Second Opinion: Clinical Investigators Provide Perspectives on the Future Role of AKT Inhibition in the Management of Prostate Cancer

A CME Symposium Held Adjunct to the
2026 ASCO® Genitourinary Cancers Symposium

Friday, February 27, 2026
6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)

Faculty

Professor Karim Fizazi, MD, PhD
Daniel George, MD

Moderator

Elisabeth I Heath, MD

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Faculty

Professor Karim Fizazi, MD, PhD
Head of Service and Full Professor
Institut Gustave Roussy
University of Paris Saclay
Villejuif, France

Moderator

Elisabeth I Heath, MD
Chair, Department of Oncology
Mayo Clinic
Rochester, Minnesota

Daniel George, MD
Eleanor Easley Distinguished Chair
Professor of Medicine, Surgery and Urology
Duke University School of Medicine
ACS Research Professor
Co-Lead, DCI Center for Prostate and Urologic Cancers
Duke Cancer Institute
Durham, North Carolina

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Second Opinion

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research
Huntsman Cancer Institute Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)
Salt Lake City, Utah

Neil Love, MD
Research To Practice
Miami, Florida

Rana R McKay, MD, FASCO
Professor of Medicine, Urology, and Radiation
Medicine and Applied Sciences
Associate Director, Clinical Research
Co-Lead, Genitourinary Program
Moores Cancer Center
University of California San Diego
San Diego, California

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Prof Fizazi — Disclosures
Faculty

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A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

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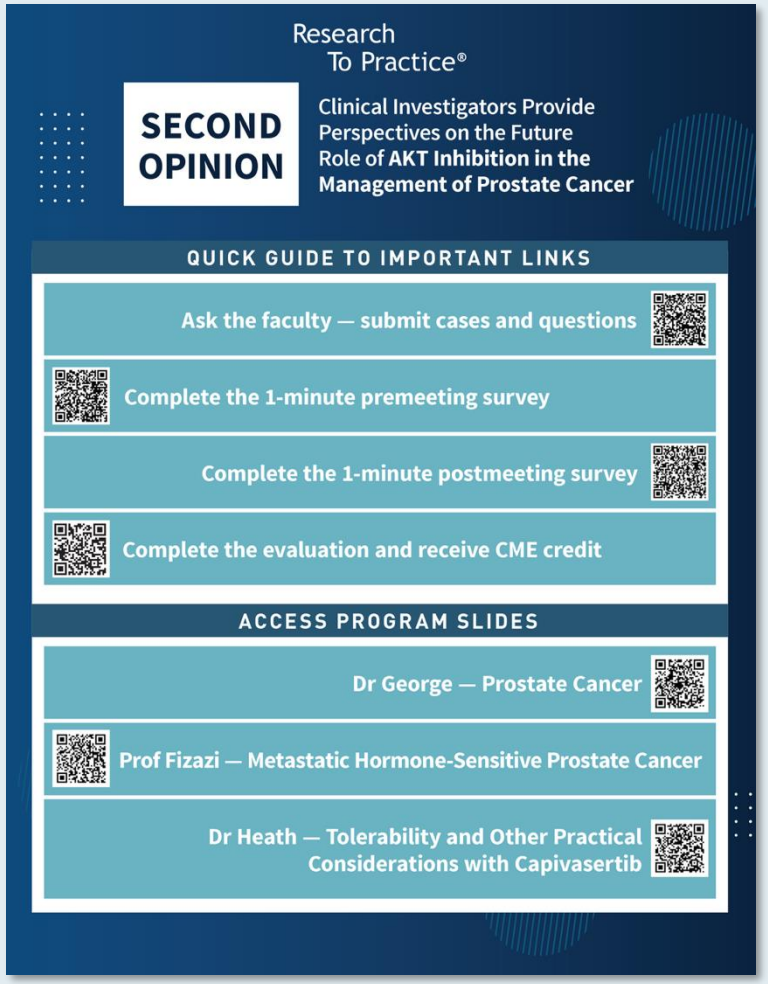

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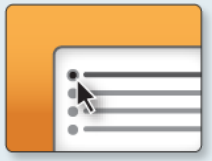

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Module 1: Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer — Dr George

Module 2: Targeting AKT in Metastatic Prostate Cancer — Prof Karim Fizazi

Module 3: Tolerability and Other Practical Considerations with Capivasertib — Dr Heath

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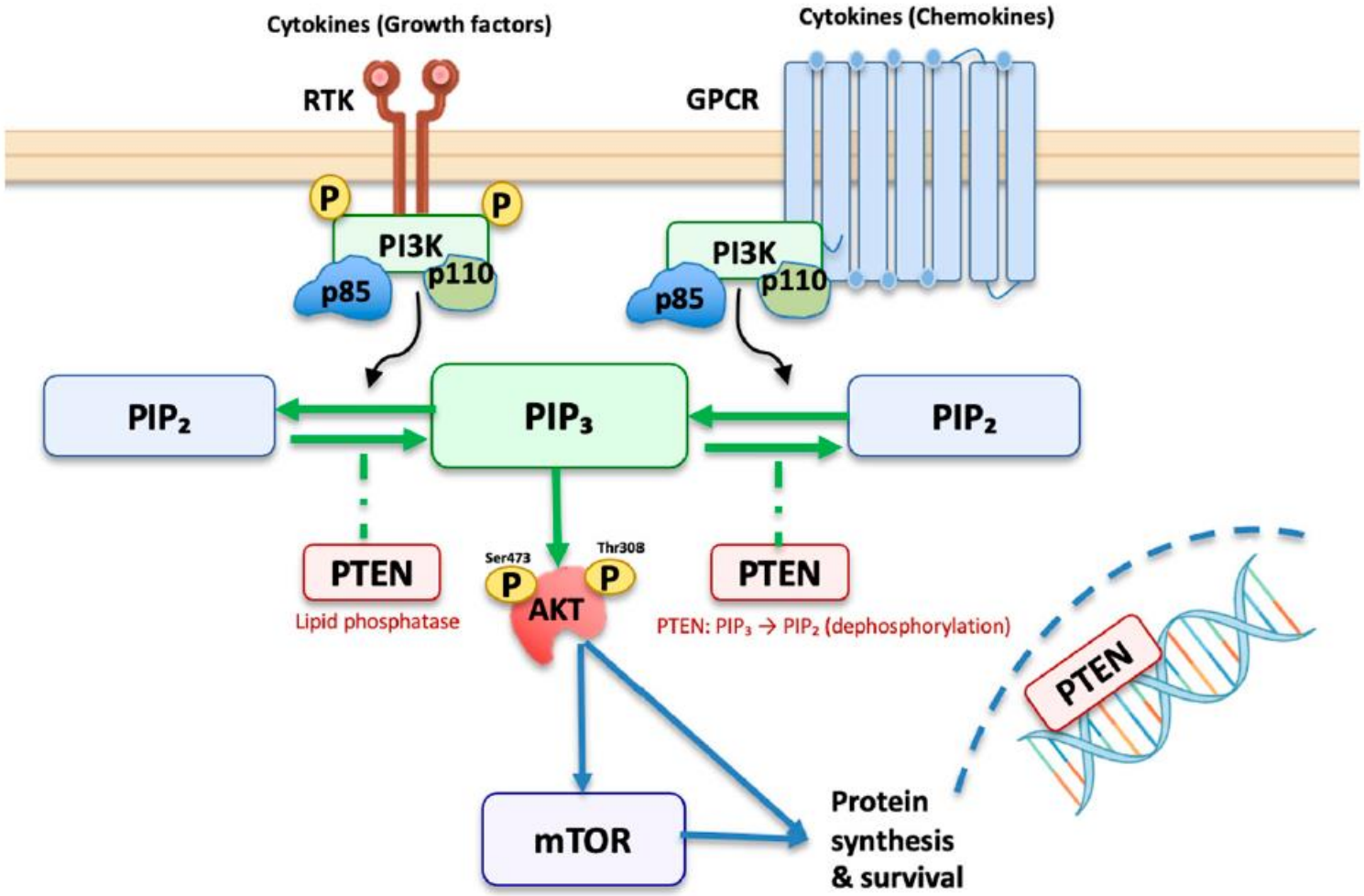
Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer —

Daniel J. George, MD FASCO
Eleanor Easley Distinguished Chair
Professor of Medicine, Surgery and Urology
Duke University School of Medicine
American Cancer Society IMPACT Research Professor
Co-lead, DCI Center for Prostate and Urologic Cancers

What Biomarkers are Recommended for Prostate Cancer Patients?

- Germline genetic testing – in case of family history, high risk localized or metastatic disease
- Somatic genetic testing – for metastatic prostate cancer (multigene assessments including HRR and MSI-H or dMMR).
  - Of these only BRCA, HRR, and MSI-H alterations are actionable
- Risk assessment of localized disease may be aided by several biomarker assays:
  - PSA – serum biomarker of AR activity, risk of recurrent/metastatic disease
  - Prolaris – 46-gene genomic risk assessment
  - Decipher – 22-gene expression risk classifier
  - Artera AI – multimodal AI test including digital path, risk assessment, predictor of ADT benefit with radiation
  - PTEN IHC – several robust, clinically validated assays are available for use

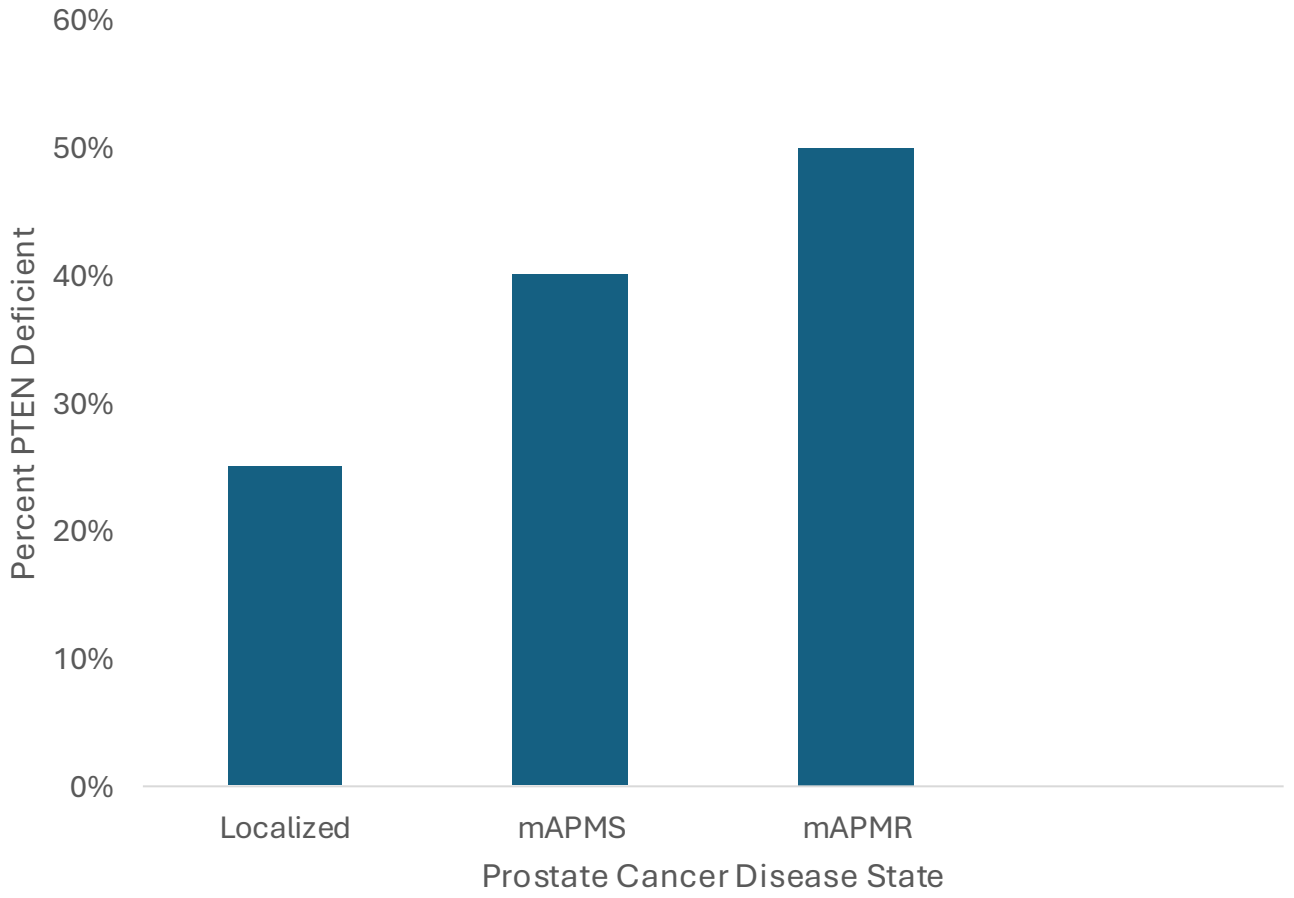
Phosphatase and TENsin homolog (PTEN) – what is it? – what does it do?



Abbreviations: RTK, receptor tyrosine kinase; GPCR, G-protein-coupled receptor; PI3K, phosphoinositide 3-kinase; p85/p110, PI3K regulatory/catalytic subunits; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homologue; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; Ser/Thr, serine/threonine; P, phosphate.

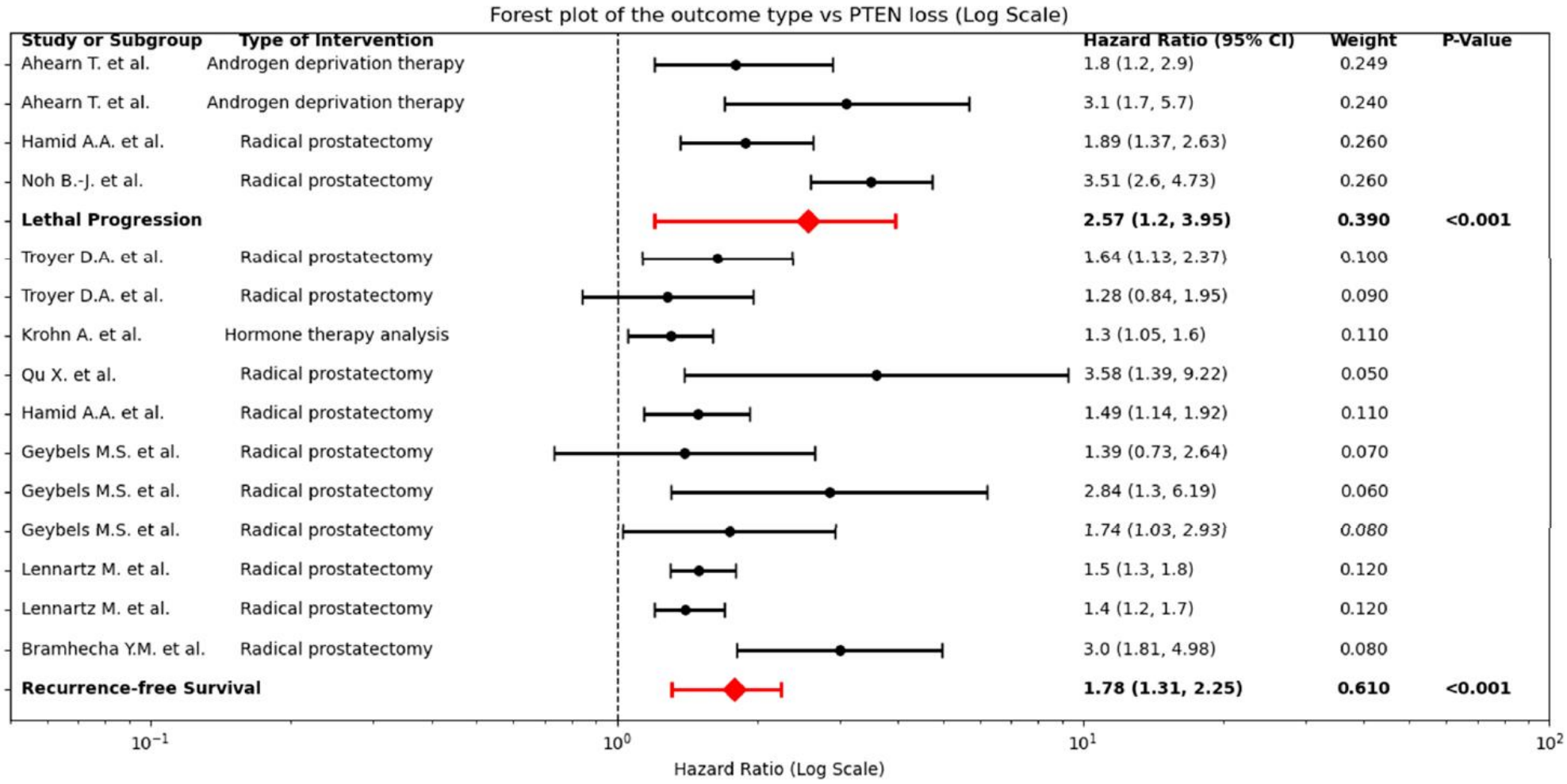
Kisiel F et al. Cancers 2025 Aug 30;17(17):2862

PTEN deficiency is common and increases with androgen pathway modulation resistance (APMR)



Ferraldeschi *Eur Urol* 2015. Velez *Prostate Cancer Prostatic Dis* 2022. Gilson *JCO Precis Oncol* 2020. Al-Toubat *Urol Oncol* 2023. Nizialek *Prostate* 2021. Fonseca *JCO Precis Oncol* 2022. Mayrhofer *Genome Med* 2018. Eule *Prostate Cancer Prostatic Dis* 2023. Hamid et al, Eur Uro 2019. Matsubara *ASCO Genitourinary Cancers Symposium* 2023. Sweeney *Lancet* 2021. Crabb *J Clin Oncol* 2021. Kolinsky *Ann Oncol* 2020. Sweeney *Clin Cancer Res* 2022. Courtney *Clin Genitourin Cancer* 2015. Alajati *J Clin Invest* 2020. Ferraldeschi *Eur Urol* 2015 Rescigno *Eur Urol Oncol* 2018. Tao *JCO Precis Oncol* 2017

Meta-analysis of PTEN status and Outcomes



Kisiel F et al. Cancers **2025**, 17, 2862

PTEN deficiency is clinically relevant across multiple cancer types

Prostate

- ↑ Gleason score
- ↑ Capsular penetration
- ↑ Recurrence
- ↓ PFS
- ↓ OS

Lung

- ↓ PFS
- ↓ OS
- ↑ Stage
- ↑ Lymph node metastasis
- ↑ Distant metastasis

Breast†

- ↓ PFS
- ↓ OS
- ↑ Stage
- ↑ Lymph node metastasis

Resistance to trastuzumab in patients with recurrent or metastatic disease

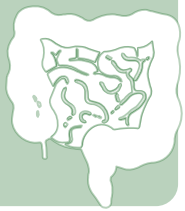
Gastric

- ↓ OS

Colorectal

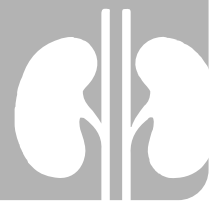
Resistance to anti-EGFR

Unclear prognostic value



Renal

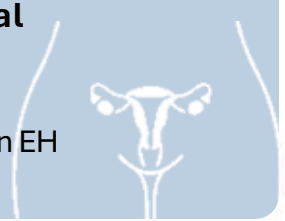
- ↓ DSS



Endometrial

Low diagnostic accuracy in EH

- ↑ risk of endometrial cancer in EH



Glioblastoma

Prognostic value in only 30% of studies

Ovarian

No prognostic value

*Note that this is not a comprehensive list; †One study found no predictive/prognostic value

EGFR, epidermal growth factor receptor; EH, endometrial hyperplasia; DSS, disease-specific survival; OS, overall survival; PFS, progression-free survival.

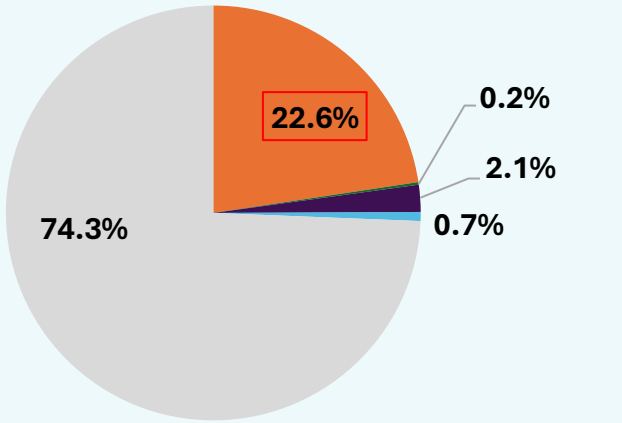
Pulido R, et al. *Cold Spring Harb Perspect Med* 2019;9:a036293

Dysregulation of the PI3K/AKT pathway in PC is predominantly caused by alterations in *PTEN*

PC/mHSPC

In PC, alterations such as *PTEN* rearrangements and deletions are the predominant causes of PI3K/AKT pathway activation[1,2]

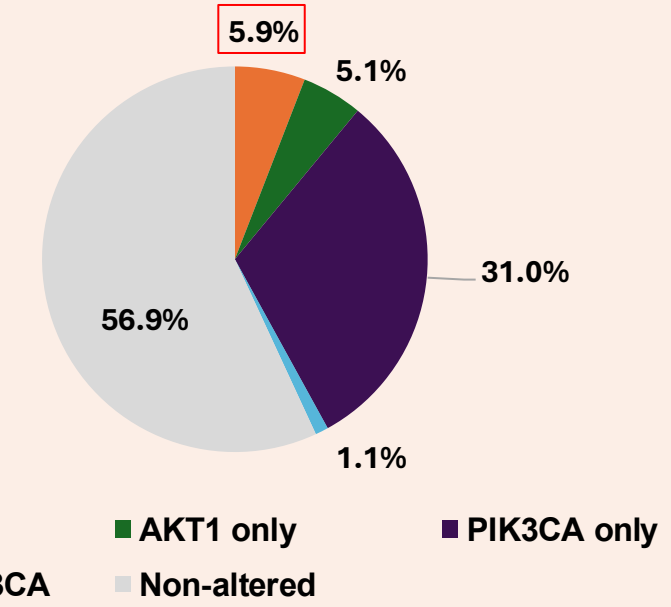
Spectrum of alterations in mHSPC[3]



ER+/HER2– mBC

In ER+ mBC, PI3K/AKT pathway activation commonly occurs through alterations in *PIK3CA*, *AKT1* and/or *PTEN*[4]

Spectrum of alterations in ER+/HER2– mBC[5]

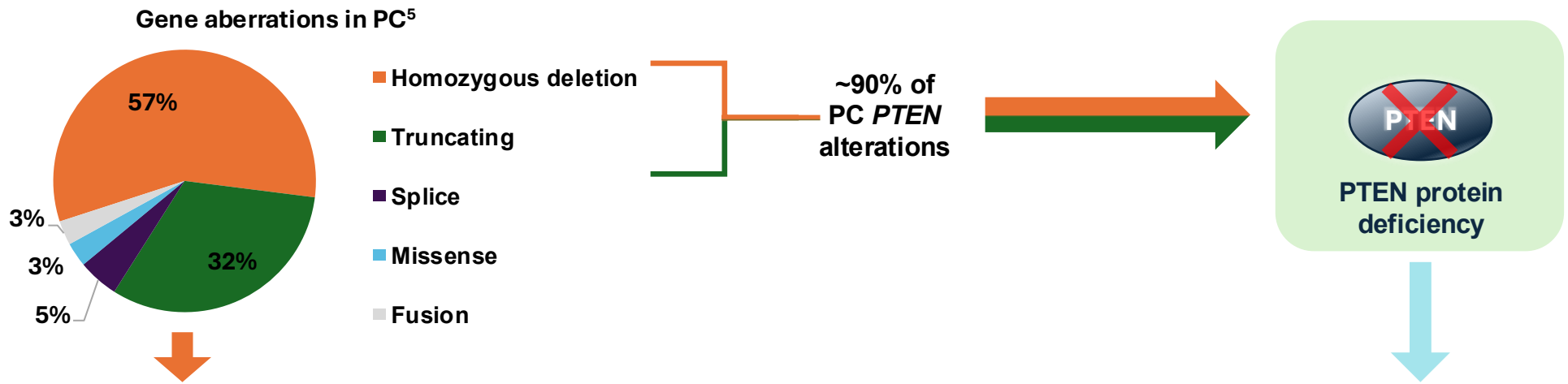


Graphical data sourced from Stopsack KH, et al. *Clin Cancer Res* 2020[3]

AKT, protein kinase B; AKT1, protein kinase B inhibitor 1; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PC, prostate cancer; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homologue.

1. Phin S, et al. *Front Oncol* 2013;3:240; 2. Ferraldeschi R, et al. *Eur Urol* 2015;67:795–802; 3. Stopsack KH, et al. *Clin Cancer Res* 2020;26:3230-3238; 4. Skolariki A, et al. *Explor Target Antitumor Ther* 2022;3:172–199; 5. Turner NC, et al. Supplementary appendix. *N Engl J Med* 2023;388:2058–2070.

PTEN deficiency in PC is primarily due to *PTEN* gene deletions, and the resulting loss of detectable PTEN protein can be assessed by IHC



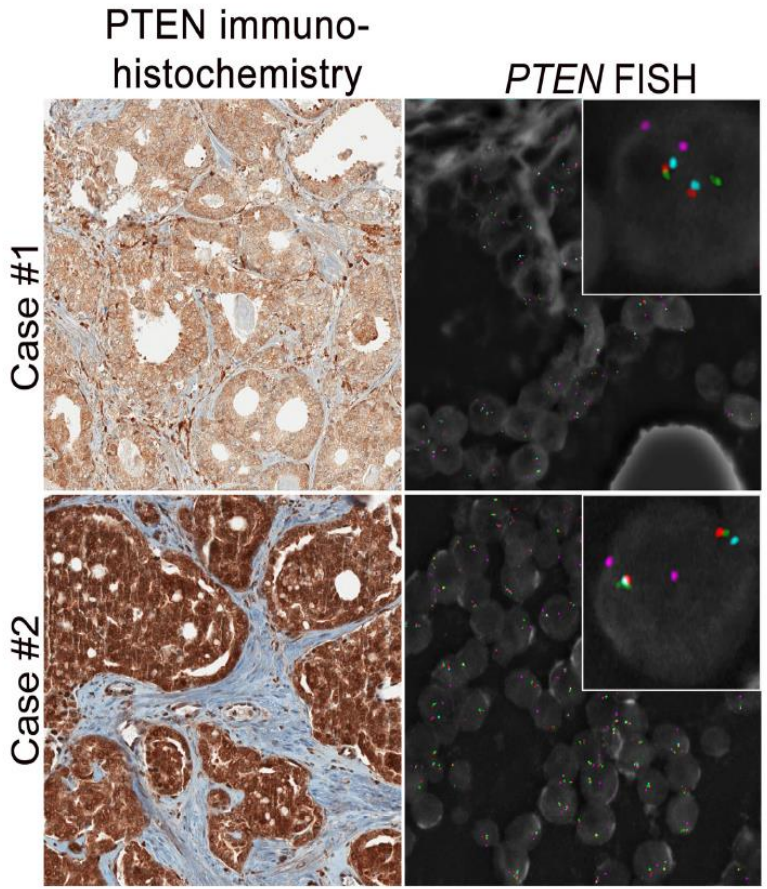
As not all *PTEN* alterations result in PTEN protein deficiency, **IHC testing for protein expression** is the most robust method to **determine actual loss of PTEN function[2–4]**

Mechanisms resulting in PTEN deficiency are diverse, but **both homozygous and heterozygous genomic *PTEN* deletions are frequent and accompanied by loss of detectable protein that can be assessed by IHC[3]**

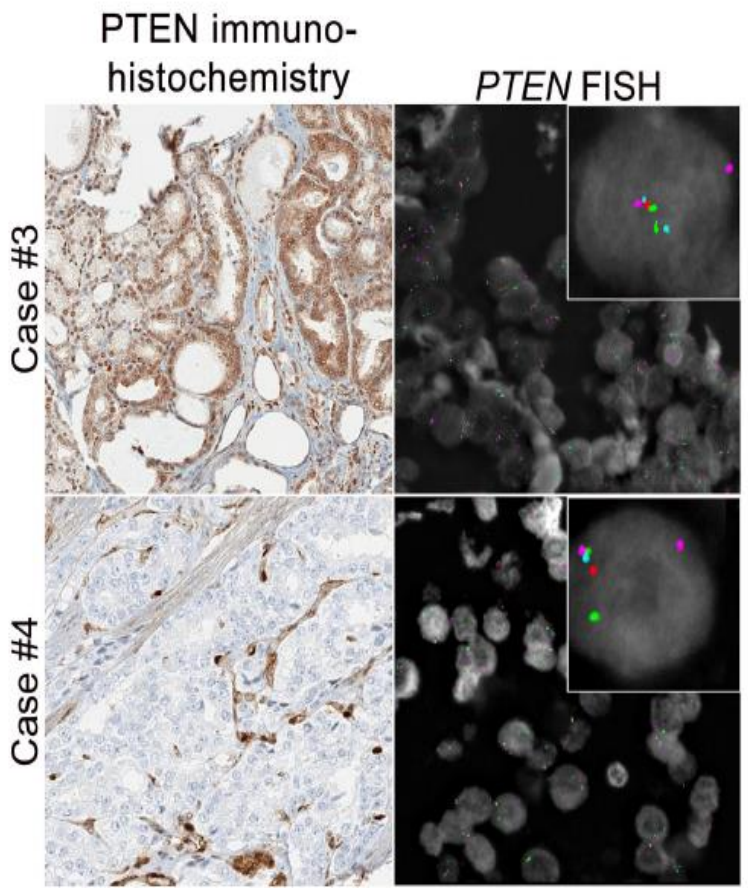
Graphical data sourced from Stopsack KH, et al. *Clin Cancer Res* 2020[5]
IHC, immunohistochemistry; mHSPC, metastatic hormone-sensitive prostate cancer; PC, prostate cancer; PTEN, phosphatase and tensin homologue.
1. Fizazi K et al. *Ann Oncol*. 2025; 2. Pulido R, et al. *Cold Spring Harb Perspect Med* 2019;9:a036293; 3. Wise HM, et al. *Clin Sci* 2017;131:197–210; 4. Lotan TL, et al. *Mod Pathol* 2016;29:904-14;
5. Stopsack KH, et al. *Clin Cancer Res* 2020;26:3230-3238.

PTEN IHC vs Genetic Loss

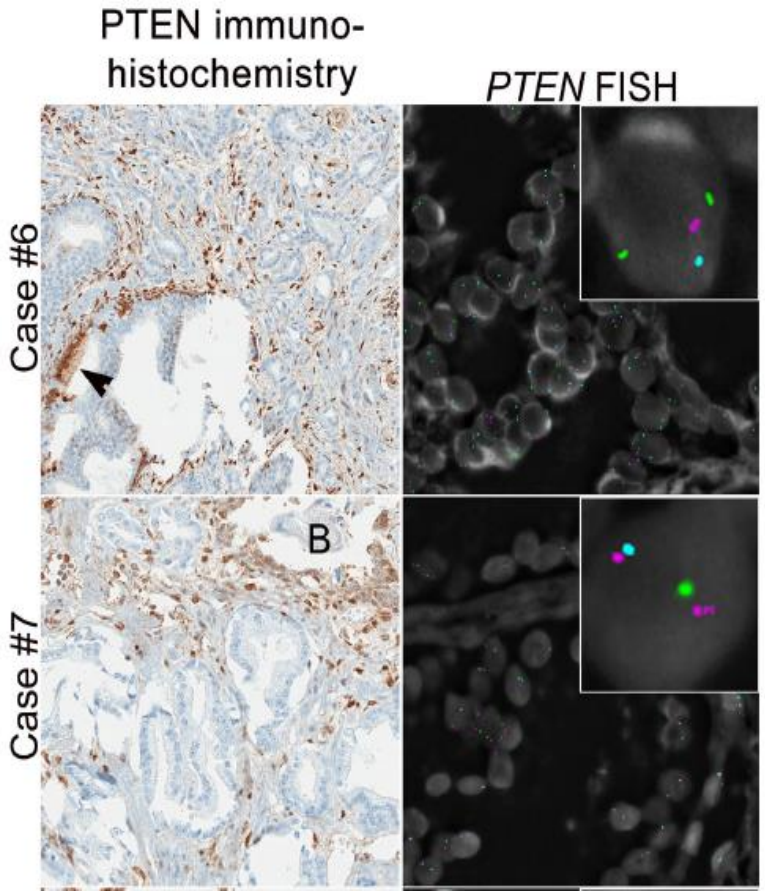
PTEN Intact



PTEN heterogenous loss



PTEN homogenous loss

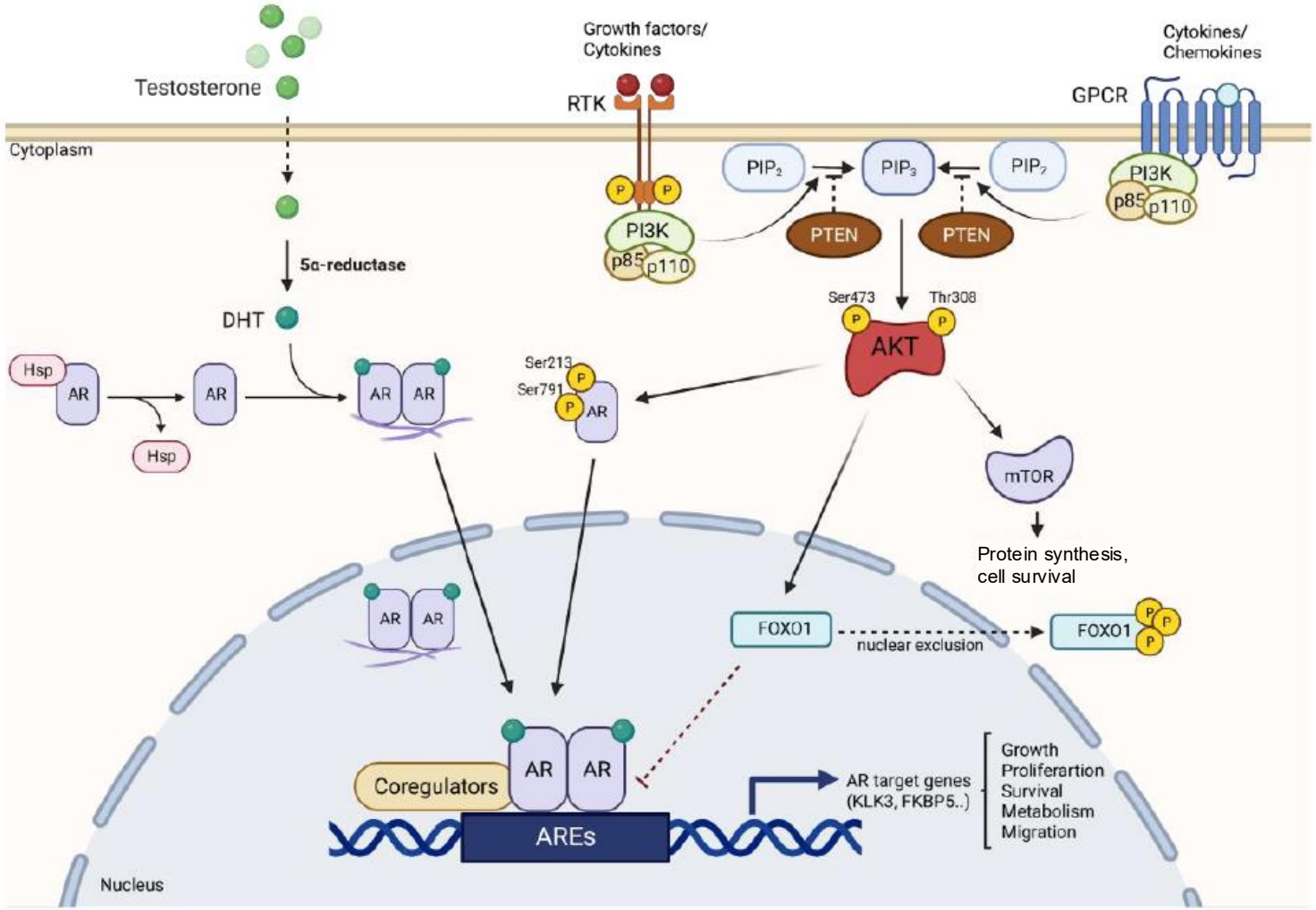


Lotan T et al. Mod Pathol. 2016 August ; 29(8): 904–914.

Biologic Implications of PTEN Deficiency in PC

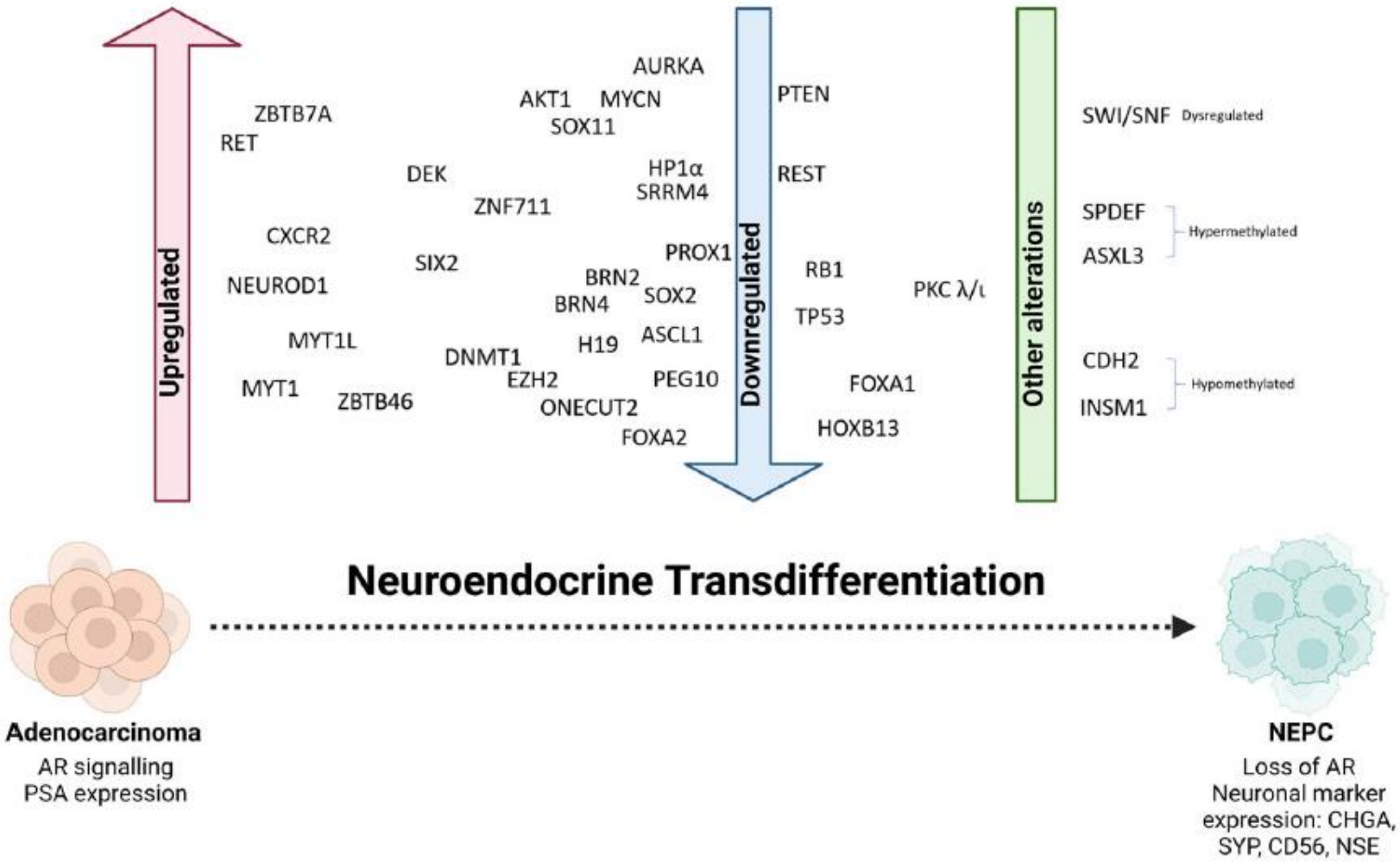
- PTEN loss in localized PC is often concurrent with genomic rearrangements involving the ETS family transcription factors
- PTEN might be a useful prognostic biomarker to distinguish potentially aggressive Grade Group 1 or 2 tumors, which might make patients poor candidates for active surveillance
- PTEN loss is associated with suppression of androgen receptor (AR) transcriptional output, and phosphoinositide 3-kinase (PI3K) inhibitors activate AR signaling, suggesting potential efficacy of combination therapies targeting the PI3K/AKT and AR signaling pathways
- PTEN loss is associated with transdifferentiation to neuroendocrine PC, in combination with other biomarkers

Crosstalk between AR and AKT signaling



Tortorella E et al. Int. J. Mol. Sci. **2023**, 24, 2046

Transition from Adeno to Neuroendocrine PC



Maylin ZR et al. Cells **2024**, 13, 1999

IHC offers the most reliable method to identify patients with PTEN-deficient tumors suitable for treatment with AKT inhibitors

IHC

Laboratory technique that uses antibodies to detect antigens (markers) in a sample of tissue[1]

- ✓ Less expensive and less time-consuming than NGS[2]
- ✓ 2.5 × less biopsy sample/tissue required than NGS[3,4]
- ✓ Can detect PTEN protein levels compromised by mutations in the gene or miRNA or epigenetic-regulated mechanisms, undetectable by NGS[5,6]
- ✓ Low testing failure rates of ~5%[7]
- ✓ High concordance with NGS for detecting PTEN deficiency (85.5%)[8]
- X Dysfunctional PTEN protein as a result of genetic point mutations, is still detected by IHC at the protein level[9]

NGS

Technology used for cfDNA and RNA sequencing and variant/mutation detection[10,11]

- ✓ Can analyse multiple mutation targets at the same time[10]
- X Longer turnaround time and higher associated costs than IHC[2]
- X High *PTEN* testing failure rates (~30%)[2]
- X May underestimate the frequency of PTEN deficiency[6]
- X Requires more tumor tissue than IHC[2]
- X Full sequencing of the gene is required to reliably detect *PTEN* alterations due to gene deletions or rearrangements[12]

cfDNA, cell-free DNA; FISH, fluorescence *in situ* hybridisation; IHC, immunohistochemistry; miRNA, microRNA; mPC, metastatic prostate cancer; NGS, next-generation sequencing; PTEN, phosphatase and tensin homologue.

1. NIH. Immunohistochemistry. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunohistochemistry (accessed September 2025); 2. Tsao MS, Yatabe Y. *J Thorac Oncol* 2019;14:2035–2038; 3. Foundation Medicine. Specimen Instructions. https://www.foundationmedicine.com/sites/default/files/media/documents/2024-04/F1CDx_Specimen_Instructions.pdf (accessed September 2025); 4. Foundation Medicine. IHC Specimen Instructions. https://www.foundationmedicine.com/media/459/fmi-view (accessed September 2025); 5. Wise HM, et al. *Clin Sci* 2017;131:197–210; 6. de Bono JS, et al. *Clin Cancer Res* 2019;25:928–936; 7. Jamaspishvili T et al. *Nat Rev Urol*. 2018;15:222–234; 8. de Bono J, et al. Presented at ASCO Genitourinary Cancers Symposium 2021; 9. Wang L, et al. *Int J Gynecol Pathol* 2022;41:12–19; 10. Qin D. *Cancer Biol Med* 2019;16:4–10; 11. Al-Toubat M, et al. *Urol Oncol* 2023;41:455.e7–455.e15; 12. Li X et al. Presented at: SABCS; December 10-13, 2024; San Antonio, Texas.

Summary

- PTEN deficiency is a common genetic alteration in PC that increases with stage and disease states.
- PTEN regulates the PI3K/AKT pathway, its loss results in unregulated AKT activity, increased cell proliferation and survival
- PTEN alterations are the most common form of PI3K/AKT dysregulation
- PTEN deficiency is associated with high grade PC and poor prognosis
- Crosstalk between androgen receptor and AKT signaling supports the concomitant inhibition strategies
- PTEN deficiency can lead to AR variant or neuroendocrine PC

Second Opinion

Neeraj Agarwal, MD, FASCO

Neil Love, MD

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QUESTIONS FOR THE FACULTY

How early in prostate tumorigenesis does PTEN loss occur, and do you view this primarily as an initiating event or a driver of disease progression?

What is the prognostic significance of PTEN deficiency, and how does this compare to other drivers of aggressive disease, such as BRCA2 or TP53 mutations?

What is the frequency of PTEN deficiency in localized versus metastatic disease? How often do you see intrapatient heterogeneity, wherein PTEN status differs between the primary tumor and metastases?

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QUESTIONS FOR THE FACULTY

What is the optimal method to assess PTEN status, and when should testing be done?

How does PTEN deficiency influence your treatment decision-making today? Do you think PTEN-deficient disease represents a distinct biological subtype that should be managed differently?

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Rana R McKay, MD, FASCO

Neil Love, MD

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QUESTIONS FOR THE FACULTY

How often have you encountered patients with aggressive disease due to PTEN deficiency but relatively low PSA? What accounts for this discordance?

What would you recommend in this scenario, and how, if at all, would your recommendation differ if capivasertib were available? Would you consider adding capivasertib for this patient who developed metastatic disease while receiving abiraterone/ADT?

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QUESTIONS FOR THE FACULTY

If capivasertib were available, would it be an appropriate option on the basis of NGS testing demonstrating PTEN homozygous deletion on archival primary tissue? Should additional testing (eg, IHC) be done?

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Module 3: Tolerability and Other Practical Considerations with Capivasertib — Dr Heath

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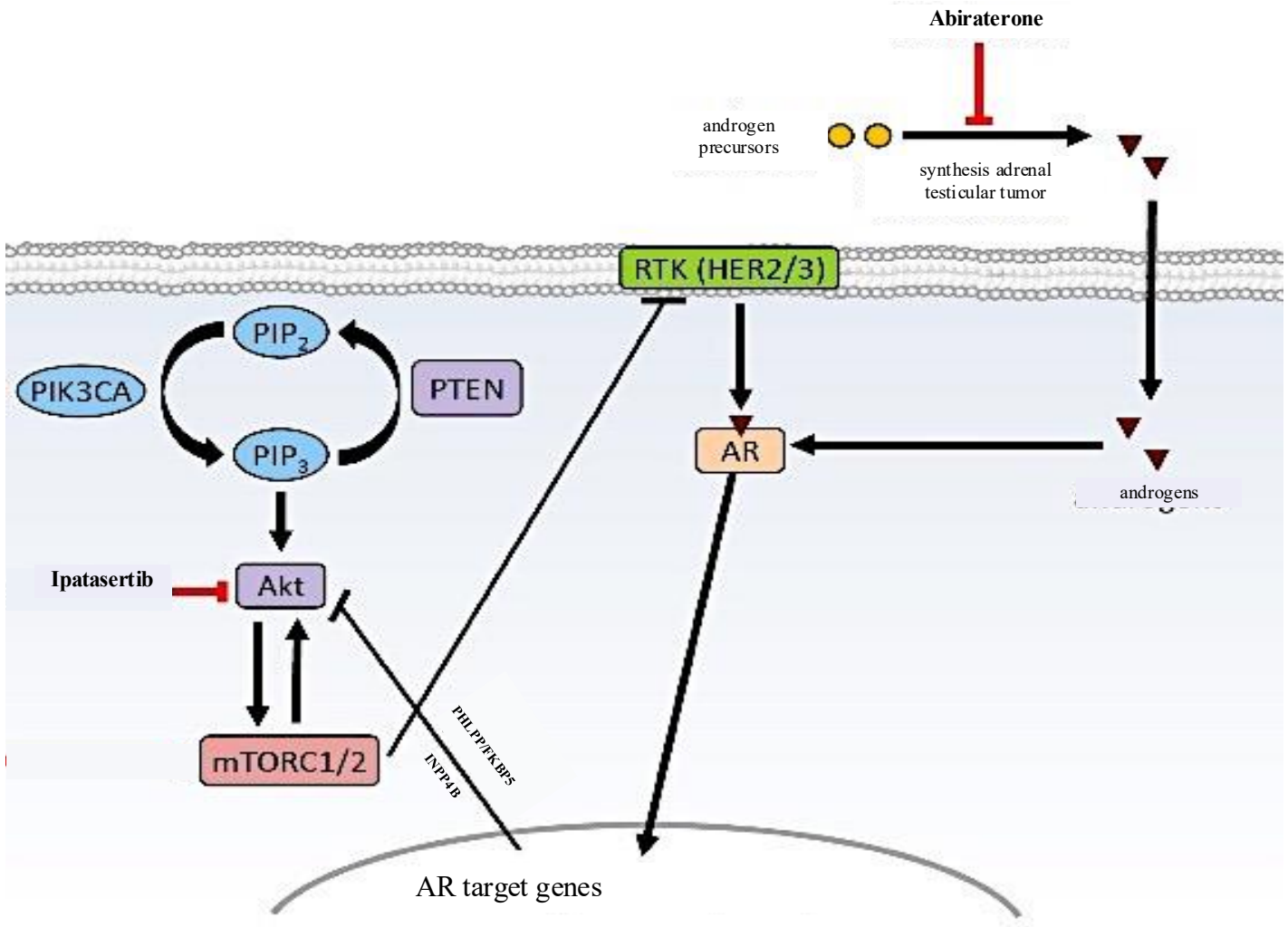
Targeting AKT in Metastatic Prostate Cancer

Karim Fizazi, MD, PhD

France

Targeting both the AKT and the AR pathways

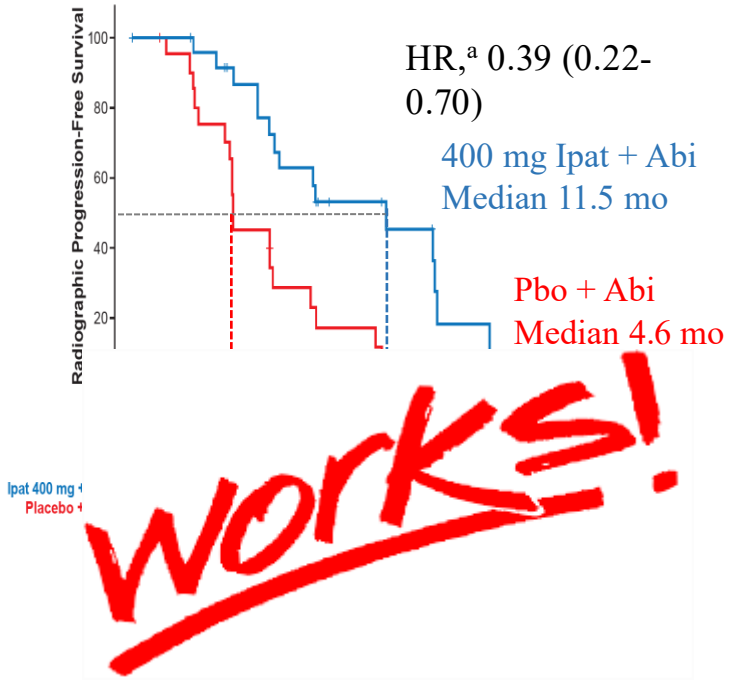


K Fizazi, personal slide

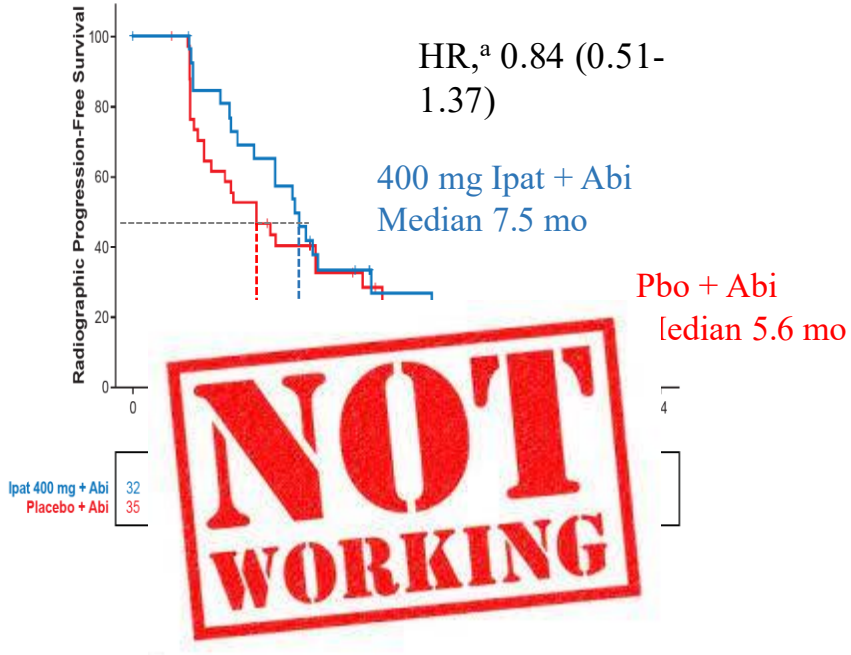
Abiraterone +/- Ipatasertib (Akt inhibitor)
Randomised phase 2 trial: PFS

400 mg Ipatasertib

PTEN loss

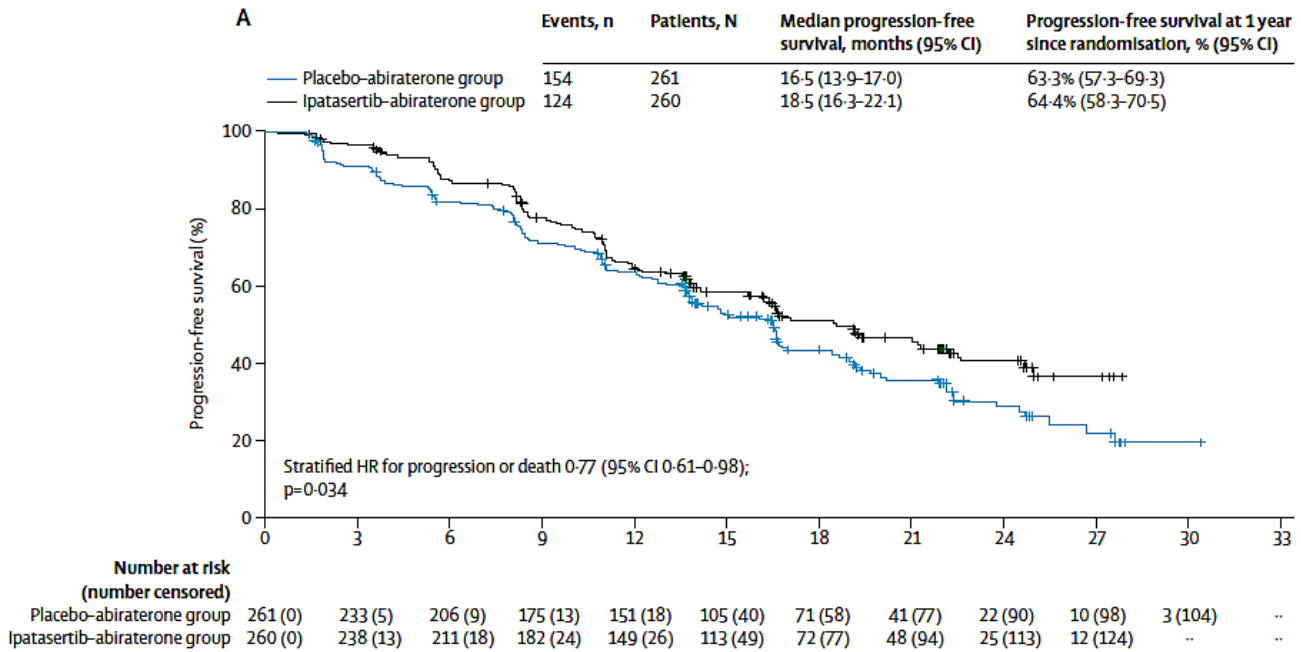


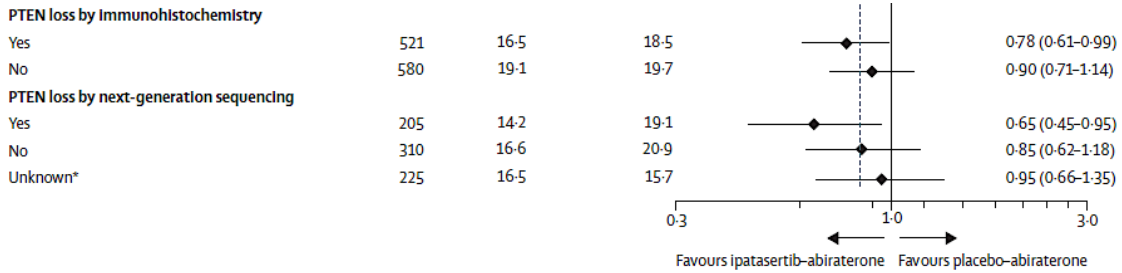
PTEN non-loss



de Bono et al, Ipatasertib, ESMO 2016

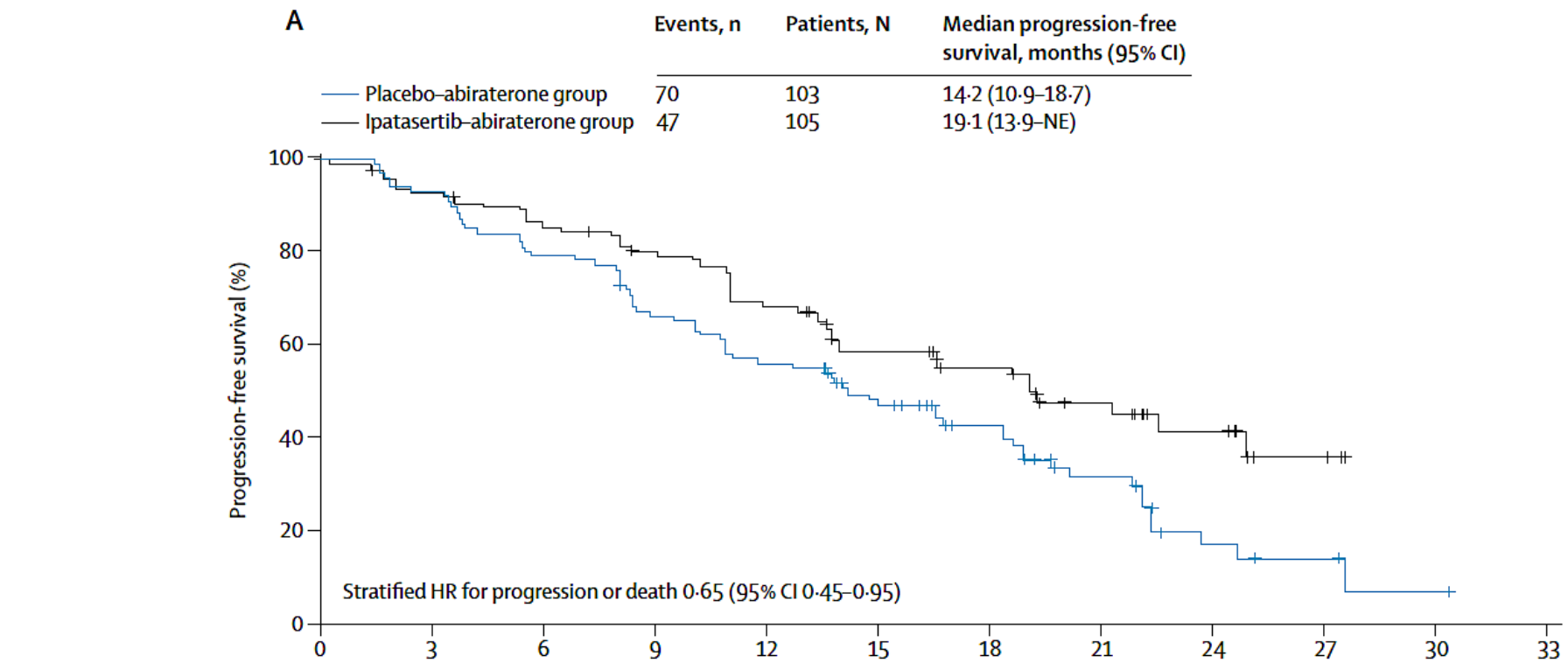
Ipatasertib-Abiraterone in mCRPC: rPFS (IPATential150 phase 3 trial)





Sweeney C, Lancet 2021

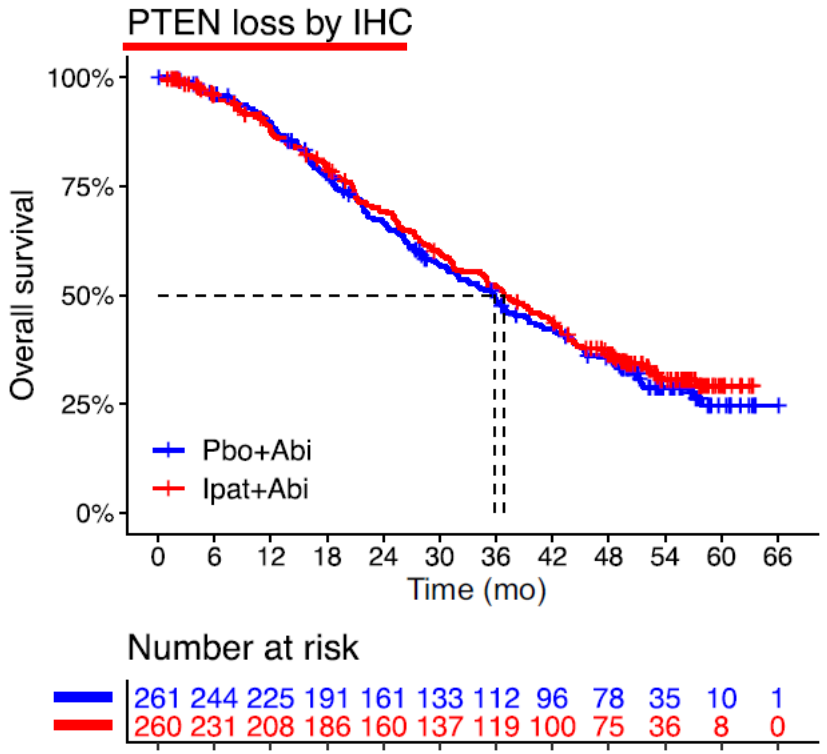
Ipatasertib-Abiraterone in mCRPC: rPFS in patients with PTEN loss by NGS



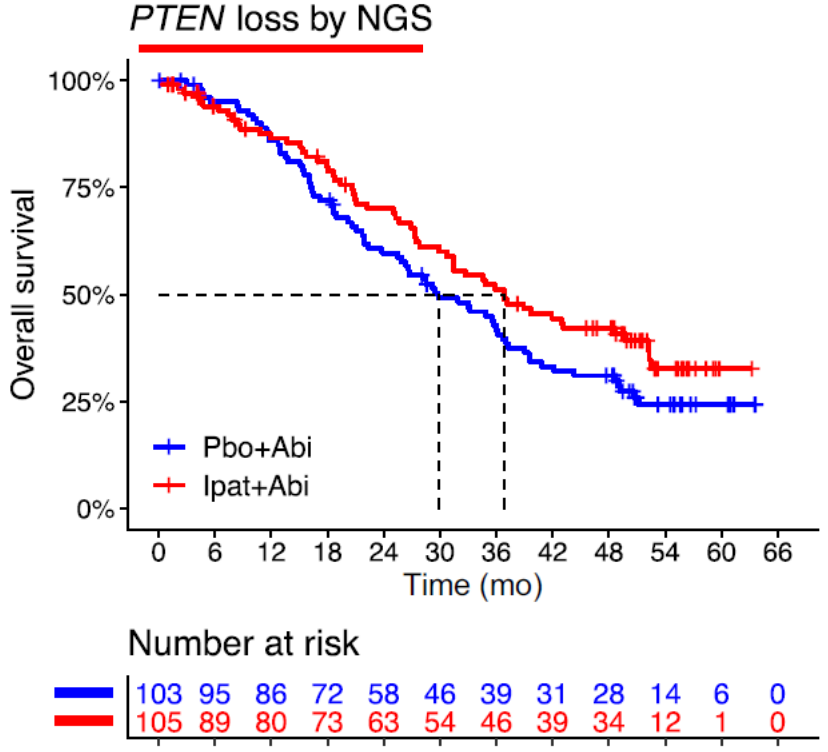
Sweeney C, Lancet 2021

Overall survival is not improved by Ipatasertib in mCRPC (IPATential 150 trial)

	Events	Patients	Median OS, mo (95% CI)	HR (95% CI), stratified	*p* value
Pbo+Abi	170	261	35.8 (30.8–39.6)	0.94 (0.76–1.17)	0.57
Ipat+Abi	158	260	36.8 (31.4–42.1)		



	Events	Patients	Median OS, mo (95% CI)	HR (95% CI), non stratified
Pbo+Abi	72	103	29.8 (25.5–37.0)	0.76 (0.54–1.07)
Ipat+Abi	58	105	36.8 (30.7–52.2)	



De Bono J, Eur Urol 2025

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

Current analysis

Enrolment period	Primary rPFS DCO	Final OS DCO
13 July 2020–5 Feb 2024	7 Oct 2024 Median rPFS follow-up:‡ ~18 mo	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

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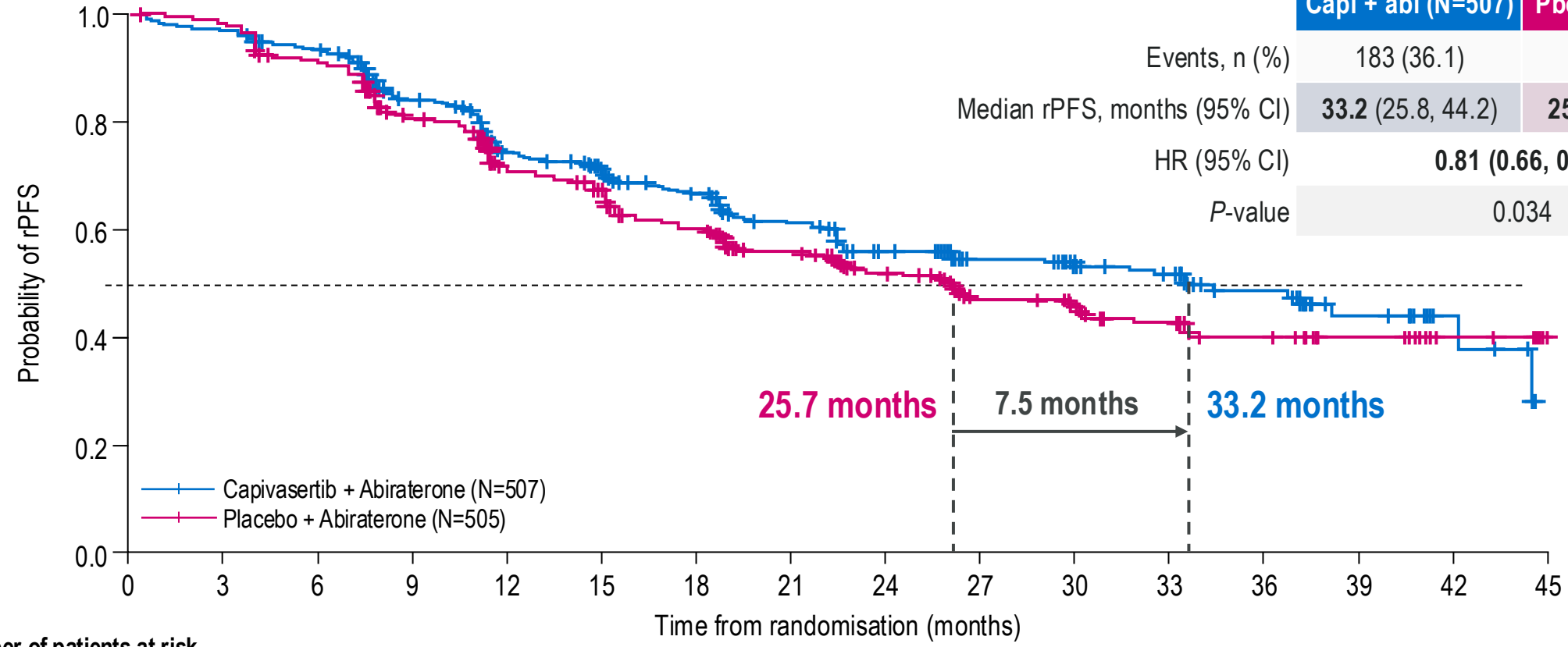
CAPItello-281 Primary endpoint: investigator-assessed rPFS

	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

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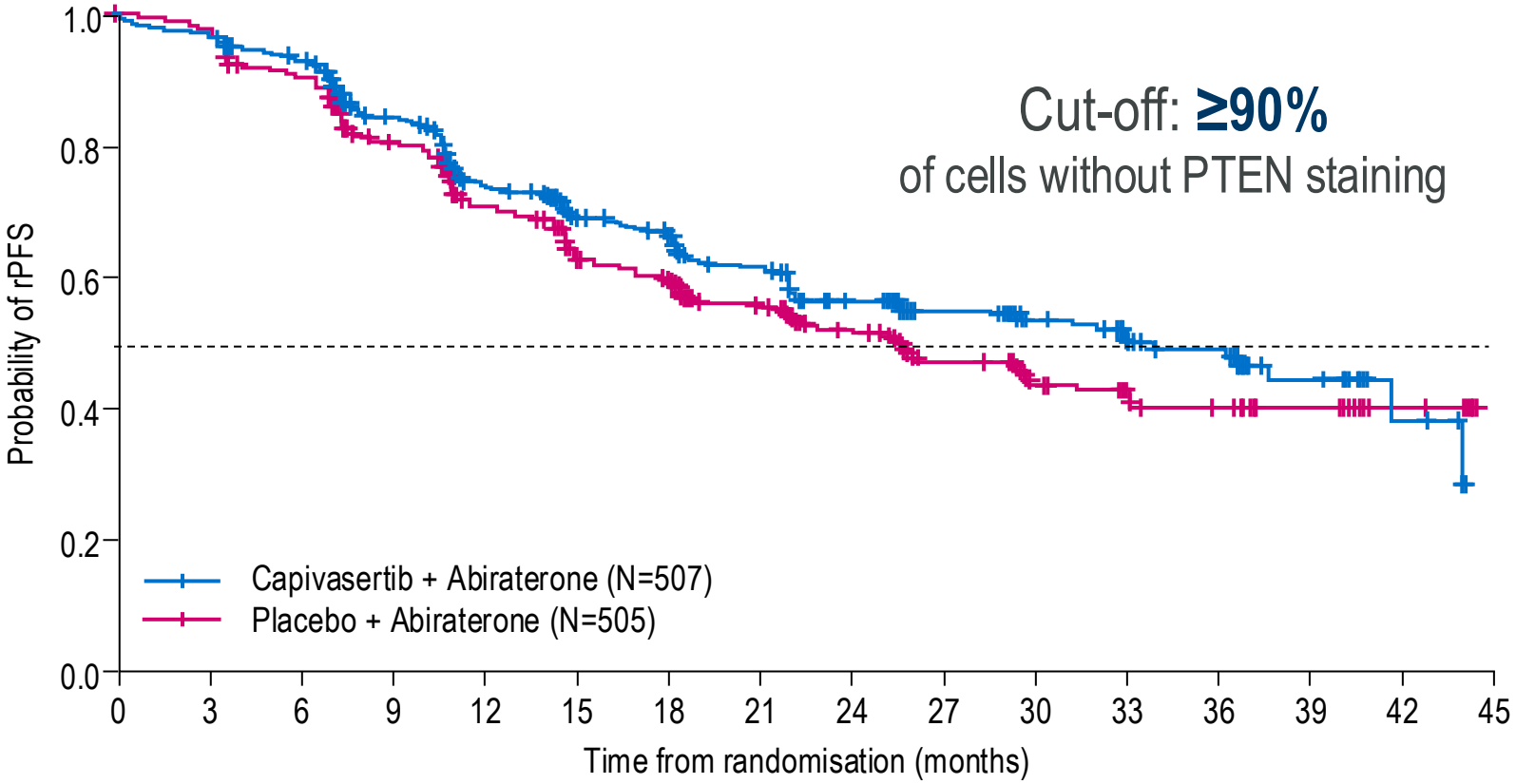
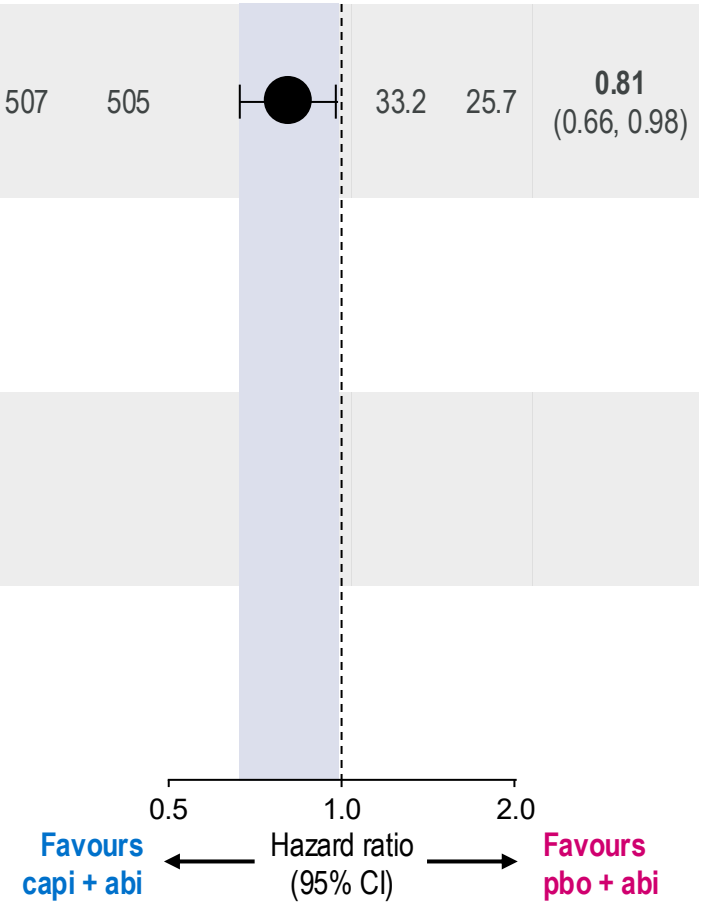
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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

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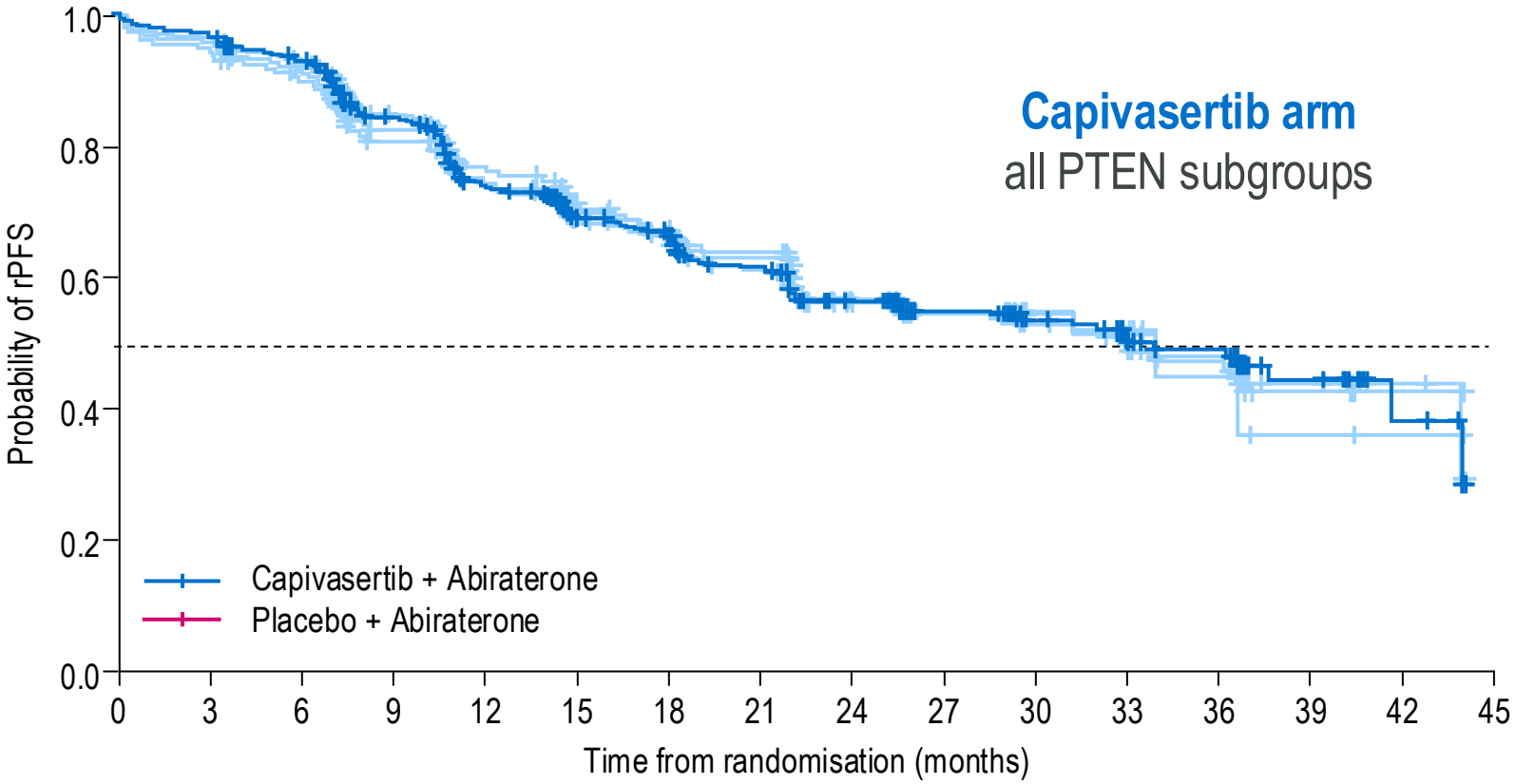
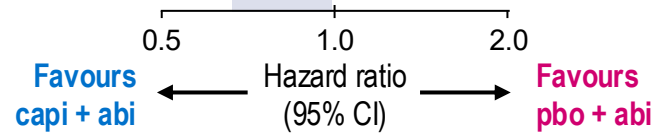
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



PTEN cutoff	Patients, n: Capi + abi	Patients, n: Pbo + abi	Median rPFS, months: Capi + abi	Median rPFS, months: Pbo + abi	HR (95% CI)
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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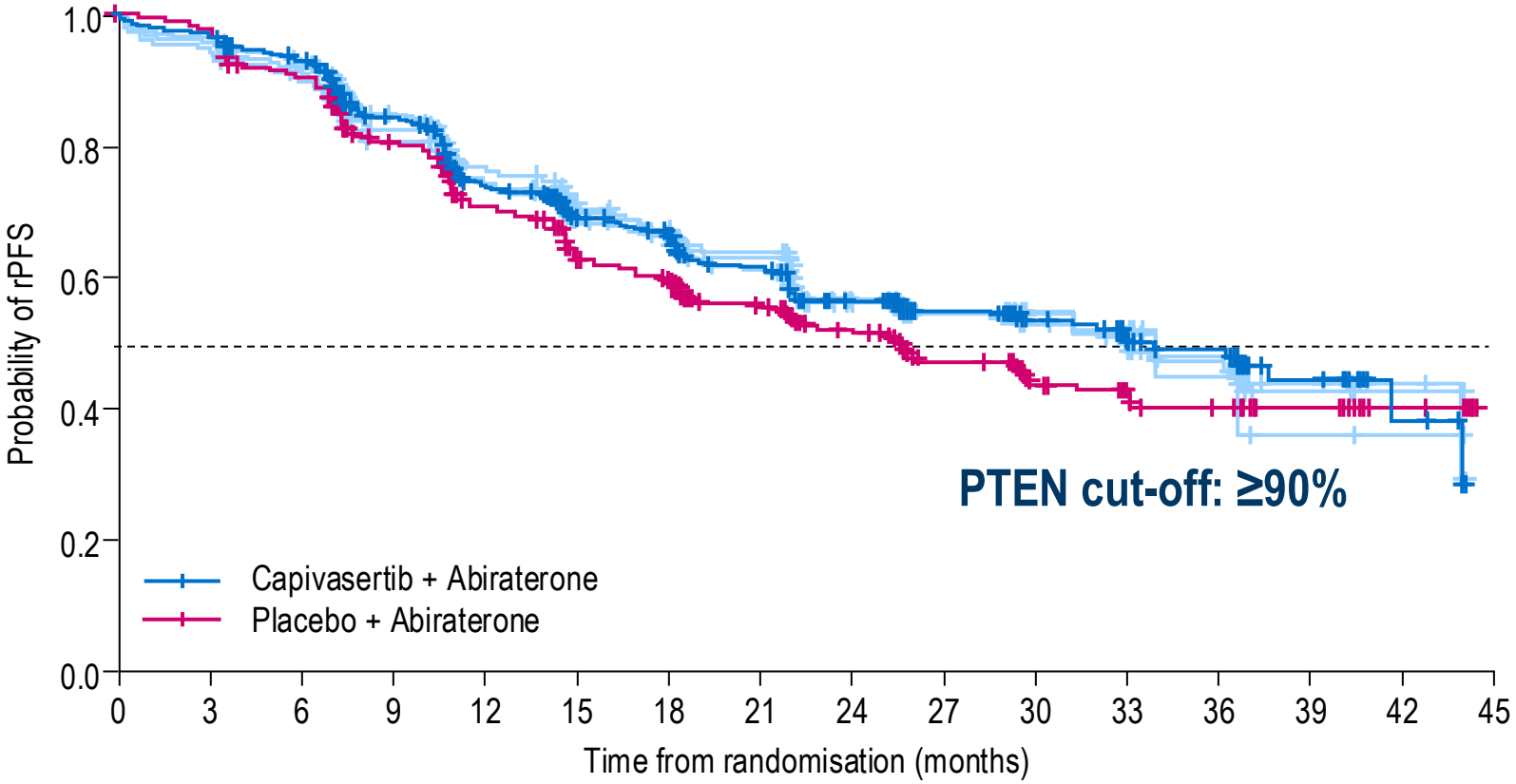
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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)
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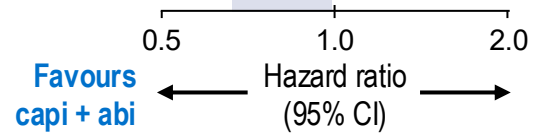

rPFS maturity in PTEN subgroups was consistent with the overall population

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

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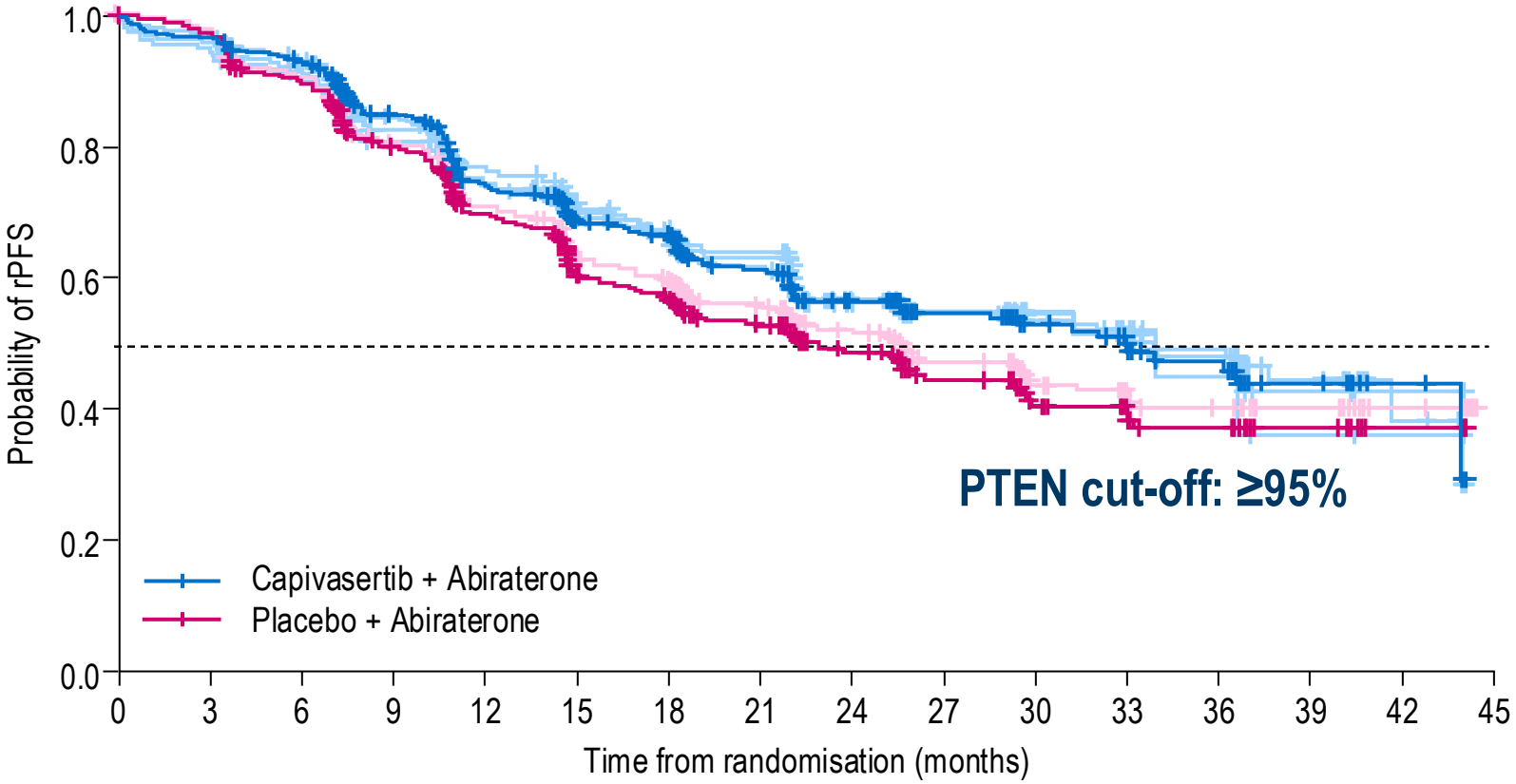
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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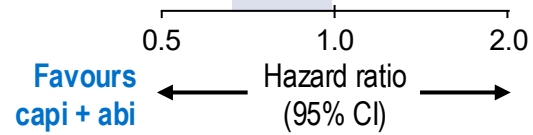

rPFS maturity in PTEN subgroups was consistent with the overall population

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

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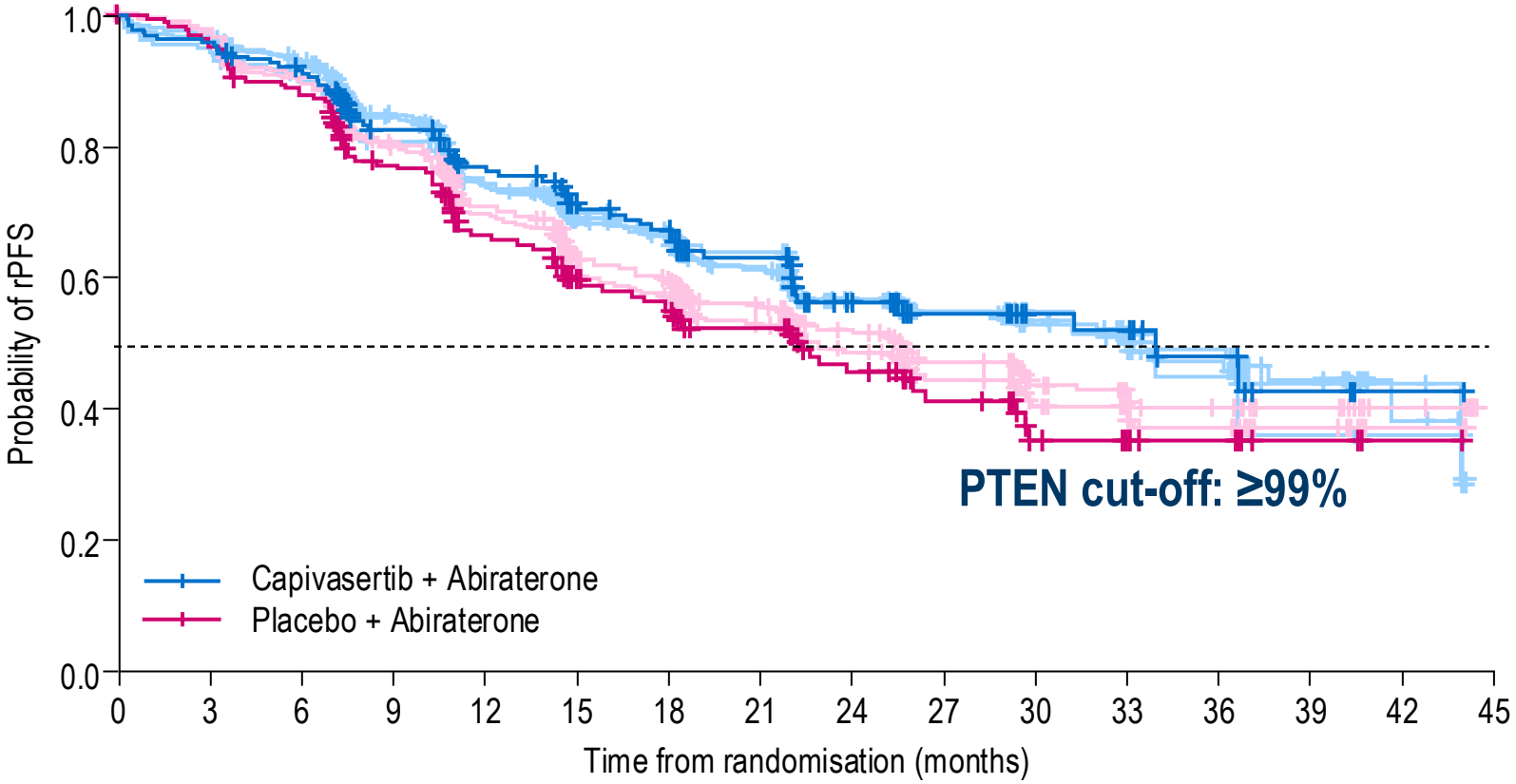
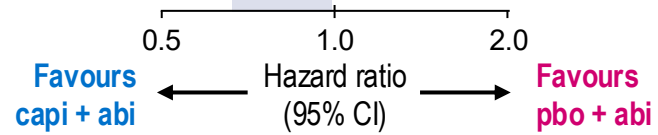
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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



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

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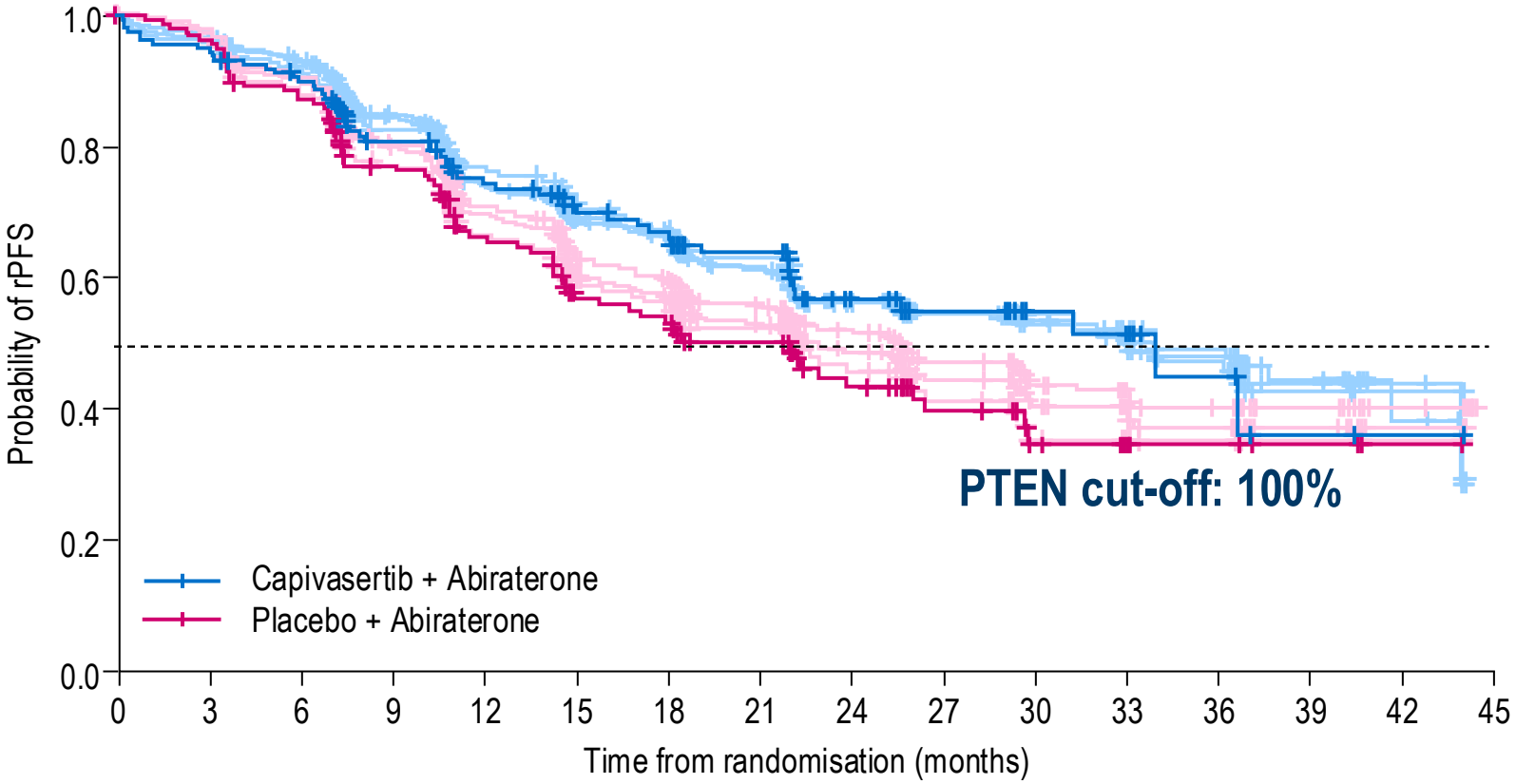
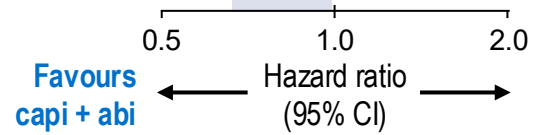
CAPItello-281 PTEN subgroups: investigator-assessed rPFS



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



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

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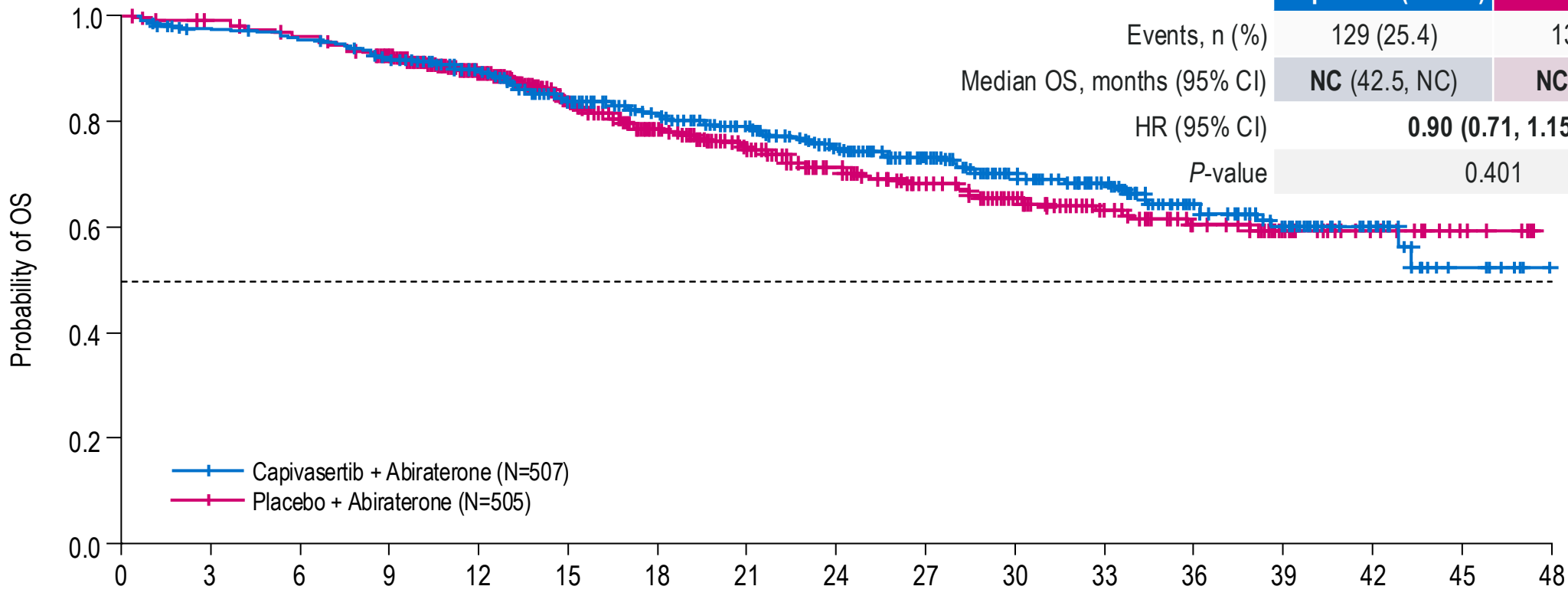
CAPItello-281: Interim OS

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

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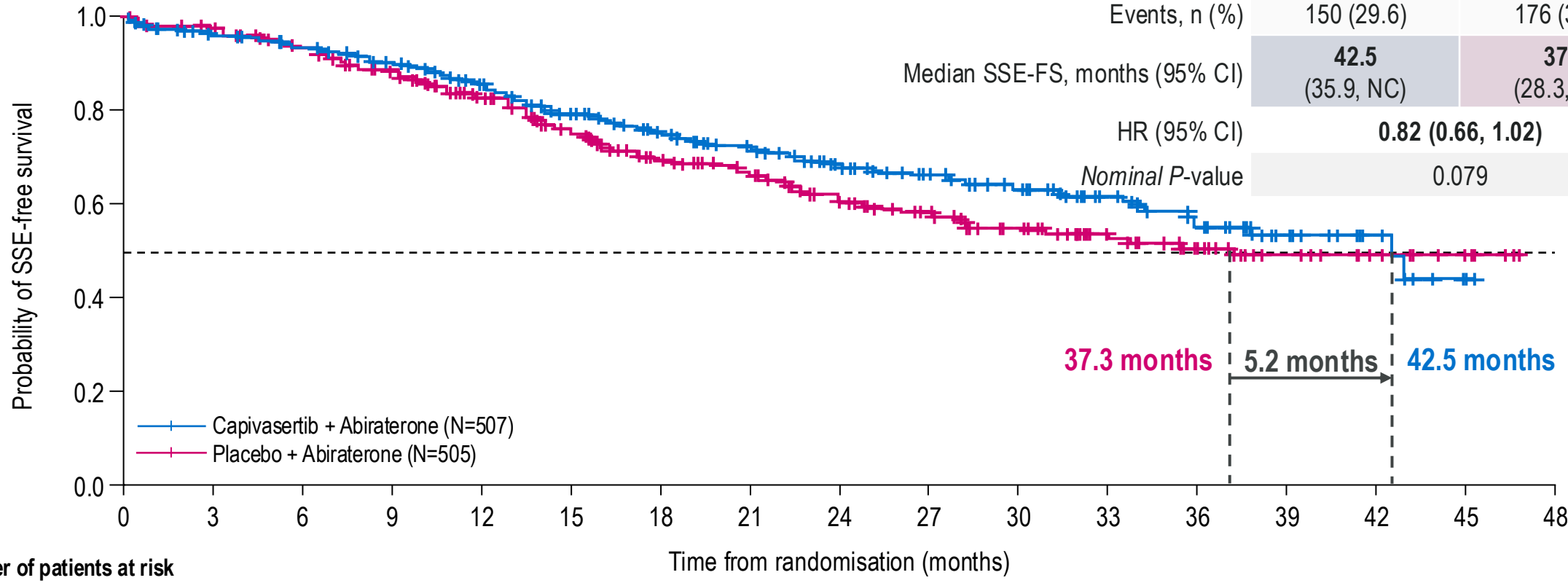
CAPItello-281: Symptomatic skeletal event-free survival

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

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



Number of patients at risk

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

CI, confidence interval; HR, hazard ratio; NC, not calculable; pbo, placebo, SSE-FS, symptomatic skeletal event-free survival

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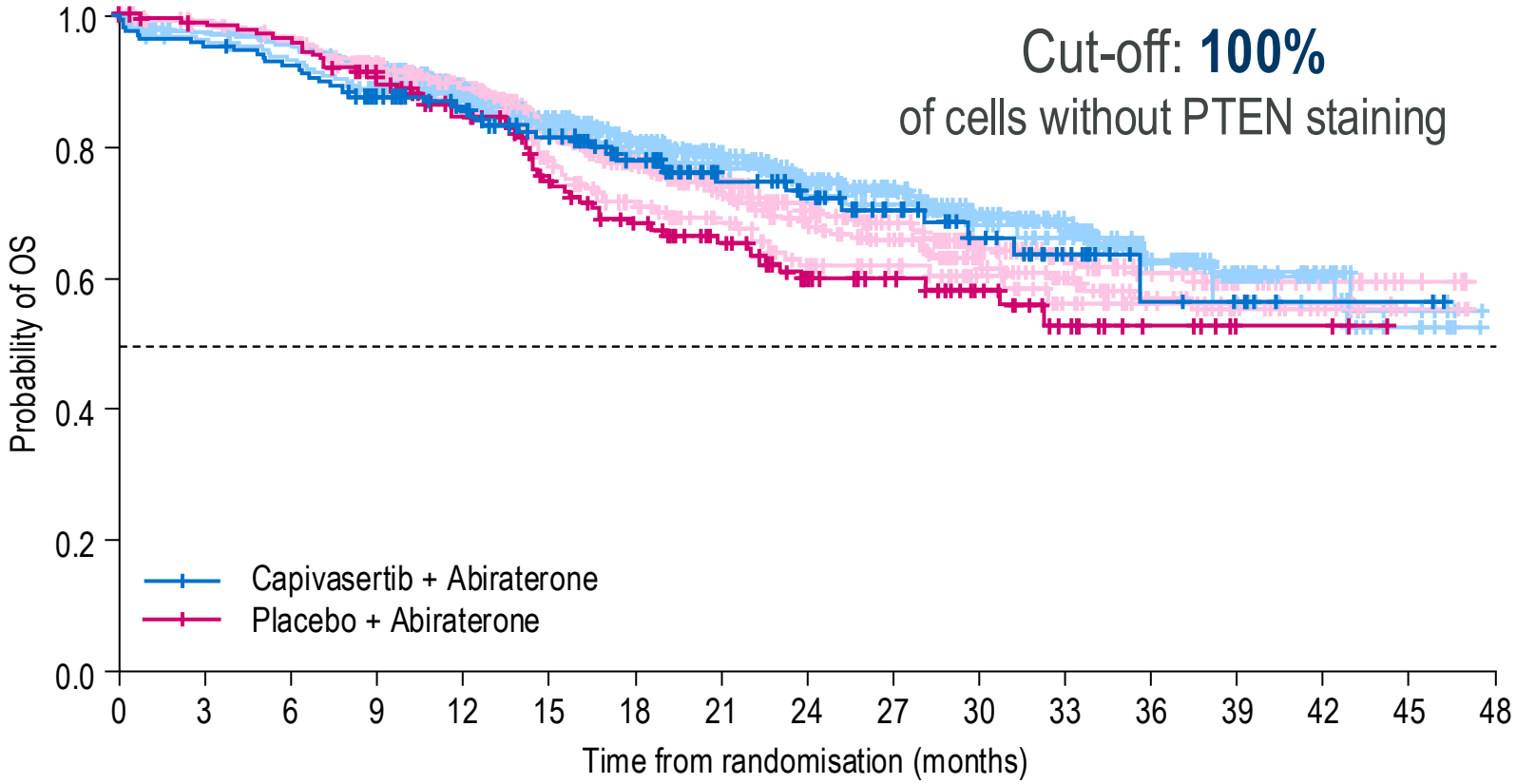
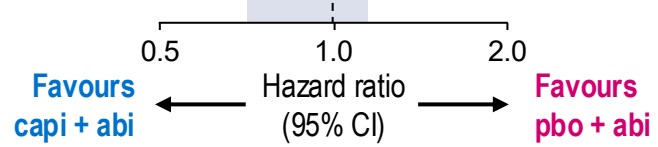
CAPItello-281 PTEN subgroups: OS



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

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CAPItello-281: Conclusions

- Patients with **PTEN deficient mHSPC** have **poor prognosis** and reduced benefit from current SoC
- CAPItello-281 met its primary objective showing a **statistically significant rPFS benefit with capi + abi** vs pbo + abi
  - Median rPFS: capi + abi arm **33.2** months vs pbo + abi **25.7** months (HR 0.81, 95% CI 0.66, 0.98; *P* = 0.034)
- Consistent benefits were also observed in **secondary endpoints** and **clinically relevant pre-defined subgroups**
  - OS was immature and further follow-up is planned
- Post-hoc analyses at **increased PTEN cutoffs** showed **greater treatment effect** with **capi + abi**
- The most common Grade ≥3 AEs of rash and hyperglycaemia are **expected with AKT inhibition**

Capivasertib in combination with abiraterone represents a potential first-in-class targeted treatment for patients with PTEN deficient mHSPC

abi, abiraterone; ADT, androgen deprivation therapy; capi, capivasertib; mHSPC, metastatic hormone-sensitive prostate cancer; pbo, placebo; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival; SoC, standard of care

Karim Fizazi MD, PhD
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Second Opinion

Neeraj Agarwal, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What were the main reasons the ipatasertib program did not move forward? What are the pharmacologic differences between ipatasertib and capivasertib?

For a fit patient with mHSPC and PTEN deficiency, how would you choose between an AR pathway inhibitor/docetaxel/ADT and capivasertib/abiraterone/ADT if capivasertib were to become available? Would the degree of PTEN loss (eg, 90% versus 100% of cells staining negative on IHC) influence this decision?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

If capivasertib/abiraterone/ADT were to reach the clinic in mHSPC, how do you envision choosing between this combination and other available and emerging biomarker-targeted therapies, such as niraparib/abiraterone/prednisone and lutetium Lu 177 vipivotide tetraxetan/AR pathway inhibitor/ADT, for patients with more than one actionable biomarker?

What's next for AKT inhibitors in prostate cancer? Do you anticipate that capivasertib will eventually be used in earlier settings or as a component of other combination strategies? Beyond PTEN deficiency, are there other genomic signatures that may predict benefit from capivasertib?

RTP
RESEARCH TO PRACTICE

Second Opinion

Rana R McKay, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

If capivasertib/abiraterone/ADT were available at the time of this patient's initial diagnosis of mHSPC, how likely would you have been to recommend it?

What would you recommend for this patient at this time? Would you consider adding capivasertib to triplet therapy with an AR pathway inhibitor, chemotherapy and ADT under any circumstances?

How would you think through next steps when this patient eventually experiences disease progression to mCRPC? Would you ever consider capivasertib for a patient with mCRPC and PTEN deficiency under any circumstances?

RTP
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TO PRACTICE

Agenda

Module 1: Clinical Implications of and Appropriate Strategies to Identify PTEN Deficiency in Prostate Cancer — Dr George

Module 2: Targeting AKT in Metastatic Prostate Cancer — Prof Karim Fizazi

Module 3: Tolerability and Other Practical Considerations with Capivasertib — Dr Heath

RTP RESEARCH TO PRACTICE

MAYO CLINIC

TOLERABILITY AND OTHER PRACTICAL CONSIDERATIONS WITH CAPIVASERTIB

Elisabeth Heath, MD

Professor of Oncology
Chair, Department of Oncology
Rochester, MN

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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)

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

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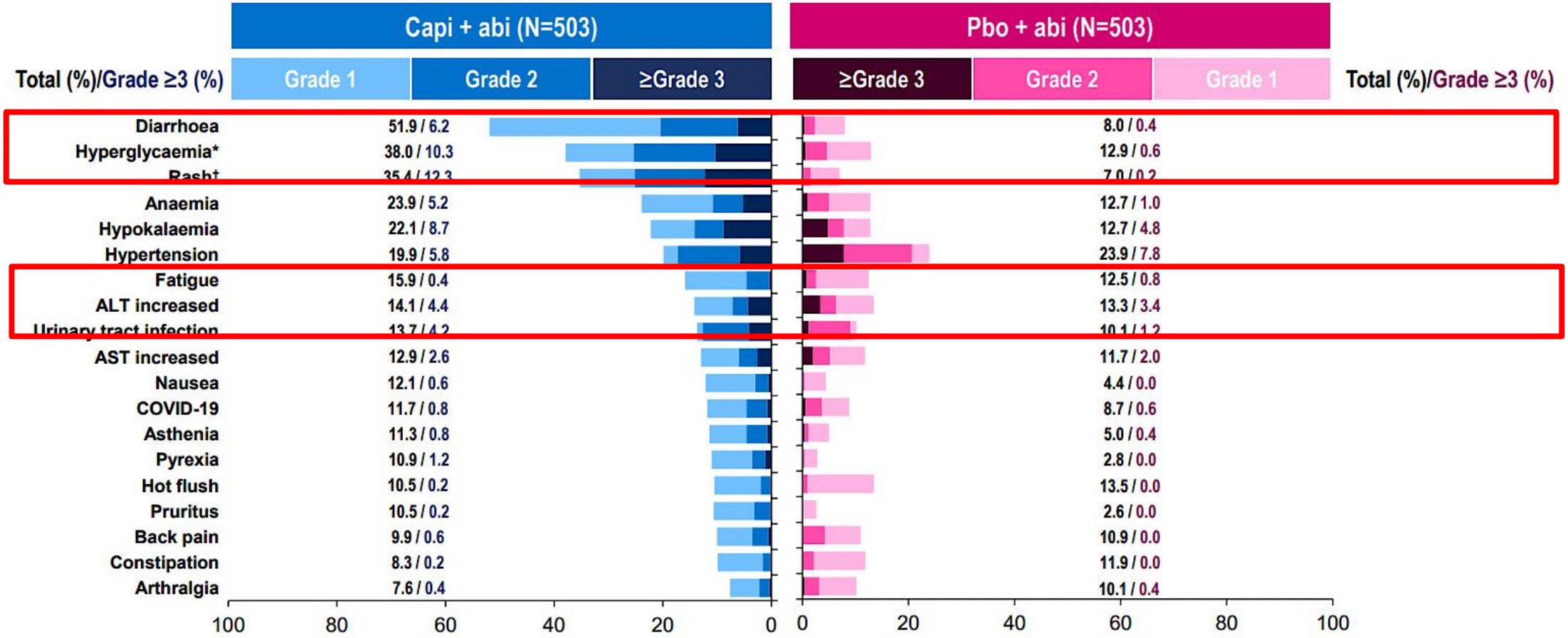
CAPITELLO-281: ADVERSE EVENTS (≥ 10% OF PATIENTS)



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

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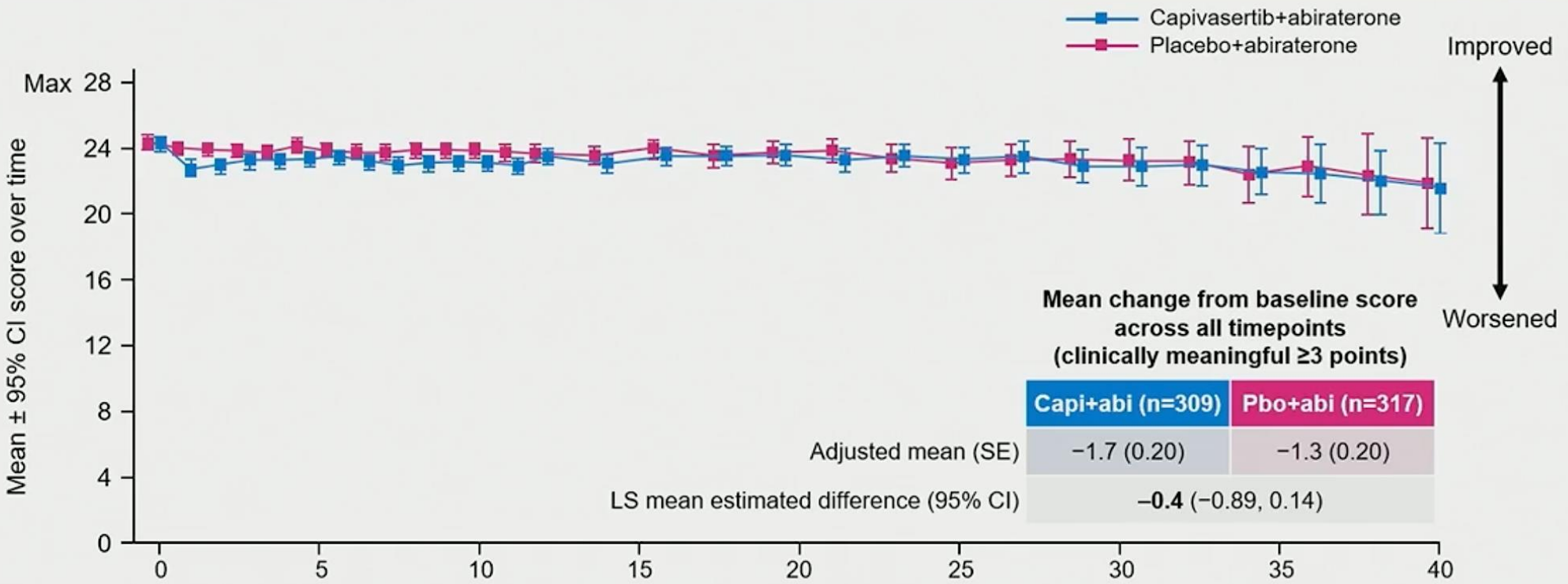
CAPItello-281: FACT–P physical wellbeing (PWB)

PWB includes outcomes such as side effects, energy, nausea and pain



Mean change from baseline score across all timepoints (clinically meaningful ≥3 points)

	Capi+abi (n=309)	Pbo+abi (n=317)
Adjusted mean (SE)	−1.7 (0.20)	−1.3 (0.20)
LS mean estimated difference (95% CI)	**–0.4** (−0.89, 0.14)	

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

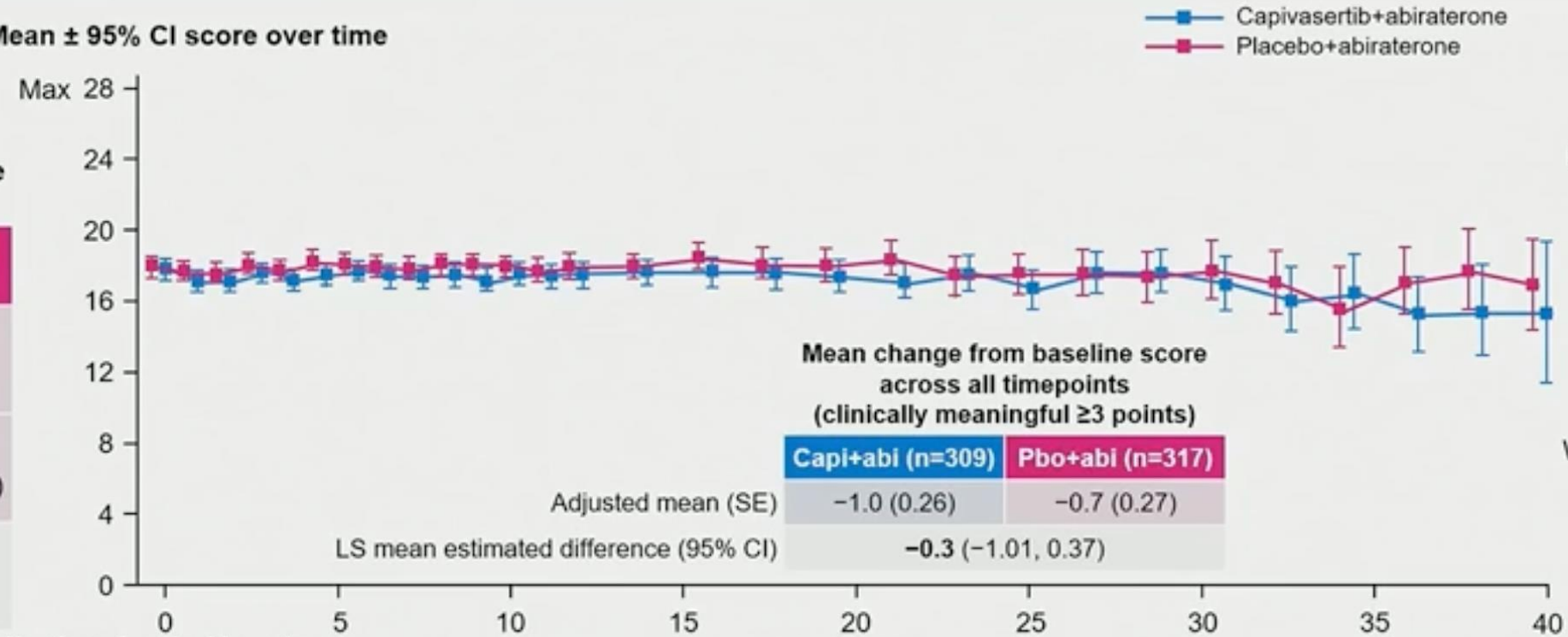
Patients were assessed every 4 weeks (±6 days) until week 52, then every 8 weeks (±6 days) until 12 months post radiographic disease progression, or subsequent anticancer therapy.
abi, abiraterone; capi, capivasertib; CI, confidence interval; FACT–P, Functional Assessment of Cancer Therapy–Prostate Cancer; LS, least squares; pbo, placebo; SE, standard error

CAPItello-281: FACT–P functional wellbeing (FWB)

FWB includes outcomes such ability to work, sleep quality and ability to enjoy life

Time to clinically meaningful decrease (≥3 points)

	Capi+abi (N=507)	Pbo+abi (N=505)
Events, n (%)	171 (33.7)	175 (34.7)
Median, months (95% CI)	6.3 (4.4, 10.9)	8.1 (5.4, 14.6)
HR (95% CI)	**1.06** (0.86, 1.32)	



Mean change from baseline score across all timepoints (clinically meaningful ≥3 points)

	Capi+abi (n=309)	Pbo+abi (n=317)
Adjusted mean (SE)	−1.0 (0.26)	−0.7 (0.27)
LS mean estimated difference (95% CI)	**−0.3** (−1.01, 0.37)	

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

Time to decrease in ≥3 points is defined as the time from randomization until date of first confirmed clinically meaningful decrease before receiving subsequent anticancer therapy (KM curves are available via QR code).
Patients were assessed every 4 weeks (±6 days) until week 52, then every 8 weeks (±6 days) until 12 months post radiographic disease progression, or subsequent anticancer therapy.
abi, abiraterone; capi, capivasertib; CI, confidence interval; FACT–P, Functional Assessment of Cancer Therapy-Prostate Cancer; HR, hazard ratio; LS, least squares; pbo, placebo; SE, standard error

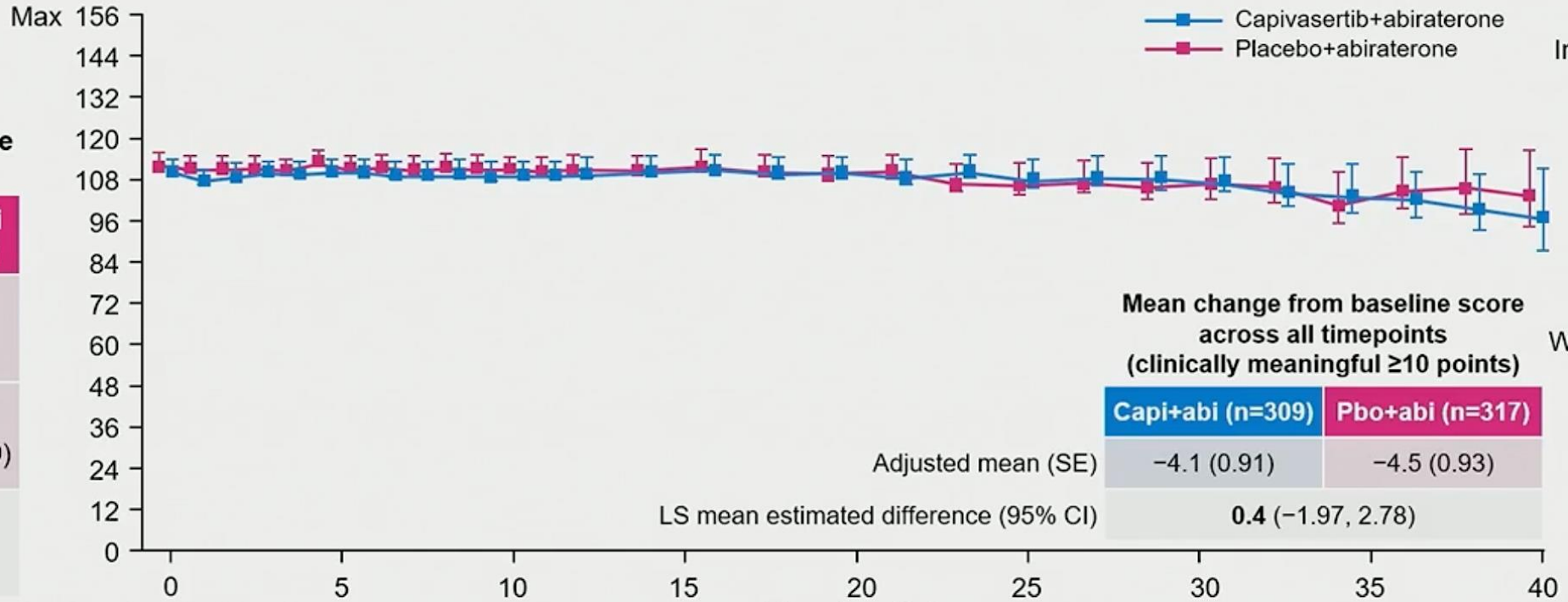
CAPItello-281: FACT–P total score

FACT–P total score includes physical, functional and emotional wellbeing, as well as prostate cancer symptoms

Time to clinically meaningful decrease (≥10 points)

	Capi+abi (N=507)	Pbo+abi (N=505)
Events, n (%)	163 (32.1)	163 (32.3)
Median, months (95% CI)	9.0 (6.3, 20.1)	12.7 (8.1, 21.9)
HR (95% CI)	**1.10** (0.89, 1.37)	

Mean ± 95% CI score over time



Mean change from baseline score across all timepoints (clinically meaningful ≥10 points)

	Capi+abi (n=309)	Pbo+abi (n=317)
Adjusted mean (SE)	−4.1 (0.91)	−4.5 (0.93)
LS mean estimated difference (95% CI)	**0.4** (−1.97, 2.78)	

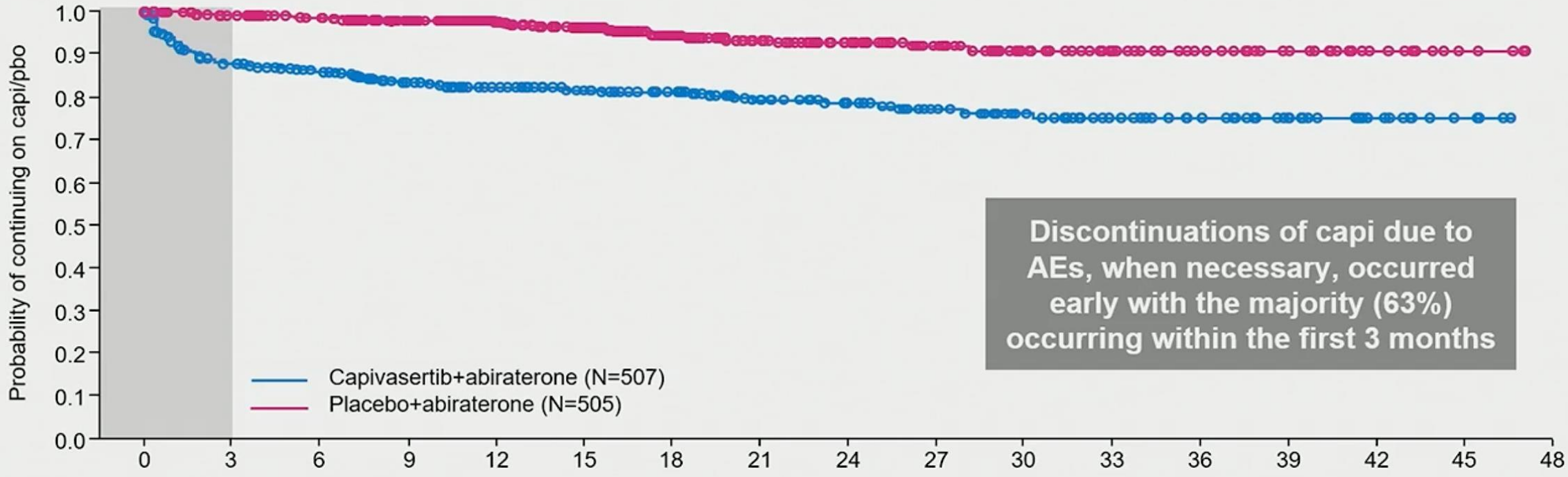
Number of evaluable patients

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	

Time to decrease in ≥10 points in FACT–P is defined as the time from randomization until date of first confirmed clinically meaningful decrease before receiving subsequent anticancer therapy (KM curves are available via QR code). Patients were assessed every 4 weeks (±6 days) until week 52, then every 8 weeks (±6 days) until 12 months post radiographic disease progression, or subsequent anticancer therapy.

abi, abiraterone; capi, capivasertib; CI, confidence interval; FACT–P, Functional Assessment of Cancer Therapy-Prostate Cancer; LS, least squares; pbo, placebo; SE, standard error

CAPItello-281: Discontinuations due to AEs



Discontinuations of capi due to AEs, when necessary, occurred early with the majority (63%) occurring within the first 3 months

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

*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. Patients not known to have discontinued capi/pbo because of AEs were censored at the earliest of the following: death date, end of study date, DCO date and when discontinuation of capi/pbo was not due to AEs. AE, adverse event; capi, capivasertib; DCO, data cutoff; pbo, placebo; SAE, serious AE

CAPItello-281: Common AEs associated with AKT inhibition

	Rash*		Diarrhea		Hyperglycemia†	
	Capi+abi (N=503)	Pbo+abi (N=503)	Capi+abi (N=503)	Pbo+abi (N=503)	Capi+abi (N=503)	Pbo+abi (N=503)
Any grade AE, n (%)	178 (35.4)	35 (7.0)	261 (51.9)	40 (8.0)	191 (38.0)	65 (12.9)
Grade ≥3 AE,‡ n (%)	62 (12.3)	1 (0.2)	31 (6.2)	2 (0.4)	52 (10.3)	3 (0.6)
Median (IQR) time to onset, days	13 (11–43)	78 (37–195)	12 (3–43)	142 (28–339)	54 (15–114)	114 (71–326)
AE leading to, n (%)						
Interruption of capi/pbo	85 (16.9)	3 (0.6)	63 (12.5)	1 (0.2)	55 (10.9)	4 (0.8)
Reduction of capi/pbo	43 (8.5)	2 (0.4)	22 (4.4)	0	33 (6.6)	1 (0.2)
Discontinuation of capi/pbo	24 (4.8)	0	5 (1.0)	0	5 (1.0)	0
Supportive treatment given, n (%)	146 (29.0)	20 (4.0)	167 (33.2)	19 (3.8)	127 (25.2)	23 (4.6)
Outcome at time of DCO, n (%)						
Recovered/recovering	164 (32.6)	28 (5.6)	238 (47.3)	36 (7.2)	140 (27.8)	43 (8.5)
Not recovered	24 (4.8)	8 (1.6)	45 (8.9)	4 (0.8)	65 (12.9)	25 (5.0)

*Grouped term including the preferred terms of erythema, rash, rash erythematous, rash macular, rash maculopapular, rash popular, rash pruritic. †Grouped term including the preferred terms of blood glucose increased, hyperglycemia. ‡A diarrhea AE of Grade 4 was reported for one patient (0.2%) in the capi+abi arm only, hyperglycemia AEs of Grade 4 and Grade 5 were reported for one patient (0.2%) each in the capi+abi arm only, no Grade 4–5 AEs of rash were reported. No primary prophylaxis interventions were used during the CAPItello-281 trial for prospective AE management. Additional data on supportive treatment received are available via QR code.
abi, abiraterone; AE, adverse event; capi, capivasertib; DCO, data cutoff; IQR, interquartile range; pbo, placebo

Conclusions

- CAPItello-281 met its primary objective showing a statistically significant rPFS benefit with capi+abi vs pbo+abi
  - Median rPFS: 33.2 months vs 25.7 months (HR 0.81, 95% CI 0.66, 0.98; *P*=0.034)
  - Post hoc analyses at increased PTEN cutoffs showed greater treatment effect with capi+abi
- Common AEs associated with AKT inhibition (diarrhea, rash, hyperglycemia) occurred early and were clinically manageable
- Despite more AEs in the capi+abi arm, addition of capivasertib did not affect other functional aspects of patient life (eg work, sleep, enjoyment of life) and overall HRQoL during mHSPC (mAPMN), allowing for continued treatment in ~80% of patients

Capivasertib in combination with abiraterone represents a potential first-in-class targeted treatment for patients with PTEN-deficient mHSPC (mAPMN)

abi, abiraterone; AE, adverse event; capi, capivasertib; CI, confidence interval; HR, hazard ratio; HRQoL, health-related quality of life; mAPMN, metastatic androgen pathway modulation naïve; mHSPC, metastatic hormone-sensitive prostate cancer; pbo, placebo; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival

GASTROINTESTINAL ADVERSE EVENT MANAGEMENT

GRADE 1	< 4 STOOLS PER DAY	• CONTINUE CAPIVASERTIB
GRADE 2	4-6 STOOLS PER DAY	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE OR ONE DOSE LOWER AS CLINICALLY INDICATED • IF RECOVERY IN > 28 DAYS, RESUME AT ONE LOWER DOSE AS CLINICALLY INDICATED • FOR RECURRENCE, REDUCE CAPIVASERTIB BY ONE LOWER DOSE
GRADE 3	≥ 7 STOOLS PER DAY	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE OR ONE DOSE LOWER AS CLINICALLY INDICATED • IF RECOVERY IN > 28 DAYS, PERMANENTLY DISCONTINUE CAPIVASERTIB
GRADE 4	LIFE THREATENING	• PERMANENTLY DISCONTINUE CAPIVASERTIB

Iyengar NM et al. NPJ Breast Cancer. 2025 Dec 4;12:16.

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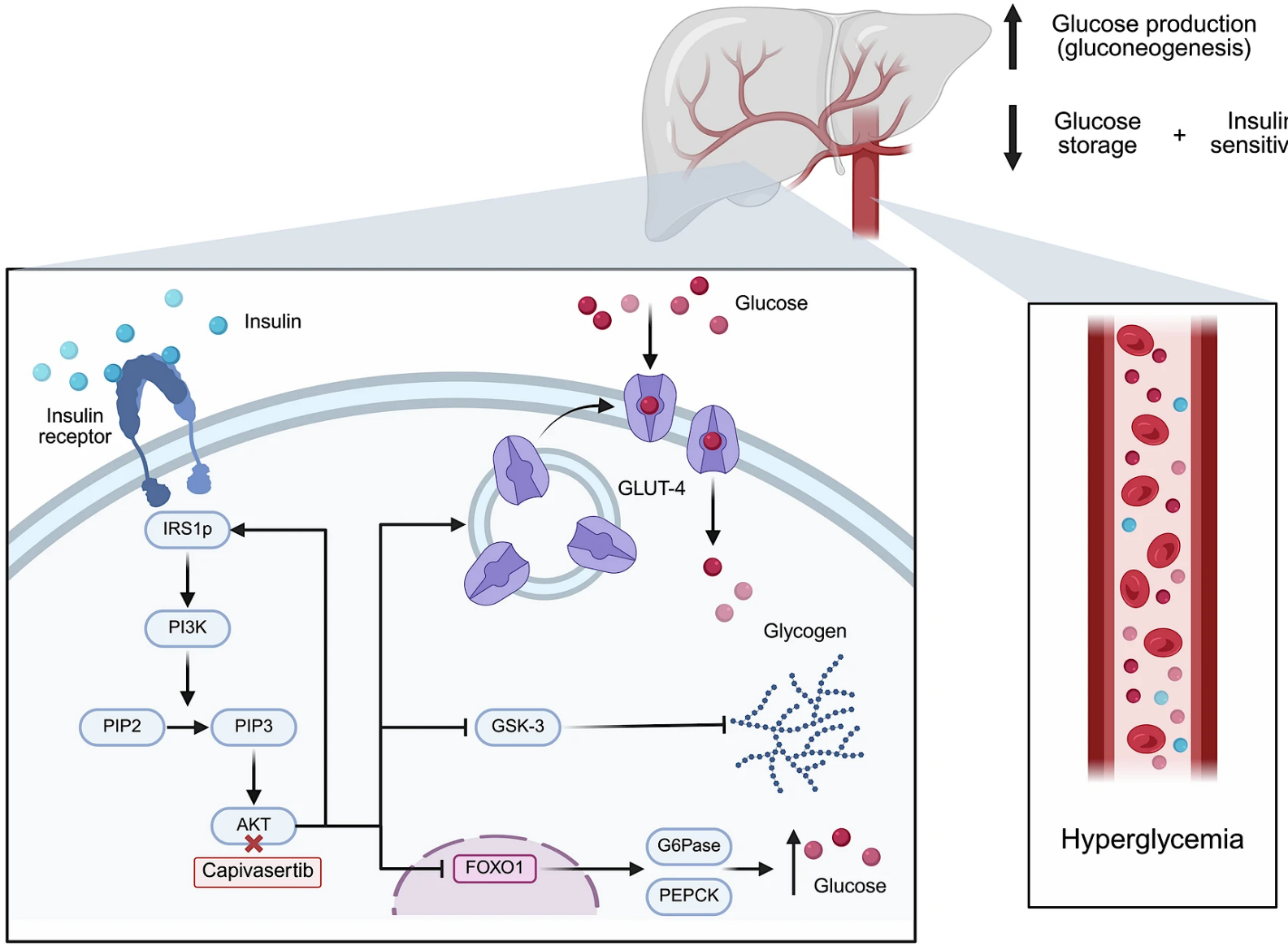
MECHANISM OF AKT INHIBITOR-INDUCED HYPERGLYCEMIA



Iyengar NM et al. *NPJ Breast Cancer* 2025 December 4;12:16.

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HYPERGLYCEMIA ADVERSE EVENT MANAGEMENT

FG > ULN-160 MG/DL OR HBA1C > 7%	• CONTINUE CAPIVASERTIB WITH NO DOSE ADJUSTMENT • CONSIDER INITIATION OR INTENSIFICATION OR ORAL ANTI-DIABETIC TREATMENT
FG > 500 OR LIFE THREATENING SEQUELAE OF HYPERGLYCEMIA AT ANY FG LEVEL	• FOR LIFE-THREATENING SEQUELAE OF HYPERGLYCEMIA OR FG PERSISTS AT ≥ 500 MG/DL AFTER 24 HOURS, PERMANENTLY DISCONTINUE CAPIVASERTIB • IF FG < 500 MG/DL WITHIN 24 HOURS, THEN FOLLOW GUIDANCE ABOVE

Clinically significant abnormalities of glucose metabolism as defined by any of the following:

- **Patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment ii. HbA1c ≥8.0% (63.9 mmol/mol)**

Iyengar NM et al. NPJ Breast Cancer. 2025 Dec 4;12:16.

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RECOMMENDED MONITORING FOR HYPERGLYCEMIA

BEFORE INITIATING TREATMENT WITH CAPIVASERTIB, TEST FG LEVELS, HBA1C, AND OPTIMIZE FG

AFTER INITIATING CAPIVASERTIB, MONITOR FG LEVELS ON DAY 3 OR 4 OF THE DOSING WEEK DURING WEEKS 1, 2, 4, 6, AND 8, THEN MONTHLY WHILE ON TREATMENT

MONITOR HBA1C Q 3 MONTHS

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CUTANEOUS ADVERSE EVENT MANAGEMENT

GRADE 1	< 10% MACULE/PAPULE WITH OR WITHOUT SYMPTOMS	• CONTINUE CAPIVASERTIB
GRADE 2	10-30% MACULE/PAPULE, WITH OR WITHOUT SYMPTOMS	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • RESUME CAPIVASERTIB AT THE SAME DOSE • PERSISTENT OR RECURRENT: REDUCE CAPIVASERTIB BY ONE LOWER DOSE
GRADE 3	> 30% MACULE/PAPULE, WITH MODERATE/SEVERE SYMPTOMS	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE • IF RECOVERY IN > 28 DAYS, RESUME CAPIVASERTIB AT ONE LOWER DOSE • FOR RECURRENT GRADE 3, PERMANENTLY DISCONTINUE CAPIVASERTIB
GRADE 4	NOT DEFINED	• PERMANENTLY DISCONTINUE CAPIVASERTIB

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FATIGUE ADVERSE EVENT MANAGEMENT

GRADE 1	FATIGUE RELIEVED BY REST	• CONTINUE CAPIVASERTIB
GRADE 2	FATIGUE NOT RELIEVED BY REST, LIMITING INSTRUMENTAL ADL	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • RESUME CAPIVASERTIB AT THE SAME DOSE
GRADE 3	FATIGUE NOT RELIEVED BY REST, LIMITING SELF CARE ADL	• WITHHOLD CAPIVASERTIB UNTIL RECOVERY TO ≤ GRADE 1 • IF RECOVERY IN ≤ 28 DAYS, RESUME CAPIVASERTIB AT SAME DOSE • IF RECOVERY IN > 28 DAYS, RESUME CAPIVASERTIB AT ONE LOWER DOSE
GRADE 4	N/A	• PERMANENTLY DISCONTINUE CAPIVASERTIB

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MANAGEMENT OF OTHER TOXICITIES

CTCAE GRADE 1	• NO DOSE ADJUSTMENT IS REQUIRED. INITIATE APPROPRIATE MEDICAL THERAPY AND MONITOR AS CLINICALLY INDICATED.
CTCAE GRADE 2	• WITHHOLD TREATMENT UNTIL SYMPTOMS IMPROVE TO ≤ GRADE 1. RESUME AT THE SAME DOSE.
CTCAE GRADE 3	• WITHHOLD TREATMENT UNTIL SYMPTOMS IMPROVE TO ≤ GRADE 1. IF SYMPTOMS IMPROVE WITHIN 28 DAYS, RESTART AT THE SAME DOSE. IF RECOVERY OCCURS LATER THAN 28 DAYS, RESUME AT ONE LOWER DOSE.
CTCAE GRADE 4	• PERMANENTLY DISCONTINUE CAPIVASERTIB.

Capivasertib [Package Insert]
NHS SWAG Cancer Alliance

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Second Opinion

Neeraj Agarwal, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

In your experience, what is the most common toxicity that affects adherence to capivasertib?

How should clinicians approach prophylaxis and early intervention for diarrhea? At what point do you hold versus dose reduce versus discontinue capivasertib for diarrhea?

Should clinicians assess baseline hemoglobin A1C in all patients before administering capivasertib? How frequently are endocrinology referrals necessary for patients receiving this drug?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How significant are cutaneous events with capivasertib? How should cutaneous reactions be managed when they occur? Are topical interventions meaningful in preventing dose interruptions with capivasertib when skin toxicities develop?

Are there any patient populations for whom you would hesitate to use capivasertib, such as those with uncontrolled diabetes, frailty or older age?

RTP
RESEARCH
TO PRACTICE

Second Opinion

Rana R McKay, MD, FASCO

Neil Love, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

If you were going to administer capivasertib to this man, what steps would you take to mitigate the risk of hyperglycemia? Would you consider a GLP-1 agonist in his case?

How do you think the patient-reported outcomes from CAPItello-281 being presented at this meeting will inform interpretation of the originally reported adverse-event data presented at ESMO?

RTP
RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

If lutetium Lu 177 vipivotide tetraxetan were to become available in mHSPC, would it be a consideration in a case like this? Do patients with mHSPC receiving lutetium Lu 177 vipivotide tetraxetan in combination with an AR pathway inhibitor and ADT need all 6 doses?

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the postmeeting survey currently available via the corresponding QR code on the printed handout for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH TO PRACTICE