VGO NORTE INTERNATIONAL GU DEBATES

The perioperative treatment of high-risk Prostate Cancer in 2026: Where do things stand after PROTEUS?

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Disclosures

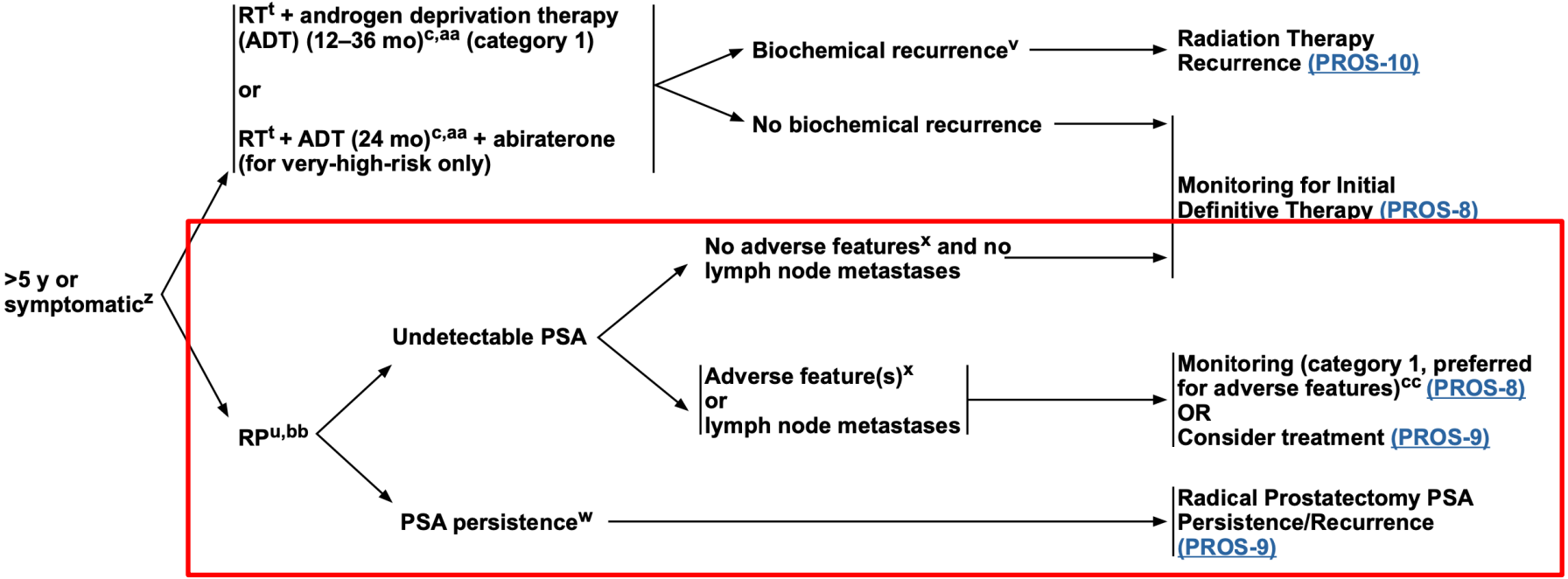
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I am not a urologist
I do not treat patients with localized disease

Localized prostate cancer is a heterogeneous disease

Classification	Very low risk	Low risk	Intermediate risk	High risk	Very high risk / Locally advanced
D'Amico	—	PSA <10 GS <7 cT1	PSA 10–20 GS 7 cT2a–b	PSA >20 GS >7 cT2c–T3a	—
NCCN	cT1c GS <7 PSA <10 PSAD <0.15 <3 positive cores	PSA <10 GS <7 cT1–T2a	PSA 10–20 GS 7 cT2b–c	PSA >20 GS >7 cT3a	cT3b–T4
EAU	—	PSA <10 GS <7 cT1–T2a	PSA 10–20 GS 7 cT2b–c	PSA >20 GS >7 ≥cT3a	—
RTOG	—	cT1–T2 GS 2–6	cT1–T2, GS 7 or cT3, GS 2–6	cT1–T2, GS 8–10 or cT3, GS 7	cT3, GS 8–10

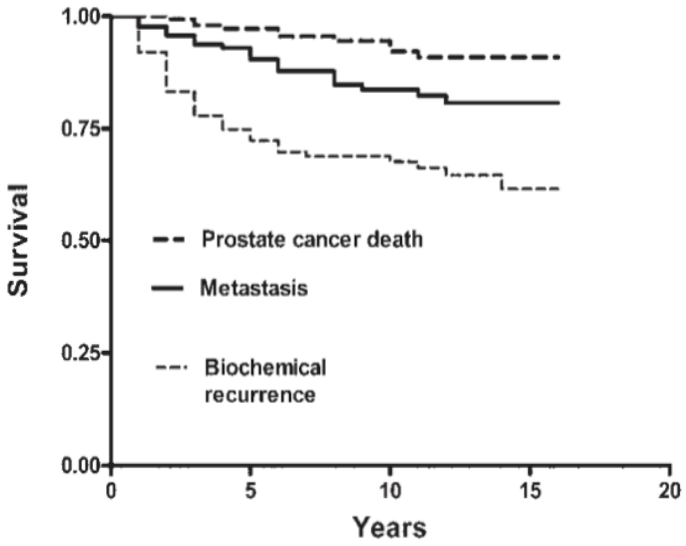
Treatment strategies for localized high-risk prostate cancer



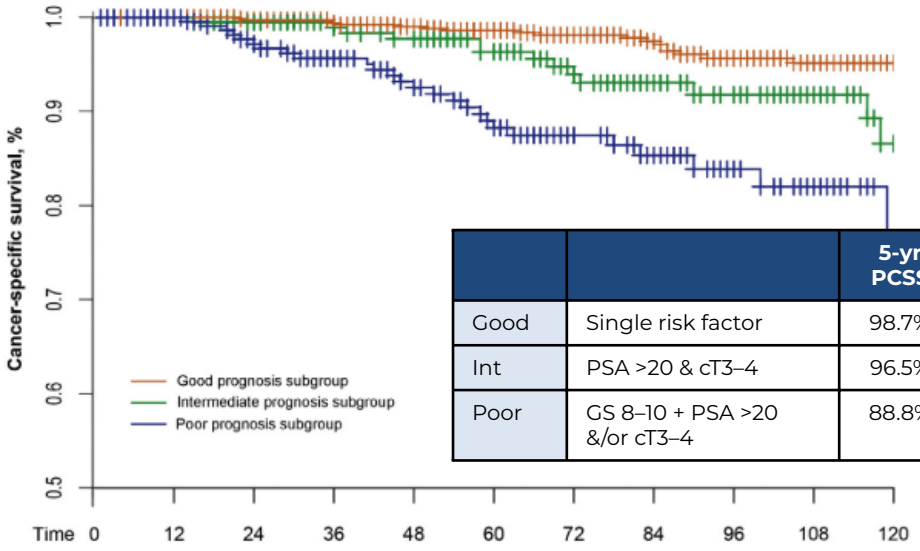
High-risk localized prostate cancer has an adverse prognosis

Increased risk of biochemical failure, need for secondary treatment, metastatic progression, and prostate cancer–specific mortality
Mortality **35.5% at 15 years** when managed with noncurative intent.

N=185. Hi risk (D'Amico). RP + PLND



High risk prostate cancer. N=1360.



		5-yr PCSS	10-yr PCSS
Good	Single risk factor	98.7%	95.4%
Int	PSA >20 & cT3–4	96.5%	88.3%
Poor	GS 8–10 + PSA >20 &/or cT3–4	88.8%	79.7%

Loeb et al. Eur Urol 2010. Joniau et al. Eur Urol 2015.

Can perioperative systemic therapy improve outcomes in high-risk prostate cancer patients?

Better treatment options are needed for high-risk localized prostate cancer

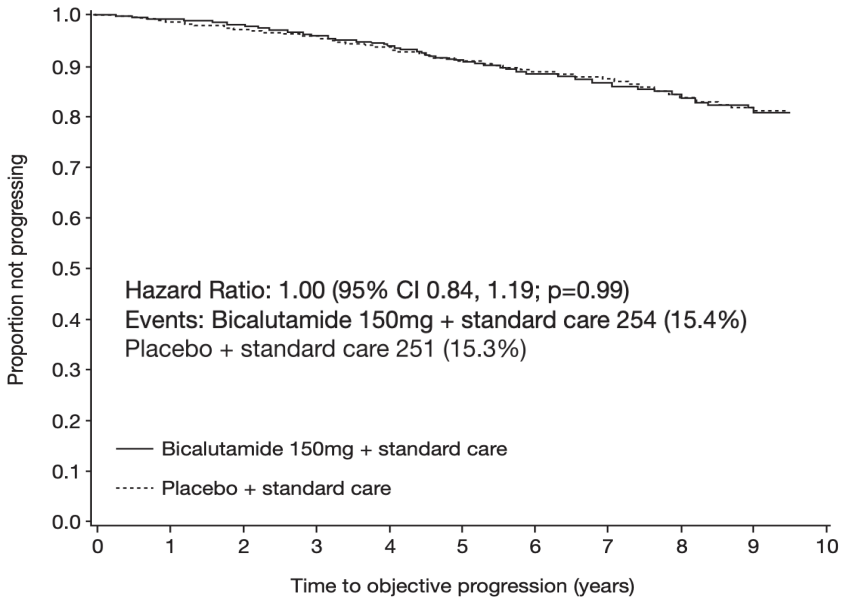
Why perioperative intensification?

- Reduction of viable tumour burden before surgery.
- Targeting occult systemic disease
- Enables direct assessment of treatment response and resistance in post-surgery
- Castration alone may incompletely suppress the androgen pathway: is ADT alone enough?

Adjuvant ADT is not standard after prostatectomy

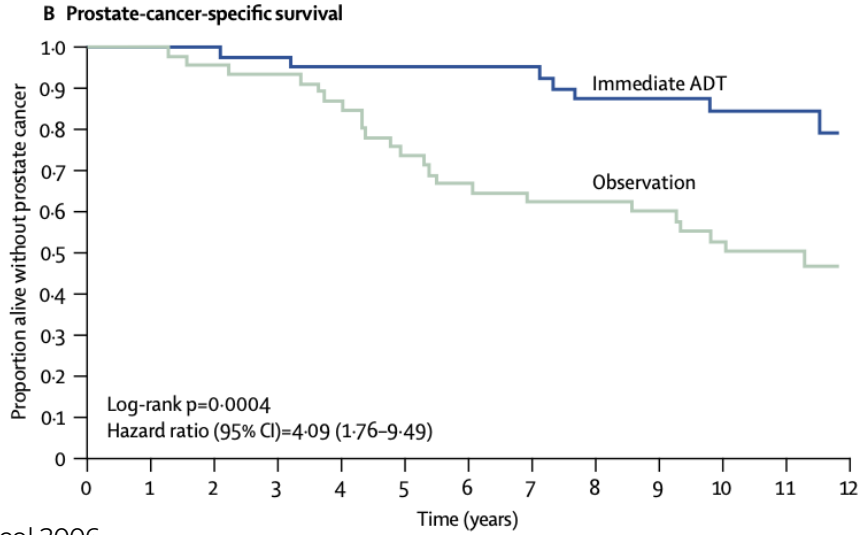
EAU	Do not prescribe adjuvant androgen deprivation therapy (ADT) to **pN0** patients.	Strong

Early Prostate Cancer (EPC) Trial Programme
No PFS benefit with adjuvant high-dose bicalutamide



EAU	In **pN1** patients, after an eLND, discuss options: - Offer adjuvant ADT. - Offer adjuvant ADT + IMRT/VMAT plus IGRT. - Offer observation to patients after eLND and ≤ 2 nodes and an undetectable PSA.	Weak

ECOG EST-3886: benefit of immediate vs deferred ADT in pN+ after prostatectomy
Benefit vs contemporary surveillance with early salvage unclear



EAU Guidelines 2026. Iversen et al. BJU Int 2010. Messing et al. Lancet Oncol 2006.

Perioperative intensification with ARPis can improve pathological outcomes from surgery

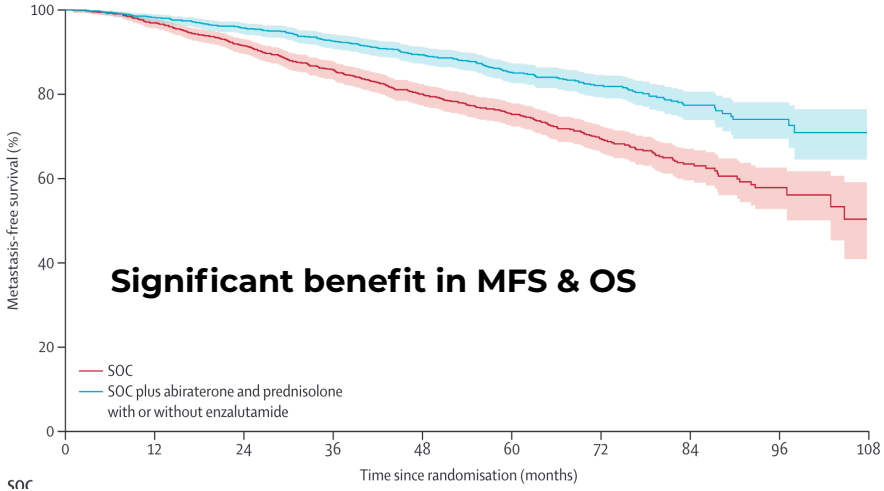
Study	Design / N	Systemic intensification	Main results
Taplin et al., 2014	RPII; N=58, high risk	Leuprolide + abiraterone	pCR: 10% vs 4%; pCR/MRD 24% vs 4%,
Montgomery et al., 2017	RPII; N=58, intermediate/high risk	Enzalutamide + leuprolide + dutasteride vs enzalutamide alone	pCR 4.3%, pCR/MRD ~ 17%;
McKay et al., 2019	RPII; N=75, intermediate/high risk	Enzalutamide + leuprolide + abiraterone vs enzalutamide + leuprolide	pCR/MRD: 30% vs 16%
McKay et al., 2021	RPII; N=118, 94% high risk	Apalutamide + abiraterone + leuprolide vs abiraterone + leuprolide	pCR/MRD: 22% vs 20%
ARNEO	RPII; N=89, high risk	Degarelix + apalutamide vs degarelix + placebo	MRD: 38% vs 9.1%

Taplin et al. J Clin Oncol 2014; Montgomery et al. Clin Cancer Res. 2017; McKay et al. J Clin Oncol. 2019; McKay et al. J Urol. 2021; Devos et al. Eur Urol 2023

Treatment intensification in high-risk / locally advanced prostate cancer

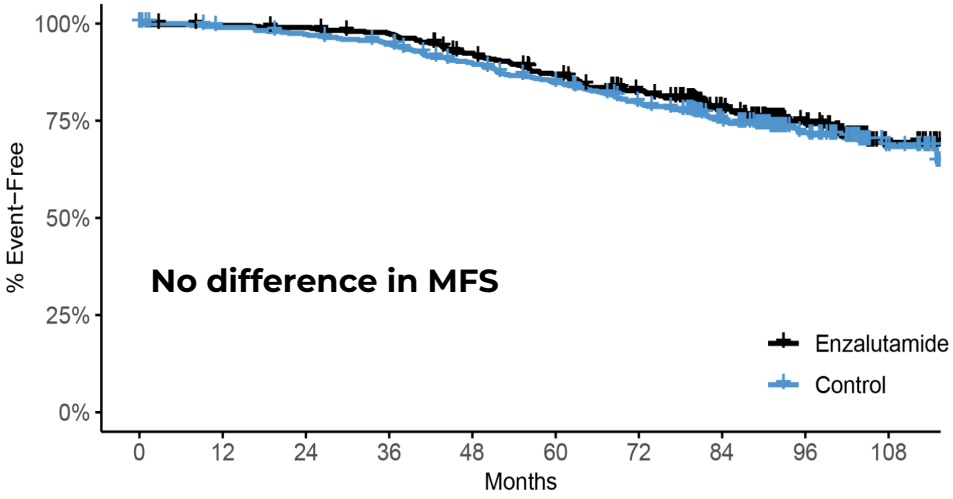
STAMPEDE

High risk localized / locally advanced prostate cancer:
GS 8-10; T3-T4, N1, PSA ≥ 40
SOC + Abi / Abi + Enz x 24m vs SOC



ENZARAD

High risk localized prostate cancer:
GS 8-10; T3-T4, N1, PSA ≥ 20
RT + LHRHA + Enzalutamide 24m vs
RT + LHRHA + NSAA



Attard et al. Lancet 2022. Nguyen et al. ESMO 2025

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Apalutamide in High-Risk Localized Prostate Cancer

M.-E. Taplin,[1] M. Gleave,[2] N.D. Shore,[3] A. Lopez-Gitlitz,[4] A. Kretschmer,[5] E. Efstathiou,[6] P.L. Nguyen,[7,8] R. Damião,[9] T. Kamoto,[10] A. Ross,[11] A. Briganti,[12] B.A. Hadaschik,[13,14] A. Heidenreich,[15] Á. Juárez Soto,[16] H. Ye,[17] G. Gotto,[18,19] B. Rooney,[20] S.K. Tian,[5] L. Wetherhold,[5] B. Miladinovic,[21] S.A. McCarthy,[5] C.P. Evans,[22,23] and A.S. Kibel,[7,8] for the PROTEUS Investigators*

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Hypothesis

(1) **neoadjuvant treatment** with ADT plus a regimen containing apalutamide **improves the pCR rate**

Or

(2) **perioperative treatment** with ADT plus a regimen containing apalutamide **improves MFS**

when compared to treatment with ADT plus placebo

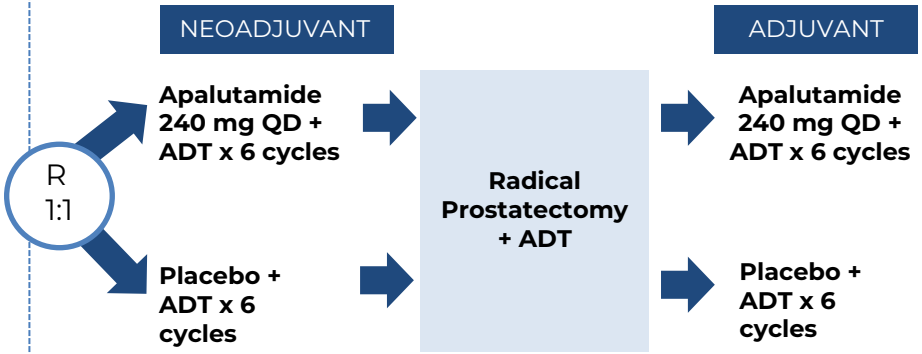
Study Design: phase III randomized double blind

High-risk localized or locally advanced disease

Total Gleason sum score ≥4+3 (ISUP group 3–5) + at least 1 of the following:

- Any combination of Gleason score 4+3 & Gleason score 8 in **≥ 6 cores** (at least 1 Gleason 8 core)
- Any combination of Gleason score 4+3 & Gleason score 8 in **≥ 3 cores & PSA ≥ 20** (at least 1 Gleason 8 core)
- **Gleason score ≥9** in **≥ 1 cores**
- Continuous Gleason score ≥8 in **≥ 1 cores** , each with ≥80% involvement

N=2109



Stratification:
cN0 vs N1
Gleason score (7 vs 8-10)
Region (North America, Europe, Rest of world)

Co-primary endpoints

Pathological Complete Response or Minimum Residual Disease

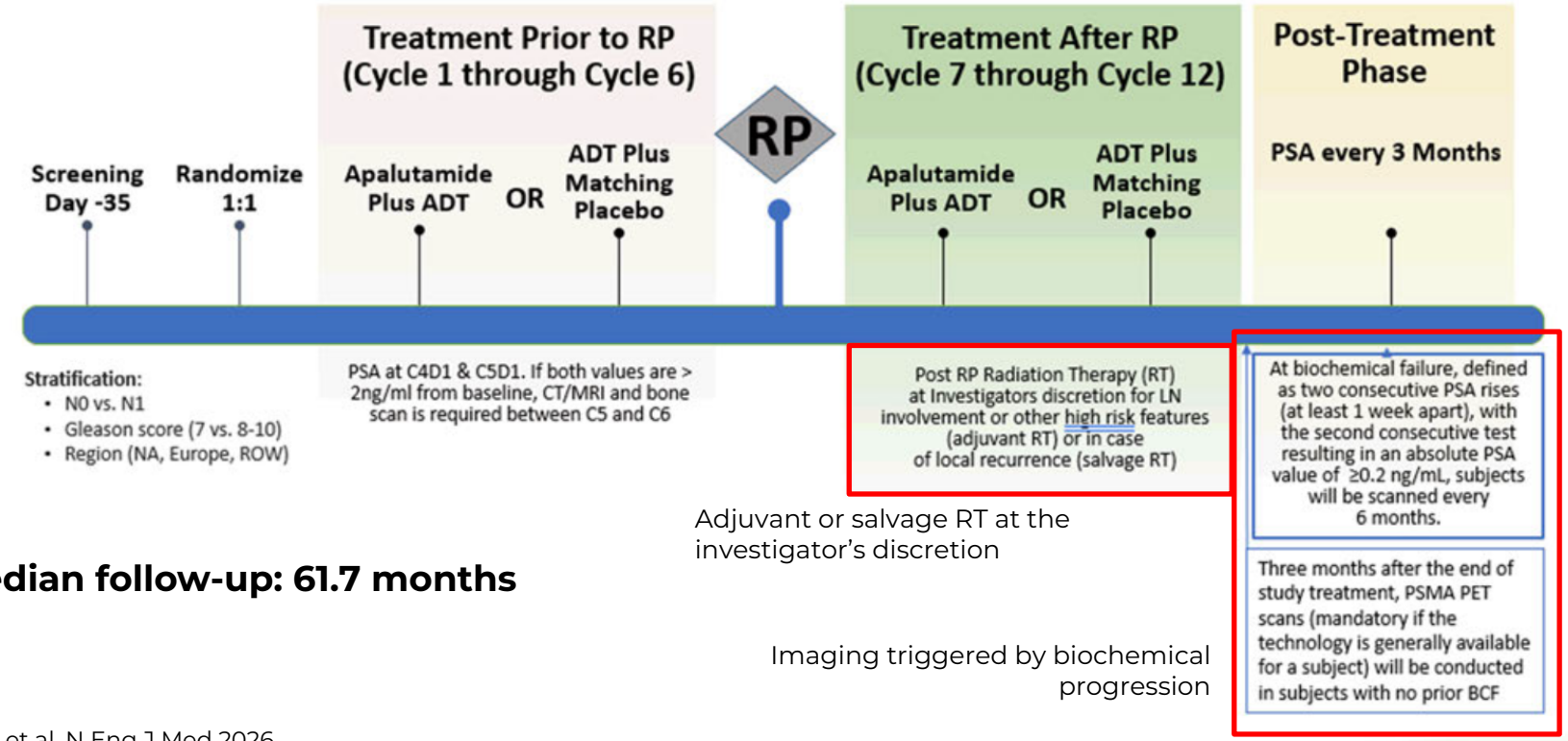
no identifiable tumor [disease stage ypT0]
or
minimal residual tumor of no more than 5 mm in the greatest dimension of the largest tumor lesion in prostate-confined disease [stage ypT2 or lower]

Metastasis-free Survival

Time from randomization to the first occurrence of any of:
· **Distant metastasis** detected on conventional imaging **or PSMA PET**
· **Pathological finding** of distant metastasis
· **Death** from any cause.

Taplin et al. N Eng J Med 2026

Follow-up during the study



Adjuvant or salvage RT at the investigator's discretion

Imaging triggered by biochemical progression

Median follow-up: 61.7 months

Taplin et al. N Eng J Med 2026

Statistical Design amended to allow for PET-PSMA MFS

Original: N = 1500

Amended: N = 2000

Metastasis-free survival

H0	Median MFS 6 yrs
H1	Median MFS 8 yrs
Alpha / Power	0.04 / 90%
Target HR	0.75
Events	559

H0	Median MFS **12 yrs**
H1	Median MFS **16 yrs**
Alpha / Power	0.04 / 85%
Target HR	0.75
Events	477

Pathological complete reponse

H0	pCR 5%
H1	pCR 10%
Alpha / Power	0.01 / 85%

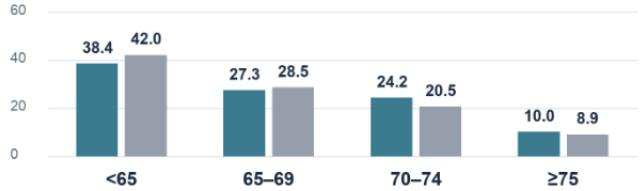
H0	pCR 5%
H1	pCR 10%
Alpha / Power	0.01 / 94%

Taplin et al. N Eng J Med 2026

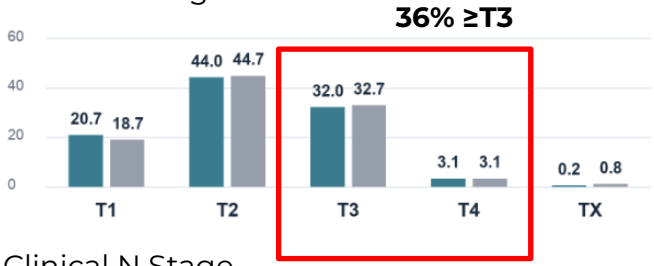
Study Population

Demographic and disease characteristics were well balanced between the two groups

Median age: 66 years



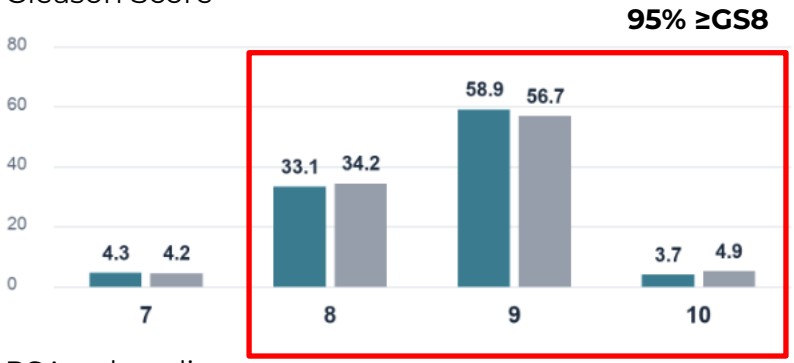
Clinical T Stage



Clinical N Stage



Gleason Score



PSA at baseline

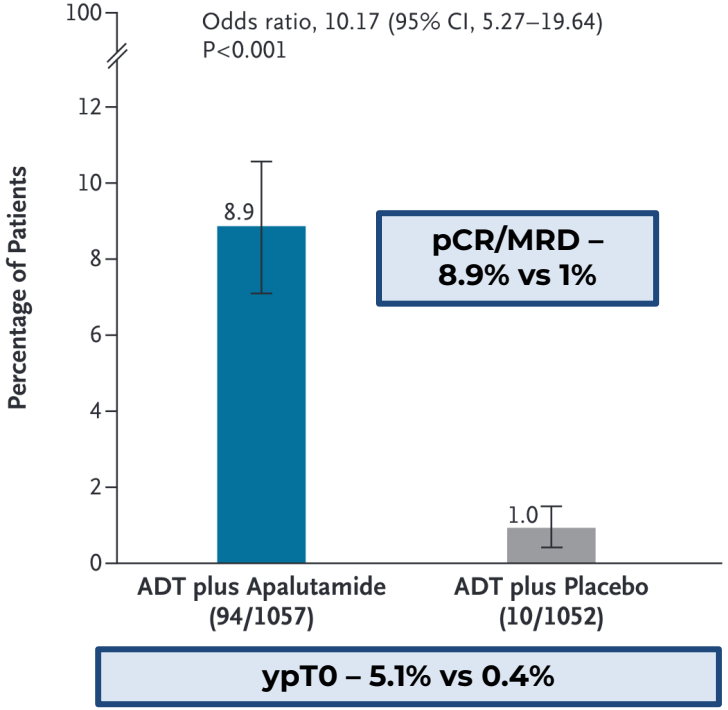


High-risk definition driven by Gleason Score

Co-primary endpoints

Pathological Complete Response or Minimum Residual Disease

No identifiable tumor [ypT0]
or
Minimal residual tumor of no more than 5 mm in the greatest dimension of the largest tumor lesion in prostate-confined disease [ypT2 or lower]



Summary of Histopathological Findings at Radical Prostatectomy

	Apalutamide+ADT	Placebo+ADT
Patients with RP	(n = 989)	(n = 1008)
Positive surgical margin — no. (%)		
Absent	650 (65.7)	547 (54.3)
Present	207 (20.9)	430 (42.7)
Unknown	132 (13.3)	31 (3.1)
Localized or locally advanced disease — no. (%)		
≤ypT2	463 (46.8)	294 (29.2)
ypT3A	185 (18.7)	218 (21.6)
ypT3B	328 (33.2)	480 (47.6)
ypT4	12 (1.2)	14 (1.4)
Unknown	1 (0.1)	2 (0.2)
Presence of pathological lymph nodes — no. (%)		
Absent	756 (76.4)	759 (75.3)
Present	230 (23.3)	246 (24.4)
Unknown	3 (0.3)	3 (0.3)

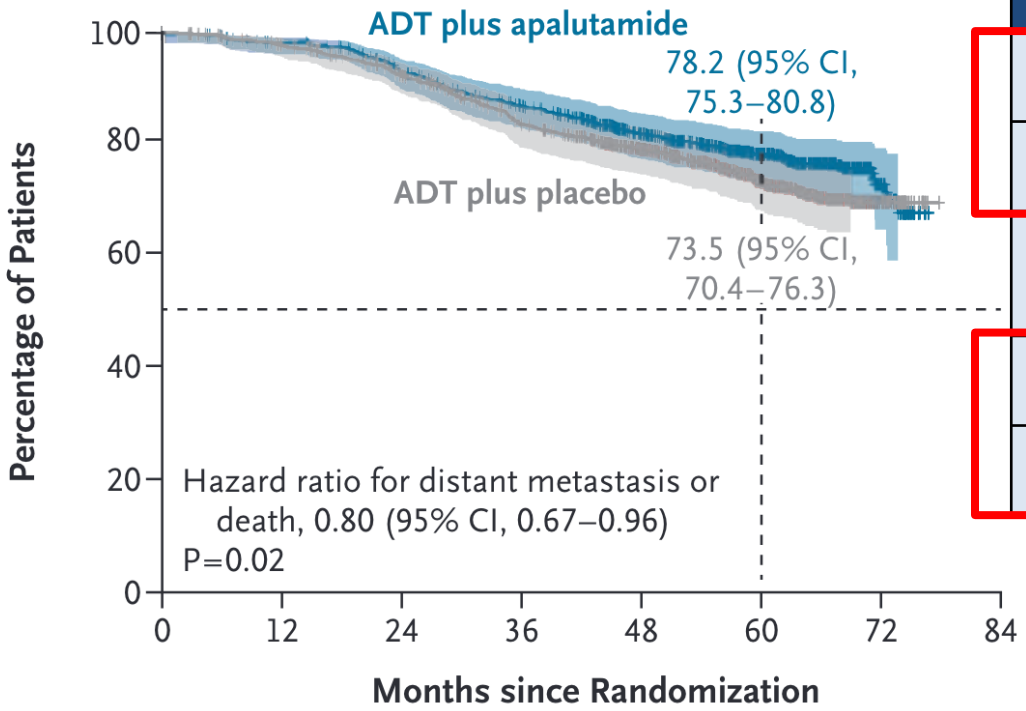
Intent-to-treat population.
RP denotes radical prostatectomy.

cN1 disease (12.2% vs 12.4%)

Taplin et al. N Eng J Med 2026

Co-primary endpoints

Metastasis-free survival

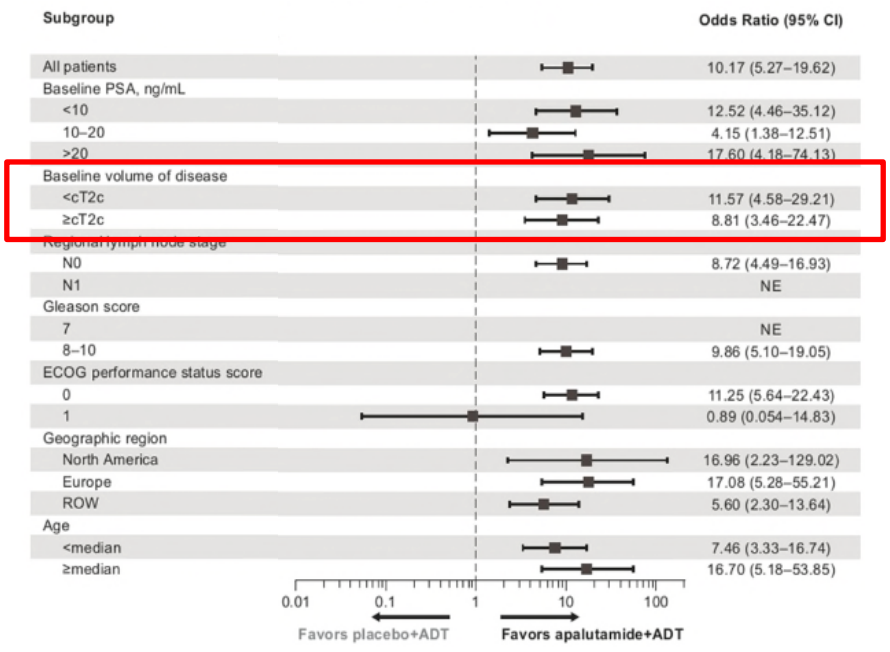


Event	ADT + Apa (n=1057)	ADT + Pbo (n=1052)
Distant metastasis by PSMA-PET	114 (10.8)	156 (14.8)
Distant metastasis by conventional imaging	35 (3.3)	58 (5.5)
Distant metastasis by histopathological assessment	7 (0.7)	7 (0.7)
Death due to prostate cancer	2 (0.2)	8 (0.8)
Death due to all other reasons	57 (5.4)	28 (2.7)

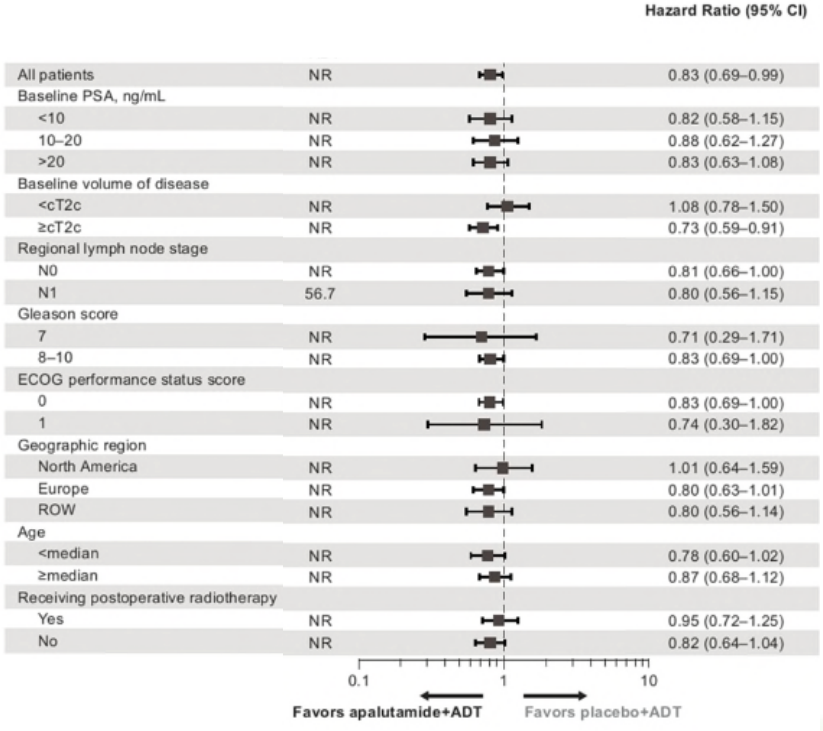
Taplin et al. N Eng J Med 2026

Subgroup analyses

Pathological Complete Response or Minimum Residual Disease



Metastases-free survival

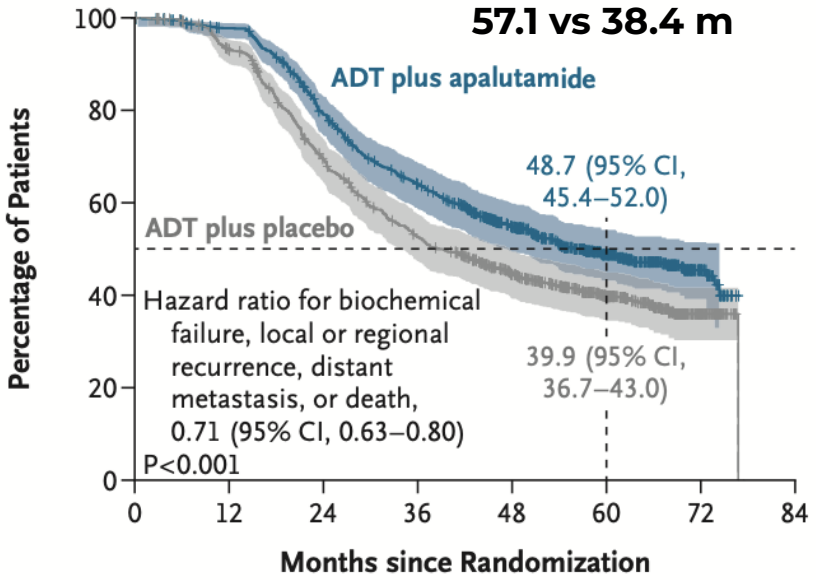


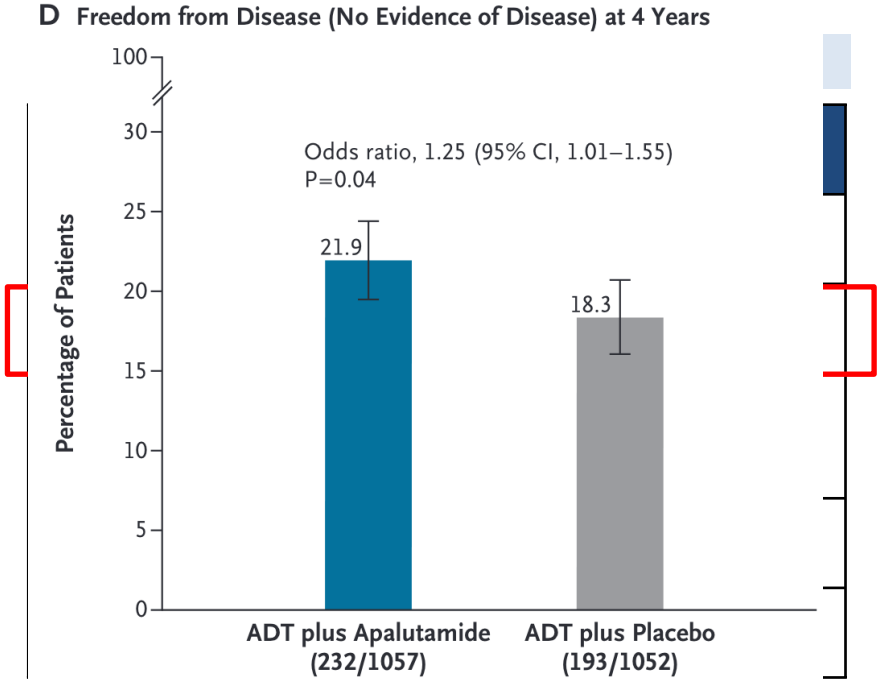
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Secondary endpoints

Event-free survival

Time from randomization to **biochemical failure, local/regional recurrence** (conventional or PET) **or distant metastases** (conventional or PET)

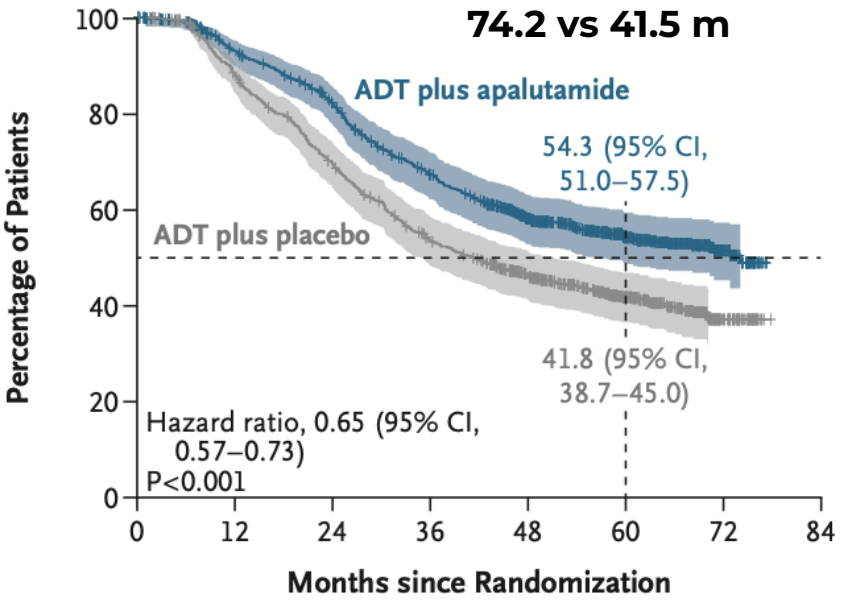




Taplin et al. N Eng J Med 2026

First subsequent local or sytemic therapy

Time from randomization to **any type of local, regional, or systemic subsequent treatment** for prostate cancer, including reinitiation of ADT



Supplementary Table S4. Subsequent Prostate Cancer Therapy.

	Apalutamide+ADT (n = 1057)	Placebo+ADT (n = 1052)
Patients with subsequent therapy/surgery/procedure, no. (%)	448 (42.4)	597 (56.7)
Systemic anticancer therapy		
Hormonal	359 (34.0)	489 (46.5)
Cytotoxic chemotherapy	39 (3.7)	62 (5.9)
Other therapy	29 (2.7)	68 (6.5)
Postoperative radiotherapy	281 (26.6)	387 (36.8)
Adjuvant*	57 (5.4)	79 (7.5)
Adjuvant only†	26 (2.5)	26 (2.5)
Salvage*	219 (20.7)	300 (28.5)
Salvage only†	46 (4.4)	66 (6.3)
Both settings	5 (0.5)	8 (0.8)
Other radiotherapy	58 (5.5)	91 (8.7)
Surgery/procedure	16 (1.5)	13 (1.2)

Intent-to-treat population.

* Includes patients without any other postoperative radiotherapy, not including stereotactic body radiation therapy or any other type of metastasis directed therapy.

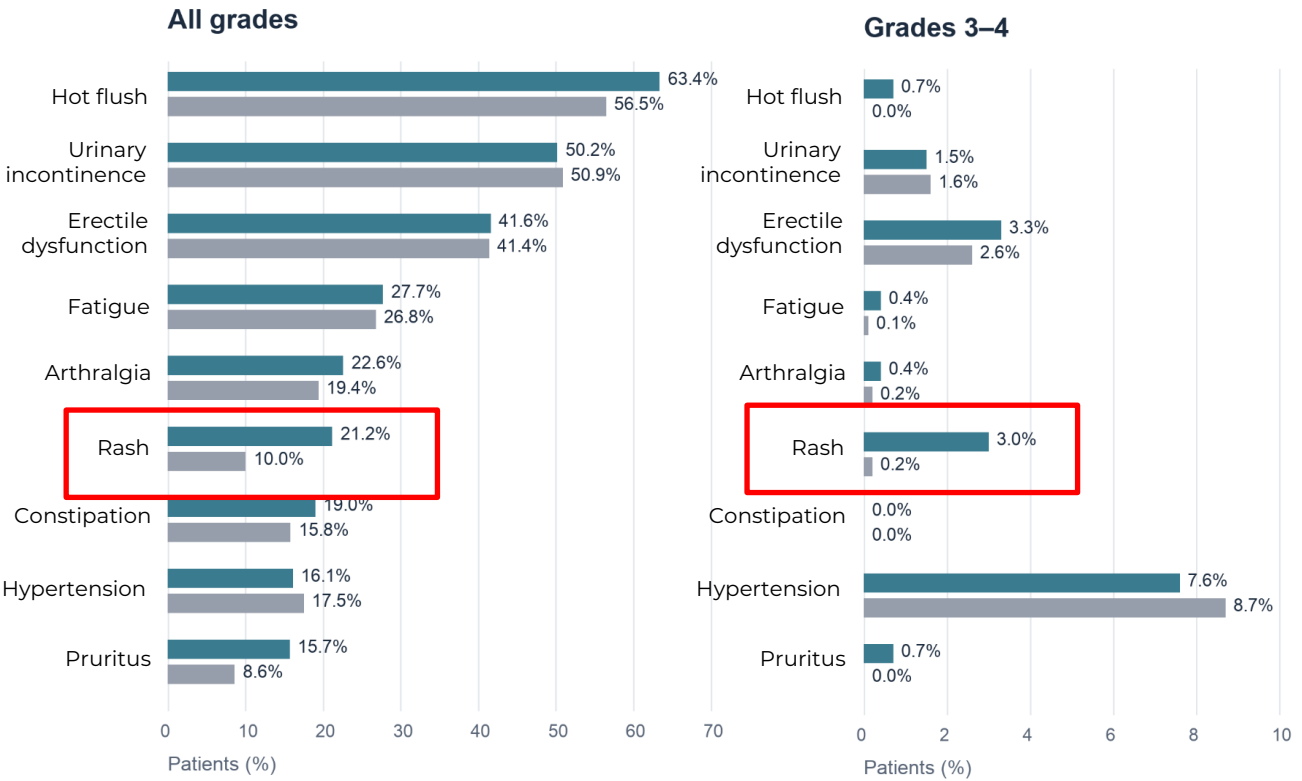
† Includes patients without any additional subsequent therapy.

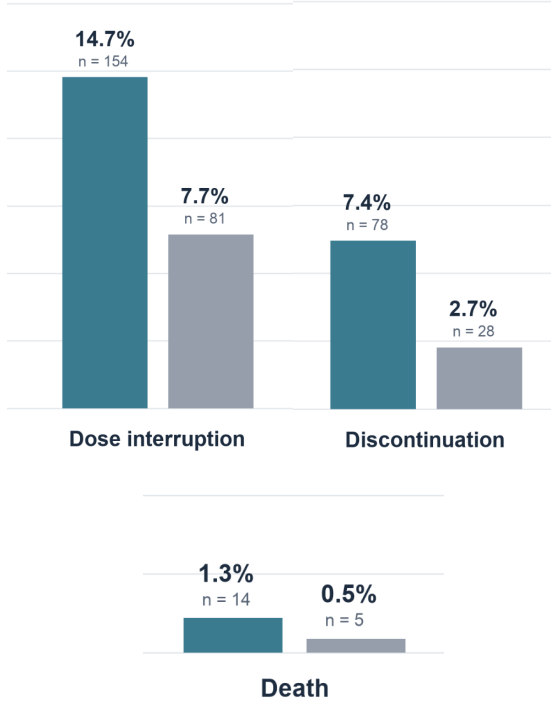
ADT denotes androgen-deprivation therapy.

Taplin et al. N Eng J Med 2026

Adverse events

Adverse events were present in **98.8% of ADT + Apalutamide** & **97.8% of ADT + Pbo treated patients**





Taplin et al. N Eng J Med 2026

DISCUSSION

Androgen-receptor pathway inhibition with 6 cycles of ADT plus apalutamide both before and after radical prostatectomy in patients with high-risk localized or locally advanced prostate cancer **led to significantly greater disease-control success** than treatment with ADT plus placebo, as well as **better patient-relevant long-term oncologic outcomes**

A **significant benefit** was observed **for pathological complete response or minimal residual disease and metastasis-free survival,** the dual primary end points.

- Pathological complete response or minimal residual disease in surgical specimens was approximately **9 times as high**

In our trial, the between-group difference in **metastasis-free survival as assessed by conventional imaging alone was not significant**.

The use of **perioperative ADT in the control arm** represents intensification of treatment beyond current clinical guideline recommendations of radical prostatectomy alone

Overall survival was evaluated as an alternative measure of safety and **showed no detrimental treatment effect**, although the **length of follow-up in this trial was short** to assess a survival outcome in this disease context.

- HR for death of 1.08 → below the prespecified threshold for an unacceptable level of detriment

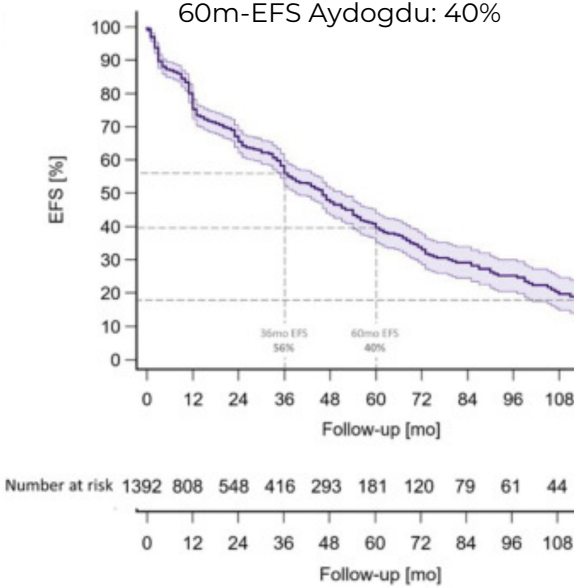
Open questions

- How do results from PROTEUS compare with real-world evidence or prior studies in this setting?
- What is the value of a complete pathological response?
- Is MFS by PSMA-PET a valid surrogate?
- Is the balance between efficacy and toxicity the same for all patients?
- Was perioperative ADT the best control arm?

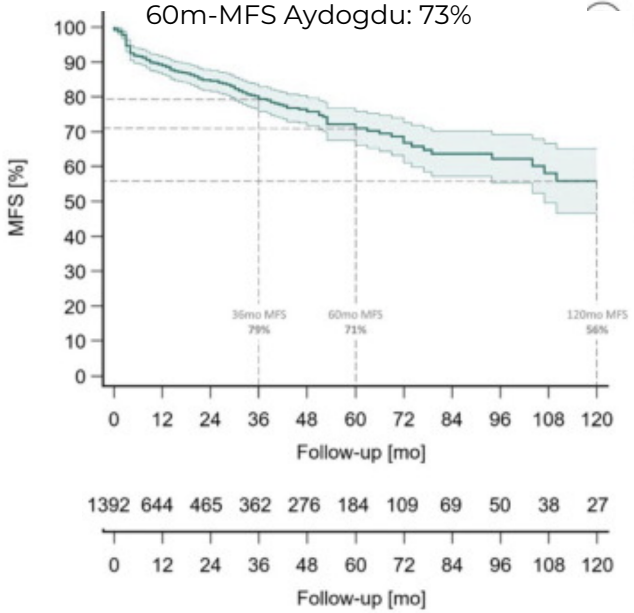
How do results compare to the real world?

Single-center cohort study of consecutive patients fulfilling PROTEUS high-risk criteria who underwent RP with lymphadenectomy without prior ADT or neoadjuvant treatment. **N=1392.**

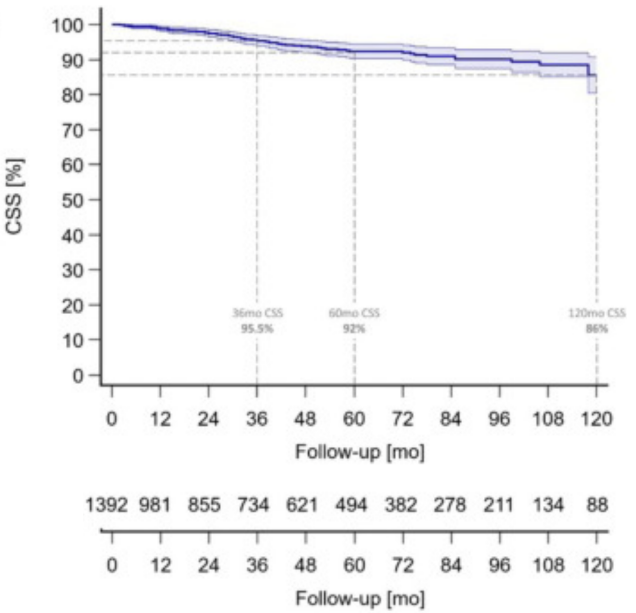
60m-EFS Proteus control arm: 39.9%
60m-EFS Aydogdu: 40%



60m-MFS Proteus control arm: 73.5%
60m-MFS Aydogdu: 73%



120m-CSS: 86%



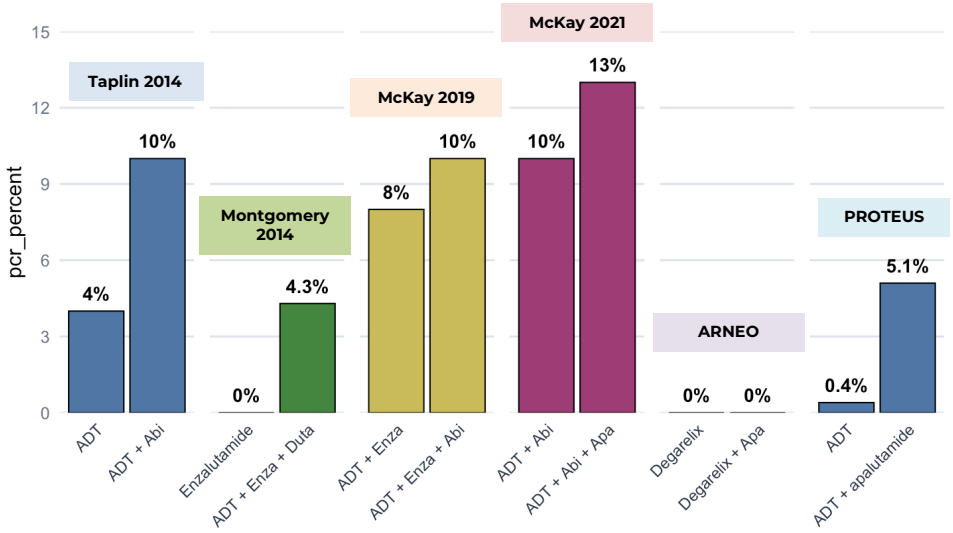
Taplin et al. N Eng J Med 2026. Aydogdu et al. Eur Urol Open Sci 2026

How do results compare to other intensification strategies?

Neoadjuvant intensification with ARPIs

pCR: absence of tumor in prostatectomy specimen (ypT0)

pCR results vary widely across studies
lack of standardization



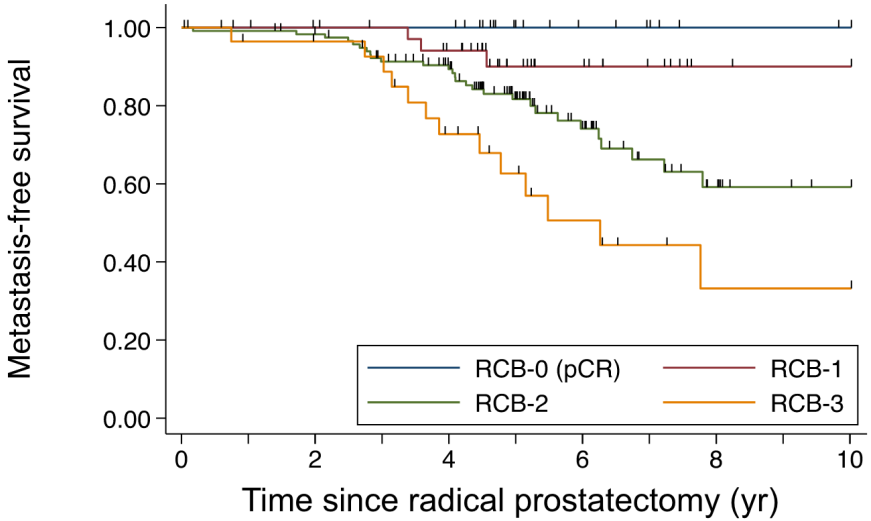
Minimal residual disease **(MRD)** and residual cancer burden **(RCB)** criteria are very variable

Trial	MRD definition	RCB-based MRD also assessed
Taplin 2014	Largest cross-sectional residual tumor dimension ≤5 mm	Yes: RCB ≤0.25 cm³
Montgomery 2017	Maximum residual tumor diameter ≤3 mm	RCB measured, but not used as the MRD definition
McKay 2019	Residual tumor ≤5 mm	RCB measured
McKay 2021	Residual tumor <5 mm	RCB measured
ARNEO	RCB ≤0.25 cm³	Yes
PROTEUS	≤ypT2, N0 + residual tumor diameter ≤5 mm	Yes:

Taplin et al. J Clin Oncol 2014; Montgomery et al. Clin Cancer Res. 2017; McKay et al. J Clin Oncol. 2019; McKay et al. J Urol. 2021; Devos et al. Eur Urol 2023

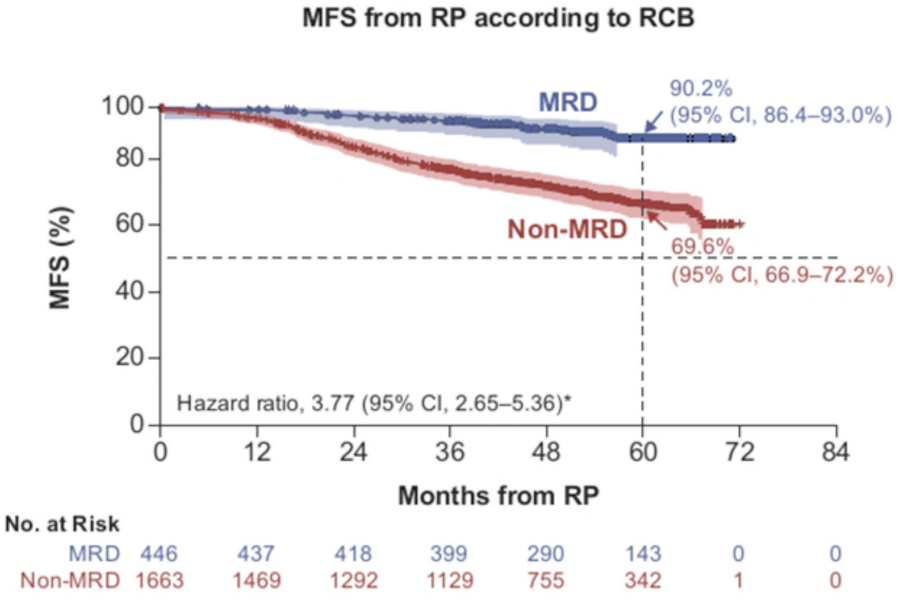
What is the value of a pathologic response?

ARNEO: low residual cancer burden is associated with a longer metastasis-free survival



PROTEUS: RCB ≤0.25 cm³ + ypT0/T2 + ypN0 + negative surgical margins

21.1% of all patients irrespective of arm



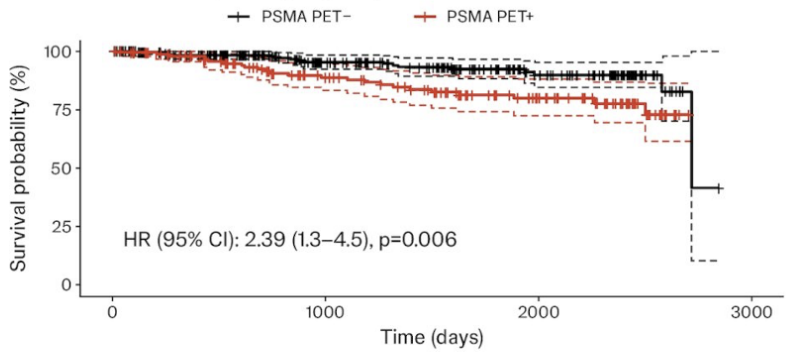
Events, no. (%)	MRD (n = 446)	Non-MRD (n = 1546)
Events	34 (7.6)	409 (26.5)
Censored	412 (92.4)	1137 (73.5)

Taplin et al. N Eng J Med 2026.

Is MFS a valid surrogate endpoint?

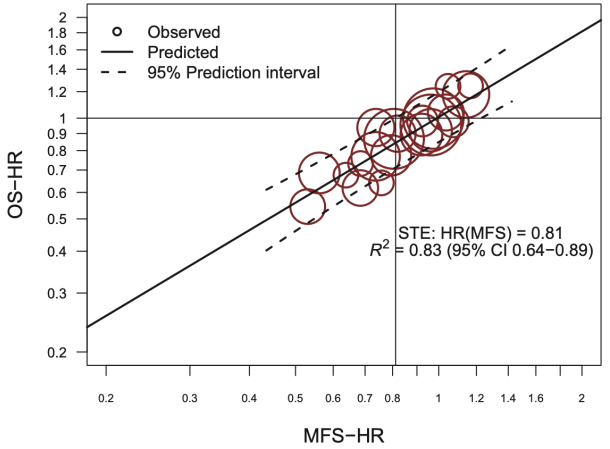
MFS by PSMA PET at biochemical recurrence after radical prostatectomy can be **three times shorter** than MFS by **conventional imaging**

Figure 1. MFS for PSMA PET+ versus PSMA PET− patients (unadjusted)



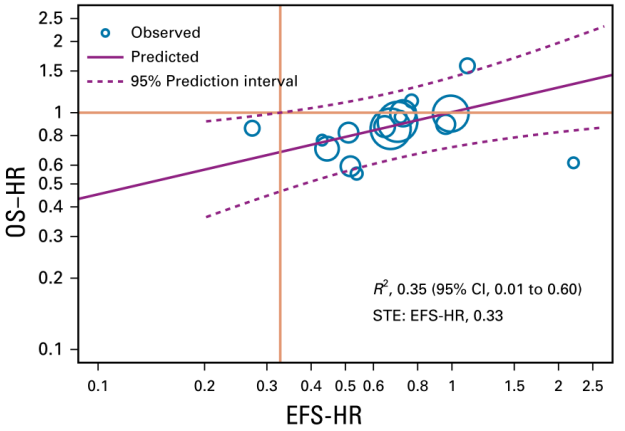
MFS by **conventional imaging** is the **only accepted surrogate** of overall survival in localized prostate cancer

STE 0.81



Event-free survival (any mode of failure including biochemical or death) has **very poor correlation to OS**

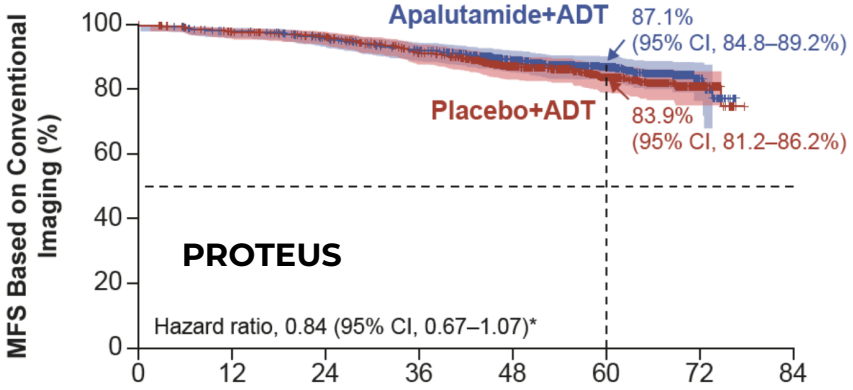
STE 0.33



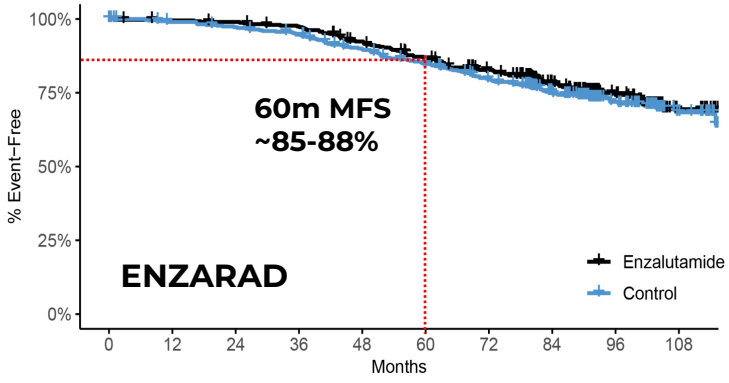
Casillas et al. ASCO GU 2025. Xie et al. Ann Oncol 2024. Xie et al. J Clin Oncol 2020.

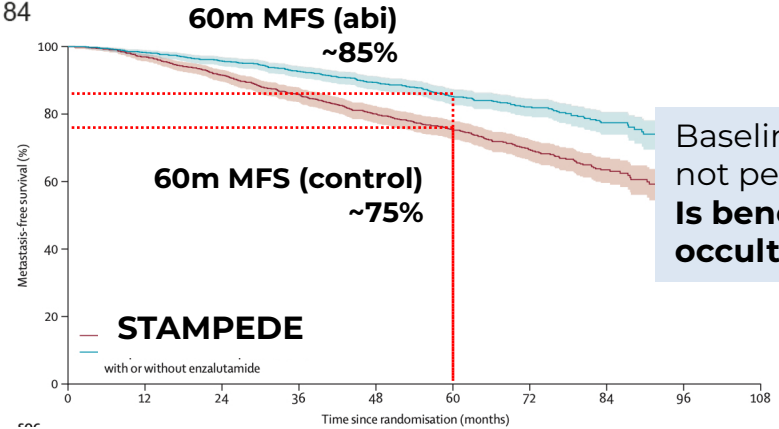
How do results compare to other intensification strategies?

MFS by conventional imaging



	STAMPEDE	ENZARAD	PROTEUS
cN1	39%	11%	12.3%
PSA	35	14	14.8
cT3-T4	92%	47%	35.4%
GS 8-10	79%	89%	95.8%





Baseline PET-PSMA not performed
Is benefit driven by occult M1?

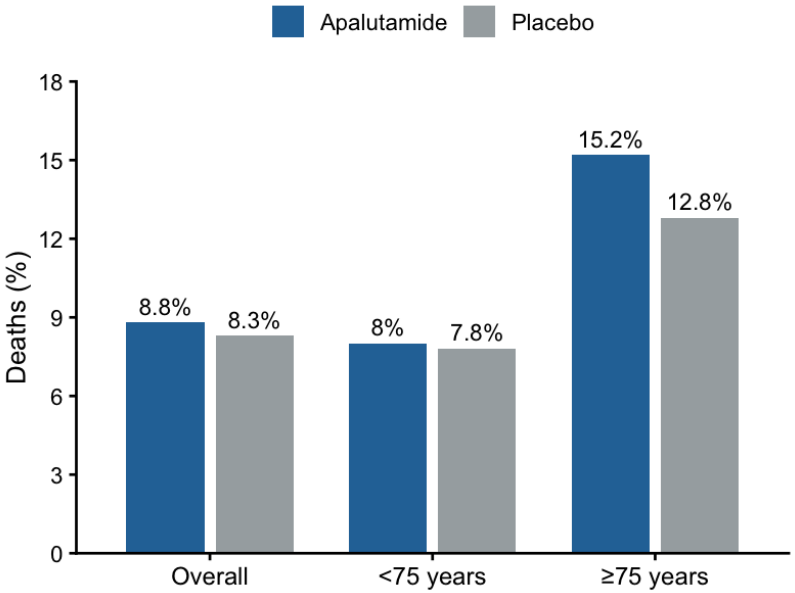
Taplin et al. N Eng J Med 2026. Attard et al. Lancet 2022. Nguyen et al. ESMO 2025

Is the balance between efficacy and toxicity the same for everyone?

Amendment 4: additional safety measures in the to reduce cardiovascular and thromboembolic complications associated with radical prostatectomy (RP) and androgen deprivation therapy (ADT).

Event	Apa	Pbo
Ischemic heart disease	25 (2.4%)	22 (2.1%)
Cerebrovascular disorders	8 (0.8%)	13 (1.2%)
Deaths due to cardiac disorders during treatment	8 (0.8%)	2 (0.2%)
Cardiac deaths within 90d of prostatectomy	6 (0.6%)	1 (0.1%)

Death rates higher in older patients

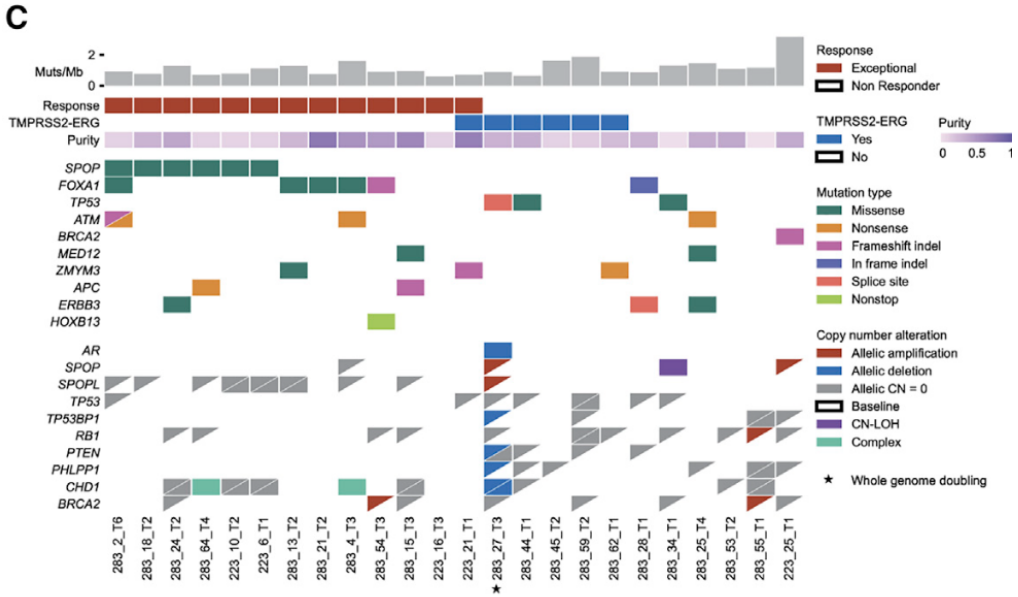


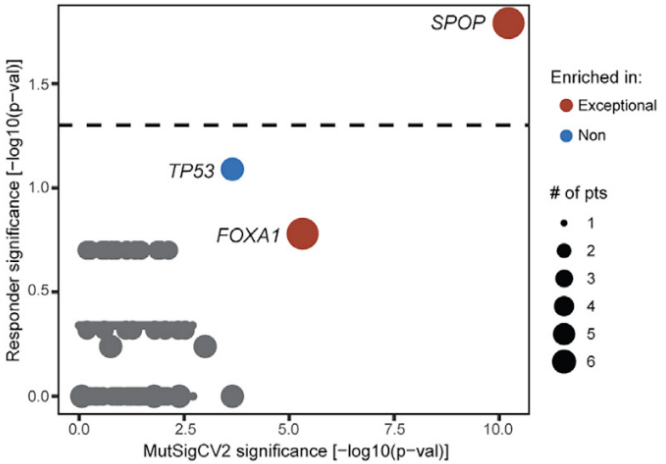
Taplin et al. N Eng J Med 2026

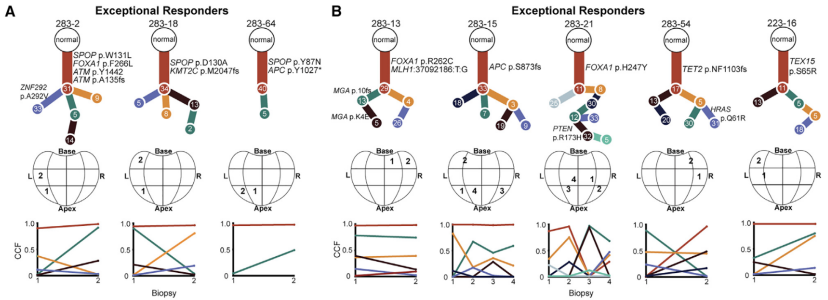
Is the balance between efficacy and toxicity the same for everyone?

Exceptional response to neoadjuvant ARPIs

N=32. Neoadjuvant ADT + ARPi
Exceptional responders vs non-responders.







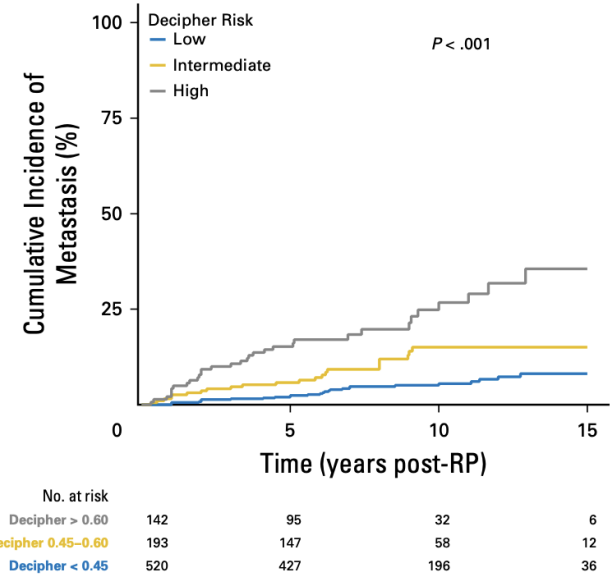
Tewari et al. Cell Rep 2021

Is the balance between efficacy and toxicity the same for everyone?

Can molecular biomarkers help us identify candidates better?

Decipher can identify patients at higher risk of developing metastases

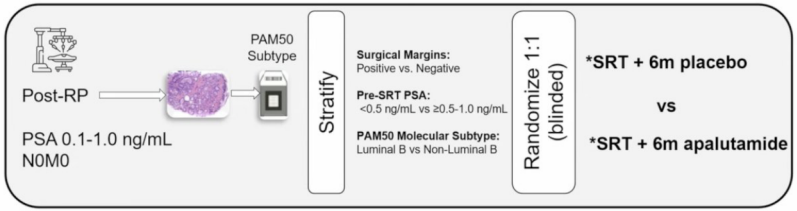
IPD metaanalysis. Localized disease treated with prostatectomy.

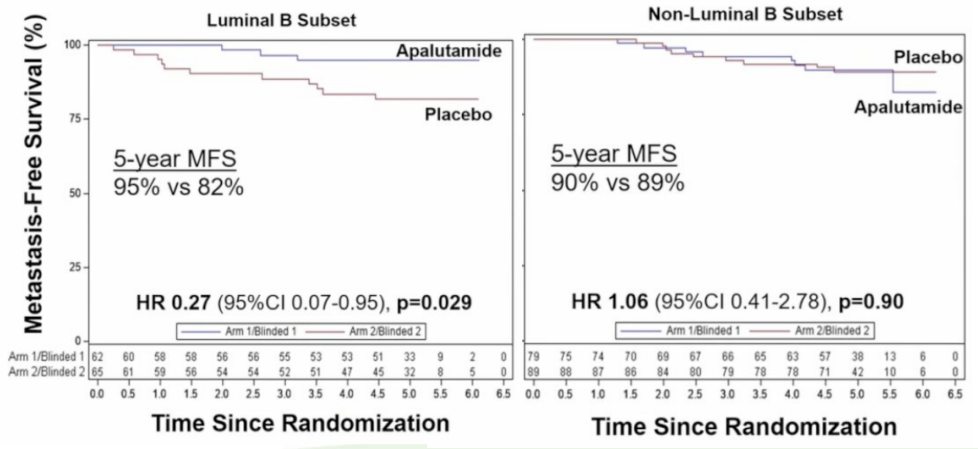


Spratt et al. J Clin Oncol 2017. Spratt et al. ASTRO 2025.

BALANCE trial: NRG GU006

PAM50 **Luminal B benefit from Apa** with SRT



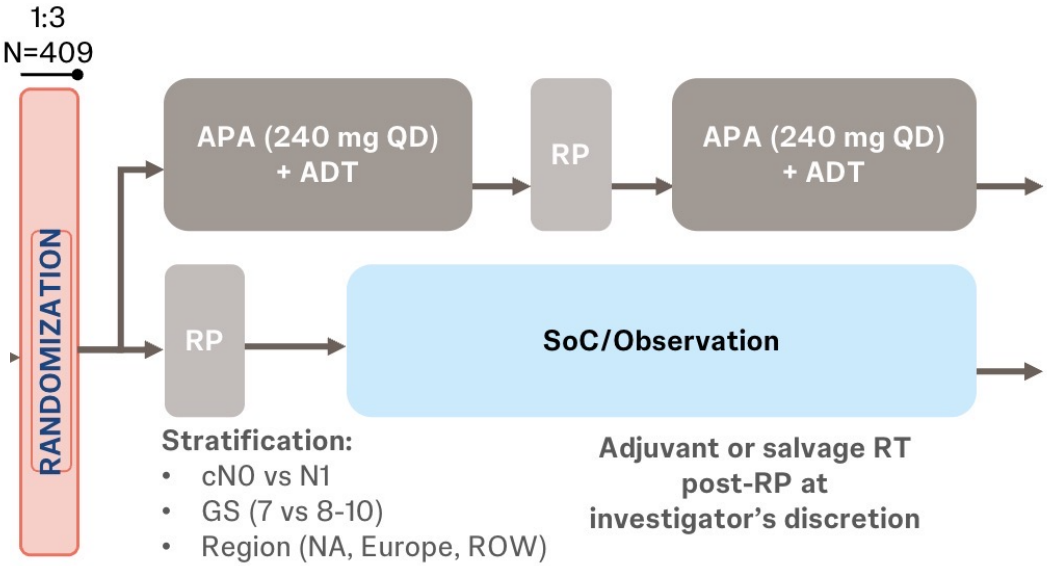


What comes next?

How does perioperative ADT + Apalutamide compare to surgery without ADT?

LBA53 - Proffered Paper Session
Saturday, 24 October 2026 10.15h

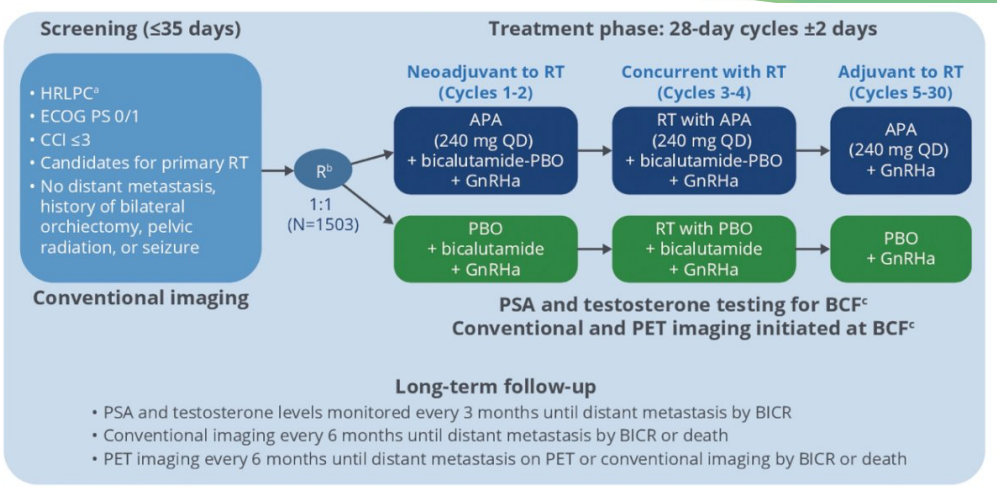
PROTEUS Substudy



- PSA levels monitored every 3 months for BCF
- local PSA testing is allowed during the follow-up phase
- At BCF (defined as 2 consecutive PSA rises ≥0.2 ng/mL), initiate PSMA PET/MRI/CT

What comes next?

The ATLAS Study



DASL-HiCaP (ANZUP 1801)

MADRID 2026 ESMO congress
MADRID SPAIN
23-27 OCTOBER 2026

LBA4 –
Presidential Session II
Sunday, 25 October
16.30h

Eligibility

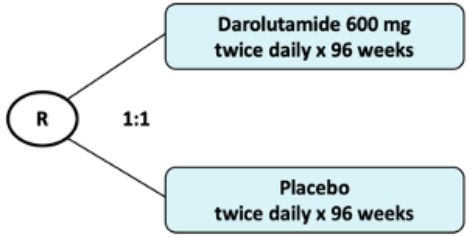
- Very high risk localised prostate cancer to be treated with definitive radiation, or
  Very high risk features + PSA persistence/rise within 12 months following radical prostatectomy (RP) to be treated with post RP radiation
- Suitable for EBRT with or without brachytherapy
- CT/MRI and bone scan negative for distant metastases (allow pelvic LN)

Statistical analysis

1100 participants:

- 3 years accrual + at least 4 years of additional follow up (until 130 events recorded)
- 80% power to detect: 40% reduction in the hazard for metastasis or death
  - assuming MFS rate at 5 years: 85% in the control group; 90.7% darolutamide group, allowing for interim analysis and missing data

All participants are also treated concurrently with an LHRHA for 96 weeks post randomisation, plus RT starting at week 8-24 post randomisation.



Endpoints

- Metastasis-free survival *(primary)*
- Overall survival
- Prostate cancer-specific survival
- PSA-progression free survival
- Time to subsequent hormonal therapy
- Time to castration-resistance
- Frequency and severity of adverse events
- Health-related quality of life
- Fear of cancer recurrence
- Incremental cost-effectiveness
- Prognostic/predictive biomarkers

Stratification

1. Previous radical prostatectomy (yes or no)
2. Planned docetaxel use (yes or no)
3. Clinical or pathological pelvic LN involvement (yes or no)

Perioperative treatment of high-risk Prostate Cancer

Perioperative **apalutamide + ADT improves pathological response and metastasis-free survival** versus ADT alone.

- **PROTEUS** is the **first randomized phase III trial shown to improve outcome** in high risk prostate cancer patients treated with surgery

Improved **clinically significant** outcomes

- Pathological response rate, negative surgical margins
- Metastasis-free survival

Does perioperative ADT + apalutamide cure more patients?

- More patients alive and free from disease at 4 years with Apalutamide (21.9% vs 18.3%)
- pN+ rate was not reduced by preoperative apalutamide
- No OS data

What do we consider a cure?

Standard follow-up strategies have changed with the **widespread implementation of PSMA-PET**

- Value of PSMA-PET as a surrogate of OS is unproven → mainly driven by PSA (EFS)
- Pathological response rate remains to be defined/validated as a biomarker

Patient selection is key to maximize benefit

- Age, comorbidities (cardiovascular)
- **Molecular biomarkers** will be paramount to identify sensitivity to hormonal approaches

How do results compare with the standard PR + LND & no ADT (efficacy and toxicity)?

- **PROTEUS substudy results** to be presented shortly

Thank you!

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@Dav_Lorente

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FUNDACIÓN
INSTITUTO VALENCIANO DE ONCOLOGÍA

