Genitourinary Masterclass

The EMBARK trial in clinical practice

Professor Dr Derya Tilki
Professor Dr Thomas Zilli
Professor Dr Thomas Steuber

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XTANDI™ (enzalutamide) indications

XTANDI is indicated, as per the EMA SmPC:

- As monotherapy or in combination with ADT for the treatment of adult men with high-risk biochemical recurrent non-metastatic HSPC who are unsuitable for salvage radiotherapy
- In combination with ADT for the treatment of adult men with mHSPC
- For the treatment of adult men with high-risk non-metastatic CRPC
- For the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated
- For the treatment of adult men with mCRPC whose disease has progressed on or after docetaxel therapy

XTANDI is subject to medicinal prescription.
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ADT, androgen deprivation therapy; EMA, European Medicines Agency; CRPC, castration-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; SmPC, Summary of Product Characteristics.
XTANDI (enzalutamide). Summary of Product Characteristics.
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Genitourinary Masterclass

Biochemical recurrence after radical prostatectomy

Prof. Dr. Derya Tilki

Professor of Urology at Martini-Klinik Prostate Cancer Centre,
Department of Urology,
University Hospital Hamburg–Eppendorf, Germany

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Disclosures

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- The speaker has received an honorarium from Astellas for this presentation

Outline

- Natural history and definition of BCR
- Imaging
- Treatment

BCR, biochemical recurrence.

Background

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J. Oldenburg, D.E. Oprea-Lager, M. Roberts, O. Rouvière, I.G. Schoots, J. Stranne, T. Wiegel
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6.4.1 Background

- Between **27% and 53%** of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Although metastatic progression is universally preceded by rising PSA levels, **physicians must inform the patient that a measurable PSA may not necessarily lead to clinically apparent metastatic disease**

- The PSA level that defines treatment failure depends on the primary treatment

EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; SIOG, International Society of Geriatric Oncology.

EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.

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Definition of BCR

After radiation

DEFINING BIOCHEMICAL FAILURE FOLLOWING RADIOTHERAPY WITH OR WITHOUT HORMONAL THERAPY IN MEN WITH CLINICALLY LOCALIZED PROSTATE CANCER: RECOMMENDATIONS OF THE RTOG-ASTRO PHOENIX CONSENSUS CONFERENCE

MACK ROACH III, M.D.,* GERALD HANKS, M.D.,† HOWARD THAMES JR., PH.D.,‡ PAUL SCHELLHAMMER, M.D.,§ WILLIAM U. SHIPLEY,‖ GERALD H. SOKOL, M.D.,¶ AND HOWARD SANDLER, M.D.**

- **RTOG-ASTRO Phoenix:**[1] A rise by ≥2 ng/ml above the post-radiation PSA nadir

After RP

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2025

- **NCCN:**[2] Undetectable PSA after RP, with a subsequent detectable PSA that increases on two or more determinations (PSA recurrence) or that increases to PSA >0.1 ng/ml

- **EAU:**[3] After RP, the threshold that best predicts further metastases is a PSA of >0.4 ng/ml and rising

BCR, biochemical recurrence; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; PSA prostate-specific antigen; RP, radical prostatectomy; RTOG-ASTRO, Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology.

1. Mack Roach III MD, et al. *Int J Radiat Oncol Biol Phys* 2006;65:965–974; 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer, Version 1.2025.
 3. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.
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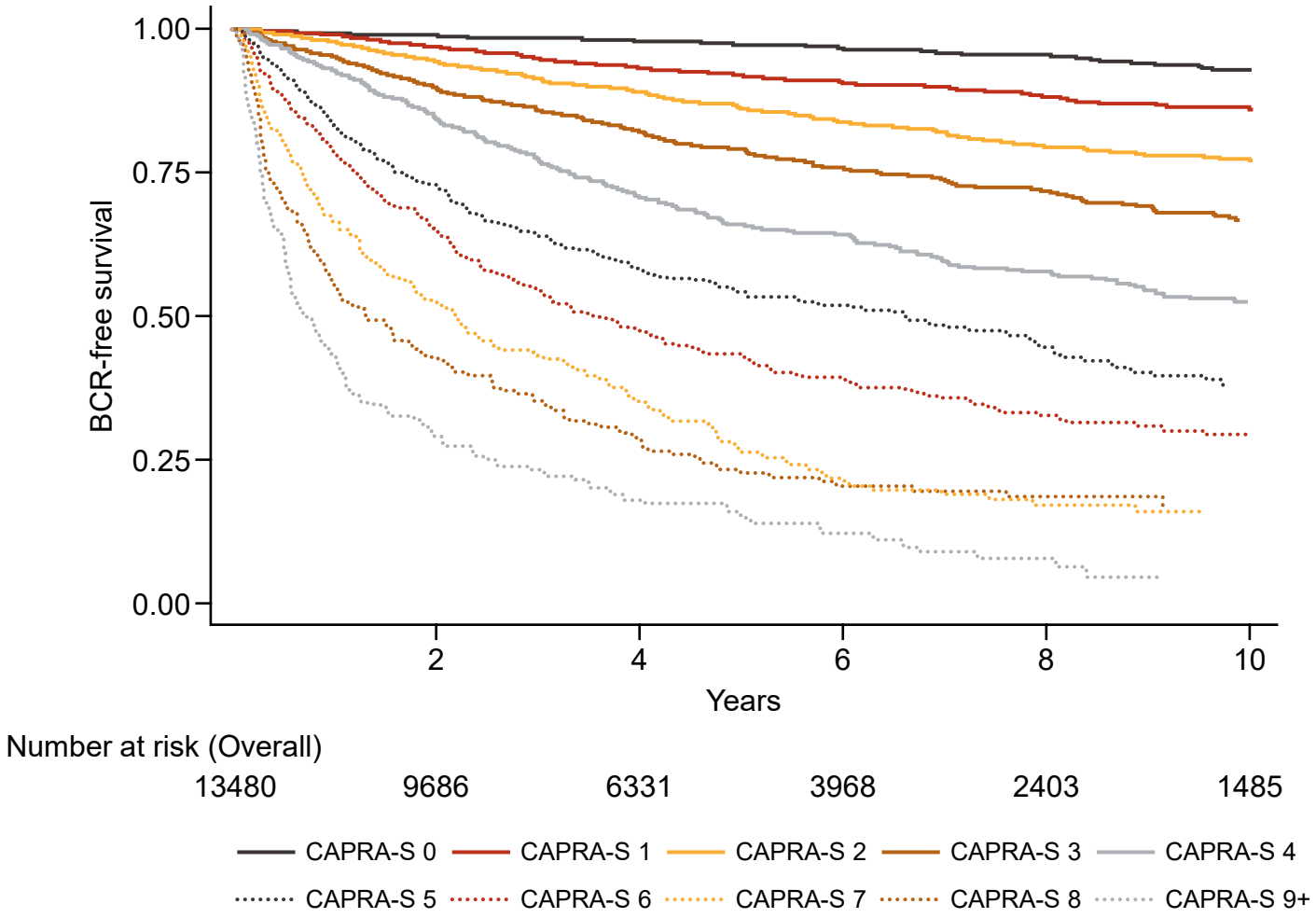
BCR after RP



CAPRA-S score	5-year BCR-free Survival, % (95% CI)
0	97.5 (96.5–98.2)
1	92.0 (90.8–93.1)
2	86.3 (84.6–87.8)
3	79.0 (76.8–81.1)
4	66.0 (62.5–69.2)
5	54.2 (49.9–58.4)
6	43.2 (38.2–48.0)
7	26.0 (20.4–32.0)
8	22.5 (16.8–28.7)
≥9	15.3 (10.6–20.8)

Variable	Level	Points
PSA	0–6	0
	6.01–10	1
	10.01–20	2
	>20	3
SM	Negative	0
	Positive	2
SVI	No	0
	Yes	2
Gleason	2–6	0
	3+4	1
	4+3	2
	8–10	3
ECE	No	0
	Yes	1
LNI	No	0
	Yes	1

Graph and tables adapted from Tilki D, et al. *J Urol* 2015.
BCR, biochemical recurrence; CAPRA-S, Cancer of the Prostate Risk Assessment Score; CI, confidence interval; ECE, extracapsular extension; LNI, lymph node involvement; PSA, prostate-specific antigen; RP, radical prostatectomy; SM, surgical margins; SVI, seminal vesicle invasion.
Tilki D, et al. J *Urol* 2015;193:1970–1975.
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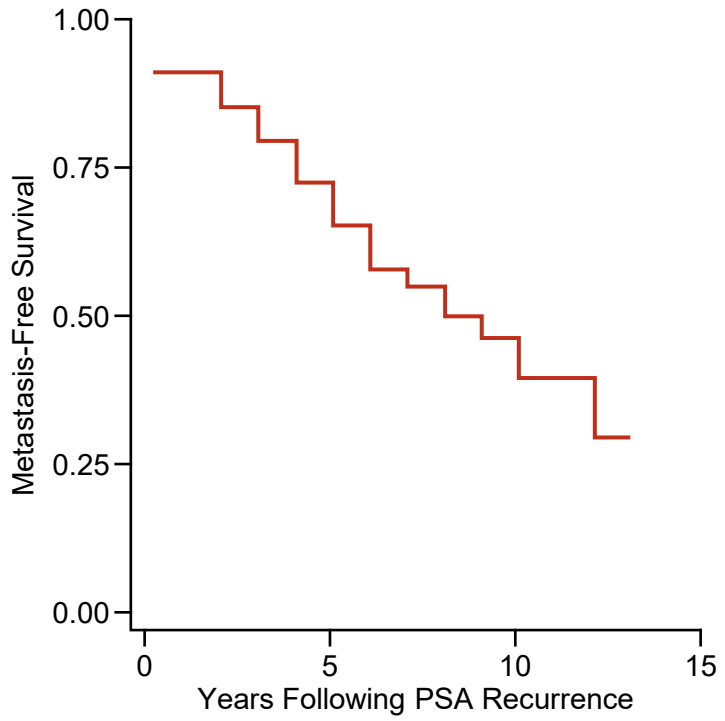
Natural history of progression after BCR following RP

Actuarial likelihood of MFS in 304 men with PSA elevation after RP



Pathological Gleason score, pathological stage and follow-up in the 304 men who had demonstrated PSA recurrence after anatomical RP

Variable	Number (%) of patients
Pathological Gleason score	
5	15 (4.9)
6	41 (13.5)
7	151 (49.7)
8–10	97 (31.9)
Total	**304 (100)**
Pathological stage	
Organ-confined	31 (10.2)
Capsular penetration	
With Gleason score ≤7	30 (9.9)
With Gleason score ≥7	108 (35.5)
Involvement of seminal vesicles, negative lymph nodes	52 (17.1)
Involvement of pelvic lymph nodes	83 (27.3)

Graph and table adapted from Pound CR, et al. *JAMA* 1999.
BCR, biochemical recurrence; MFS, metastasis-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy.
Pound CR, et al. *JAMA* 1999;281:1591–1597.
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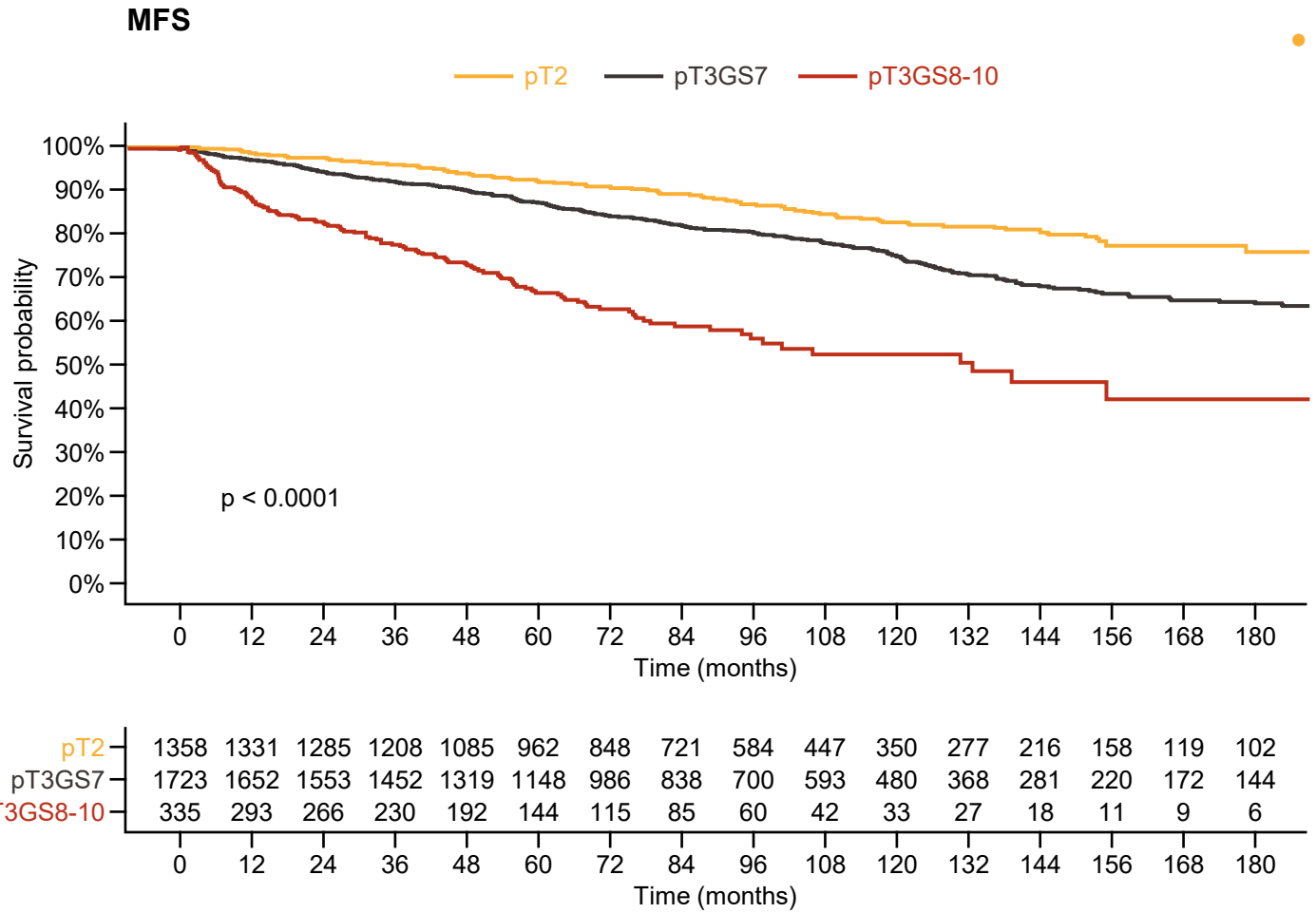
Long-term oncological outcomes of patients with BCR



- **A total of 3416 patients** with RP (1992–2017) **who experienced BCR** (PSA level ≥0.2 ng/ml)

pT stage, Gleason score	5-year MFS (95% CI), %
pT2	92.1 (90.6–93.6)
pT3, Gleason 7	87.3 (85.6–88.9)
pT3, Gleason 8–10	66.6 (61.4–72.4)

pT stage, Gleason score	10-year MFS (95% CI), %
pT2	82.7 (80.0–85.4)
pT3, Gleason 7	74.9 (72.3–77.5)
pT3, Gleason 8–10	52.5 (45.6–60.5)

Graph adapted from Unpublished data provided by Tilki D.
BCR, biochemical recurrence; CI, confidence interval; MFS, metastasis-free survival; PSA, prostate-specific antigen; pT, pathological tumour stage; RP, radical prostatectomy.
Unpublished data provided with permissions by the presenter.
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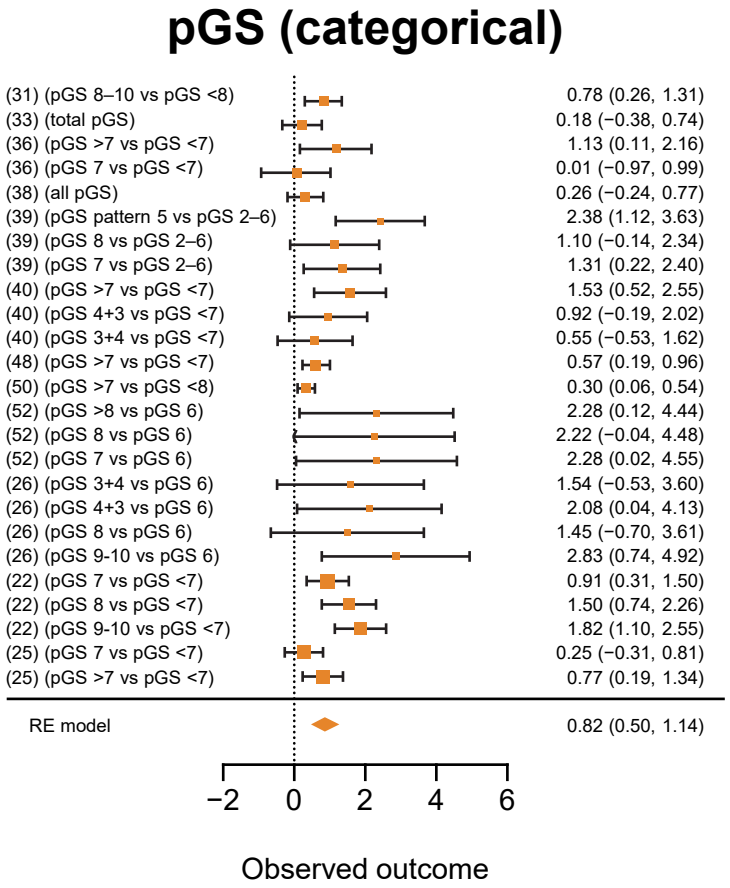
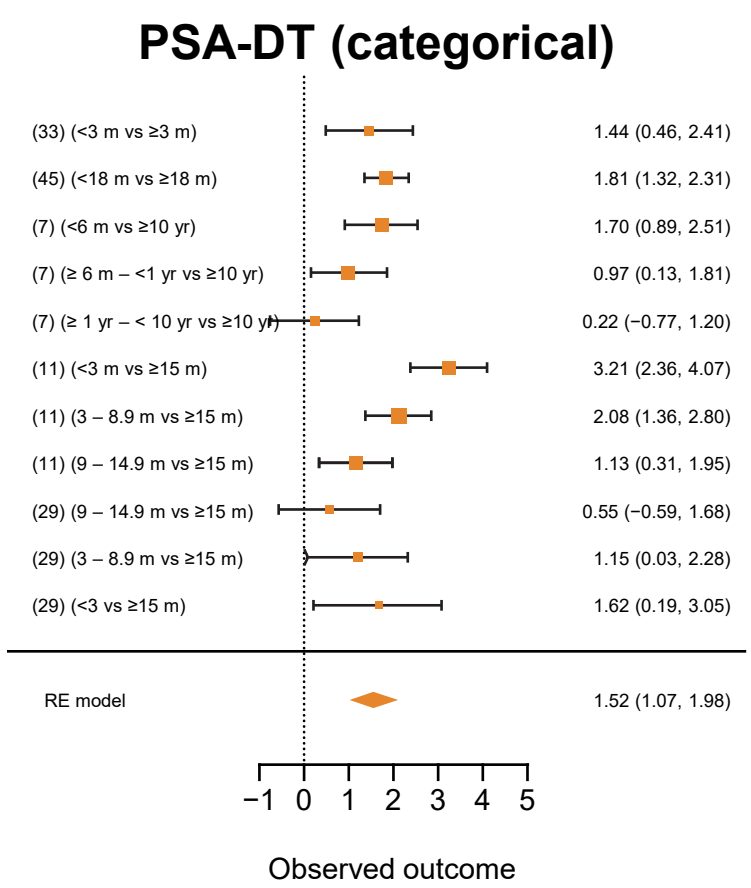
Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review

Thomas Van den Broeck [a,b,1,], Roderick C.N. van den Bergh [c,1], Nicolas Arfi [d,1], Tobias Gross [e], Lisa Moris [a,b], Erik Briers [f], Marcus Cumberbatch [g], Maria De Santis [h,i], Derya Tilki [j,k], Stefano Fanti [l], Nicola Fossati [m,n], Silke Gillessen [o,p,q], Jeremy P. Grummet [r], Ann M. Henry [s], Michael Lardas [t], Matthew Liew [u], Olivier Rouvière [v], Jakub Pecanka [w,x], Malcolm D. Mason [y], Ivo G. Schoots [z], Theo H. van Der Kwast [aa], Henk G. van Der Poel [c], Thomas Wiegel [bb], Peter-Paul M. Willemse [cc], Yuhong Yuan [dd], Thomas B. Lam [ee,ff], Philip Cornford [gg], Nicolas Mottet [hh]*





EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

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Guidelines Associates: P. Chiu, A. Farolfi, G. Gandaglia, N. Grivas, E. Linares Espinós, A. Sachdeva
Guidelines Office: E.J. Smith, C. Bezuidenhout

Figures adapted from Van den Broeck T, et al. *Eur Urol* 2019.
EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; m, month; pGS, pathological Gleason score; PSA-DT, prostate-specific antigen doubling time; RE, random effect; SIOG, International Society of Geriatric Oncology; yr, year.
Van den Broeck T, et al. *Eur Urol* 2019;75:967–987.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

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The EAU prostate cancer guidelines recommend **stratifying patients with BCR into EAU low-risk and high-risk BCR groups**[1]

Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations

Thomas Van den Broeck[a,], Roderick C.N. van den Bergh[b], Erik Briers[c], Philip Cornford[d], Marcus Cumberbatch[e], Derya Tilki[f,g], Maria De Santis[h,i], Stefano Fanti[j], Nicola Fossati[k,l], Silke Gillessen[m,n,o], Jeremy P. Grummet[p], Ann M. Henry[q], Michael Lardas[r], Matthew Liew[s], Malcolm Mason[t], Lisa Moris[a,u], Ivo G. Schoots[v], Theodorus van der Kwast[w], Henk van der Poel[x], Thomas Wiegel[y], Peter-Paul M. Willemse[z], Olivier Rouvière[A], Thomas B. Lam[B,C], Nicolas Mottet[D]*

Summary of the EAU low-risk and high-risk BCR definitions stratified by primary treatment[2]

Risk group	Characteristics
BCR after RP	
Low-risk BCR	PSA-DT >1 yr and pGS <8 (ISUP grade <4)
High-risk BCR	PSA-DT ≤1 yr **or** pGS 8–10 (ISUP grade 4–5)
BCR after RT	
Low-risk BCR	IBF ≤18 mo and bGS <8 (ISUP grade <4)
High-risk BCR	IBF ≤18 mo and bGS 8–10 (ISUP grade 4–5)

Table adapted from Van den Broeck T, et al. *Eur Urol Focus* 2020.
BCR, biochemical recurrence; bGS, biopsy Gleason score; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ; IBF, interval from primary therapy to biochemical failure; ISUP, International Society of Urological Pathology; mo, months; pGS, pathological Gleason score; PSA-DT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy; SIOG, International Society of Geriatric Oncology; yr, year.

1. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025; 2. Van den Broeck T, et al. *Eur Urol Focus* 2020;6:231–234.

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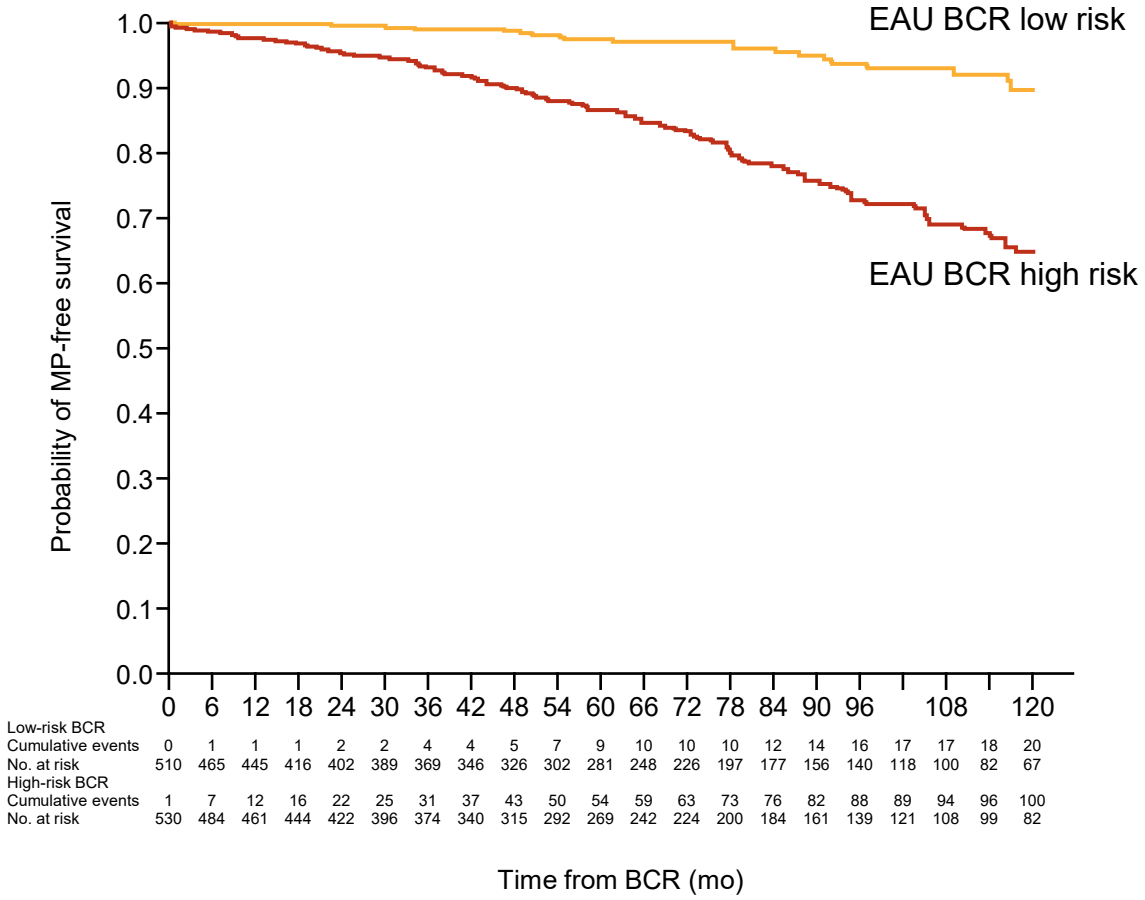
External Validation of the European Association of Urology Biochemical Recurrence Risk Groups to Predict Metastasis and Mortality After Radical Prostatectomy in a European Cohort

MP-free survival stratified according to the EAU BCR risk groups



- **There were 510 patients with EAU low-risk BCR**
- **There were 530 patients with EAU high-risk BCR**
- RP between 1992 and 2006

Graph adapted from Tilki D, et al. *Eur Urol* 2019.
BCR, biochemical recurrence; EAU, European Association of Urology; mo, months; MP, metastatic progression; RP, radical prostatectomy.
Tilki D, et al. *Eur Urol* 2019;75:896–900.
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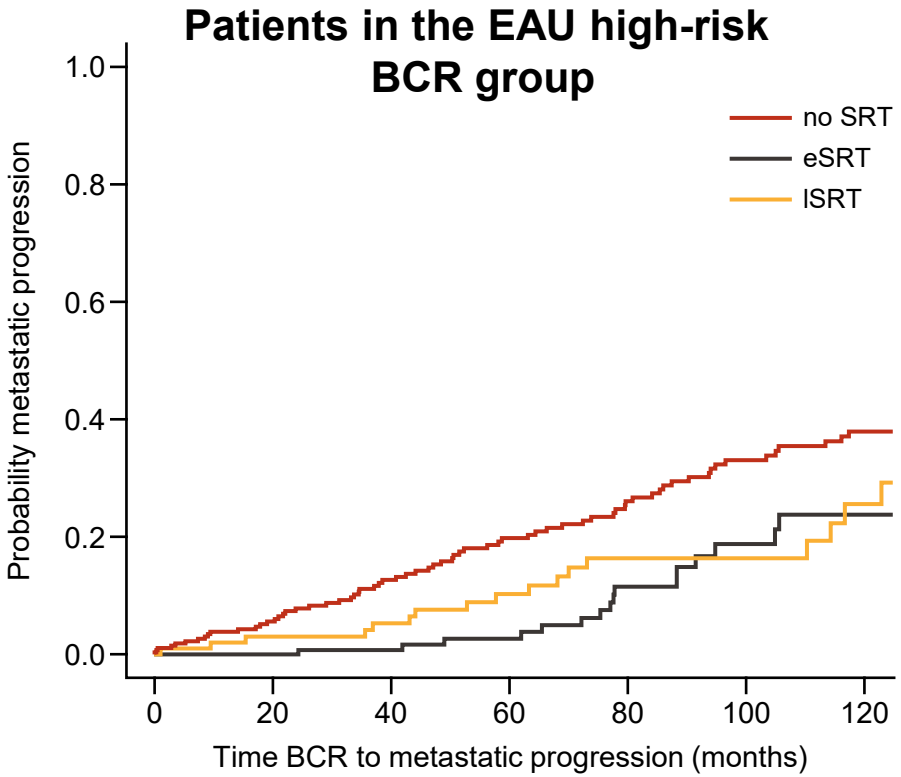

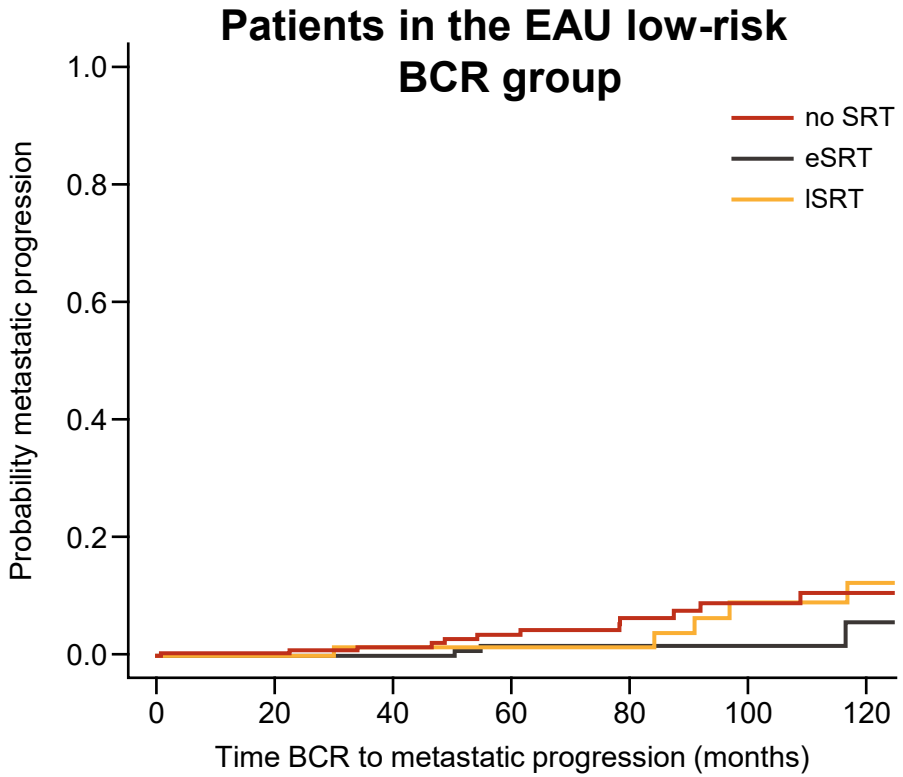

Patients in the **EAU high-risk BCR group had better survival after early SRT** (PSA <0.5 ng/ml) compared with no SRT or late SRT

Within the **EAU low-risk BCR group, there was no protective effect of early SRT** or late SRT with regard to MP or PCSM (p>0.5)

Graph adapted from Unpublished data provided by Tilki D.
BCR, biochemical recurrence; EAU, European Association of Urology; eSRT, early salvage radiotherapy; lSRT, late salvage radiotherapy; MP, metastatic progression; PCSM, prostate cancer-specific mortality; PSA, prostate-specific antigen; SRT, salvage radiotherapy.
Unpublished data provided with permissions by the presenter.
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Outline

- Natural history and definition of BCR
- Imaging
- Treatment

BCR, biochemical recurrence.

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6.4.4.3 Summary of evidence of imaging in case of BCR

In patients with BCR, imaging can detect both local recurrences and distant metastases; however, **the sensitivity of detection depends on the PSA level. After RP, PSMA PET/CT is the imaging modality with the highest sensitivity at low PSA levels (<0.5 ng/ml)**

Table 6.4.2: PSMA positivity separated by PSA level category

PSA (ng/ml)	^{68}Ga-PSMA PET positivity, % (CI)
<0.20	33 (16–51)
0.20–0.49	45 (39–52)
0.50–0.99	59 (50–68)
1.00–1.99	75 (66–84)
≥2.00	95 (92–97)

6.4.4.4 Summary of evidence and guidelines for imaging in patients with BCR

Recommendation	Strength rating
PSA recurrence after RP	
Perform PSMA PET/CT **if the PSA level is >0.2 ng/ml and if the results will influence subsequent treatment decisions (EAU BCR risk groups)**	Weak

Tables adapted from EAU Prostate Cancer Guidelines.
^{68}Ga, gallium-68; BCR, biochemical recurrence; CI, confidence interval; CT, computed tomography; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; SIOG, International Society of Geriatric Oncology.
EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.
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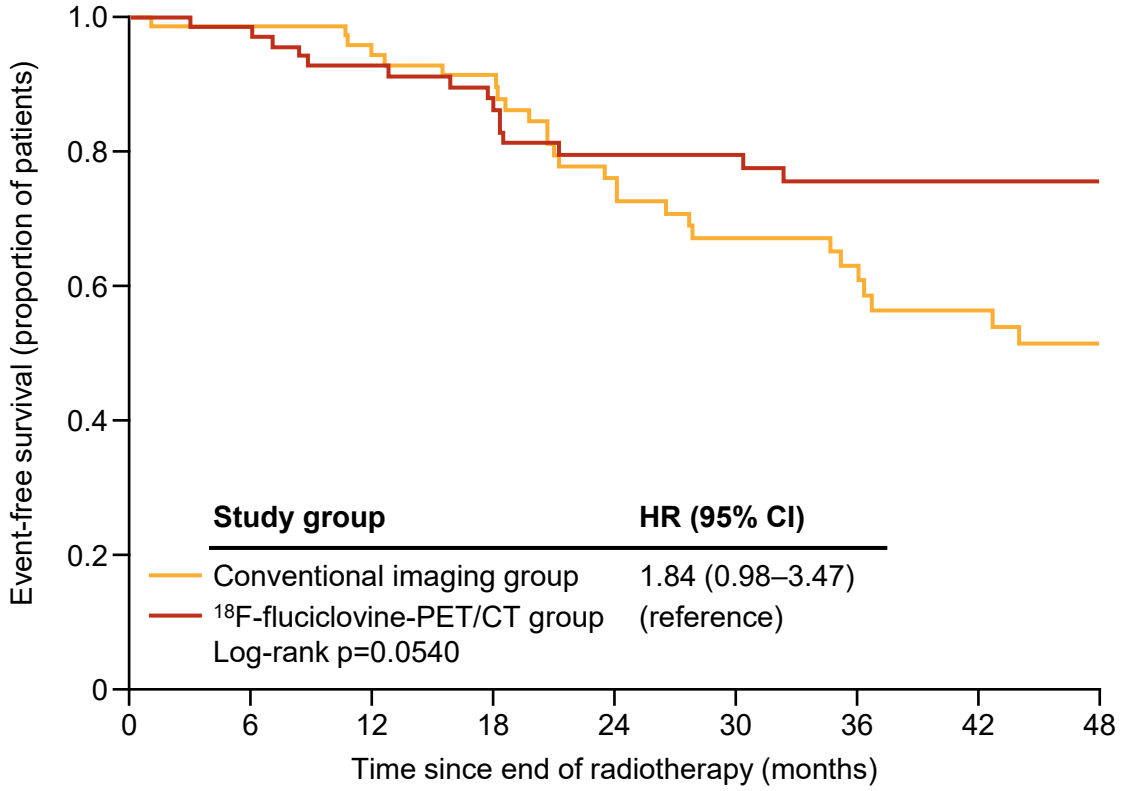
^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial

Event-free survival among the modified ITT population, consisting of all patients assigned to a study group who received RT



- Molecular imaging is increasingly used to guide treatment decisions and planning
- Inclusion of ^{18}F-fluciclovine-PET into post-prostatectomy radiotherapy planning significantly improved event-free survival

Graph adapted from Jani AB, et al. *Lancet* 2021.
^{18}F, fluorine-18; CI, confidence interval; CT, computed tomography; HR, hazard ratio; ITT, intention-to-treat; PET, positron emission tomography; RT, radiotherapy.
Jani AB, et al. *Lancet* 2021;397:1895–1904.
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6.4.8 Recommendations for 2L therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for BCR after RP	
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises	Strong
A negative PET/CT scan should not delay SRT if otherwise indicated	Strong
Offer monitoring, including PSA, to EAU low-risk patients with BCR	Weak
Do not wait for a PSA threshold before starting treatment. After the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible	Strong
Offer hormonal therapy in addition to SRT to men with BCR	Weak

The potential benefits and toxicities of salvage treatment should be discussed with each individual patient, considering both the EAU BCR risk stratification and the patient's life expectancy

Table adapted from EAU Prostate Cancer Guidelines.
2L, second line; BCR, biochemical recurrence; CT, computed tomography; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy; SIOG, International Society of Geriatric Oncology.
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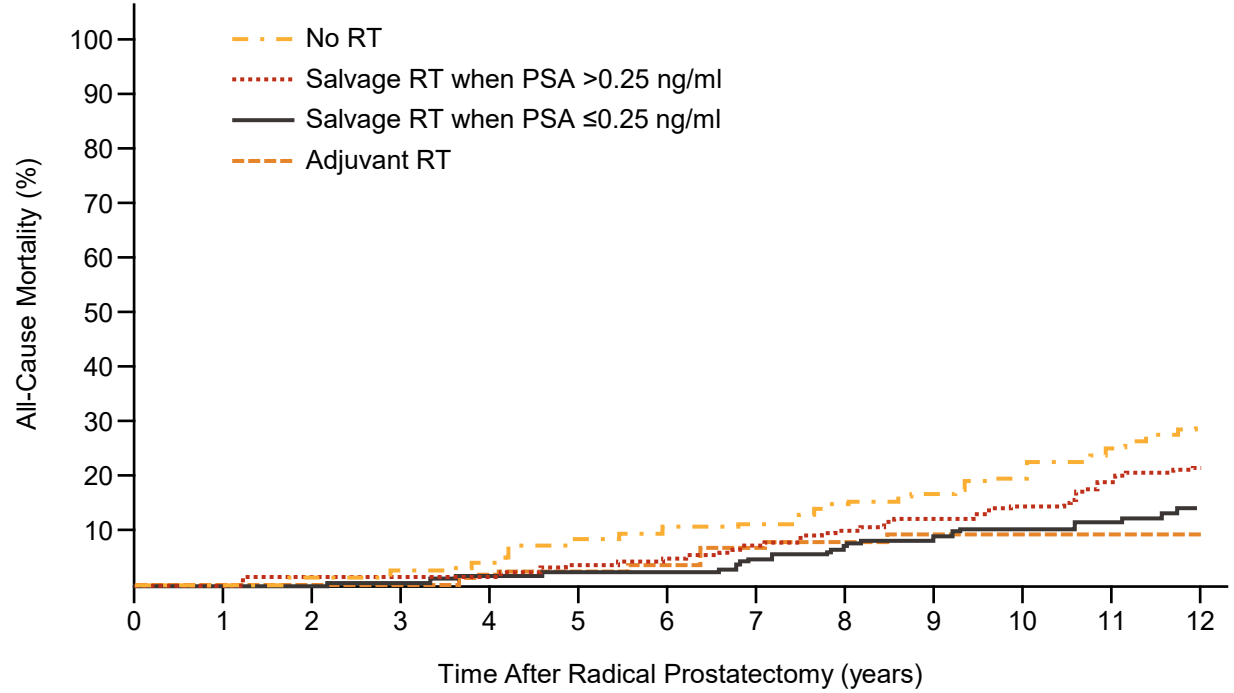
Offer hormonal therapy in addition to SRT to men with BCR	Weak

Table adapted from EAU Prostate Cancer Guidelines.
2L, second-line; BCR, biochemical recurrence; CT, computed tomography; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy; SIOG, International Society of Geriatric Oncology.
EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Prostate-Specific Antigen Level at the Time of Salvage Therapy After Radical Prostatectomy for Prostate Cancer and the Risk of Death

Derya Tilki, MD[1,2,3]; Ming-Hui Chen, PhD[4]; Jing Wu, PhD[5]; Hartwig Huland, MD[1]; Markus Graefen, MD[1]; Osama Mohamad, MD, PhD[6]; Janet E. Cowan, MA[7]; Felix Y. Feng, MD[6]; Peter R. Carroll, MD, MPH[7]; and Anthony V. D'Amico, MD, PhD[8]

Adjusted estimates of ACM by post-RP RT and PSA level groups



No. at risk:

No RT	25,551	22,324	19,813	16,887	14,455	12,367	10,474	8,816	7,274	5,949	4,598	3,567	2,722
Salvage RT when PSA >0.25 ng/ml	0	436	707	843	915	908	874	768	676	581	465	354	269
Salvage RT when PSA ≤0.25 ng/ml	0	323	671	830	882	856	801	722	603	492	372	286	216
Adjuvant RT	0	623	567	459	367	296	241	194	155	130	100	76	54

- Among patients with a single high-risk factor (i.e. pT3/4 or prostatectomy Gleason score 8–10), initiating SRT when PSA >0.25 ng/ml was associated with increased ACM risk

Graph adapted from Tilki D, et al. *J Clin Oncol 2023.*
ACM, all-cause mortality; PSA, prostate-specific antigen; pT, pathological tumour stage; RT, radiotherapy; SRT, salvage radiotherapy.
Tilki D, et al. *J Clin Oncol* 2023;41:2428–2435.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J. Oldenburg, D.E. Oprea-Lager, M. Roberts, O. Rouvière, I.G. Schoots, J. Stranne, T. Wiegel
Patient Advocate: E. Briers
Guidelines Associates: P. Chiu, A. Farolfi, G. Gandaglia, N. Grivas, E. Linares Espinós, A. Sachdeva
Guidelines Office: E.J. Smith, C. Bezuidenhout

6.4.8 Recommendations for 2L therapy after treatment with curative intent

Recommendations for systemic salvage treatment	Strength rating
Recommendations for BCR after RP	
Do not offer ADT to M0 patients with a PSA-DT of >12 months	Strong
Offer enzalutamide with or without ADT to M0 patients with high-risk BCR, defined as a PSA-DT of ≤9 months and a PSA level of ≥2 ng/ml above nadir after RT or ≥1 ng/ml after RP with or without post-operative RT	Strong

Table adapted from EAU Prostate Cancer Guidelines.
2L, second-line; ADT, androgen deprivation therapy; BCR, biochemical recurrence; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; M, metastases; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy; SIOG, International Society of Geriatric Oncology.
EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Metastasis-directed therapy for recurrent nodal disease

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J. Oldenburg, D.E. Oprea-Lager, M. Roberts, O. Rouvière, I.G. Schoots, J. Stranne, T. Wiegel
Patient Advocate: E. Briers
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Guidelines Office: E.J. Smith, C. Bezuidenhout

Salvage LN dissection: no standard treatment

6.4.5.1.3 Salvage LN dissection

The reported 5-year BCR-free survival rates ranged from 6% to 31%; 5-year OS rate was approximately 84% (1103).

In a multicentre retrospective study, long-term outcomes of salvage LN dissection were reported to be worse than previously described in studies with shorter follow-up (1063).

High-level evidence for the oncological value of salvage LN dissection is still lacking (1060).

BCR, biochemical recurrence; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Therapeutic Radiology and Oncology; ESUR, European Society of Urogenital Radiology; ISUP, International Society of Urological Pathology; LN, lymph node; OS, overall survival; SIOG, International Society of Geriatric Oncology

EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Radioguided surgery

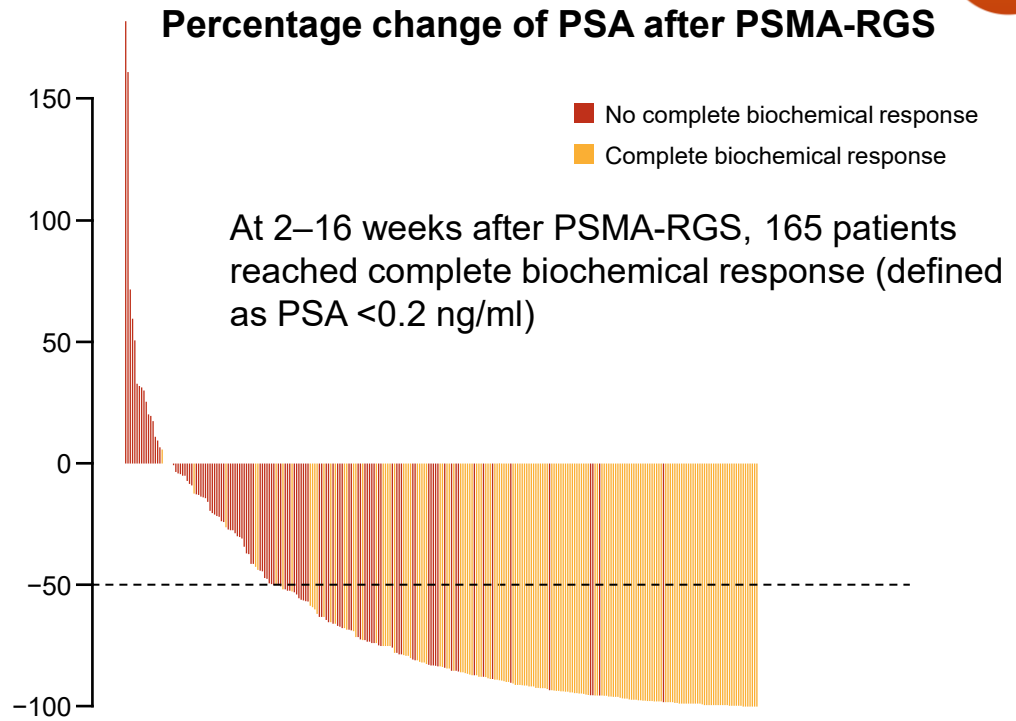
Prostate Cancer

Cohort Study of Oligorecurrent Prostate Cancer Patients: Oncological Outcomes of Patients Treated with Salvage Lymph Node Dissection via Prostate-specific Membrane Antigen–radioguided Surgery

456 consecutive PSMA-RGS patients between 2014 and 2022

Excluded (n=92)
- Included in prospective ProSTone trial (27)
- Refused data collection (22)
- Received two PSMA-RGSs (17)
- ADT prior to PSMA-RGS (16)
- Primary treatment with RT (5) or IRE (1)
- Had Osseous metastases (3)
- Had Surgery abortion (1)

364 PSMA-RGS patients included in this study



- Within the overall follow-up, 225/364 patients experienced BCR, and 121 patients received further therapy during follow-up
- At 2 years, BFS and TFS rates were 32% and 58%, respectively
- Careful patient selection is mandatory based on life expectancy, low PSA values and low number of PSMA PET-avid lesions located in the pelvis

Figures adapted from Knipper S, et al. *Eur Urol* 2023.
BCR, biochemical recurrence; BFS, BCR-free survival; PSA, prostate-specific antigen; PET, positron-emission tomography; PSMA, prostate-specific membrane antigen; RGS, radioguided surgery; TFS, therapy-free survival.
Knipper S, et al. *Eur Urol* 2023;83:62–69.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Summary

- Patients with BCR who have received local treatment represent a heterogeneous population with diverse prognosis[1]
- The EAU prostate cancer guidelines recommend stratifying patients with BCR into EAU low risk and high risk groups[2]
- Most available studies included in systematic reviews did not use PET. PET can detect more metastases at BCR than conventional imaging and potentially improve oncological outcomes[3]
- Risk stratification of patients is essential for personalised treatment approaches[4]
- Limiting salvage treatments to patients who might benefit from them should be considered a priority to avoid overtreatment[4]

BCR, biochemical recurrence; EAU, European Association of Urology; PET, positron emission tomography.

1. Tilki D, et al. *Eur Urol* 2019;75:896–900; 2. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025;
3. Jani AB, et al. *Lancet* 2021;397:1895–1904; 4. Speaker's own opinion.

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Thank you

Genitourinary Masterclass

High-risk BCR: Not all patients are equal

The radiation oncologist point of view

Prof. Dr. med. Thomas Zilli, MD

Oncology Institute of Southern Switzerland (IOSI),
Ente Ospedaliero Cantonale, Bellinzona, Switzerland

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astellas

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Disclosures

Honoraria and travel costs

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- Debiopharm, Varian Medical Systems,

Advisory boards

- Accord, Astellas, Janssen, Teleflex

- The speaker has received an honorarium from Astellas for this presentation

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The “eligible” and the “real” EMBARK patient

EMBARK inclusion criteria[1]

- PSA ≥1 ng/ml after RP
- PSA ≥2 ng/ml after RT above nadir
- PSA DT ≤9 months

The EMBARK patient[1]

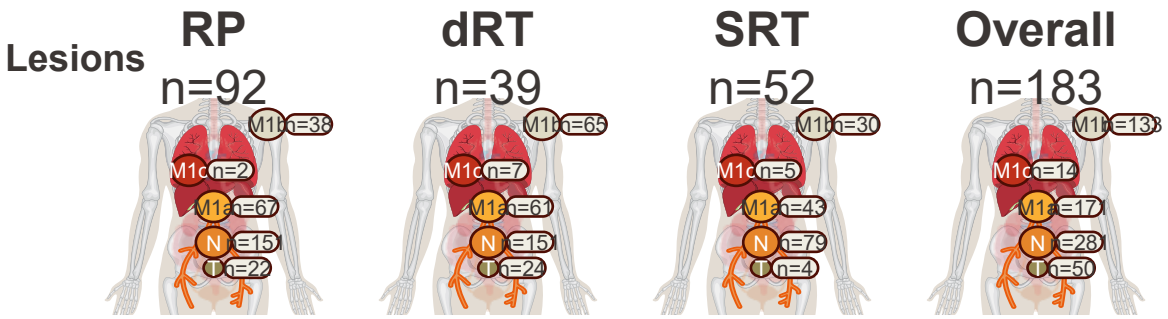
Characteristic	Enzalutamide + Leuprolide (n=355)	Leuprolide alone (n=358)	Enzalutamide monotherapy (n=355)
PSA DT, n (%)			
≤3 m	69 (19.4)	80 (22.3)	76 (21.4)
>3 to 6 m	187 (52.7)	142 (39.7)	164 (46.2)
>6 to 9 m	98 (27.6)	135 (37.7)	114 (32.1)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)
Median PSA DT (range), m	4.6 (0.9–9.6)	5.0 (1.1–10.8)	5.0 (1.0–18.9)
Median serum PSA level (range), ng/ml	5.0 (1.0–308.3)	5.5 (1.1–163.3)	5.3 (1.1–37.0)
Primary definitive therapy, n (%)			
RP alone	90 (25.4)	75 (20.9)	99 (27.9)
RT alone	86 (24.2)	104 (29.1)	90 (25.4)
RP and RT therapy	179 (50.4)	179 (50.0)	166 (46.8)

The EMBARK population is more aggressive than defined by eligibility criteria.
A subset of 'early EMBARK-eligible' patients may still benefit from combined systemic therapy and local radiotherapy[2]

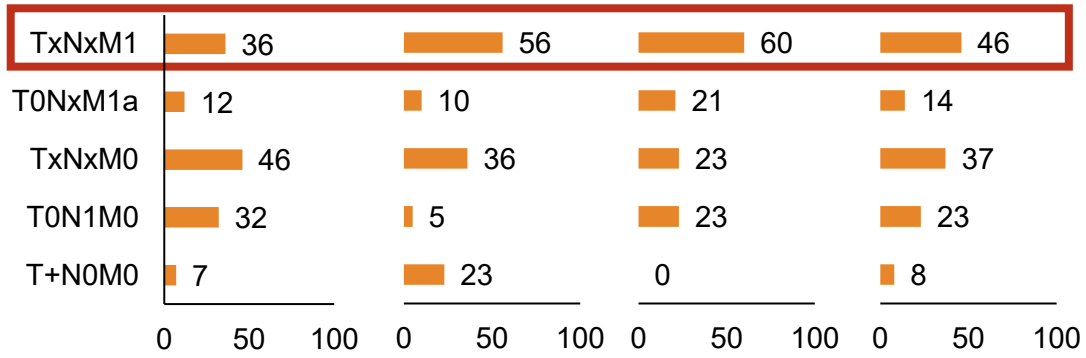
DT, doubling time; m, months; RP, radical prostatectomy; RT, radiotherapy; PSA, prostate-specific antigen.
Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.
1. Date of preparation: July 2025 | MAT-NL-XTD-2025-00033; 2. Speaker’s own opinion.

PSMA restaging of high-risk BCR nmHSPC disease

Lesion staging and distributions by treatment[1]



miTNM[1]



Lesion-based assessment was reported as the total number of lesions reported per category.

Baseline characteristics[2]

Characteristic	RP (n=91)	dRT (n=39)	SRT (n=52)	Overall (N=182)
Median age at PSMA PET/CT (IQR), years	69 (64–72)	67 (63–77)	70 (66–73)	69 (64–73)
Last PSA value before enrolment, median (IQR), ng/ml	2.4 (1.4–4.8)	6.9 (3.5–18.5)	2.6 (1.6–5.2)	2.8 (1.7–6.6)
Median time between last therapy and PSMA PET/CT scan (IQR), mo	28 (8–62)	40 (26–72)	92 (53–124)	43 (18–93)

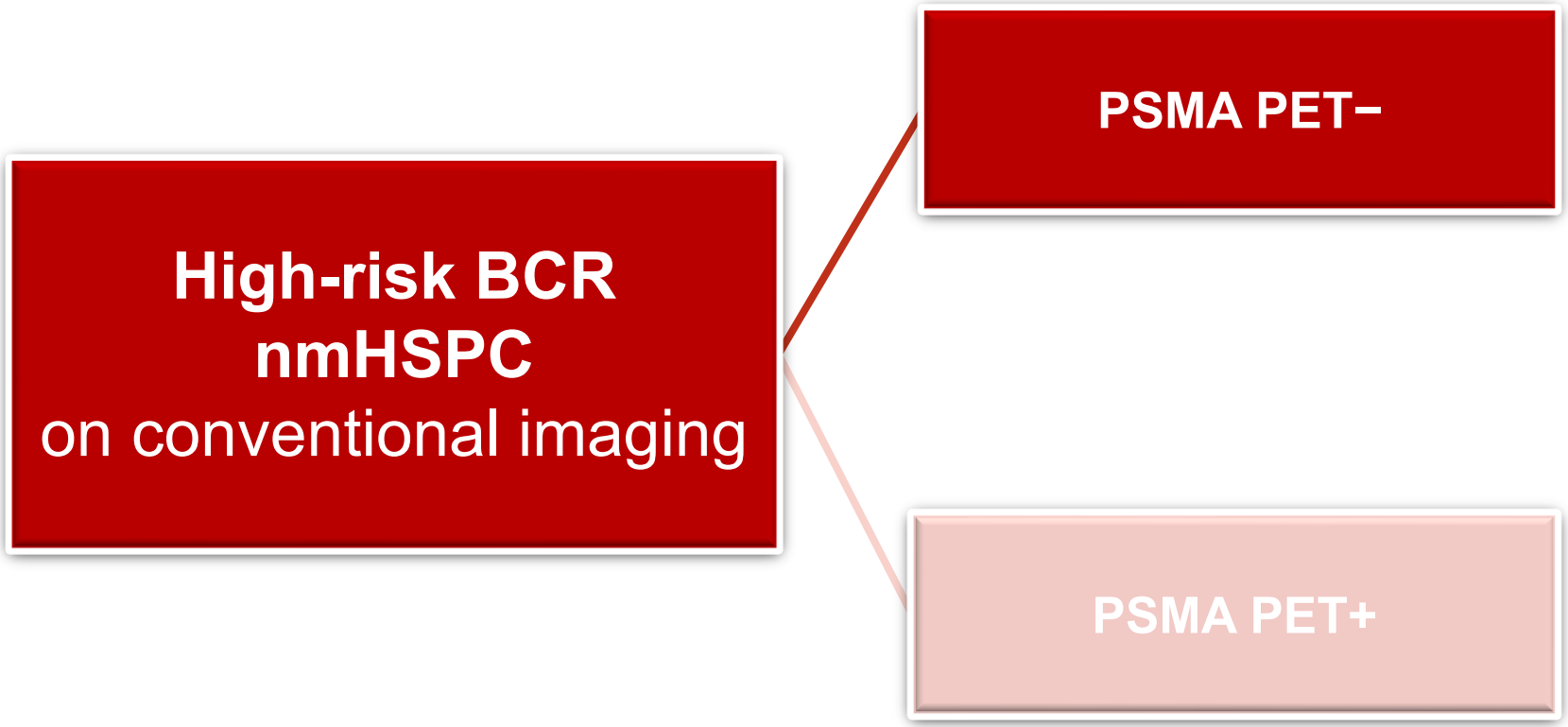
Disease distribution by primary treatment[2]

	RP, % (n=91)	dRT, % (n=39)	RP and SRT, % (n=52)	Overall, % (N=182)
TxNxM1	34	56	60	46
T0NxM1a	11	13	21	14
T0NxMx	58	36	75	58
TxNxM0	46	36	25	38
T0N1M0	32	5	23	24
T+N0M0	7	23	2	9
Positive scan	80	92	85	84
≥5 Lesions	19	36	23	24
T0NxMx	58	36	75	58
TxN1M0	40	13	23	29
M1b	18	36	31	25

In 83% of patients with high-risk BCR nmHSPC, disease was confirmed by conventional imaging PSMA PET/CT. M1 disease is observed in 46% of the cases (1–4 lesions: 22%; and ≥5 lesions: 24%)[1]

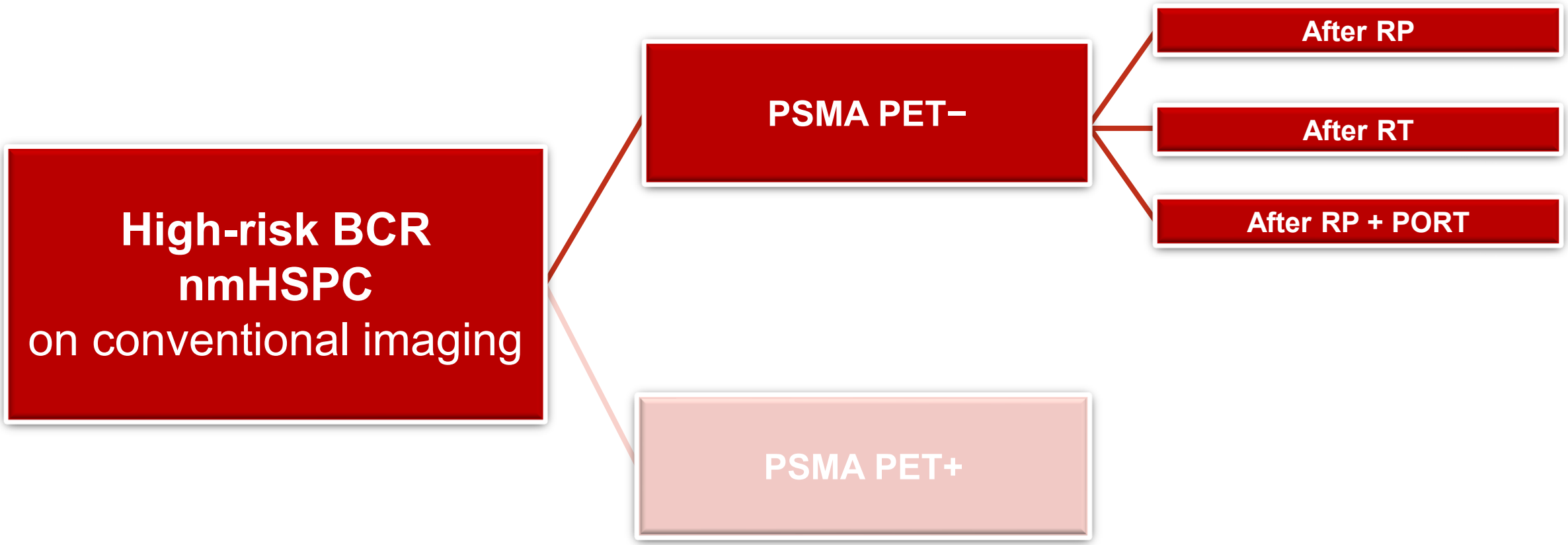
Figures and tables adapted from Armstrong WR, et al. Presented at ASCO 2023[1] and Holzgreve A, et al. *JAMA Netw Open* 2025.[2]
BCR, biochemical recurrence; CT, computed tomography; dRT, definitive radiotherapy; IQR, interquartile range; M, metastasis; miTNM, molecular imaging tumour node metastasis staging; N, nodal involvement; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; SRT, salvage radiotherapy; T, tumour.
1. Armstrong WR, et al. Presented at ASCO 2023, 2–6 June 2023, Chicago, IL, USA, Abstract 5091; 2. Holzgreve A, et al. *JAMA Netw Open* 2025;8:e2452971.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033.

High-risk BCR: Same disease, different settings



BCR, biochemical recurrence; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

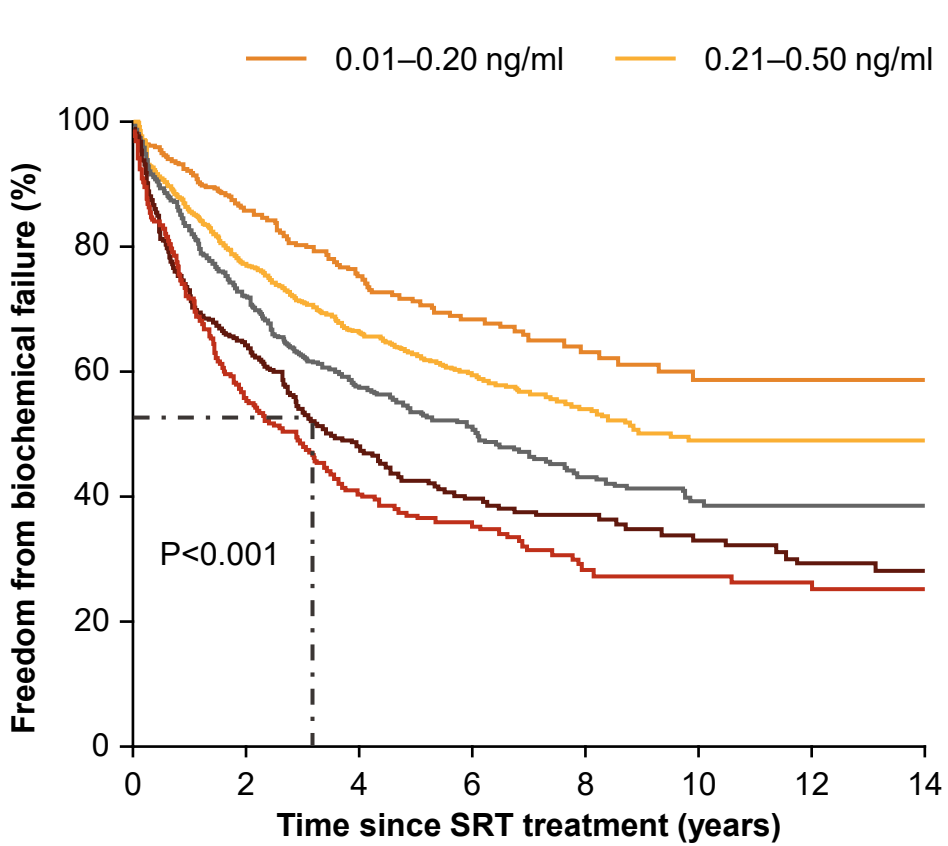
High-risk BCR: Same disease, different settings



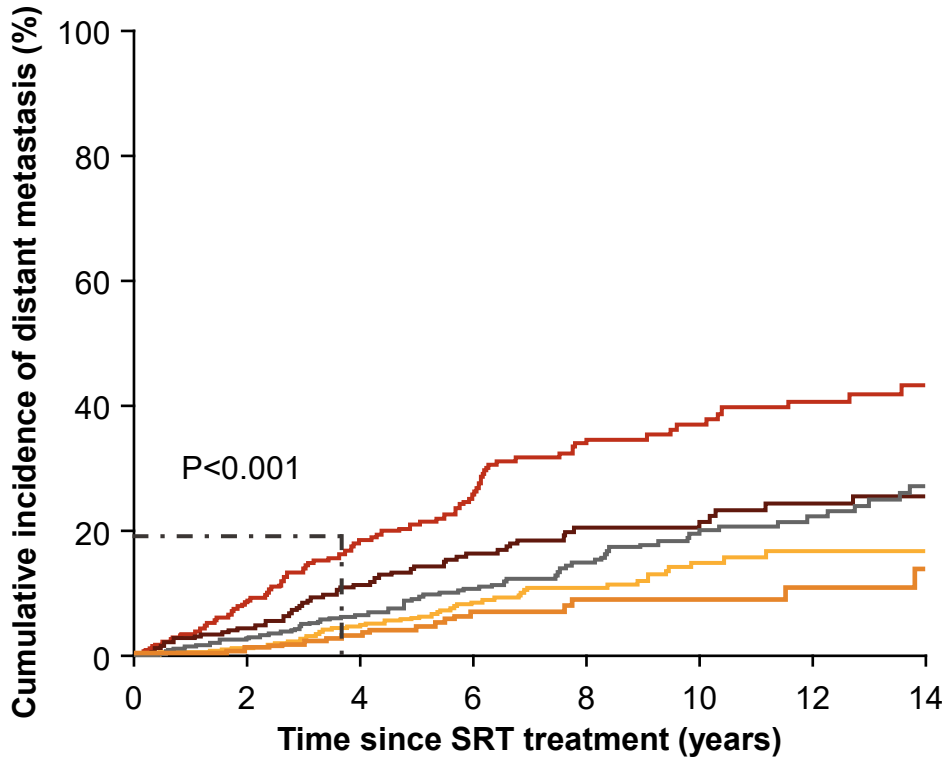
BCR, biochemical recurrence; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PORT, post-operative radiotherapy; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Late salvage radiotherapy: Still an option?

Estimated rates of freedom from biochemical failure by pre-SRT PSA level



Estimated cumulative incidence rates of distant metastasis by pre-SRT PSA level

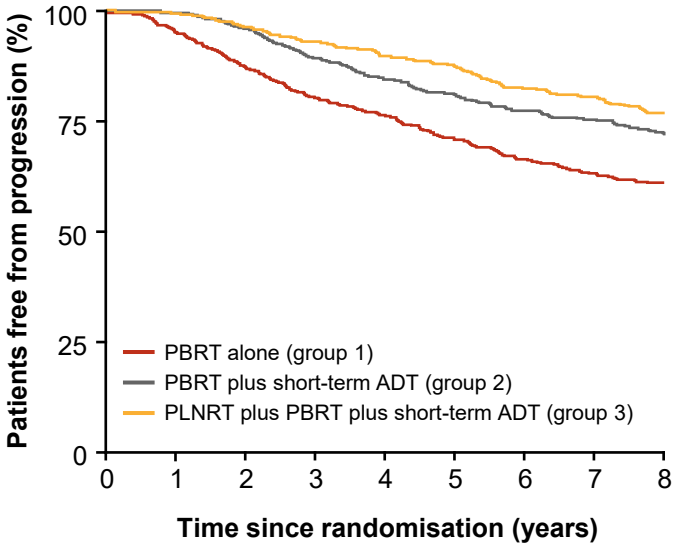


Late prostate bed SRT (PSA >1 ng/ml) is associated with poor outcomes, but the risk of metastases remains below 20% at 5 years

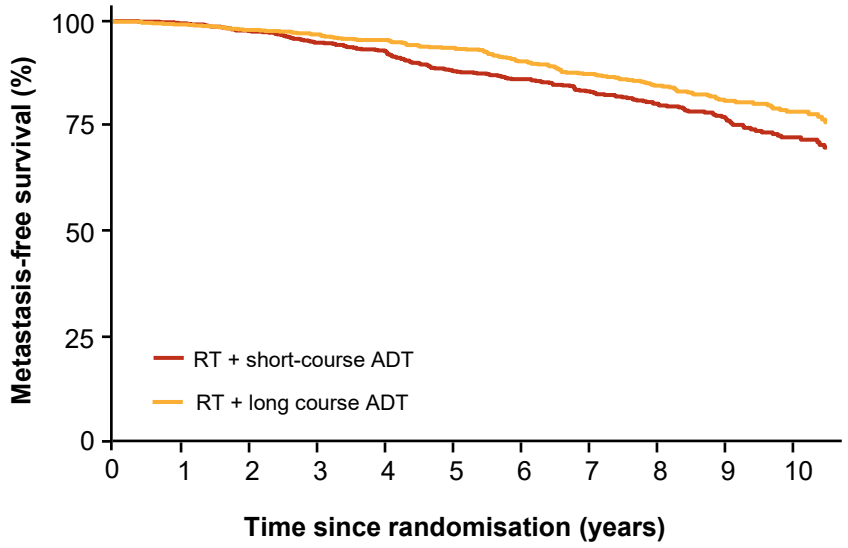
Graphs adapted from Tendulkar RD, et al. *J Clin Oncol* 2016.
*WPRT: 17%; ADT: 16%, SRT <66 Gy: 47%.
ADT, androgen deprivation therapy; PSA, prostate specific antigen; SRT, salvage radiotherapy; WPRT, whole pelvis radiotherapy.
Tendulkar RD, et al. *J Clin Oncol* 2016;34:3648–3654.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Late salvage radiotherapy: Can we do better?

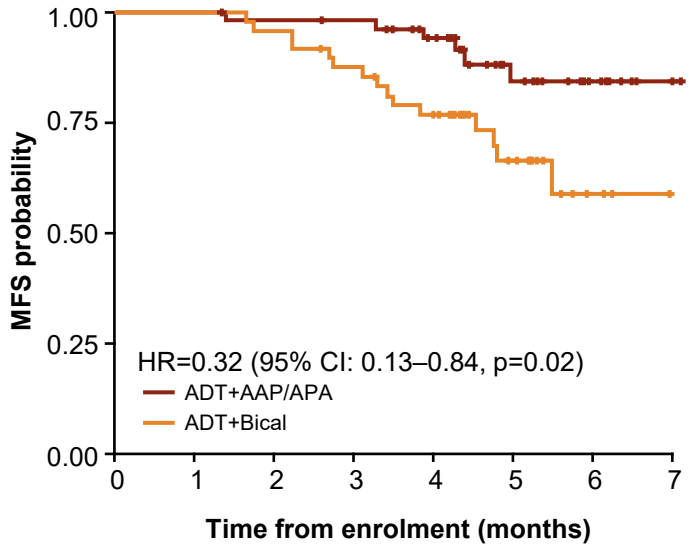
RTOG 0534/SPPORT: WPRT[1]



RADICALS HD: 24 mo ADT[2]



FORMULA 509: ARPI[3]



WPRT, long-term ADT and ARPI can help improve outcome of patients with late BCR treated with SRT

Graphs adapted from Pollack A, et al. *Lancet* 2022,[1] Parker C et al. *Lancet* 2024[2] and Nguyen P et al. Presented at ASCO GU 2023.[3]

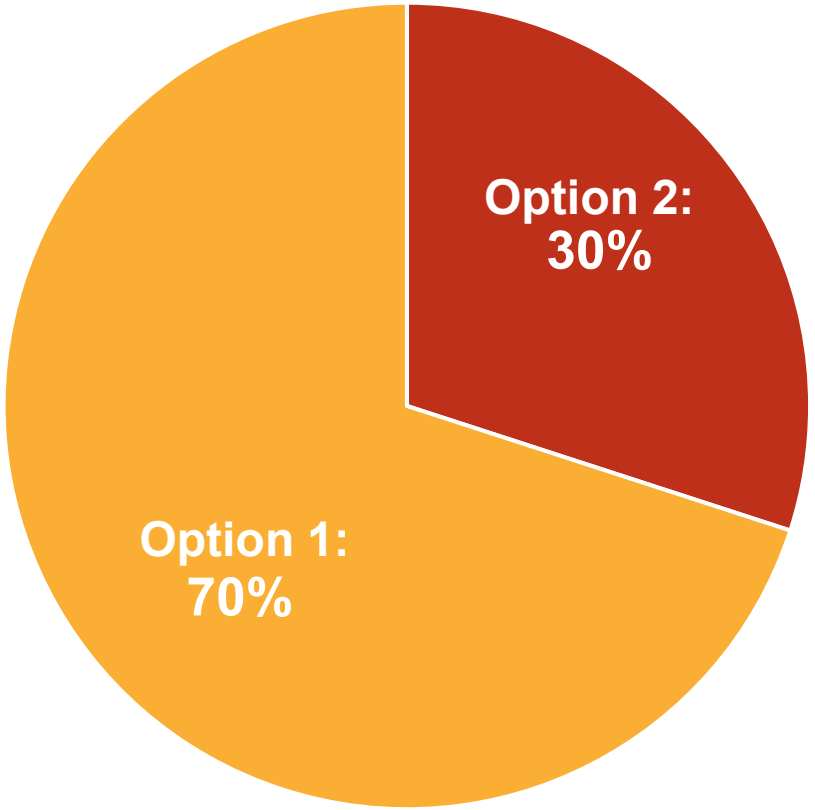
AAP, abiraterone acetate + prednisone; ADT, androgen deprivation therapy; APA, apalutamide; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; CI, confidence interval; HR, hazard ratio; MFS, metastasis-free survival; mo, month; PBRT, prostate bed radiotherapy; PLNRT, pelvic lymph node radiotherapy; PSA, prostate specific antigen; RT, radiotherapy; SRT, salvage radiotherapy; WPRT, whole pelvis radiotherapy.

1. Pollack A, et al. *Lancet* 2022;399:1886–1901; 2. Parker C, et al. *Lancet* 2024;403:2416–2425; 3. Nguyen P, et al. Presented at ASCO GU 2023. Abstract 303. UroToday. ASCO GU 2023: FORMULA-509. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2023/asco-gu-2023-prostate-cancer/142429-asco-gu-2023-formula-509-a-multicenter-randomized-trial-of-post-operative-salvage-radiotherapy-and-6-months-of-gnrh-agonist-with-or-without-abiraterone-acetate-prednisone-and-apalutamide-post-radical-prostatectomy.html. Last accessed June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

APCCC: PSA persistence and BCR

60. For the majority of patients with high-risk nmHSPC and negative PSMA PET imaging, what do you recommend?[1]



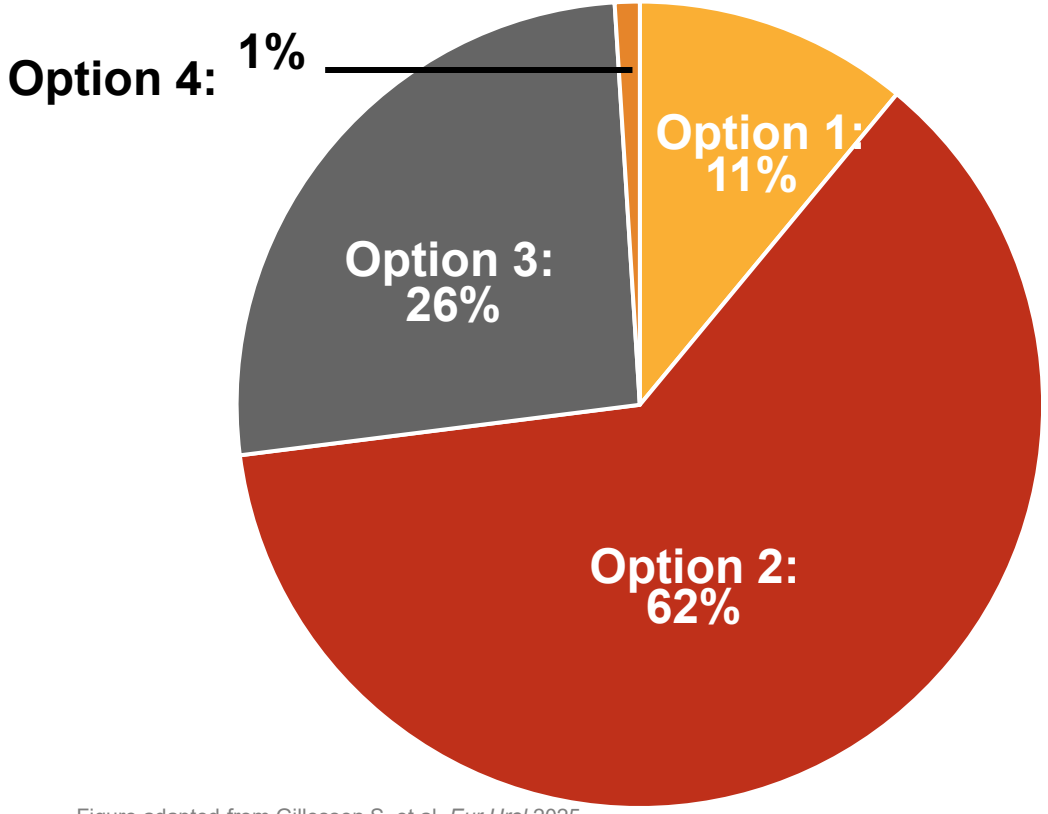
EMBARK definition:[2] PSA ≥1 ng/ml after RP
PSA >2 ng/ml after RT above nadir
PSA DT ≤9 mo

Option[1]	Votes, n
1. Immediate systemic therapy	73
2. Monitoring and deferred treatment	31
Abstain/unqualified to answer	2

Figure adapted from Gillessen S, et al. *Eur Urol* 2025.
APCCC, Advanced Prostate Cancer Consensus Conference; BCR, biochemical recurrence; DT, doubling time; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.
1. Gillessen S, et al. *Eur Urol* 2025;87:157–216; 2. Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

APCCC 2024: PSA persistence and BCR

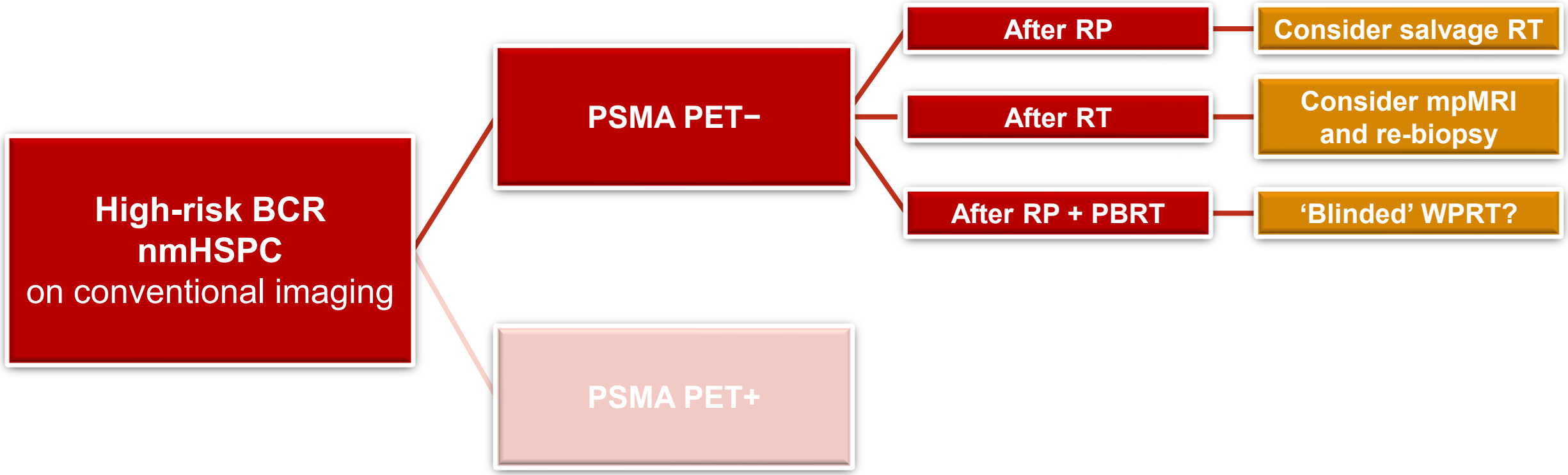
44. For the majority of patients with a confirmed rising PSA after radical prostatectomy and PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 and no or negative PSMA PET imaging, what is your management recommendation regarding salvage therapy?



Option	Votes, n
1. Radiation therapy alone	11
2. Radiation therapy plus short-term (e.g. 6 months) systemic hormonal therapy	63
3. Radiation therapy plus long-term (e.g. 24 months) systemic hormonal therapy	27
4. Systemic therapy alone	1
Abstain/unqualified to answer (including I do not recommend salvage therapy)	4

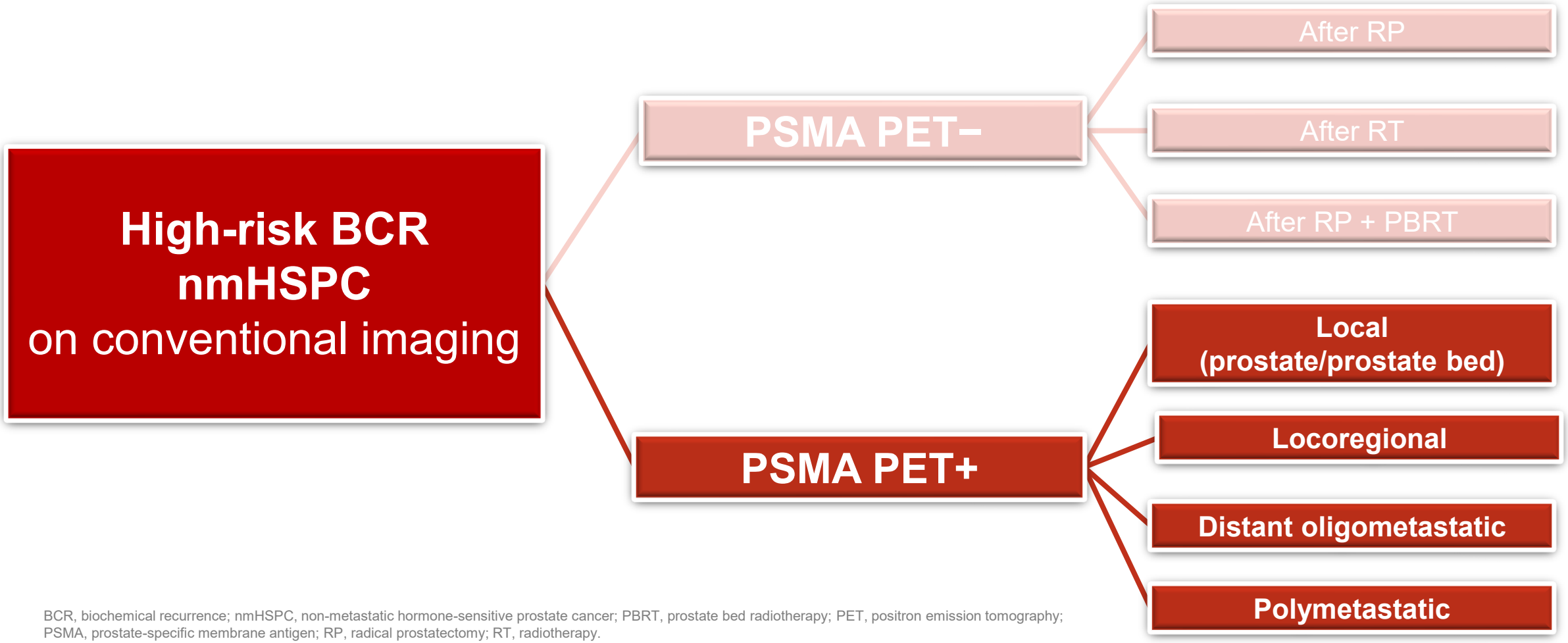
Figure adapted from Gillessen S, et al. *Eur Urol* 2025
APCCC, Advanced Prostate Cancer Consensus Conference; BCR, biochemical recurrence; DT, doubling time; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.
Gillessen S, et al. *Eur Urol* 2025;87:157–216.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

High-risk BCR: Same disease, different settings



BCR, biochemical recurrence; mpMRI, multi-parametric magnetic resonance imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PBRT, prostate bed radiotherapy; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; WPRT, whole pelvis radiotherapy.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

High-risk BCR: Same disease, different settings

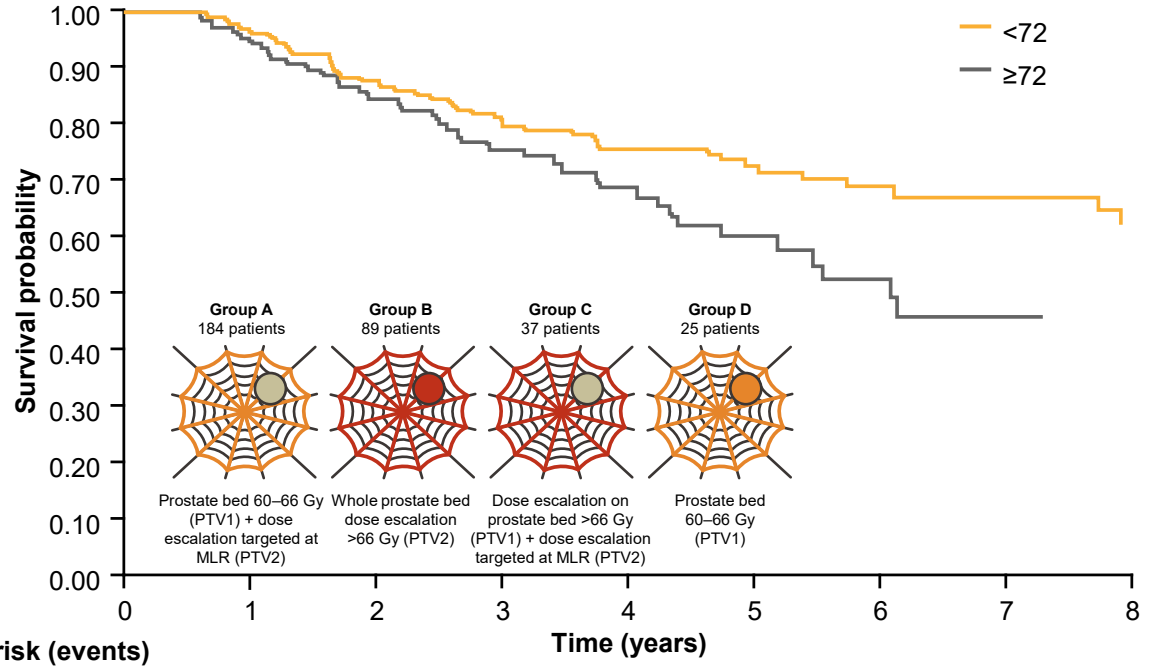


BCR, biochemical recurrence; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PBRT, prostate bed radiotherapy; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Local PET-positive disease

SPIDER: SRT to prostate bed with dose escalation[1]

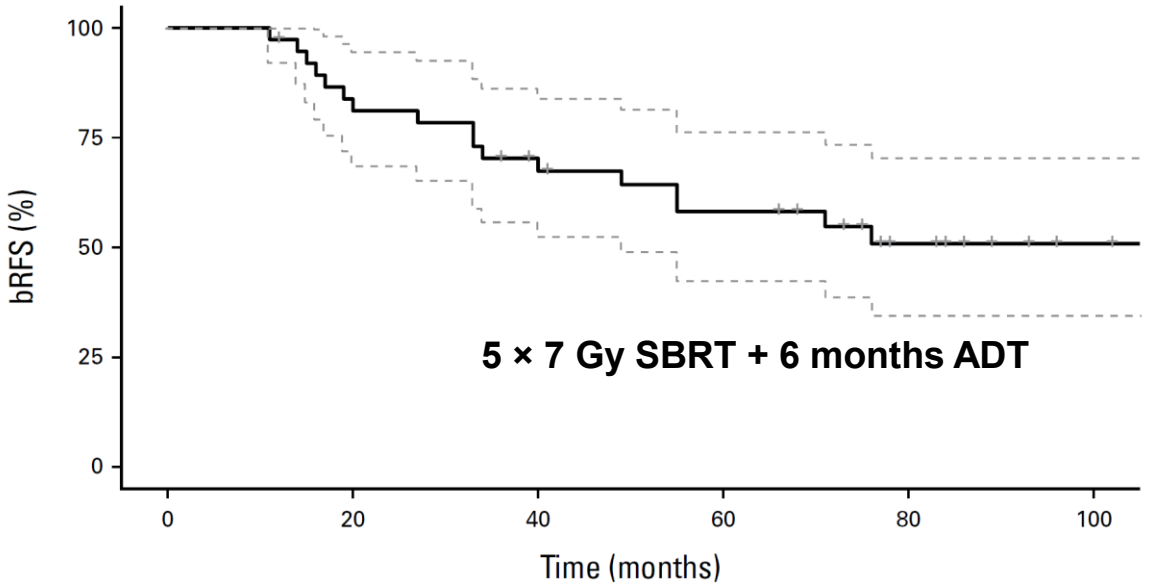
(macroscopic local recurrence in prostate bed)



At risk (events)									
<72	115	(16)	82	(13)	44	(8)	16	(2)	9
≥72	194	(21)	143	(17)	88	(6)	46	(3)	24

Swedish trial: Re-irradiation SBRT[2]

(locally recurrent after primary RT)



Patients with PET-positive local recurrence in the prostate bed or who received 1L RT to the prostate could be salvaged with radiotherapy ± ADT[1,2]

Graphs adapted from Benziane-Ouaritini N, et al. *Eur Urol Oncol* 2023 and Ekanger C, et al. *J Clin Oncol* 2024.[1,2]

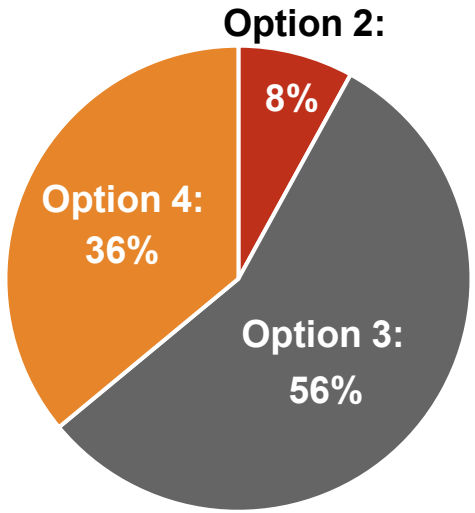
ADT, androgen deprivation therapy; bRFS, biochemical recurrence-free survival; PET, positron emission tomography; PTV, planning target volume; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SRT, salvage radiotherapy;

1. Benziane-Ouaritini N, et al. *Eur Urol Oncol* 2023;390–398; 2. Ekanger C, et al. *J Clin Oncol* 2024;42:1934–1942.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

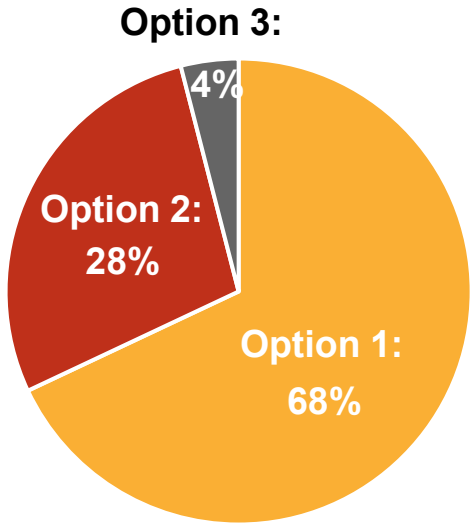
APCCC 2024: Local treatment for prostate local recurrence

53. In the majority of patients with PSA rise after RP and a local relapse in the prostate bed detected on MRI and/or PSMA PET (no prior local SRT) confirmed by biopsy and a PSA-DT ≤1 year or pathological ISUP grade group 4 or 5 what do you recommend?



Option	Votes, n
1. Monitoring	0
2. Radiation therapy of the prostatic bed ± boost the lesion ± pelvis	8
3. Radiation therapy of the prostatic bed ± boost the lesion ± pelvis plus short-term (e.g. 6 months) systemic therapy	57
4. Radiation therapy of the prostatic bed ± boost the lesion ± pelvis plus long-term (e.g. 24 months) systemic therapy	36
Abstain/unqualified to answer	5

55. What do you recommend for the majority of patients with a confirmed local recurrence in the prostate after radical RT (interval to biochemical failure <18 months and/or ISUP grade group 4–5) and a PSA-DT ≤9 months and no detectable metastases on imaging?



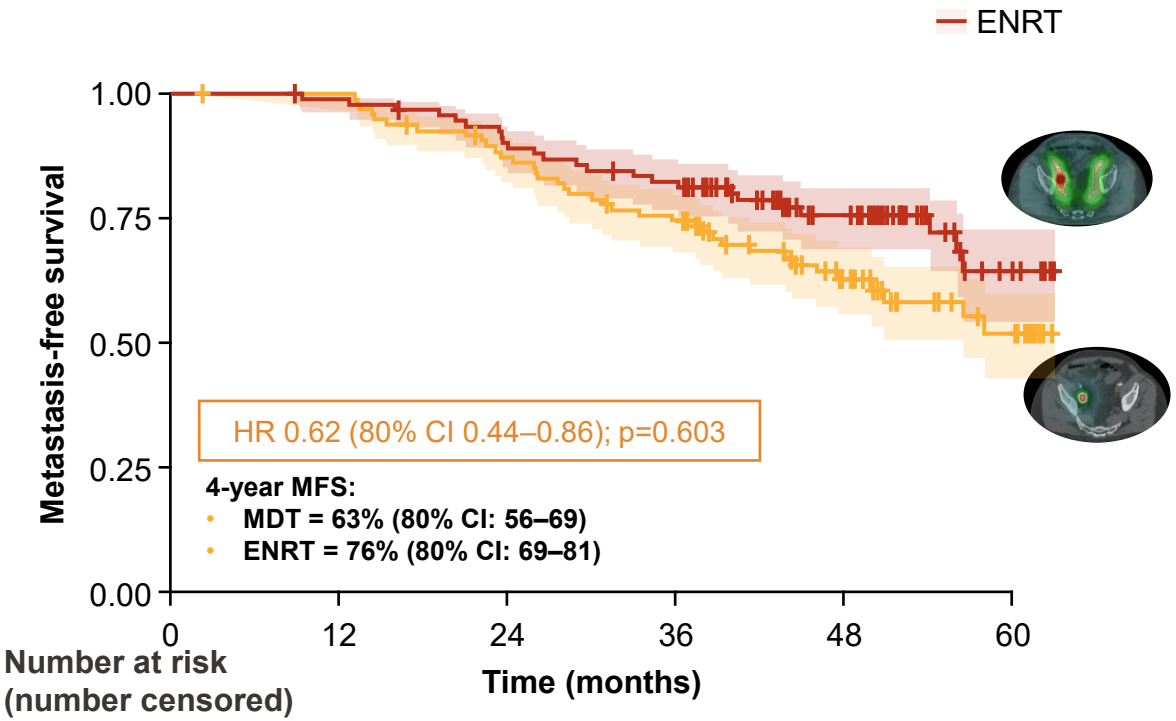
Option	Votes, n
1. Local salvage therapy (± systemic therapy)	71
2. Systemic therapy alone	30
3. Monitoring	4
Abstain/unqualified to answer	1

Figures adapted from Gillessen S, et al. *Eur Urol* 2025.
APCCC, Advanced Prostate Cancer Consensus Conference; DT, doubling time; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy.
Gillessen S, et al. *Eur Urol* 2025;87:157–216.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Locoregional, PET-positive nodal disease

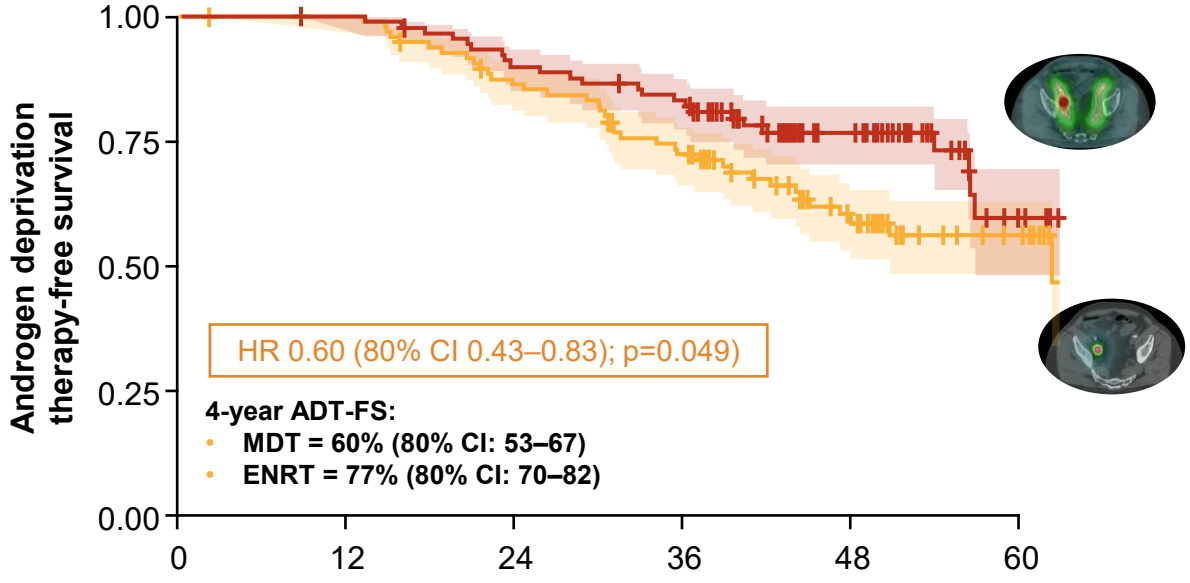
PEACE V-STORM

MFS



Number at risk (number censored)						
ENRT	93 (0)	91 (1)	82 (2)	74 (3)	46 (26)	13 (57)
MDT	97 (0)	96 (1)	82 (3)	68 (5)	39 (25)	15 (45)

ADT-free survival



Number at risk (number censored)						
ENRT	91 (0)	90 (1)	80 (2)	73 (3)	43 (28)	11 (57)
MDT	97 (0)	96 (1)	81 (3)	66 (5)	36 (26)	13 (47)

In oligorecurrent, PSMA-detected nodal disease, elective nodal RT combined with 6 months of ADT is associated with improved DMFS, locoregional control and ADT-free survival compared with MDT

Figures adapted from Ost P, et al. *Lancet Oncol* 2025.
ADT, androgen deprivation therapy; CI, confidence interval; DMFS, distant metastasis-free survival; ENRT, elective nodal radiotherapy; HR, hazard ratio; MDT, metastasis-directed therapy; MFS, metastasis-free survival; PSMA, prostate-specific membrane antigen; RT, radiotherapy.
Ost P, et al. *Lancet Oncol* 2025;26:695–706.
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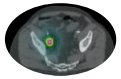
Oligometastatic disease: The clinical evidence

Observation



MDT

MDT + systemic therapy

Systemic therapy

STOMP, ORIOLE (MDT > observation)[1,2]

RADIOSA (MDT + 6 months ADT > MDT)[3]

EXTEND (MDT + int. hormonal therapy > int. hormonal therapy)[4]

Combination of MDT with systemic therapy delays progression and helps to improve clinical outcomes compared with observation, MDT alone or systemic therapy alone[1-4]

ADT, androgen deprivation therapy; int, intermittent; MDT, metastasis-directed therapy.

1. Deek M, et al. *J Clin Oncol* 2022;40:3377–3382; 2. Philips R, et al. *JAMA Oncol* 2020;6:650–659; 3. Marvaso G, et al. *Lancet Oncol* 2025;26:300–311; 4. Tang C, et al. *JAMA Oncol* 2023;9:825–834.

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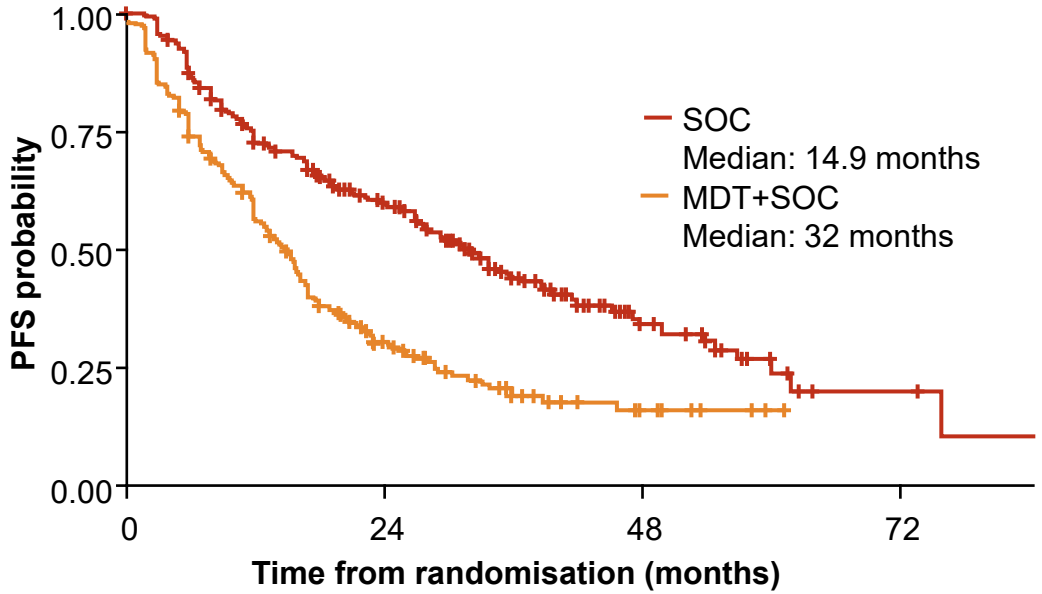
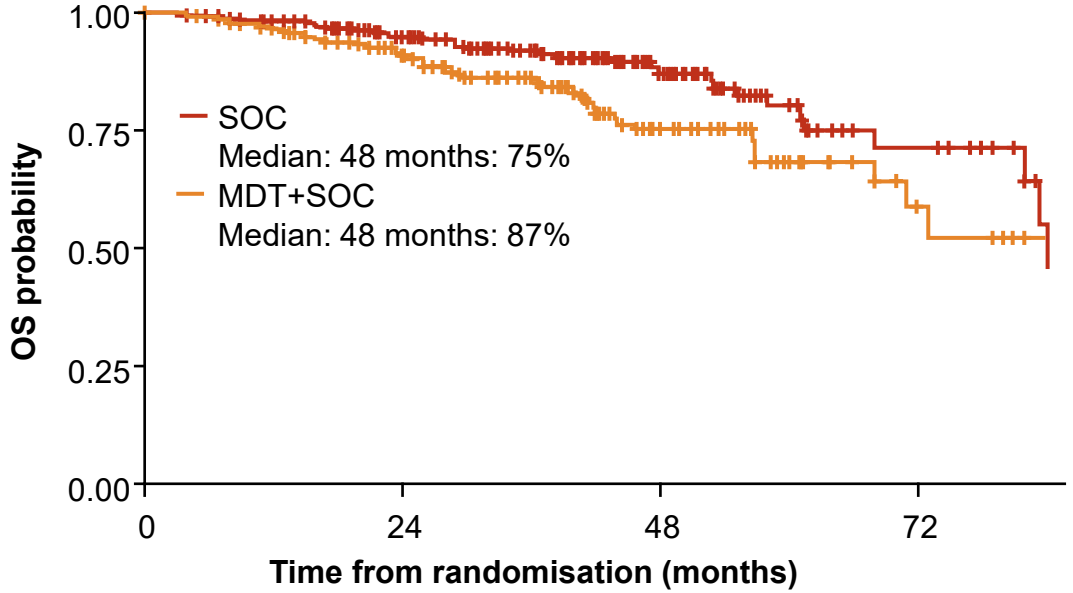
Oligometastatic disease: WOLVERINE meta-analysis

MDT vs. SOC
HR 0.45 (95% CI: 0.35–0.58; p<0.001)



Number at risk (number censored)				
SOC	224	50	7	0
MDT+SOC	248	112	24	3

MDT vs. SOC
HR 0.64 (95% CI: 0.40–1.01; p=0.057)



Number at risk (number censored)				
SOC	224	159	52	11
MDT+SOC	248	185	75	20

Individual data meta-analysis of five prospective trials (COMET, EXTEND, ORIOLE, STOMP and ARTO; 472 patients with oligometastatic disease)

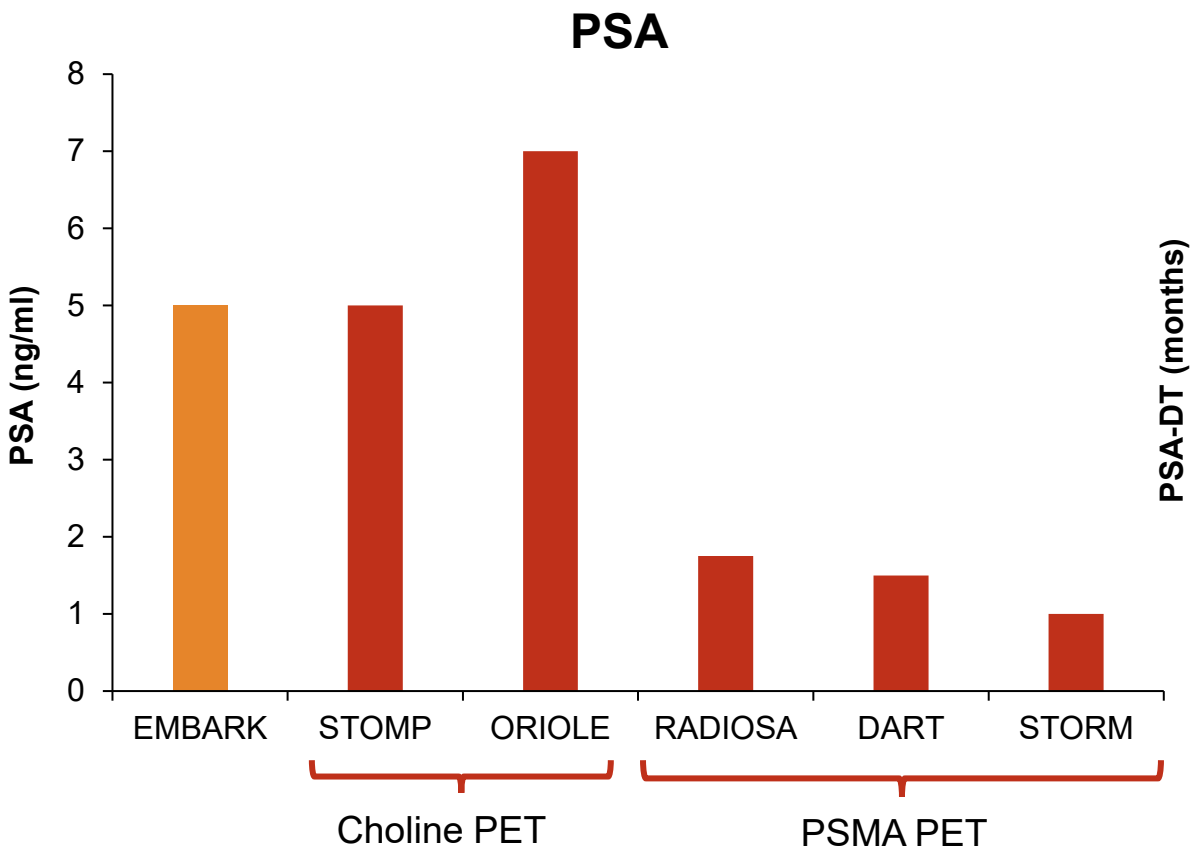
MDT consistently helps to improve PFS, rPFS, CRPC-free survival (random effects model) across subgroups (including treatment with or without systemic therapies), in addition to a near significant association with OS

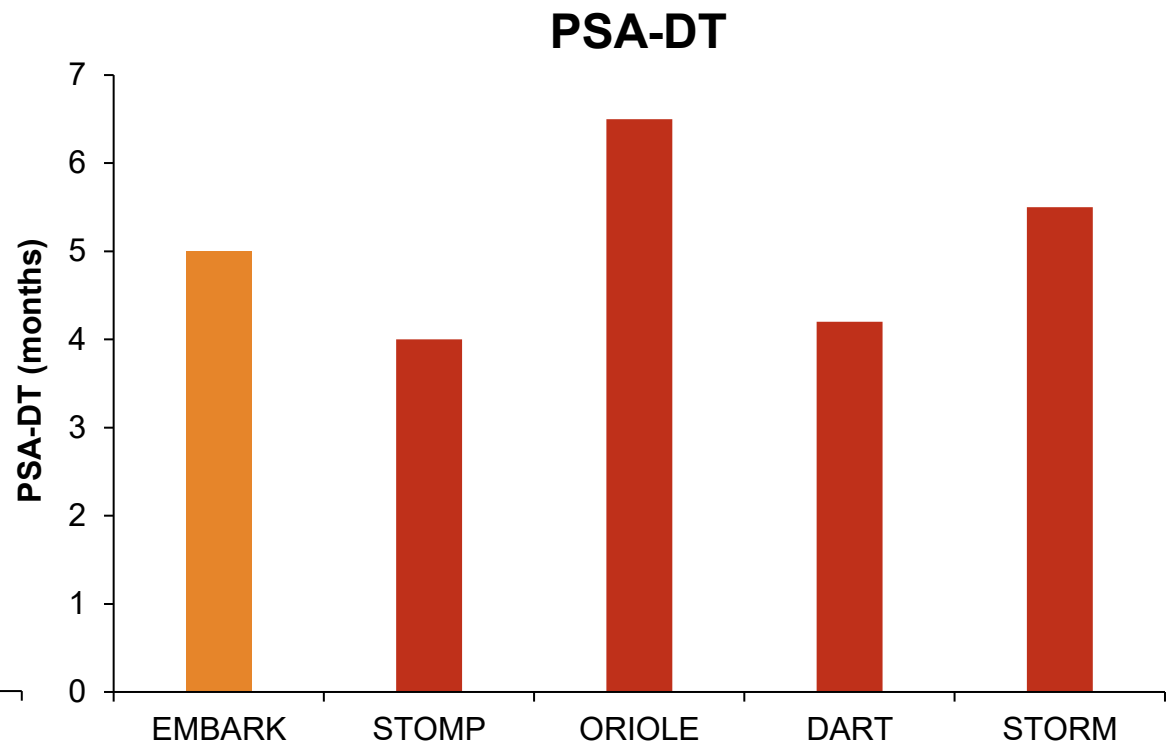
Graphs adapted from Tang C ET AL. Presented at ASCO GU 2025. CI, confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; MDT, metastasis-directed therapy; mo, months; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival; SOC, standard of care.

Tang C, et al. Presented at ASCO GU 2025, 13–15 February 2025, San Francisco, CA, USA, Abstract 15.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Translating EMBARK in MDT trials



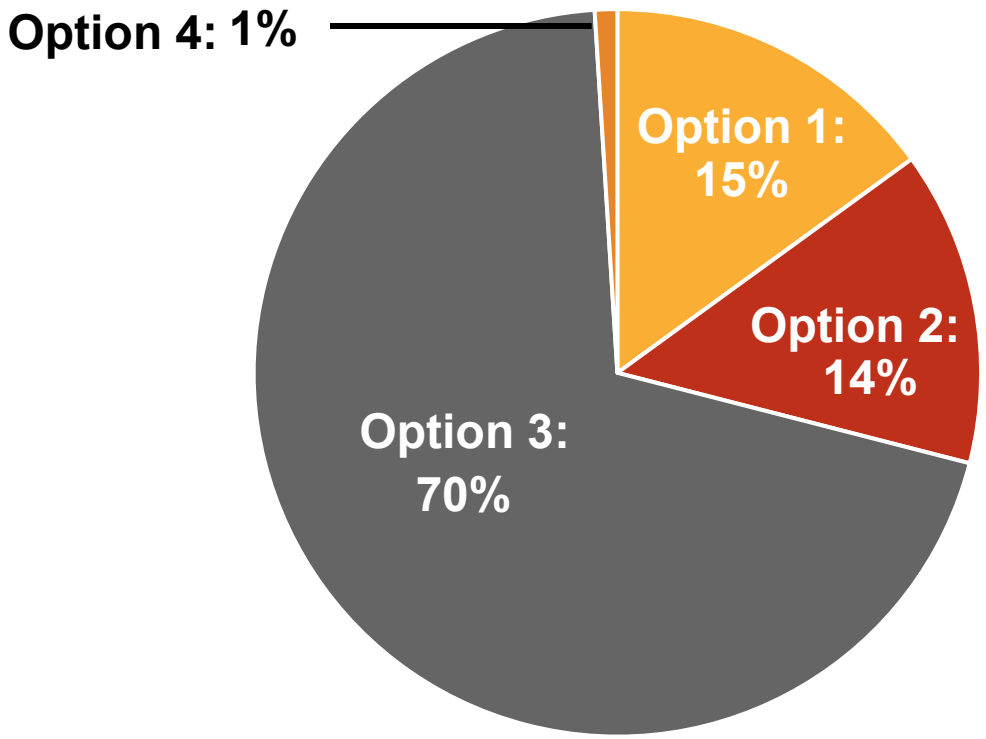


PSA at inclusion in recent MDT trials is lower compared with EMBARK
(PSMA PET imaging detects earlier oligometastatic disease), but PSA-DT remains accelerated (<9 months)

Graphs adapted from Ost P, et al., 2025.
DT, doubling time; MDT, metastasis-directed therapy; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
Ost P. Presented at ESTRO 2025, 2–5 May 2025, Vienna, Austria, Abstract 4858.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

APCCC 2024: PSA persistence and biochemical recurrence

58. For the majority of patients with high-risk nmHSPC and oligometastatic disease on PSMA PET imaging, what do you recommend?



Option	Votes, n
1. Immediate systemic therapy	15
2. Immediate MDT	15
3. Immediate combination of both options above	73
4. Monitoring only and deferred treatment	1
Abstain/unqualified to answer	2

APCCC, Advanced Prostate Cancer Consensus Conference; MDT, metastasis-directed therapy; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Gillessen S, et al. *Eur Urol* 2025;87:157–216.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Improving systemic therapy with MDT: EORTC 2391 – ESCALATE-RT study design

Population

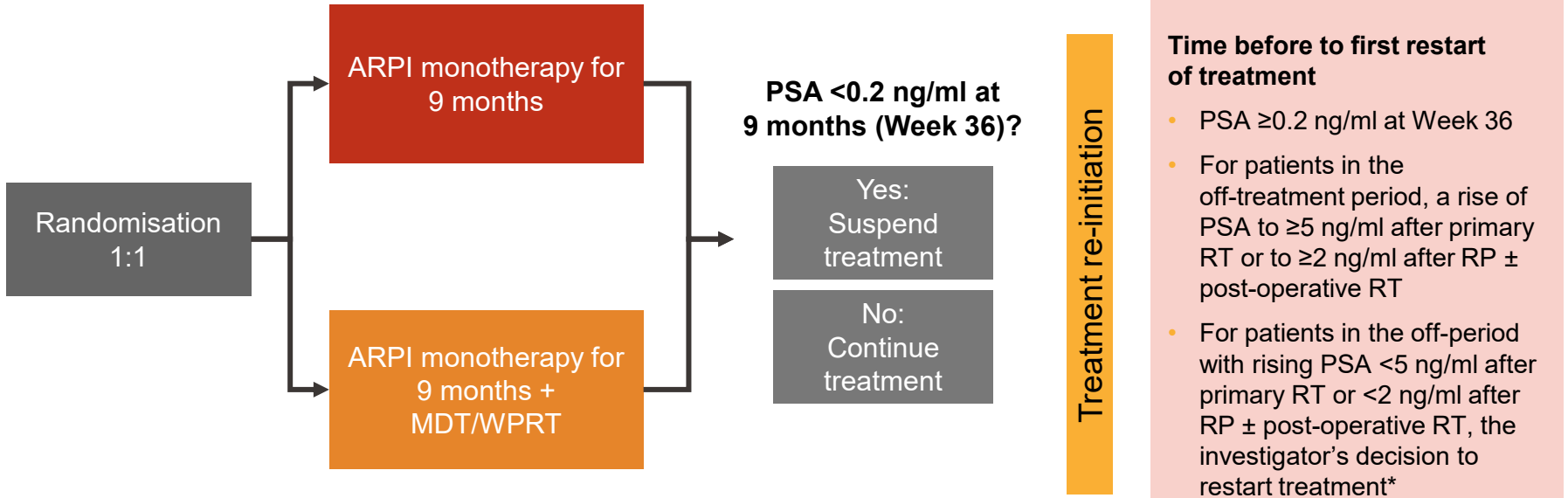
- High-risk HSPC
- PSA ≥0.2 ng/ml after RP ± post-operative RT or ≥2 ng/ml after RT
- PSA-DT ≤9 months
- Testosterone >150 ng/dL
- On PSMA PET/CT restaging, presence of:
  - A total of 1–5 metastases that are amenable to MDT (M1) ± pelvic nodes (N1)

Stratification

- Previous pelvis RT or not
- PSA-DT (≤3 months vs. >3 to ≤9 months)

Primary endpoint

- Time to first re-initiation of treatment



Time before to first restart of treatment

- PSA ≥0.2 ng/ml at Week 36
- For patients in the off-treatment period, a rise of PSA to ≥5 ng/ml after primary RT or to ≥2 ng/ml after RP ± post-operative RT
- For patients in the off-period with rising PSA <5 ng/ml after primary RT or <2 ng/ml after RP ± post-operative RT, the investigator's decision to restart treatment*

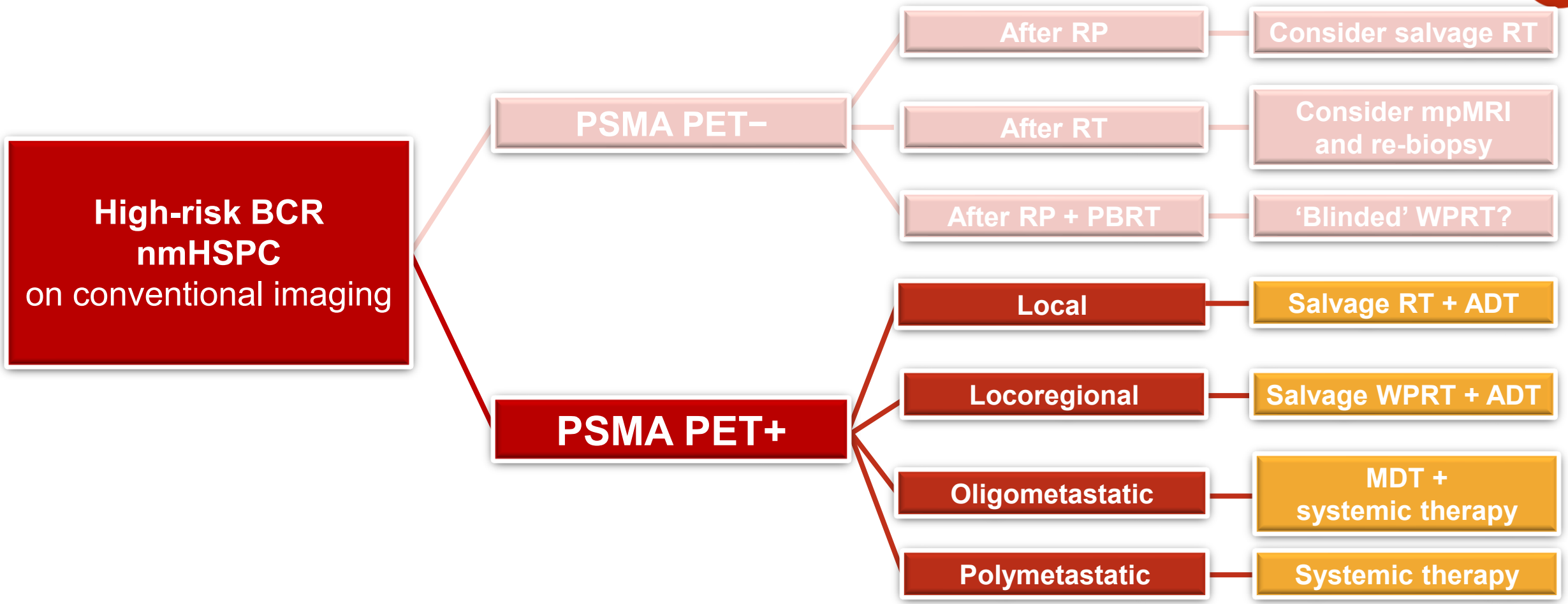
*In case of oligometastatic progression (N1 and/or M1), use of MDT and/or WPRT is allowed.

DT, doubling time; EORTC, European Organisation for Research and Treatment of Cancer; HSPC, hormone-sensitive prostate cancer; MDT, metastasis-directed therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; WPRT, whole pelvis radiotherapy.

McDermott R. Presented at APCCC 2024, 25–27 September, 2024. Lugano, Switzerland. UroToday. APCCC2024. Available at: https://www.urotoday.com/conference-highlights/apccc-2024/151506-apccc-2024-second-bcr-without-correlate-on-ngi-after-salvage-radiation-and-or-after-metastases-directed-therapy-how-to-manage-these-patients.html. Last accessed: June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

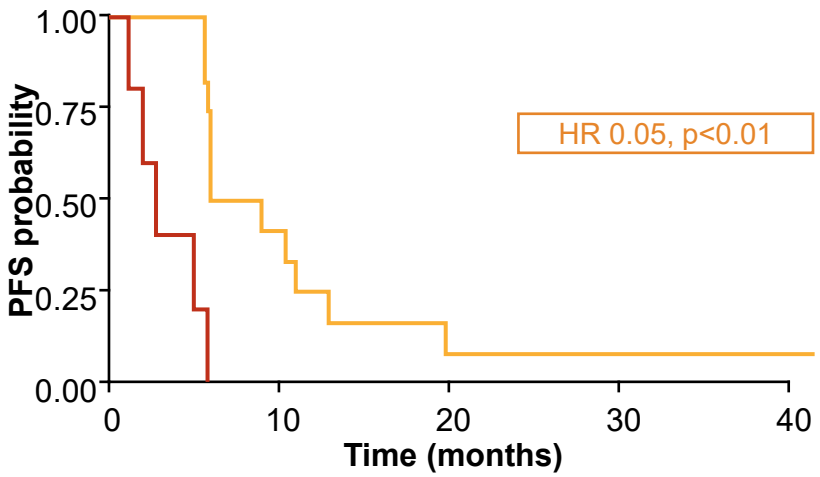
High-risk BCR: Same disease, different settings



ADT, androgen deprivation therapy; BCR, biochemical recurrence; MDT, metastasis-directed therapy; mpMRI, multi-parametric magnetic resonance imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PBRT, prostate bed radiotherapy; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; WPRT, whole pelvis radiotherapy.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

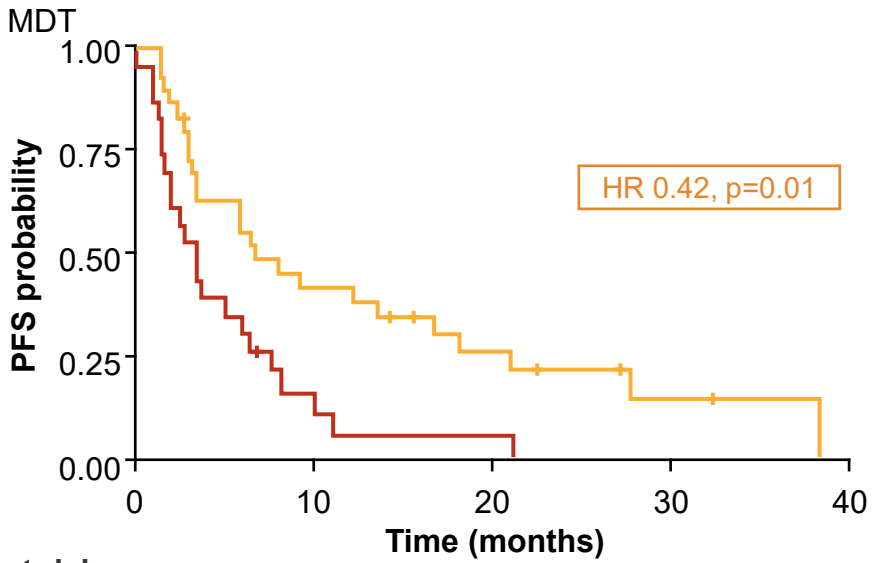
Patient selection: Biology matters

Patients with high-risk mutations



Number at risk					
Observation	5	0	0	0	0
MDT	12	5	2	1	1

Patients without high-risk mutations



Number at risk					
Observation	23	3	1	0	0
MDT	30	12	6	2	0

The study included 70 males with oligorecurrent disease from **STOMP** and **ORIOLE** for whom genomic data was available.
High-risk mutations: ***ATM, BRCA1/2, Rb1*** and ***TP53***

In men without high-risk mutations, outcomes were improved with MDT vs. observation (median PFS 13.4 vs. 7.0 months). In men with high-risk mutations, outcomes were poorest in those who received observation vs. MDT (median PFS 2.8 months vs.7.5 months)

Graphs adapted from Deek M, et al. *J Clin Oncol* 2022.
HR, hazard ratio; MDT, metastasis-directed therapy; PFS, progression-free survival.
Deek M, et al. *J Clin Oncol* 2022;40:3377–3382.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Take-home messages

High-risk nmHSPC identified via conventional imaging represents a **heterogeneous disease spectrum**

NGI redefines disease burden and guides treatment strategies in high-risk nmHSPC

RT and **MDT** may **delay progression** and **help improve clinical outcomes** and **quality of life**

Combination of **MDT** with **optimised systemic therapy** may offer an opportunity to help maximise clinical benefit and decrease exposure to ARPIs

Integration of **new biomarker signatures with NGI imaging** will reshape **patient selection** and **treatment optimisation**

ARPI, androgen receptor pathway inhibitor; MDT, metastasis-directed therapy; NGI, next-generation imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; RT, radiotherapy.
Speaker's own opinion.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Genitourinary Masterclass

astellas

The importance of early treatment intensification in patients with nmHSPC and high-risk BCR

Professor Dr Thomas Steuber

Faculty member, Martini-Klinik;
Professor of Urological Oncology, University Medical Center Hamburg-Eppendorf,
Hamburg, Germany

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

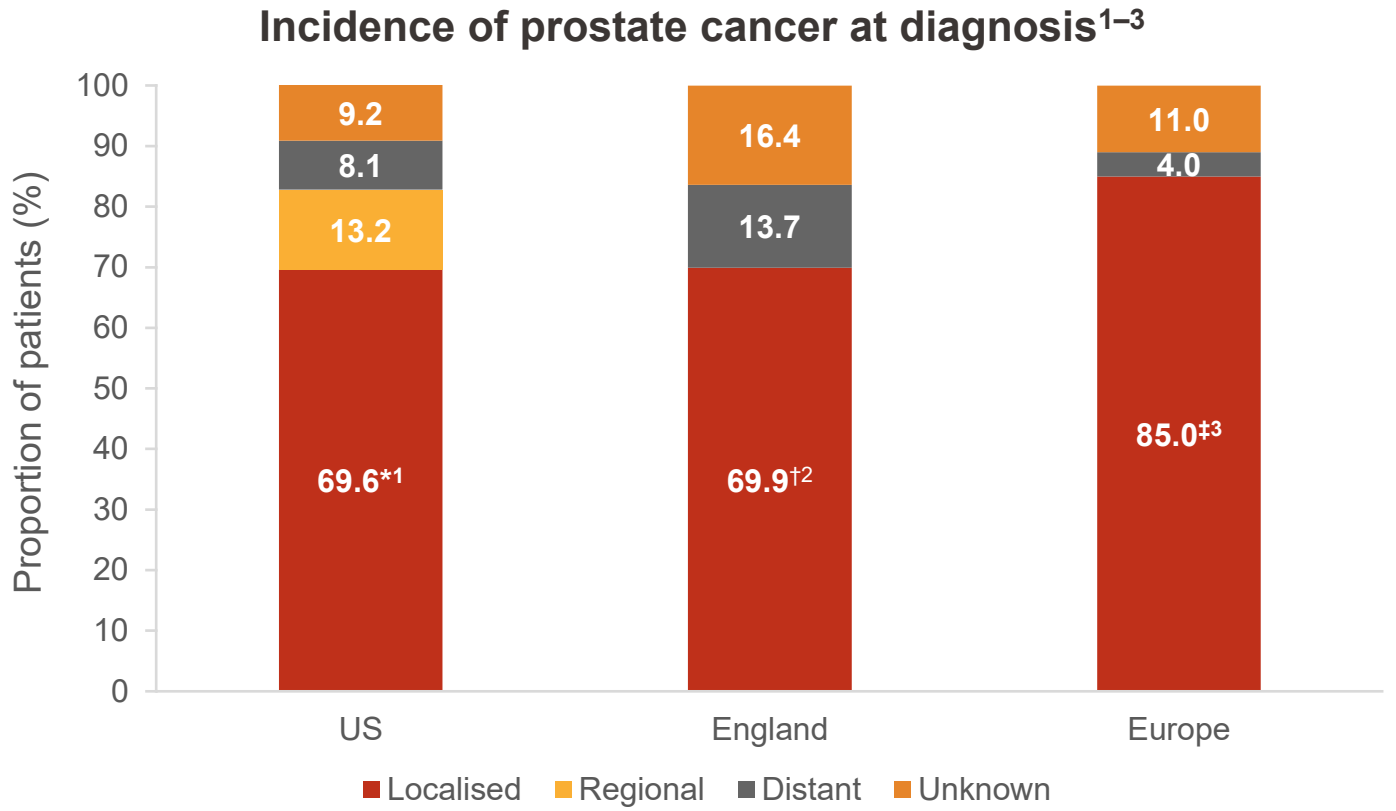
Disclosures

Consultant to:

- Amgen, Astellas Pharma Inc., AstraZeneca, Bayer, Janssen/J&J, MSD, Novartis, and Sanofi

- The speaker has received an honorarium from Astellas for this presentation

Patients with prostate cancer are frequently diagnosed at the non-metastatic stage, providing an opportunity for early treatment



Early diagnosis gives us an opportunity to start treatment as soon as possible. But should we?

*Between 2013 and 2022; †Between 2015 and 2019; ‡Between 1993 and 2010.

Figures adapted from National Cancer Institute. SEER Program Cancer Statistics Explorer Network, National Prostate Cancer Audit, and Buzzoni C, et al. *Eur Urol* 2015[1–3]

1. National Cancer Institute. SEER Program Cancer Statistics Explorer Network. Stage Distribution of SEER Incidence Cases, 2013-2022. Available at https://seer.cancer.gov/statistics-network/explorer/application.html?site=66&data_type=1&graph_type=4&compareBy=race&chk_race_1=1&hdn_sex=2&age_range=1&advopt_precision=1&hdn_view=1&advopt_show_apc=on&advopt_display=2#resultsRegion1. Last accessed: June 2025; 2. National Prostate Cancer Audit. Patient and tumour characteristics associated with metastatic prostate cancer at diagnosis in England. NPCA: Short report 2022. Available at: 69.969. Last accessed: June 2025; 3. Buzzoni C, et al. *Eur Urol* 2015;68:885–890.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

The incidence of BCR at 10 years for patients with nmHSPC varies by treatment type and disease stage when treated

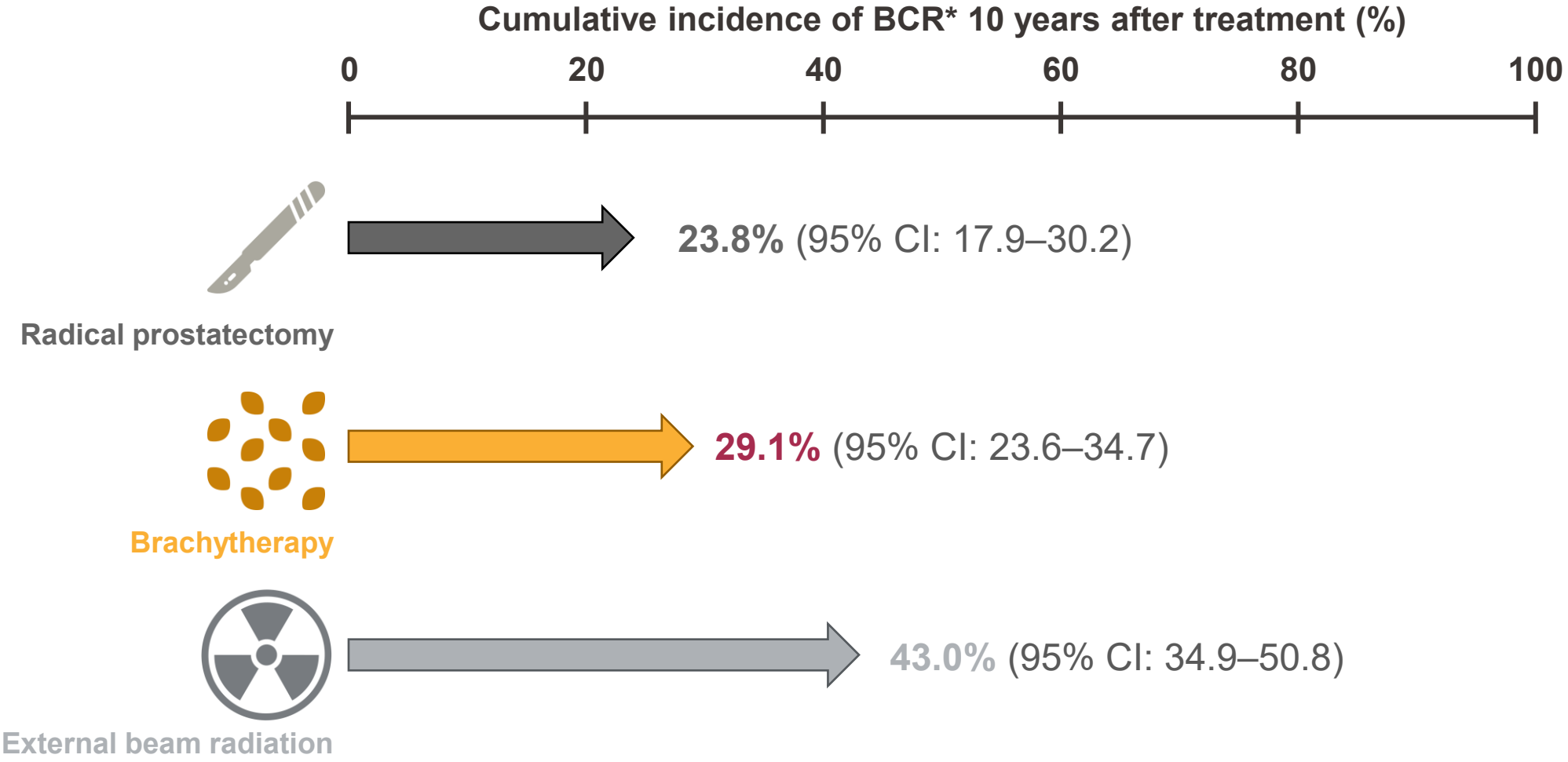
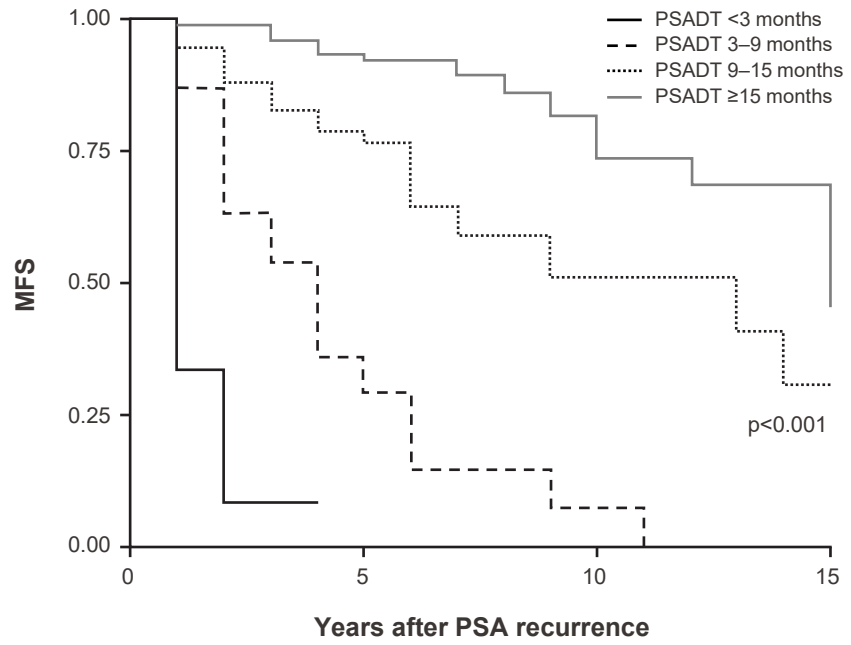
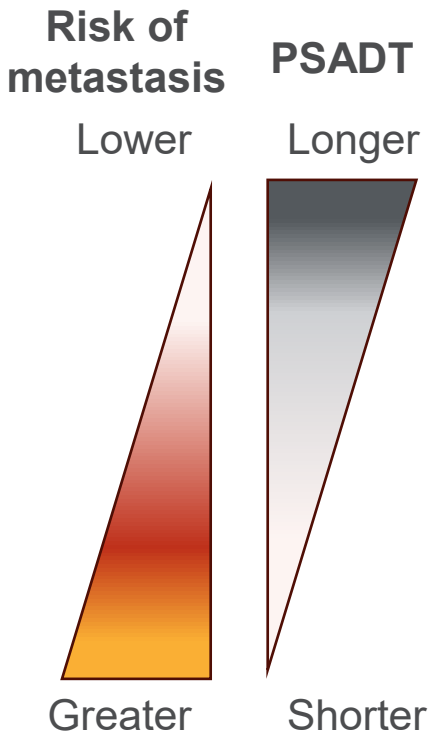


Figure adapted from Suarez JF, et al. *Sci Rep* 2022.
*BCR appeared at a median of 4.4 years after treatment.
BCR, biochemical recurrence; CI, confidence interval; nmHSPC, non-metastatic hormone-sensitive prostate cancer.
Suarez JF, et al. *Sci Rep* 2022;12:12589.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Patients with short PSADTs are at higher risk of metastasis than those with longer PSADT

Kaplan–Meier estimates for MFS,* stratified by PSADT

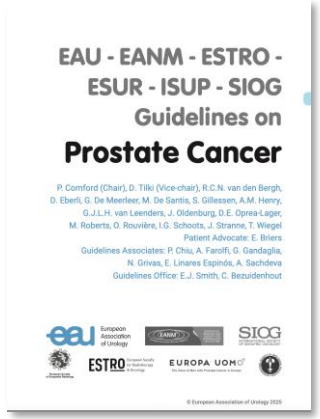




Treatment is required to delay the onset of metastases for patients with high-risk disease

Figure adapted from Antonarakis ES, et al. *BJU Int* 2012.
*Defined as the time interval from BCR to initial metastasis.
BCR, biochemical recurrence; MFS, metastasis-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.
Antonarakis ES, et al. *BJU Int* 2012;109:32–39.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

EAU risk categories for patients developing BCR



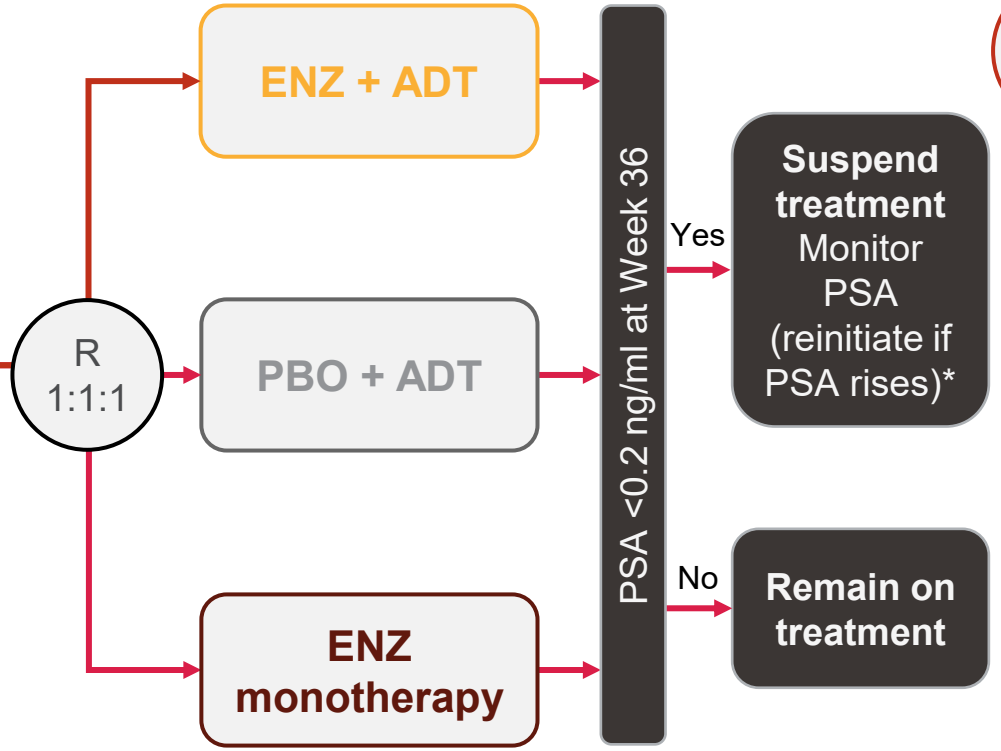
	Low risk	High risk
After RP	PSADT >1 year AND Pathological ISUP grade group <4	PSADT ≤1 year OR Pathological ISUP grade group 4–5
After RT	Interval to biochemical failure >18 months AND Biopsy ISUP grade group <4	Interval to biochemical failure ≤18 months OR Biopsy ISUP grade group 4–5

Table adapted from EAU Guidelines on prostate cancer.
BCR, biochemical recurrence; EAU, European Association of Urology; ISUP, International Society of Urological Pathology; PSADT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy.
EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer/. Last accessed: June 2025
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

EMBARK was an international, randomised, Phase III trial investigating ENZ ± ADT vs. PBO + ADT in patients with nmHSPC with high-risk BCR

Patient population

- High-risk disease: PSADT ≤9 months; PSA ≥2 ng/ml above nadir after RT *or* PSA ≥1 ng/ml after RP ± postoperative RT
- Serum testosterone ≥150 ng/dl
- ECOG PS 0/1
- No distant metastases via bone scans, CT or MRI
- No prior hormonal therapy, unless given ≥9 months before R, as neoadjuvant/adjuvant therapy to treat prostate cancer ≤36 months in duration, or a single dose or a short course (≤6 months) given for rising PSA



Primary endpoint:
MFS†
(ENZ + ADT group vs. PBO + ADT group)

Key secondary endpoints

- MFS (ENZ monotherapy group vs. PBO + ADT group)
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- Safety

Stratification factors: Screening PSA (≤10 vs. >10 ng/ml); PSADT (≤3 months vs. >3 to ≤9 months); prior hormonal therapy (yes vs. no)

*Treatment was suspended at Week 37 if PSA was <0.2 ng/ml and restarted when PSA was ≥5.0 ng/ml (without prior RP) and ≥2 ng/ml (prior RP); †MFS was defined as the time from R to the date of earliest objective evidence of imaging-based progression according to central imaging or death from any cause.

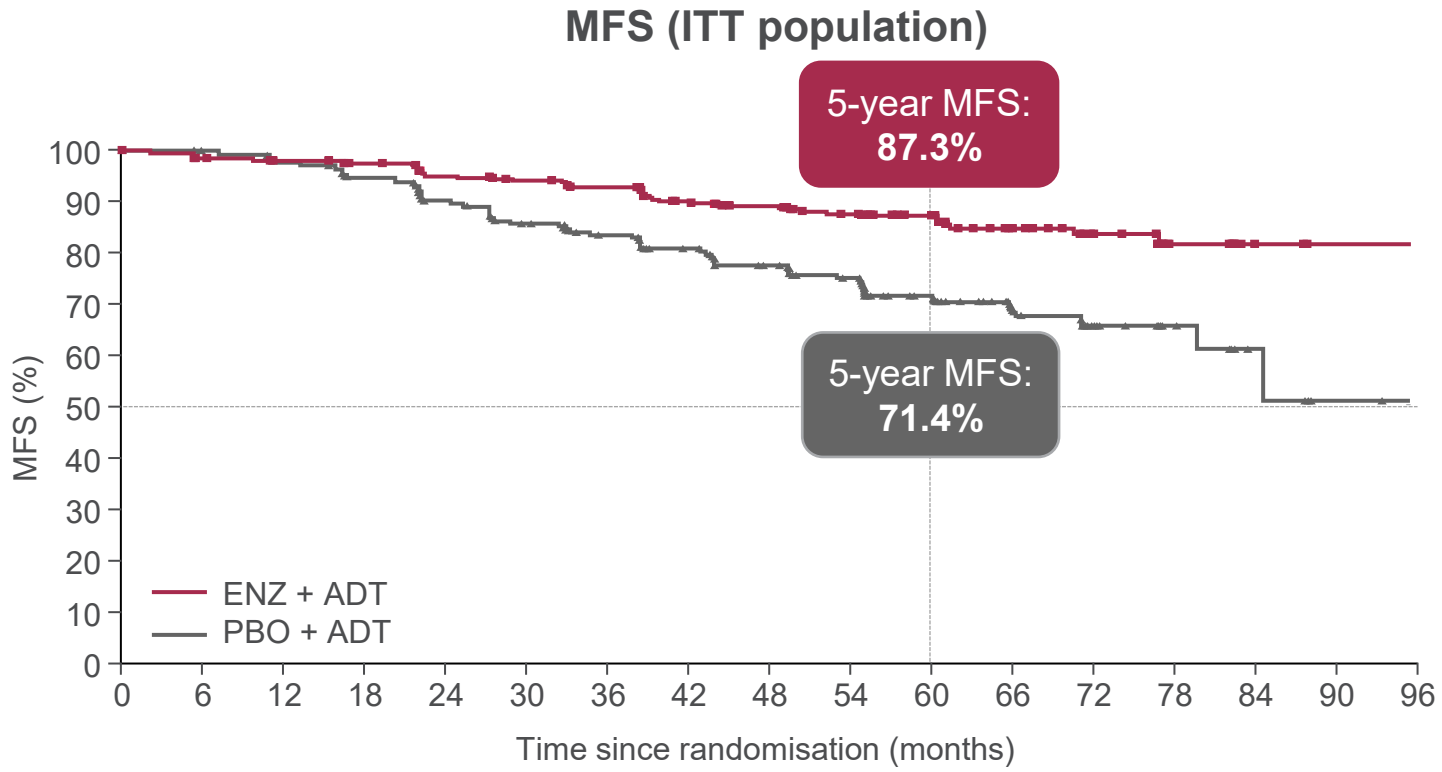
Figure adapted from Freedland SJ, et al. *N Engl J Med* 2023.

ADT, androgen deprivation therapy; BCR, biochemical recurrence; CT, computerised tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; ENZ, enzalutamide; MFS, metastasis-free survival; MRI, magnetic resonance imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; OS, overall survival; PBO, placebo; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; R, randomisation; RP, radical prostatectomy; RT, radiotherapy.

Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Treatment intensification with ENZ + ADT was associated with significantly improved MFS* over PBO + ADT

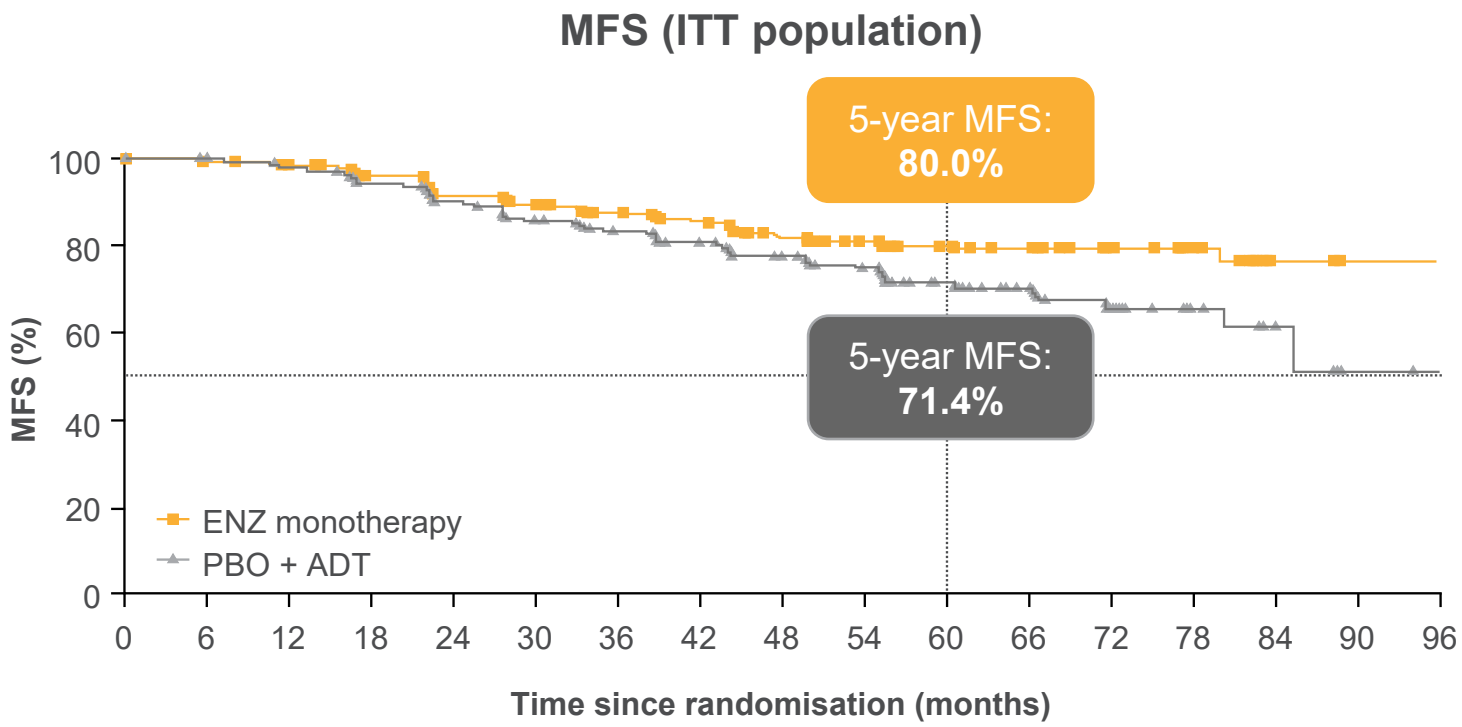


	ENZ + ADT (n=355)	PBO + ADT (n=358)
Image-based progression or death events, n (%)	45 (12.7)	92 (25.7)
Median MFS, per BICR	NYR	NYR
Median follow-up, months	60.7	60.6

ENZ + ADT was associated with a significant 58% reduction in the risk of metastasis or death vs. PBO + ADT **HR 0.42 (95% CI: 0.30–0.61); p<0.001**

*MFS defined as the time from randomisation to the date of earliest objective evidence of imaging-based progression by central imaging or death due to any cause.
Table adapted from Freedland SJ, et al. *N Engl J Med* 2023.
ADT, androgen deprivation therapy; BICR, blinded independent central review; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; ITT, intention-to-treat; MFS, metastasis-free survival; NYR, not yet reached; PBO, placebo.
Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Treatment with ENZ monotherapy was also associated with significantly improved MFS* over PBO + ADT

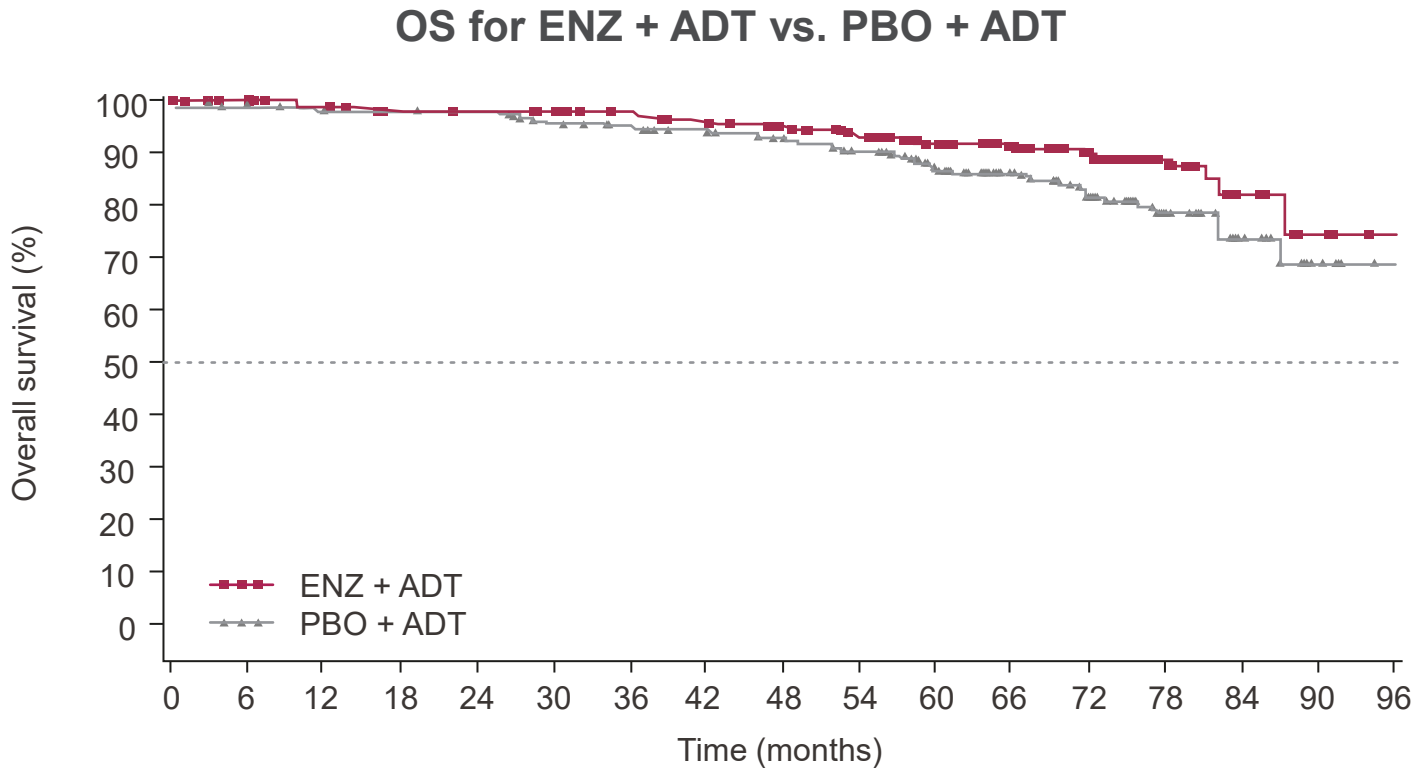


	ENZ monotherapy (n=355)	PBO + ADT (n=358)
Image-based progression or death events, n (%)	63 (17.7)	92 (25.7)
Median MFS, per BICR	NYR	NYR
Median follow-up, months	60.7	60.6

ENZ monotherapy was associated with a significant 36.9% reduction in the risk of metastasis or death compared with PBO + ADT **HR 0.63 (95% CI: 0.46–0.87); p=0.005**

*MFS defined as the time from randomisation to the date of earliest objective evidence of imaging-based progression by central imaging or death due to any cause.
Figure adapted from Freedland SJ, et al. *N Engl J Med* 2023.
ADT, androgen deprivation therapy; BICR, blinded independent central review; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; ITT, intention-to-treat; MFS, metastasis-free survival; NYR, not yet reached; PBO, placebo.
Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Median OS was not yet reached for either trial arm, but favoured ENZ + ADT over PBO + ADT



	ENZ + ADT (n=355)	PBO + ADT (n=358)
Death events, n (%)	33 (9.3)	55 (15.4)
Median OS	NYR	NYR
Median follow-up, months	60.7	60.6

OS for ENZ + ADT vs. PBO + ADT:

HR 0.59 (95% CI: 0.38–0.91); p=0.02 (interim efficacy boundary, p≤0.0001)

Figures adapted from Freedland SJ, et al. *N Engl J Med* 2023.
ADT, androgen deprivation therapy; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; NYR, not yet reached; OS, overall survival; PBO, placebo.
Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465 (supplementary appendix).
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Overall rates of AEs were comparable across treatment arms, regardless of intensification

Event, n (%)*[1]	ENZ + ADT (n=353)		PBO + ADT (n=354)		ENZ monotherapy (n=354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related AE	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious AE	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious AE	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
AE leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
AE leading to permanent discontinuation of study treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
AE leading to death†	6 (1.7)	–	3 (0.8)	–	8 (2.3)	–
Median treatment duration, excluding treatment suspension, months (range)	32.4 (0.1–83.4)		35.4 (0.7–85.7)		45.9 (0.4–88.9)	

Safety profiles were consistent with the known side effects of ENZ in advanced prostate cancer.[2]
Discontinuation rates due to AEs were similar to previous ENZ studies.[1]

Disclaimer: Please consult SmPC for full safety information.

*Patients in the safety population were evaluated according to the treatment they received. Shown are AEs that occurred from the time of the first dose of the trial regime through 30 days after permanent discontinuation. The median duration of treatment, excluding treatment suspension, was 32.4 months (range, 0.1–83.4) among patients who received enzalutamide plus leuprolide, 35.4 months (range, 0.7–85.7) among patients who received leuprolide alone, and 45.9 months (range, 0.4–88.9) among patients who received enzalutamide monotherapy. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Percentages may not total 100 because of rounding; †AEs leading to death were Grade 5 adverse events; none were considered by the investigator to be related to treatment.

Table adapted from Freedland SJ, et al. *N Engl J Med* 2023.

ADT, androgen deprivation therapy; AE, adverse event; ENZ, enzalutamide; PBO, placebo.

1. Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465; 2. XTANDI (enzalutamide). Prescribing Information.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Safety profiles of each trial arm differed (1/2)

Most common AEs that occurred in ≥10% of patients, n (%)	ENZ + ADT (n=353)		PBO + ADT (n=354)		ENZ monotherapy (n=354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hot flash	**243 (68.8)***	2 (0.6)	**203 (57.3)***	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	**151 (42.8)***	12 (3.4)	116 (32.8)	5 (1.4)	**165 (46.6)***	14 (4.0)
Arthralgia	97 (27.5)	7 (2.0)	75 (21.2)	1 (0.3)	81 (22.9)	2 (0.6)
Hypertension	82 (23.2)	24 (6.8)	69 (19.5)	18 (5.1)	67 (18.9)	19 (5.4)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Back pain	60 (17.0)	3 (0.8)	54 (15.3)	1 (0.3)	62 (17.5)	3 (0.8)
Diarrhoea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	1 (0.3)
Constipation	46 (13.0)	1 (0.3)	31 (8.8)	0	34 (9.6)	1 (0.3)
Haematuria	42 (11.9)	8 (2.3)	44 (12.4)	4 (1.1)	45 (12.7)	9 (2.5)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	1 (0.3)	29 (8.2)	1 (0.3)	54 (15.3)	2 (0.6)
Pain in arm or leg	41 (11.6)	3 (0.8)	36 (10.2)	2 (0.6)	40 (11.3)	1 (0.3)

Disclaimer: Please consult SmPC for full safety information.

Table adapted from Freedland SJ, et al. *N Engl J Med* 2023.

*These events were among the most common treatment-related AEs (occurring in ≥30% of patients).

ADT, androgen deprivation therapy; AE, adverse event; ENZ, enzalutamide; PBO, placebo.

Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Safety profiles of each trial arm differed (2/2)

Most common AEs that occurred in ≥10% of patients, n (%)	ENZ + ADT (n=353)		PBO + ADT (n=354)		ENZ monotherapy (n=354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	2 (0.6)	37 (10.5)	2 (0.6)	41 (11.6)	3 (0.8)
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	4 (1.1)	28 (7.9)	3 (0.8)	36 (10.2)	6 (1.7)
Gynaecomastia	29 (8.2)	0	32 (9.0)	0	**159 (44.9)***	3 (0.8)
Coronavirus disease 2019 (COVID-19)	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	2 (0.6)
Peripheral oedema	27 (7.6)	1 (0.3)	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	7 (2.0)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

Disclaimer: Please consult SmPC for full safety information.

Table adapted from Freedland SJ, et al. *N Engl J Med* 2023.

*These events were among the most common treatment-related AEs (occurring in ≥30% of patients).

ADT, androgen deprivation therapy; AE, adverse event; ENZ, enzalutamide; PBO, placebo.

Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.

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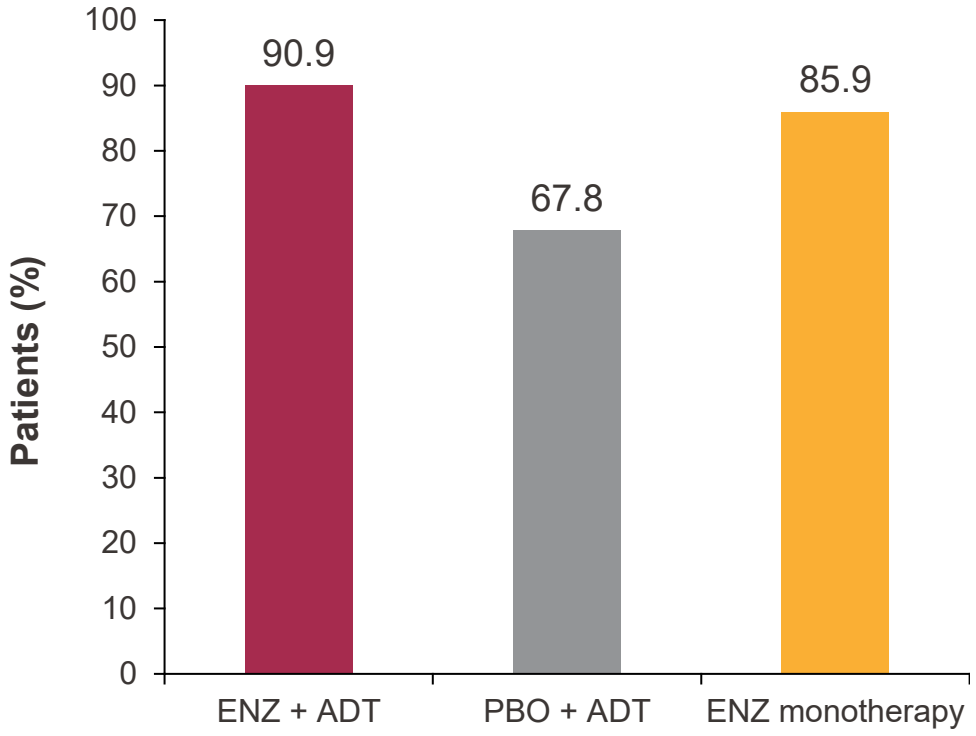
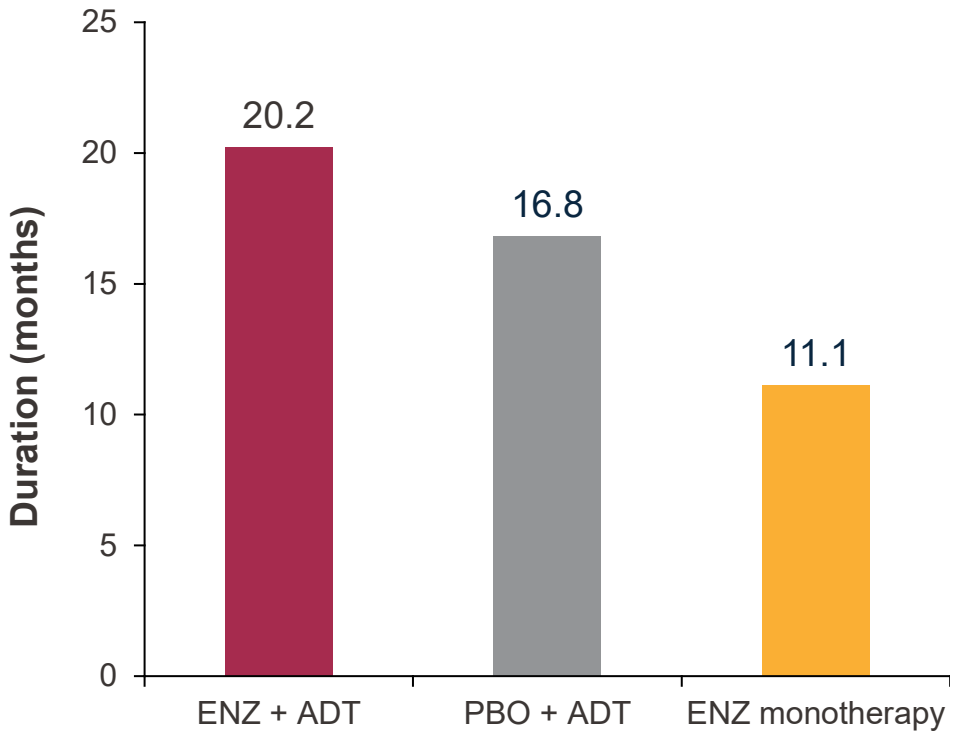
Secondary endpoint: Percentage of patients who achieved undetectable PSA* (ITT population)

Patients with PSA <0.2 ng/ml at Week 36



Median duration of treatment suspension†



Graphs adapted from Freedland SJ, et al. *N Engl J Med* 2023.
*<0.2 ng/ml; †Last date of suspension without treatment.
ADT, androgen deprivation therapy; ENZ, enzalutamide; ITT, intention-to-treat; PBO, placebo; PSA, prostate-specific antigen.
Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465 (supplementary appendix).
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Genitourinary Masterclass

astellas

How to implement findings in your daily clinical practice?

Andreas initially presented with a high PSA and Gleason score

68 years old

Mediterranean male

Patient disease profile

- PSA: **8 ng/ml**
- ISUP: **4 (Gleason 4+4)**

Initial presentation

- PSMA PET-CT imaging: **negative**

Initial treatment

RALP

Fictitious clinical case provided by the speaker.

CT, computed tomography; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RALP, robot-assisted laparoscopic prostatectomy.

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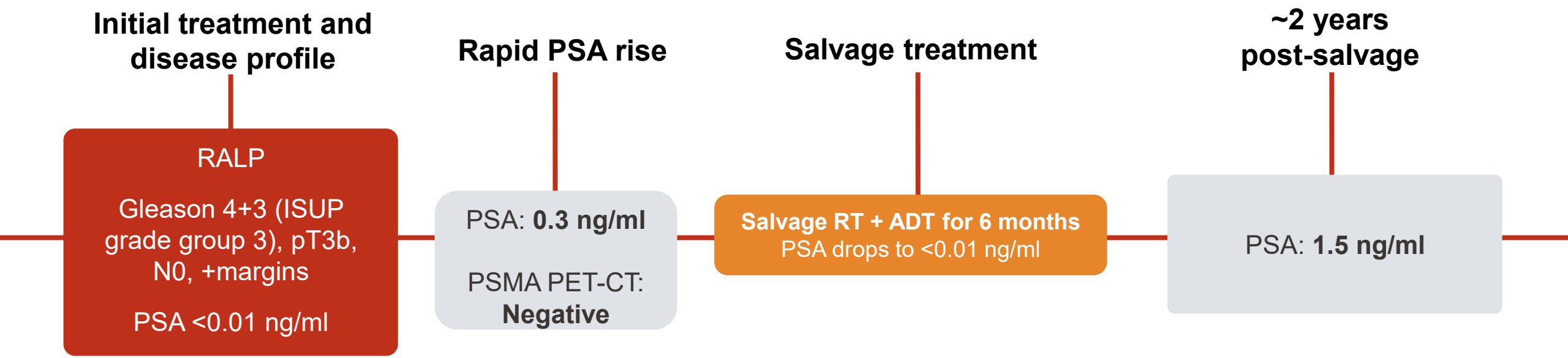
Andreas was diagnosed with EAU high-risk PCa and was initially treated with RALP



Fictitious clinical case provided by the speaker.

ADT, androgen deprivation therapy; BCR, biochemical recurrence; CT, computerised tomography; N, node; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RALP, robot-assisted laparoscopic prostatectomy; RT, radiotherapy; T, tumour.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

pT3b, Gleason 4+3, ISUP 3, pN0, PSA 1.5 ng/ml 2 years after salvage radiation for BCR?

Fictitious clinical case provided by the speaker.

BCR, biochemical recurrence; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSMA, prostate-specific membrane antigen; RALP, robot-assisted laparoscopic prostatectomy.

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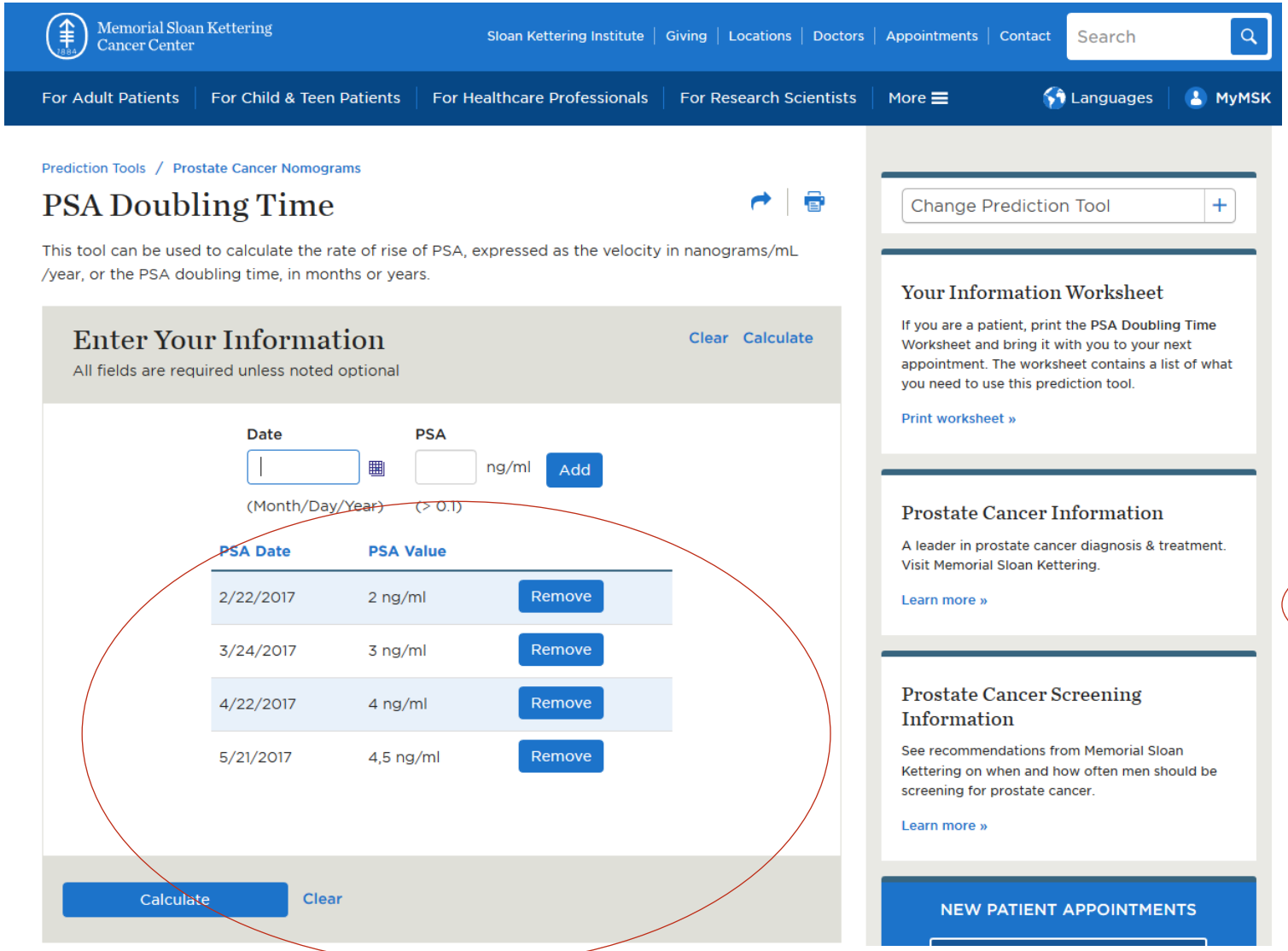
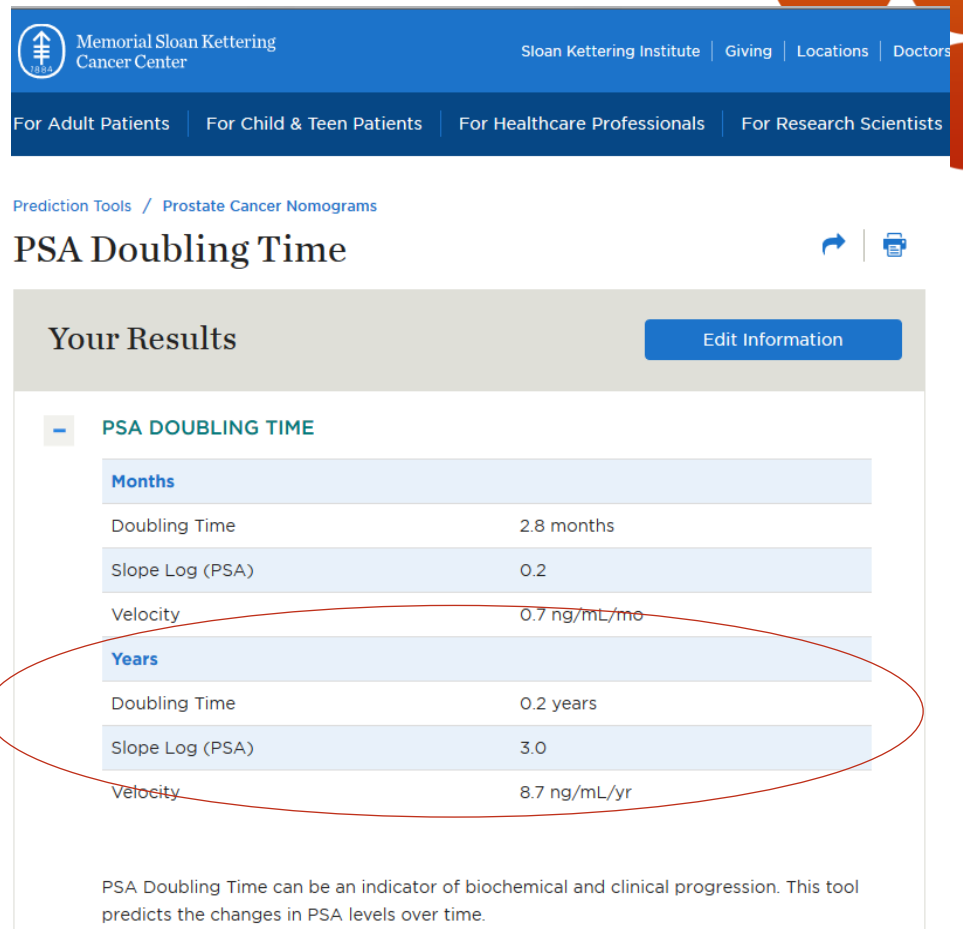
How to calculate PSA-DT





PSA-DT, prostate-specific antigen doubling time.

Memorial Sloan Kettering Cancer Center. PSA doubling time [Prediction tool]. Available at: https://www.mskcc.org/nomograms/prostate/psa_doubling_time. Last accessed: June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

pT3b, Gleason 4+3, ISUP 3, pN0, PSA 1.5 ng/ml 2 years after salvage radiation for BCR?

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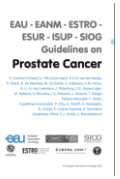
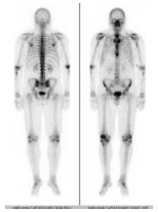
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Key considerations for imaging in men with nmHSPC



'Perform prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) if the PSA level is >0.2 ng/mL and if the results will influence subsequent treatment decisions (EAU BCR risk groups).' WEAK[1]



Patients in EMBARK were negative on conventional imaging (M0)[2]

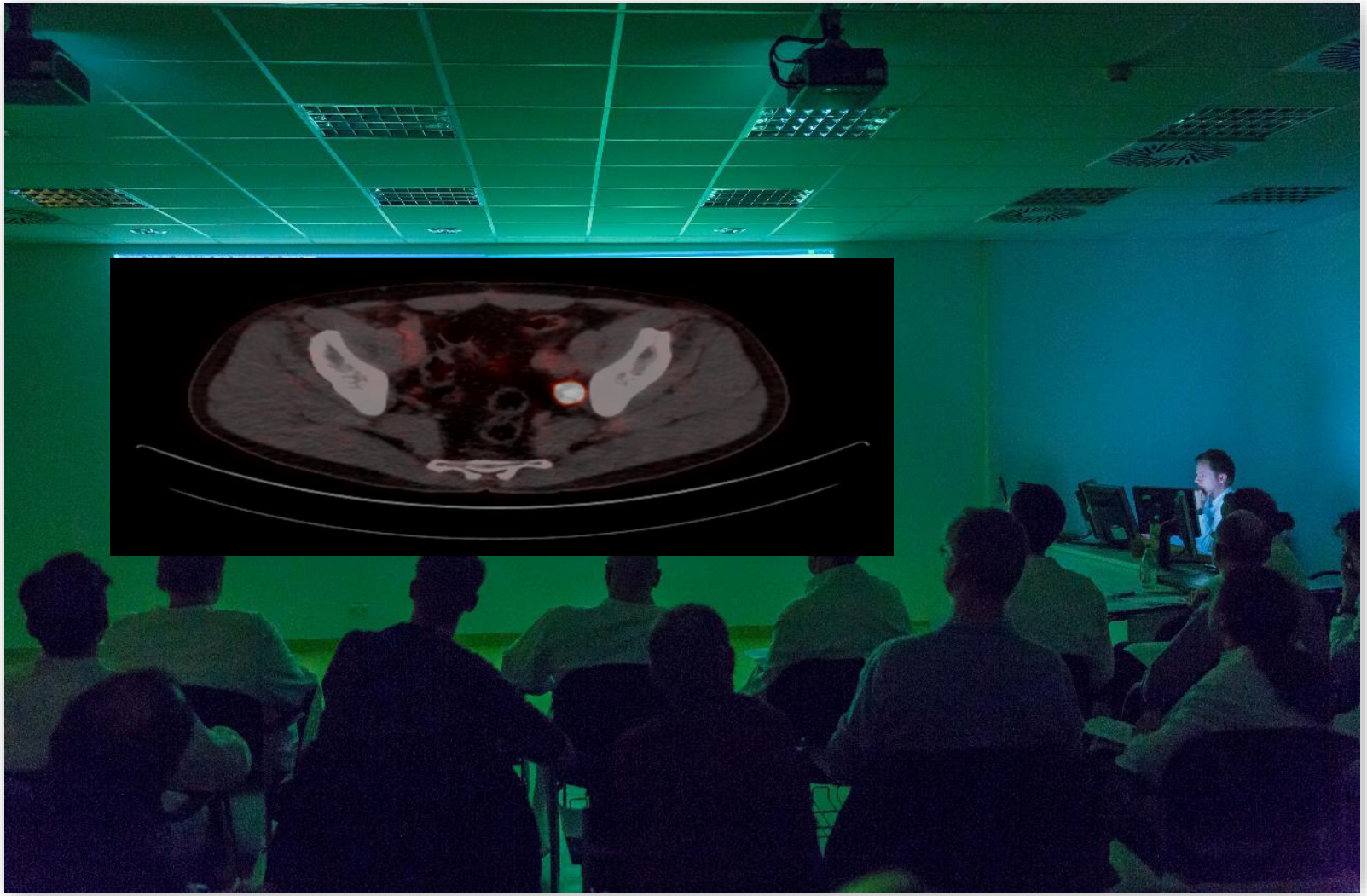
Overall population n=182, high-risk BCR (EMBARK), negative on conventional imaging (M0): 46% miM1, 24% polymetastatic (≥5 lesions)[3]

BCR, biochemical recurrence; EAU, European Association of Urology; M0, non-metastatic; miM1, metastatic by molecular imaging; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PET/CT, positron emission tomography//computed tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

1. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer. Last accessed: June 2025; 2. Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465;
3. Holzgreve A, et al. *JAMA Netw Open* 2025;8:e2452971.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

pT3b, Gleason 4+3, ISUP 3, pN0, PSA 1.5 ng/ml 2 years after salvage radiation for BCR?



Fictitious clinical case provided by the speaker.

BCR, biochemical recurrence; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSMA, prostate-specific membrane antigen; RALP, robot-assisted laparoscopic prostatectomy.

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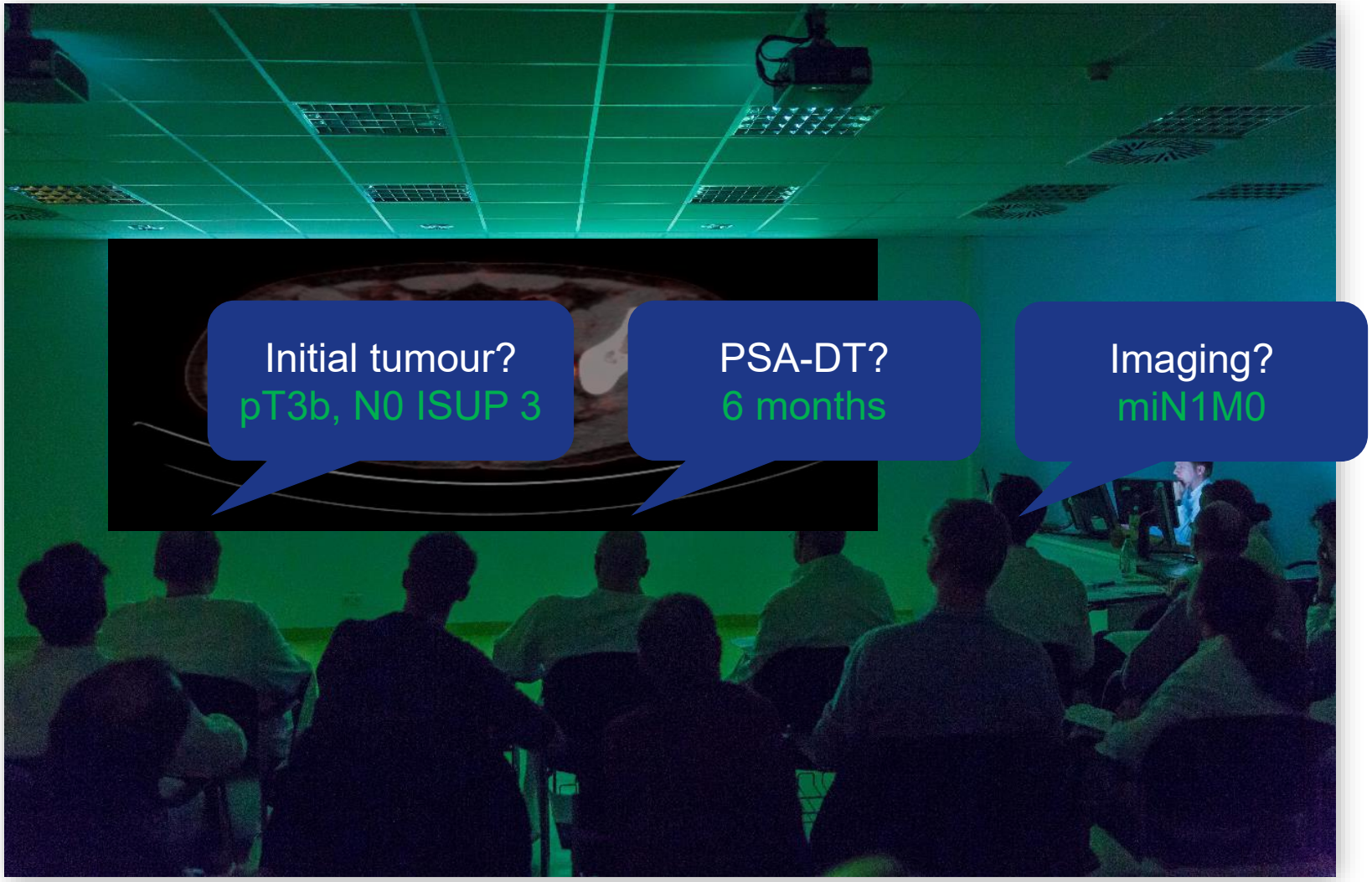
pT3b, Gleason 4+3, ISUP 3, pN0, PSA 1.5 ng/ml 2 years after salvage radiation for BCR?



Fictitious clinical case provided by the speaker.

BCR, biochemical recurrence; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSMA, prostate-specific membrane antigen; RALP, robot-assisted laparoscopic prostatectomy.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Andreas’s disease profile following BCR

Can’t we treat the lesion? Or cure?

Now 70 years old

Patient disease profile

- PSA: 1.5 ng/ml
- PSA-DT: 6 months
- PSMA PET-CT: miN1(6 mm), M0

Personal considerations

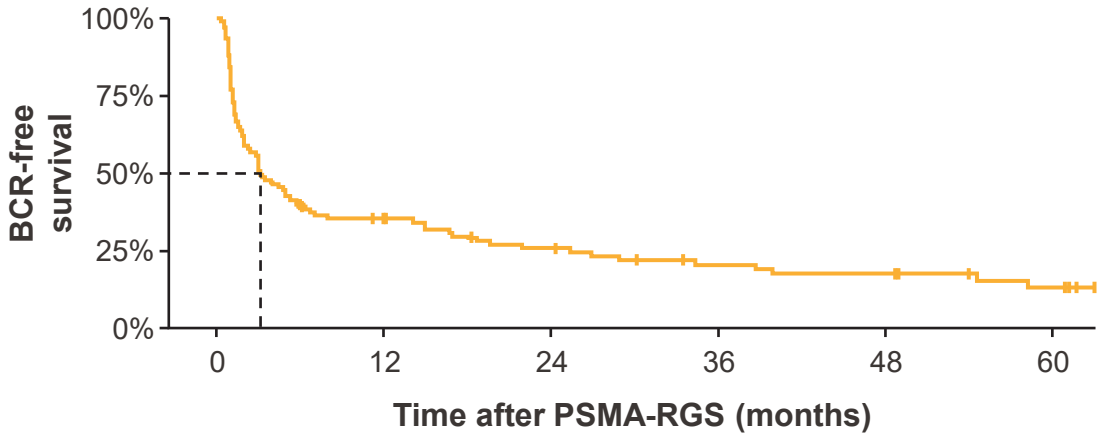
- Not sexually active since salvage RT – not important to him
- Had fatigue/sweats with initial ADT during RT (no treatment administered)

Fictitious clinical case provided by the speaker.
ADT, androgen deprivation therapy; BCR, biochemical recurrence; CT, computerised tomography; PET, positron emission tomography; PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time; PSMA, prostate-specific membrane; RT, radiotherapy.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

MDT (radio-guided surgery) in miN1 M0 patients with EMBARK high-risk BCR

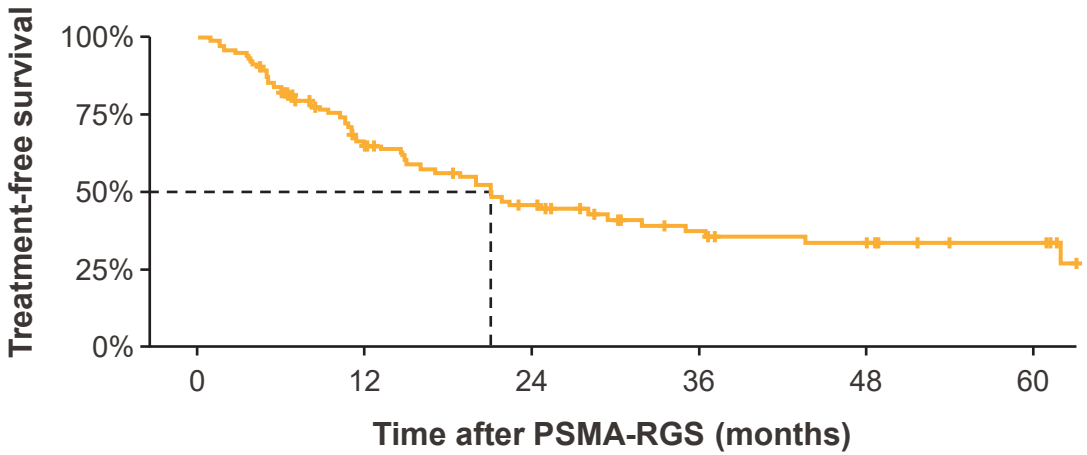
- N=111
- Median PSA 1.9 ng/ml
- Median PSA-DT 4.0 months
- 63.1% one lesion, 74.8% pelvis only

Overall cohort: BCR-free survival



Number at risk						
Overall	99	33	21	14	12	6

Overall cohort: Treatment-free survival



Number at risk						
Overall	100	56	33	20	16	11

Graphs adapted from Falkenbach F, et al. *Eur Urol Focus* 2025.
BCR, biochemical recurrence; MDT, metastasis-directed therapy; mo, months; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSMA-RGS, prostate-specific membrane antigen radio-guided surgery.
Falkenbach F, et al. *Eur Urol Focus* 2025;25:S2405-4569.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

How would you treat Andreas following BCR?

- **A** Watch and wait
- **B** ADT alone
- **C** ENZ alone
- **D** ENZ + ADT

Fictitious clinical case provided by the speaker.
ADT, androgen deprivation therapy; BCR, biochemical recurrence; ENZ, enzalutamide.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

To ensure appropriate intensification of therapy, it was necessary to consider Andreas's preferences and most important concerns

Treatment options

- **Pros and cons of ENZ + ADT vs. ENZ alone discussed with Andreas**
  - Not sexually active, so no expectations of any sexual benefits from ENZ monotherapy
  - Given the patient experienced depression with ADT, he wanted the best chance for treatment suspension and greatest chance for the longest suspension possible

- **Andreas chose to be treated with ENZ + ADT for 9 months**
  - Approved by FDA and EMA[1,2]
  - Recommended in ESMO and EAU guidelines[3,4]

Fictitious clinical case provided by the speaker.

ADT, androgen deprivation therapy; EAU, European Association of Urology; EMA, European Medicines Agency; ENZ, enzalutamide; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration.

1. XTANDI (enzalutamide). Summary of Product Characteristics; 2. XTANDI (enzalutamide). Prescribing Information; 3. Fizazi K, et al. *Ann Oncol* 2023;34:557–563;
4. EAU. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer. Last accessed: June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

2025 EAU guidelines recommend ENZ ± ADT for patients with nmHSPC with high-risk BCR

2025 EAU guidelines

6.4.8 Recommendations for second-line therapy after treatment with curative intent

✓ *Offer enzalutamide with or without ADT to M0 patients with a high-risk BCR, defined as a PSADT of ≤9 months and a PSA level of ≥2 ng/ml above nadir after RT or ≥1 ng/ml after RP with or without postoperative RT (STRONG)*

ADT, androgen deprivation therapy; BCR, biochemical recurrence; EAU, European Association of Urology; ENZ, enzalutamide; M0, non-metastatic; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy.

EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer. Available at: uroweb.org/guideline/prostate-cancer. Last accessed: June 2025.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

EMA enzalutamide Summary of Product Characteristics

4.4 Special warnings and precautions for use

Enzalutamide as monotherapy in patients with high-risk BCR nmHSPC

Results of the EMBARK study suggest that enzalutamide as monotherapy and in combination with ADT are not equivalent treatment options in patients with high-risk BCR nmHSPC.

ENZ + ADT is considered the preferred treatment option *except for cases in which the addition of ADT may result in unacceptable toxicity or risk*.

ADT, androgen deprivation therapy; BCR, biochemical recurrence; EMA, European Medicines Agency; ENZ, enzalutamide; nmHSPC, non-metastatic hormone-sensitive prostate cancer.

XTANDI (enzalutamide). Summary of Product Characteristics.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

Key considerations for treatment intensification in patients with nmHSPC

To ensure appropriate intensification of therapy, it is critical to ensure eligible patients are identified based on their disease status (tumour, PSA-DT, imaging)[1]

Both ENZ + ADT and ENZ monotherapy resulted in significantly longer MFS ($p<0.01$) compared with PBO + ADT, and did not further alter QoL[2]

It is important to consider patient preferences and their most important concerns when making treatment decisions[1]

ADT, androgen deprivation therapy; ENZ, enzalutamide; MFS, metastasis-free survival; nmHSPC, non-metastatic hormone-sensitive prostate cancer; PBO, placebo; PSA-DT, prostate-specific antigen doubling time; QoL, quality of life.

1. Speaker's own conclusions; 2. Freedland SJ, et al. *N Engl J Med* 2023;389:1453–1465.

Date of preparation: July 2025 | MAT-NL-XTD-2025-00033

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Please refer to the EMA SmPC for XTANDI™ (enzalutamide) via the following link: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf

Scan/click here for the XTANDI™ UK prescribing information

Scan/click here for the XTANDI™ NL SmPC

XTANDI is subject to medicinal prescription.
Astellas Pharma B.V., Sylviusweg 62, 2333 BE Leiden, The Netherlands.
EMA, European Medicines Agency; SmPC, Summary of Product Characteristics.
Date of preparation: July 2025 | MAT-NL-XTD-2025-00033