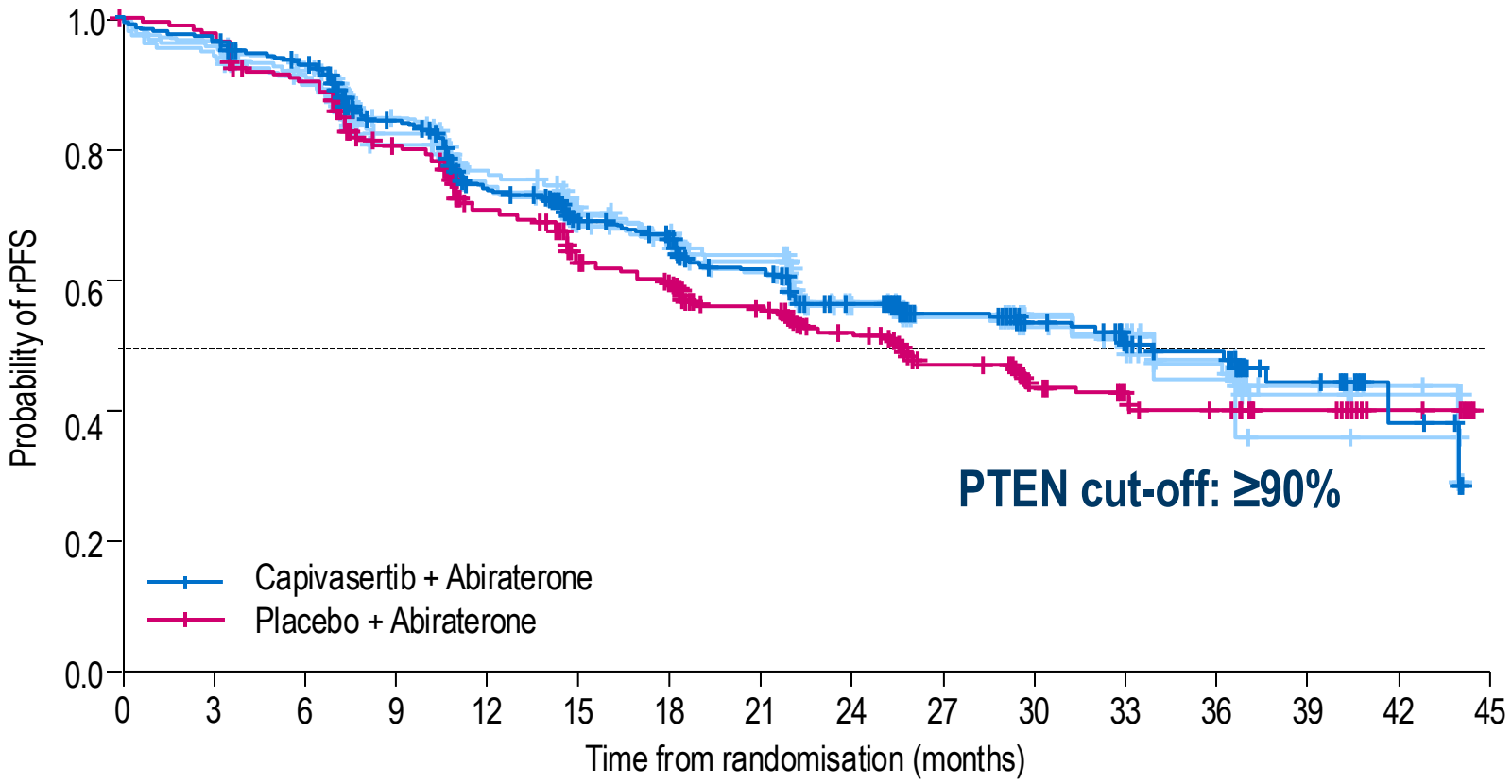
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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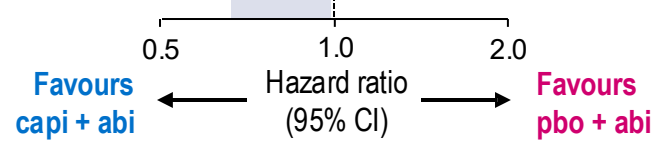

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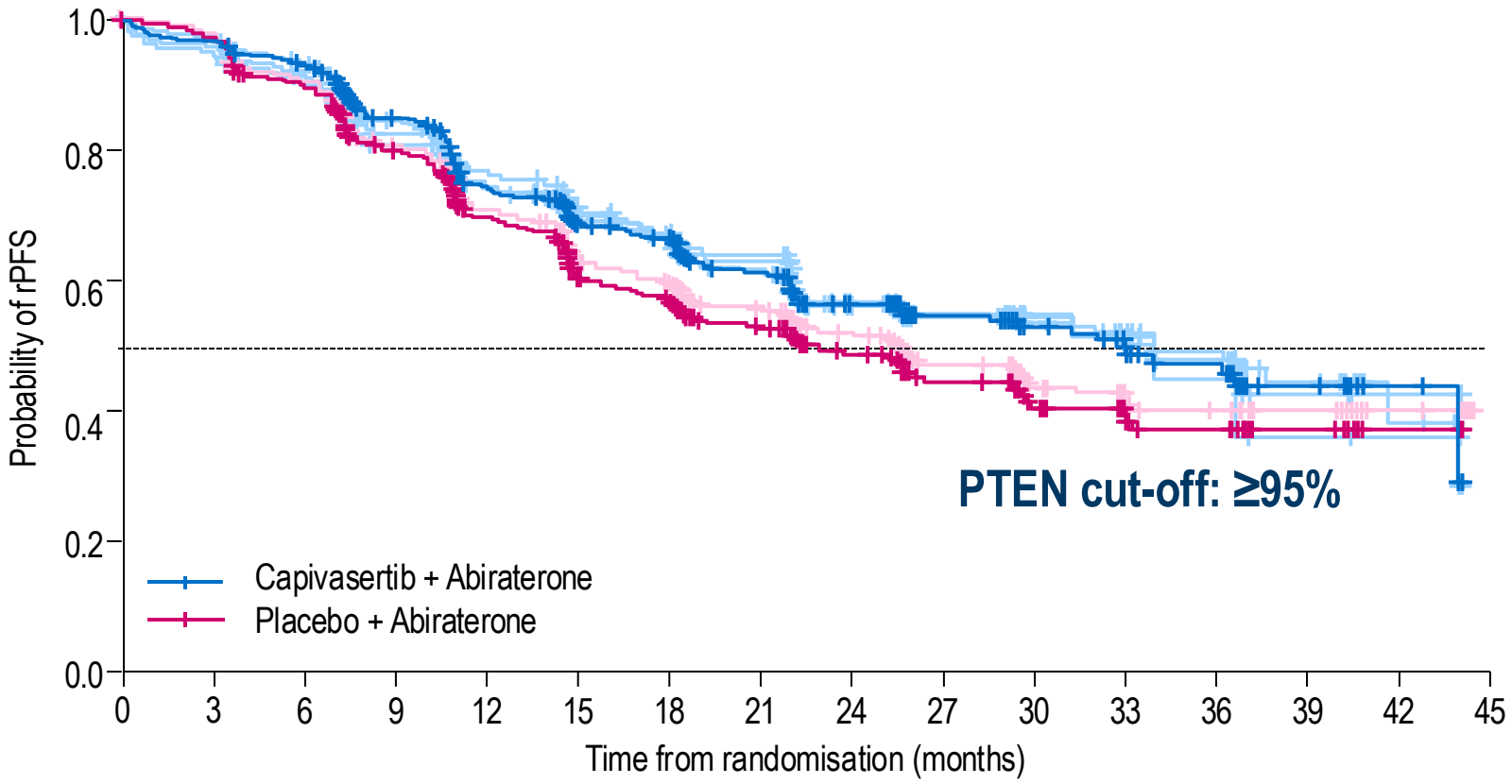
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median rPFS, months: Capi + abi	Median rPFS, months: Pbo + abi	HR (95% CI)
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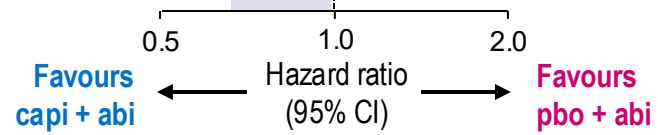

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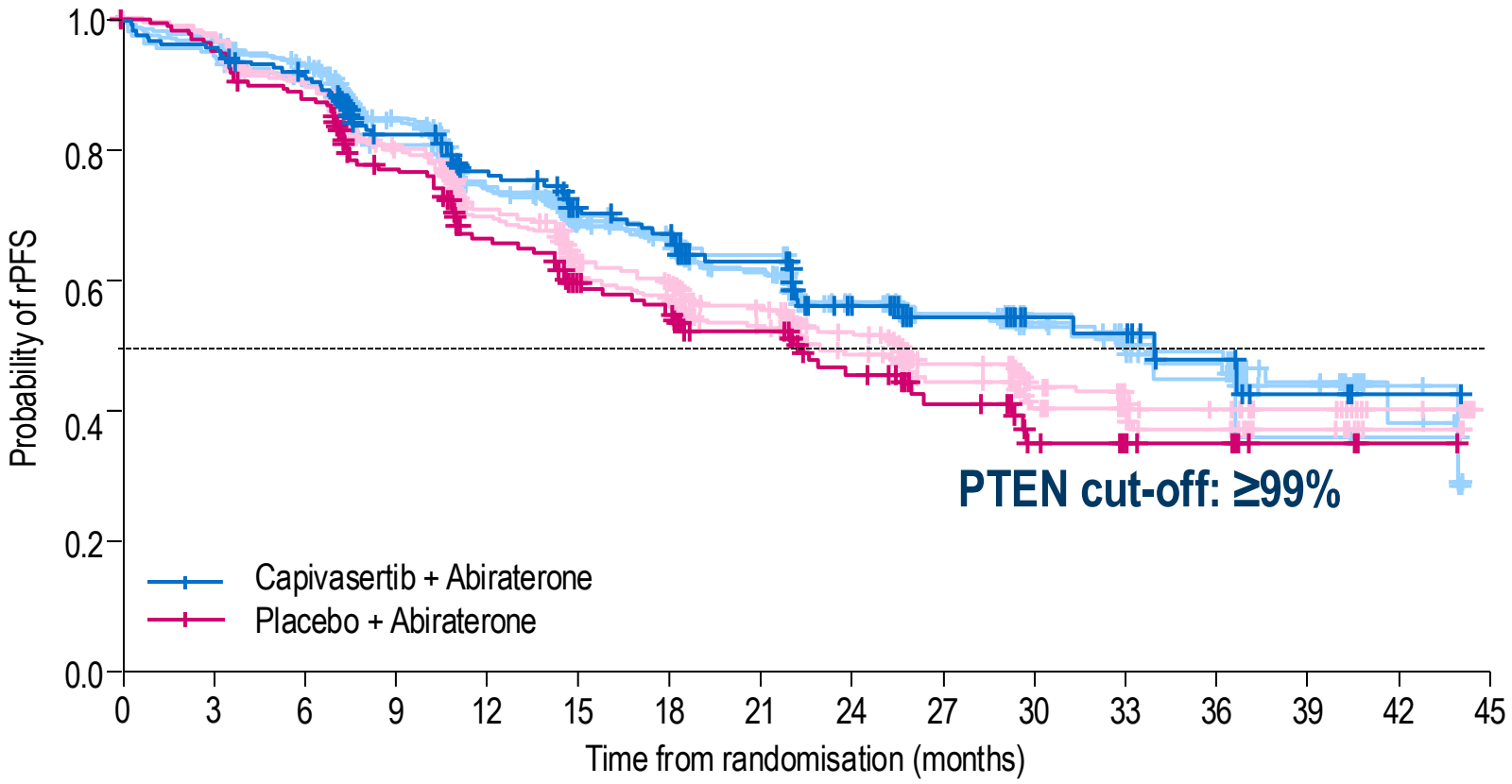

PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median rPFS, months: Capi + abi	Median rPFS, months: Pbo + abi	HR (95% CI)
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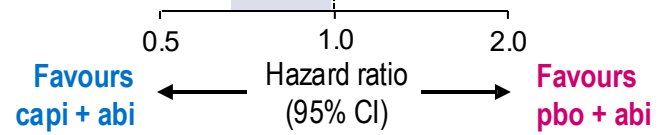

rPFS maturity in PTEN subgroups was consistent with the overall population

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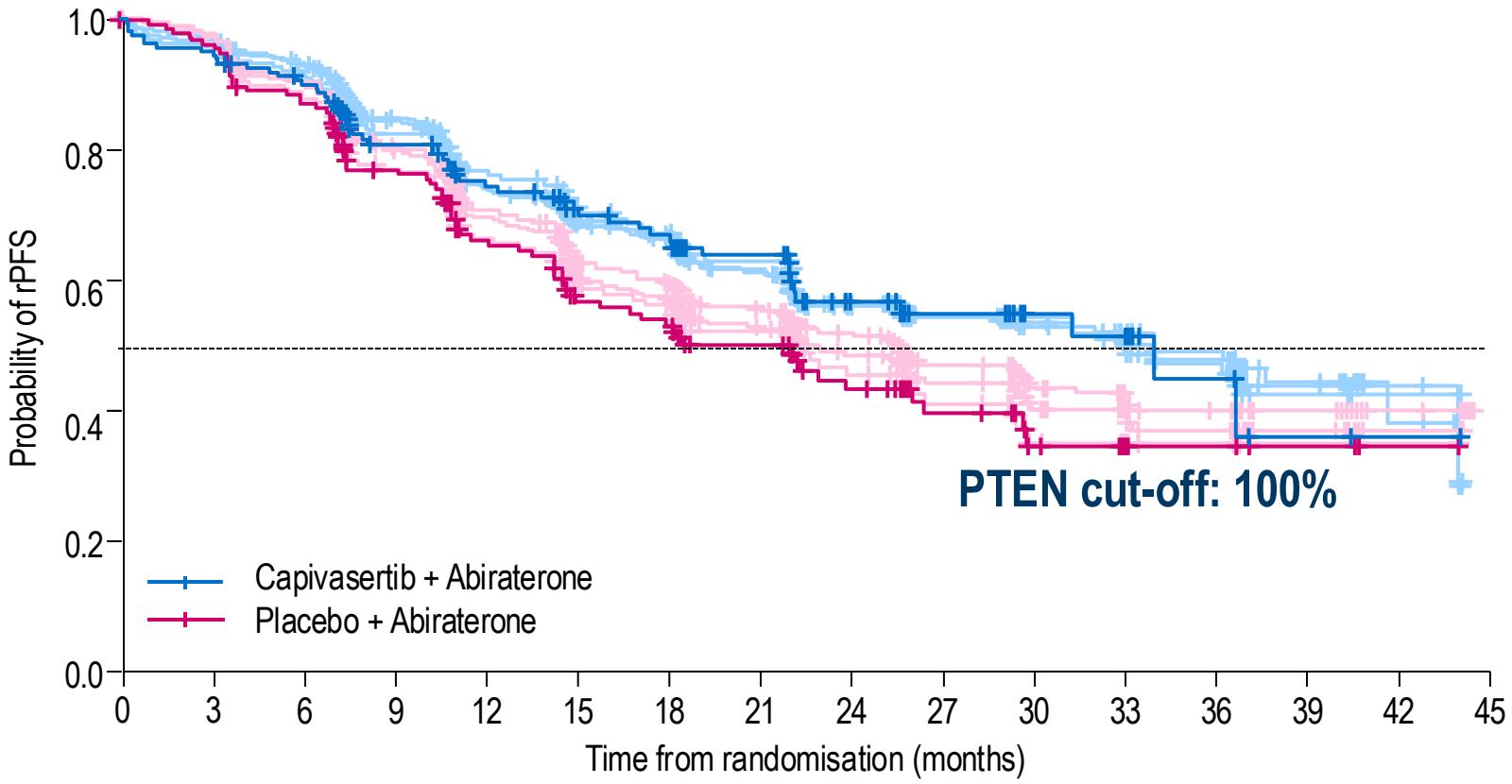
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median rPFS, months: Capi + abi	Median rPFS, months: Pbo + abi	HR (95% CI)
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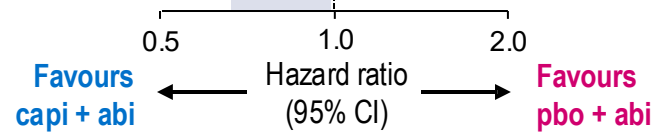
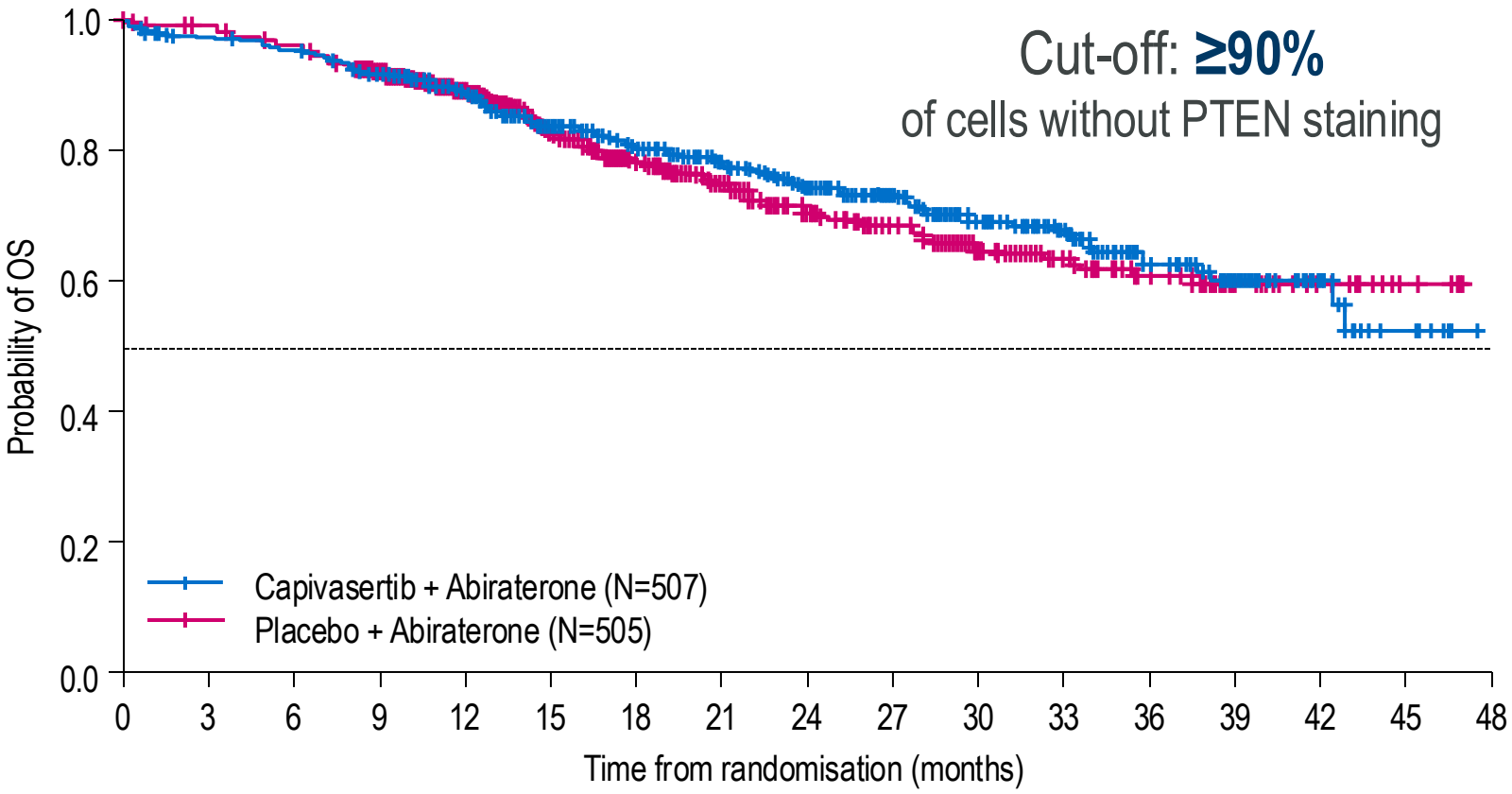
≥99%	205	196	34.1	22.4	**0.71** (0.52, 0.97)
100%	169	162	34.1	22.1	**0.68** (0.48, 0.96)

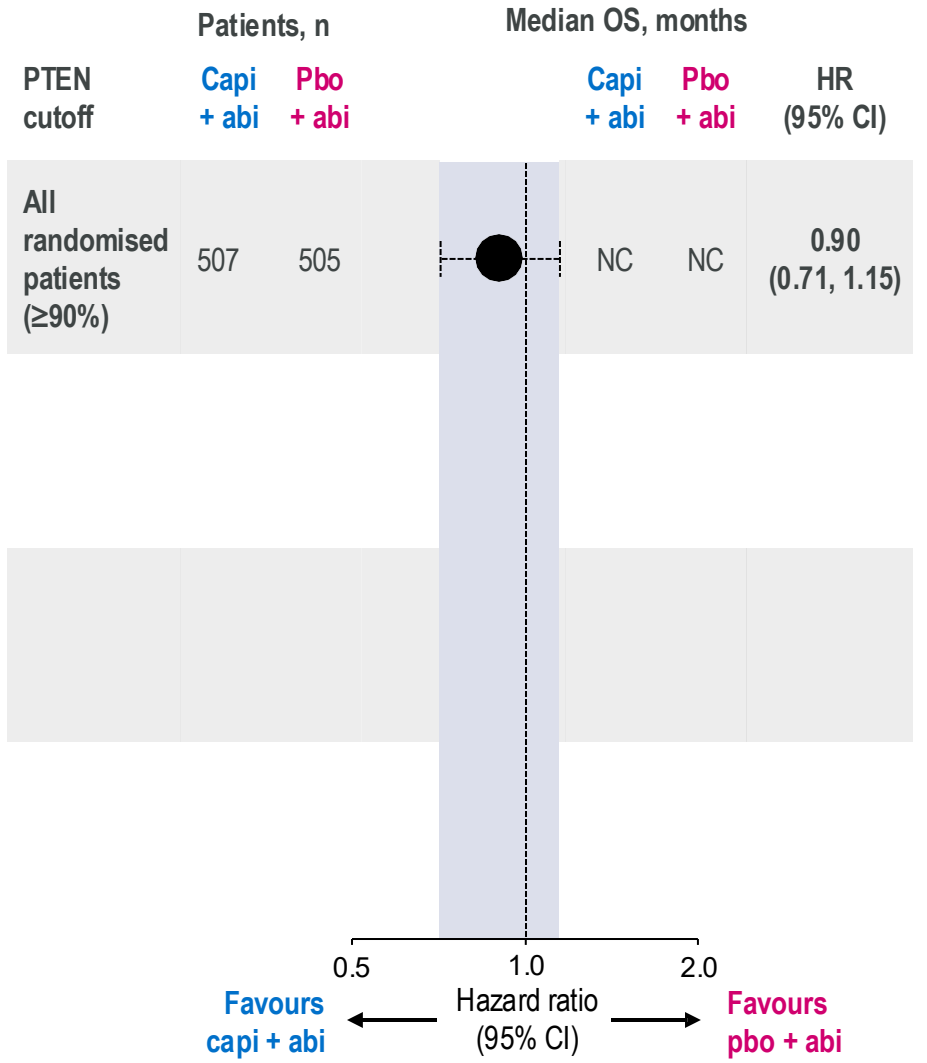


rPFS maturity in PTEN subgroups was consistent with the overall population

abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; pbo, placebo; rPFS, radiographic progression-free survival

CAPItello-281 PTEN subgroups: OS

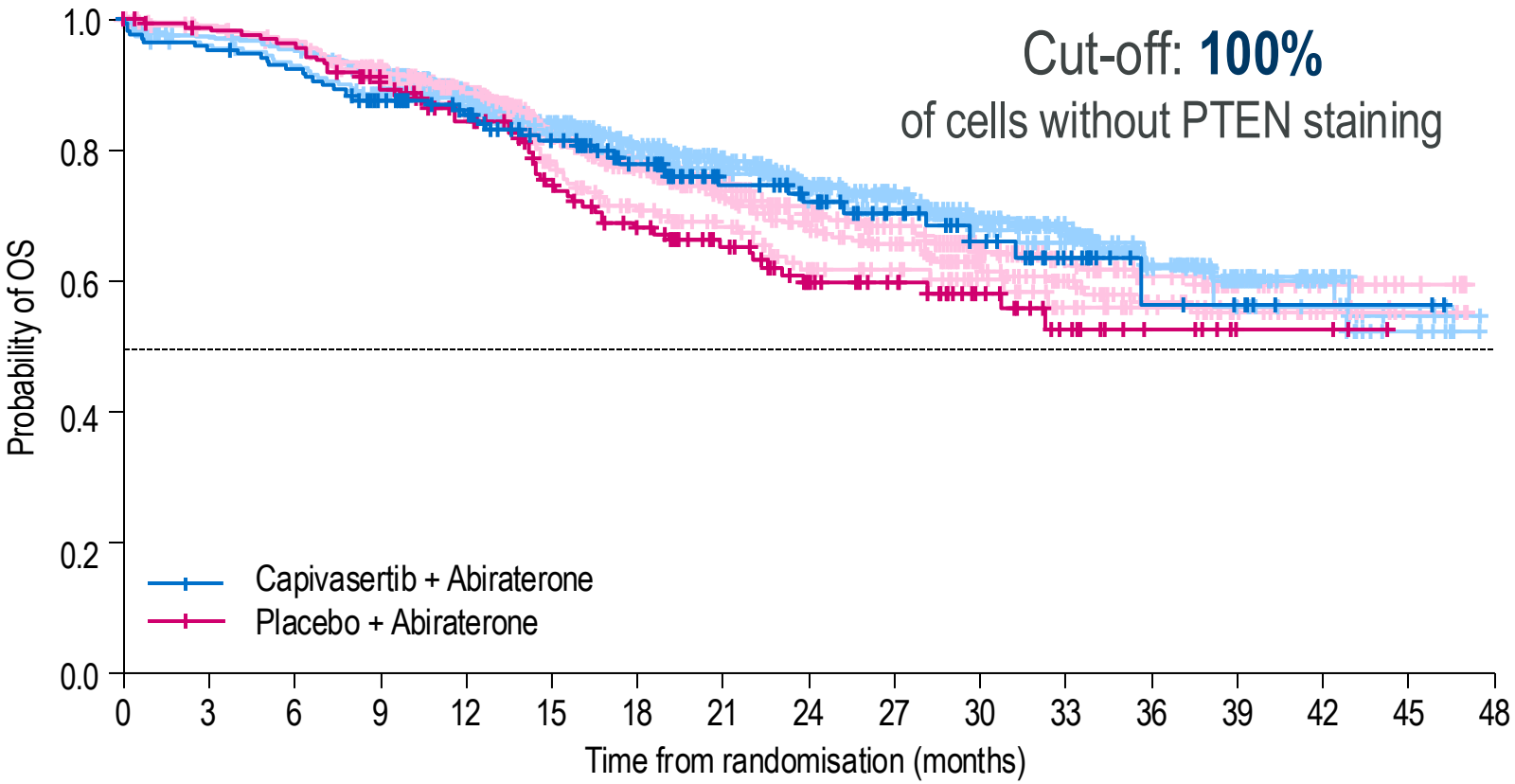




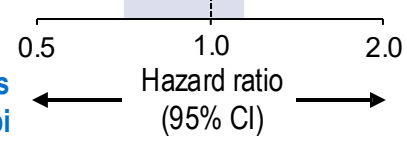
OS maturity in PTEN subgroups was broadly consistent with the overall population

abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; pbo, placebo

CAPItello-281 PTEN subgroups: OS



PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median OS, months: Capi + abi	Median OS, months: Pbo + abi	HR (95% CI)
All randomised patients (≥90%)	507	505	NC	NC	0.90 (0.71, 1.15)
≥95%	404	410	NC	NC	0.80 (0.62, 1.04)
≥99%	205	196	NC	NC	0.77 (0.53, 1.12)
100%	169	162	NC	NC	0.77 (0.51, 1.14)

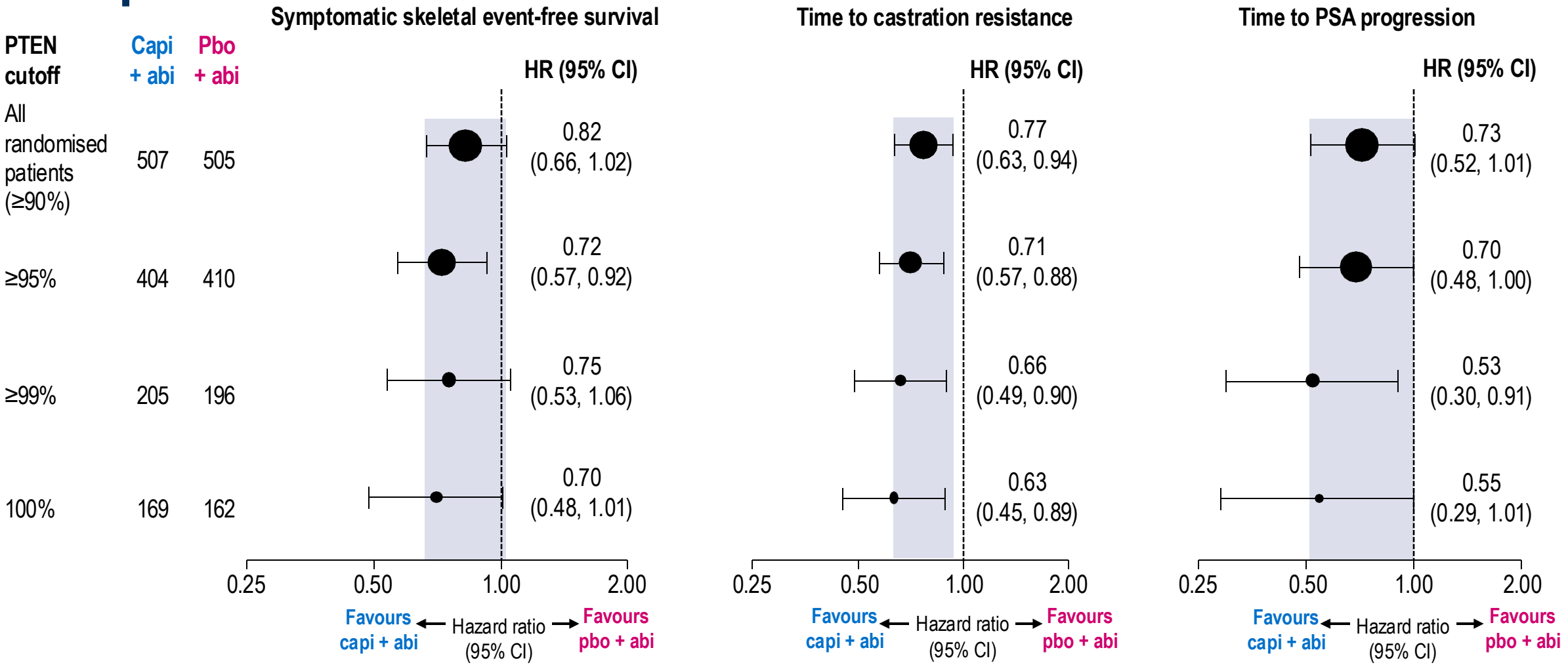


OS maturity in PTEN subgroups was broadly consistent with the overall population

abi, abiraterone; capi, capivasertib; CI, confidence interval; HR, hazard ratio; NC, not calculable; OS, overall survival; pbo, placebo

CAPItello-281 PTEN subgroups: Secondary endpoints

95% CI:
Overall population (≥90%)



abi, abiraterone; capi, capivasertib; CI, confidence interval; pbo, placebo; rPFS, radiographic progression-free survival; SSE-FS, symptomatic skeletal event-free survival; TTCR, time to castration resistance; TTPSA, time to PSA progression

CAPItello-281: Safety summary

n (%)	Capi + abi (n=503)	Pbo + abi (n=503)
Any AE	497 (98.8)	463 (92.0)
Any AE Grade ≥3	337 (67.0)	203 (40.4)
Any SAE	214 (42.5)	131 (26.0)
Any AE leading to death*	36 (7.2)	26 (5.2)
Any AE leading to discontinuation of capivasertib/placebo	92 (18.3)	24 (4.8)
Any AE leading to discontinuation of abiraterone	48 (9.5)	27 (5.4)
Any AE leading to dose interruption of capivasertib/placebo	316 (62.8)	135 (26.8)
Any AE leading to dose interruption of abiraterone	238 (47.3)	127 (25.2)
Any AE leading to dose reduction of capivasertib/placebo	146 (29.0)	18 (3.6)
Any AE leading to dose reduction of abiraterone	49 (9.7)	27 (5.4)

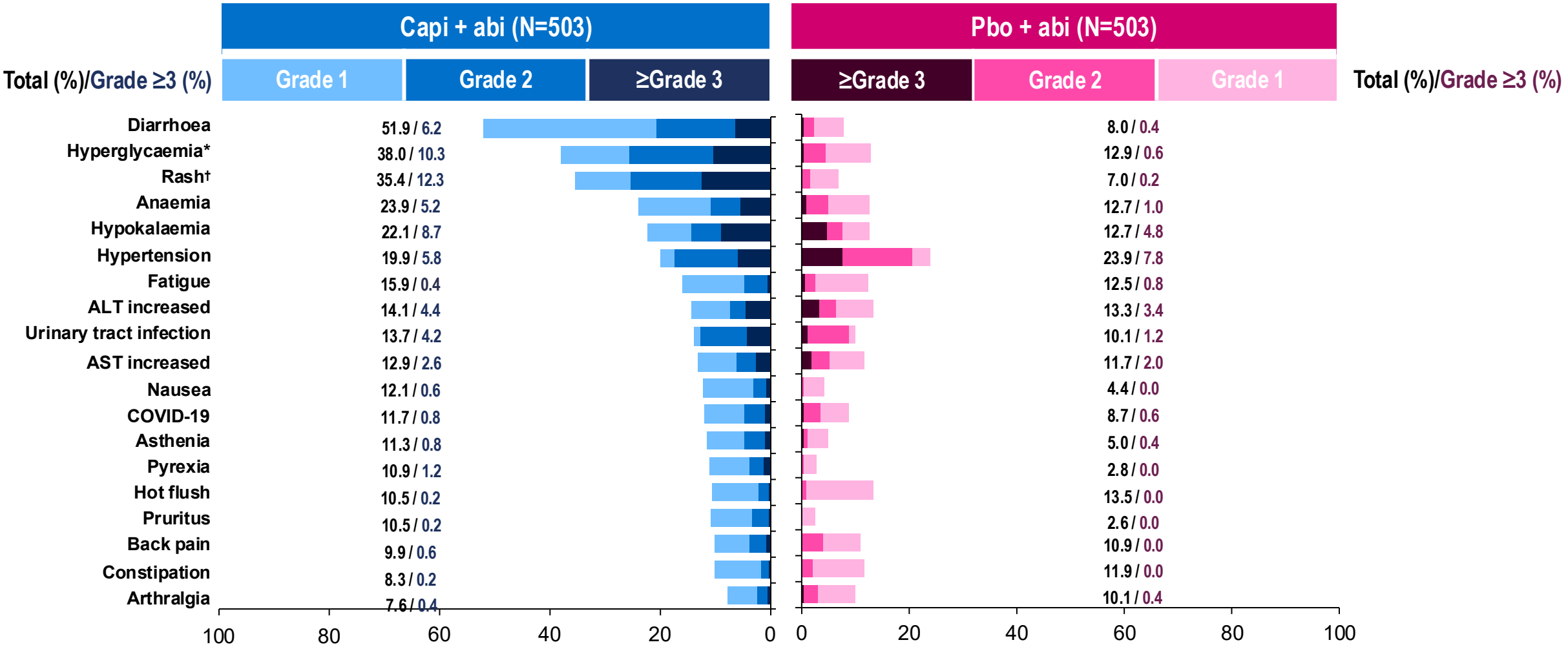
x2-3

The adverse event profile of capivasertib plus abiraterone was consistent irrespective of PTEN deficiency cutoff

Median (range) total duration of treatment with capivasertib/placebo was **13.6 (0.1, 46.6) months** in the capi + abi arm, compared with **14.9 (0.1, 47.1) months** with pbo in the pbo + abi arm

*AEs leading to death, considered by the investigator to be related to capi/pbo were reported in 6 (1.2%) and 1 (0.2%) patient(s), respectively.
abi, abiraterone; AE, adverse event; capi, capivasertib; pbo, placebo; SAE, serious adverse event

CAPItello-281: Adverse events (≥10% of patients)



Diabetic ketoacidosis was reported in 6 patients (1.2%) in the capi + abi arm, and 0 patients in the pbo + abi arm.

*Grouped term (includes the preferred terms of blood glucose increased, hyperglycaemia). †Grouped term (includes the preferred terms of erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic).

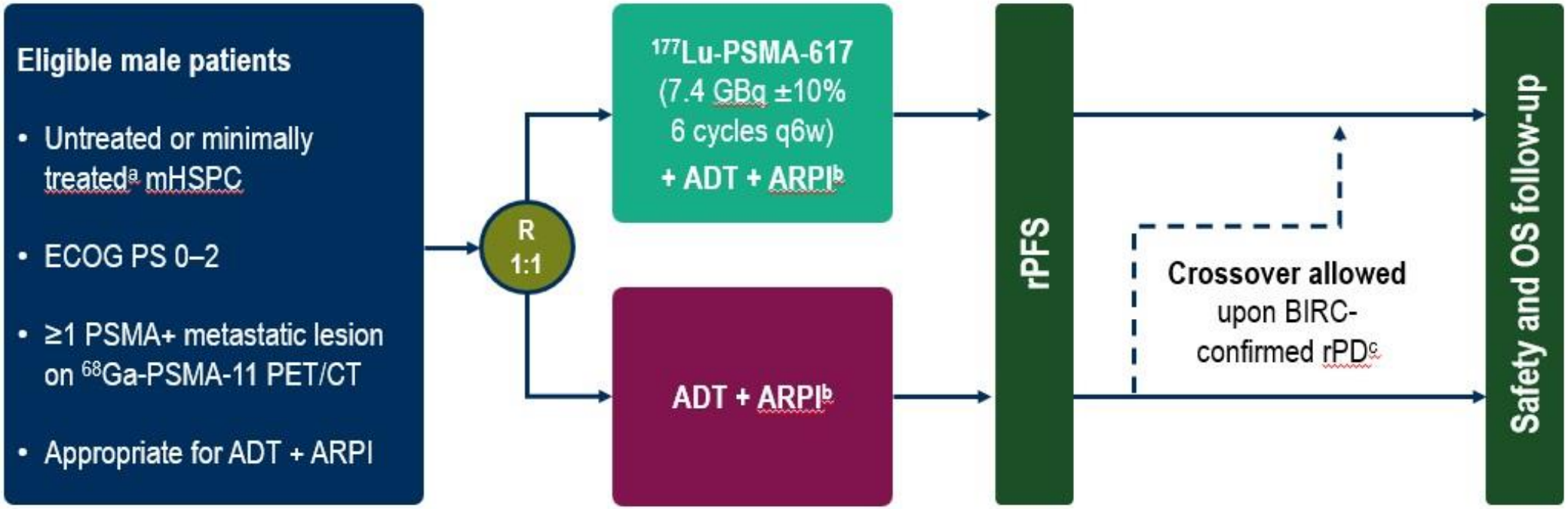
abi, abiraterone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; capi, capivasertib; pbo, placebo

CAPItello-281Conclusions

- Adding Capivasertib to AAP improves rPFS in mHSPC PTEN loss (IHC) but also increases AEs
- No benefit in OS (immature data)

PSMAddition

PSMAddition: randomized phase 3 trial of 177Lu-PSMA-617 in mHSPC



Stratification factors

- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

Docetaxel : not allowed

Follow-up periods

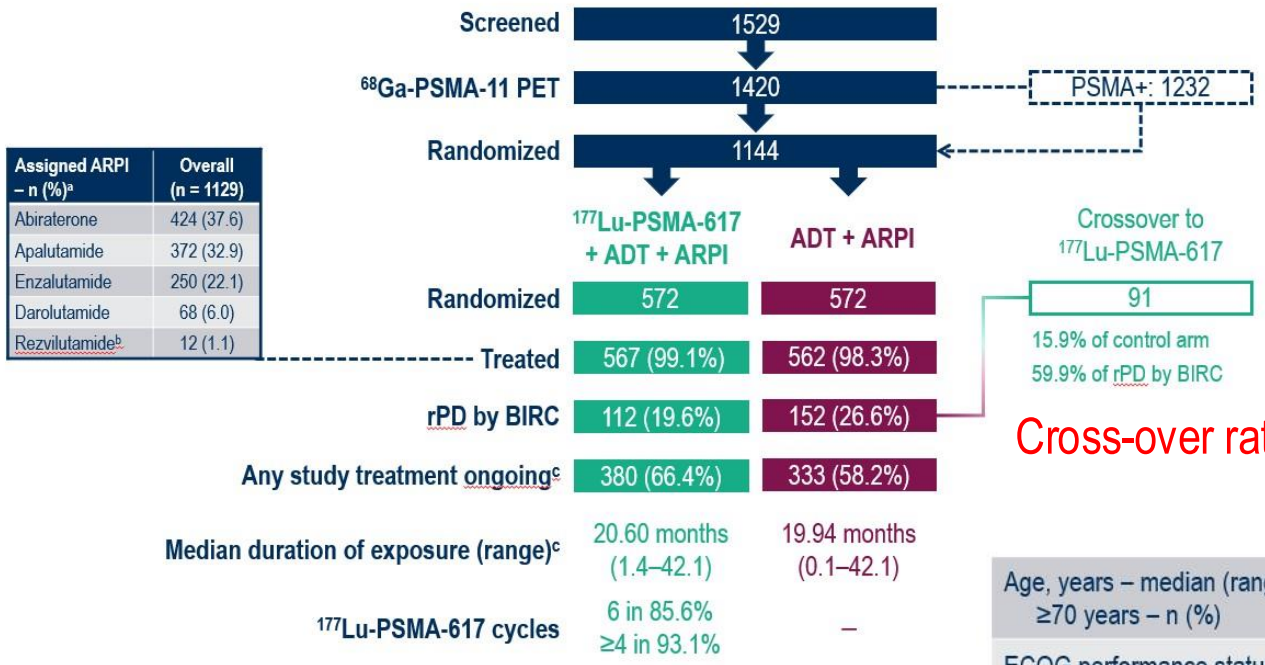
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

[a] ≤45 days before consent | [b] Any ARPI with one switch allowed | [c] ADT/ARPI not mandatory after crossover

ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PET/CT, positron-emission tomography/computed tomography; q6w, every 6 weeks; rPD, radiographic disease progression; rPFS, radiographic progression-free survival

1. Sweeney CT *et al. N Engl J Med* 2015;373:737–46

PSMAddition: population



Assigned ARPI – n (%)[a]	Overall (n = 1129)
Abiraterone	424 (37.6)
Apalutamide	372 (32.9)
Enzalutamide	250 (22.1)
Darolutamide	68 (6.0)
Rezvilutamide[b]	12 (1.1)

Positive PSMA PET: 87%

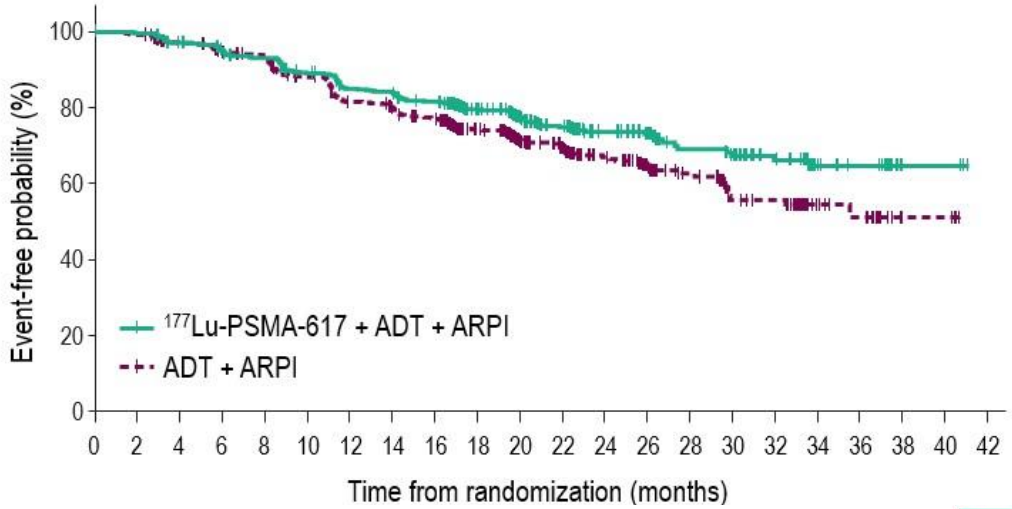
Cross-over rate : 60%

	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)	Overall (N = 1144)
Age, years – median (range)	68.0 (38–91)	68.0 (36–90)	68.0 (36–91)
≥70 years – n (%)	246 (43.0)	246 (43.0)	492 (43.0)
ECOG performance status – n (%)			
0	397 (69.4)	407 (71.2)	804 (70.3)
1	174 (30.4)	155 (27.1)	329 (28.8)
2	1 (0.2)	7 (1.2)	8 (0.7)
Site of disease – n (%)			
Soft tissue	342 (59.8)	338 (59.1)	680 (59.4)
Bone	522 (91.3)	521 (91.1)	1043 (91.2)
Visceral	225 (39.3)	238 (41.6)	463 (40.5)
PSA level, ng/mL – median (interquartile range)	12.06 (3.16–53.24)	11.64 (2.83–44.15)	11.91 (3.01–50.34)
Gleason score 8–10 (grade group 4–5) – n (%)	389 (68.0)	406 (71.0)	795 (69.5)
High tumour volume[a] – n (%)	389 (68.0)	390 (68.2)	779 (68.1)
De novo mHSPC[b] – n (%)	298 (52.1)	274 (47.9)	572 (50.0)

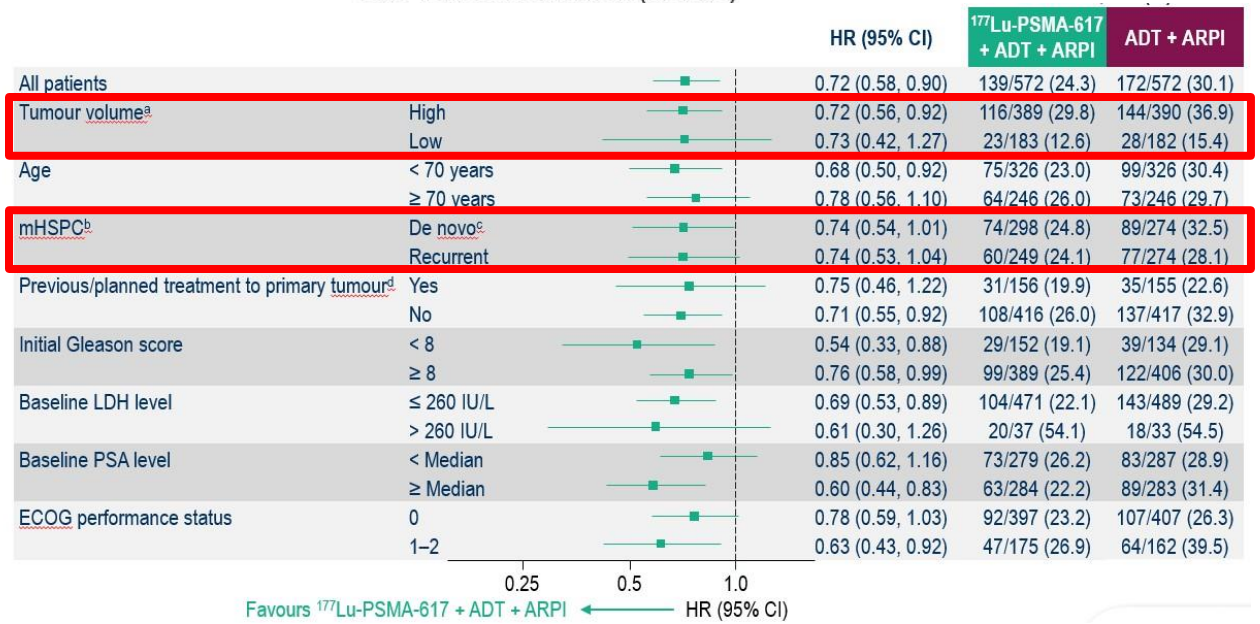
PSMAddition: Results

rPFS

2nd interim rPFS
Primary efficacy



	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	139 (24.3)	172 (30.1)
rPD	112 (19.6)	152 (26.6)
Death without rPD	27 (4.7)	20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

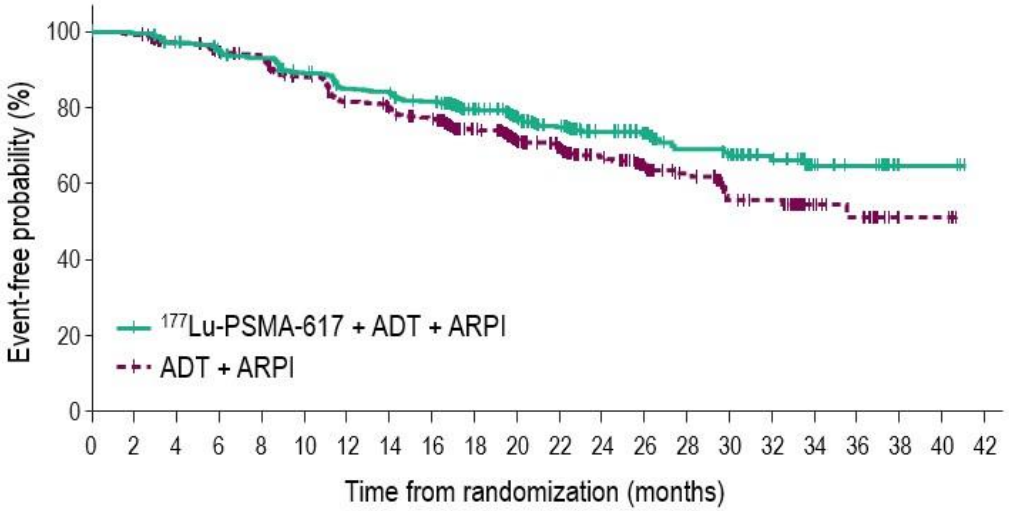


Subgroup missing :
- Visceral metastasis: YES or NO

PSMAddition: Results

rPFS

2nd interim rPFS
Primary efficacy



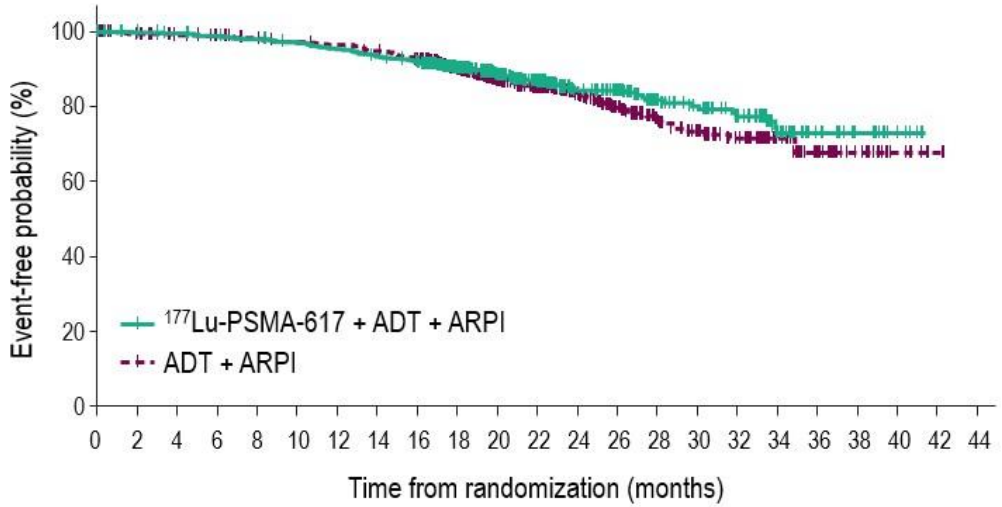
Number of patients still at risk

572	558	539	524	512	485	458	452	436	337	252	212	153	134	79	73	59	23	18	3	3	0
572	550	527	507	495	461	424	408	391	304	225	195	134	99	74	50	47	19	15	4	4	0

	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

OS

1st interim OS



Number of patients still at risk

572	566	562	556	550	543	533	521	512	424	336	267	195	174	109	94	78	45	27	12	5	0	0
572	561	551	547	539	531	526	516	501	432	315	268	196	159	118	91	72	46	28	16	7	2	0

	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	85 (14.9)	99 (17.3)
Censored – n (%)	487 (85.1)	473 (82.7)
HR (95% CI)	0.84 (0.63, 1.13)	
p value	0.125[a]	
Median OS (95% CI) – months	NR (NE, NE)	NR (NE, NE)

PSMAddition: Safety

Patients with on-treatment AE – n (%)[a]	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	555 (98.4)	286 (50.7)	546 (96.6)	243 (43.0)
Related to any study treatment	504 (89.4)	128 (22.7)	394 (69.7)	69 (12.2)
^{177}Lu-PSMA-617-related	441 (78.2)	78 (13.8)	–	–
ADT and/or ARPI-related	418 (74.1)	81 (14.4)	394 (69.7)	69 (12.2)
Serious	180 (31.9)	150 (26.6)	162 (28.7)	129 (22.8)
Related to any study treatment	39 (6.9)	31 (5.5)	14 (2.5)	12 (2.1)
^{177}Lu-PSMA-617-related	17 (3.0)	13 (2.3)	–	–
ADT and/or ARPI-related	27 (4.8)	22 (3.9)	14 (2.5)	12 (2.1)
Leading to death	15 (2.7)	15 (2.7)	14 (2.5)	14 (2.5)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16.1)	46 (8.2)	51 (9.0)	23 (4.1)
Leading to ^{177}Lu-PSMA -617…				
Discontinuation	45 (8.0)	28 (5.0)	–	–
Dose reduction	22 (3.9)	13 (2.3)	–	–
Dose delay	68 (12.1)	27 (4.8)	–	–

Patients with AE in grouping – n (%)	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dry mouth[a]	262 (46.5)	0	22 (3.9)	0
Cytopenias	248 (44.0)	81 (14.4)	115 (20.4)	28 (5.0)
Anaemia[b]	158 (28.0)	28 (5.0)	79 (14.0)	16 (2.8)
Neutropenia[c]	83 (14.7)	21 (3.7)	24 (4.2)	5 (0.9)
Thrombocytopenia[d]	63 (11.2)	10 (1.8)	19 (3.4)	3 (0.5)
Fractures	52 (9.2)	16 (2.8)	43 (7.6)	15 (2.7)
Renal events[e]	40 (7.1)	9 (1.6)	26 (4.6)	5 (0.9)
Second primary malignancies	37 (6.6)	24 (4.3)	31 (5.5)	14 (2.5)
Dry eye	33 (5.9)	0	3 (0.5)	0
Intracranial haemorrhage	6 (1.1)	4 (0.7)	4 (0.7)	2 (0.4)

PSMAddition conclusions

- Combining 177Lu-PSMA-617 with ADT+ARPI improves rPFS
- OS data is immature
- Acceptable safety profile, with no new signal

ARASAFE

ARASAFE: randomised, open-label, multicentre phase 3 trial (NCT05676203)

Patients (N=250)
- mHSPC
- ECOG PS 0 or 1
- Candidates for darolutamide, ADT and docetaxel

Stratification
- Extent of disease: high vs. low volume
- ALP < vs ≥ ULN

Enrolment
FPFV: May 2023
LPFV: Dec 2024

1:1 Randomization (N=250)

STD: Darolutamide 600 mg twice daily + ADT + 6 x Docetaxel *75 mg/m²* every 3 weeks (3 week cycle)

Total expected docetaxel dose: 450 mg/m²

EXP: Darolutamide 600 mg twice daily + ADT + 6 x Docetaxel *50 mg/m²* every 2 weeks (4 week cycle)

Total expected docetaxel dose: 600 mg/m²

Primary analysis (at week 26)

Endpoints
Primary:
- Safety: Grade 3-5 AEs
- Safety: Grade 3-4 Neutropenia or death of any reason

Secondary
- Time to CRPC
- Overall survival
- Time to pain progression
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- QoL (exploratory)

Standard arm (STD) Experimental arm (EXP)

Marc-Oliver Grimm

Primary Endpoint

ARASAFE

Endpoint	Docetaxel 75 mg/m² Q3W, N=128	Docetaxel 50 mg/m² Q2W, N=121	p-value
Grade 3-5 AE rates, % (95% CI)	78.9 (70.8, 85.6)	61.2 (51.9, 69.9)	**0.0024**
Grade 3-4 neutropenia/death, % (95% CI)	64.1 (55.1, 72.3)	24.0 (16.7, 32.6)	**<0.00001**

Efficacy: PSA Response at Week 26

PSA response at week 26		Docetaxel 75 mg/m² Q3W, N=129	Docetaxel 50 mg/m² Q2W, N=121
PSA, median (IQR), ng/ml		0.16 (0.03, 1.00)	0.26 (0.05, 1.55)
PSA subgroups, n (%)	PSA ≤ 0.2 ng/ml	63 (48.8)	50 (41.3)
	0.2 ng/ml < PSA ≤ 4.0 ng/ml	43 (33.3)	52 (43.0)
	PSA > 4 ng/ml	14 (10.9)	12 (9.9)
	Not applicable	6 (4.7)	4 (3.3)
	Missing	3 (2.3)	3 (2.5)

But no data on rPFS or OS

ARASAFE conclusions

- Docetaxel Q3W + ADT + ARPI is standard of care

- Docetaxel Q2W + ADT + ARPI might be an option for frail/old patients with “very high” volume disease

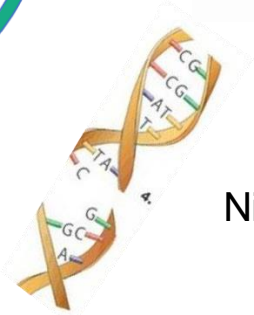
Therapeutic landscape for mCRPC patients

Chemotherapy
Docetaxel
Cabazitaxel
Carboplatine +/- VP16

Radioligand therapy
^{177}LuPSMA-617
Radium-223

mCRPC

ARPI
Abiratérone
Enzalutamide



PARP inhibitors
Olaparib (*BRCA* mutated)
Olaparib + abiraterone
Niraparib + abiraterone (*BRCA* mutated)
Talazoparib + enzalutamide

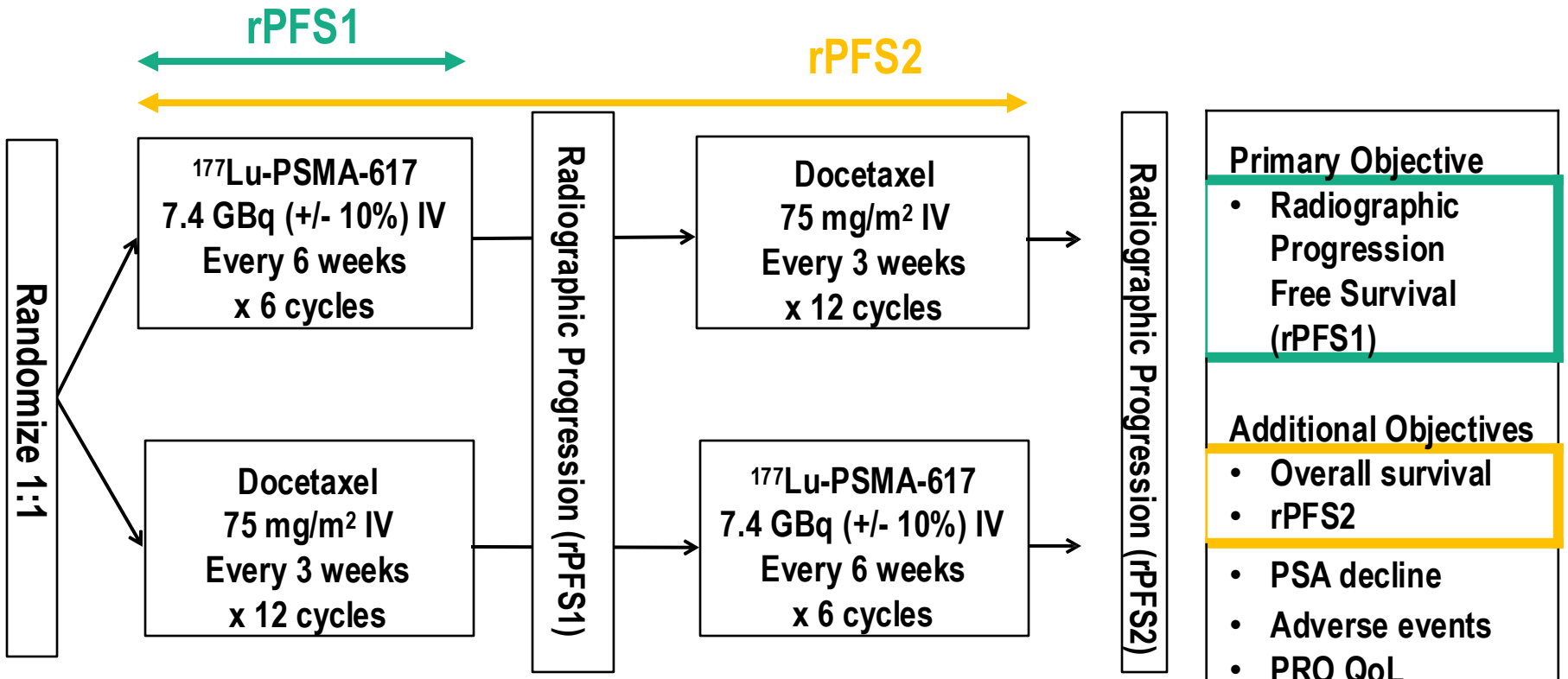
PR21

Canadian Cancer Trials Group (CCTG) PR21

Open label randomized phase II with cross-over

Key Eligibility

- Chemotherapy-naïve mCRPC progressing after ARPI
- PSMA PET positive (uptake >liver)
  - Excluded if >50% of extra-osseous lesions or >5 cm soft tissue lesion were PSMA negative
- ANC ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥ 90 g/L
- CrCl ≥ 30 ml/min
- Bilirubin < 1.5 x ULN
- ALT < 3.5 x ULN (<5 x UN for liver metastases)
- ECOG PS of 0 - 2
- Prior docetaxel for mHSPC permitted if ≥12 months prior



Stratification factors:

- ECOG PS (0-1 vs 2)
- LDH (>ULN, yes vs no)
- Visceral metastases (yes vs no)
- Prior docetaxel for mHSPC (yes vs no)

Primary Objective

- Radiographic Progression Free Survival (rPFS1)

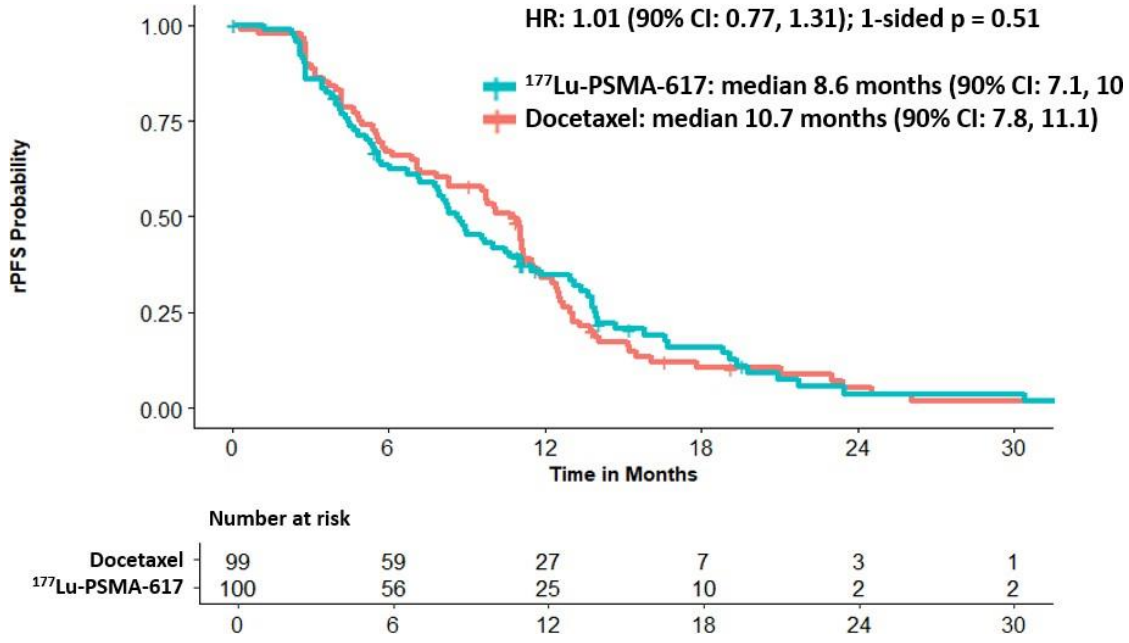
Additional Objectives

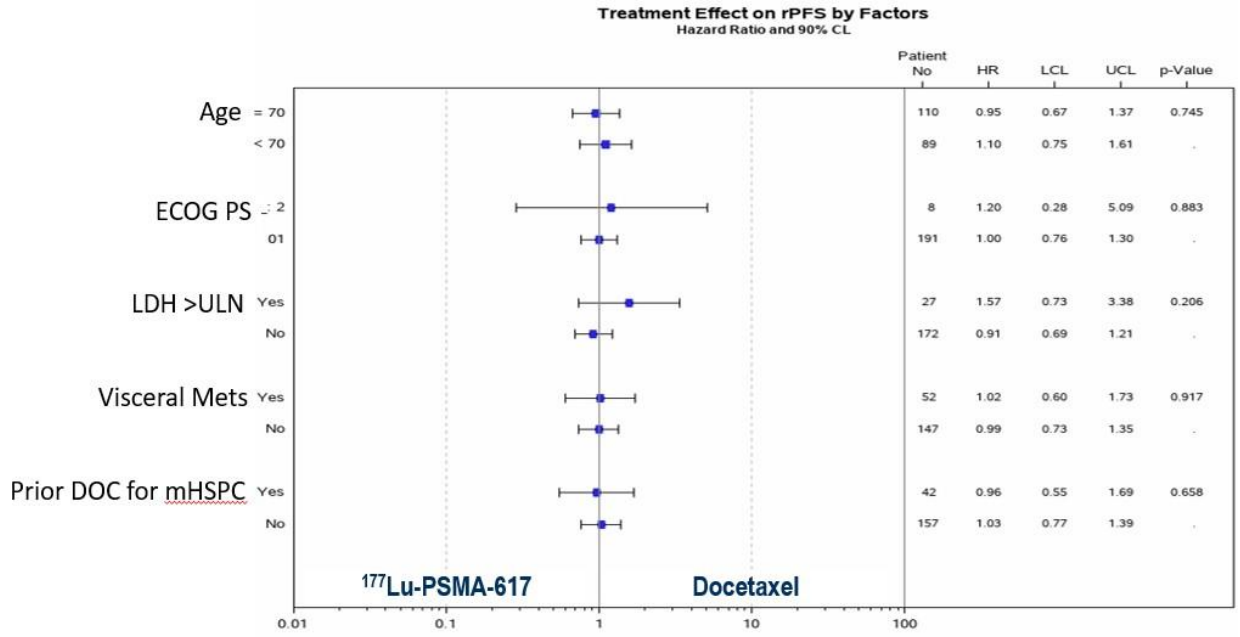
- Overall survival
- rPFS2
- PSA decline
- Adverse events
- PRO QoL
- Correlative studies

Presenter: Dr. Kim N. Chi

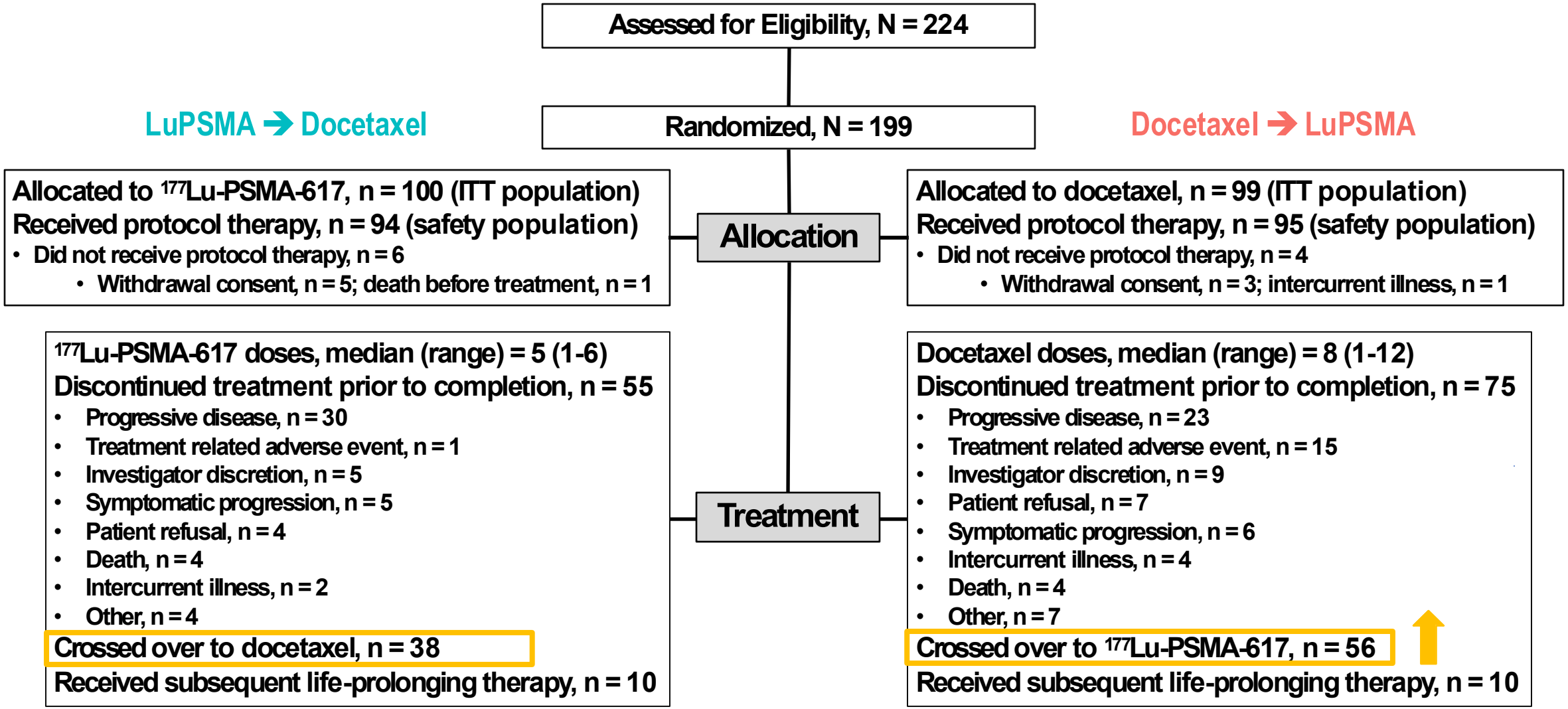
Results

rPFS1



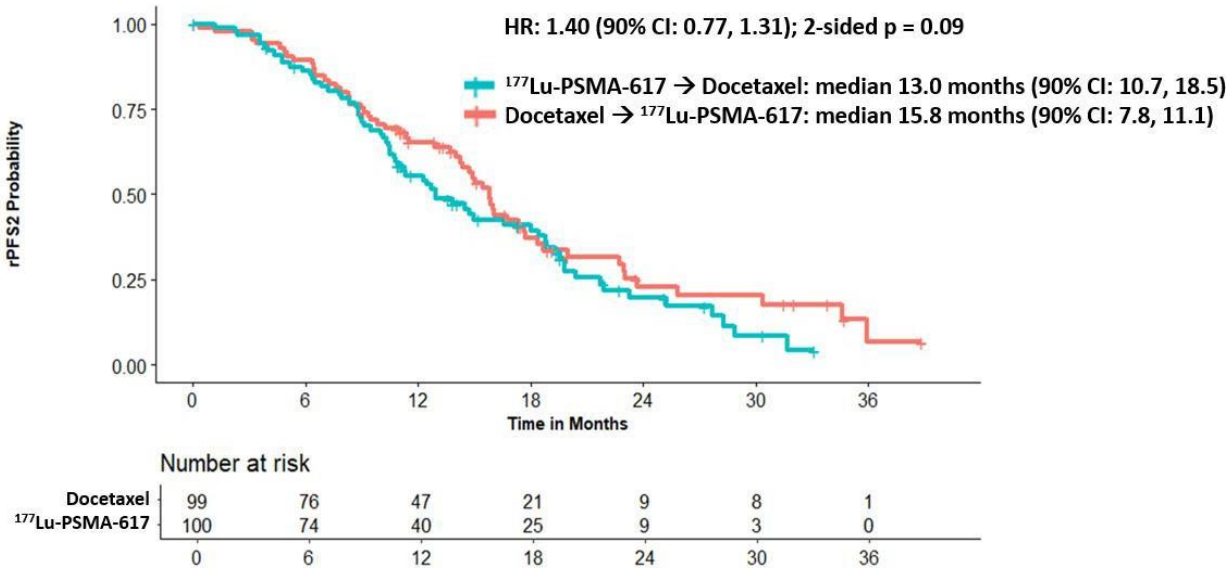


Results

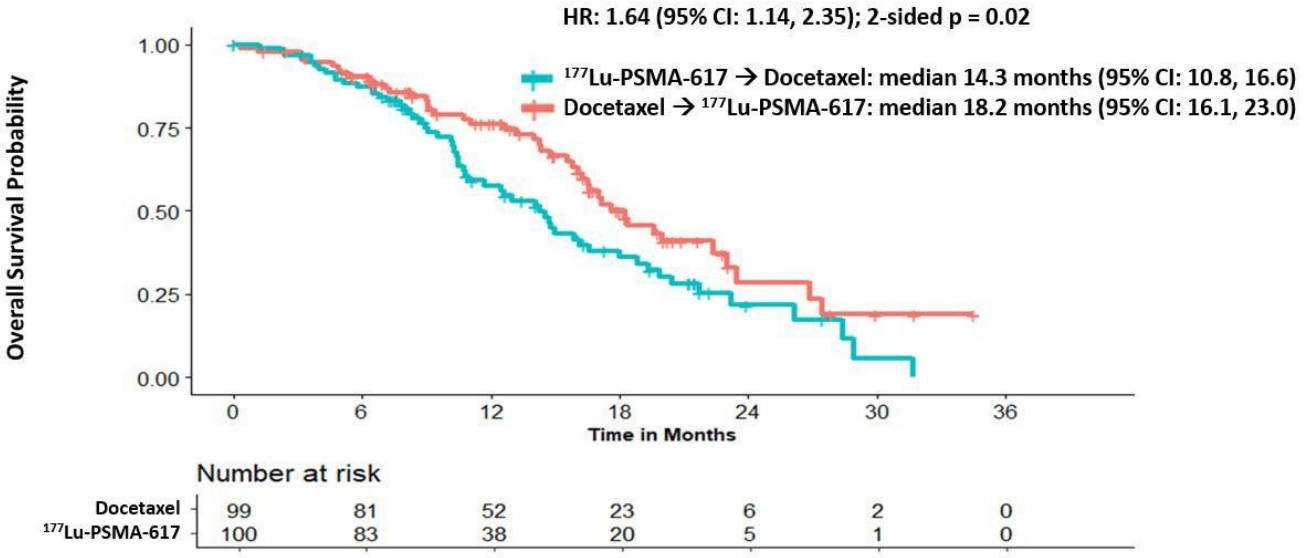

Assessed for Eligibility, N = 224
Randomized, N = 199
LuPSMA → Docetaxel
Docetaxel → LuPSMA
Allocated to 177Lu-PSMA-617, n = 100 (ITT population)
Received protocol therapy, n = 94 (safety population)
• Did not receive protocol therapy, n = 6
• Withdrawal consent, n = 5; death before treatment, n = 1
Allocation
Allocated to docetaxel, n = 99 (ITT population)
Received protocol therapy, n = 95 (safety population)
• Did not receive protocol therapy, n = 4
• Withdrawal consent, n = 3; intercurrent illness, n = 1
177Lu-PSMA-617 doses, median (range) = 5 (1-6)
Discontinued treatment prior to completion, n = 55
• Progressive disease, n = 30
• Treatment related adverse event, n = 1
• Investigator discretion, n = 5
• Symptomatic progression, n = 5
• Patient refusal, n = 4
• Death, n = 4
• Intercurrent illness, n = 2
• Other, n = 4
Crossed over to docetaxel, n = 38
Received subsequent life-prolonging therapy, n = 10
Treatment
Docetaxel doses, median (range) = 8 (1-12)
Discontinued treatment prior to completion, n = 75
• Progressive disease, n = 23
• Treatment related adverse event, n = 15
• Investigator discretion, n = 9
• Patient refusal, n = 7
• Symptomatic progression, n = 6
• Intercurrent illness, n = 4
• Death, n = 4
• Other, n = 7
Crossed over to 177Lu-PSMA-617, n = 56
Received subsequent life-prolonging therapy, n = 10

Results

rPFS2



OS



Take Home Message : It's not Lu-PSMA *or* docetaxel — it's Lu-PSMA *and* docetaxel.

Conclusiones

ENZARAD: The addition of Enzalutamide to ADT – Radiotherapy in unslected high-risk prostate cancer didn’t improve MFS or OS

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AMPLITUDE: Patients harbouring HRR alterations, specially BRCA1-2, benefit of addition of niraparib to abiraterone-prednisone in radiologic PFS

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CAPItello-281: Patients with PTEN loss (IHC) show worse prognosis. Addition of Capivasertib to Abiraterone improves rPFS.

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PSMAddition: 177Lu-PSMA-617 plus ADT+ARPI improves rPFS in mHSPC