

Updates in GU Oncology: Science and Practice Changes in 2026

Jorge A. Garcia, MD, MSc, FACP.

Professor of Medicine and Urology

George and Edith Richman Distinguished Scientist Chair

Chief, Division of Solid Tumor Oncology

Senior Distinguished Physician

University Hospitals Seidman Cancer Center

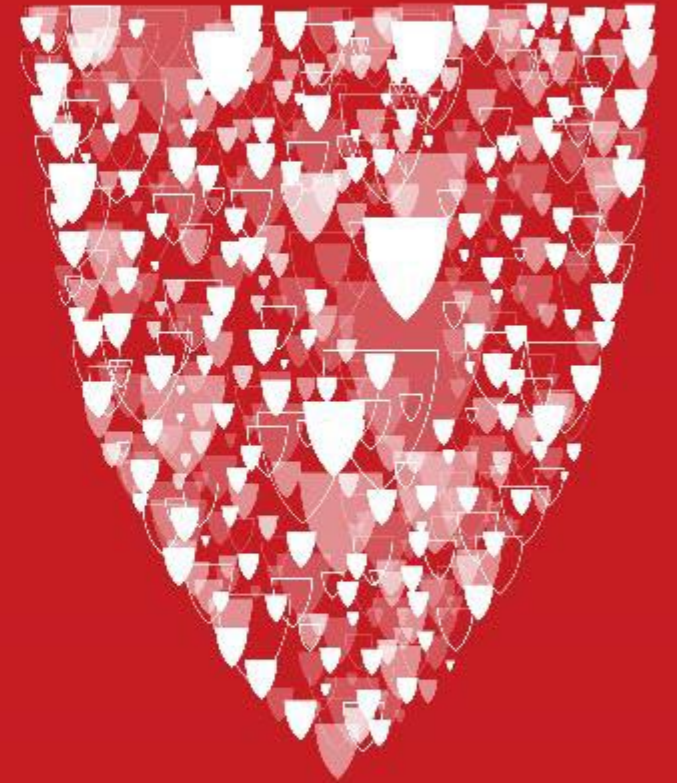
Case Western Reserve University

Case Comprehensive Cancer Center



University Hospitals
Seidman Cancer Center

Cleveland | Ohio



36 Months Conflict of Interest

Jorge A. Garcia, MD, MSc, FACP

- **Advisory Consultant:** Aptitude Health, MJH Associates, Dava Oncology, Pfizer, Astellas, GSK, Janssen, BeiGene, Urogene, AstraZeneca, Premier Inc.
- **Data Safety Committee:** MacroGenetics, Takeda
- **Research (Paid to the Institution):** Pfizer, Merck, Exelixis, Premier Inc,
- **Federal Agency:** Chairman Food Drug Administration Oncology Drug Advisory (ODAC)
 - Appointment completed late summer 2023
 - Active AdHoc Voting Member for FDA Panels

Three shifts are redefining GU oncology

PROSTATE

**Biomarker-defined
intensification enters
mHSPC**

PTEN • HRR • PSMA

KIDNEY

**Adjuvant therapy
gains OS—and a new
doublet in mRCC**

IO • HIF-2 α • VEGF

UROTHELIAL

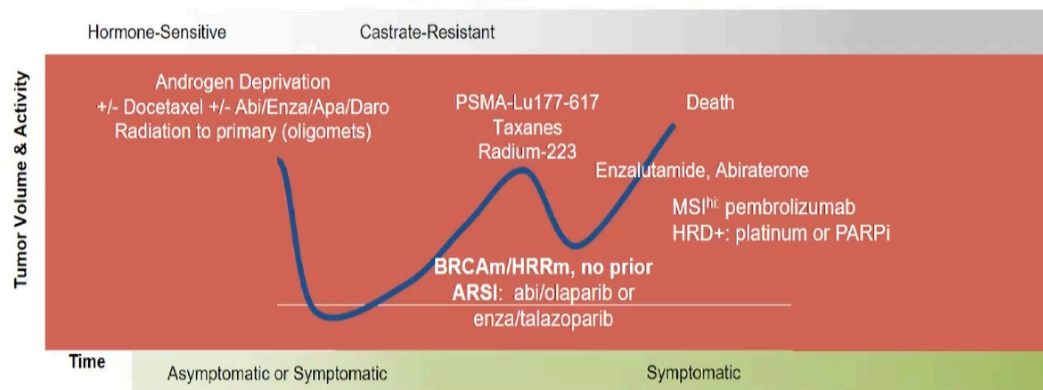
**ADC–IO displaces
chemotherapy and
moves perioperative**

EV • ctDNA • MRD

rPFS and OS improved but Progress Remains Imperfect

Men who Present with Metastatic Disease Have a Truncated Natural History

mHSPC at diagnosis comprises 5-10% of patients in the US, 30-70% of patients ex-US including India



Key Trials: STAMPEDE, LATTITUDE, CHAARTED, ARCHES, ENZAMET, TITAN, ARASENS, PEACE-1

Earlier use of potent AR therapy is changing our algorithm for subsequent therapy
Integration of chemo-hormonal therapy with ADT OR novel AR therapies
Triplet therapy with abi/darolutamide and docetaxel in high volume disease

Therapy	Prior Docetaxel	Comparator	FFS/PFS benefit, HR, p-value	OS benefit, HR; p-value
Radiation to the Primary	No	No radiation, ADT alone +/- docetaxel	Yes: low volume HR 0.59 p<0.0001	Yes: low volume HR 0.68 p=0.007
Enzalutamide ARCHES ENZAMET	18% 44-45%	Placebo/ADT ADT/Bicalutamide	Yes HR 0.39 p<0.0001 Yes HR 0.39 p<0.0001	Yes HR 0.66 p<0.0001 all volumes Yes HR 0.67 p=0.002 all volumes
Docetaxel/prednisone: STAMPEDE	No	ADT	Yes HR 0.61 p<0.0001	Yes HR 0.76 p=0.005 all volumes Yes HR 0.63 p<0.001 high volume HR 1.04 low volume
Docetaxel: CHAARTED	No	ADT	Yes HR 0.61 p<0.0001	
Docetaxel/Abiraterone	Yes	Docetaxel/ADT	Yes HR 0.47-0.58 p=0.006, <0.0001	Yes HR 0.72 p=0.019 high volume de novo
Apalutamide	11%	Placebo/ADT	Yes HR 0.48 p<0.001	Yes HR 0.67 p=0.0053 all volumes
Abiraterone/Prednisone LATTITUDE	No	Prednisone	Yes HR 0.47 p<0.0001	Yes HR 0.66 p<0.001 high risk
Abiraterone/Prednisone STAMPEDE	No	Prednisone	Yes HR 0.31 p<0.0001	Yes HR 0.61 p<0.001 all risk/volumes
Abiraterone/prednisone (PEACE-1)	100% (concurrent)	ADT/Docetaxel	Yes HR 0.50 p<0.0001	Yes HR 0.75 p=0.017; HV: HR 0.72 p=0.019
Darolutamide	100% (concurrent)	Placebo/ADT/ Docetaxel	Yes CRPC HR 0.35 p<0.0001	Yes HR 0.675 p<0.0001 de novo 86%

Parker et al Lancet 2018; Armstrong et al JCO 2019 and ESMO/JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2019; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

mHSPC intensification is becoming biologically segmented

Universal backbone
ADT + ARPI

PTEN loss	Capivasertib + abiraterone CAPItello-281
PSMA-positive	¹⁷⁷ Lu-PSMA-617 + ADT/ARPI PSMAAddition
HRR alteration	Talazoparib + enzalutamide TALAPRO-3

The next decision is no longer simply “doublet or triplet?”

CAPitello-281 study design

A global, multicenter, randomized, double-blind, Phase III study

Patients with PTEN-deficient *de novo* mHSPC (mAPMN)

- PTEN deficiency: (diagnostic cutoff of **≥90%** of viable malignant cells with **no specific cytoplasmic staining** by IHC)*
 - ie ≤10% of cells expressing PTEN by IHC

Of ~6200 patients submitting tumor tissue, **97%** had a valid IHC result and **25%** were **PTEN deficient**

Stratification factors:†

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

1012 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

Key secondary endpoints

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

PRO/tolerability endpoints

- FACT-P (including PWB and FWB)
- AE assessment
- PGI-S

Study timeline

Enrollment period
July 13, 2020–February 5, 2024

Current analysis

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

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

*Determined using investigational antibody for PTEN (SP218) (Roche Diagnostics); †High-volume disease with visceral mets, high-volume disease without visceral mets, low-volume disease; North America; Western Europe and Australia; Latin America and Eastern Europe; Asia; ‡In censored patients. ADT, androgen deprivation therapy; AE, adverse event; bid, twice daily; DCO, data cutoff; FACT-P, Functional Assessment of Cancer Therapy – Prostate; FWB, functional wellbeing; IHC, immunohistochemistry; mAPMN, metastatic androgen pathway modulation naïve; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; pred, prednisone/prednisolone; PGI-S, Patient Global Impression of Severity; PRO, patient reported outcomes; PTEN, phosphatase and tensin homolog; PWB, physical wellbeing; qd, once daily; rPFS, radiographic progression-free survival. Fizazi K *et al.* *Ann Oncol* 2026;37:53–68

ASCO Genitourinary
Cancers Symposium

#GU26

PRESENTED BY: Professor Daniel J. George

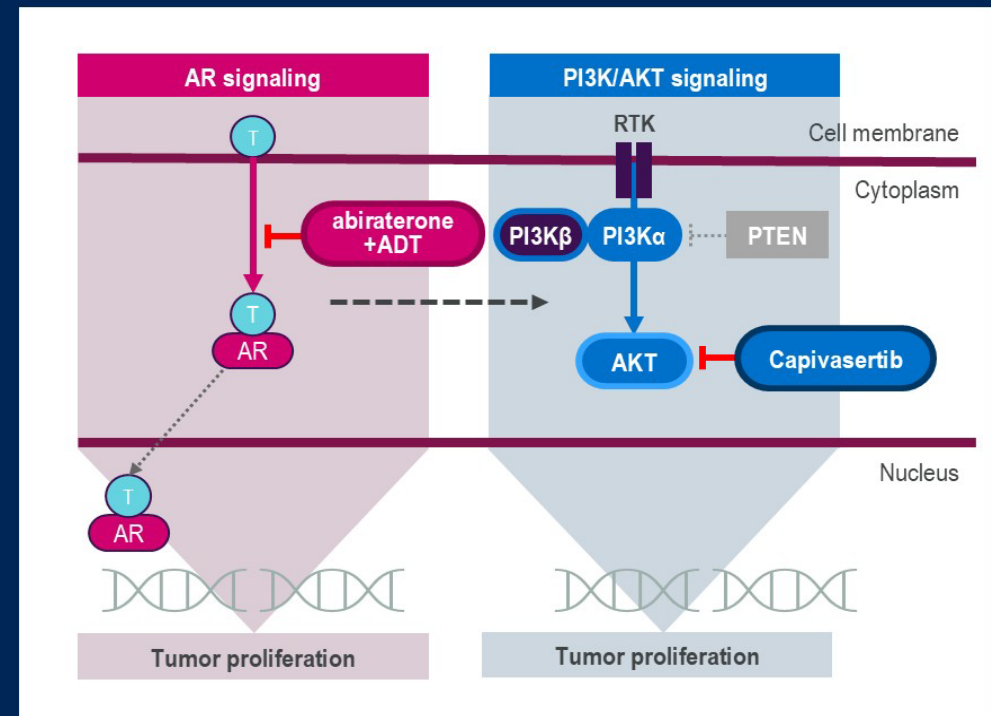
Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org.

ASCO[®] AMERICAN SOCIETY OF
CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

PTEN deficiency in prostate cancer

- In **PTEN-proficient** hormone-sensitive tumor cells, **AR signaling** is the key driver of proliferation¹
- In PTEN-deficient tumor cells, there is an **additional proliferative drive** from upregulation of the PI3K/AKT pathway that complements and provides an alternative survival mechanism to AR signaling²
- **PTEN deficiency** is associated with poor prognosis²⁻⁴
- **Capivasertib** is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- **Phase II/III evidence** showed benefits with ipatasertib (AKTi) plus abiraterone in **PTEN-deficient mCRPC (mAPMR)**^{2,3}

PTEN-deficient cell



AR, androgen receptor; mAPMR, metastatic androgen pathway modulation resistant; mCRPC, metastatic castration resistant prostate cancer; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; T, testosterone

1. Quistini A *et al. Res Rep Urol* 2025;17:211-23; 2. De Bono JS *et al. Clin Cancer Res* 2019;25:928-36; 3. Sweeney C *et al. Lancet* 2021;398:131-42; 4. Rathkopf D *et al. J Clin Oncol* 2025;43:abst 5096

CAPitello-281 met rPFS—but the absolute gain is modest

33.2 mo

Median rPFS: capivasertib +
abiraterone

25.7 mo

Median rPFS: placebo +
abiraterone

HR 0.81

95% CI 0.66–0.98; P=0.034

- PTEN deficiency: $\geq 90\%$ malignant cells with absent cytoplasmic staining by central IHC
- OS immature: HR 0.90; no proven survival advantage
- Added hyperglycemia, diarrhea and cutaneous toxicity; benefit–risk requires selection

My interpretation: FDA approval supports access—not automatic treatment of every PTEN-deficient patient.

Use capivasertib selectively—and test early

Strongest rationale

- Near-complete PTEN loss
- De novo / high-volume biology
- Fit, motivated patient
- Low metabolic/dermatologic risk

Reasons to pause

- Low-volume or metachronous disease
- Poorly controlled diabetes
- Baseline rash / frailty / polypharmacy
- Preference for proven OS-based triplet

Delayed testing

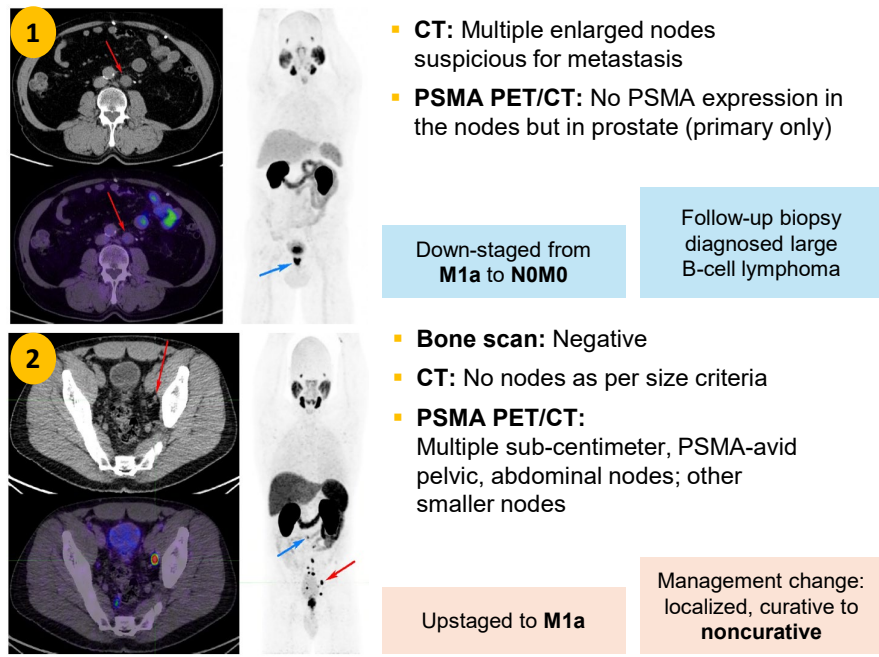
Trial entry allowed limited prior ADT/abiraterone; evidence does not define late “add-on” after a prolonged response assessment.

Do not extrapolate intact PTEN + isolated AKT1 mutation: CAPitello-281 selected by PTEN IHC.

RLT Progress is Promising but Challenges Remain

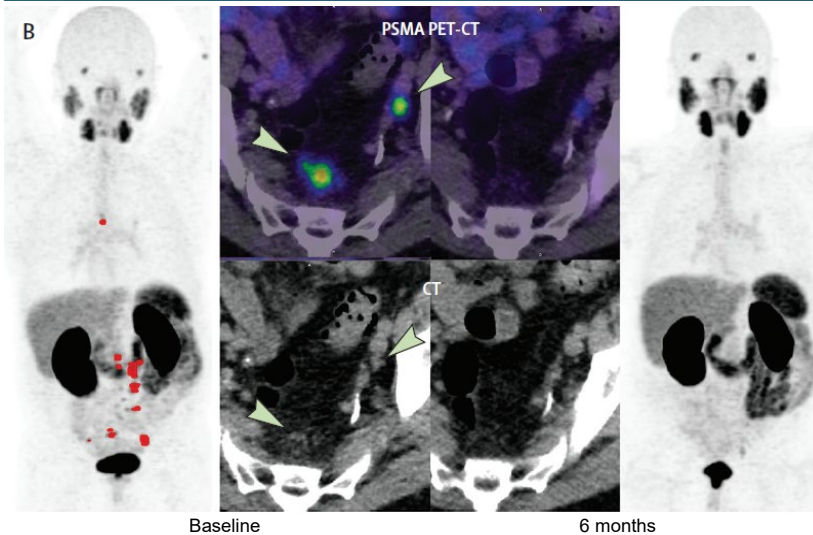
Imaging Success has been transformational but challenges in interpretation and applicability for some remains

Case studies: impact of PSMA PET/CT on disease staging¹



Alipour R, et al. Ther Adv Med Oncol. 2019;11:1–14; Sonni I, et al. J Nucl Med. 2020;61(8):1153–1160; von Klot CJ, et al. Nucl Med Mol Imaging. 2017;51(4):314–322; Ferraro DA, et al. Eur J Nucl Med Mol Imaging. 2020;47(1):147–159.

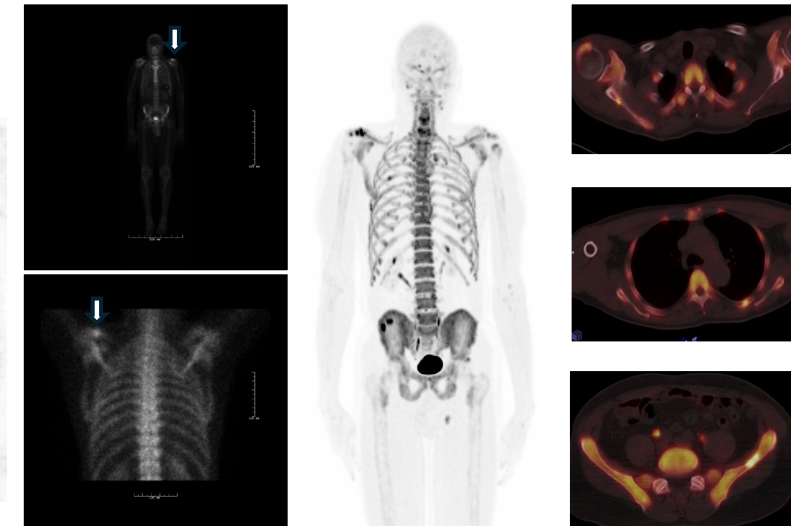
ProPSMA: PSMA PET/CT images show multiple metastases in a patient with normal results from baseline conventional imaging



⁶⁸Ga-PSMA-11 PET/CT showed multiple sub-cm pelvic and distant nodal metastases with regression at 6-month follow-up

Hofman MS, et al. Lancet. 2020;395(10231):1208–1216.

Traditional Clinical Case Scenario Upstaging to Metastatic CSPC



2015 HR PCa pt (IPSA21/cT2/GS8) with baseline WBS showing questionable uptake in L clavicle
Underwent PET imaging that showed HV disease

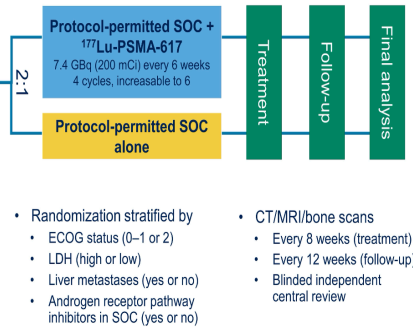
JAGR – CCF Case

Earlier Therapeutic Successes of RLT in CRPC

Open-label study of protocol-permitted standard of care ± ¹⁷⁷Lu-PSMA-617 in adults with PSMA-positive mCRPC

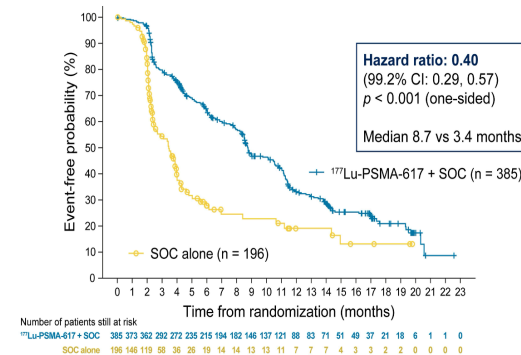
Eligible patients

- Previous treatment with both
 - ≥ 1 androgen receptor pathway inhibitor
 - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
 - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ⁶⁸Ga-PSMA-11



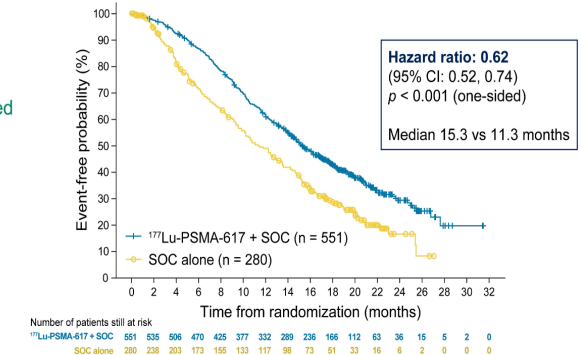
Primary endpoints: ¹⁷⁷Lu-PSMA-617 improved rPFS

Primary analysis rPFS analysis set (n = 581)

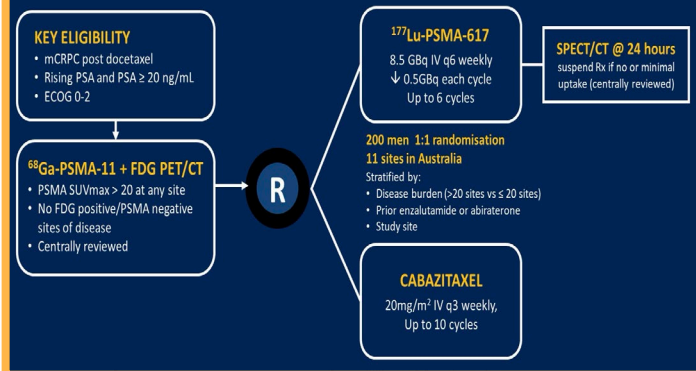


Primary endpoints: ¹⁷⁷Lu-PSMA-617 prolonged OS

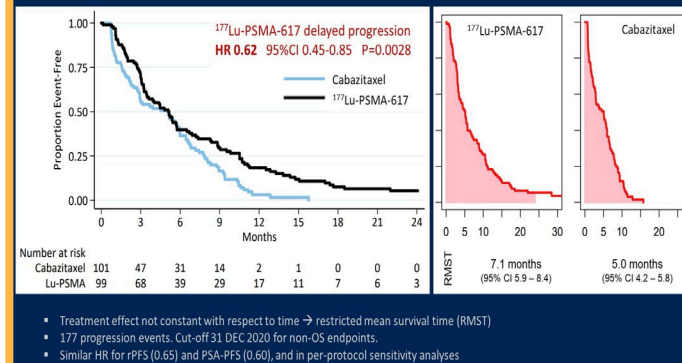
Primary analysis All randomized patients (N = 831)



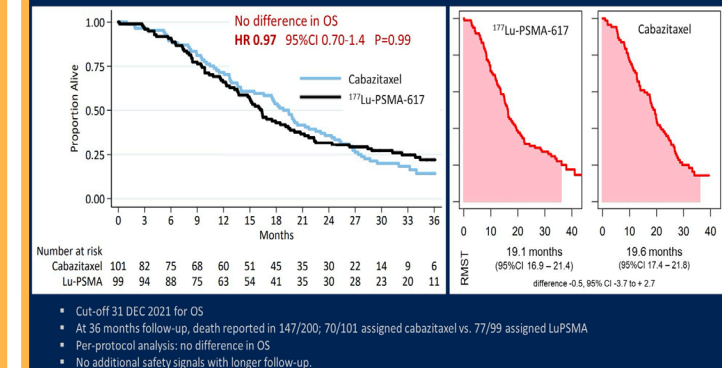
TheraP Trial Schema



Progression Free Survival (PSA and radiographic)

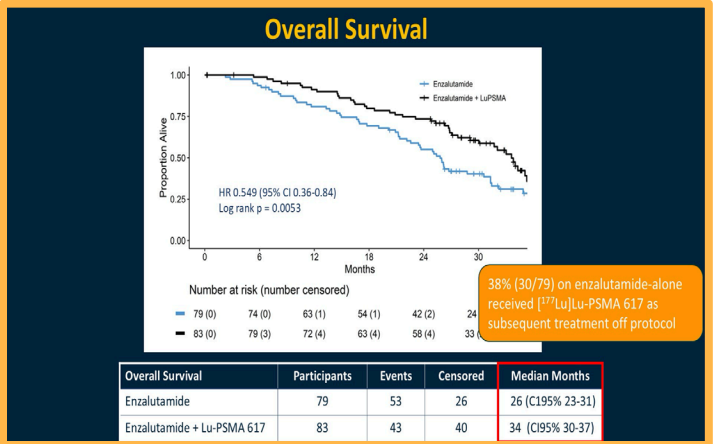
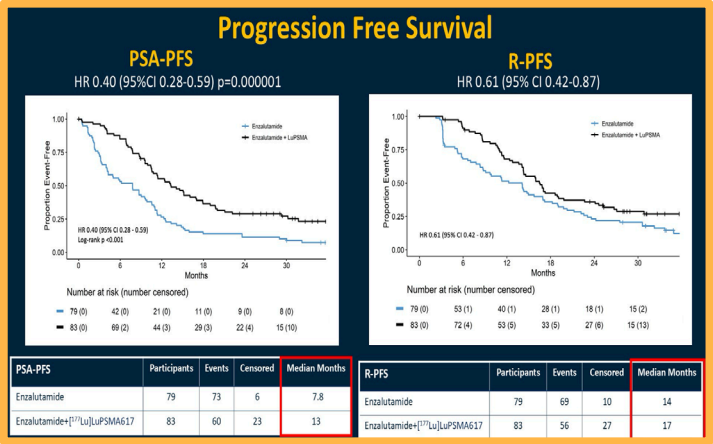
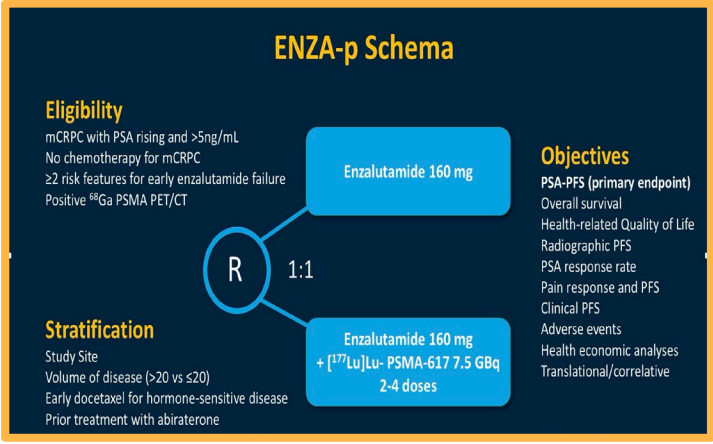
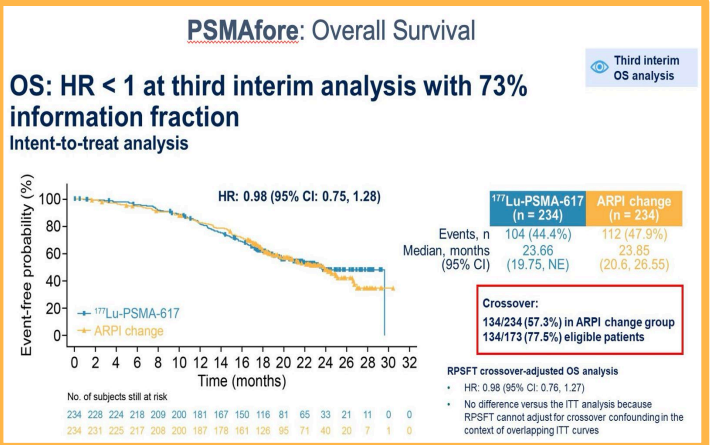
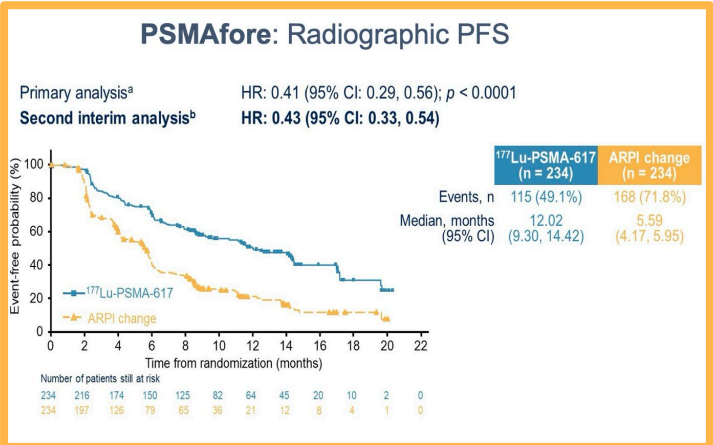
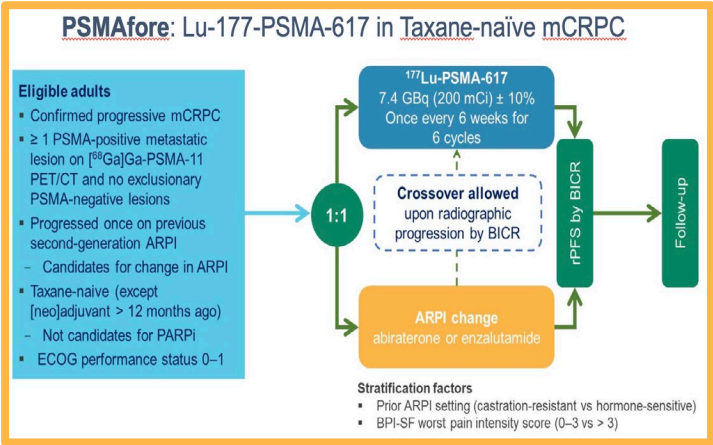


Overall survival (ITT)



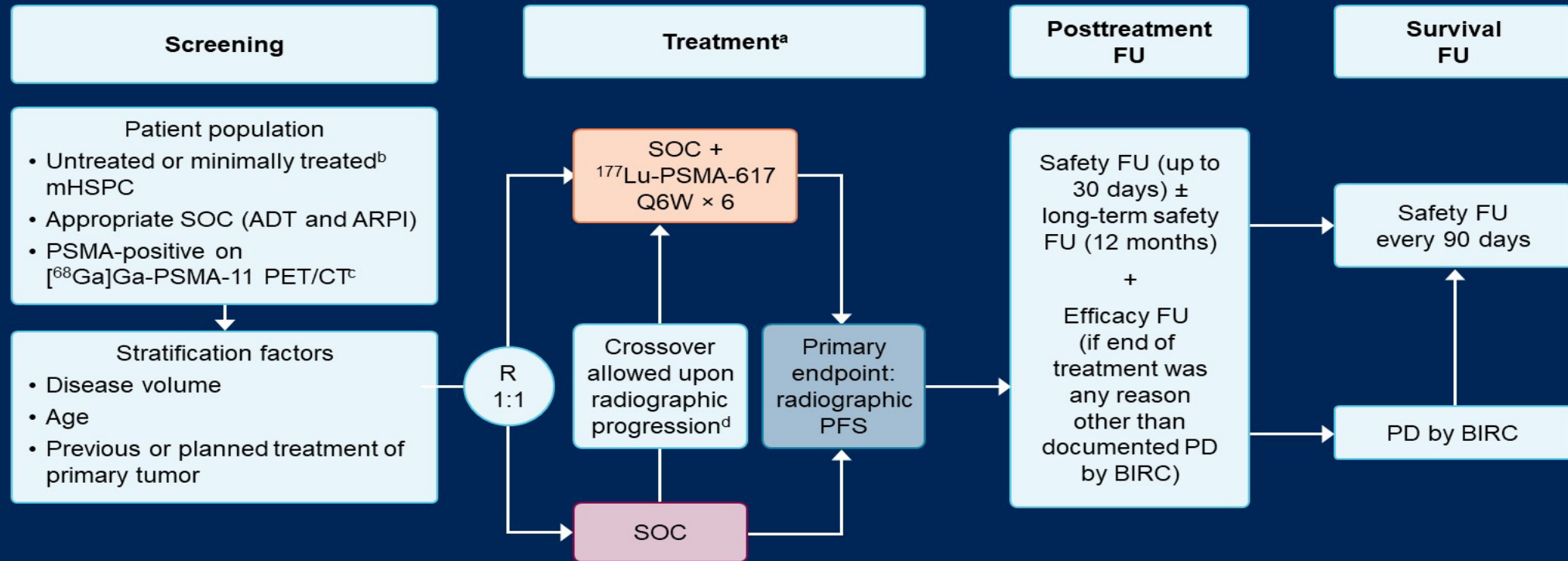
Sartor O, et al. N Engl J Med 2021;385:1091; Hofman MS, et al. The Lancet 2021, 397:797-804; Hofman MS, et al. Lancet Oncol 2024,25:99-107

Additional Therapeutic Successes of RLT in CRPC



Morris M, et al. The Lancet, 2024, 404:1227-1239 Emmett, L, et al. The Lancet Oncology, 2024, 5:563-571; Emmett L, et al. J Clin Oncol 43, 2025 (suppl 5; abstr 17); Emmett L, et al. The Lancet Oncology, 2025, 26:291-299

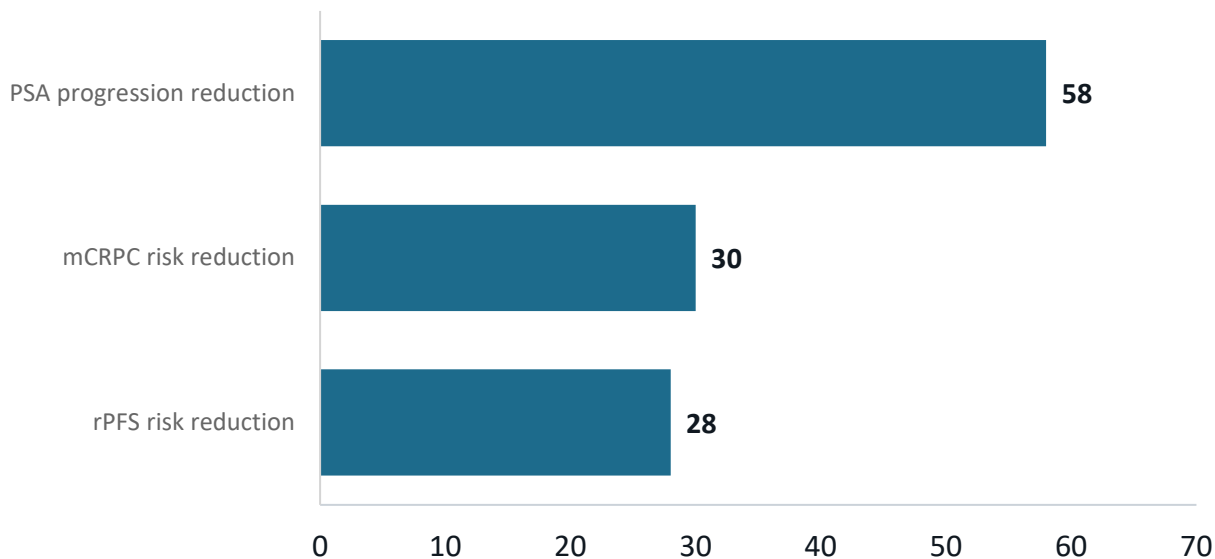
PSMAAddition Study Design



^aTreatment until radiographic progression or no longer clinically benefitting. ^bUp to 45 days of ADT and/or an ARPI for metastatic prostate cancer prior to screening. ^cPositive lesions defined as having [68Ga]Ga-PSMA-11 uptake higher than noncancerous liver parenchyma by visual assessment. Lesion(s) can be in any system. PSMA expression qualification will be determined by central readers. ^dCrossover to ¹⁷⁷Lu-PSMA-617 + SOC allowed upon radiographic progression confirmed by BIRC.

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BIRC, blinded independent review committee; CT, computerized tomography; FU, follow-up; mHSPC, metastatic hormone-sensitive prostate cancer; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; Q6W, once every 6 weeks; R, randomization; SOC, standard of care.

PSMAAddition brings radioligand therapy into mHSPC



HR 0.72

rPFS; median not reached in either arm

HR 0.84

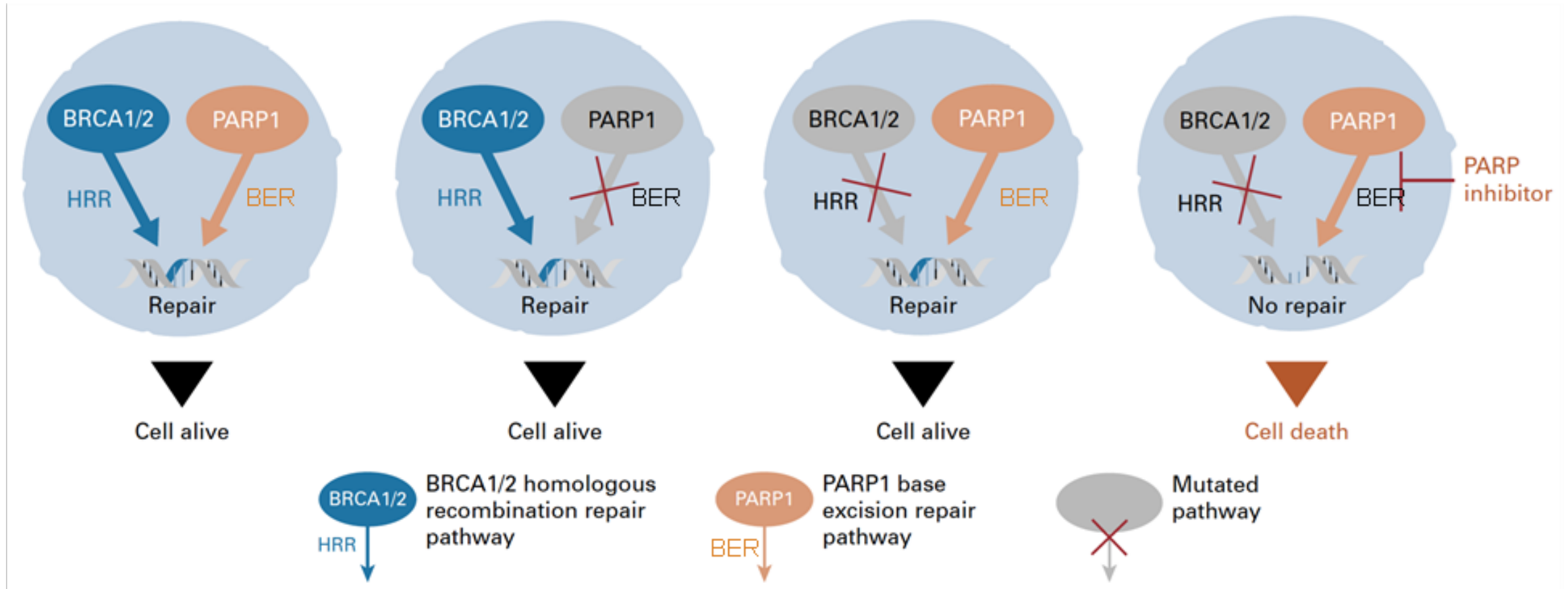
Interim OS; 95% CI 0.63–1.13

Trade-off

Grade ≥ 3 treatment-related AEs: 22.7% vs 12.2%; six cycles; capacity and access matter.

**Practice point: promising intensification; await mature OS and regulatory positioning now allows for universal use.
The question is: Should we?**

PARP Inhibition is Synthetic Lethal in HRR Deficient Cells



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

PARP Inhibitors in Metastatic Prostate Cancer: Biomarker Matters

THERAPY	ELIGIBLE / STUDIED ALTERATIONS	SETTING	TRIAL	KEY POINT
Olaparib	ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	mCRPC after ARPI	PROfound	Broad HRR label*
Rucaparib	BRCA1, BRCA2	mCRPC	TRITON2 / 3	BRCA-driven
Talazoparib + enzalutamide	ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C	1L mCRPC	TALAPRO-2	HRR-selected
Olaparib + abiraterone	BRCA1, BRCA2	1L mCRPC	PROpel	US label: BRCA
Niraparib + abiraterone	BRCA1, BRCA2	1L mCRPC	MAGNITUDE	BRCA-selected
Niraparib + abiraterone	BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L	mCSPC upfront	AMPLITUDE	rPFS HR 0.63 BRCA1/2 HR 0.52

Clinical pearl: Do not equate “HRR-positive” with uniform PARP sensitivity — BRCA2 remains the clearest predictive alteration.

TALAPRO-3: Trial Design

Key eligibility criteria

- HRR gene-altered mCSPC
- Metastatic disease confirmed by positive bone scan or metastatic lesion by CT or MRI scan
- ECOG PS 0 or 1
- Ongoing ADT
- ≤3 months of prior ADT with/without ARPI for mCSPC
- Prior docetaxel for mCSPC not permitted†

Stratification factors

- De novo vs relapsed mCSPC
- High- vs low-volume disease
- *BRC*Am vs non-*BRC*Am

1:1

N=599

TALA 0.5 mg* + ENZA 160 mg QD

PBO + ENZA 160 mg QD

Data cutoff: February 18, 2026

Primary endpoint

- rPFS by investigator assessment

Key secondary endpoint

- OS (alpha-protected)

Other secondary endpoints

- ORR per RECIST v1.1
- Duration of soft tissue response
- PSA response
- Time to PSA progression
- Time to subsequent antineoplastic therapy
- Time to first SSE
- Safety
- PROs

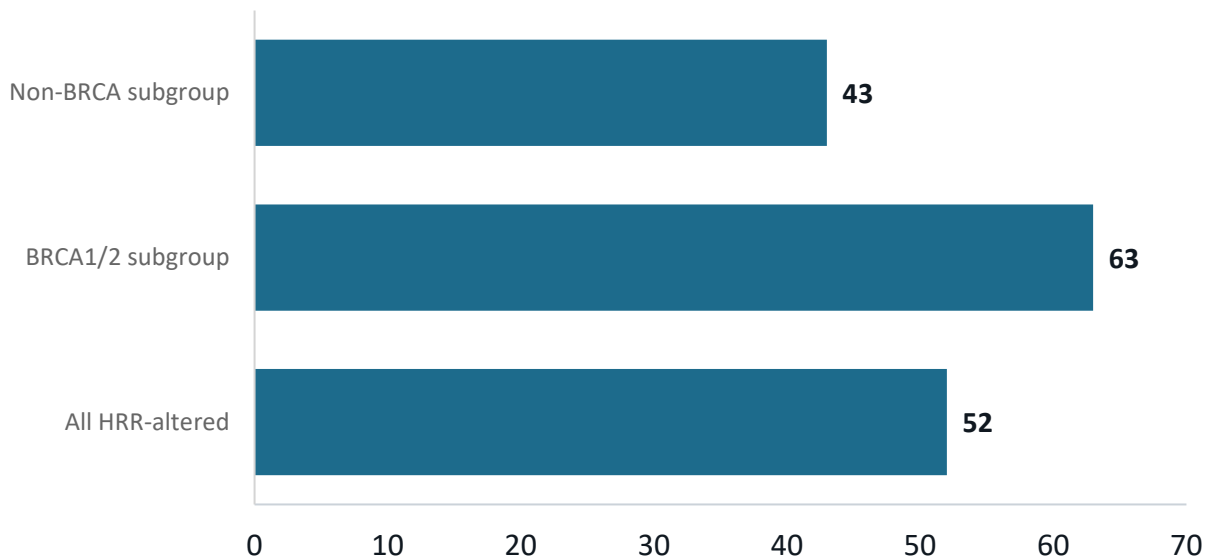
Exploratory endpoint

- PFS2

HRRm: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*‡

*0.35 mg QD if the patient has moderate renal impairment; †As per the protocol amendment (September 2021). ClinicalTrials.gov identifier: NCT04821622. ‡HRR testing using FoundationOne®/FoundationOne®CDx and FoundationOne®Liquid CDx. *BRC*Am=*BRCA* alterations; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; HRRm=HRR gene alterations; MRI=magnetic resonance imaging; ORR=objective response rate; OS=overall survival; PFS2=time to second progression or death; PRO=patient-reported outcome; PSA=prostate-specific antigen; QD=once daily; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SSE=symptomatic skeletal event.

TALAPRO-3 shows the clearest biomarker-gradient signal



HR 0.481

rPFS; NR vs 45.8 months

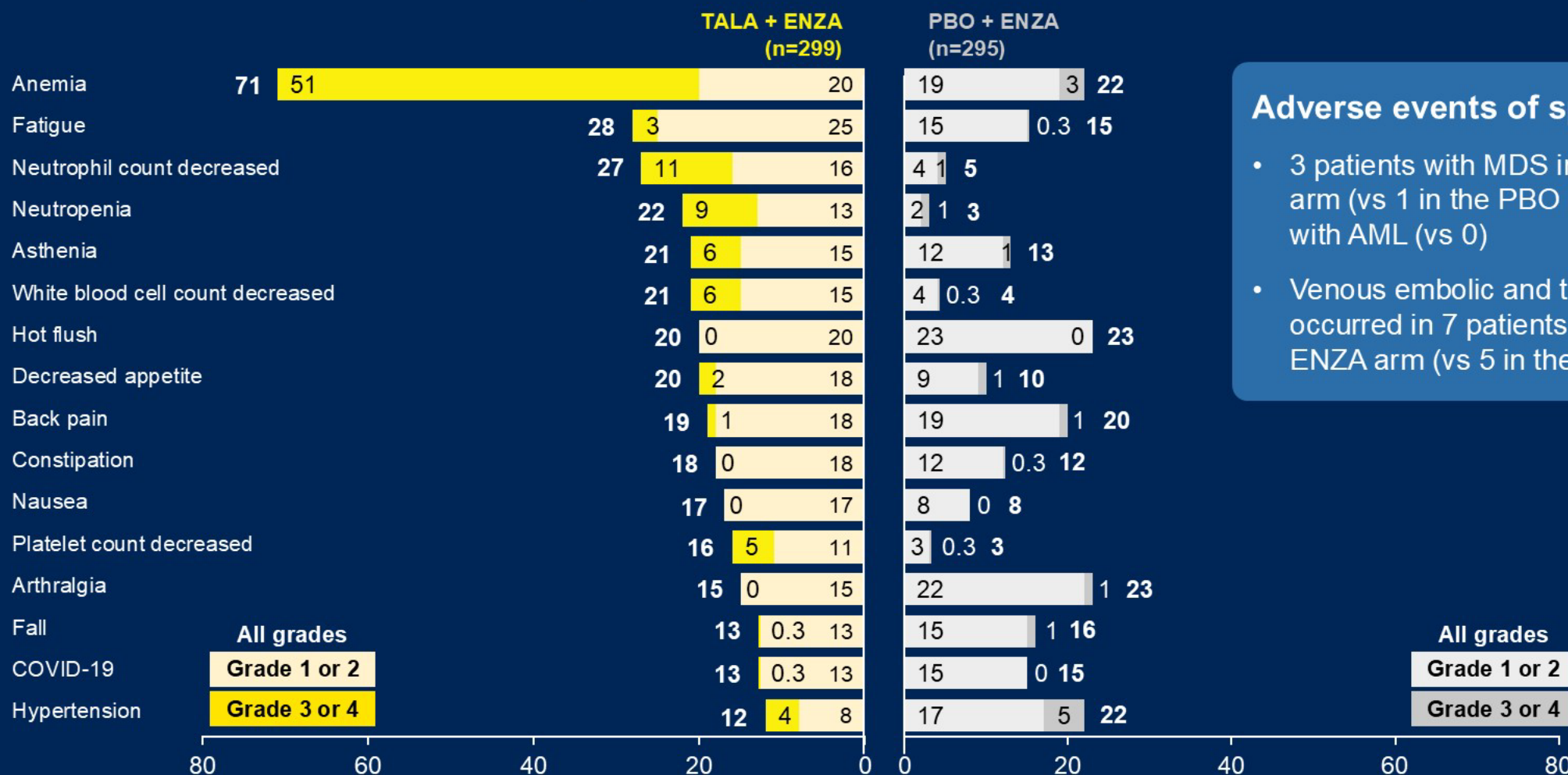
HR 0.767

Interim OS; not statistically significant

- Anemia 71.2%
- Talazoparib discontinuation for AEs 18.7%

Practice point: prioritize BRCA2/BRCA1; discuss hematologic toxicity and uncertain OS before extending broadly across HRR genes.

Most Common ($\geq 15\%$) All-Cause TEAEs



Data cutoff: February 18, 2026 (Safety population). Includes AEs occurring from the time of the first dose of study treatment through 28 days after the last dose of study treatment or before initiation of new systemic antineoplastic therapy, excluding ADT, whichever occurs first. TEAEs were graded according to NCI CTCAE v4.03.

AESI=AE of special interest; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; NCI CTCAE v4.03=National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

A practical mHSPC selection matrix

Clinical situation	Preferred discussion	Why
Near-complete PTEN loss	ADT + abi + capivasertib	Approved; modest rPFS gain; select for fitness
BRCA1/2 alteration	ADT + enza + talazoparib	Large rPFS effect; anemia monitoring
PSMA+ high-volume disease	ADT + ARPI ± ¹⁷⁷ Lu-PSMA	Promising rPFS; OS/access unresolved
Fit de novo high-volume, no target	ADT + ARPI + docetaxel	OS-established triplet evidence
Low-volume / metachronous	ADT + ARPI; consider MDT	Avoid reflexive toxicity escalation

No head-to-head trial answers these choices. Patient phenotype, toxicity tolerance and strength of endpoint remain decisive.

JG's approach: "PPP" prolong, prevent and protect.....

Renal Cell Carcinoma

Adjuvant RCC: pembrolizumab remains the OS benchmark

60.9%

5-year DFS with pembrolizumab

52.2%

5-year DFS with placebo

HR 0.66

5-year OS analysis; 95% CI 0.48–0.90

Why this matters

- Only single-agent adjuvant ICI trial with reproducible DFS and OS benefit¹
- Negative trials with atezolizumab, nivolumab–ipilimumab and perioperative nivolumab caution against a class effect
- Selection remains clinical: clear-cell component, KEYNOTE-564 risk, recovery from surgery, informed preference.
- Role of Kidney Injury Molecule-1 **KIM-1**² (emergent serum/plasma biomarker remains experimental)

Study Design: LITESPARK-022 (NCT05239728)

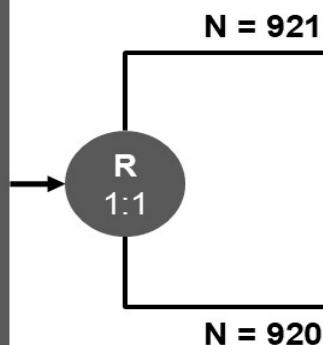
Key Eligibility Criteria

- Histologically confirmed ccRCC with no prior systemic therapy
- Surgery ≤12 weeks prior to randomization
- ECOG PS 0 or 1
- One of the following:
 - Intermediate-high risk of recurrence (M0):
 - pT2, grade 4 or sarcomatoid, N0
 - pT3, any grade, N0
 - High risk of recurrence (M0):
 - pT4, any grade, N0
 - Any pT, any grade, N+
 - M1 NED

Stratification Factors

- Intermediate-high vs high vs M1 NED
- Tumor grade 1-2 vs 3-4

Median follow-up (data cutoff, Aug 23, 2025):
28.4 months (range, 15.0–40.1)



Pembrolizumab 400 mg Q6W
for ~1 year (≤9 cycles)
+ **belzutifan 120 mg QD**
for ≤54 weeks

Pembrolizumab 400 mg Q6W
for ~1 year (≤9 cycles)
+ **placebo QD**
for ≤54 weeks

Primary endpoint: DFS by investigator

Key secondary endpoint: OS

Other secondary endpoints include: safety

NED, no evidence of disease; QD, daily; Q6W; every six weeks.

Belzutifan adds DFS—and substantially more toxicity

LITESPARK-022	Pembro + belzutifan	Pembro + placebo
24-month DFS	80.7%	73.7%
DFS hazard ratio	0.72 (0.59–0.87)	Reference
24-month OS	96.2%	95.7%
Grade ≥3 AEs	52.1%	30.2%
Key added toxicity	Anemia • hypoxia	Immune-mediated AEs

FDA approved

June 12, 2026

OS immature

HR 0.78
95% CI 0.51–1.19

The choice is now pembro alone vs an approved, more toxic DFS-intensified doublet.

Adjuvant RCC now requires an explicit intensity conversation

Pembrolizumab alone

Established DFS + OS benefit

Default for many KEYNOTE-564–eligible patients

Pembrolizumab + belzutifan

Greater DFS; OS immature; more anemia/hypoxia

Consider highest-risk, fit patients after shared decision-making

Surveillance

Avoids toxicity and overtreatment

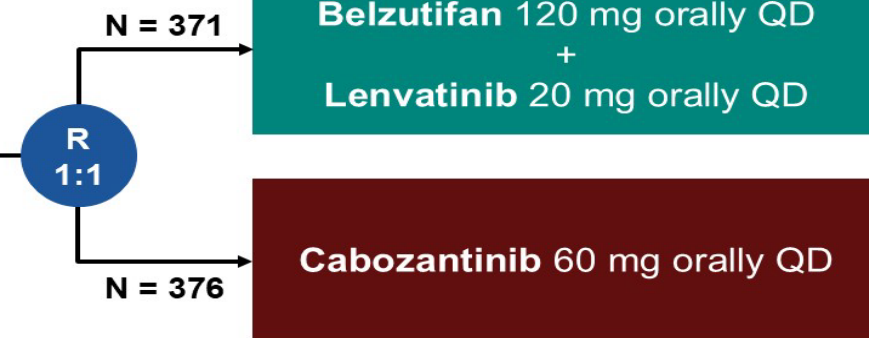
Reasonable when recurrence risk, comorbidity or preference argues against therapy

Still missing: a validated predictive biomarker that separates who needs no therapy, pembro alone, or doublet.

LITESPARK-011 Study (NCT04586231)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Karnofsky Performance Status score $\geq 70\%$
- ≤ 2 prior systemic regimens
- Progression on/after anti-PD-(L)1 mAb as 1L or 2L therapy or progression ≤ 6 months of the last dose of adjuvant anti-PD-(L)1 mAb
- Prior VEGFR-TKI was permitted



Stratification Factors

- IMDC prognostic score:^a 0 vs. 1-2 vs. 3-6
- Line of treatment for prior anti-PD-(L)1: 1L, adjuvant, neoadjuvant-adjuvant vs. 2L
- Geographic region: North America vs. western Europe vs. rest of world

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety

Exploratory Endpoints Include:

- Time to deterioration in patient-reported outcomes

BICR, blinded independent central review; QD, daily.

^aBased on the number of present risk factors (KPS score $< 80\%$; time from diagnosis to 1L treatment < 1 year; low hemoglobin; high corrected serum calcium; high neutrophils; high levels of platelets) according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

LITESPARK-011 establishes an active post-IO oral doublet

14.8 mo

Median PFS: belzutifan +
lenvatinib

10.7 mo

Median PFS: cabozantinib

HR 0.70

95% CI 0.59–0.84; $P < 0.0001$

OS is not yet definitive

34.9 vs 27.6 months • HR 0.85 • $P = 0.061$

Toxicity is substantial in both arms

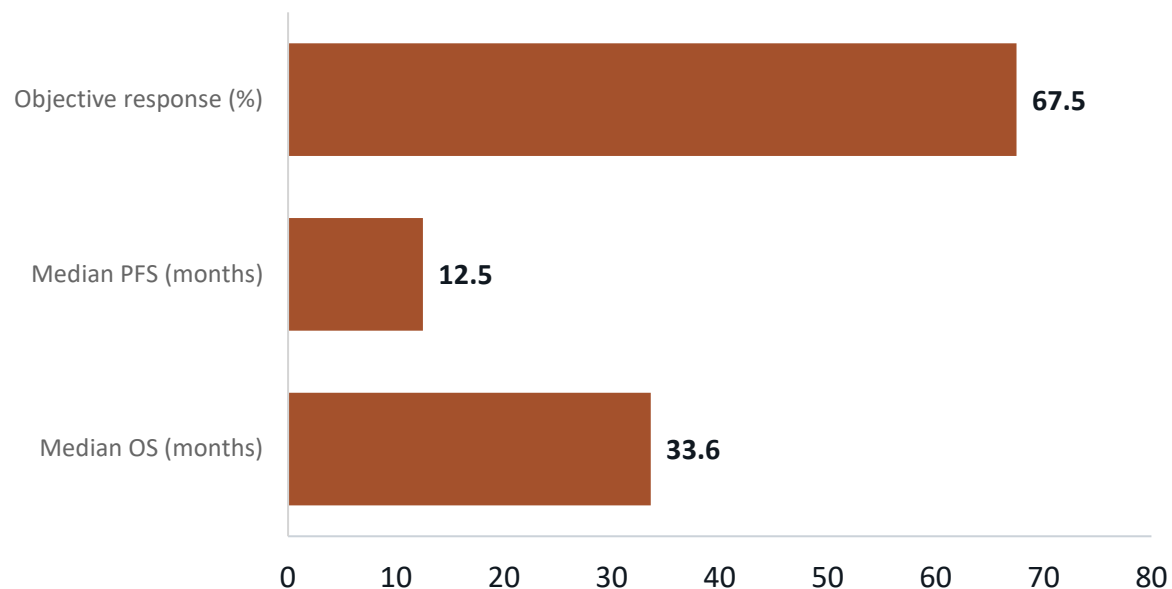
Grade ≥ 3 TEAEs: 84% vs 83%

Hypertension: 31% vs 29%

Practice point: compelling option after PD-(L)1; choose against cabozantinib based on prior VEGF exposure, anemia/hypoxia, BP, tempo and patient preference.

Urothelial Cancer

EV+pembrolizumab is the advanced UC standard



EV + pembrolizumab

Chemotherapy comparator: OS 15.9 mo • PFS 6.3 mo • ORR 44.2%

HR 0.53

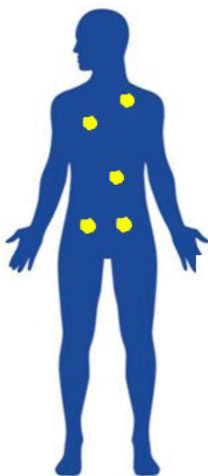
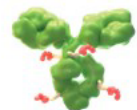
Overall survival at 42.8-month follow-up

44.0%

42-month OS vs 24.6% with chemotherapy

The survival effect is durable across major clinical subgroups.

At 3.5 years of follow-up EV+Pembro has a consistent overall survival in advanced/metastatic urothelial carcinoma

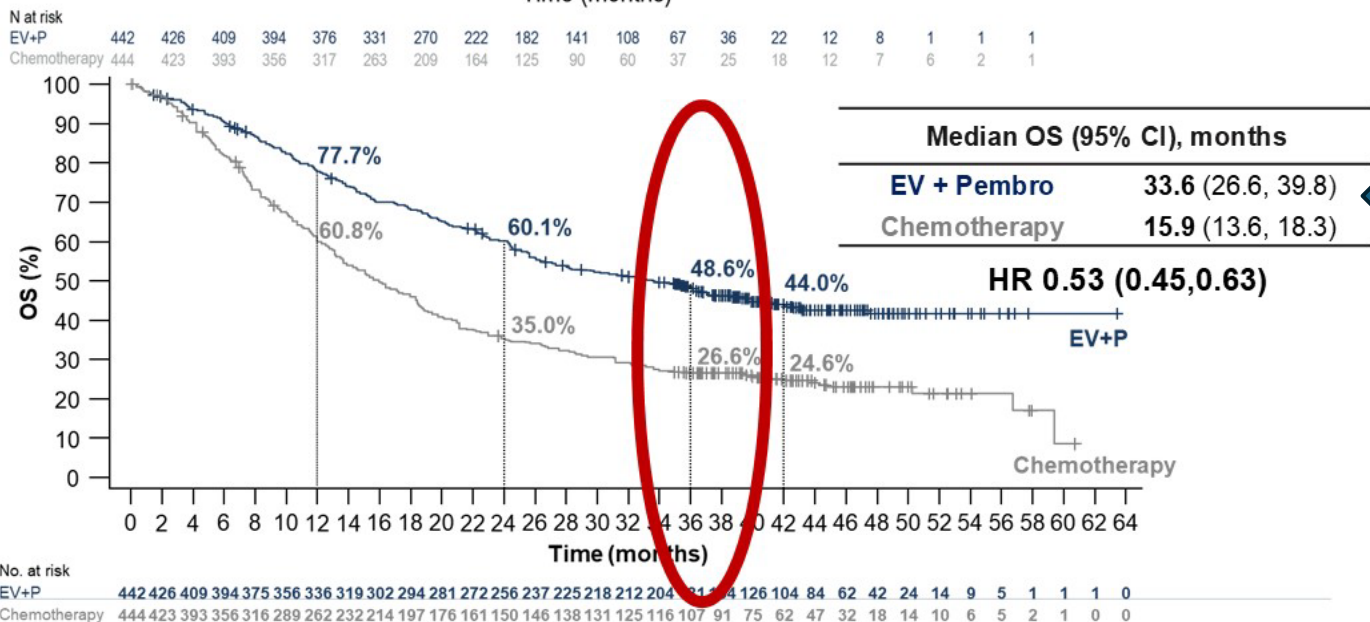
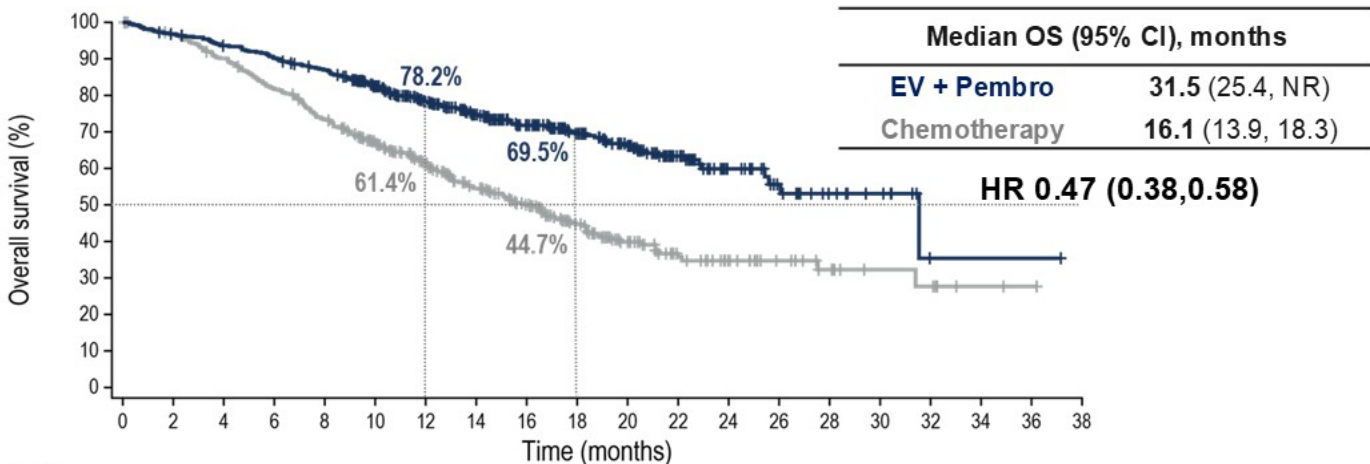


First-Line
Enfortumab vedotin
+ Pembrolizumab



~1.5 years
Median Follow-up

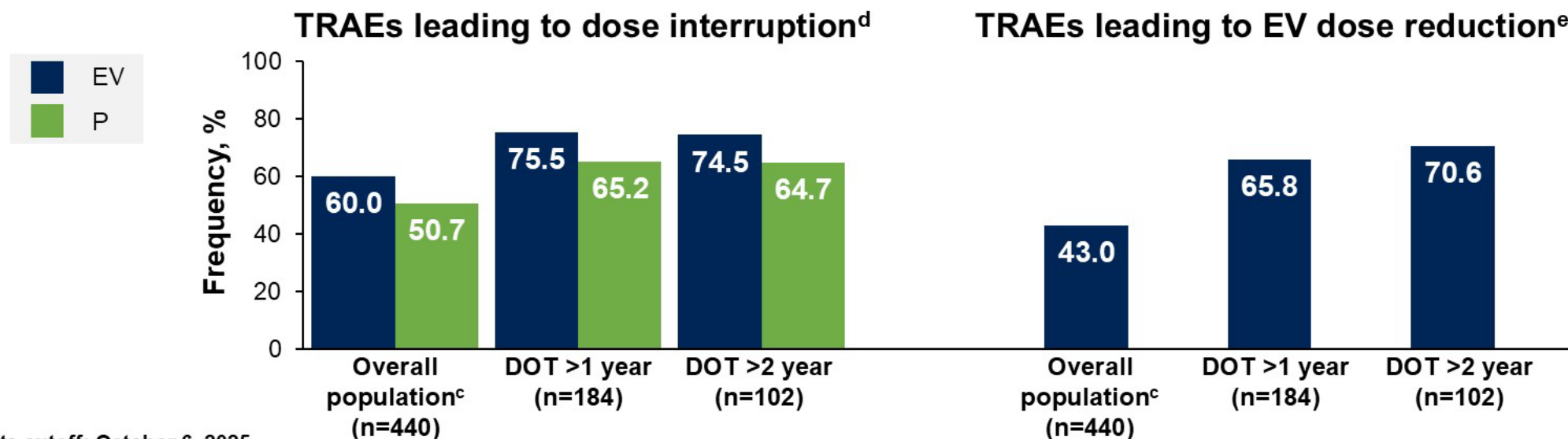
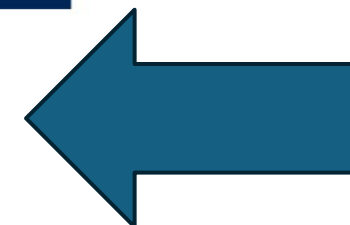
3.5 years
Median Follow-up



Powles T et al., NEJM 2024;390:875-88

Patients Remaining on Treatment and Dose Modifications (EV+P arm)^a

Time point	Patients on treatment ^b / Overall population, n/n ^c	Percentage on treatment, % ^b
6 months	297/440	67.5%
12 months (1 year)	184/440	41.8%
18 months	139/440	31.6%
24 months (2 years)	102/440	23.2%

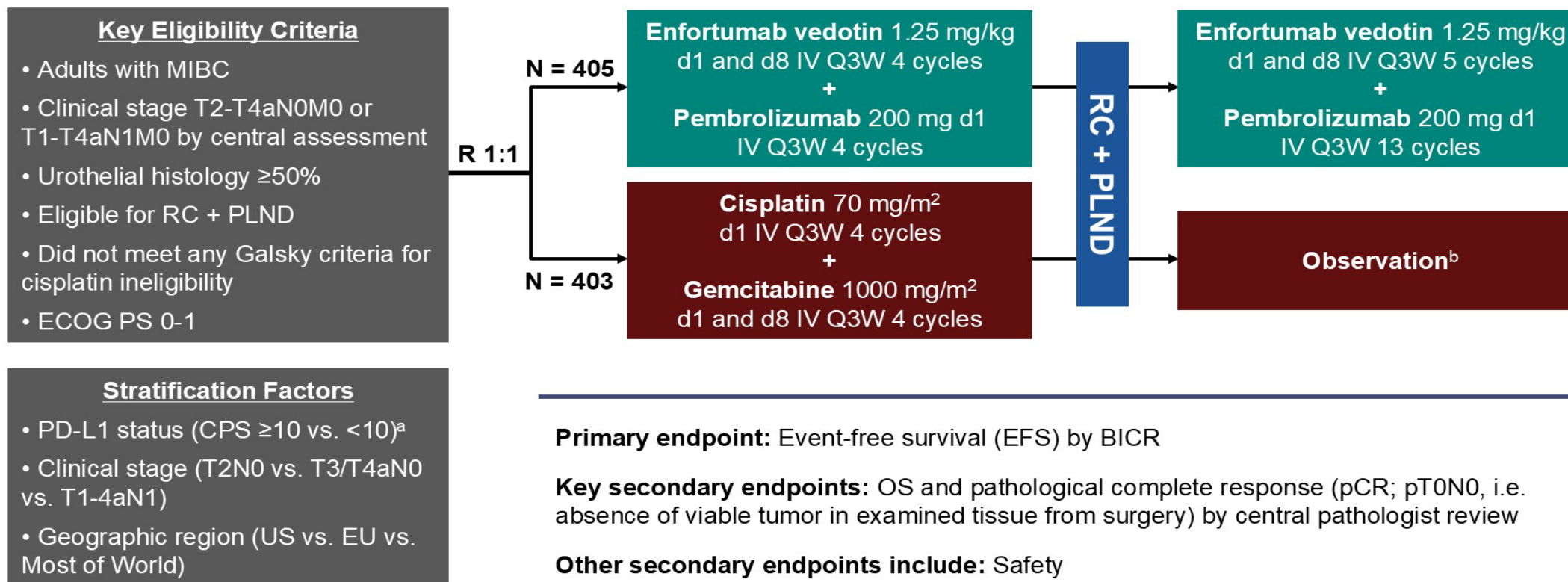


Data cutoff: October 6, 2025.

DOT, duration of treatment; EV, enfortumab vedotin; P, pembrolizumab; TRAE, treatment-related adverse event.

^aMaximum number of 35 treatment cycles for P per protocol. ^bEither EV+P, EV only, or P only. ^cSafety analysis set. ^dDose interruption includes dose elimination (scheduled dose being skipped) and dose delay (dose not occurring on the scheduled dosing day) as collected on the case report form. ^eNo dose reduction was permitted for P.

KEYNOTE-B15/EV-304 Study (NCT04700124)



BICR, blinded independent central review; CPS, combined positive score; IV, intravenous; Q3W, every 3 weeks.

^aAssessed by PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA); CPS = # PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) ÷ total # viable tumor cells × 100.

^bAs of Feb 2023, adjuvant nivolumab was permitted when clinically indicated and regionally available.

Data cutoff date: 27 October 2025

Perioperative EV–pembro changes MIBC care

Trial / population	Comparator	pCR	EFS	OS
KEYNOTE-905 / cisplatin-ineligible 3 cycles Pre-op followed by 6 cycles POP	Cystectomy alone	57.1% vs 8.6%	HR 0.40	HR 0.50
KEYNOTE-B15 / cisplatin-eligible 4 cycles Pre-op followed by 5 cycles POP	Neoadjuvant GC	55.8% vs 32.5%	HR 0.53	HR 0.65

- Both regimens include neoadjuvant and adjuvant therapy: phase contribution cannot be isolated
- KEYNOTE-B15 directly beat cisplatin-based neoadjuvant chemotherapy
- FDA approval now extends perioperative EV–pembrolizumab to cystectomy candidates regardless of cisplatin eligibility

Toxicity prevention replaces platinum selection

Neuropathy	Document baseline; assess every cycle; hold early rather than “treat through”
Skin toxicity	Early rash education; rapid evaluation; stop for severe or suspected SCAR
Hyperglycemia	Check glucose/A1c; recognize DKA risk; coordinate diabetes management
Pneumonitis / irAEs	Distinguish EV toxicity, immune toxicity, infection and progression
Response depth	Reassess duration and dose intensity; durable CR does not eliminate surveillance

Community implementation succeeds when dose modification is treated as good oncology—not treatment failure.

ctDNA detects molecular relapse before imaging

After cystectomy

No radiographic
disease

Tumor-informed assay

Personalized variants
tracked in plasma

ctDNA positive

Molecular residual
disease detected

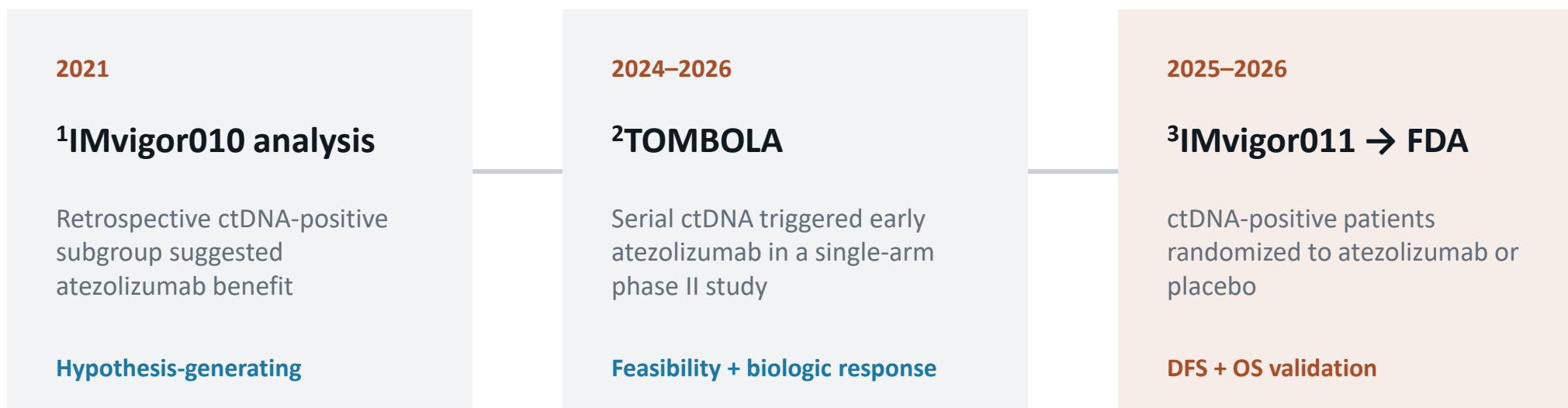
What it can do

- Identify a much higher-risk population
- Trigger treatment before radiographic recurrence
- Support serial postoperative surveillance

What it cannot do

- Prove that every negative patient is cured
- Replace imaging, pathology or clinical judgment
- Establish interchangeability across MRD assays

The evidence evolved from signal to prospective validation



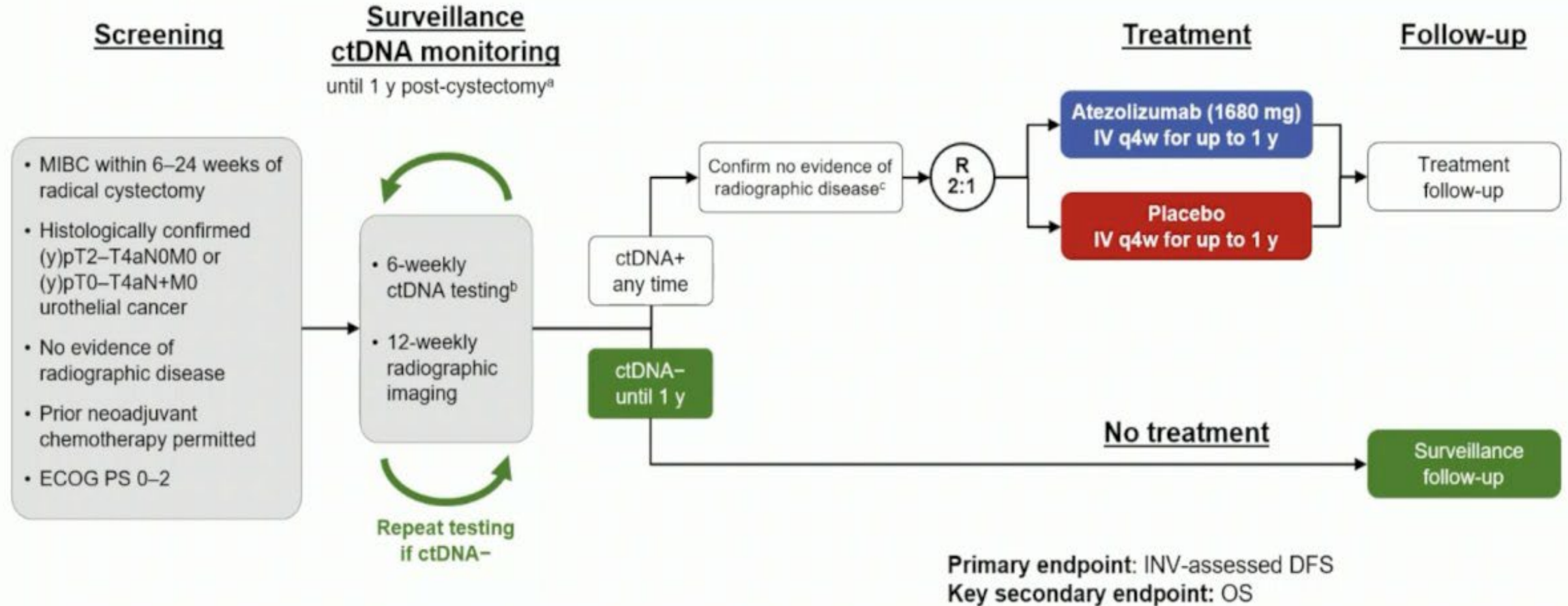
The decisive advance was not prognostic association—it was randomized evidence of treatment benefit in MRD-positive disease.

¹Bellmunt J, Hussain M, Gschwend JE, et al; IMvigor010 Study Group. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma: a multicentre, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2021;22(4):525-537.

²Dyrskjöt L, Birkenkamp-Demtröder K, Nordentoft I, et al. ctDNA-guided immunotherapy following radical cystectomy for muscle-invasive bladder cancer: results from the TOMBOLA trial. *Ann Oncol*. 2026;37(5):712-724.

³Powles T, Kann AG, Castellano D, et al; IMvigor011 Investigators. ctDNA-guided adjuvant atezolizumab in muscle-invasive bladder cancer. *N Engl J Med*. 2025;393(24):2395-2408.

IMvigor011 study design



IMvigor011 improved both DFS and Overall Survival

9.9 vs 4.8 mo

Median DFS • HR 0.64 (95% CI 0.47–0.87)

32.8 / 21.1 mo

Median OS • HR 0.59 (95% CI 0.39–0.90)

28% vs 22%

Grade 3–4 adverse events

Persistently ctDNA-negative cohort

95%

DFS at end of 1-year monitoring

88%

DFS at 2 years

Why it is practice-changing

A biomarker-selected adjuvant strategy produced an OS benefit—while observation spared persistently negative patients from protocol therapy.

Caution: negative patients were not randomized to treatment versus observation.

Adapted from Powles T, Kann AG, Castellano D, et al; IMvigor011 Investigators. ctDNA-guided adjuvant atezolizumab in muscle-invasive bladder cancer. *N Engl J Med*. 2025;393(24):2395-2408.

The FDA label is specific—and operational

May 15, 2026

Adjuvant atezolizumab approved after cystectomy for adults with MIBC and ctDNA-defined MRD by an FDA-authorized test.

Companion diagnostic

Signatera CDx selects post-cystectomy MIBC patients with ctDNA MRD for Tecentriq or Tecentriq Hybreza.

Testing instruction

If the initial Signatera CDx result is negative, continue serial testing until positivity or completion of the recommended 12-month window.

What was approved

A specific assay–drug pairing in a defined post-cystectomy population.

What was not approved

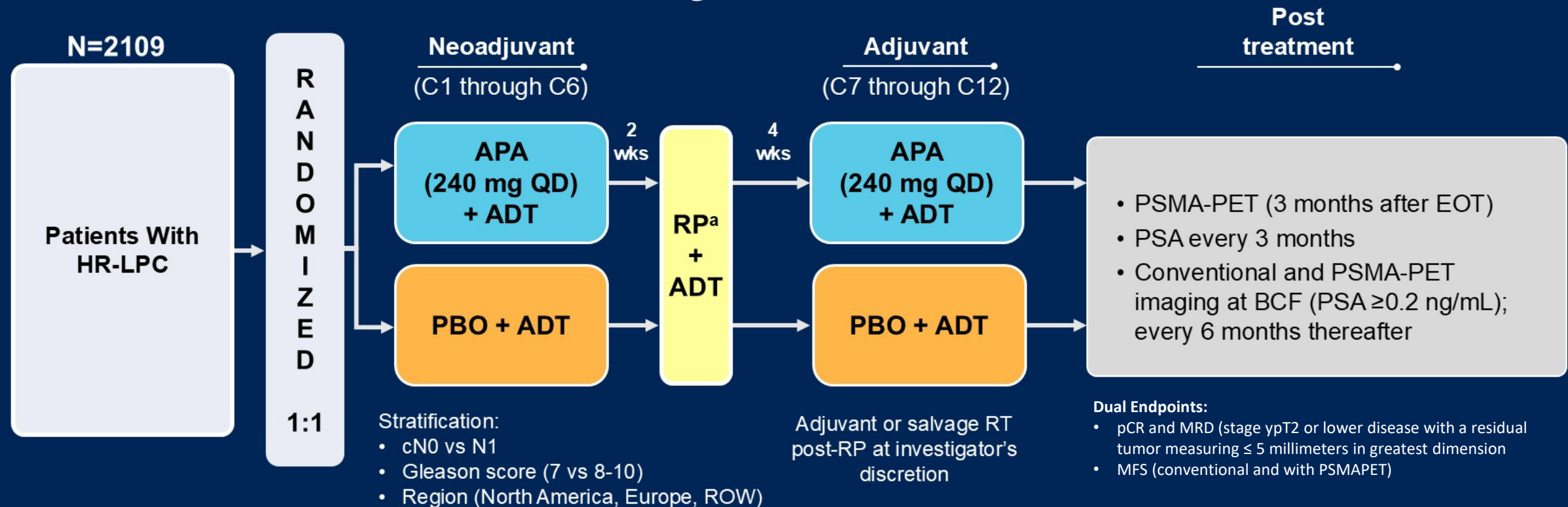
All ctDNA assays, all adjuvant drugs, or ctDNA-guided omission after modern perioperative EV–pembrolizumab.

TAKE-HOME: What should change in practice now?

- | | | |
|---|---------------------------------------|--|
| 1 | Test early in mHSPC | PTEN IHC, germline/somatic HRR and PSMA imaging now influence intensification— but endpoint maturity and toxicity still debatable. |
| 2 | Risk-adapt adjuvant RCC | Pembrolizumab has OS evidence; Pembro/Belzutifan adds DFS and toxicity with immature OS. Predictive biomarkers will be introduced soon. |
| 3 | Make EV–pembro the UC backbone | It is the SOC for advanced disease and now a perioperative standard across all patients regardless of CCDP fitness |
| 4 | Use ctDNA as MRD | IMvigor011 validates treatment at molecular relapse; sequencing after modern perioperative therapy remains unresolved. |
-



PROTEUS: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in HR-LPC



- To complement these data, a substudy is ongoing to further inform on the role of APA + ADT + RP versus RP alone

Patients randomized from July 15, 2019, to June 30, 2022.

Protocol Amendment 7 for including PSMA-PET into MFS assessment (April 14, 2022).

APA, apalutamide; BCF, biochemical failure; C, cycle; EOT, end of treatment; PBO, placebo; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron emission tomography; QD, daily; ROW, rest of the world; RT, radiation therapy.

^aAPA/PBO is stopped 2 weeks prior to planned RP and then resumed 4 weeks after RP. Cardiovascular risk prophylaxis and venous thromboembolism prophylaxis given based on risk.

Baseline Characteristics Were Well Balanced

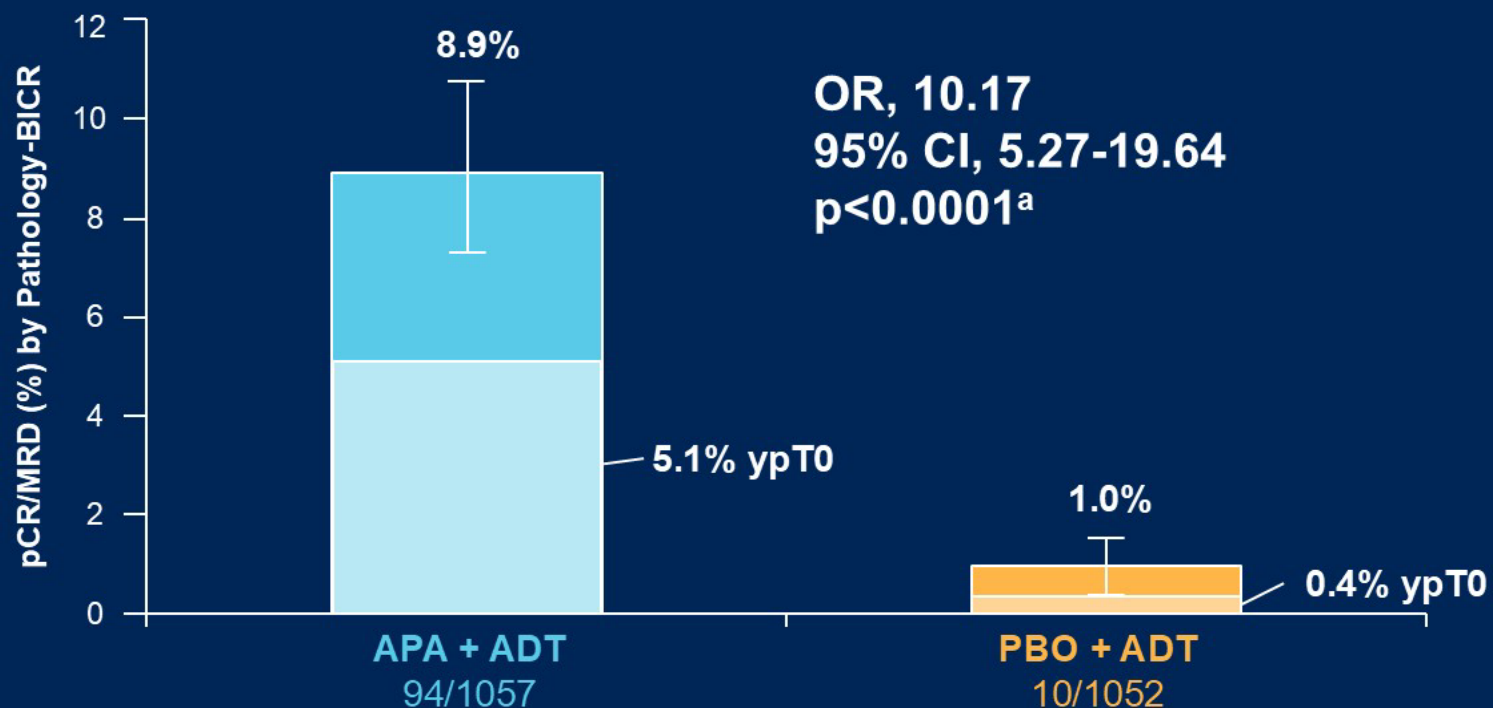
		APA + ADT (n=1057)	PBO + ADT (n=1052)
Median age (IQR), years		66.0 (62-71)	66.0 (61-70)
≥75, n (%)		106 (10.0)	94 (8.9)
Gleason score at initial diagnosis, n (%)	7	45 (4.3)	44 (4.2)
	≥8	1012 (95.7)	1008 (95.8)
Baseline PSA ^a	Median (IQR), ng/mL	14.4 (8.3-29.2) ^b	15.1 (8.1-33.7) ^c
	<20, n (%)	630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

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

IQR, interquartile range.

^aPSA before first dose was the closest value assessment on or prior to ADT or APA start date. ^bn=1025. ^cn=1033. ^dTx: APA + ADT, 2 (0.2); PBO + ADT, 8 (0.8).

Dual Primary End Point Met: pCR/MRD



9-fold improvement in pCR/MRD at RP after 6-cycle neoadjuvant APA + ADT vs PBO + ADT

Exploratory end point of RCB ($\leq$ ypT2, N0, $\leq$ 0.25 cm³) corroborates pCR/MRD:

- APA + ADT vs PBO + ADT, 30.6% vs 11.7%
- OR, 3.36; 95% CI, 2.67-4.23; p<0.0001

pCR/MRD: Minimal residual tumor $\leq$ 5 mm (greatest dimension of largest tumor lesion) in prostate-confined disease ($\leq$ ypT2, N0) or no tumor identified (ypT0)

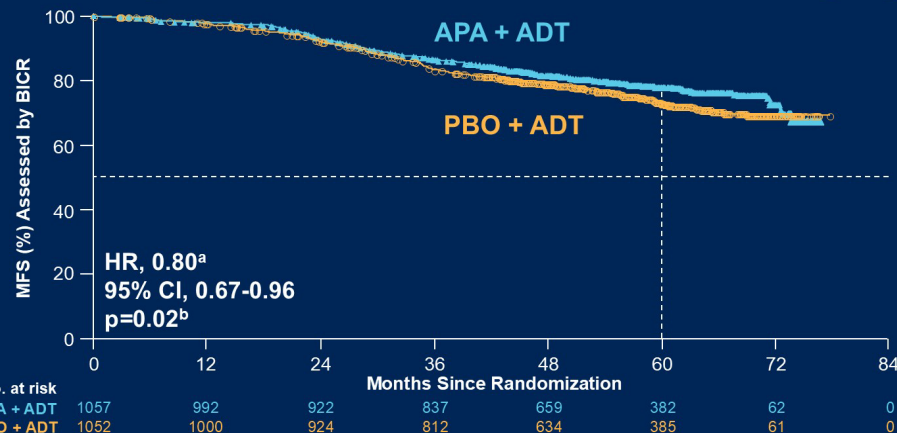
RCB: Residual cancer burden $\leq$ 0.25 cm³ in prostate-confined disease ($\leq$ ypT2, N0)

Error bars indicate 95% confidence intervals (CIs). Odds ratio (OR) is from a logistic regression adjusted for stratification factor; OR >1 favors APA + ADT.

^ap Value is based on Cochran-Mantel-Haenszel test stratified by Gleason score (7, $\geq$ 8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

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

PRIMARY END POINT



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

Investigator-assessed MFS was consistent:

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

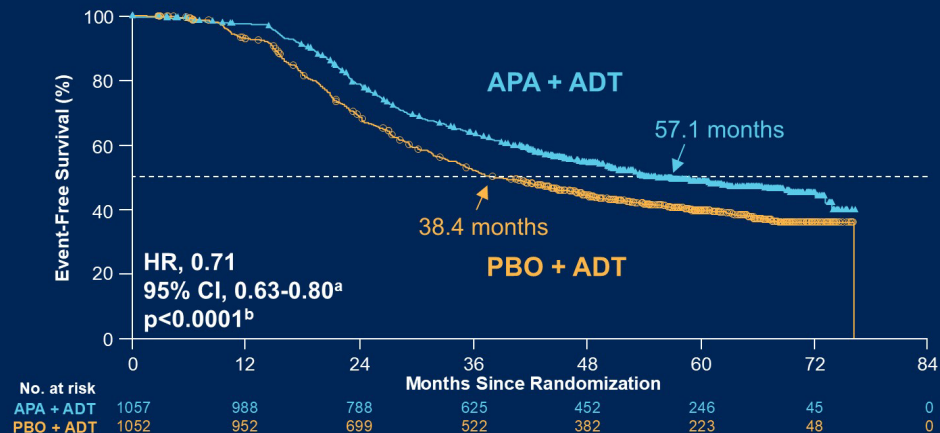
MFS: Time to first occurrence of radiographic distant metastasis based on conventional imaging or PSMA-PET imaging, pathologic finding of distant metastasis, or death from any cause

^aHazard ratio (HR) is from stratified proportional hazards model. HR <1 favors APA + ADT.

^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

Event-Free Survival

KEY SECONDARY END POINT



29% reduction in the risk of oncologic event or death

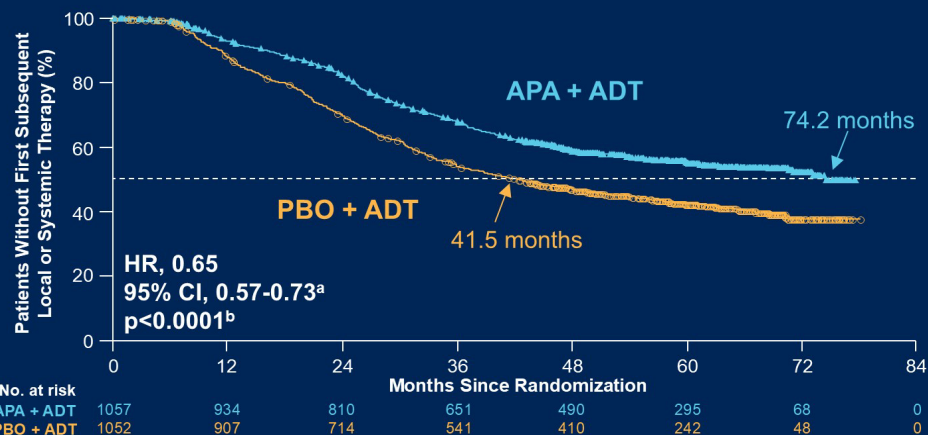
EFS: Time to first of BCF (PSA progression) or local or regional recurrences or distant metastasis, or death by any cause

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

Time to First Subsequent Therapy

KEY SECONDARY END POINT



Nearly 3 years' treatment-free interval added with APA + ADT compared with PBO + ADT

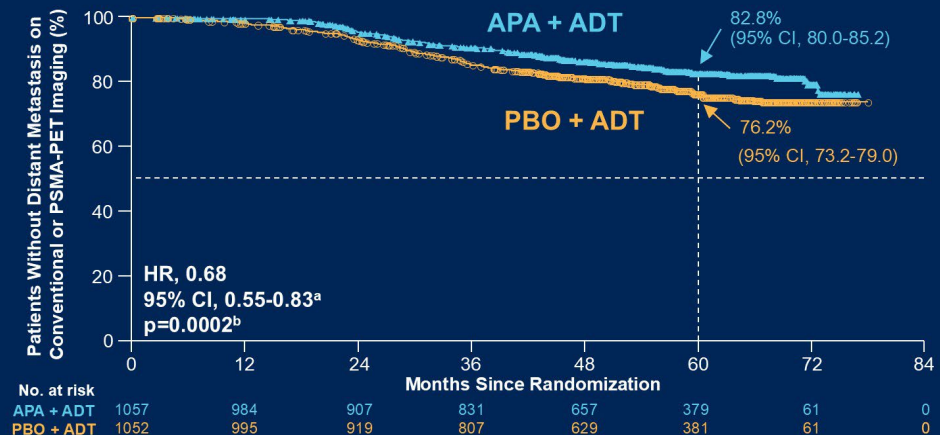
Time to first subsequent therapy: Time to local, regional, or systemic therapy, including reinitiation of ADT

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, and rest of the world).

Time to Distant Metastases

KEY SECONDARY END POINT



32% reduced risk of distant metastasis after APA + ADT, with 83% patients without distant metastasis at 5 years

Time to distant metastasis: Time to first distant metastasis by conventional or PSMA-PET imaging, or pathologic finding of distant metastasis

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), geographic region (North America, Europe, rest of the world).

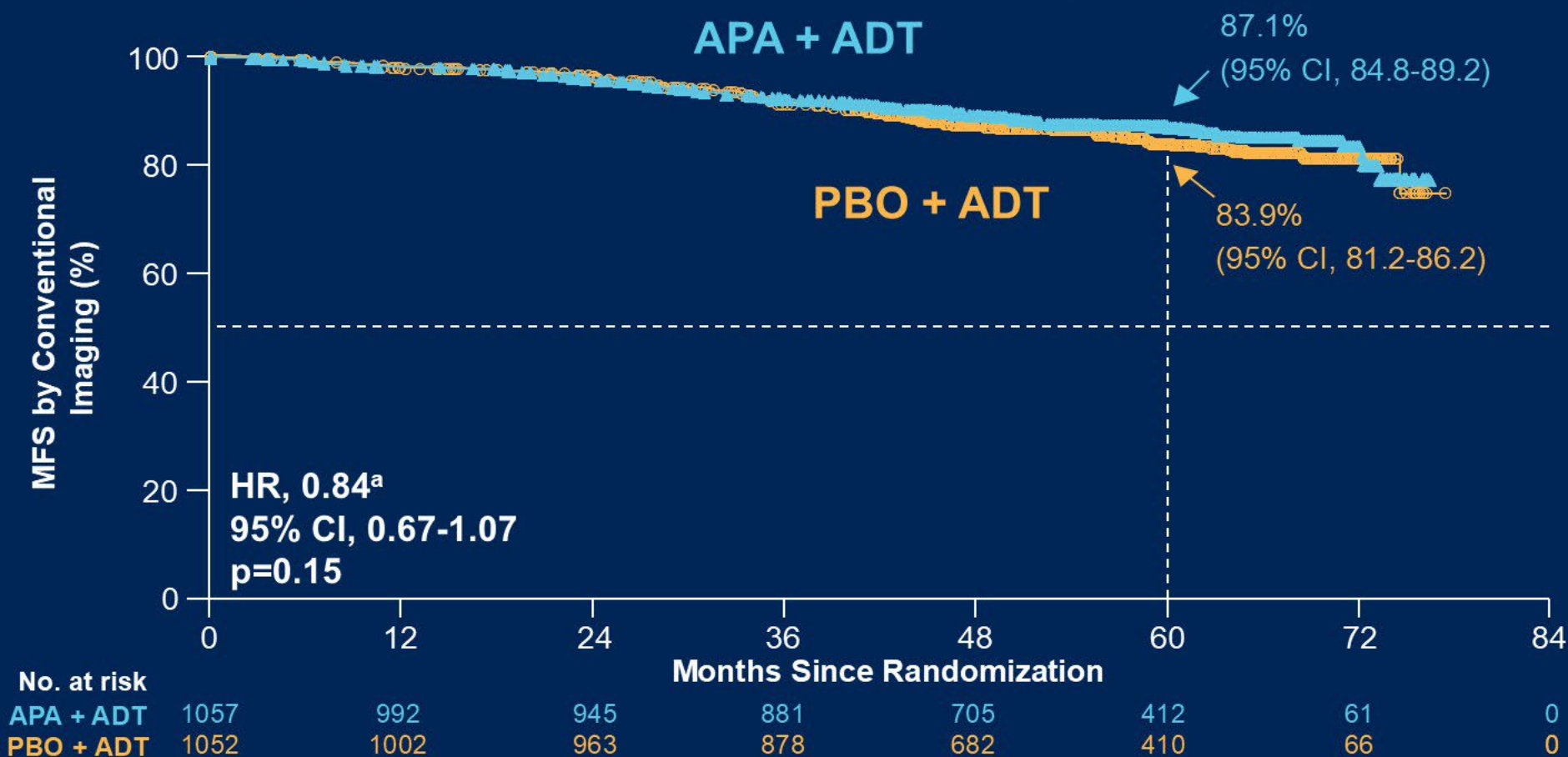
Time to First Subsequent Therapy

ITT Population	APA + ADT (n=1057)	PBO + ADT (n=1052)
Events, n (%)	448 (42.4)	597 (56.7)
Subsequent systemic therapy	282 (26.7)	383 (36.4)
Postoperative radiotherapy	137 (13.0)	194 (18.4)
Other radiotherapy	20 (1.9)	13 (1.2)
Subsequent surgery	9 (0.9)	7 (0.7)

Time to first subsequent therapy: Time to local, regional, or systemic therapy, including reinitiation of ADT

ITT, intent to treat.

MFS by Conventional Imaging



Use of PSMA-PET with potential early detection of metastasis and subsequent therapy may impact MFS by conventional imaging

MFS: Time to first occurrence of radiographic distant metastasis based on conventional imaging, pathologic finding of distant metastasis, or death from any cause
Patients progressing on PSMA-PET and receiving subsequent treatments are included in this analysis which may delay the onset of metastasis on conventional imaging

NS, not significant.

^aHR is from stratified proportional hazards model. HR <1 favors APA + ADT.

Testosterone Recovery

- For the patients who had testosterone recovered to ≥ 200 ng/dL,
 - Median testosterone value was 270 ng/dL (range, 200-1797) with **APA+ADT** compared with 290 ng/dL (200-1134) with **PBO+ADT**
 - Median time from EOT to testosterone recovery was 8.1 months with **APA+ADT** compared with 6.6 months with **PBO+ADT**

Testosterone group	APA + ADT (n=1050)			PBO + ADT (n=1050)		
	≥ 200	100-199	50-99	≥ 200	100-199	50-99
n (%)	857 (81.6)	72 (6.9)	51 (4.9)	871 (83.0)	60 (5.7)	44 (4.2)
Median age, years (range)	66 (41-83)	71 (57-84)	69 (49-83)	66 (44-81)	69 (52-80)	69.5 (51-82)

Frequency of Treatment-Related Adverse Events

Safety Population, n (%)		APA + ADT (n=1050)	PBO + ADT (n=1050)
All grades	Treatment-related AE	1000 (95.2)	985 (93.8)
Grade 3/4	Treatment-related AEs	289 (27.5)	198 (18.9)
	Treatment-related AEs leading to dose reduction ^a	118 (11.2)	24 (2.3)
	Treatment-related AEs leading to dose interruption ^a	126 (12.0)	46 (4.4)
All grades	Treatment-related AEs leading to death ^b	7 (0.7)	1 (0.1)

AE, adverse event.
 Treatment-related AEs are those that occurred on or after the first dose of study drug through the last dose of study treatment + 30 days or prior to the start of subsequent therapy, whichever is earlier, or any AE that is considered treatment related regardless of the start date of the event. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study drug (apalutamide or placebo), ADT, or RP.
^aAEs leading to treatment interruption or dose reduction are based on AE action taken. ^bIncludes grade 5 events; AEs leading to death are based on AE outcome of fatal.

Treatment-Emergent Adverse Events of Special Interest

Special Interest Category, n (%)	APA + ADT (n=1050)		PBO + ADT (n=1050)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
≥ 1 TEAE of special interest	398 (37.9)	90 (8.6)	214 (20.4)	23 (2.2)
Skin rash	346 (33.0)	62 (5.9)	161 (15.3)	3 (0.3)
Fall	34 (3.2)	6 (0.6)	29 (2.8)	5 (0.5)
Ischemic heart disease	25 (2.4)	13 (1.2)	22 (2.1)	9 (0.9)
Nonpathological fracture	22 (2.1)	6 (0.6)	19 (1.8)	5 (0.5)
Cerebrovascular disorders	8 (0.8)	5 (0.5)	13 (1.2)	6 (0.6)
Seizure	2 (0.2)	2 (0.2)	1 (0.1)	0
Fatigue	291 (27.7)	4 (0.4)	281 (26.8)	1 (0.1)

TEAE, treatment-emergent AE.
 TEAEs are those that occurred on or after the first dose of study drug through the last dose of study treatment plus 30 days or prior to the start of subsequent therapy, whichever is earlier, or any AE that is considered treatment related regardless of the start date of the event. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. The event with the worst toxicity grade is used. If a patient has all adverse events with missing toxicity grades, the patient is only counted in the total column.

PROTEUS: Why a “positive” trial is not automatically practice changing

The central issue is not whether apalutamide has activity — it clearly does — but whether PROTEUS proves that this perioperative strategy should become the new standard.

- **No true contemporary standard-of-care control.** Both arms received 12 months of perioperative ADT, although ADT with prostatectomy has not been established to improve meaningful long-term outcomes. The clinically relevant comparison remains perioperative intensification vs upfront RP alone — and, more broadly, versus modern RT + ADT/ARPI strategies.
- **The MFS endpoint changed during the trial.** PSMA PET was incorporated after trial initiation. The positive primary MFS analysis combined conventional imaging and PSMA PET (HR 0.80), whereas conventional-imaging MFS alone was not statistically significant (HR $\approx$ 0.84; $p \approx$ 0.15).
- **PSMA-PET MFS is not a validated OS surrogate.** Conventional-imaging MFS has established surrogacy in localized prostate cancer; the same cannot yet be assumed when PET detects metastases earlier and is triggered by biochemical recurrence.
- **The absolute MFS gain is modest.** At 5 years: 78.2% vs 73.5% — an absolute difference of 4.7%, despite one year of ADT plus perioperative apalutamide and greater toxicity.

PROTEUS: Additional concerns — and the Spratt critique

Daniel E. Spratt: “How positive was PROTEUS? Reconsidering success when most patients never reach no evidence of disease” (Nature Reviews Clinical Oncology, Aug 2026)

- **Most patients were not rendered disease free.** Despite striking relative improvement in pCR/MRD, pCR/MRD was only 8.9% vs 1.0%; freedom from disease at 4 years was reported at only ~21.9% vs 18.3%. A 10-fold odds ratio can obscure a small absolute pathologic response rate.
- **Overall survival remains immature.** For a curative-intent population with long life expectancy, whether earlier PET-detected metastasis translates into longer survival — or merely earlier labeling/treatment of recurrence — remains unresolved.
- **Treatment burden and toxicity matter.** Grade 3/4 treatment-emergent AEs were 39.6% vs 31.0%; discontinuation for AEs 7.4% vs 2.7%. Mature patient-reported outcomes are needed to judge the net value of treating >1,000 men for a modest absolute MFS gain.
- **Postoperative salvage therapy complicates interpretation.** Postoperative radiotherapy — a proven potentially curative intervention after RP — was used in only a minority of patients, raising questions about how PROTEUS maps onto optimized contemporary multimodality care.
- **Who actually needs both neoadjuvant AND adjuvant therapy?** The design cannot determine the contribution of the preoperative vs postoperative components or whether pathologic/PSA response could identify patients who can safely avoid additional treatment.

PROTEUS: practice-changing, but not practice-simple

My threshold for adoption: highest-risk surgical candidates, multidisciplinary selection

Why I would use it

- Very high-risk biology
- Clear MFS + EFS signal
- Delays salvage therapy
- One-year finite systemic course

Why I would hesitate

- No mature OS yet
- Absolute MFS gain modest
- More grade 3/4 toxicity
- No direct comparison vs intensified RT

What I would do now

- Discuss at diagnosis
- Stage carefully with PSMA PET
- Avoid “surgery alone” framing
- Use shared decision-making
- RT plus ADT has OS benefit – if pt refuses RT, approach is feasible

