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MODERN RADIATION ONCOLOGY
35° RESIDENTIAL COURSE

From guidelines to 'living' practice: the role of modern integrated approach among local and systemic therapies

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Advanced Radiation Therapy

Disclosures

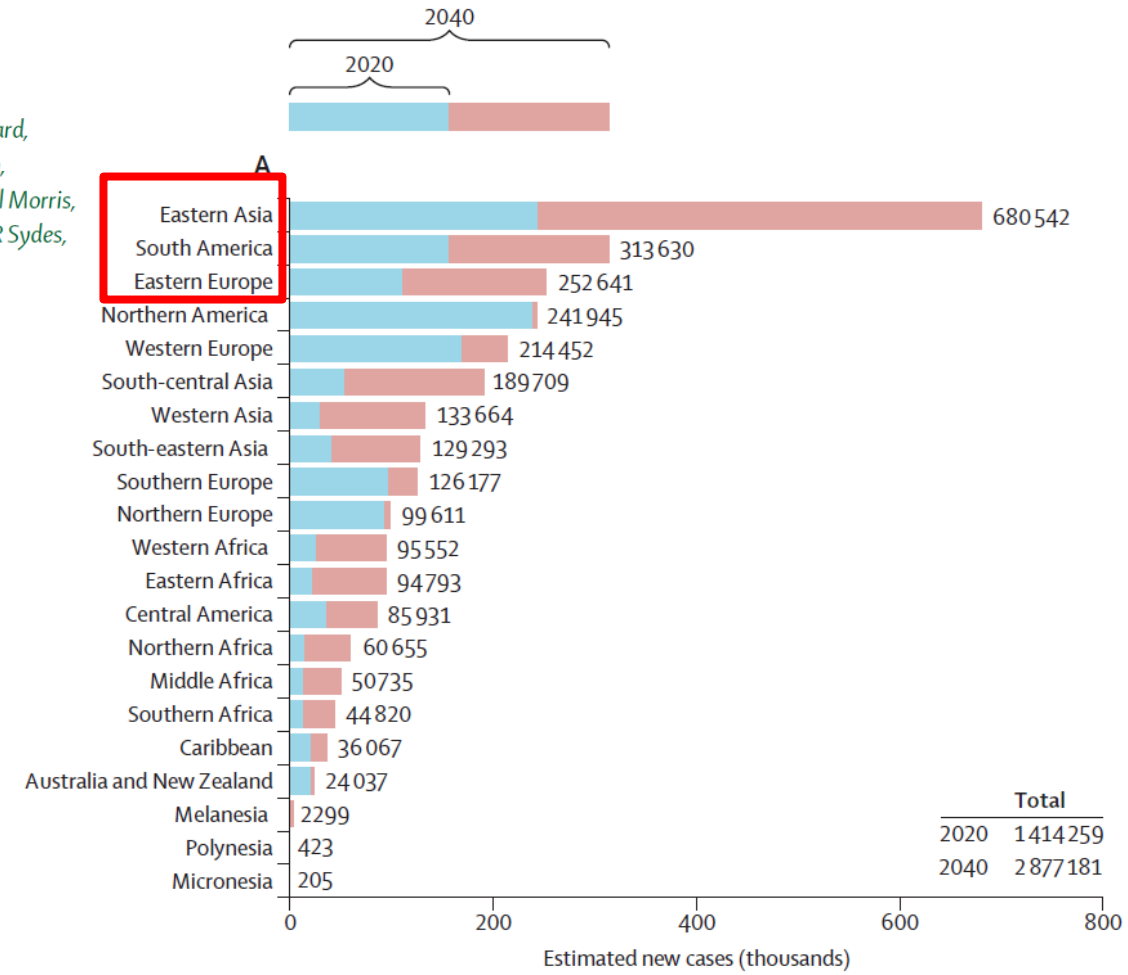
- Honoraria - Travel costs: Janssen, Amgen, Ferring, Debiopharm, Bayer, Astellas, Recordati, Telix, MVision
- Research Grants: Varian Medical Systems, Debiopharm
- Advisory Boards: Janssen, Accord, Astellas

The prostate cancer reality

The *Lancet* Commission on prostate cancer: planning for the surge in cases

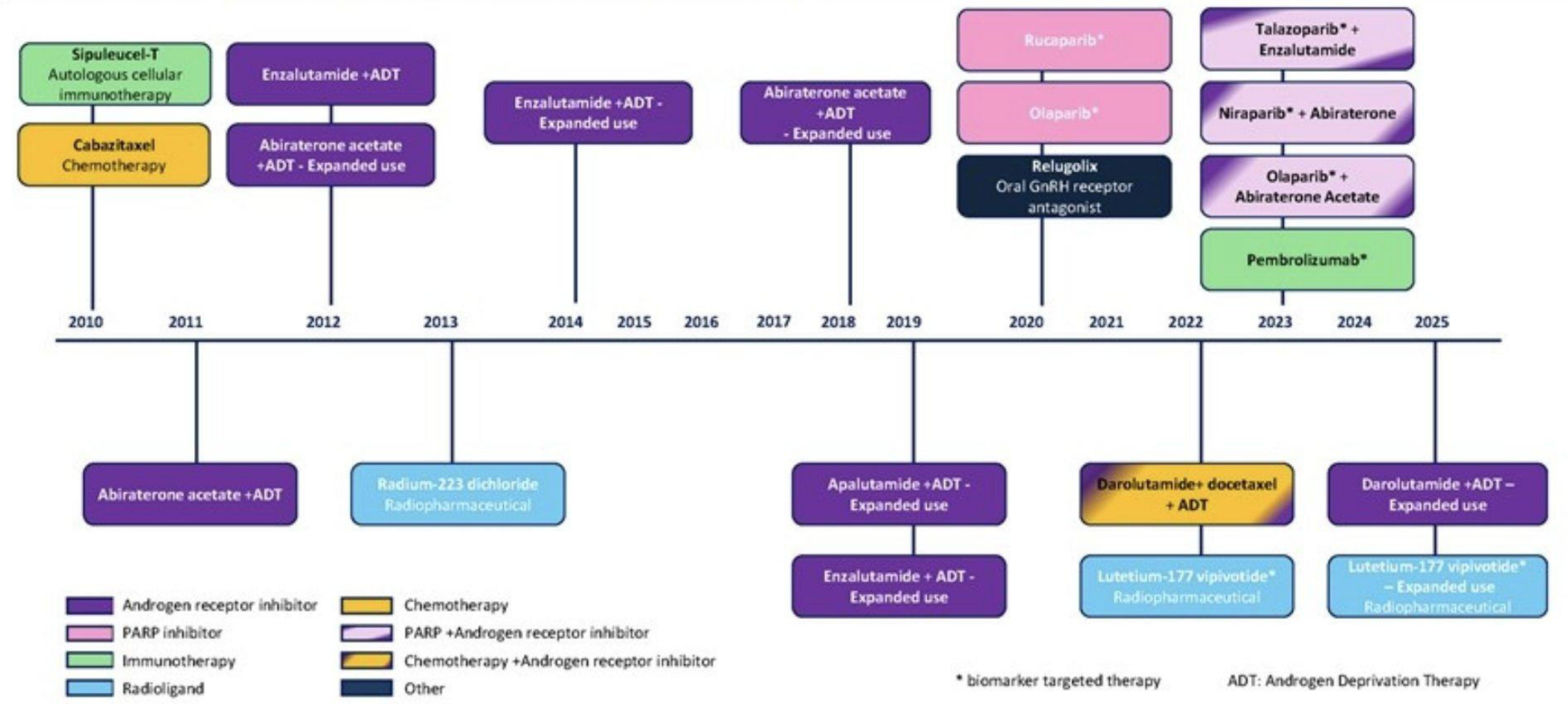
Nicholas D James, Ian Tannock, James N'Dow, Felix Feng, Silke Gillessen, Syed Adnan Ali, Blanca Trujillo, Bissan Al-Lazikani, Gerhardt Attard, Freddie Bray, Eva Compérat, Ros Eeles, Omolara Fatiregun, Emily Grist, Susan Halabi, Áine Haran, Daniel Herchenhorn, Michael S Hofman, Mohamed Jalloh, Stacy Loeb, Archie MacNair, Brandon Mahal, Larissa Mendes, Masood Moghul, Caroline Moore, Alicia Morgans, Michael Morris, Declan Murphy, Vedang Murthy, Paul L Nguyen, Anwar Padhani, Charles Parker, Hannah Rush, Mark Sculpher, Howard Soule, Matthew R Sydes, Derya Tilki, Nina Tunariu, Paul Villanti, Li-Ping Xie

- Prostate cancer is the **commonest male cancer** in 112/185 countries and is **15%** of **all male cancers**
- New cases will rise annually **from 1.4 million in 2020** to approximately **3 millions in 2040**

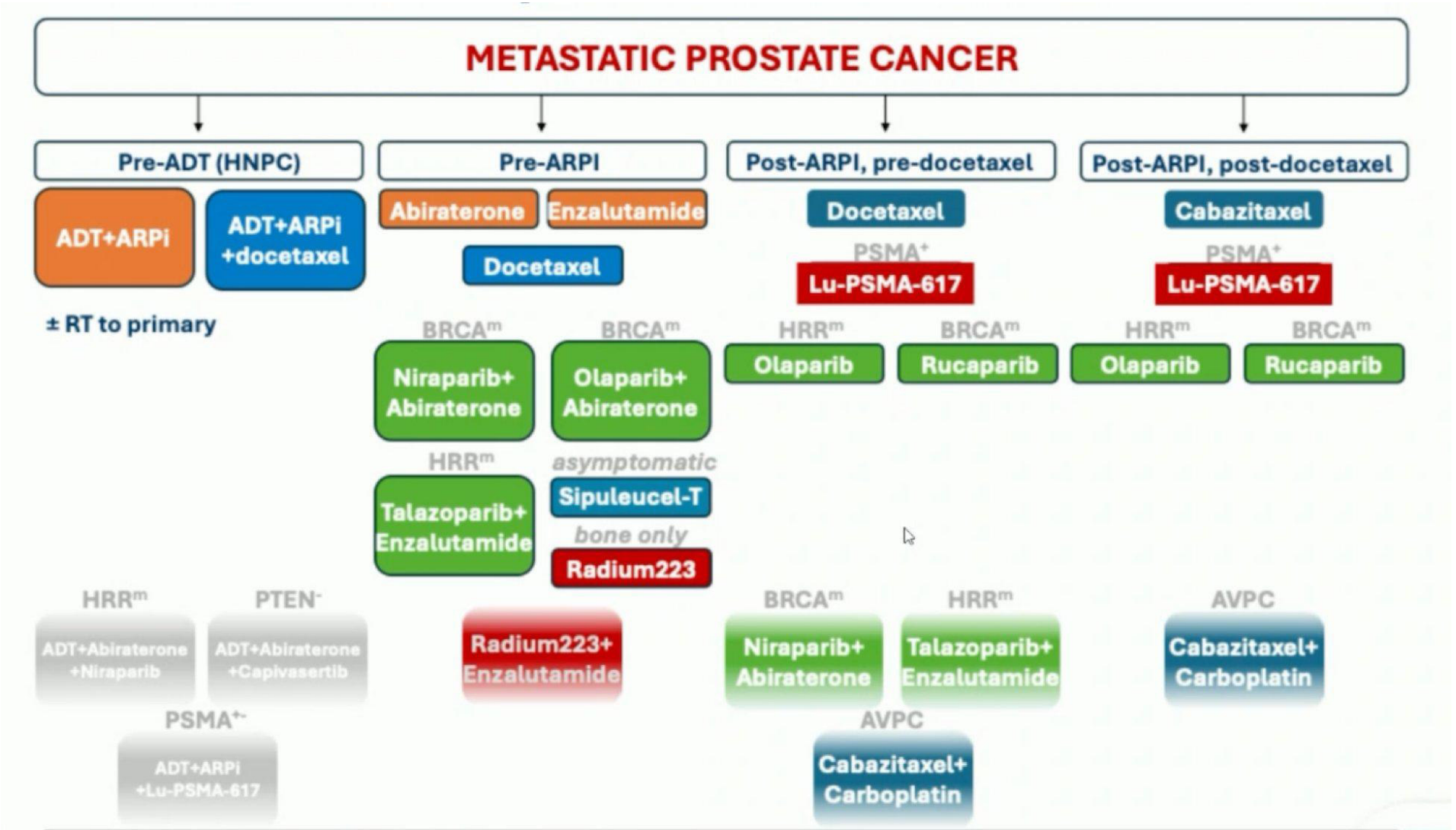


James N et al. Lancet 2024

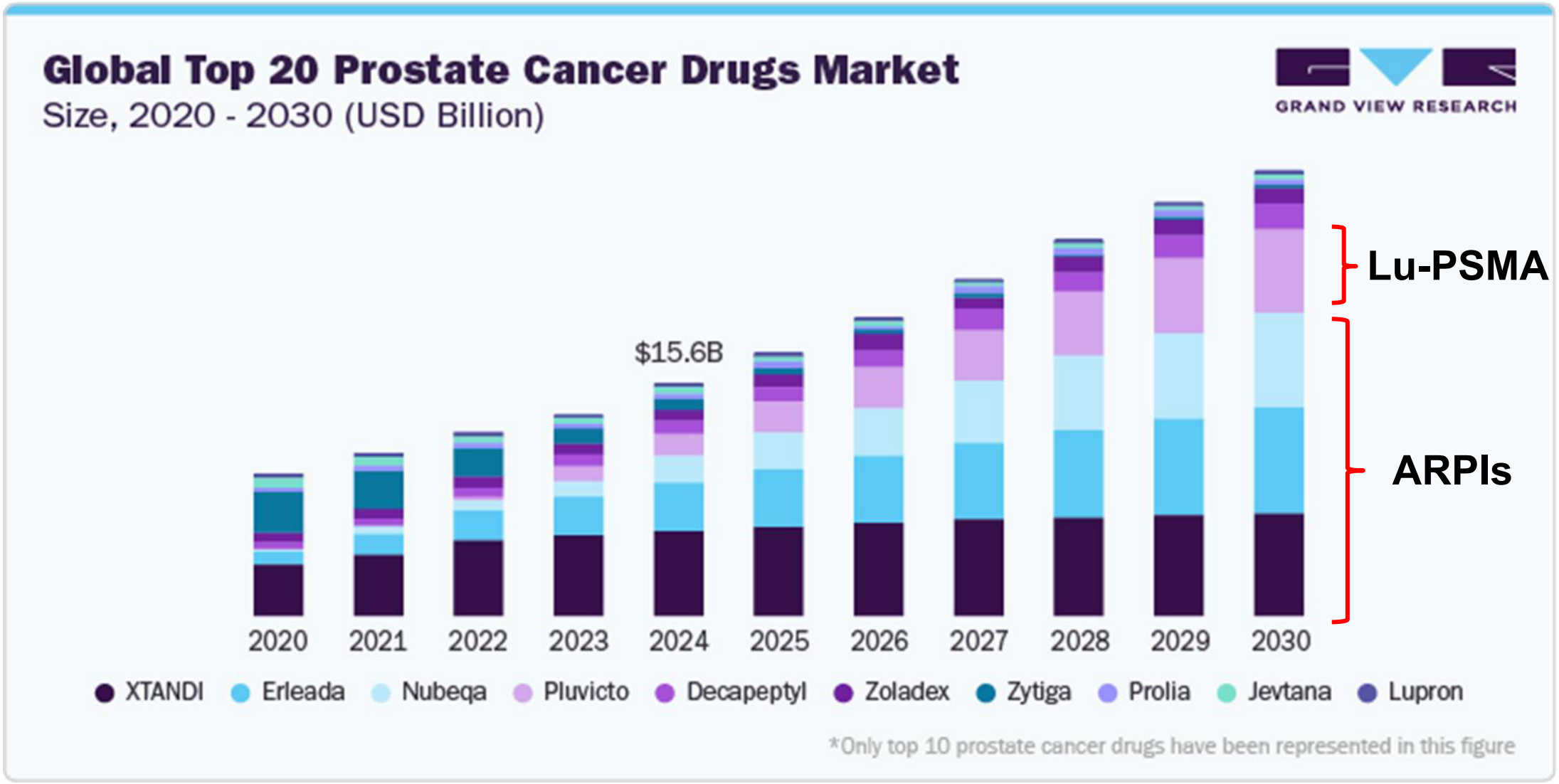
The evolving treatment landscape for prostate cancer



The treatment choices in metastatic prostate cancer



Expanding treatment options means rising costs



https://www.grandviewresearch.com/market-trends/top-20-prostate-cancer-drugs-market#

The mHPSC example: outcome benefit *vs* toxicity risk

- The **current standard of care** for metastatic hormone-sensitive prostate cancer (**mHSPC**) combines **ADT with an ARPI, with or without docetaxel and/or prostate radiotherapy**.

- This approach improves overall survival by about **30%**, but increases toxicity risks, including:

🫀 - **Cardiovascular events:** RR 1.71 (95% CI 1.29–2.27) and grade 3–4 hypertension RR 1.53 (95% CI 1.19–1.97).

🤸 - **Falls and fractures:** grade ≥3 falls RR 1.6; all-grade fractures RR 1.59; grade ≥3 fractures RR 1.71.

🧠 - **Cognitive effects and fatigue:** cognitive toxicity RR 2.10 (95% CI 1.30–3.38); fatigue RR 1.34 (95% CI 1.16–1.54).

💲 - **This undoubtedly increases the healthcare costs!**

Wala J et al. JCO 2023; Rizzo A et al. Expert Opin Drug Metab Toxciol 2021; Myint ZW et al. JAMA Netw Open 2020; Nowakowska MK JAMA Oncol 2023

Goals of **sustainable** and **equitable** oncologic treatments

1. Prolong **quantity** of life
2. Improve **quality** of life
3. Increase **cost-effectiveness**

1. Need to demonstrate **equivalent** or **better outcome** compared to other strategies
2. Need to have a **better toxicity** profile
3. Need to **limit** the healthcare **costs**

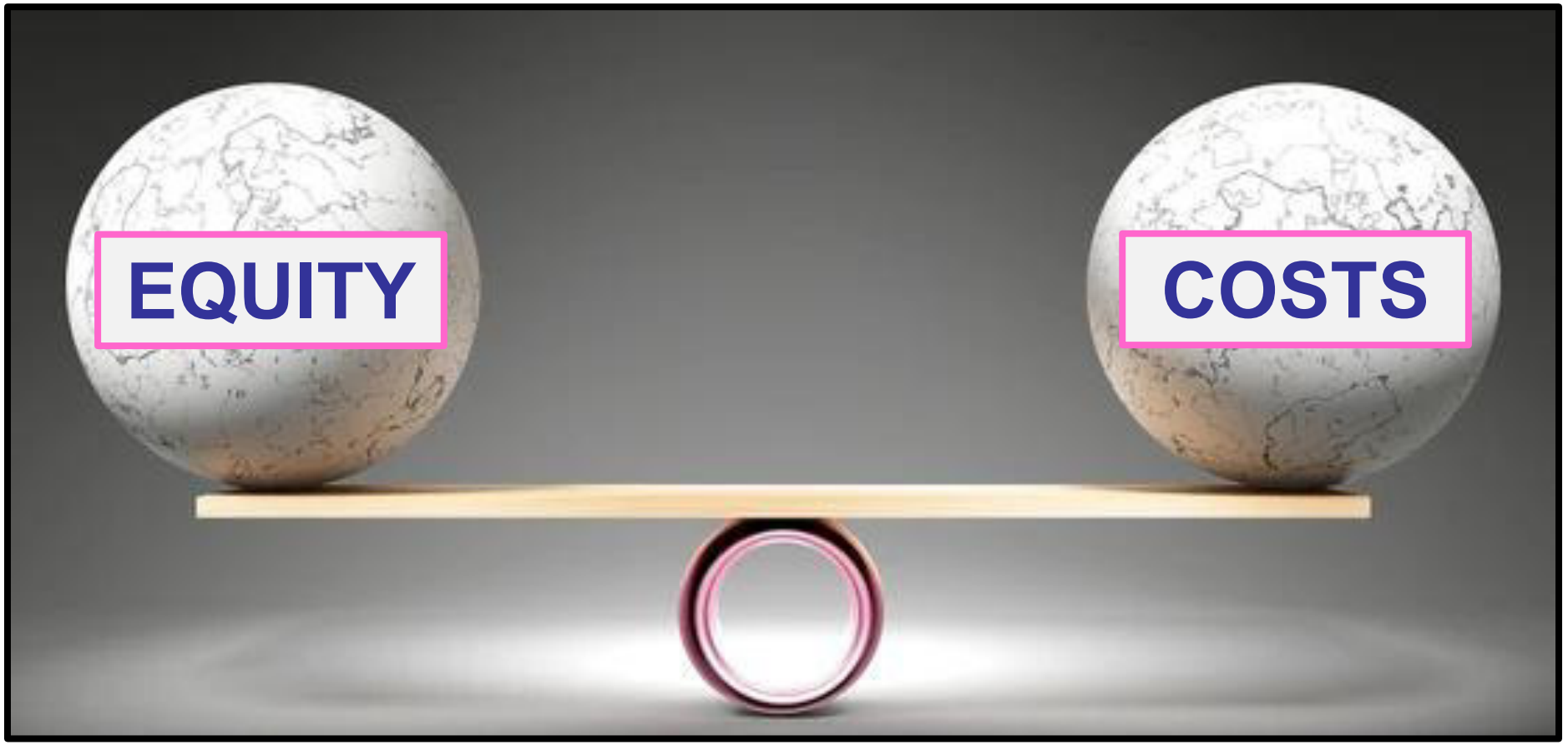
The equity challenge in prostate cancer treatment

- **Geographical disparities:** Access to ARPIs, PARP-inhibitors and PSMA agents varies significantly between high-income countries *vs* low- and middle-income countries.

- **Economic disparities:** Health systems with limited budgets may prioritize cost-effective population strategies (ADT ± docetaxel) over precision options.

- **Implementation gaps:** Even within high-income countries, differences exist between academic centers and community settings in testing and treatment delivery

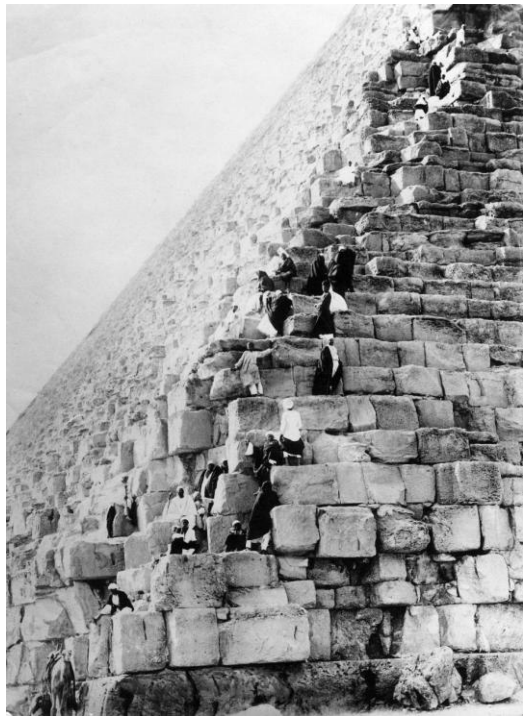
Equity *vs* cost-effectiveness: the core dilemma

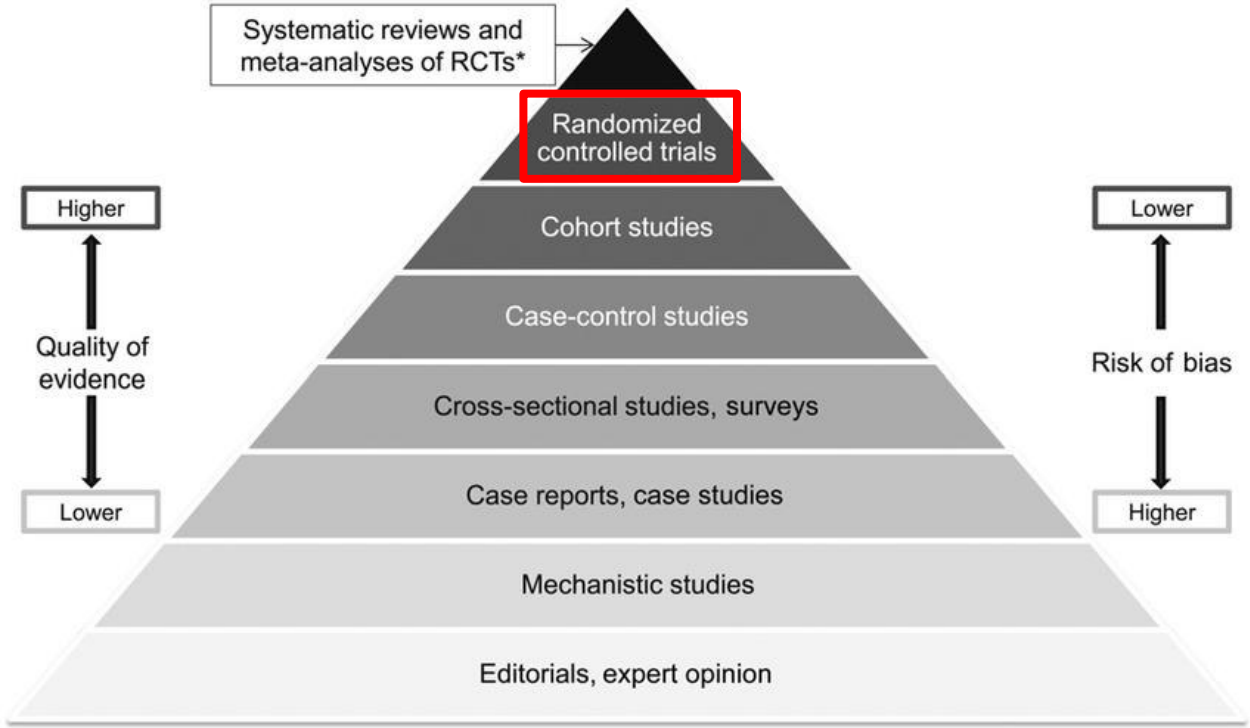


*How can **radiation therapy** contribute to achieving **value-based care** while promoting **equitable access** to **high-quality treatment** standards?*

Climbing the pyramid of evidence for treatment decision

Overall survival assessment in cancer drug trials: a luxury or a necessity?

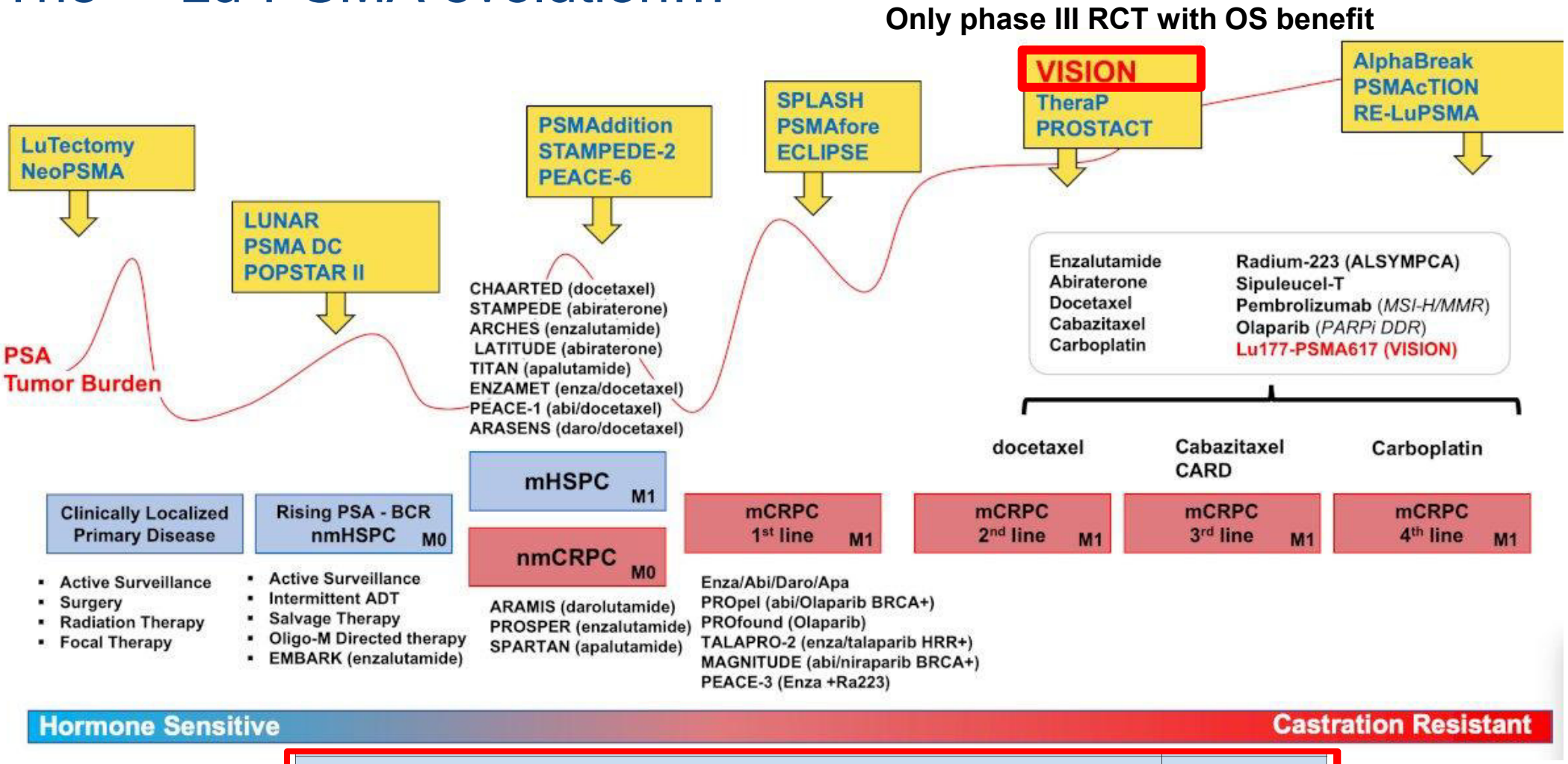




Overall survival and quality of life are the most important clinical endpoints to confirm the potential benefit of a therapeutic intervention (FDA guidance 2025)

Stevens SX et al. Lancet Oncol 2025

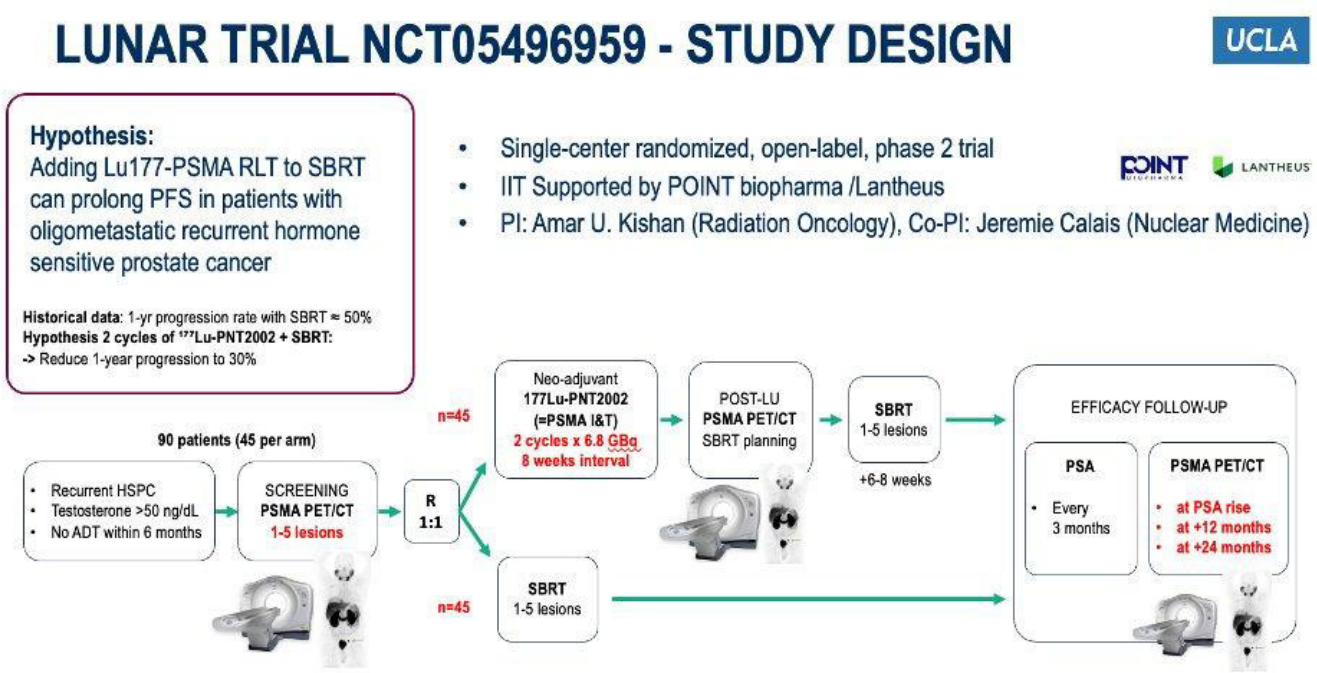
The ^{177}Lu-PSMA evolution…

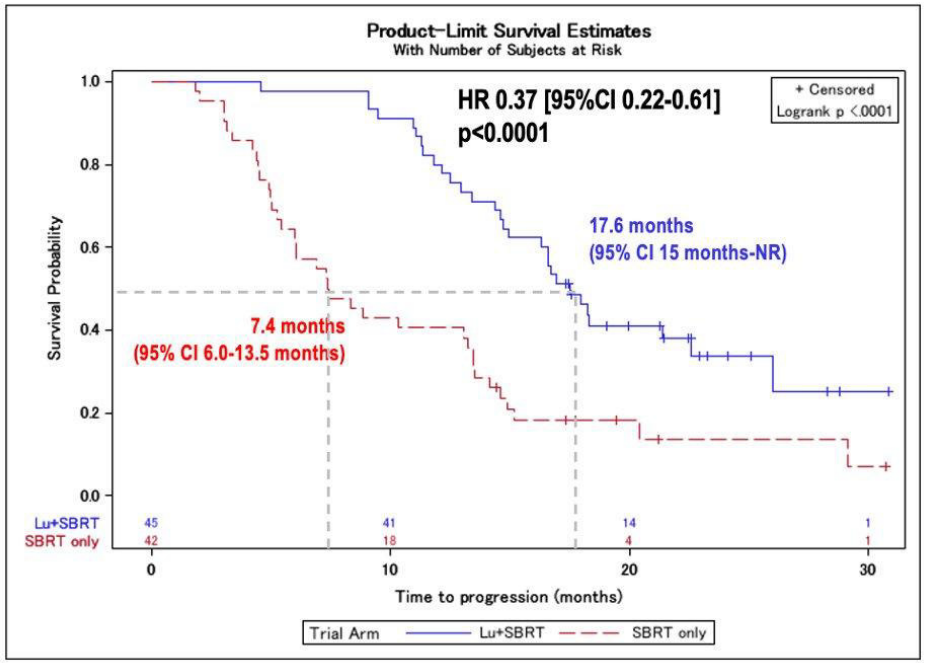


Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

Fendler W. EAU 2025

Do we need to add ^{177}Lu-PSMA to SBRT in oligometastatic HSPC?





SBRT + ^{177}Lu-PSMA improves PFS from 7.4 to 17.6 months compared to SBRT alone, with ADT-free survival extending from 14.1 to 24.3 months

Kishan A et al. ASTRO 2025

Lu-PSMA and SBRT: a rapidly evolving field

Unlocking New Therapeutic Strategies in Oligometastatic Prostate Cancer with Radioligand and Metastasis-directed Radiation Therapy

Salvatore Cozzi[a,b], *Camille Roukoz*[a], *Thomas Zilli*[b,c,d,*]

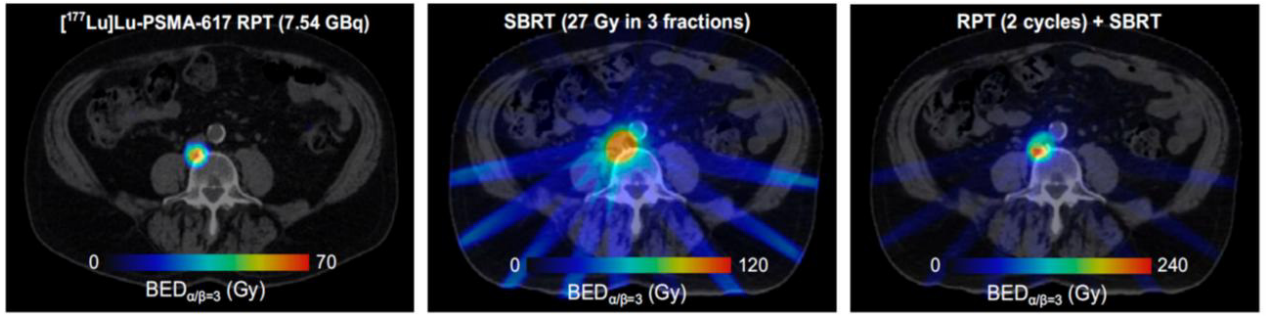


Table 2 – Summary of the main ongoing trials on combined radioligand therapy and SBRT in omHSPC

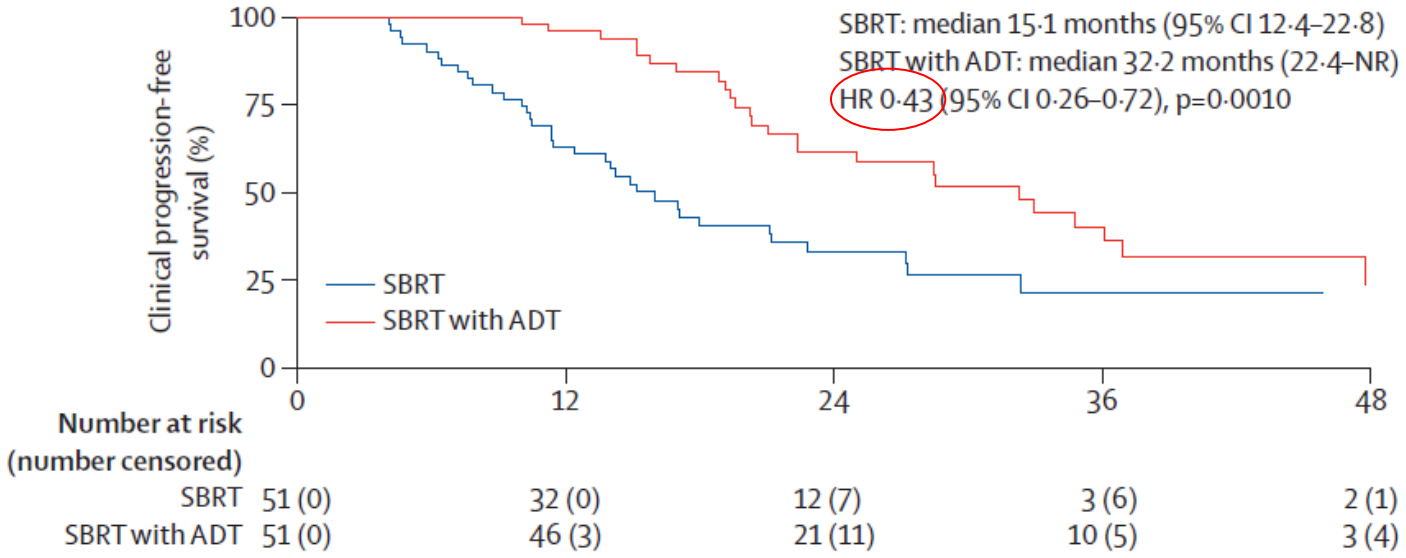
Trial	Sponsor	Year started	Design	Pts	Population	Arms		Primary endpoint
						Intervention	Control	
POPSTAR II NCT05560659	Peter MacCallum Cancer Centre	2023	Phase 2 Randomized, two arms	92	Metachronous omHSPC (≤ 5 mets on PSMA PET)	2 cycles of ^{177}Lu-PSMA-I&T with SBRT between cycles 1 and 2	SBRT alone	PFS (biochemical or clinical)
NCT05079698	Memorial Sloan Kettering Cancer Center	2023	Prospective Single institution Pilot study	6	MTC omHSPC (≤3 mets on PSMA PET)	Neoadjuvant ^{177}Lu-PSMA-I&T (2 cycles) followed by SBRT	–	Feasibility
ProstACT TARGET NCT05146973	Telix	2022	Phase 2, single arm Prospective Multicenter	5	MTC omHSPC (≤5 mets)	SBRT + adjuvant ^{177}Lu-J591 (2 cycles)	/	PSA-based PFS
PSMA-DC NCT05939414	Novartis	2024	Phase 3 Randomized, two arms Multicenter	450	MTC omHSPC (≤5 mets on PSMA PET)	SBRT + adjuvant ^{177}Lu-PSMA-617 (4 cycles)	SBRT alone	MFS

MTC = metachronous; mets = metastases; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SBRT = stereotactic body radiotherapy; da-SBRT = dose-adapted SBRT; PFS = progression-free survival; ADT = androgen deprivation therapy; MFS = metastasis-free survival; PSA = prostate-specific antigen; omHSPC = oligometastatic hormone-sensitive prostate cancer.

Cozzi S et al. Eur Urol Focus 2025

SBRT with 6-months ADT: a safe alternative?

ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial



	SBRT group (n=51)		SBRT with ADT group (n=51)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
SBRT related (n=2)				
Diarrhoea	1 (2%)	0	0	0
Left ureter stenosis	0	0	0	1 (2%)
ADT related				
Hot flushes	..	..	22 (43%)	0
Asthenia	..	..	8 (16%)	0
Insomnia	..	..	4 (8%)	0
Muscular pain	..	..	2 (4%)	0

Data are n (%). ADT=androgen deprivation therapy. SBRT=stereotactic body radiotherapy. Maximum toxicity grade reported according to the Common Terminology Criteria for Adverse Events.

Table 3: Adverse events by grade and treatment group

Median time to testosterone recovery: 9 months (IQR 9-12)

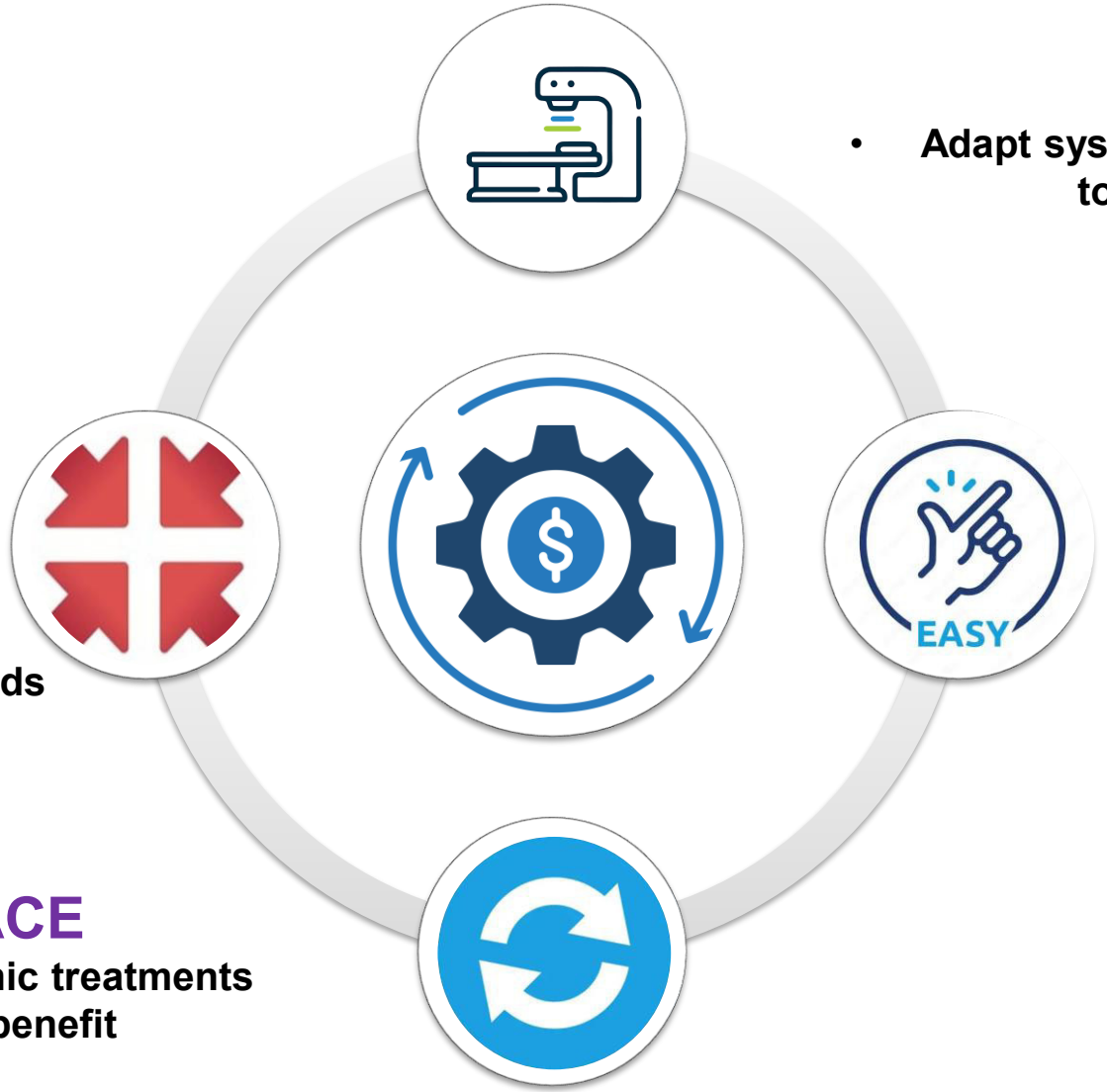
SBRT + 6-mo ADT improves PFS compared to SBRT alone, achieving a clinical benefit comparable to Lu-PSMA therapy (HR 0.43 vs. 0.37)

Marvaso G et al. Lancet Oncol 2025

The equity *vs* cost-effectiveness conundrum

⚖️ **Treatment**	Duration	Approx. Total Cost	Notes
☢️ **2 cycles Lu-PSMA**	~ 8 weeks	**€50,000 – €70,000** Approximate cost per cycle: €25,000 – €35,000	High cost due to radiopharmaceutical & nuclear medicine infrastructure
💉 **ADT (6 months)**	6 months	**€1,000 – €3,000** Leuprolide depot 22.5 mg q3mo × 2: €800 – €1,200	Widely available, reimbursed in most health systems

Ways to **improve cost-efficiency** with radiotherapy



INDIGENIZE

- **Adapt systemic therapies and radiotherapy to local contexts and resources**

REDUCE

- **Duration of systemic therapy**
- **Systemic therapy doses**
- **Number of RT fractions**
- **Travel and accommodation needs**

SIMPLIFY

- **Simple" approaches are more reproducible**
- **Streamlined SBRT protocols**
- **Accessible, easy-to-implement biomarkers**

REPLACE

- **Complex systemic treatments lacking proven benefit**

Indigenize & **Simplify**: ultra-hypofractionated radiotherapy

1200 men with intermediate risk prostate cancer with 1 or 2 risk factors
- T1c – T3a
- Gleason ≥ 7
- PSA ≤20 ng/mL

- No ADT

Randomised 1:1

Conventional RT
78 Gy in 39 fx
7.5 weeks

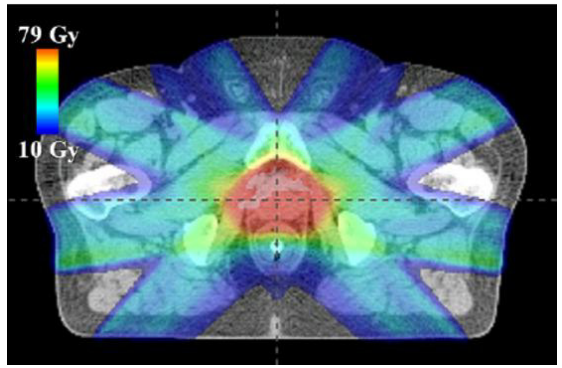
Extreme Hypofx
42.7 Gy in 7 fx
2.5 weeks

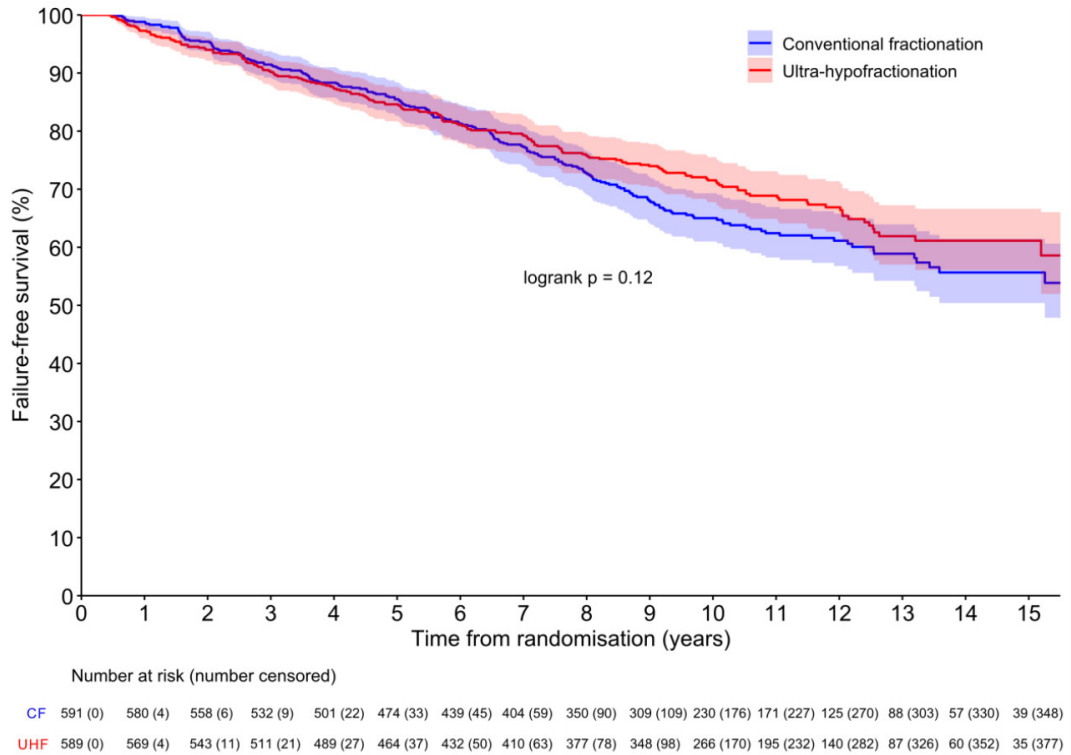
Endpoints
Primary:
- Biochemical/clinical failure

Secondary endpoints included:
- Overall and prostate cancer-specific survival
- CRO – acute and late
- PRO – acute and late

Non inferiority design
Image guided RT (80% 3DCRT- 20% VMAT)

3D-CRT with IGRT: 80%

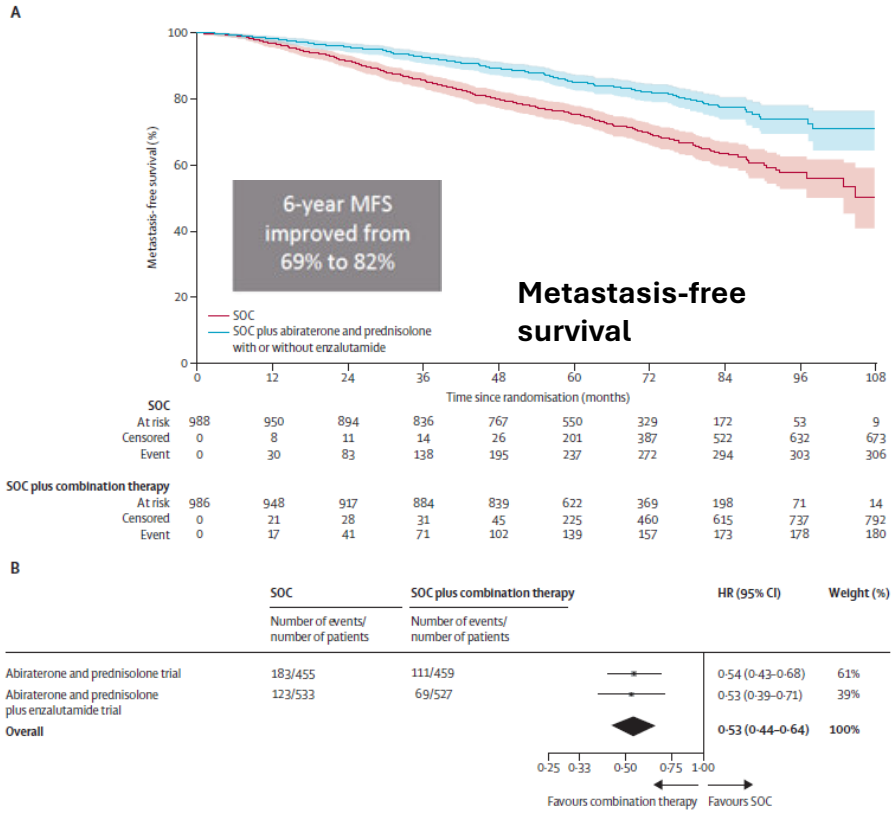


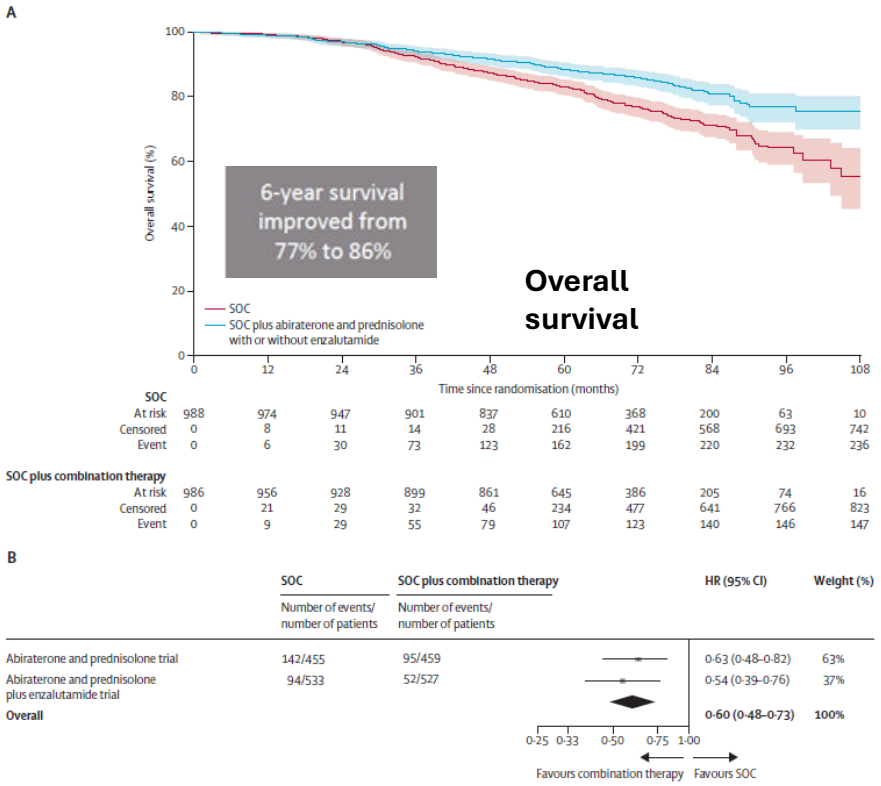


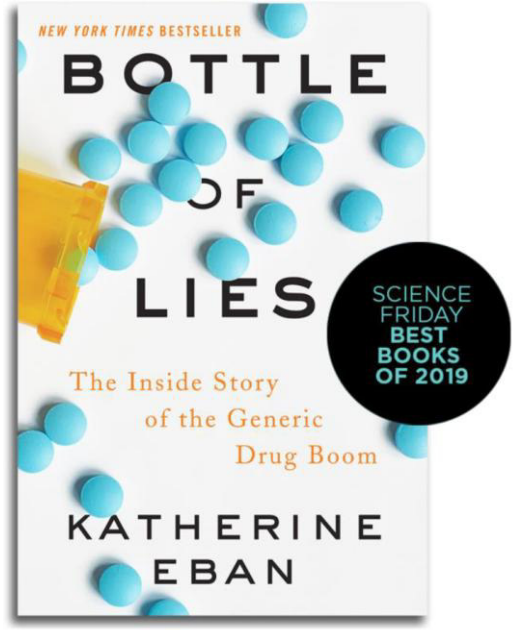
Ultra-hypofractionated prostate EBRT in 7 fx delivered with 3D-CRT techniques is non-inferior to conventional fractionation using 78Gy/39 fx

Widmark A et al. Lancet 2019; Thellenberg-Karlsson, Radioth Oncol suppl. ESTRO 2025

Intensify in high-risk PCa and **Replace** with generic drug?





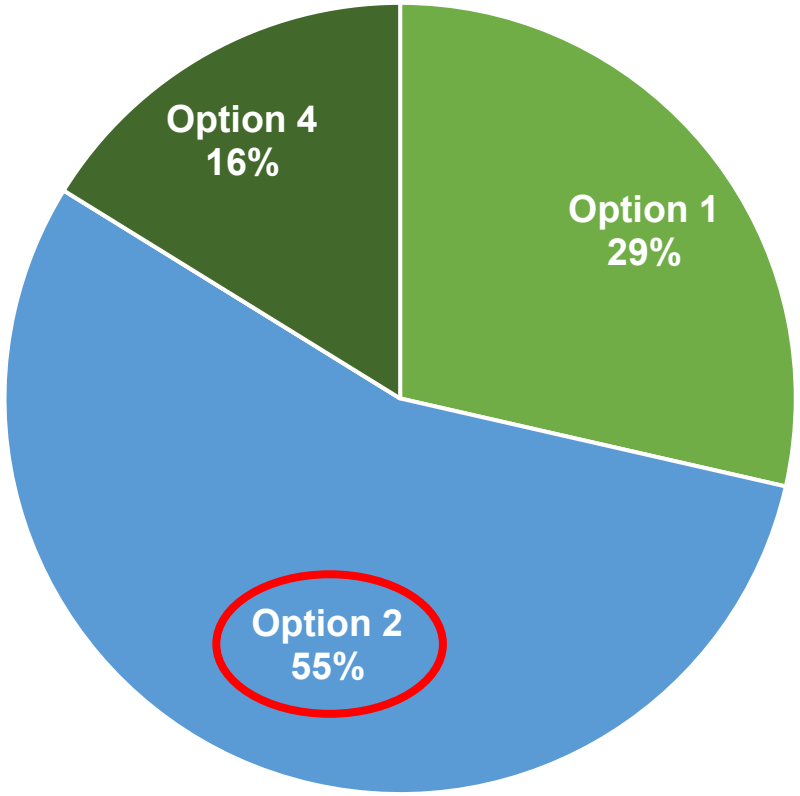


Two years of abiraterone added to long-term ADT improves significantly MFS and OS in very high-risk and cN1 prostate cancer patients (potential for generic abiraterone?)

Attard G et al. Lancet 2022

4. In the majority of patients with very high-risk localised prostate cancer (NCCN definition) and NOT high-risk localised/locally advanced prostate cancer (STAMPEDE definition) N0 M0 on next-generation imaging, what is your recommended treatment?

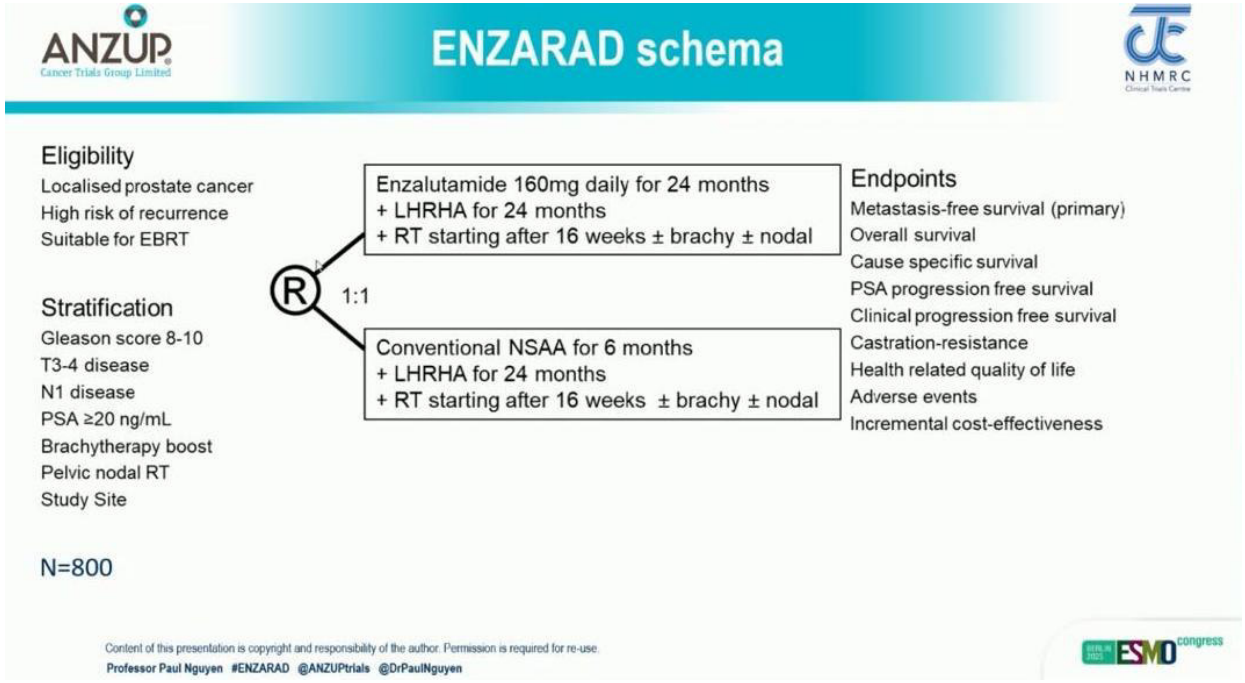
1. Radiation plus long-term ADT alone
2. Radiation plus long-term ADT plus abiraterone for 2 years
3. Radiation plus long-term ADT plus docetaxel
4. Surgery, recognising that it may be part of a multimodality approach
5. Abstain/unqualified to answer

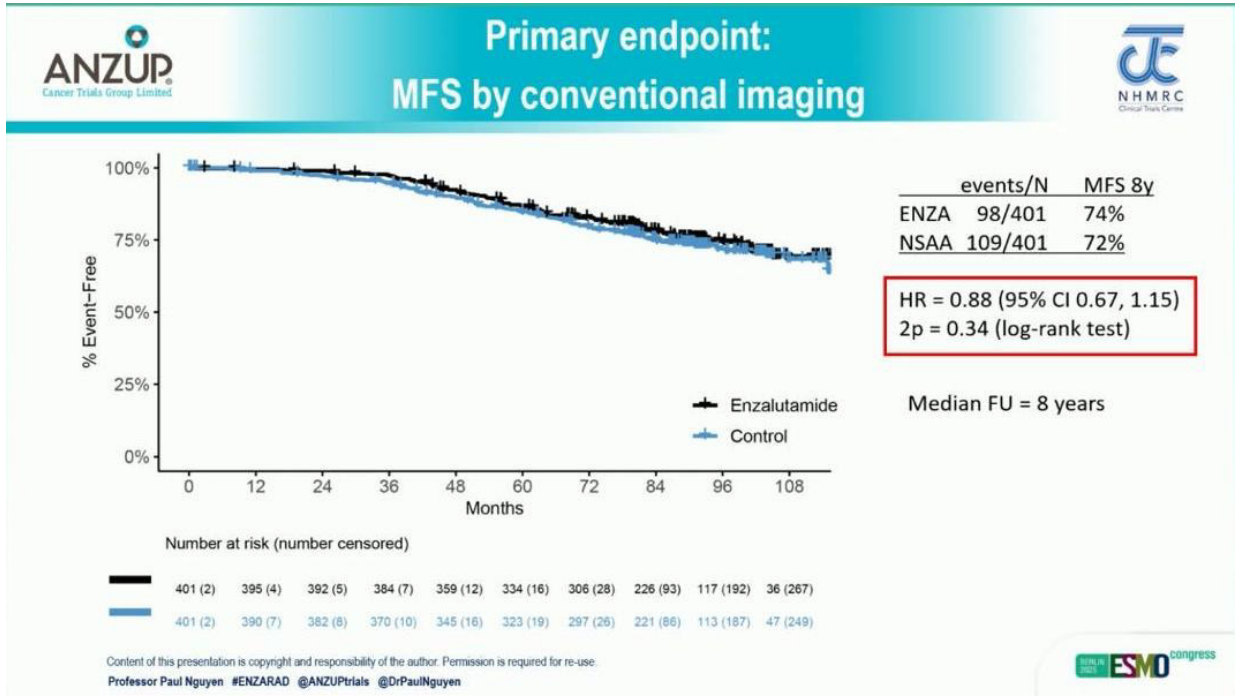


Option	Votes
Option 1	30
Option 2	58
Option 3	0
Option 4	17
Abstain	1

Gillessen S et al. Eur Urol 2025

Reduce systemic therapies in high-risk PCa: patient selection





Most high-risk prostate cancer patient receiving high-dose radiation and 2 years of ADT do not need intensification with Enzalutamide

Nguyen P et al. ESMO 2025

Not all high-risk patients are the same

ENZARAD Benefit in cN1 is consistent with STAMPEDE but ENZARAD enrolled more favorable risk patients

	STAMPEDE (abiraterone)	ENZARAD (enzalutamide)
HR for MFS in cN1	0.49	0.43
HR for MFS in all patients	0.53 (p<0.0001)	0.88 (p=.34)
cN1	39%	11%
Median PSA	35	14
Clinical T3-4	92%	47%
Received radiation	82%	100%
Gleason 8-10	79%	89%

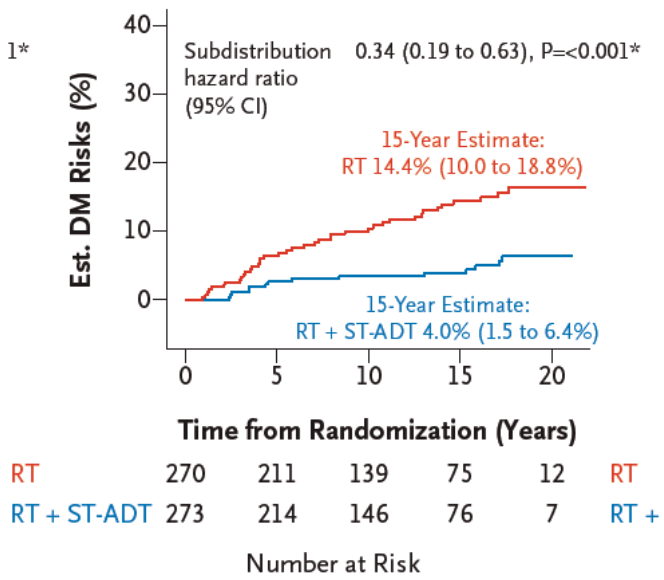
Reduce systemic therapies: new AI-derived biomarkers

Artificial intelligence-based digital pathology predictive model

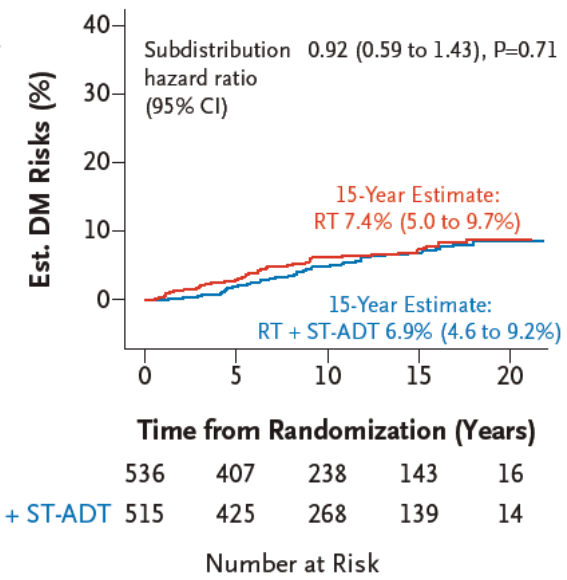
NRG/RTOG 9408 RT +/- short course ADT – results in model positive and model negative populations

Distant Metastases Risk

Predictive model positive

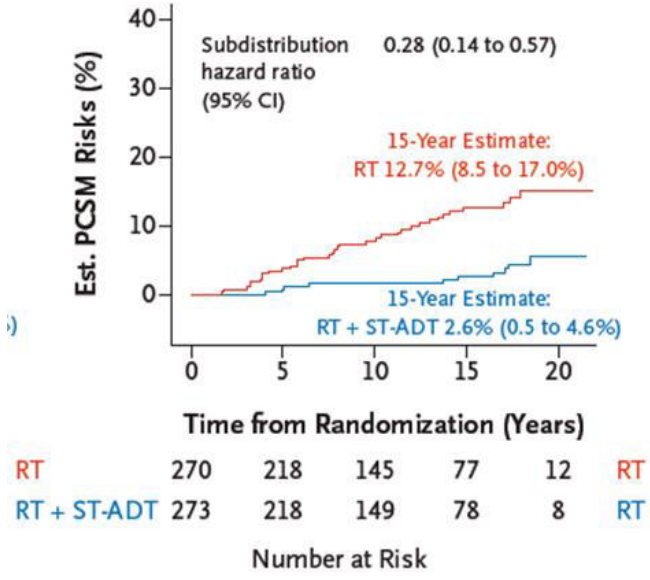


Predictive model negative

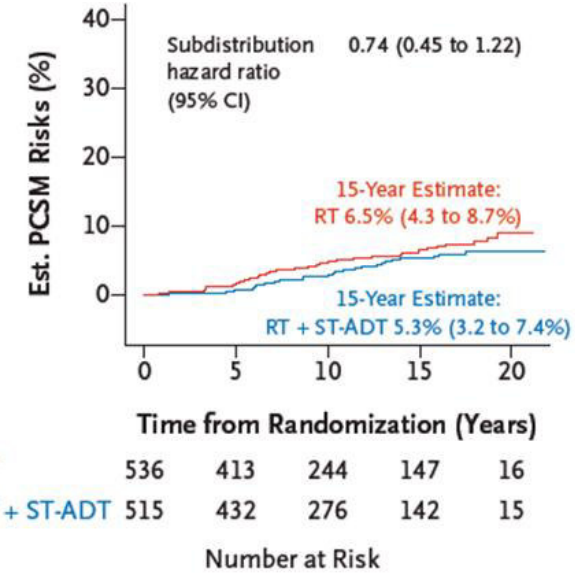


Prostate Cancer Mortality Risk

Predictive model positive



Predictive model negative

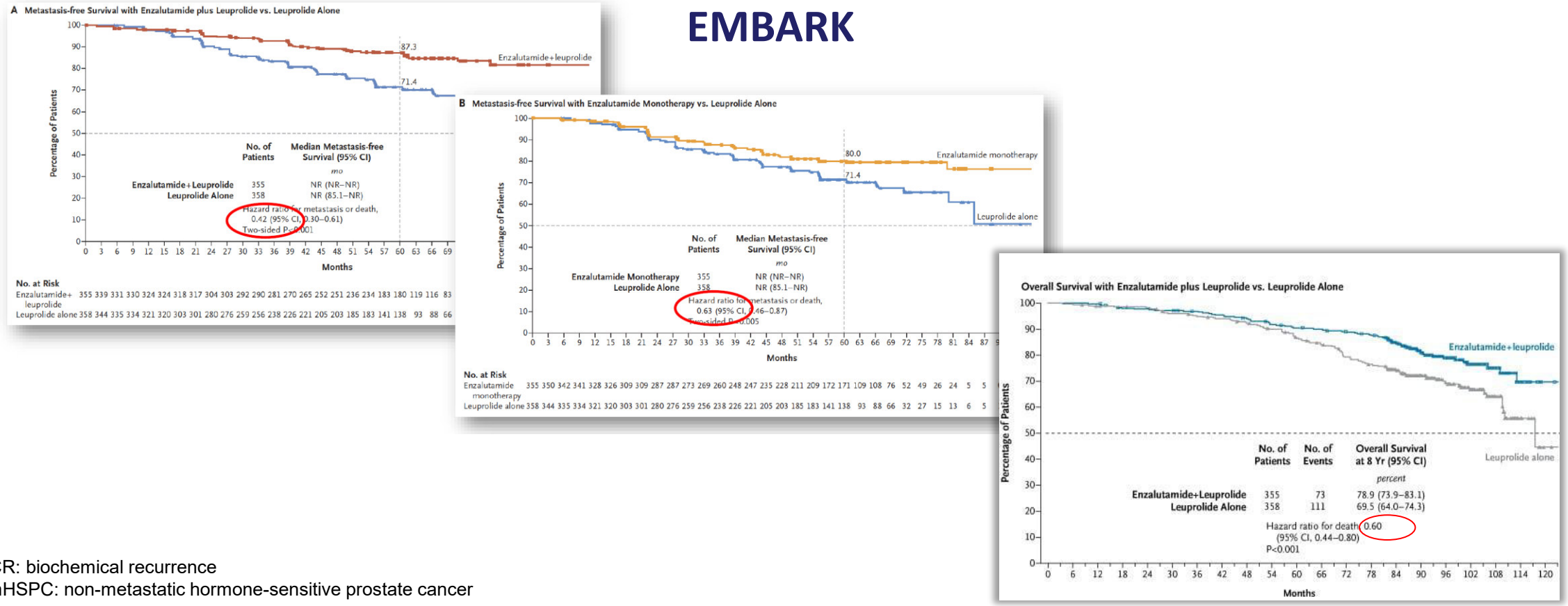


Only 34% of patients (model positive patients) benefit from short-term ADT to reduce the risk of distant metastases

Spratt DE et al. NEJM Evid 2023

Reduce systemic therapies **duration** in high-risk BCR nmHSPC

EMBARK



BCR: biochemical recurrence
nmHSPC: non-metastatic hormone-sensitive prostate cancer

Intermittent enzalutamide and leuprolide than with leuprolide alone improves OS among patients with prostate cancer with high-risk biochemical recurrence

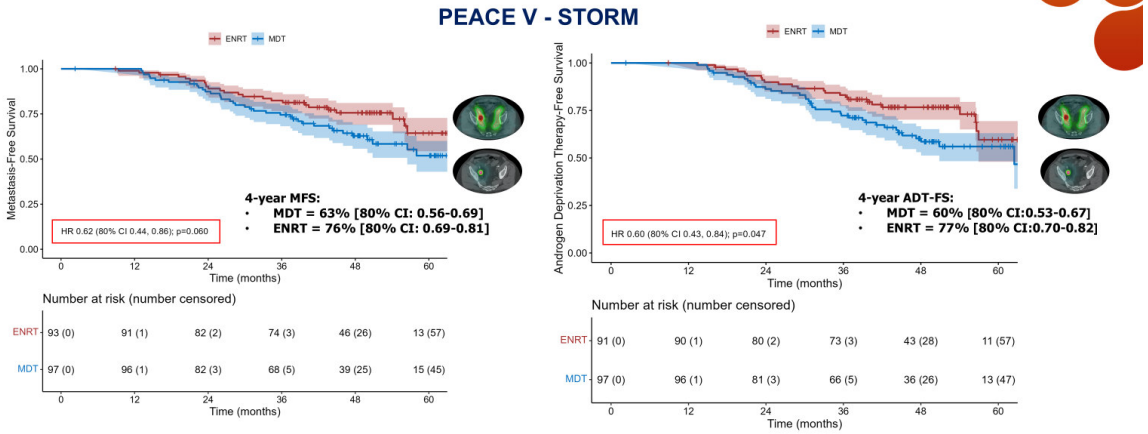
Freedland S et al. NEJM 2023; Shore N et al NEJM 2025

Replace long-term systemic therapies **with radiotherapy**

Should We Embark on "EMBARK"? Reassessing the Role of Radiotherapy and Androgen Receptor Pathway Inhibitors in the Era of Next-generation Imaging

Giulia Marvaso [a,b,†,], Giulio Francolini [c,†], Vérane Achard [d,e], Alfonso Gomez-Iturriaga [f,g], Finbar Slevin [h,i], Thomas Zilli [j,k,l,‡], Piet Ost [m,n,‡], on behalf of the Urology Focus Group of the European Society for Radiotherapy and Oncology [§]*

Loco-regional PET positive nodal disease



In oligorecurrent PSMA detected nodal disease, elective nodal RT combined with 6 mo ADT improves DMFS, loco-regional control and ADT-free survival compared to MDT

Ost P, Zilli T et al. Lancet Oncol 2025

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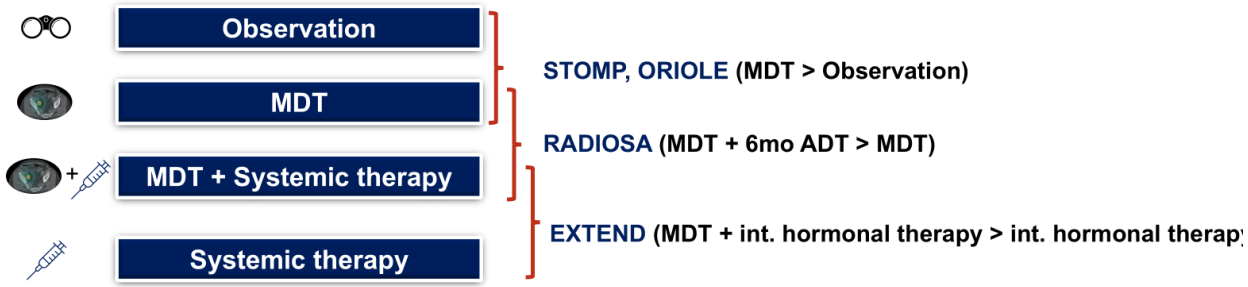
Oligometastatic disease: the clinical evidence



Combination of MDT with systemic therapy delays progression and improves clinical outcome compared to observation, MDT alone or systemic therapy alone

Ost et al. JCO 2018 – ASCO GU 2020; Philips R et al. JAMA Oncol 2020; Marvaso G et al. Lancet Oncol 2025; Tang C et al. JAMA Oncol 2023

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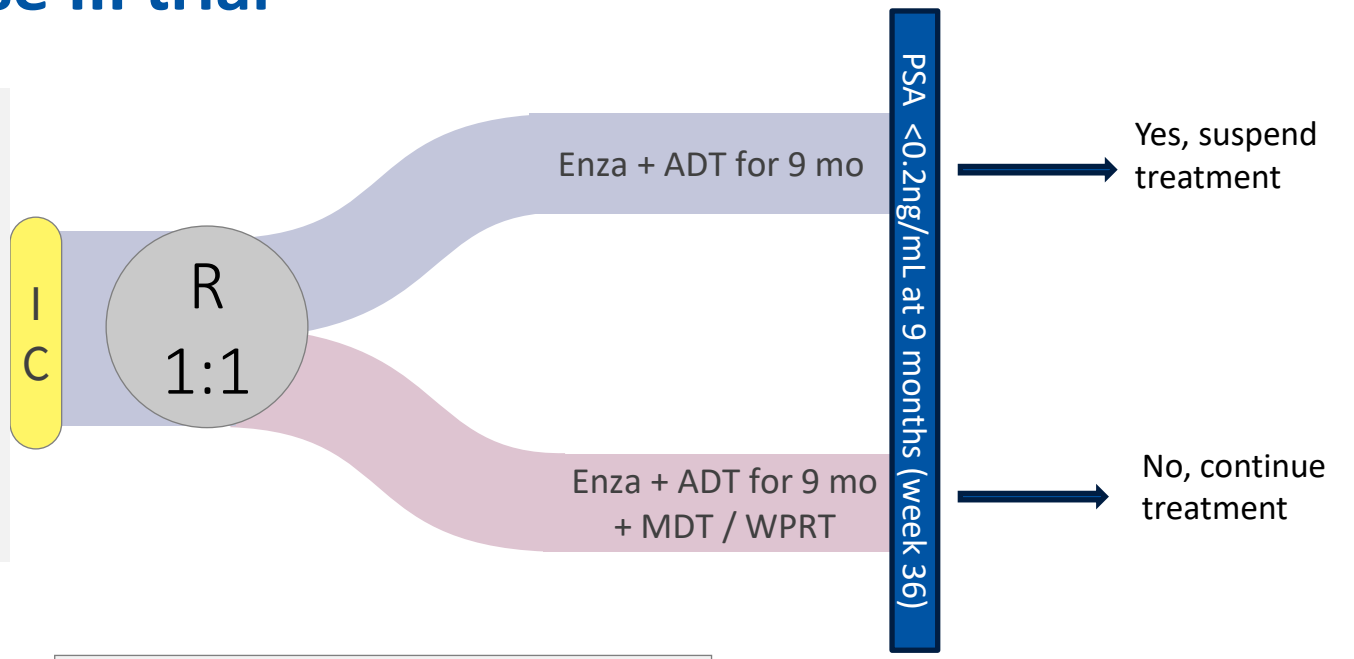
In selected high-risk BCR patients radiotherapy and metastasis-directed therapy may delay progression and improve clinical outcome and quality of life

Marvaso G et al. Eur Urol 2025; Zilli T. personal slides 2025

Reduce systemic therapies in high-risk BCR **with SBRT**?

ESCALATE-RT phase III trial

High-risk hormone-sensitive prostate PCa
- PSA ≥ 0.2 ng/mL after RP± postoperative RT or ≥ 2 ng/mL after RT
- PSADT ≤ 9 months
- Testosterone > 150 ng/dL
- On PSMA PET/CT restaging presence of:
  - 1 to 5 metastases that are amenable to MDT (M1) ± pelvic nodes (N1)



Time before to first restart of treatment

- PSA ≥ 0.2 ng/mL at week 36
- For patients in the off-period, a rise of PSA to ≥ 5 ng/mL after primary RT or to ≥ 2 ng/mL after RP ± postoperative RT
- For patients in the off-period with rising PSA < 5 ng/mL after primary RT or < 2ng/mL after RP ± postoperative RT, the investigator decision to restart treatment*

Stratification factors:
- Previous pelvic radiotherapy or not
- PSA doubling time (≤3 mo vs. > 3 to ≤ 9 mo)

Primary endpoint:
Time to first re-initiation of treatment

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

PCa: prostate cancer
PSA: prostate-specific antigen
RP: radical prostatectomy
RT: radiotherapy
PSADT: PSA doubling time
ADT: androgen deprivation therapy
WPRT: whole pelvis radiotherapy
MDT: metastasis-directed therapy

PI: Zilli T, Tombal B, Ost P, Gillessen S

Istituto Oncologico della Svizzera Italiana
Oncology Institute of Southern Switzerland

Reduce systemic therapies: the value of PSA nadir

On-Treatment Serum Prostate Specific Antigen (PSA) and Metastatic Burden at Treatment Start: Landmark Analysis of 7129 Patients Starting Long-Term Androgen Deprivation (ADT) and Randomised in the **STAMPEDE** Platform Protocol

Figure 1. Landmark Kaplan–Meier analysis of OS in the metastatic cohort, stratified by PSA level at 24 weeks post-randomization.

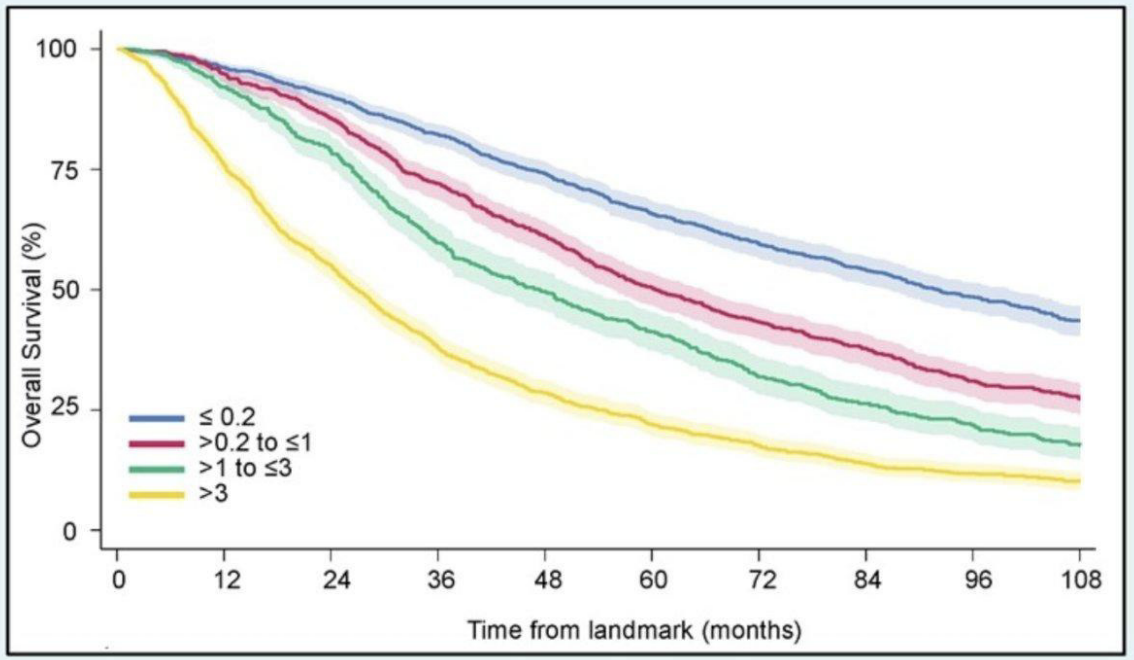


Table 2. 96-month survival rates of patients randomised to abiraterone +/- enzalutamide (PSA categories measured at 24 weeks)

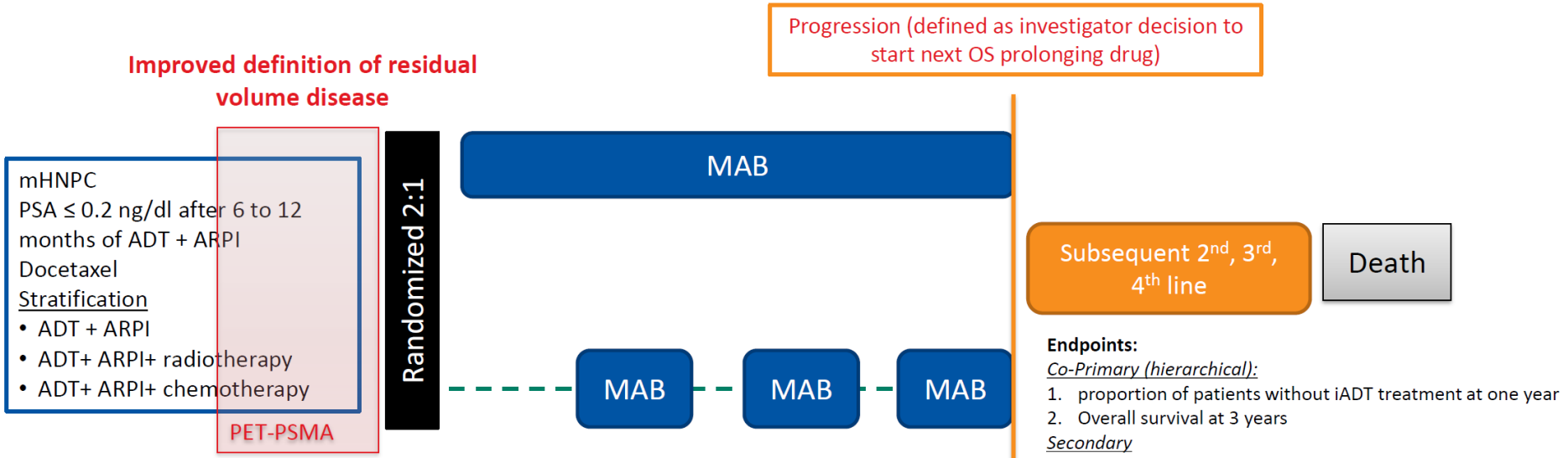
PSA Category	≤0.2		>0.2 to ≤1		>1 to ≤3		>3	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Non-metastatic Node-negative	415	82.8% (78.7--86.1)	86	73.2% (62.1--81.5)	10	60.0% (25.3--82.7)	6	100.0% (NA--NA)
Non-metastatic Node-positive	263	79.4% (73.8--83.9)	47	53.9% (38.3--67.1)	18	35.7% (13.7--58.7)	17	37.8% (15.6--60.1)
Metastatic Low-volume	253	64.1% (57.8--69.8)	68	42.9% (30.8--54.4)	32	28.1% (14.0--44.1)	25	21.7% (8.0--39.6)
Metastatic High-volume	177	44.6% (37.1--51.9)	88	28.4% (19.2--38.4)	55	9.1% (3.3--18.4)	89	7.7% (3.3--14.5)

Achieving a PSA ≤ 0.2 ng/mL within 6–12 weeks strongly predicts favorable long-term survival

Reduce systemic therapies in mHSPC

DE-ESCALATE Intermittent ADT in the era of AR pathway inhibitors; a phase 3 pragmatic randomized trial (EORTC 2238)

Funded by the European Union



Sratification
- 2:1 ratio,
- stratified by country and
- ARPI alone, ARPI + docetaxel, ARPI + radiotherapy)
- PSA ≤0.1 vs >0.1 - ≤ 0.2 ng/dl

EORTC

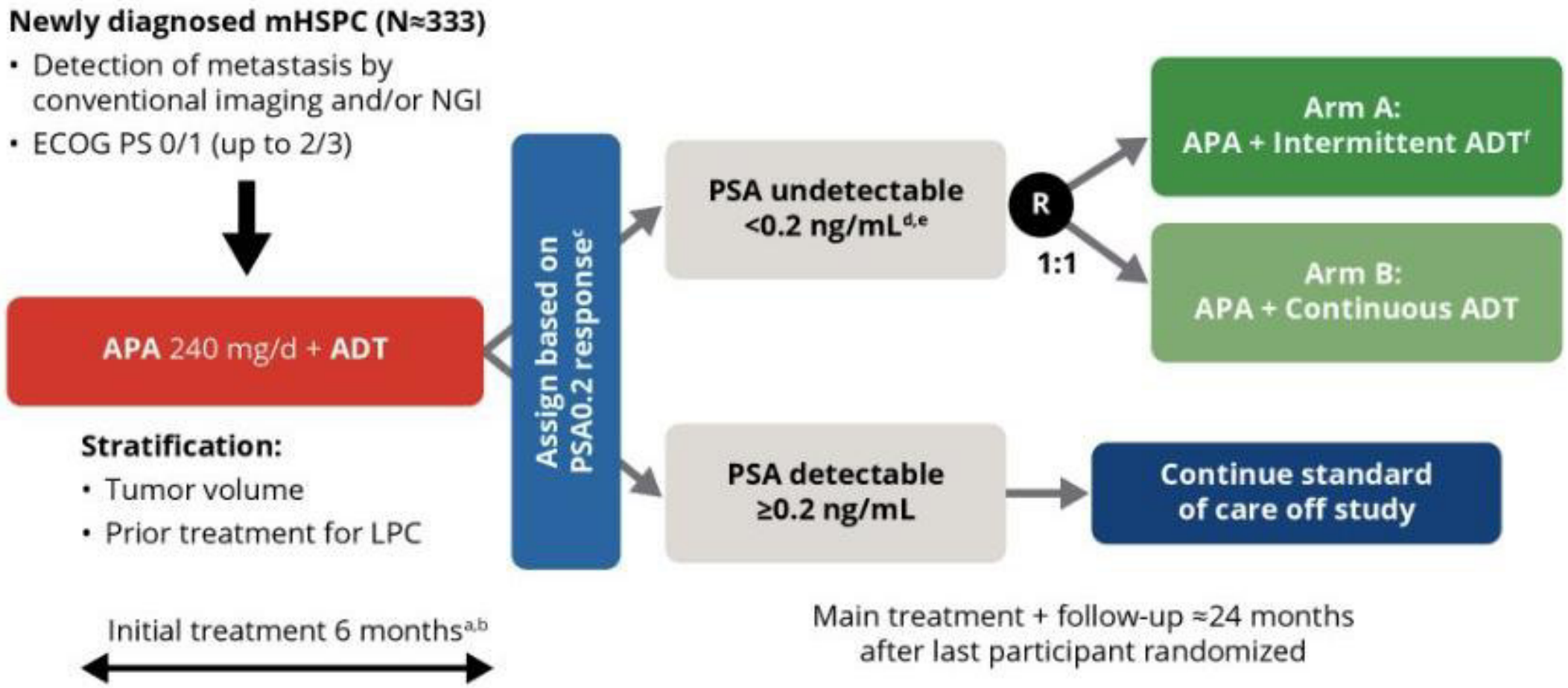
mHNPC: metastatic hormone naïve prostate cancer patients;

The future of cancer therapy

mHSPC: metastatic hormone-sensitive prostate cancer

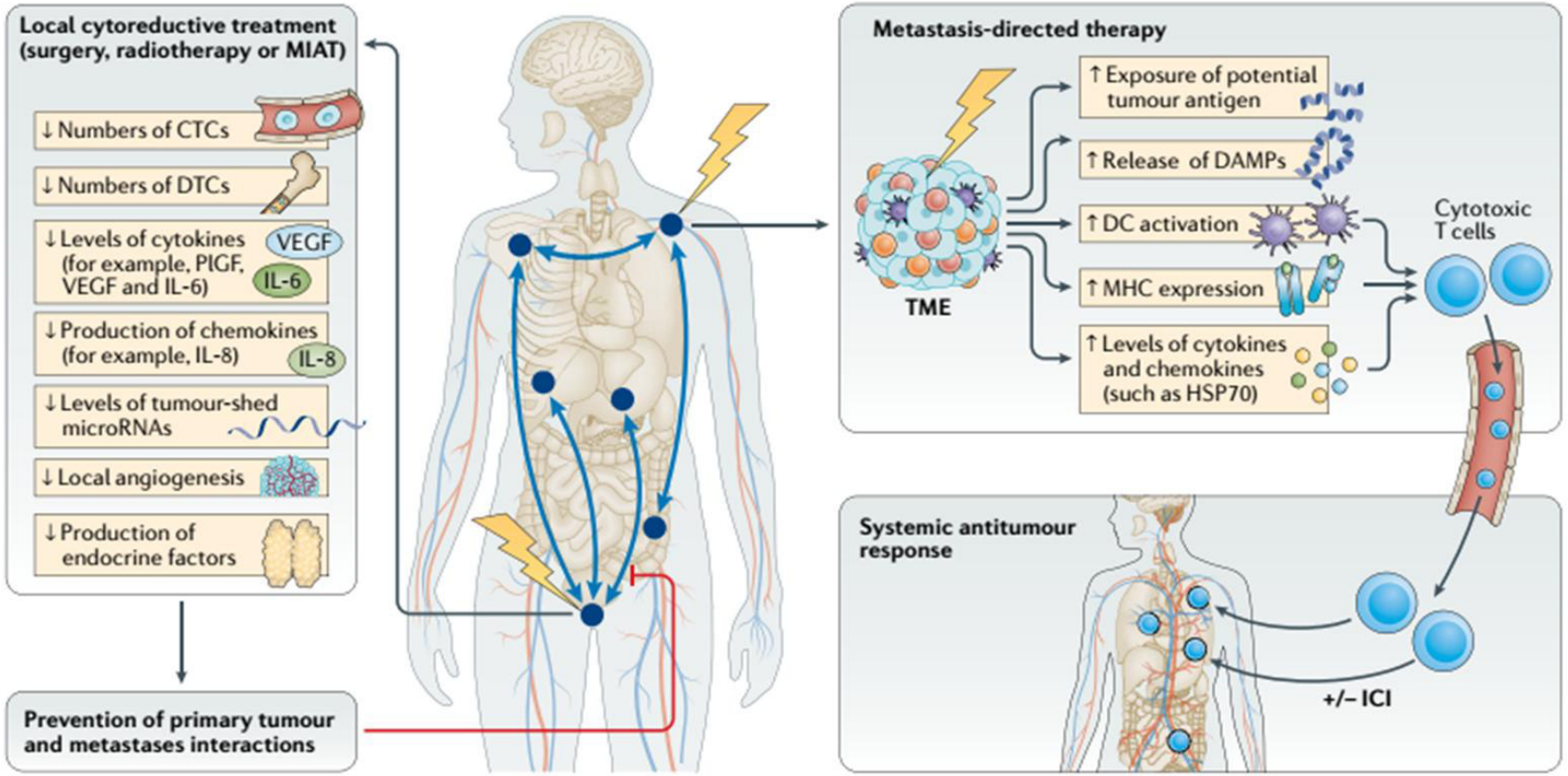
Reduce systemic therapies in mHSPC

LIBERTAS

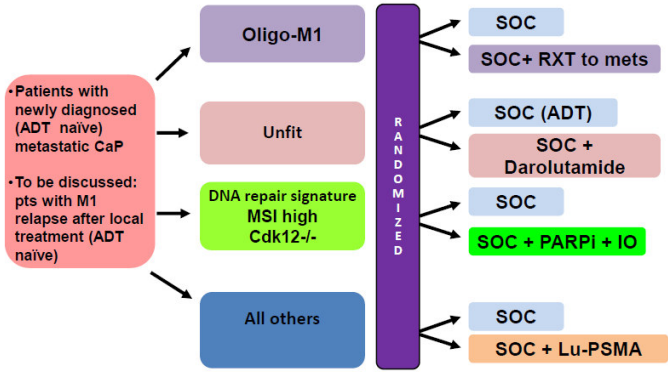


mHSPC: metastatic hormone-sensitive prostate cancer

Reduce systemic therapies **with SBRT** in oligometastatic HSPC

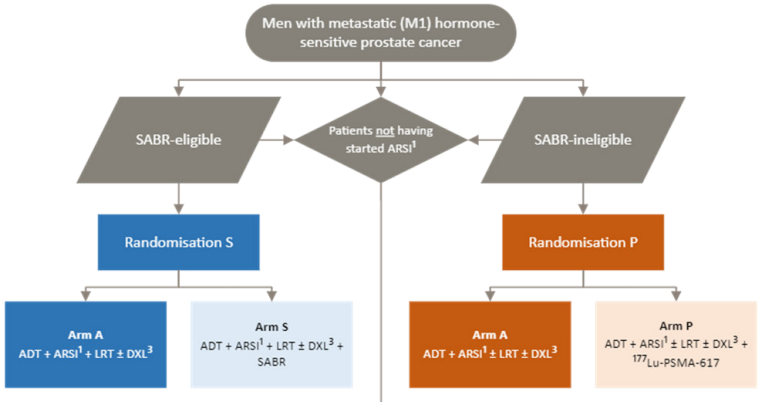


PEACE-6 OligoPRESTO



Study sponsor: Unicancer

STAMPEDE 2

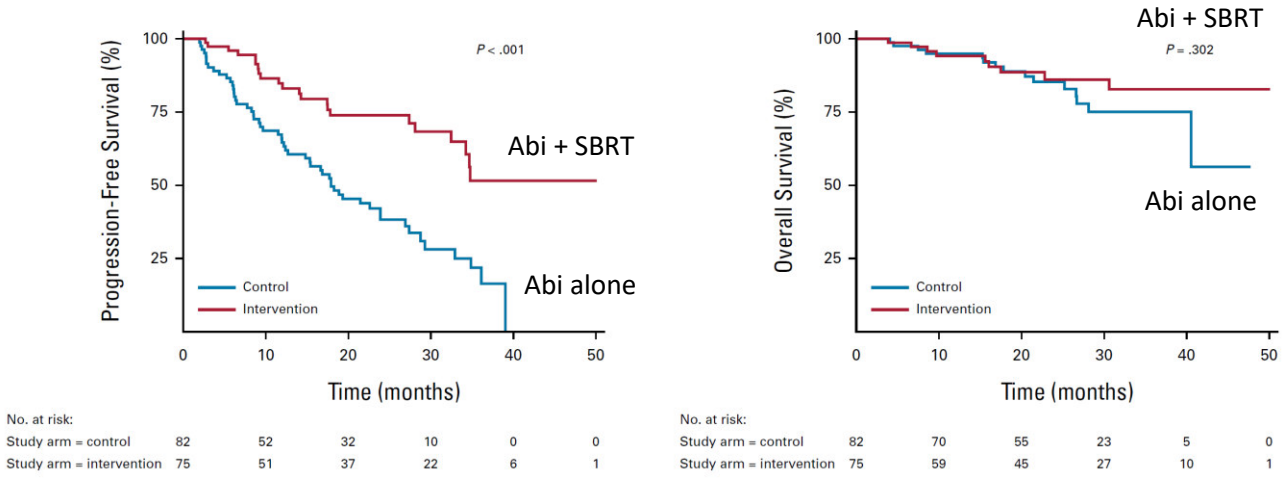


Comprehensive radiotherapy of all metastatic sites plus SOC systemic therapy may potentially improve long-term outcomes of oligometastatic patients (but yet to be demonstrated)

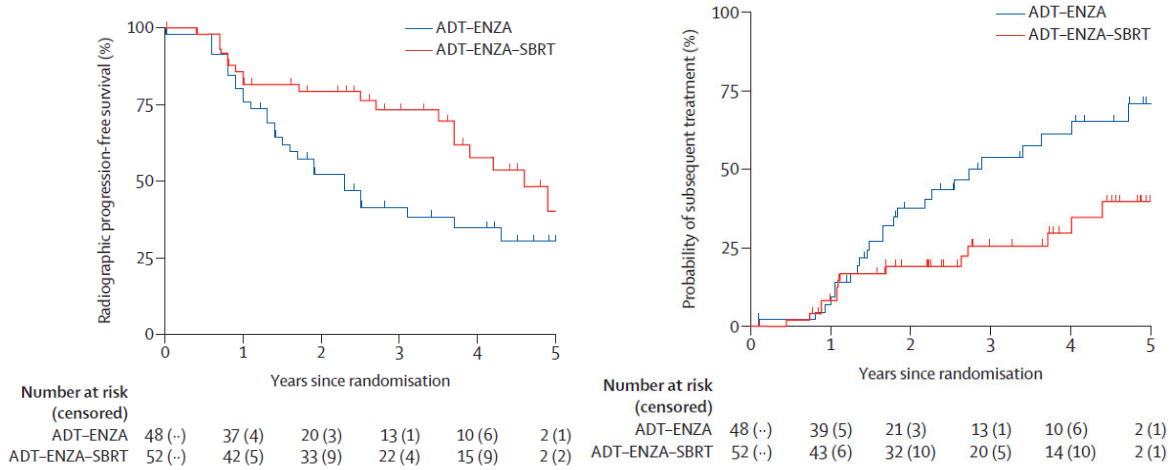
Connor MJ et al. Nat Rev Clin Oncol 2020

Reduce systemic therapies **with SBRT** in oligometastatic CRPC

Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic Castrate-Resistant Prostate Cancer: A Randomized Phase II Trial (ARTO)



Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration-resistant prostate cancer in Canada (GROUQ-PCS 9): a multicentre, open-label, randomised, phase 2 trial



Addition of SBRT to 1st line ARPI improves progression-free survival and postpone subsequent line of systemic therapy in oligoprogressive CRPC patients

CRCP: castration-resistant prostate cancer

Francolini G et al. JCO 2023; Niazi T et al. Lancet Oncol 2025

Modern integrated approaches: a vision for the future

🧬 **Prostate cancer management has evolved remarkably.**

🛡️ **Focus on reducing toxicity and enhancing QoL** — finding the right balance between benefit and burden of new therapies.

❤️ **Future goals**: Preserve function. Minimize side effects. Improve life and sustainability.

⚡ **Radiotherapy offers a cost-effective path** to improve efficacy with minimal toxicity while preserving QoL and healthcare costs.

THANK YOU FOR YOUR ATTENTION

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