FDA is committed to ensuring digital accessibility for people with disabilities. We are continually improving the user experience for everyone and applying the relevant accessibility standards. At the time of initial posting on **April 30, 2026**, the attached **Event Materials** may not be fully accessible to users using assistive technology. A fully accessible version of the **Event Materials** is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

Please let us know if you encounter accessibility barriers by contacting **Division of Advisory Committee and Consultant Management (DACCM)** at:

- **ODAC@fda.hhs.gov**

AstraZeneca

Capivasertib (TRUQAP®) in Combination With Abiraterone for the Treatment of Patients With PTEN-Deficient Metastatic Hormone-Sensitive Prostate Cancer

United States Food and Drug Administration
Oncologic Drugs Advisory Committee

April 30, 2026

AstraZeneca

Introduction

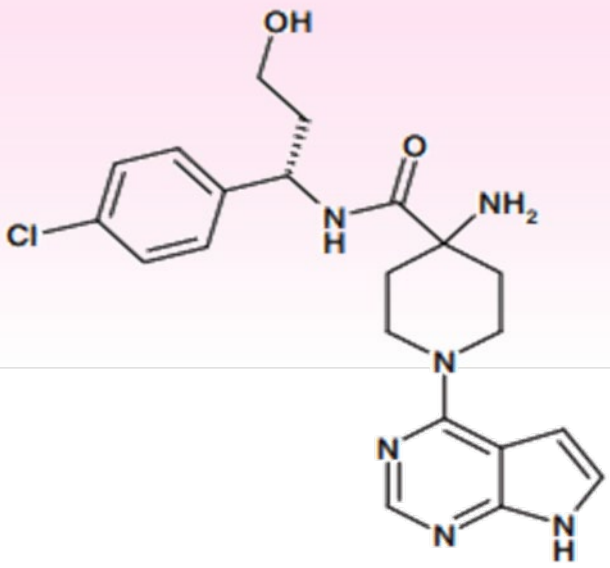
Andrew Foxley, MFPM (Hon)

VP, Late Development Franchise Head

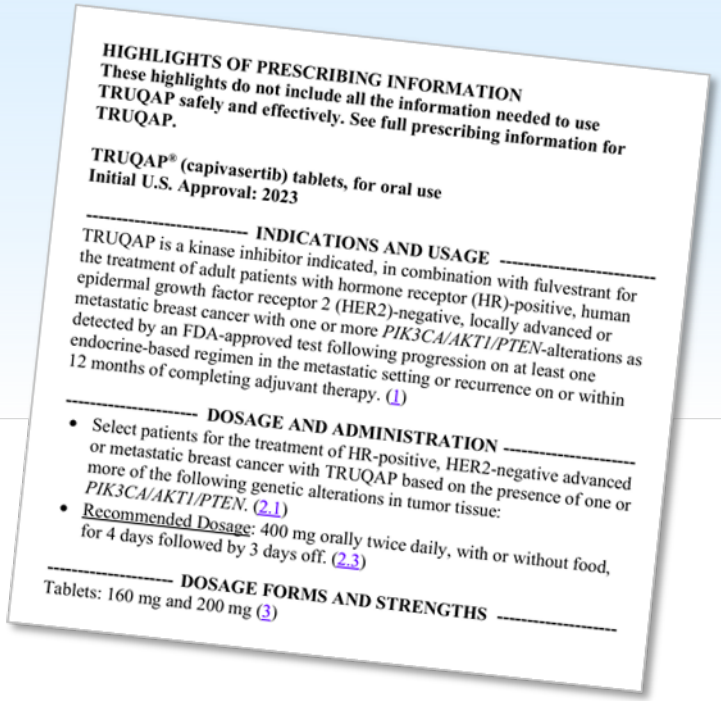
Oncology Small Molecules
AstraZeneca

Capivasertib

A first-in-class AKT inhibitor



Approved in 2023 for *PIK3CA/AKT1/PTEN*-altered, HR-positive, HER2-negative breast cancer



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRUQAP safely and effectively. See full prescribing information for TRUQAP.

TRUQAP® (capivasertib) tablets, for oral use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

TRUQAP is a kinase inhibitor indicated, in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. (1)

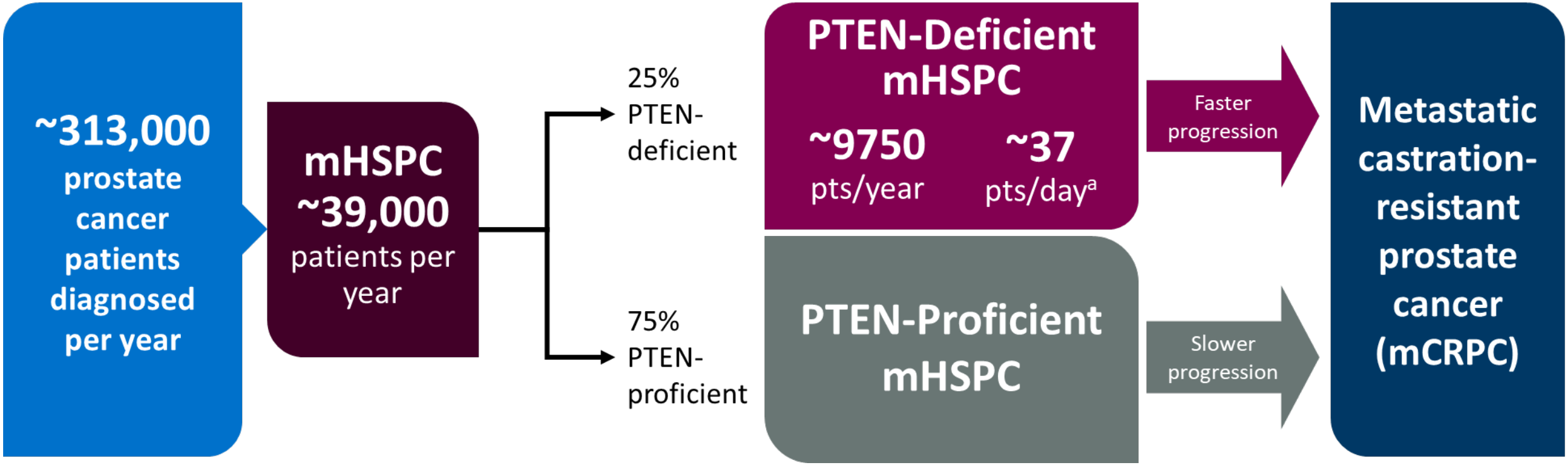
DOSAGE AND ADMINISTRATION

- Select patients for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer with TRUQAP based on the presence of one or more of the following genetic alterations in tumor tissue: *PIK3CA/AKT1/PTEN*. (2.1)
- Recommended Dosage: 400 mg orally twice daily, with or without food, for 4 days followed by 3 days off. (2.3)

DOSAGE FORMS AND STRENGTHS

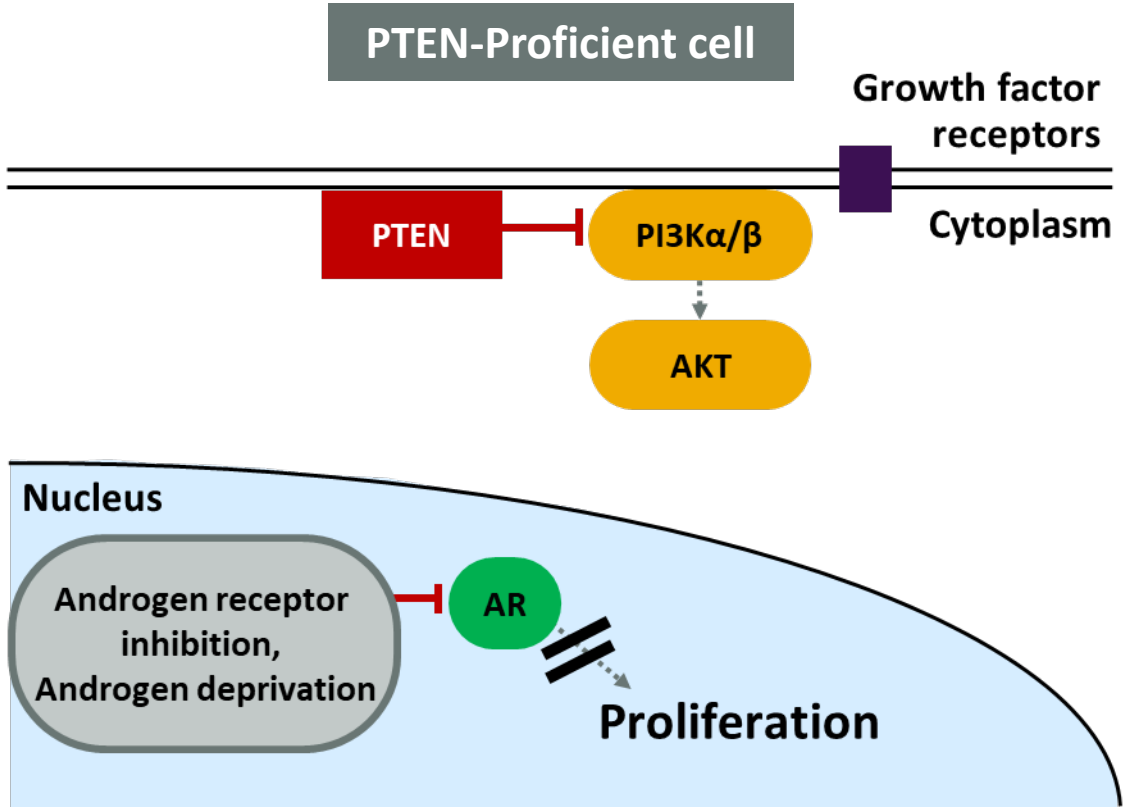
Tablets: 160 mg and 200 mg (3)

25% of Men With mHSPC Have Tumor PTEN Deficiency Associated With More Rapid Onset of Castration Resistance

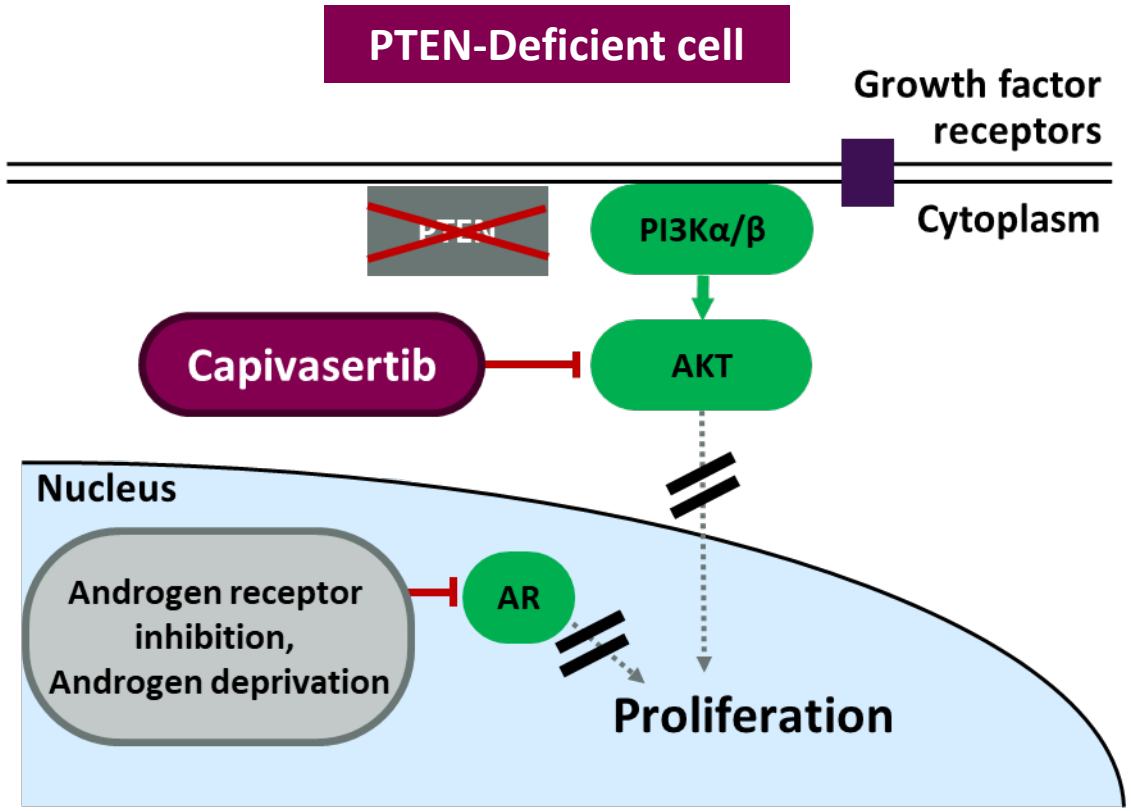


mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; PTEN=phosphatase and tensin homolog.
a. Calculated based on PTEN deficiency (defined as ≥90% of viable malignant cells with no specific cytoplasmic staining) having a prevalence of 25% in mHSPC, and 260 days per year on which diagnosis can be made in the clinic.
Oracle Life Science – CancerMPact; NIH, NCI, SEER. Cancer Stat Facts: Prostate Cancer. Accessed January 20, 2026. https://seer.cancer.gov/statfacts/html/prost.html.

PTEN Deficiency in mHSPC Ungates an Additional Driver of Cell Proliferation Via the PI3K-AKT Pathway



In PTEN-proficient cells, AR is the primary proliferation drive



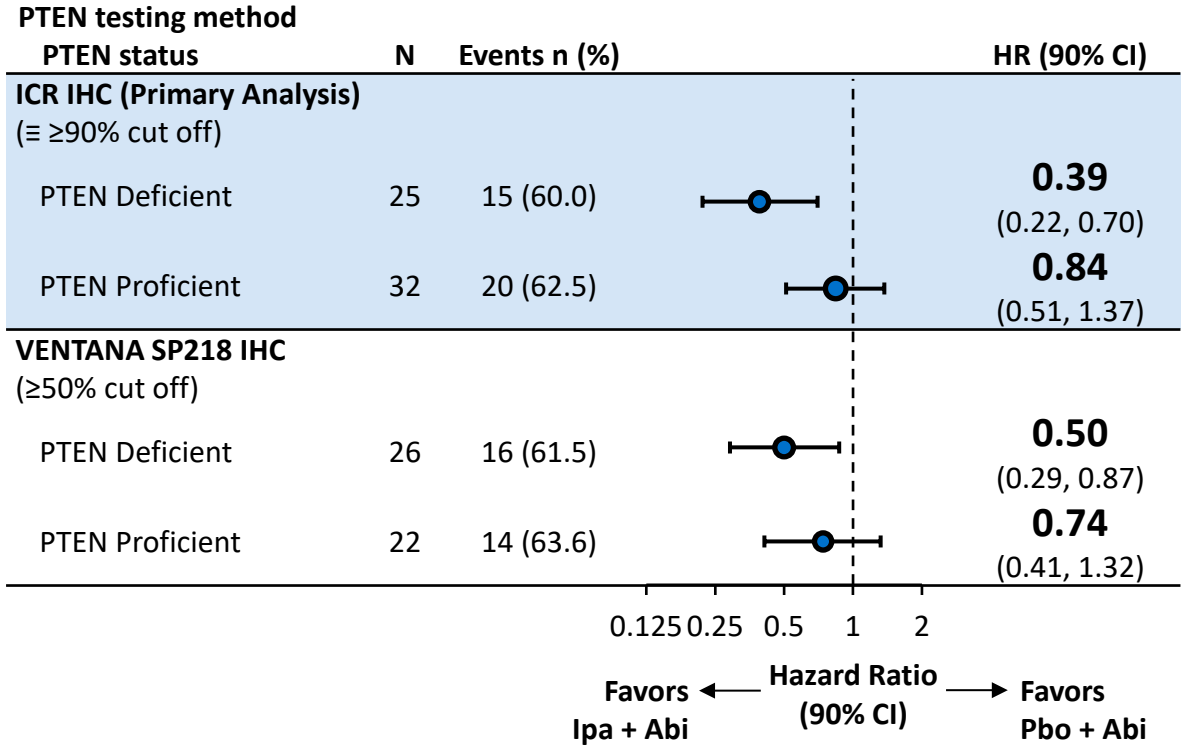
In PTEN-deficient cells, AKT pathway provides an additional proliferation drive

AR=androgen receptor; mHSPC=metastatic hormone-sensitive prostate cancer; PTEN=phosphatase and tensin homolog.

Key Design Choices for CAPItello-281

1. Selection of an IHC diagnostic to identify PTEN-deficiency

ASTON MARTIN Phase 2 rPFS: mCRPC[1]



2. mHSPC to address early PTEN deficiency

- PTEN deficiency is present in 25% of mHSPC
- Additional proliferation drive not addressed by current therapies

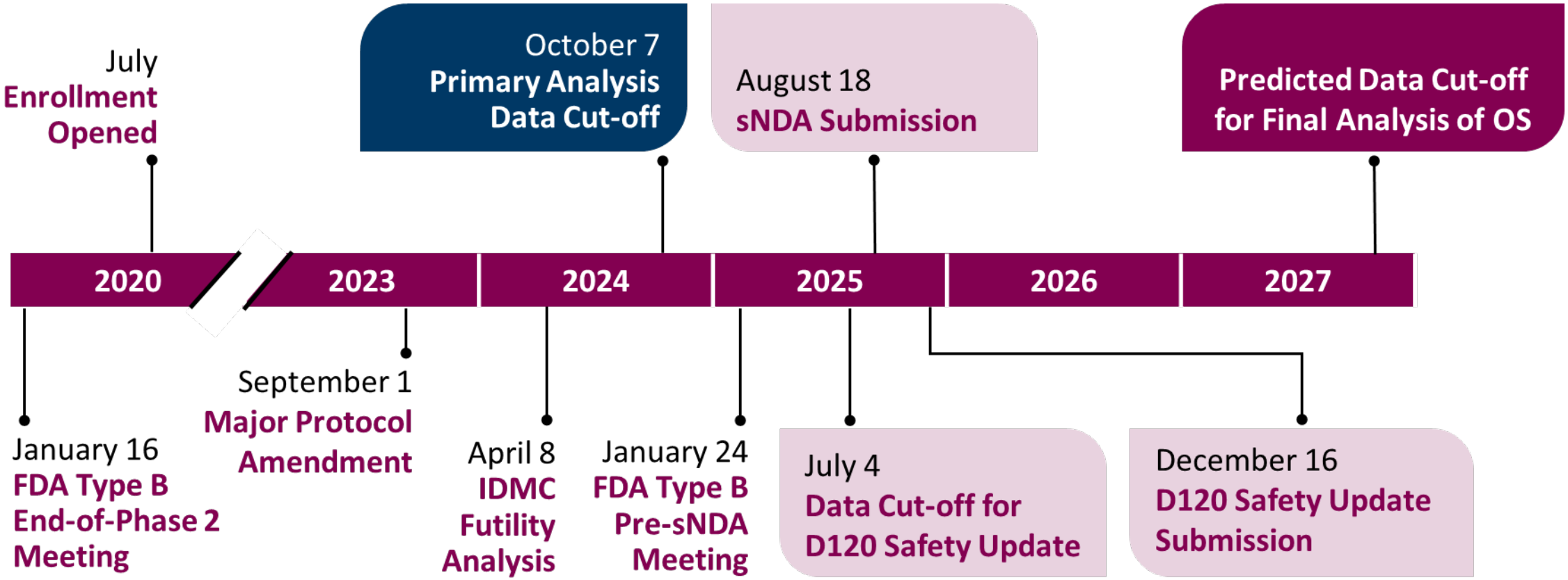
3. Selection of abiraterone as ARPI combination partner

- One of the two most common therapies in mHSPC available in 2019
- Enzalutamide has negative impact on capivasertib PK

abi=abiraterone; ARPI=androgen receptor pathway inhibitors; CI=confidence interval; HR=hazard ratio; IHC=immunohistochemistry; ipa=ipatasertib; mCRPC=metastatic castration-resistant prostate cancer; rPFS=radiographic progression-free survival.

1. de Bono JS, et al. *Clin Cancer Res*. 2019;25(3).

CAPItello-281 Key Regulatory Milestones



IDMC=independent data monitoring committee; OS=overall survival; sNDA=supplemental new drug application.

Proposed Indication

Capivasertib in combination with abiraterone is indicated for treatment of adult patients with metastatic hormone-sensitive prostate cancer that is PTEN-deficient as detected by an FDA-approved test.

PTEN, phosphatase and tensin homolog.
Companion diagnostic: VENTANA PTEN (SP218) RxDx IHC assay

CAPItello-281 Demonstrates a Positive Risk-Benefit Profile

Primary Endpoint Met

- Radiographic progression-free survival (rPFS) (HR=0.81; 95% CI: 0.66, 0.98)
- 7.5-month improvement in median rPFS

Clinically Impactful Benefits in Secondary / Exploratory Endpoints

- Reduced/delayed symptomatic skeletal events
- Delayed time to chemotherapy
- Delayed time to castration resistance

Manageable Toxicity Profile

- AEs were predictable and manageable with established mitigation strategies
- Exposure to abiraterone was not compromised by addition of capivasertib
- No detriment to interim overall survival
- Impact on patient reported symptoms
- Limited effect on functional wellbeing; majority of patients report either no or low bother from side effects

Presenters

Disease Background & Unmet Need

Elisabeth I. Heath, MD, FACP
Chair, Department of Oncology/Professor of Oncology
Mayo Clinic

CAPItello-281 Clinical Efficacy

Gaia Schiavon, MD, PhD
Global Clinical Head – Capivasertib
AstraZeneca

CAPItello-281 Clinical Safety & PROs

Mayur Patel, PharmD
VP, Patient Safety, Oncology
AstraZeneca

Benefit:Risk & Clinical Perspective

Daniel J. George, MD
Professor of Medicine, Surgery and Urology
Duke University School of Medicine

Additional Expert Responders

Tamara L. Lotan, MD
Professor of Pathology, Oncology and Urology
The Johns Hopkins University School of Medicine

Niara B. Oliveira, MD, FRACP
Staff Specialist, Medical Oncologist
Mater Hospital Brisbane

Hope S. Rugo MD, FASCO
Director, Women's Cancers Program; Division Chief, Breast Medical Oncology
City of Hope

Disease Background & Unmet Need

Elisabeth I. Heath, MD, FACP
Chair, Department of Oncology

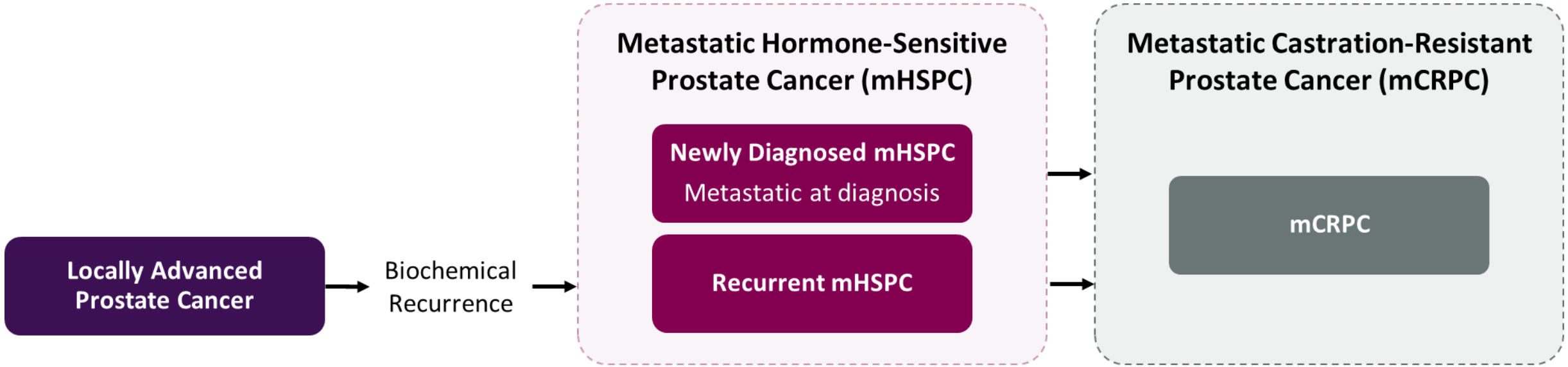
Professor of Oncology
Mayo Clinic
Rochester, Minnesota

Prostate Cancer Across the Clinical Disease Spectrum

PROSTATE CANCER

Prostate cancer significantly impacts **millions of men worldwide**

~313,000 new patients in the US in 2025[1]



1. NIH, NCI, SEER. Cancer Stat Facts: Prostate Cancer. Accessed January 20, 2026. https://seer.cancer.gov/statfacts/html/prost.html.

Current Treatment Landscape in mHSPC

Standard-of-Care Treatment

Doublet therapy with ADT + ARPI[a]

ARPIs include abiraterone, darolutamide, enzalutamide, and apalutamide

Triplet therapy with ADT + ARPI + docetaxel

Appropriate only for certain patients[1]

Treatment Decision Factors

Guided by disease burden and risk

- Visceral metastasis
- Number of bone metastasis
- Gleason Score

Monitoring

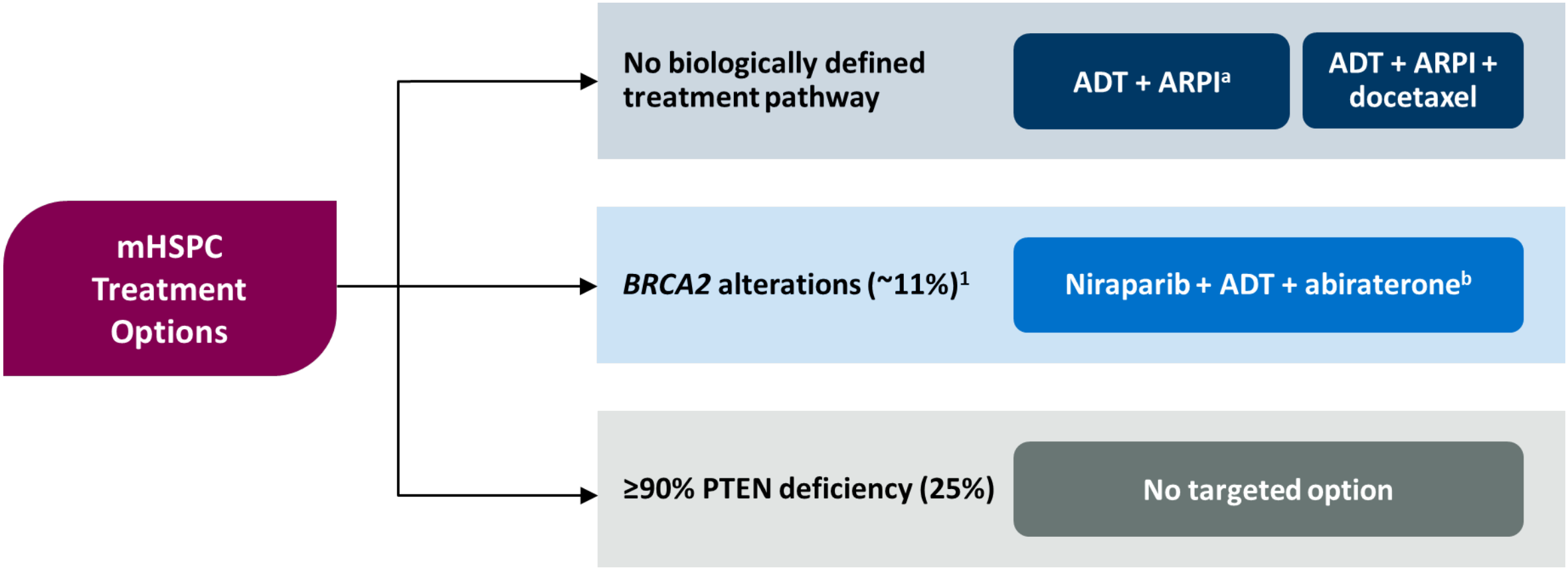
- Clinical Symptoms
- Prostate-Specific Antigen (PSA)

ADT=androgen deprivation therapy; ARPI=androgen receptor pathway inhibitor.

a. ARPIs include: abiraterone, darolutamide, enzalutamide, and apalutamide.

1. National Comprehensive Cancer Network® (NCCN®). NCCN Clinical Practice Guidelines in Oncology—Prostate Cancer. Version 5.2026; January 23, 2026. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

Evolving Treatment Paradigm Moving Toward Biologically Defined Subpopulations

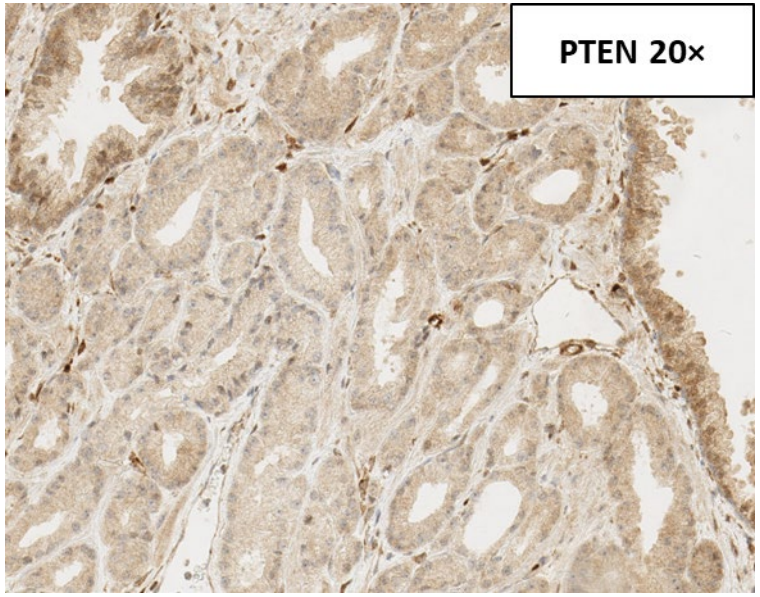


a. ARPIs include: abiraterone, darolutamide, enzalutamide, and apalutamide; b. For *BRCA2*-mutated tumors.
ADT=androgen deprivation therapy; ARPI=androgen receptor pathway inhibitor; BRCA2=breast cancer gene 2; mHSPC=metastatic hormone-sensitive prostate cancer; PTEN=phosphatase and tensin homolog.
1. Olmos D, et al. *Ann Oncol*. 2025;36(10):1190-1202

Detecting PTEN Deficiency in Clinical Practice: Role of Immunohistochemistry (IHC)

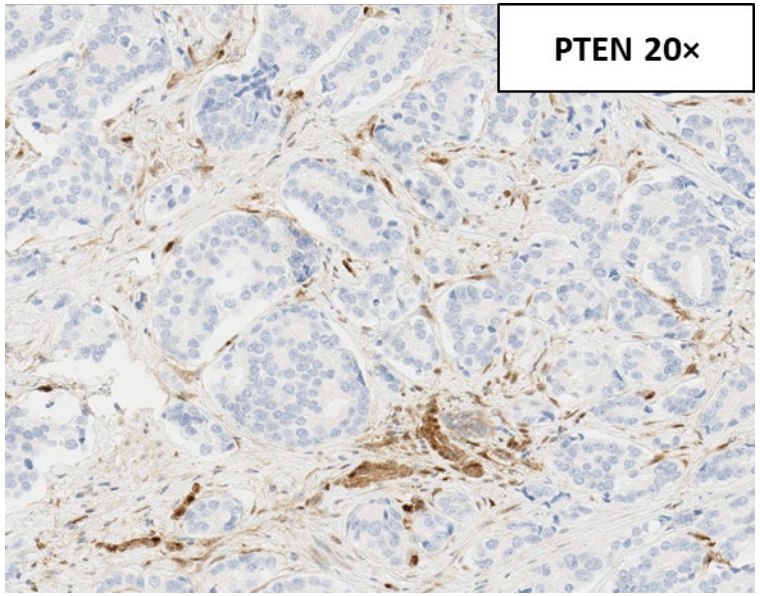
PTEN-Proficient

(>10% of viable malignant cells with any cytoplasmic staining)

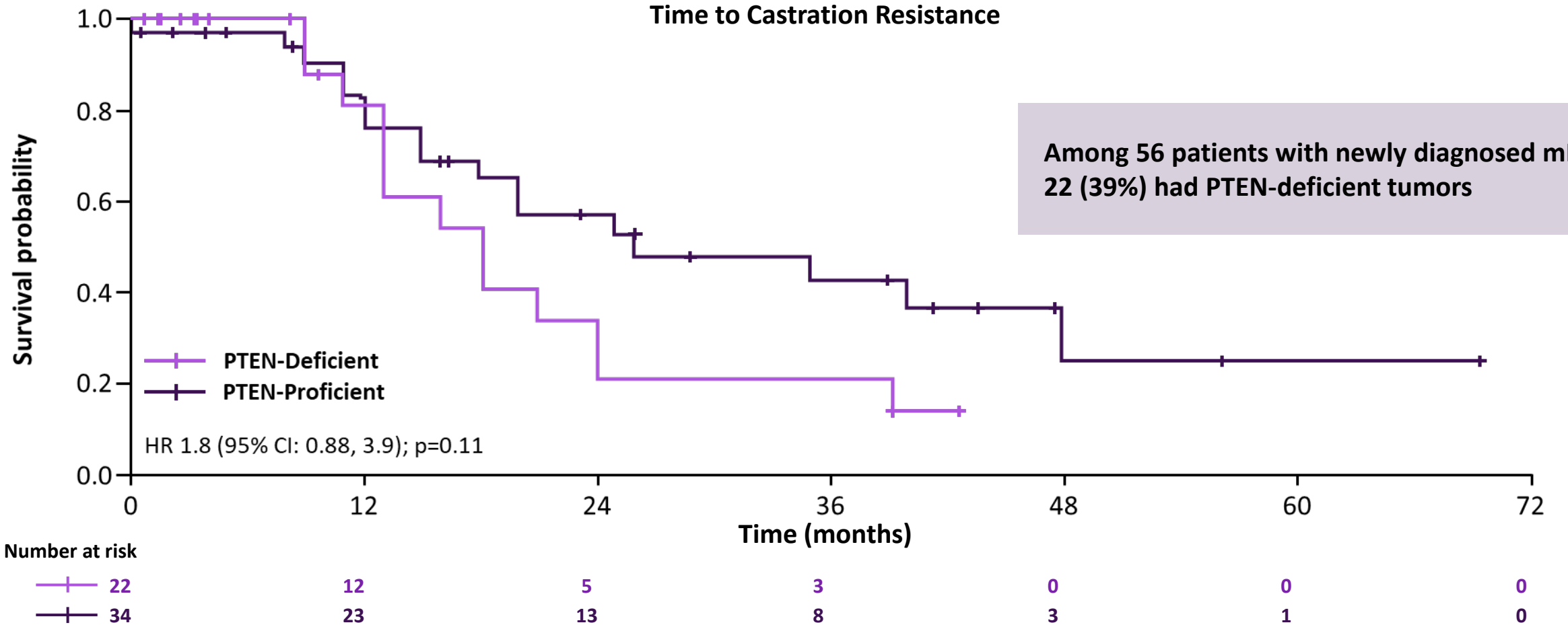


PTEN-Deficient

(≥90% of viable malignant cells with no cytoplasmic staining)



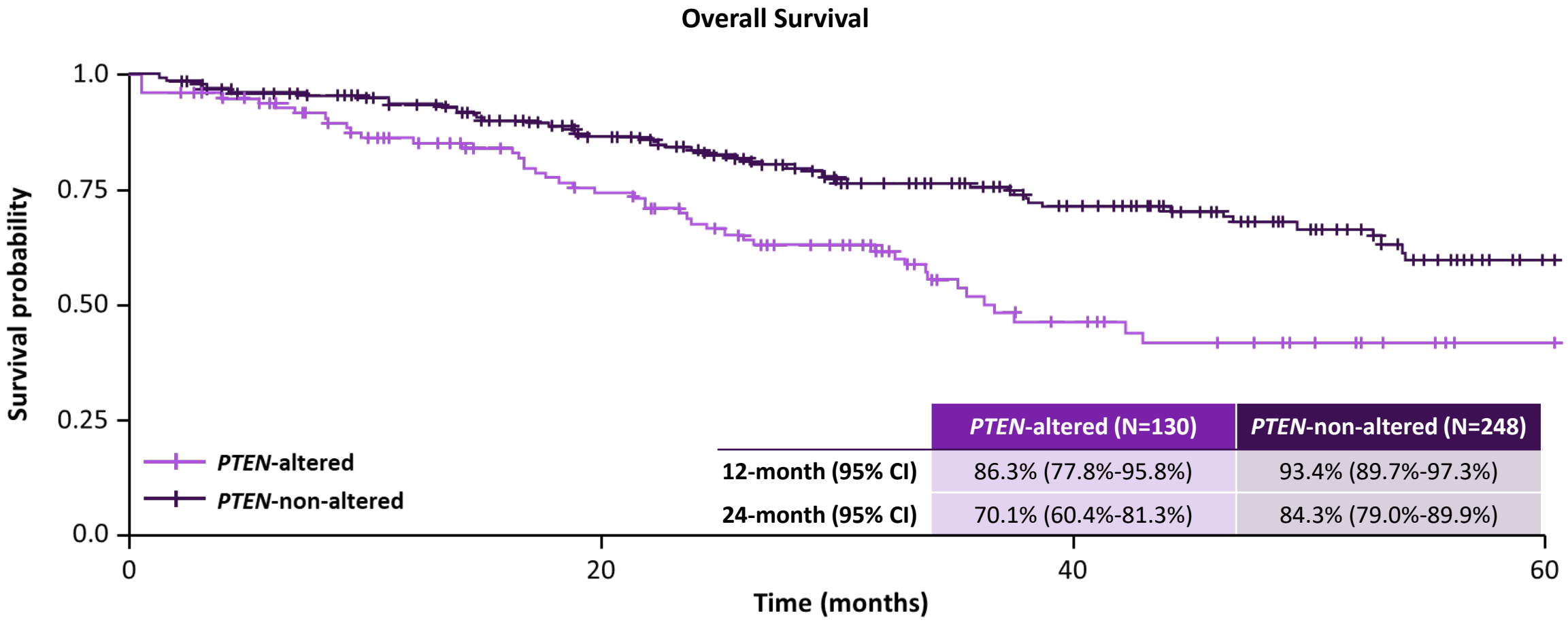
PTEN Deficiency in mHSPC Is Associated With Shorter Time to Castration Resistance in Real-World Patients



Among 56 patients with newly diagnosed mHSPC, 22 (39%) had PTEN-deficient tumors

PTEN expression was assessed by IHC in primary tumor biopsy; loss was defined as absence or weak intensity staining in > 10% of cells.

PTEN Deficiency in mHSPC Is Associated With Reduced Real-World Overall Survival in Patients Who Received ARPI



	PTEN-altered (N=130)	*PTEN*-non-altered (N=248)
12-month (95% CI)	86.3% (77.8%-95.8%)	93.4% (89.7%-97.3%)
24-month (95% CI)	70.1% (60.4%-81.3%)	84.3% (79.0%-89.9%)

ARPIs include: abiraterone, darolutamide, enzalutamide, and apalutamide.
PTEN-altered group included patients with a tumor harboring a homozygous deletion (copy number variant = 0) or mutation (known or likely pathogenic short variant alterations or rearrangements).
Reproduced with permission from Rathkopf et al. Poster presented at the 2025 ASCO congress; May 30-June 3, 2025; Chicago, IL. Abstract 5096.

Significant Unmet Need for PTEN-Deficient mHSPC

Worse Prognosis	Critical Oncogenic Driver	Identifiable and Actionable	Opportunity
Faster disease progression Shorter survival SoC therapies are inadequate	Activation of the PI3K/AKT pathway accelerates progression	Biologically-defined population	AKT inhibition improves outcomes

AstraZeneca

CAPItello-281 Clinical Efficacy

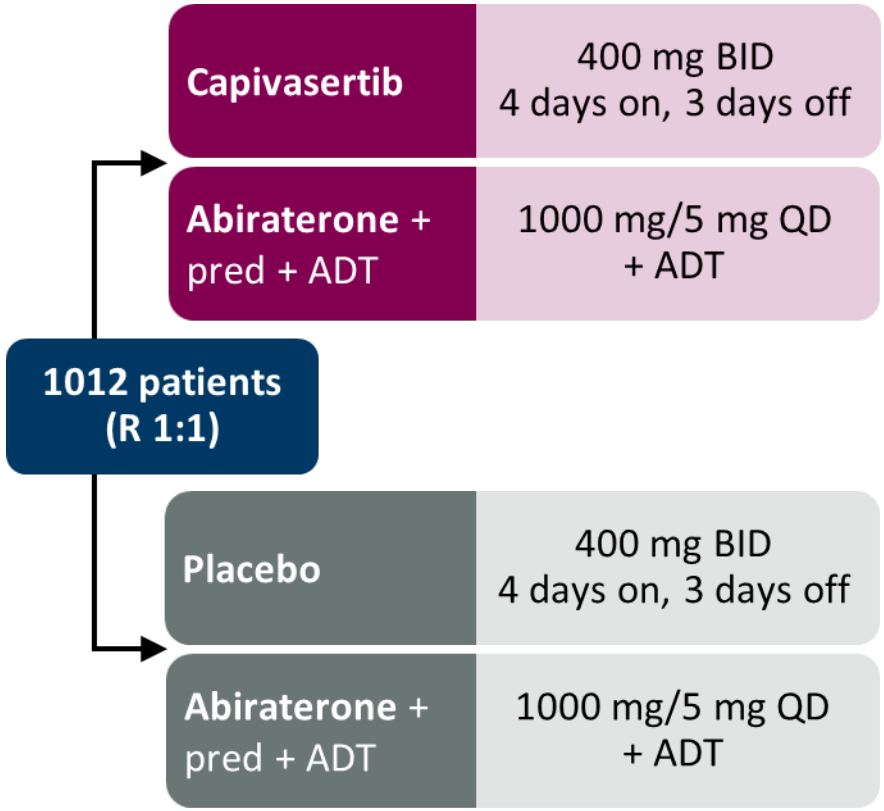
Gaia Schiavon, MD, PhD

Global Clinical Head - Capivasertib
AstraZeneca

CAPItello-281 Is the First Pivotal Phase 3 Study in Patients With PTEN-Deficient mHSPC

Population

- Newly diagnosed (within 6 months) PTEN-deficient mHSPC
- Prior ADT ± abiraterone up to 3 months
- All patients receiving ADT and background prednisone/prednisolone
- High-risk and low-risk disease allowed
- Type 1 diabetes mellitus, type 2 requiring insulin treatment, HbA1c ≥8% excluded



Endpoints

Primary endpoint

- Investigator-assessed rPFS[a]

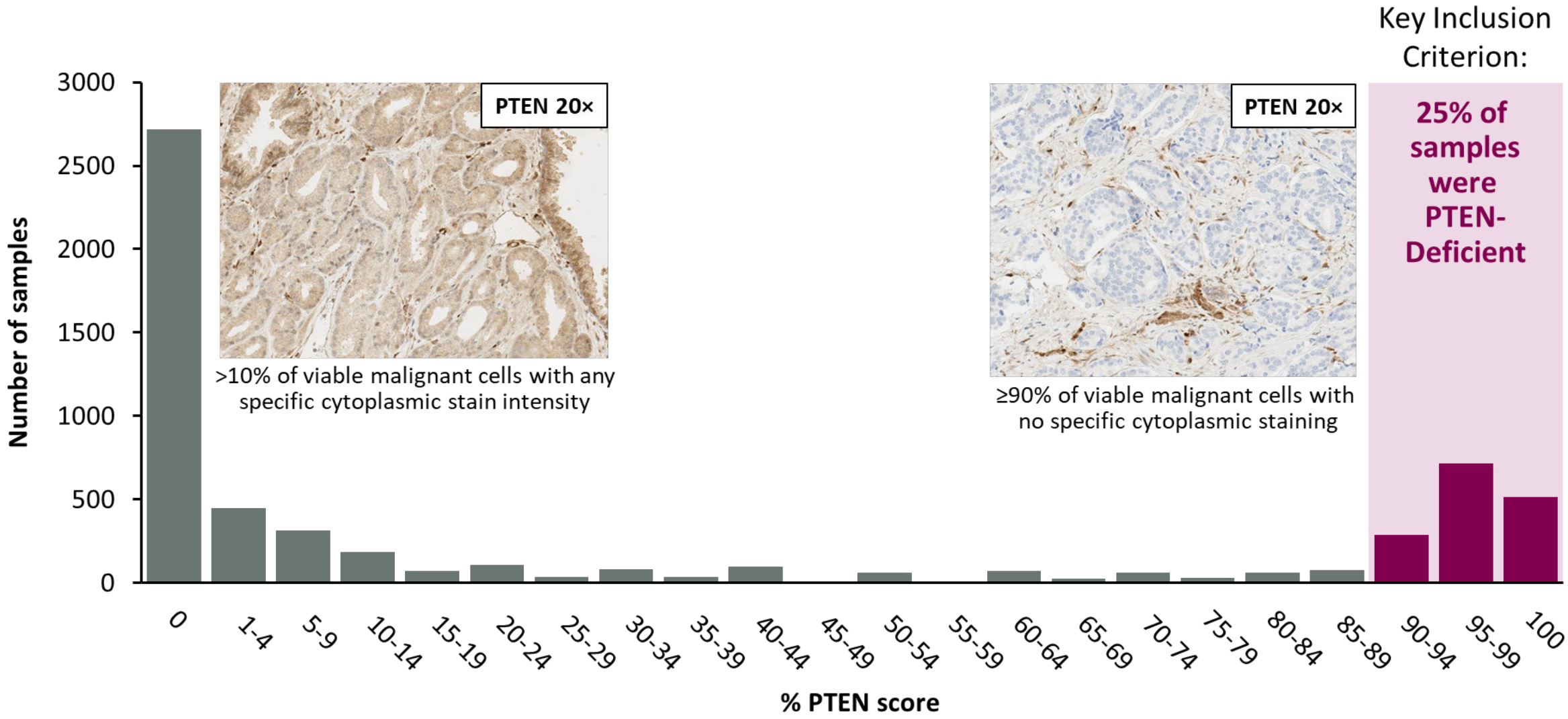
Secondary & exploratory endpoints include

- Overall survival
- Symptomatic skeletal event-free survival
- Castration resistance
- PSA progression
- Time to chemotherapy
- Safety, tolerability, QoL

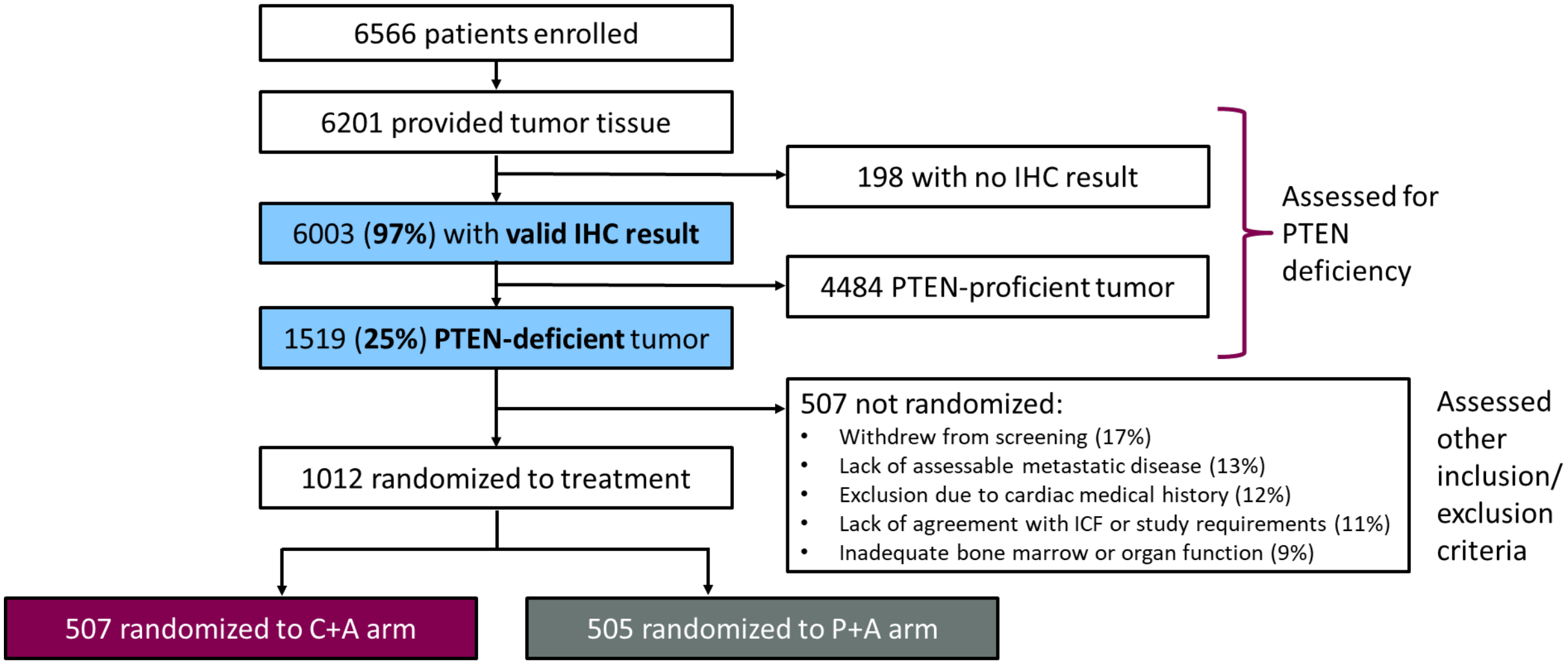
a. Determined by RECIST and PCWG3 or early death.

ADT=androgen deprivation therapy; BID=twice daily; mHSPC=metastatic hormone-sensitive prostate cancer; pred=prednisone/prednisolone; QD=once daily; rPFS=radiographic progression-free survival.

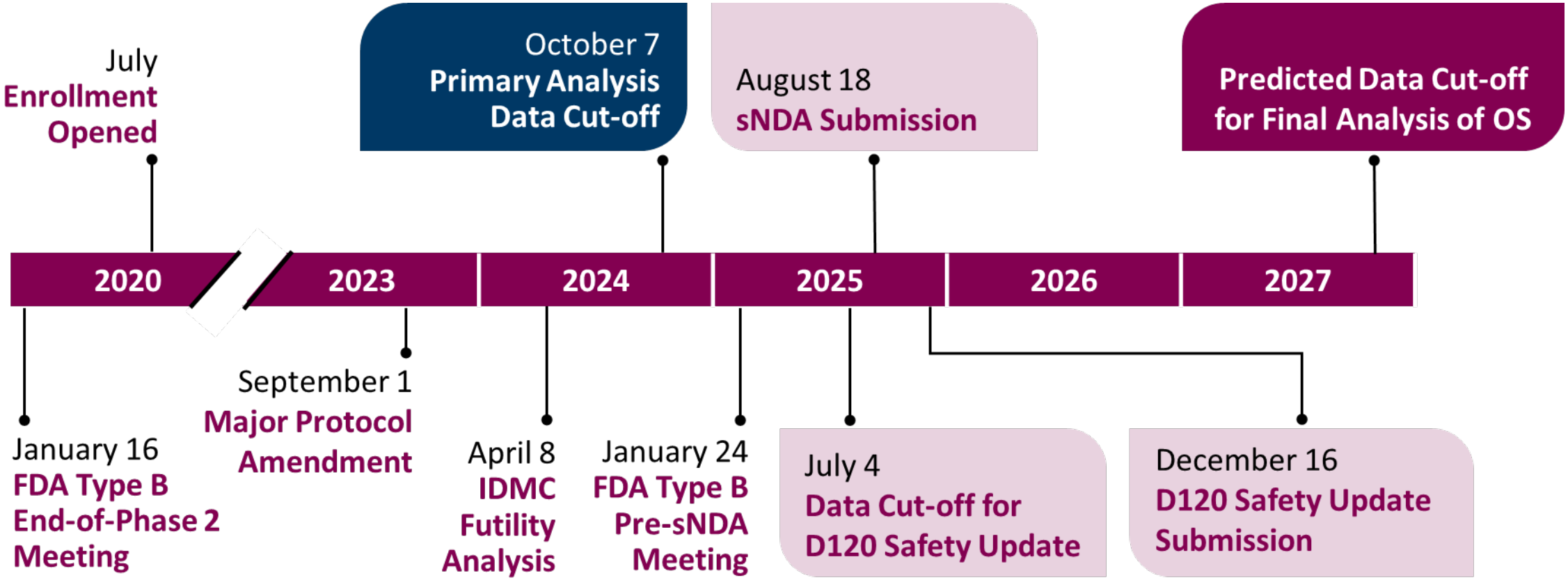
PTEN-Deficiency Prospectively Tested by Immunohistochemistry (IHC)



IHC Testing Had a 97% Success Rate

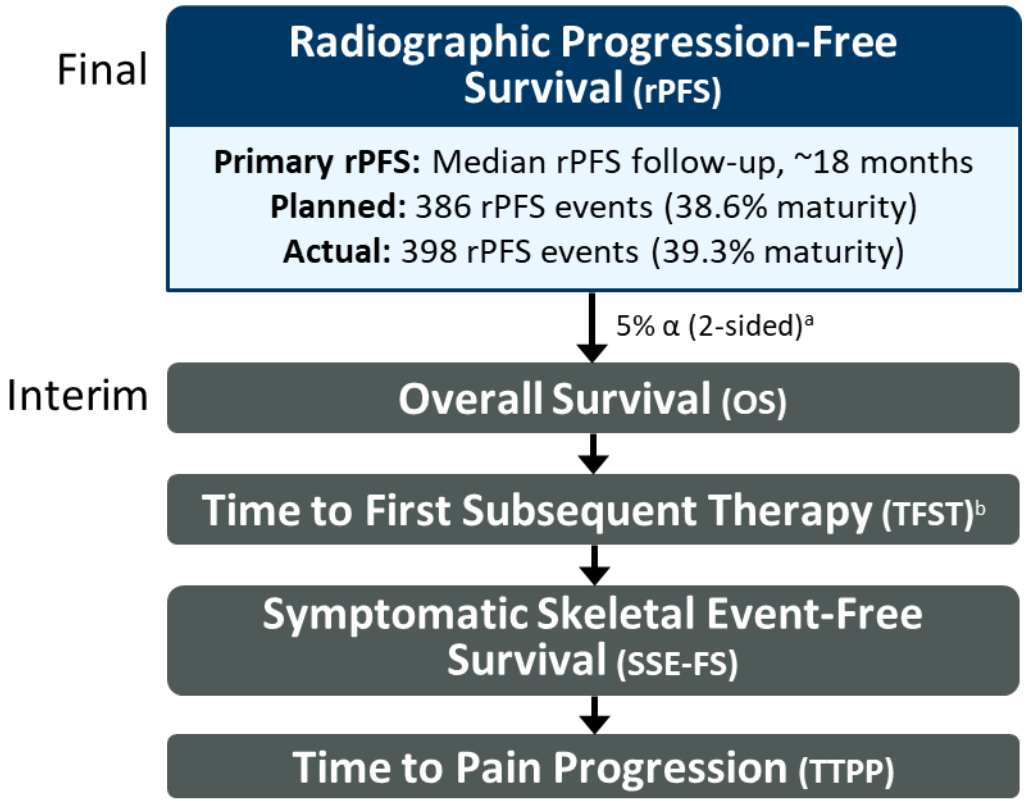


CAPItello-281 Study Timeline



IDMC=independent data monitoring committee; OS=overall survival; sNDA=supplemental new drug application.

Multiple Testing Procedure



a. Alpha spending functions were planned for each key secondary endpoint with an interim analysis (OS, SSE-FS and TTPP) in order to preserve the overall type-1-error (familywise error rate) at 5% in the strong sense.
b. TFST was to be analyzed only once at the Primary analysis and therefore no alpha spending function was required.

Patient Demographics & Characteristics Broadly Balanced

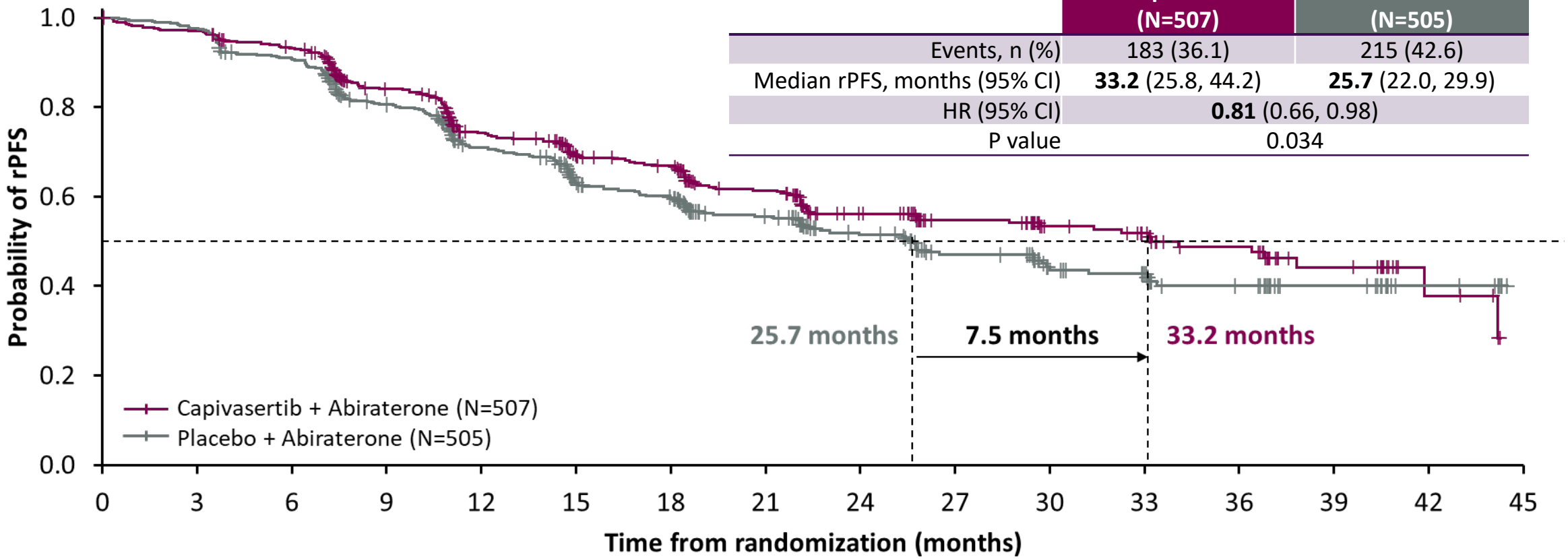
Full Analysis Set (FAS)

		Capivasertib + Abiraterone (N=507)	Placebo + Abiraterone (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,[a] n (%)	High	311 (61.3)	333 (65.9)
	Low	184 (36.3)	164 (32.5)
M1 volume/visceral metastases, n (%)	High-volume[b] disease with visceral mets	98 (19.3)	95 (18.8)
	High-volume disease without visceral mets	276 (54.4)	283 (56.0)
	Low-volume disease	131 (25.8)	126 (25.0)

a. High-risk disease is defined as having any 2 of the following: 4 or more bone metastases on bone scan, Gleason sum ≥8, any visceral metastases.
b. High-volume disease is defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis (CHAARTED criteria).

Primary Endpoint: Significant Improvement in 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	



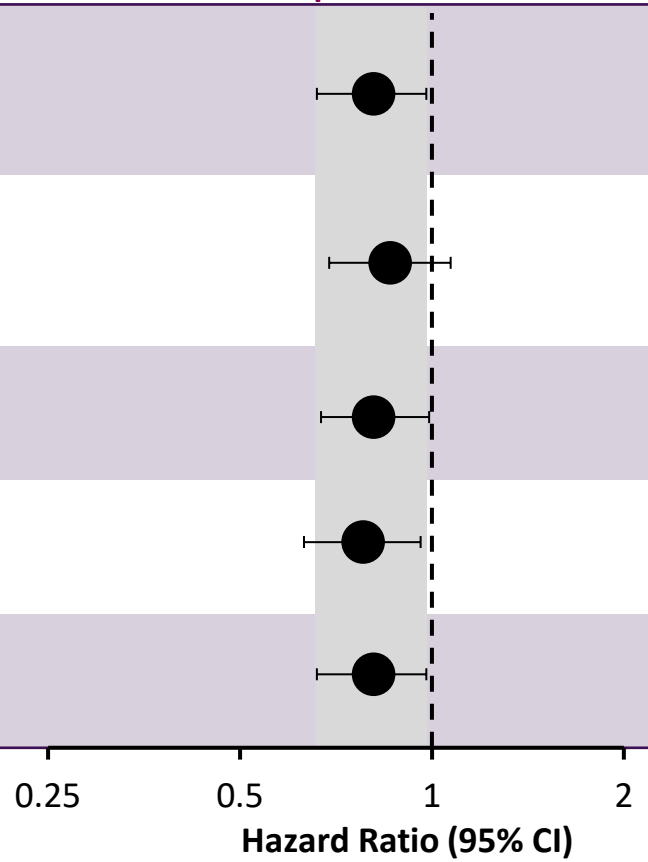
Number of patients at risk

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 2-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model.
Median rPFS follow-up in censored patients: 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.

Prespecified rPFS Sensitivity Analyses

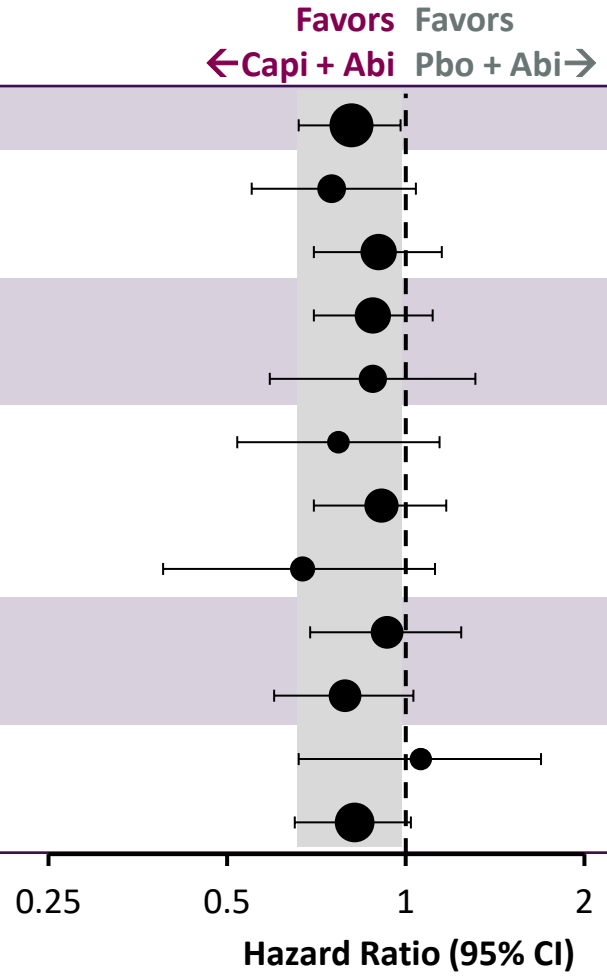
	Treatment	N	Events (%)	Median (95% CI), months	HR (95% CI)
rPFS by Investigator assessment (Primary Endpoint)	Capi + abi	507	183 (36.1)	33.2 (25.8, 44.2)	0.81 (0.66, 0.98)
	Pbo + abi	505	215 (42.6)	25.7 (22.0, 29.9)	
Blinded independent central review (BICR)	Capi + abi	507	149 (29.4)	37.8 (29.5, NC)	0.86 (0.69, 1.07)
	Pbo + abi	505	168 (33.3)	29.8 (22.7, NC)	
Evaluation-time bias[a]	Capi + abi	507	183 (36.1)	35.0 (27.1, NC)	0.81 (0.67, 0.99)
	Pbo + abi	505	215 (42.6)	24.0 (20.5, 31.2)	
Attrition bias[b]	Capi + abi	507	164 (32.3)	36.4 (29.7, 44.2)	0.78 (0.63, 0.96)
	Pbo + abi	505	202 (40.0)	25.8 (22.1, 33.1)	
Censoring COVID-19 deaths[c]	Capi + abi	507	182 (35.9)	34.1 (25.8, 44.2)	0.81 (0.66, 0.98)
	Pbo + abi	505	214 (42.4)	25.7 (22.0, 30.0)	



a. Analysis was performed using mid-point between time of progression and previous evaluable assessment (RECIST v1.1 or PCWG3). For patients whose death was used as the rPFS event, the date of death was used.
b. Patients who took subsequent therapy prior to progression or death were censored at their last evaluable assessment prior to taking subsequent therapy. In addition, analysis was performed using the actual rPFS event times, rather than the censored times, for patients who progressed or died following 2 or more missed visits.
c. Patients with confirmed/suspected COVID-19 deaths were censored at their last evaluable assessment prior to death.

Investigator-Assessed rPFS: Treatment Effect Consistent Across Prespecified Subgroups

		Events/Patients, n/N (%)		
		Capi + Abi	Pbo + Abi	HR (95% CI)
All randomized 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[a]	≤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)

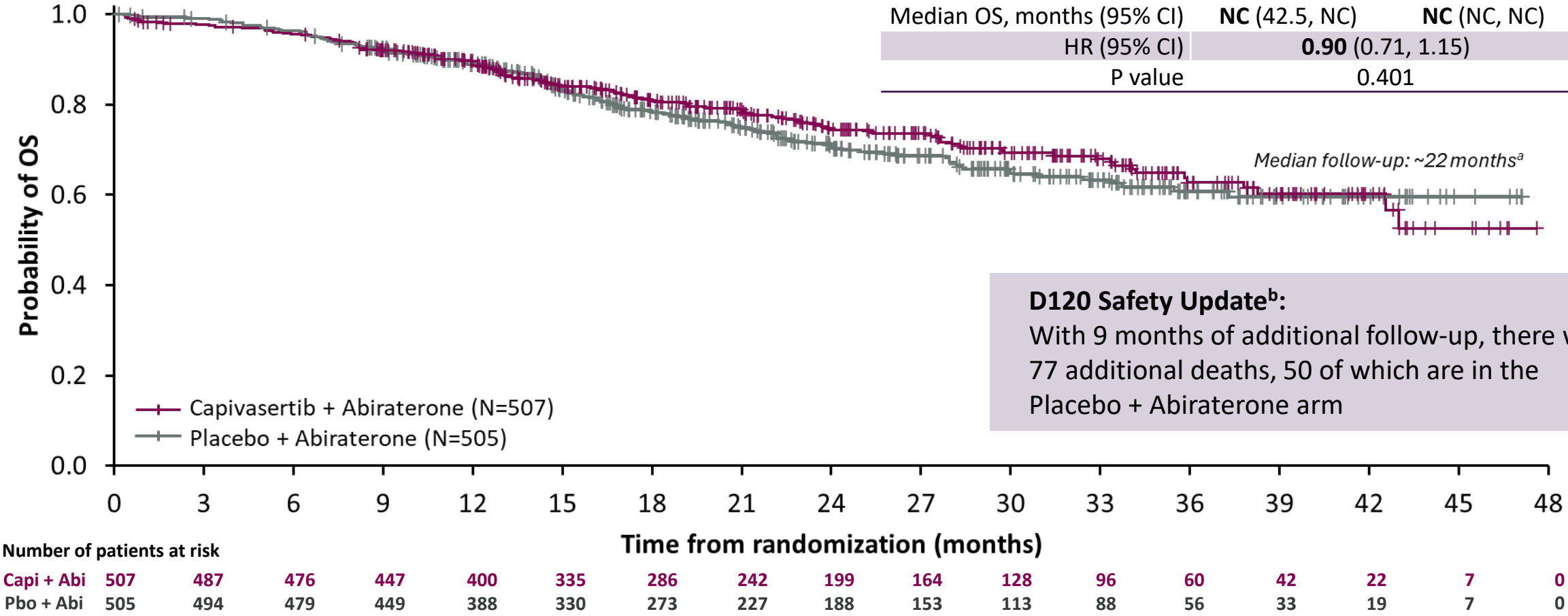


a. Baseline PSA may have been impacted by earlier initiation of ADT.

abi=abiraterone; capi=capivasertib; CI=confidence interval; HR=hazard ratio; pbo=placebo; PSA=prostate-specific antigen.

Key Secondary Endpoint: Interim Overall Survival

	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

D120 Safety Update[b]:
With 9 months of additional follow-up, there were 77 additional deaths, 50 of which are in the Placebo + Abiraterone arm

OS analysis was conducted at 26% maturity, and further follow-up is planned; final OS is expected ~Q4 2027

A stratified log-rank test was used to calculate 2-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model.
a. Median follow-up in censored patients: 22.9 months (Capi + abi) vs 22.3 months (Pbo + abi). b. Data cutoff July 2025. Efficacy endpoints were not analyzed with this update.
CI=confidence interval; HR=hazard ratio; NC=not calculable; OS=overall survival; pbo=placebo.

Endpoints Most Impactful in Clinical Practice

Radiographic Progression-Free Survival (rPFS)

Time to
- Radiographic progression, as assessed by the investigator per RECIST v1.1 (soft tissue) and/or PCWG3 criteria (bone)
- Death due to any cause

Overall Survival (OS)

Time to death due to any cause, regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy

Symptomatic Skeletal Event-Free Survival (SSE-FS)

Time to
- Use of radiation therapy to prevent or relieve skeletal symptoms
- New symptomatic bone fracture
- Spinal cord compression
- Surgical intervention for bone metastasis
- Death due to any cause

Time to Castration Resistance (TTCR)

Time to
- Radiographic progression, including death
- PSA progression[a]
- Skeletal event

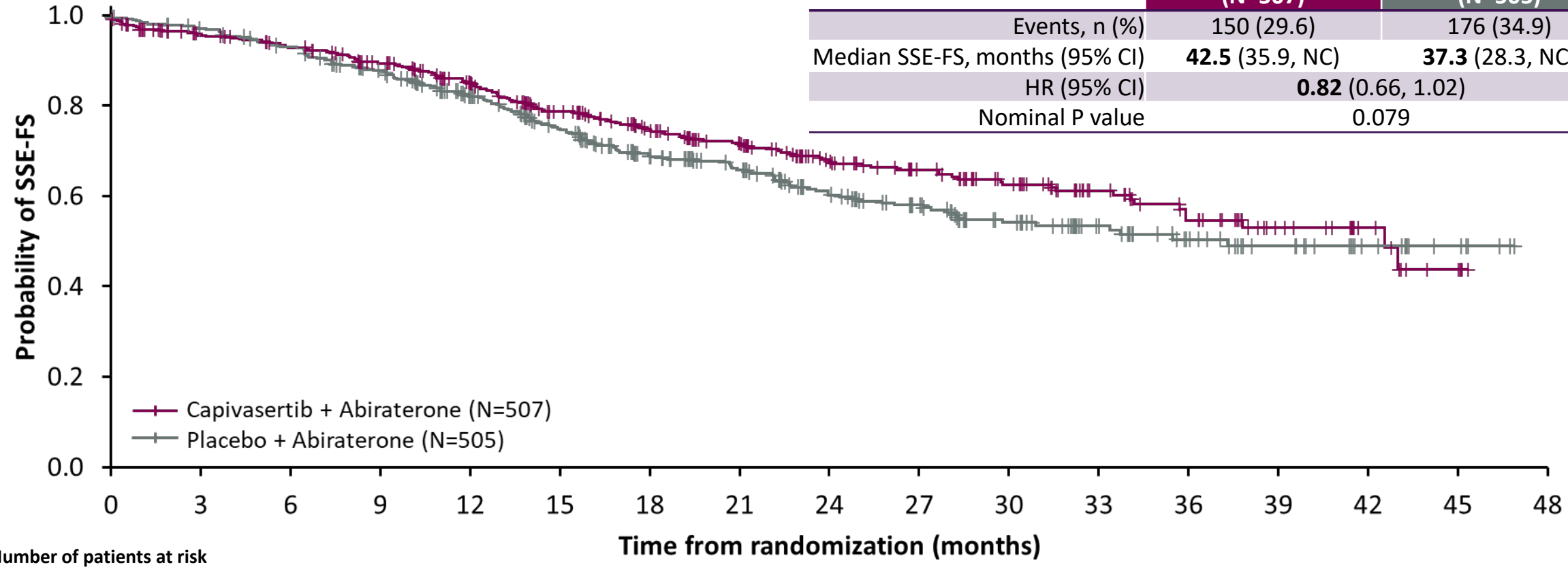
Time to First Subsequent Chemotherapy (TFSC)

Time to
- Start date of subsequent chemotherapy
- Death due to any cause

a. PSA progression by PCWG3 criteria: at least a 25% increase and an absolute value above 2 ng/mL, confirmation required.

Symptomatic Skeletal Event (SSE)-Free Survival: Fewer and Delayed Events With Capivasertib

	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	



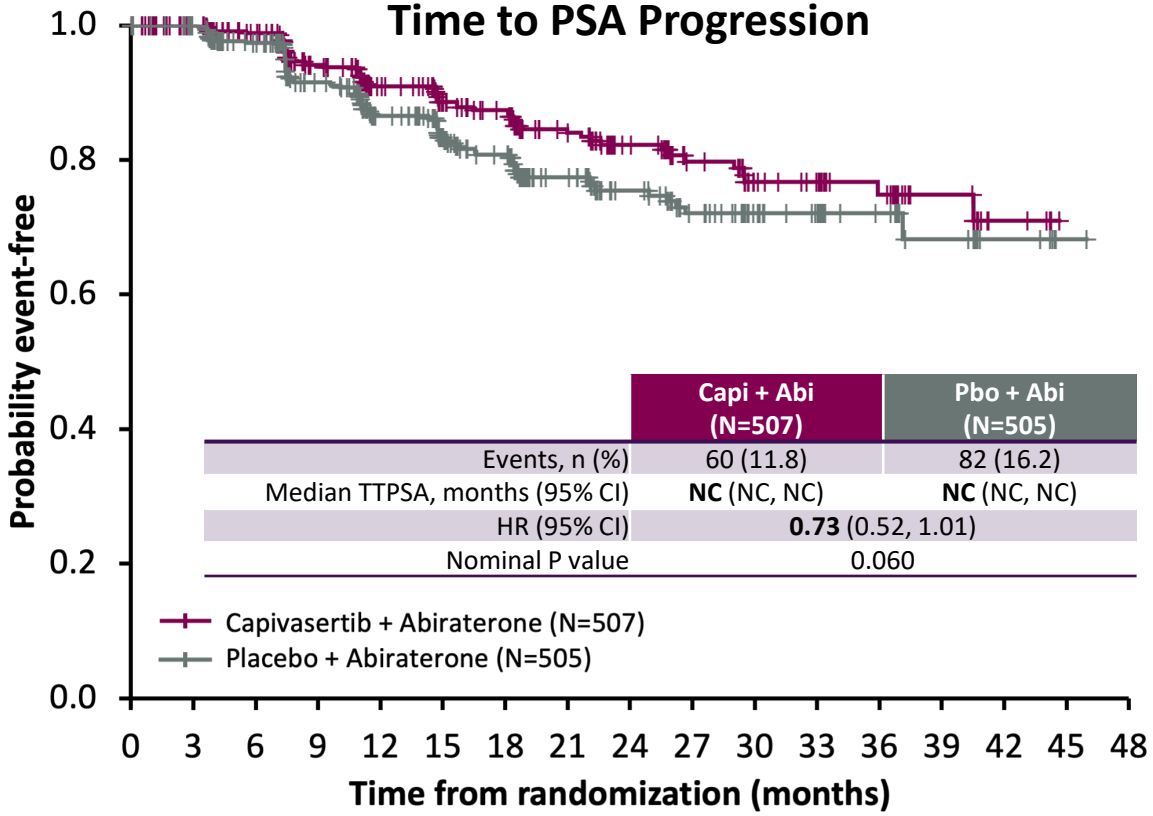
Number of patients at risk

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

A stratified log-rank test was used to calculate 2-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; pbo=placebo; SSE-FS=symptomatic skeletal event-free survival.

Time to Castration Resistance and PSA Progression Is Prolonged With Capivasertib

Time to PSA Progression

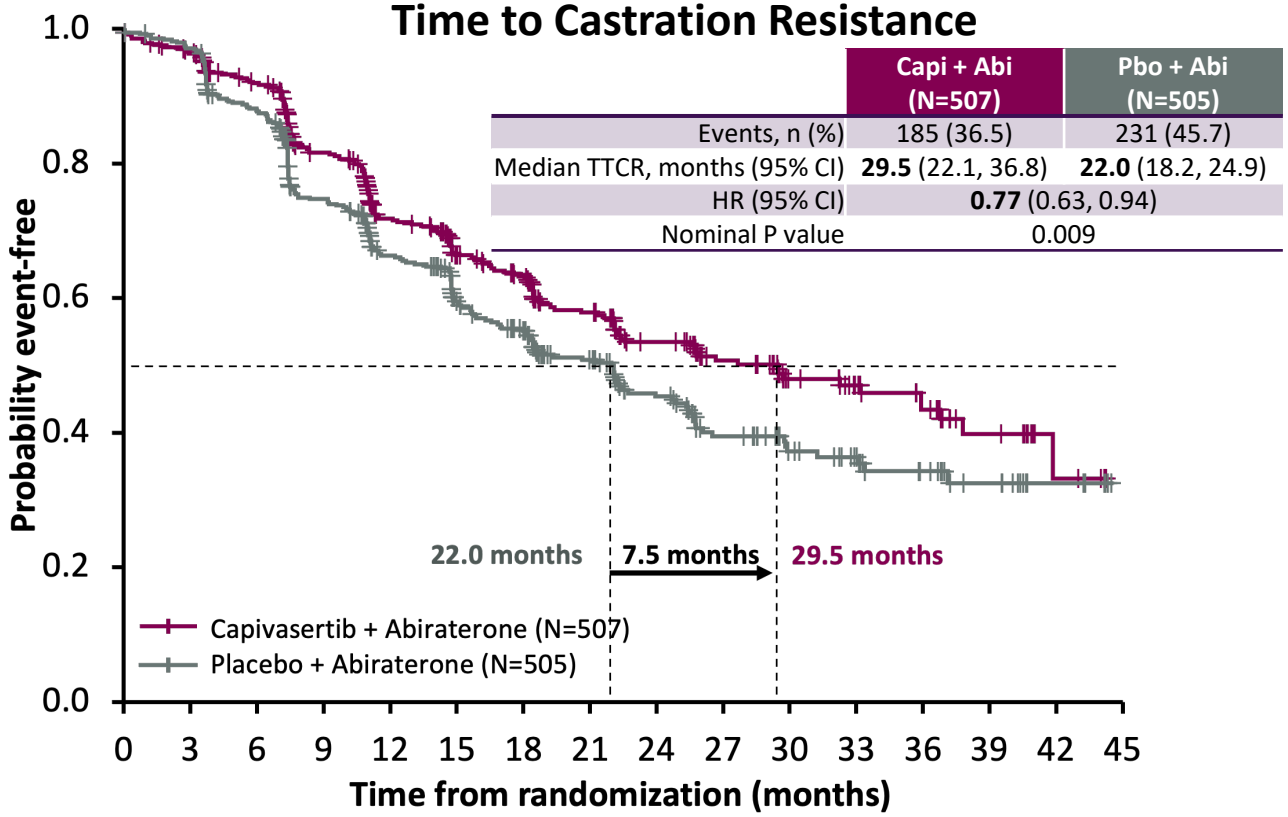


	Capi + Abi (N=507)	Pbo + Abi (N=505)
Events, n (%)	60 (11.8)	82 (16.2)
Median TTPSA, months (95% CI)	**NC** (NC, NC)	**NC** (NC, NC)
HR (95% CI)	**0.73** (0.52, 1.01)	
Nominal P value	0.060	

Number of patients at risk

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

Time to Castration Resistance



	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

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

71% of patients who progressed to castration resistance did so in the absence of, or prior to, biochemical progression

A stratified log-rank test was used to calculate 2-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; pbo=placebo; PSA=prostate-specific antigen; TTCR=time to castration resistance; TTPSA=time to PSA progression.

Treatment With Capivasertib Does Not Limit Ability to Receive Subsequent Therapy

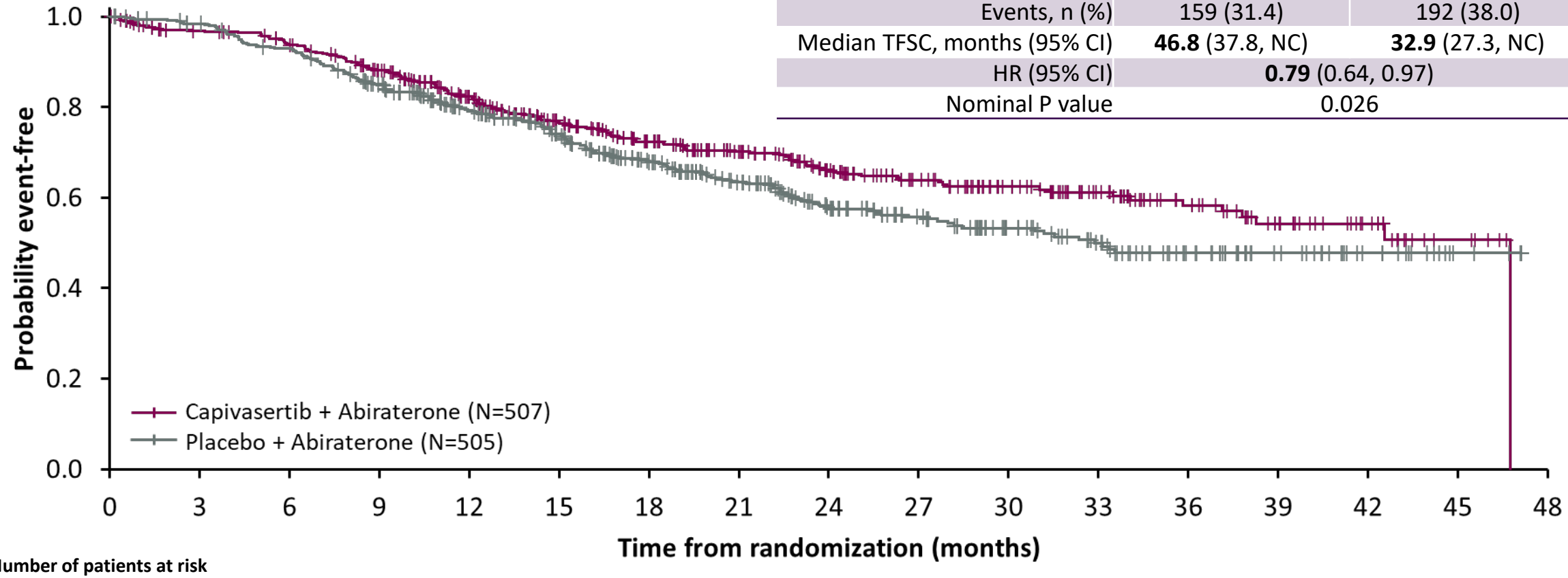
	Capivasertib + Abiraterone (N=507) n (%)	Placebo + Abiraterone (N=505) n (%)
Patients with any post-discontinuation anticancer therapy	131 (25.8)	151 (29.9)
Anticancer therapy[a]	**(N=131) n (%)**	**(N=151) n (%)**
Cytotoxic chemotherapy	87 (66.4)	121 (80.1)
ARPIs	53 (40.5)	34 (22.5)
Immunotherapy	6 (4.6)	2 (1.3)
Radiopharmaceuticals	6 (4.6)	9 (6.0)
Other	6 (4.6)	12 (7.9)
Other hormonal agents	4 (3.1)	6 (4.0)
PARP inhibitors	4 (3.1)	4 (2.6)

Among the patients who received subsequent therapy after study treatment discontinuation due to radiographic disease progression, the use of cytotoxic chemotherapy was balanced between the arms (81% and 82%, respectively)

ARPI=androgen receptor pathway inhibitor; PARP=poly-ADP ribose polymerase; pbo=placebo.
a. % values for types of anticancer therapy are calculated from the number of patients with any subsequent anticancer therapy in each study arm: 131 and 151, respectively.
Patients may be counted in more than one anticancer therapy.

Exploratory Endpoint: Time to First Subsequent Chemotherapy

	Capi + Abi (N=507)	Pbo + Abi (N=505)
Events, n (%)	159 (31.4)	192 (38.0)
Median TFSC, months (95% CI)	**46.8** (37.8, NC)	**32.9** (27.3, NC)
HR (95% CI)	**0.79** (0.64, 0.97)	
Nominal P value	0.026	



Number of patients at risk

Capi + Abi	507	474	454	413	353	295	246	204	166	133	105	79	52	34	20	6	0
Pbo + Abi	505	488	458	408	341	292	235	189	146	118	89	70	47	29	16	4	0

A stratified log-rank test was used to calculate 2-sided P values. HRs and 95% CIs were calculated using a stratified Cox proportional-hazards model.
TFSC=time to first subsequent chemotherapy

Totality of Evidence Across Clinically Relevant Endpoints Demonstrates Meaningful Benefit

Radiographic Progression-free Survival (rPFS)

- 7.5-month improvement in median rPFS
- HR (95% CI): 0.81 (0.66, 0.98)

Overall Survival (OS)

- No evidence of detriment at interim analysis
- HR (95% CI): 0.90 (0.71, 1.15)

Symptomatic Skeletal Event-free Survival (SSE-FS)

- Fewer and delayed symptomatic skeletal events
- HR (95% CI): 0.82 (0.66, 1.02)

Time to Castration Resistance (TTCR)

- Prolonged time to castration resistance
- HR (95% CI): 0.77 (0.63, 0.94)

Time to First Subsequent Chemotherapy (TFSC)

- Delayed need to require chemotherapy
- HR (95% CI): 0.79 (0.64, 0.97)

AstraZeneca

CAPItello-281 Clinical Safety and PROs

Mayur Patel, PharmD

VP, Patient Safety, Oncology
AstraZeneca

Capivasertib and Abiraterone Have Well-Established Safety Profiles

Capivasertib

- **Approved for use in breast cancer[a] (2023)**
  - 3348 patients in the clinical program
  - ~6050 patient-years in marketed use[b]
- **Safety profile includes**
  - Diarrhea
  - Rash including cutaneous reactions
  - Hyperglycemia

Abiraterone

- **Approved in mCRPC (2011) & in mHSPC (2018)**
  - In mHSPC used with prednisone 5 mg and ADT
- **Safety profile includes**
  - Cardiometabolic effects (hypertension, hypokalemia, heart failure, MI, arrhythmia)
  - Infections
  - Hepatotoxicity

a. HR+, HER2-, locally advanced or metastatic with *PIK3CA*/*AKT1*/*PTEN* alterations.
b. PBRER DLP November 15, 2025.

Capivasertib and Abiraterone Exposure Profile

Primary Analysis, Safety Analysis Set (SAS)

	Capivasertib + Abiraterone (N=503)	Placebo + Abiraterone (N=503)
Capivasertib/Placebo		
Actual treatment duration (median)	12.1 months	14.7 months
Relative dose intensity (median)	96.3%	99.9%
Percentage intended dose (median)	87.0%	98.9%
Abiraterone		
Actual treatment duration (median)	14.5 months	14.7 months
Relative dose intensity (median)	99.7%	100%
Percentage intended dose (median)	97.5%	99.3%

The addition of capivasertib did not compromise exposure to abiraterone

Actual treatment duration = total treatment duration minus the total duration of dose interruptions.
Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.
Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to radiological progression.

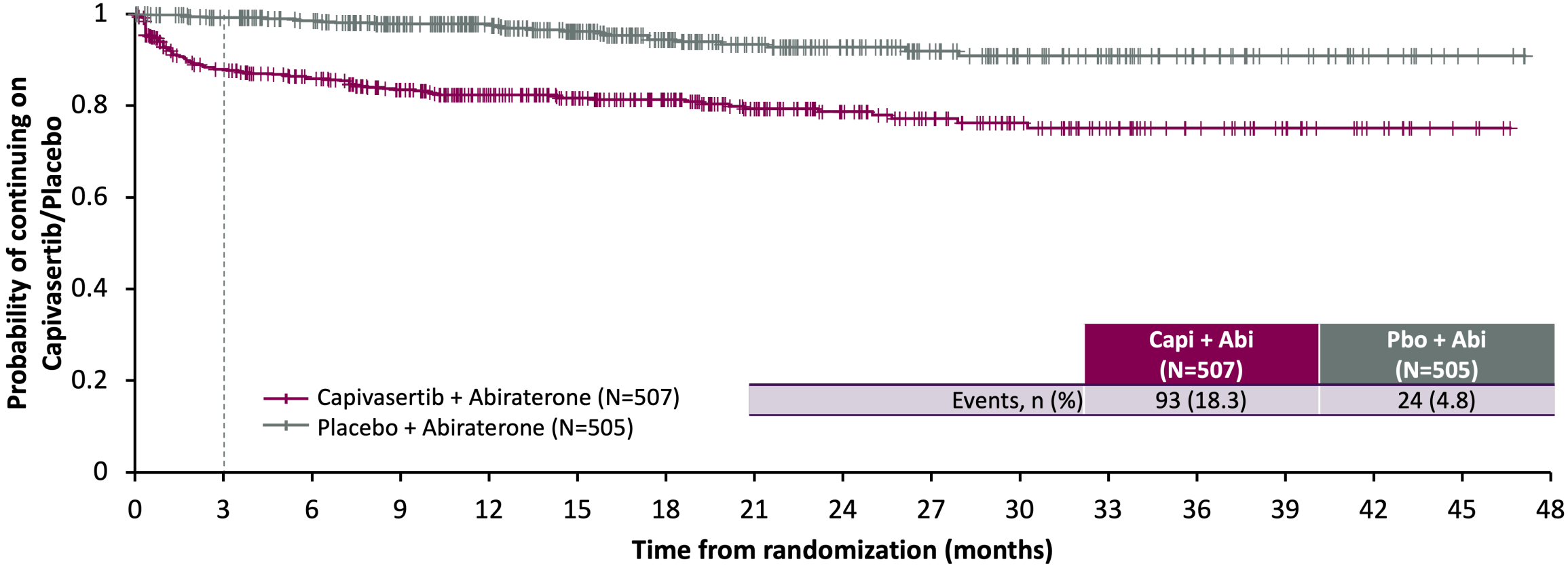
Overview of Safety
Primary Analysis, SAS

	Capivasertib + Abiraterone (N=503) n (%)	Placebo + Abiraterone (N=503) n (%)
Any AE	497 (98.8)	463 (92.0)
Any SAE (including events with outcome of death)	214 (42.5)	131 (26.0)
Any AE with outcome of death[a]	36 (7.2)	26 (5.2)
Any AE of CTCAE Grade 3 or higher	337 (67.0)	203 (40.4)
Any AE leading to dose interruption of Capivasertib/Placebo	316 (62.8)	135 (26.8)
Any AE leading to dose reduction of Capivasertib/Placebo	146 (29.0)	18 (3.6)
Any AE leading to discontinuation of Capivasertib/Placebo	92 (18.3)	24 (4.8)

a. Included deaths where prostate cancer and AEs were contributing factors.

Two-thirds of Capivasertib Discontinuations Due to AEs Are in the First 3 Months

Primary Analysis, SAS



Number of patients at risk

Capi + Abi	507	403	369	321	271	230	191	147	113	91	70	53	35	24	13	4	0
Pbo + Abi	505	473	435	376	309	253	197	158	124	97	72	57	38	25	13	4	0

Patients not known to have discontinued capivasertib/placebo due to AEs are censored at the earliest of the following: death date, end of study date, DCO date, and when discontinuation of capivasertib/placebo was not due to AEs.

Deaths Were Distributed Across System Organ Classes
Primary Analysis

Full analysis set (FAS)	Capivasertib + Abiraterone (N=507) n (%)	Placebo + Abiraterone (N=505) n (%)
Total number of deaths	**129 (25.4)**	**138 (27.3)**
Safety analysis set (SAS)	**(N=503) n (%)**	**(N=503) n (%)**
Patients with any AE with outcome of death[a]	**36 (7.2)**	**26 (5.2)**
Infections and Infestations	11 (2.2)	10 (2.0)
General Disorders and Administration Site Conditions	5 (1.0)	3 (0.6)
Nervous System Disorders	3 (0.6)	1 (0.2)
Cardiac Disorders	3 (0.6)	3 (0.6)
Vascular Disorders	3 (0.6)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	3 (0.6)	0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	2 (0.4)	6 (1.2)
Metabolism and Nutrition Disorders	2 (0.4)	0
Injury, Poisoning and Procedural Complications	2 (0.4)	0
Gastrointestinal Disorders	1 (0.2)	0
Hepatobiliary Disorders	1 (0.2)	0
Renal and Urinary Disorders	1 (0.2)	1 (0.2)
Psychiatric Disorders	0	1 (0.2)

a. AEs with Outcome of death ONLY (capivasertib + abiraterone arm, N=25; placebo + abiraterone arm, N=23), plus Death related to disease under investigation and AE with outcome of death (capivasertib + abiraterone arm, N=11; placebo + abiraterone arm, N=3).

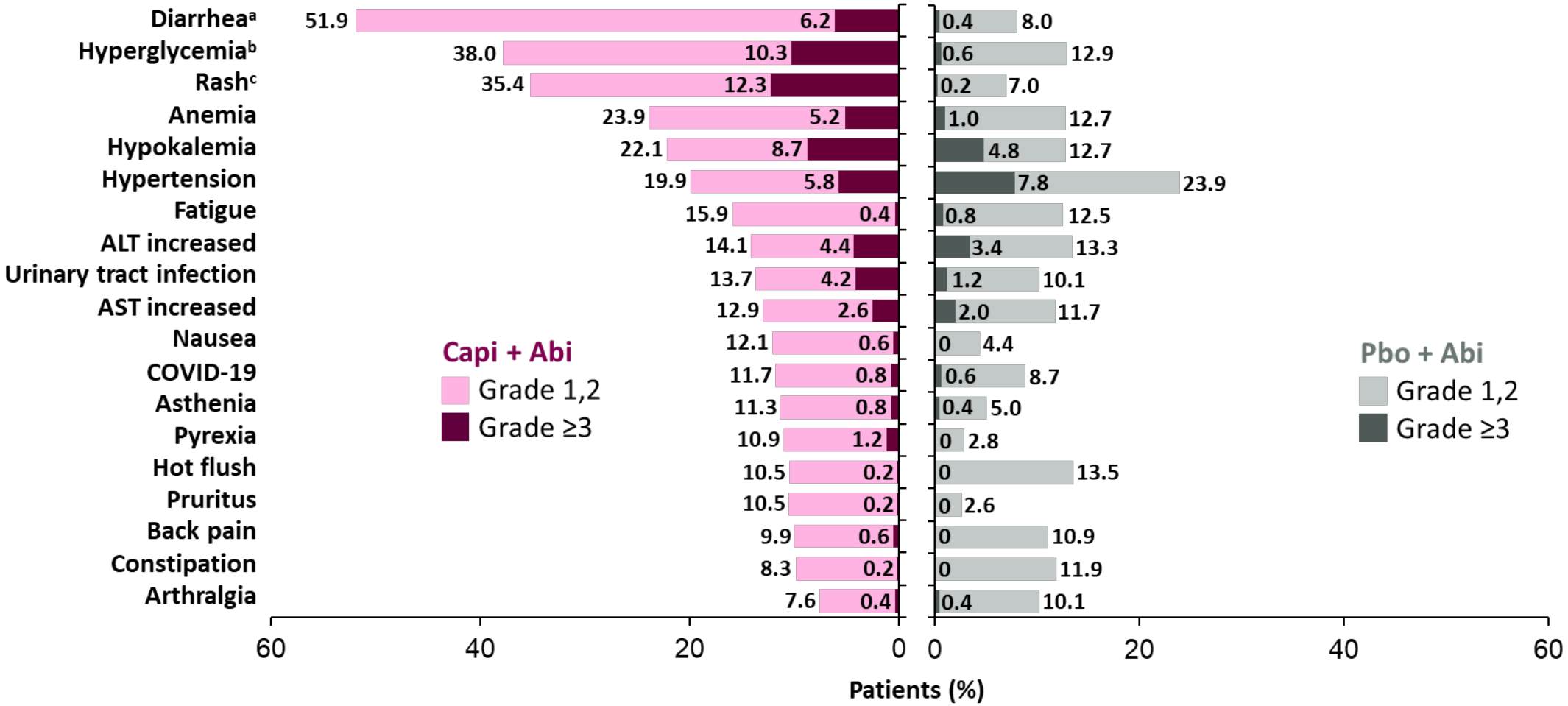
Serious Adverse Events (>1% of Patients)
Primary Analysis, SAS

	Capivasertib + Abiraterone (N=503) n (%)	Placebo + Abiraterone (N=503) n (%)
Any SAE[a]	**214 (42.5)**	**131 (26.0)**
Pneumonia	19 (3.8)	12 (2.4)
Hyperglycemia	18 (3.6)	0
Urinary tract infection	15 (3.0)	4 (0.8)
Rash maculo-papular	12 (2.4)	0
Acute kidney injury	9 (1.8)	5 (1.0)
Hypokalemia	9 (1.8)	2 (0.4)
Urosepsis	9 (1.8)	2 (0.4)
Diabetic ketoacidosis	6 (1.2)	0
Diarrhea	6 (1.2)	1 (0.2)
Pyrexia	6 (1.2)	0

a. PTs listed for events that were reported in >1% of patients in any arm.

Common Adverse Events (≥10% of Patients)

Primary Analysis, SAS



abi=abiraterone; ALT=alanine aminotransferase; AST=aspartate aminotransferase; capi=capivasertib; pbo=placebo.

a. Diarrhea is a medical concept including the following PTs: Diarrhea, Frequent bowel movements, and Gastrointestinal hypermotility.

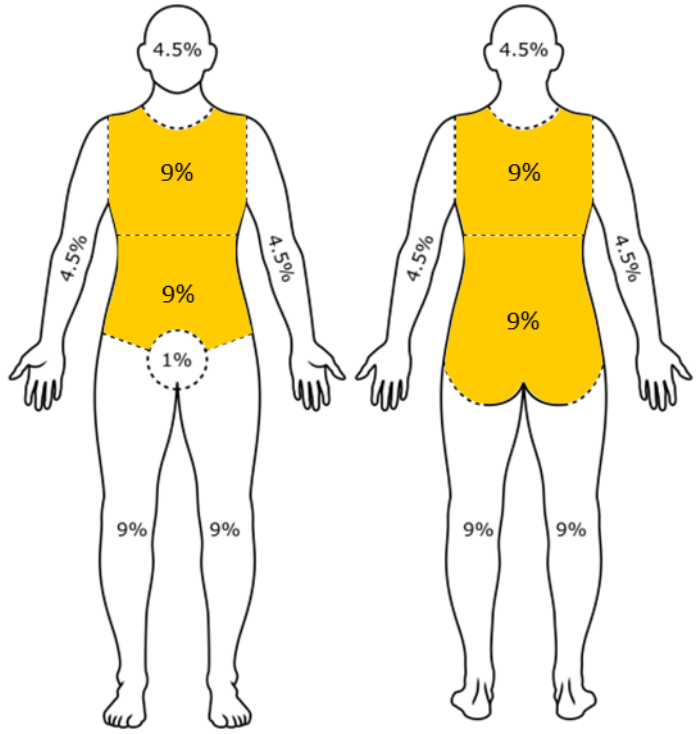
b. Grouped term (includes the PTs of Blood glucose increased, Hyperglycemia).

c. Grouped term (includes the PTs of Erythema, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic).

Key Adverse Event: Rash
Primary Analysis, SAS

	Capi + Abi (N=503) n (%)	Pbo + Abi (N=503) n (%)
Patients with an AE of rash[a]	178 (35.4)	35 (7.0)
Grade 1	51 (10.1)	27 (5.4)
Grade 2	65 (12.9)	7 (1.4)
Grade 3	62 (12.3)	1 (0.2)
Dose modifications of capivasertib		
Dose interruption	85 (16.9)	3 (0.6)
Dose reduction	43 (8.5)	2 (0.4)
Discontinuation	24 (4.8)	0
Treatment	146 (29.0)	20 (4.0)
Antihistamines	103 (20.5)	5 (1.0)
Topical corticosteroids	97 (19.3)	13 (2.6)
Systemic corticosteroids	43 (8.5)	1 (0.2)

Patients with an AE of Rash	**(N=178) n (%)**	**(N=35) n (%)**
Patients with reported outcome for event(s) of rash[b]		
Recovered/Recovering	154 (86.5)	27 (77.1)
Not reported as recovered	24 (13.5)	8 (22.9)



Shaded area represents example of Grade 3 event (>30% BSA)[c]

a. Grouped term (includes the preferred terms of Erythema, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic).
b. Includes terms of Recovered, Recovered with sequelae, and Recovering.
c. CTCAE Version 5 defines Grade 3 Rash as >30% body surface area (BSA), with moderate or severe symptoms; limiting self care activities of daily living.

Key Adverse Event: Diarrhea
Primary Analysis, SAS

	Capivasertib + Abiraterone (N=503) n (%)	Placebo + Abiraterone (N=503) n (%)
Patients with an AE of diarrhea[a]	261 (51.9)	40 (8.0)
Dose modifications of capivasertib		
Dose interruption	63 (12.5)	1 (0.2)
Dose reduction	22 (4.4)	0
Discontinuation	5 (1.0)	0
Treatment	167 (33.2)	19 (3.8)
Treatment with loperamide	130 (25.8)	11 (2.2)

Patients with an AE of Diarrhea	**(N=261) n (%)**	**(N=40) n (%)**
Patients with reported outcome		
Recovered/Recovering[b]	216 (82.8)	36 (90.0)
Not reported as recovered	45 (17.2)	4 (10.0)

Of the 5 patients who discontinued capivasertib, 4 continued on study abiraterone

a. Diarrhea is a medical concept including the following PTs: Diarrhea, Frequent bowel movements, and Gastrointestinal hypermotility.
b. Includes terms of Recovered, Recovered with sequelae, and Recovering.

Key Adverse Event: Hyperglycemia
Primary Analysis, SAS

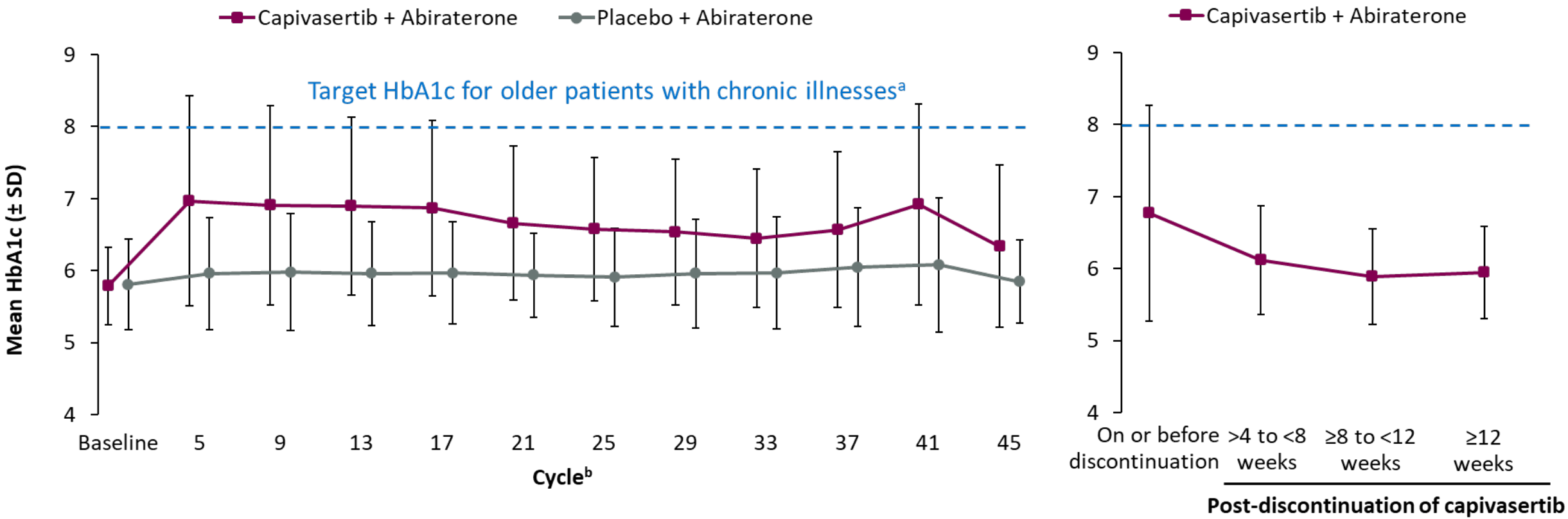
	Capivasertib + Abiraterone (N=503) n (%)	Placebo + Abiraterone (N=503) n (%)
Patients with AE of hyperglycemia[a]	232 (46.1)	72 (14.3)
Grade 1: Abnormal glucose	62 (12.3)	40 (8.0)
Grade 2: Oral medication	100 (19.9)	29 (5.8)
Grade ≥3: Hospitalization or insulin	70 (13.9)	3 (0.6)
Dose modifications of capivasertib		
Dose reduction	40 (8.0)	1 (0.2)
Dose interruption	71 (14.1)	4 (0.8)
Discontinuation	11 (2.2)	0
Treatment	171 (34.0)	30 (6.0)
Metformin	121 (24.1)	25 (5.0)
Other antidiabetics[b]	91 (18.1)	12 (2.4)
Insulin	67 (13.3)	4 (0.8)

Patients with an AE of Hyperglycemia	(N=232) n (%)	(N=72) n (%)
Patients with reported outcome[c]		
Recovered/Recovering	136 (58.6)	40 (55.6)
Not reported as recovered[d]	96 (41.4)	32 (44.4)

a. Grouped term (included PTs of Hyperglycemia, Blood glucose increased, Type 2 diabetes mellitus, and Diabetes mellitus).
b. Other antidiabetics category does not include patients that also received metformin or insulin.
c. Includes terms of Recovered, Recovered with sequelae, and Recovering.
d. Includes one additional patient with a fatal outcome.

Capivasertib's Impact on HbA1c Over Time

Primary Analysis, SAS



Number of patients																
Capi + Abi	500	401	360	299	233	190	148	117	86	64	41	22	153	90	29	69
Pbo + Abi	499	426	390	315	243	174	131	100	77	52	31	17				

a. According to the American Diabetes Association.
b. Each treatment cycle is 28 days.

Capivasertib Pharmacovigilance and Risk Management

Safety Surveillance

Post-marketing Surveillance

- **Routine signal detection/evaluation:**
  - Individual case safety report reviews
  - Periodic trend analyses
  - Literature searches
  - External databases (Eudravigilance, and FDA Adverse Event Monitoring System [AEMS])
- Detailed questionnaires for post-marketing hyperglycemia evaluation

Education and Communication

Risk Communication

- **US Prescribing Information** includes warnings and precautions for rash, diarrhea, and hyperglycemia
- **Patient Information Leaflet** describes key safety risks

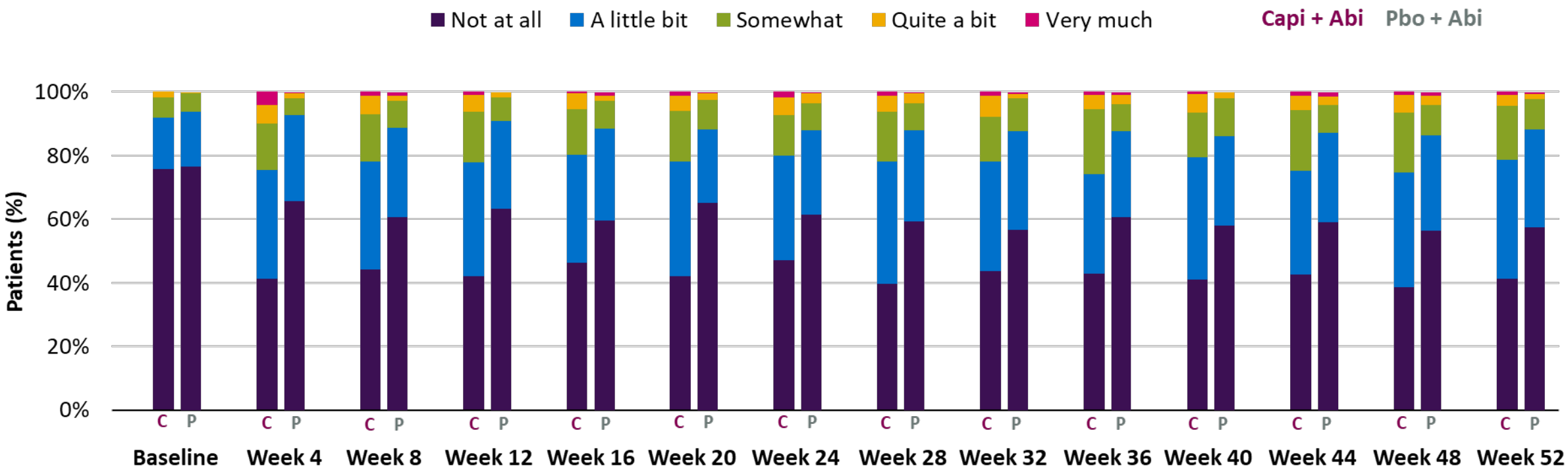
Education for HCPs and Patients

- **Prescriber Education:** Dosing & Adverse Reaction Handbooks and interactive case-based tools support clinical decision-making and dose-modification strategies
- **Patient Education:** Educational materials and symptom trackers enable patients to identify key AEs (hyperglycemia, rash, diarrhea) and report promptly to healthcare teams

https://www.truqap.com/.

FACT-P-GP5 Bothered by Treatment Side Effect

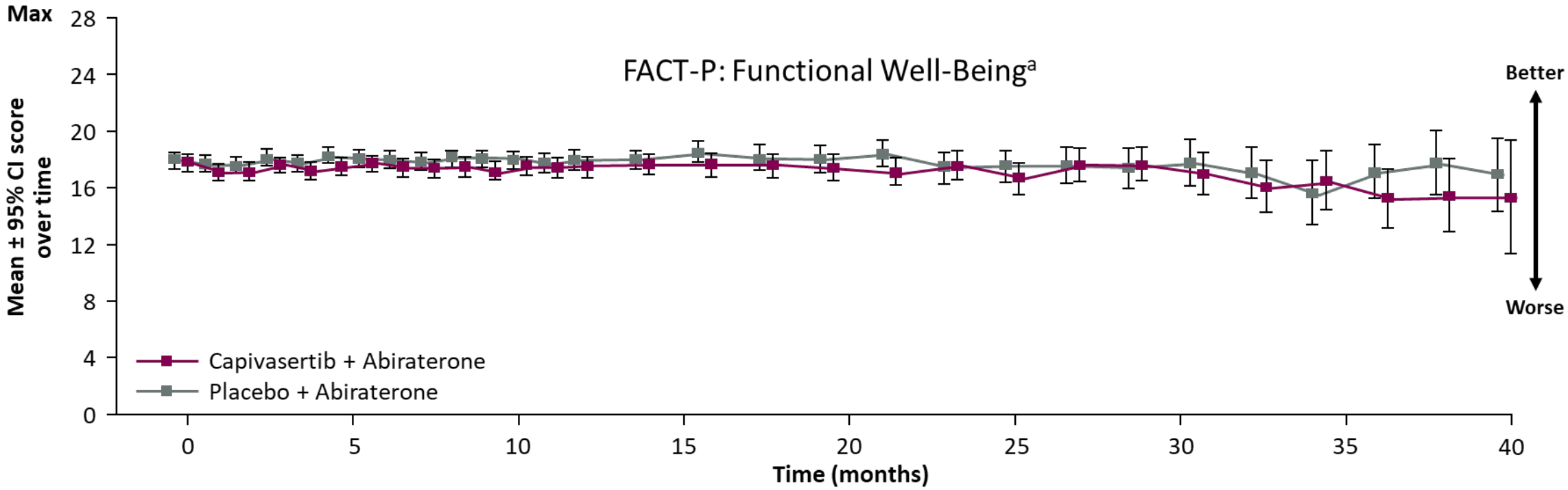
Primary Analysis, SAS



	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
PRO Completed (n)	331 325	404 416	396 420	390 411	381 398	372 389	369 377	357 374	350 368	329 349	310 332	301 325	287 306	247 248
PRO Not Completed (n)	176 180	78 81	75 73	73 73	78 78	81 72	72 78	74 70	71 63	79 65	76 56	69 52	70 44	72 68
Patients on Study (n)	507 505	482 497	471 493	463 484	459 476	453 461	441 455	431 444	421 431	408 414	386 388	370 377	357 350	319 316

Patients' Functioning Was Generally Stable

Primary Analysis, SAS



Weeks	0	8	16	24	32	40	48	60	76	92	108	124	140	156	172
Number of evaluable patients															
Capi + Abi	331	396	381	369	350	310	287	225	185	142	109	82	53	32	16
Pbo + Abi	325	420	399	377	368	332	306	231	173	132	98	68	50	32	20

abi=abiraterone; capi=capivasertib; CI=confidence interval; FACT-P=Functional Assessment of Cancer Therapy-Prostate Cancer; pbo=placebo.
a. Functional well-being includes outcomes such as Ability to work, Sleep quality, and Ability to enjoy life.

Safety Profile Stable at Day 120 Safety Update[a]

+ 9 months

Full analysis set (FAS)	Primary Analysis		Day 120 Safety Update	
	Capi + Abi (N=507) n (%)	Pbo + Abi (N=505) n (%)	Capi + Abi (N=507) n (%)	Pbo + Abi (N=505) n (%)
Total deaths by arm	**129 (25.4)**	**138 (27.3)**	**156 (30.8)**	**188 (37.2)**
Safety analysis set (SAS)	**(N=503) n (%)**	**(N=503) n (%)**	**(N=503) n (%)**	**(N=503) n (%)**
Any AE	497 (98.8)	463 (92.0)	499 (99.2)	469 (93.2)
Any SAE (including events with outcome of death)	214 (42.5)	131 (26.0)	234 (46.5)	152 (30.2)
Any AE with outcome of death	36 (7.2)	26 (5.2)	39 (7.8)	32 (6.4)
Any AE of CTCAE Grade 3 or higher	337 (67.0)	203 (40.4)	357 (71.0)	224 (44.5)
Any AE leading to dose interruption of Capivasertib/Placebo	316 (62.8)	135 (26.8)	328 (65.2)	148 (29.4)
Any AE leading to dose reduction of Capivasertib/Placebo	146 (29.0)	18 (3.6)	159 (31.6)	19 (3.8)
Any AE leading to discontinuation of Capivasertib/Placebo	92 (18.3)	24 (4.8)	100 (19.9)	28 (5.6)

a. Data cutoff July 2025. Efficacy endpoints were not analyzed with this update.

CAPItello-281 Summary of Clinical Safety and PROs

Well-established safety profile, with experience from breast cancer

Capivasertib targets the AKT pathway; AEs include on-target effects

The addition of capivasertib to abiraterone increased side-effect bother but did not translate into meaningful health-related quality-of-life limitations

In mHSPC patients, clinically important AEs are manageable and may require proactive monitoring, prompt intervention, and dose modification

Benefit:Risk & Clinical Perspective

Daniel J. George, MD

Professor of Medicine, Surgery and Urology

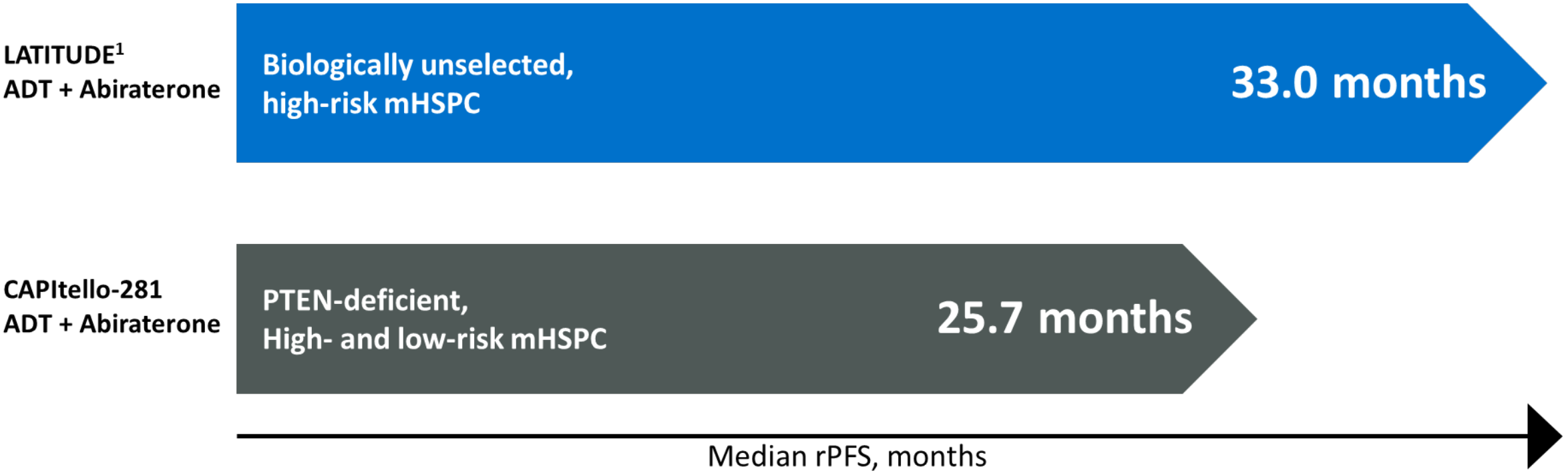
Divisions of Medical Oncology and Urology

Director, Genitourinary Oncology

Duke Cancer Institute

Duke University School of Medicine

PTEN-Deficient mHSPC Is a Biologically-Defined Subpopulation of Prostate Cancer With Poor Prognosis



Shorter rPFS on standard-of-care doublet therapy with abiraterone and ADT in PTEN-deficient mHSPC

1. Fizazi K, et al. *N Engl J Med.* 2017;377(4):352-360.

PTEN-Deficient Tumors Can Be Easily and Frequently Identified in Clinical Practice

Evaluation of Newly Diagnosed mHSPC Patients

Initial Assessment

Tumor biopsy

Standard Labs, PSA testing

Imaging (CT, bone scan, or PET and Dexa scans)

Consultation for physical and medical assessment:
- **Discussion of hormonal therapies**
- **Fitness for potential chemotherapy**

+

Genetic and Molecular Profiling

Profiling should include
- **IHC testing for ≥90% PTEN deficiency**
- **Somatic and germline testing**

Follow-up consultation
- **Discussion of results of profiling and additional treatment options as appropriate**

25% of patients have PTEN-deficient mHSPC

Capivasertib Provides Clinically Meaningful Benefits for Patients With PTEN-Deficient mHSPC

Prolonged Radiographic Progression-free Survival

Improvement in median rPFS of 7.5 months

Fewer and Delayed Bone Complications

Longer Time Until Hormone Therapy Stops Working

Delayed Time to Needing Chemotherapy

Practicalities of Managing AEs Associated With Capivasertib

- Treatment with capivasertib adds side effects, which some patients may not tolerate
- Early onset of rash, diarrhea, and hyperglycemia requires proactive monitoring and intervention
- Established management strategies for on-target key capivasertib AEs should be employed
- Functional well-being was maintained

Clinical Perspective: I Would Recommend the Addition of Capivasertib to Abiraterone, Prednisone, and ADT

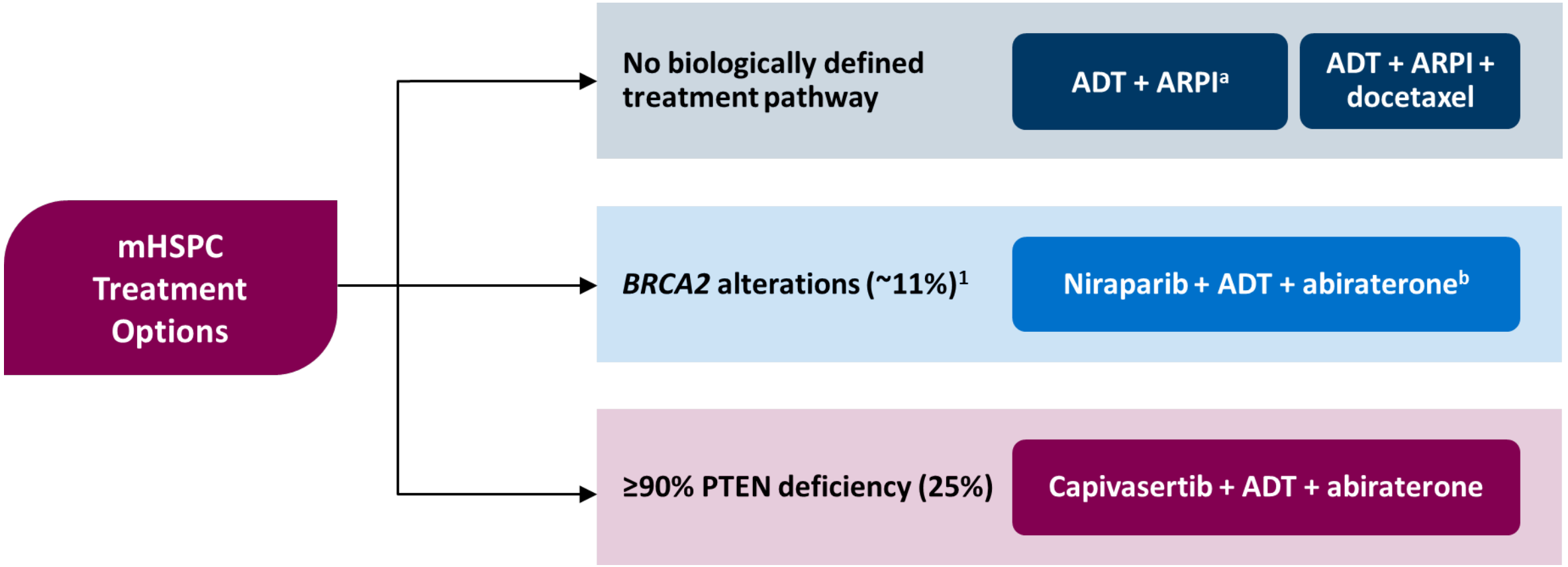
The Benefits of Capivasertib Outweigh the Risks of Treatment

First Targeted Therapy to Delay Progression and Alter Clinical Course in Patients With PTEN-Deficient mHSPC

Addresses Unmet Need for 25% of mHSPC Driven by PTEN-Deficient Biology

Maximizing the First Remission Is the Most Important Treatment Goal for Our Patients

Opportunity to Improve Outcomes With Personalized Treatment in mHSPC



Capivasertib with abiraterone and ADT should be the first choice for PTEN-deficient mHSPC

a. ARPIs include: abiraterone, darolutamide, enzalutamide, and apalutamide; b. For BRCA2-mutated tumors.
ADT=androgen deprivation therapy; ARPI=androgen receptor pathway inhibitor; BRCA2=breast cancer gene 2; mHSPC=metastatic hormone-sensitive prostate cancer; PTEN=phosphatase and tensin homolog.

1. Olmos D, et al. *Ann Oncol*. 2025;36(10):1190-1202.