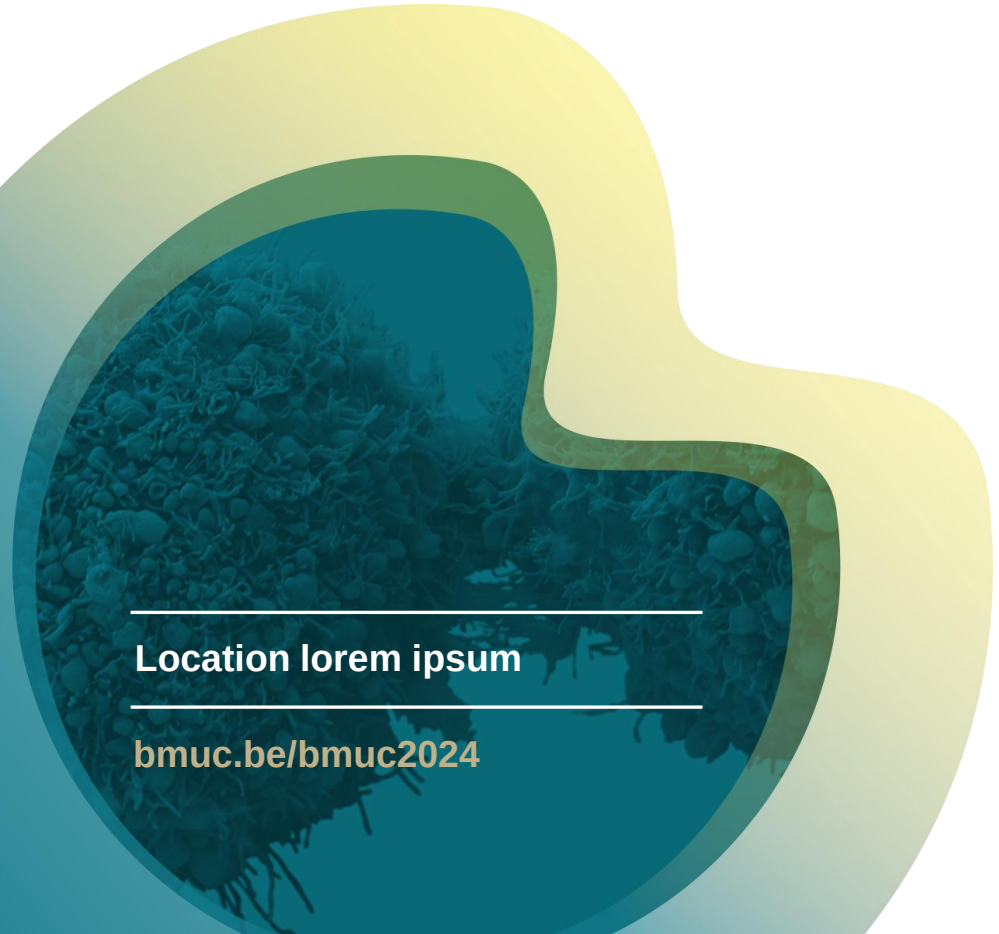
Systemic therapy optimisation

Bertrand TOMBAL

Cliniques universitaires Saint Luc

Brussels, Belgium



Location lorem ipsum

bmuc.be/bmuc2024

BMUC

UROLOGY - RADIATION ONCOLOGY - MEDICAL ONCOLOGY

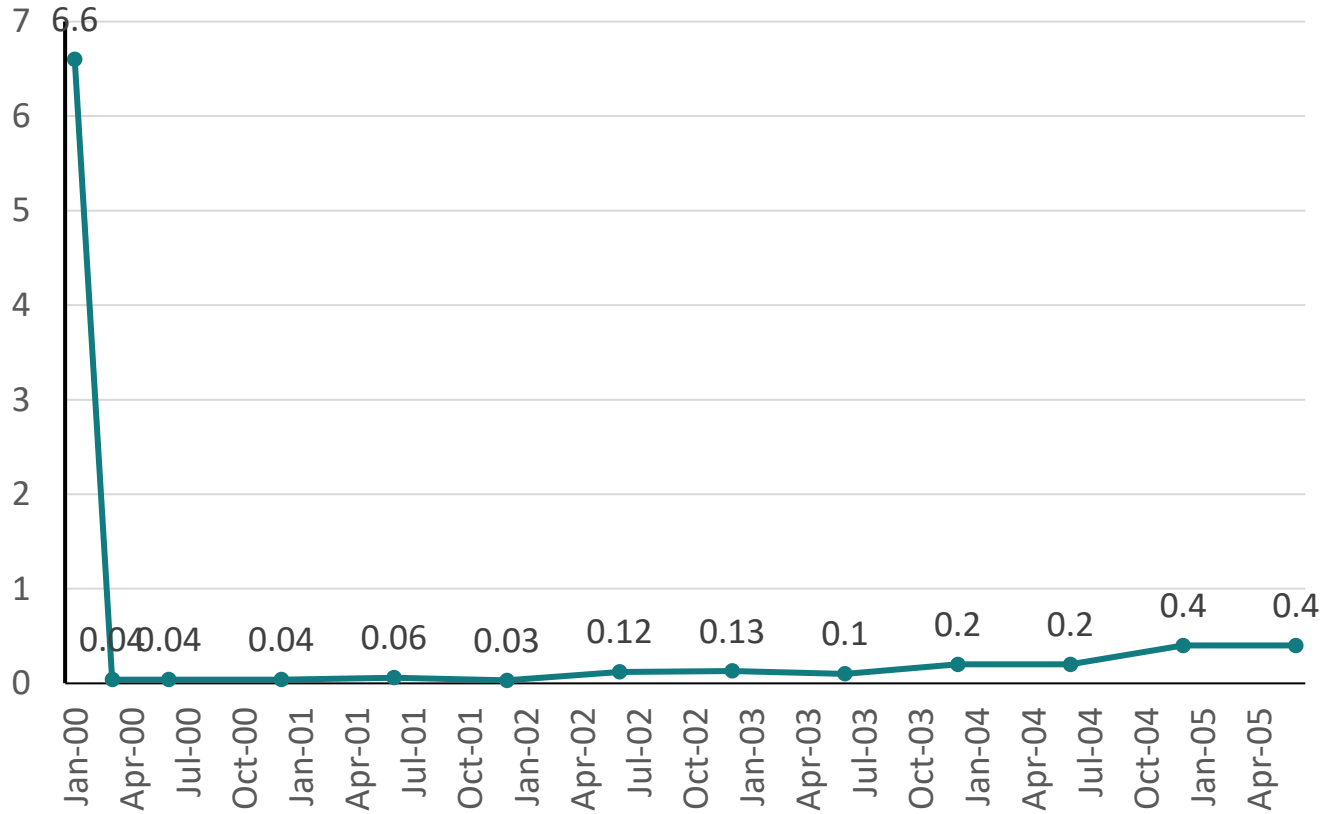
11th Belgian Multidisciplinary Meeting on Urological Cancers

Credentials and conflict of interests

- Professor and Chairman, Division of Urology, Cliniques universitaires Saint Luc, Brussels, BE
- Past-President, European Organization Of Research and Treatment of Cancer (EORTC)
- Investigator and paid advisor for Amgen, Astellas, Bayer, Janssen, Ferring, Pfizer, Sanofi, Myovant.
- This presentation reflects the personal view of Bertrand TOMBAL

Clinical case…

- 61-y.o. intermediate risk localized (PSA 7 ng/ml, T1c, 3/12 Bx Gleason 7 (4+3), mpMRI T2c)
- RP + limited LND 01/2000: pT3a Gleason 7 (4+3), R1, N0 (8 Ln), M0



What would you recommend?

- Do nothing; keep monitoring
- Salvage radiotherapy (± ADT)
- Do a PET-PSMA first, and treat accordingly
- Start ADT
- Start Enzalutamide (± ADT) and then PET-PSMA

Case and images courtesy of Bertrand Tombal and Frederic Lecouvet, CUSL, Brussels

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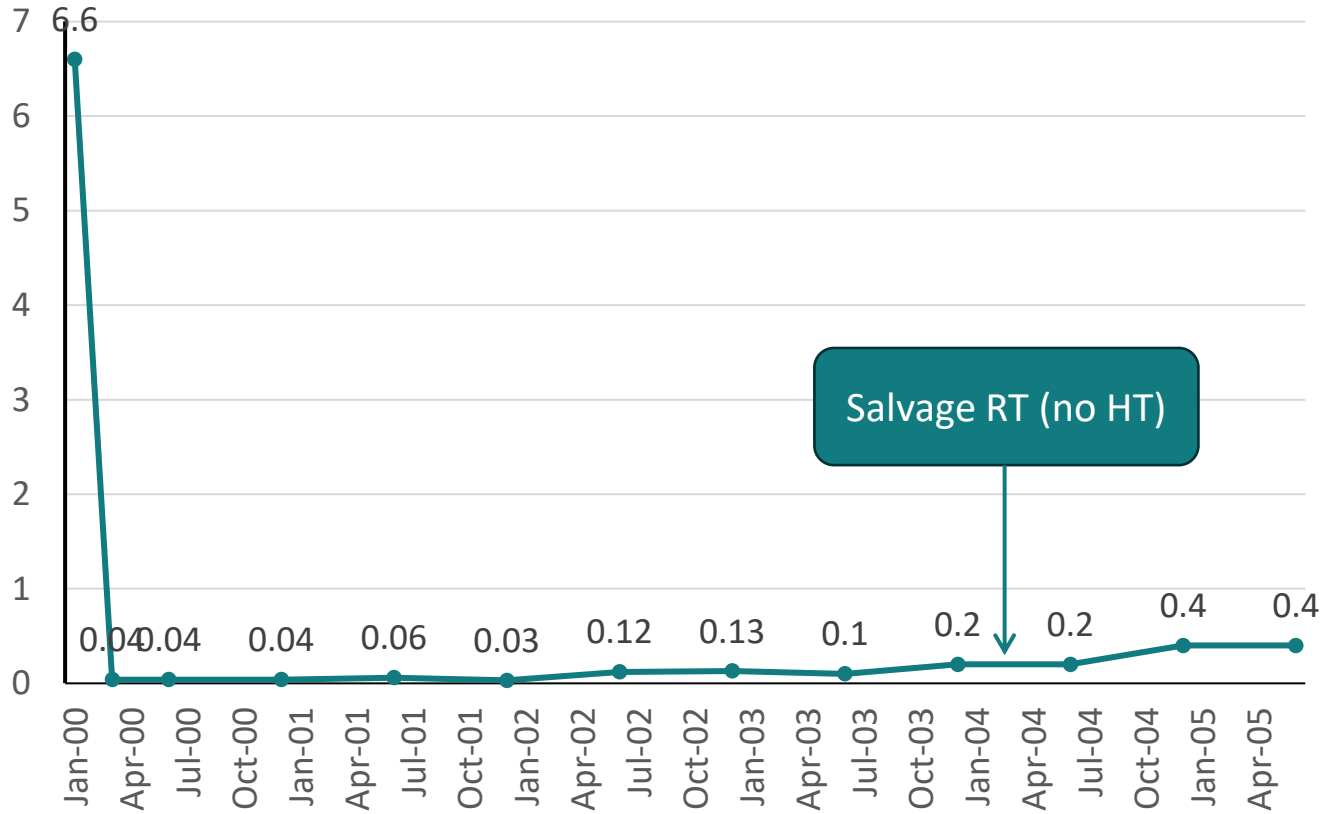
- Salvage RT administered; no hormone therapy



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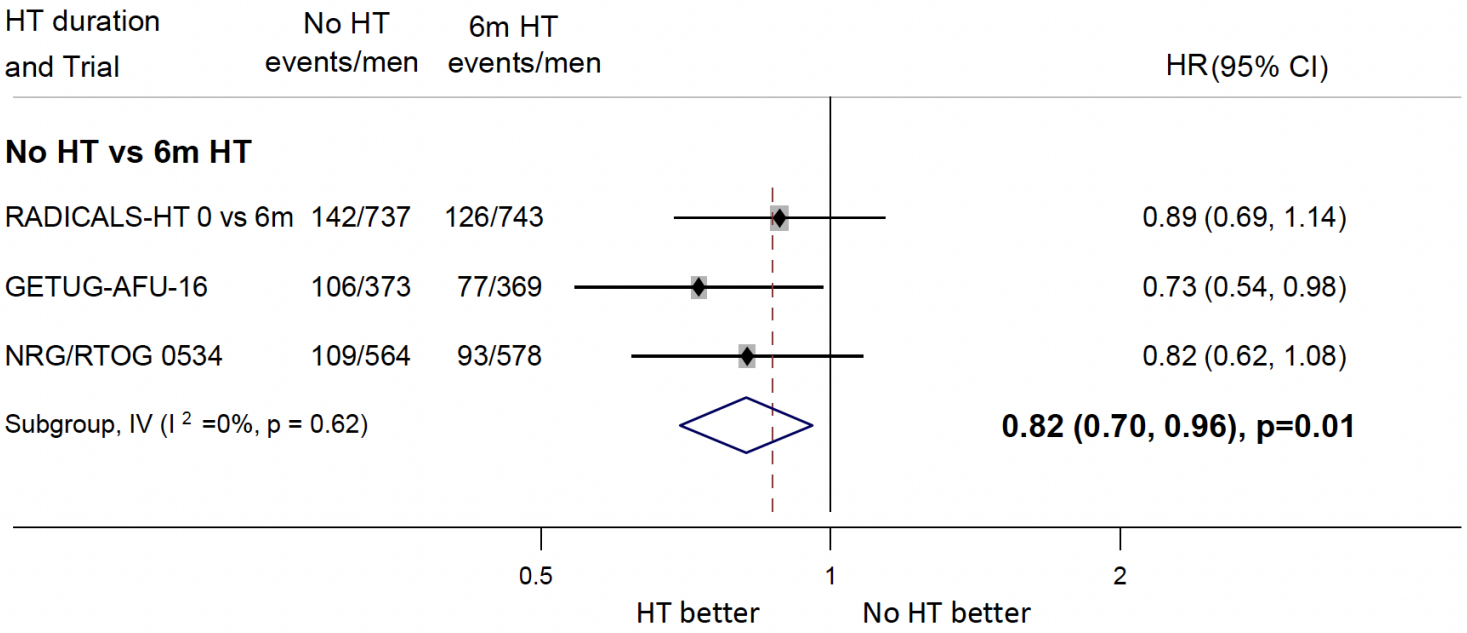
https://uroweb.org/guidelines/prostate-cancer/chapter/treatment, accessed on 1/02/2022

Duration of androgen suppression with postoperative radiotherapy (DADSPORT): A collaborative meta-analysis of aggregate data



Evidence of improved MFS with 6 vs 0m of HT

5 yr absolute improvement 0 vs 6m = 2% (0%-3%)

Short-term ADT improves 5-yr MFS from 90% to 92%

PFS: progression-free survival; MFS: metastatic-free survival; ADT: androgen deprivation therapy

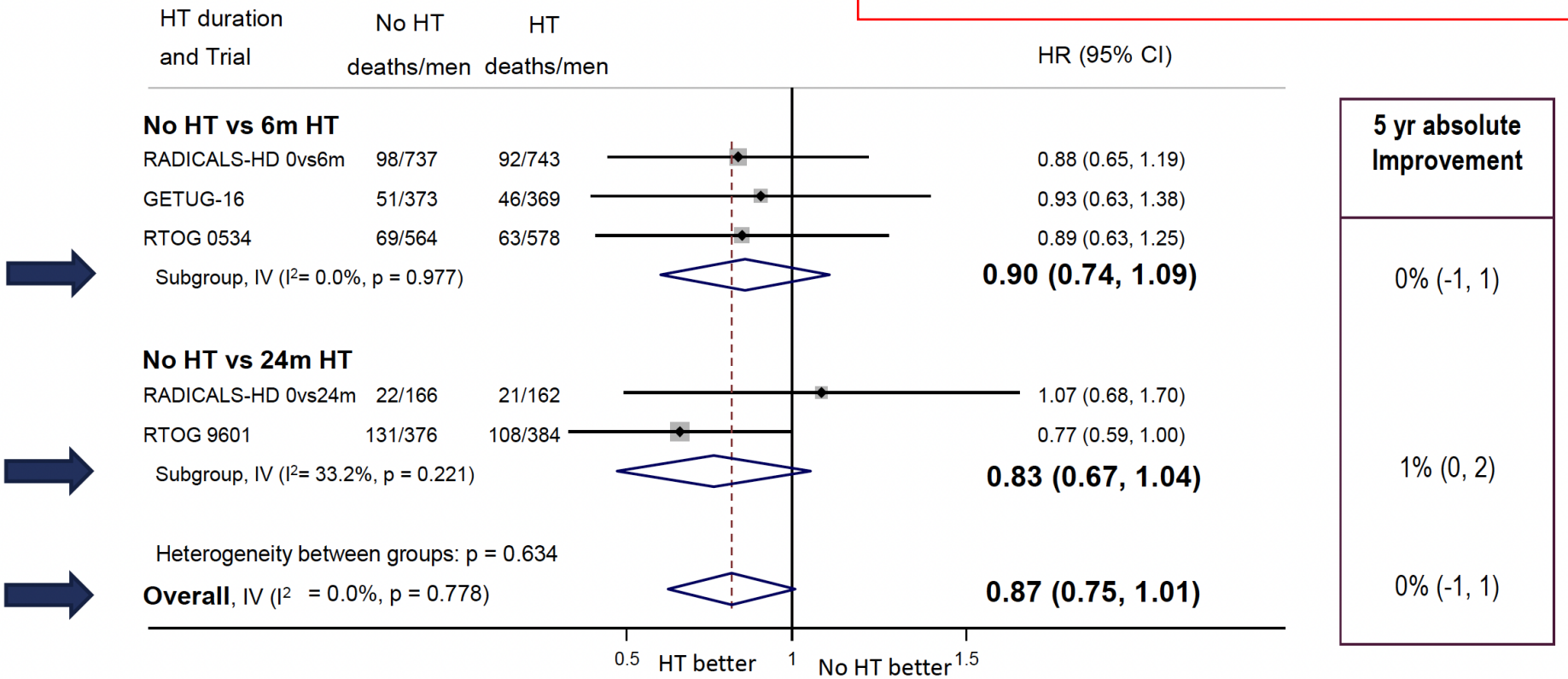
Burdett et al. ESMO 2022 https://doi.org/10.1016/j.annonc.2022.08.067

Duration of androgen suppression with postoperative radiotherapy (DADSPORT): A collaborative meta-analysis of aggregate data

Median follow-up at least 8 years

No clear evidence of a difference in survival with HT versus none, irrespective of whether 6m or 24m

Results: Overall survival



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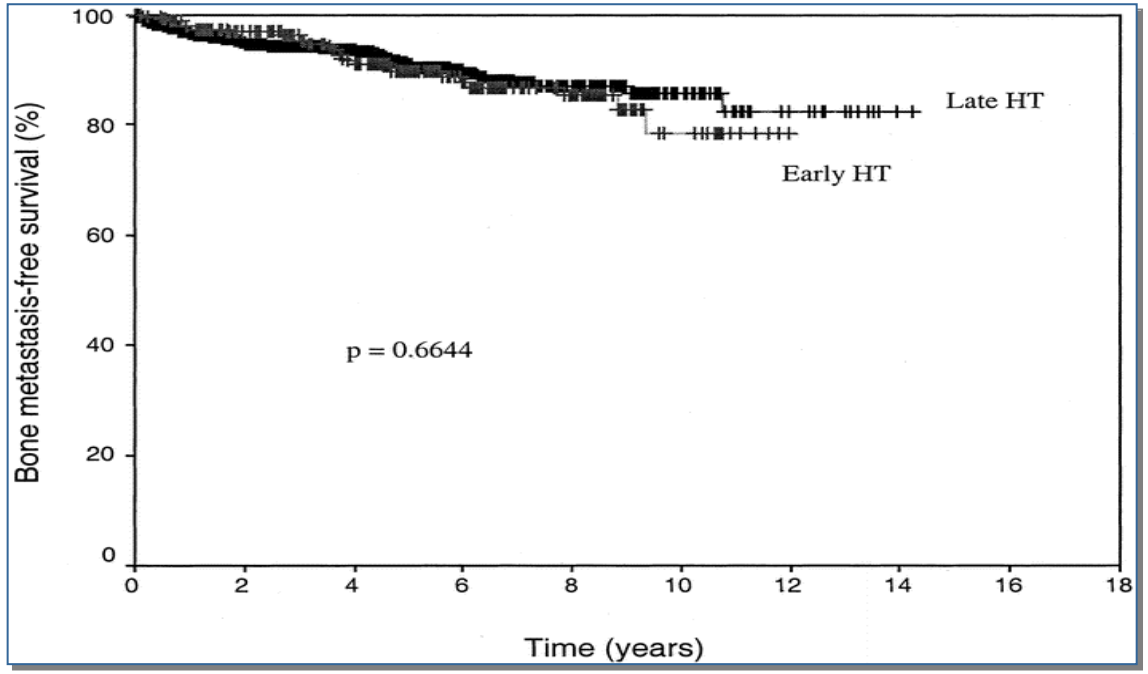
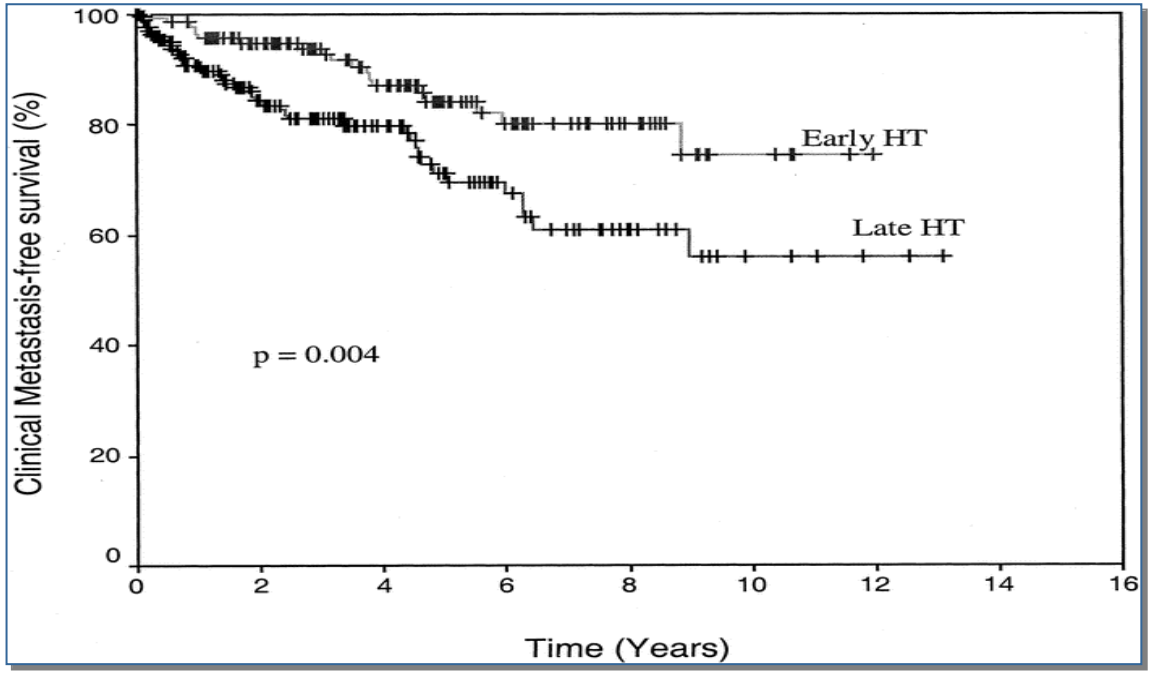
Early versus delayed hormonal therapy for PSA only recurrence of prostate cancer after radical prostatectomy.

ADT for PSA ≤5 ng/ml
All patients (n=1352)



ADT for PSA ≤5 ng/ml
Gleason> 7 and/or PSADT < 12 mths.

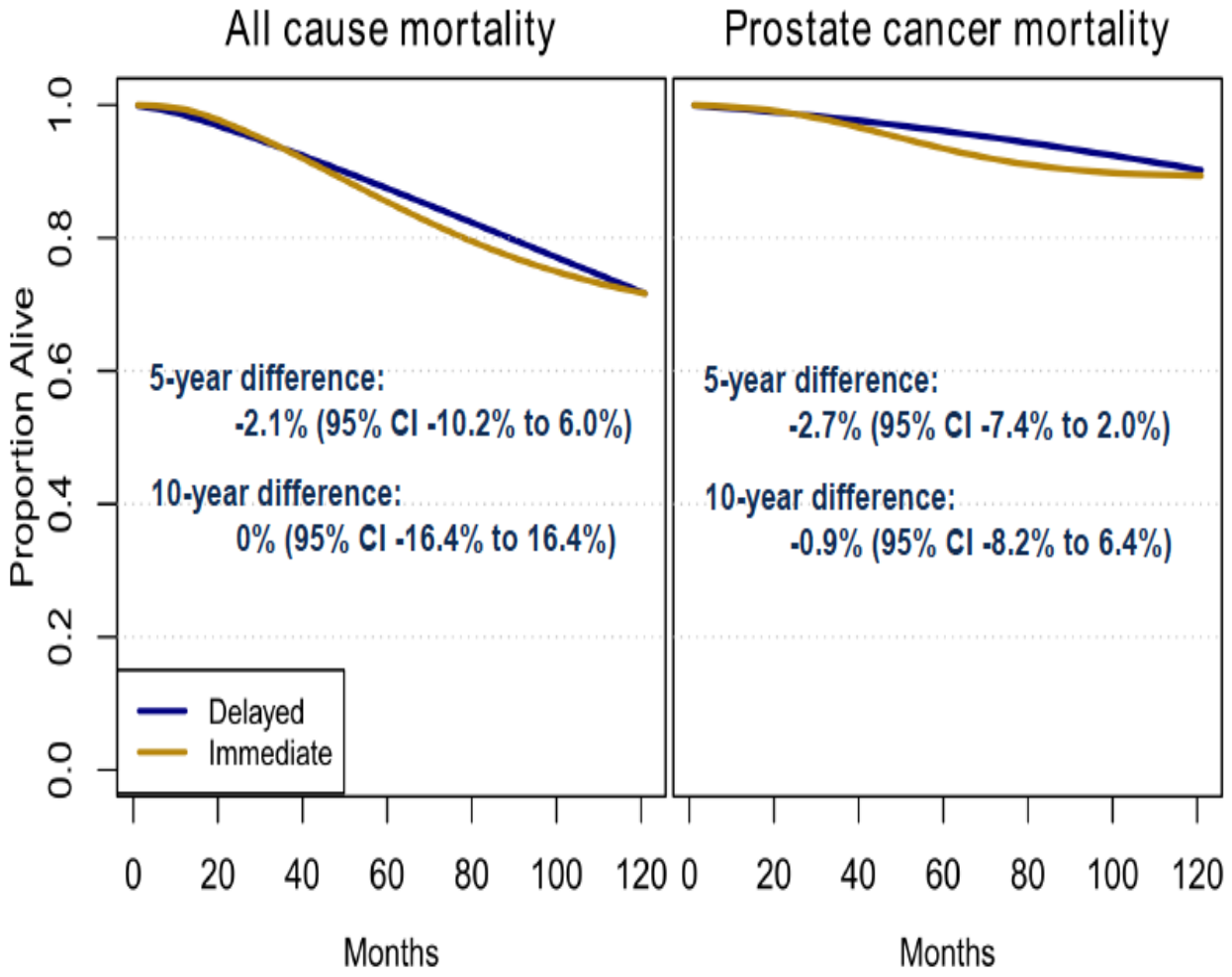


Moul JW et al. J Urol. 2004 Mar;171(3):1141-7

Immediate versus deferred initiation of ADT in prostate cancer patients with PSA-only relapse. An observational follow-up study

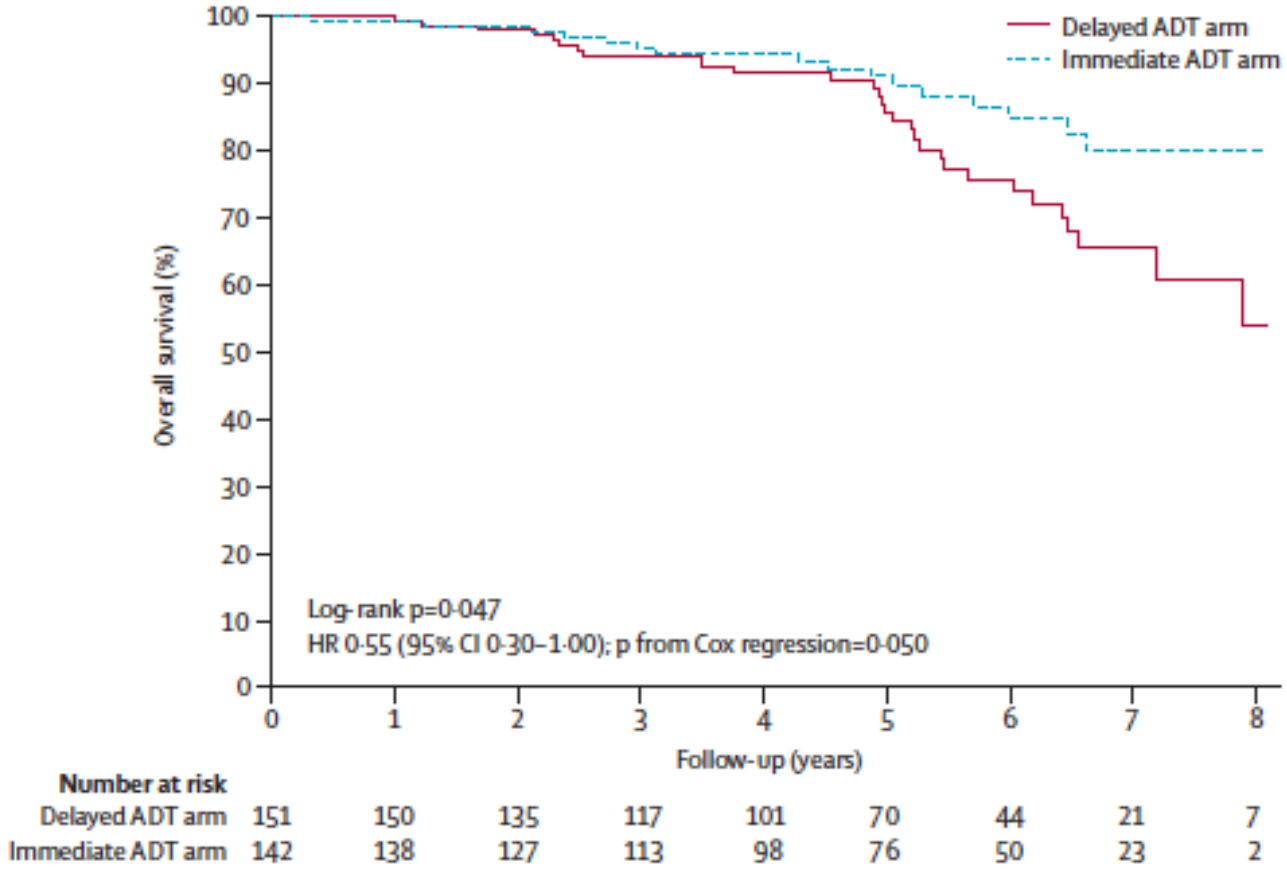
Definition early or late.

- metastasis in any imaging technique,
- severe cancer-related symptoms,
- PSA doubling time <12 m. if PSA ≥ 10 ng/ml
- PSA doubling time ≤ 6 m. based on 3 measurements



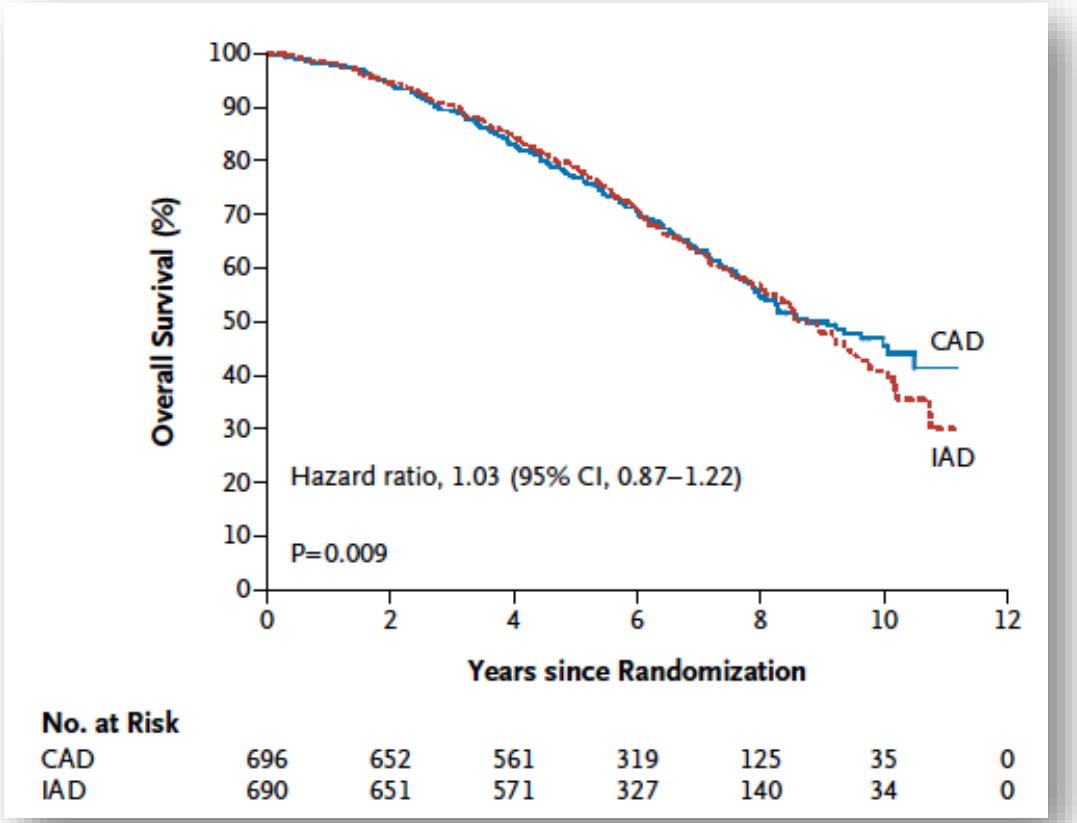
Timing of androgen-deprivation therapy in patients with PCa with a rising PSA (TROG 03.06 and VCOG PR01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial.

- 261 PSA relapse after previous attempted curative therapy and 32 PCa not suitable for curative treatment
- Randomized to immediate ADT or to delayed ADT with a recommended interval of at least two years unless clinically contraindicated



Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

- Rising PSA > 3.0 ng/ml >1 year post RRT, either initial or salvage, for localized PSA.
- 1,386 patients; 524 deaths were observed (268 on IAS vs. 256 on CAD).



Median OS

- 8.8 years in the intermittent therapy group
- 9.1 years in the continuous-therapy group.

HR for death with IAD
1.03; 95% CI, 0.86 to 1.23.
P for non-inferiority: 0.01.

JM. Crook et al. N Engl J Med 2012;367:895-903.

Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Table 2. Investigator-Reported Causes of Death (Intention-to-Treat Population).

Cause	Deaths in Intermittent-Therapy Group (N=268)	Deaths in Continuous-Therapy Group (N=256)	Total Deaths (N=524)
		number (percent)	
Disease-specific			
Prostate cancer	110 (41.0)	87 (34.0)	197 (37.6)
Prostate cancer and off-protocol treatment	10 (3.7)	5 (2.0)	15 (2.9)
Complication of per-protocol treatment	0	2 (0.8)	2 (0.4)
Unrelated to prostate cancer			
Complication of off-protocol treatment*	2 (0.7)	5 (2.0)	7 (1.3)
Other primary cancer	59 (22.0)	54 (21.1)	113 (21.6)
Other cause	75 (28.0)	92 (35.9)	167 (31.9)
Unknown	12 (4.5)	11 (4.3)	23 (4.4)

* Treatment was initiated off protocol after the development of castration-resistant disease.

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Recommendations	Strength rating
Offer hormonal therapy in addition to SRT to men with BCR.	Weak
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling time > 12 months.	Strong

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

https://uroweb.org/guidelines/prostate-cancer/chapter/treatment, accessed on 1/03/2024

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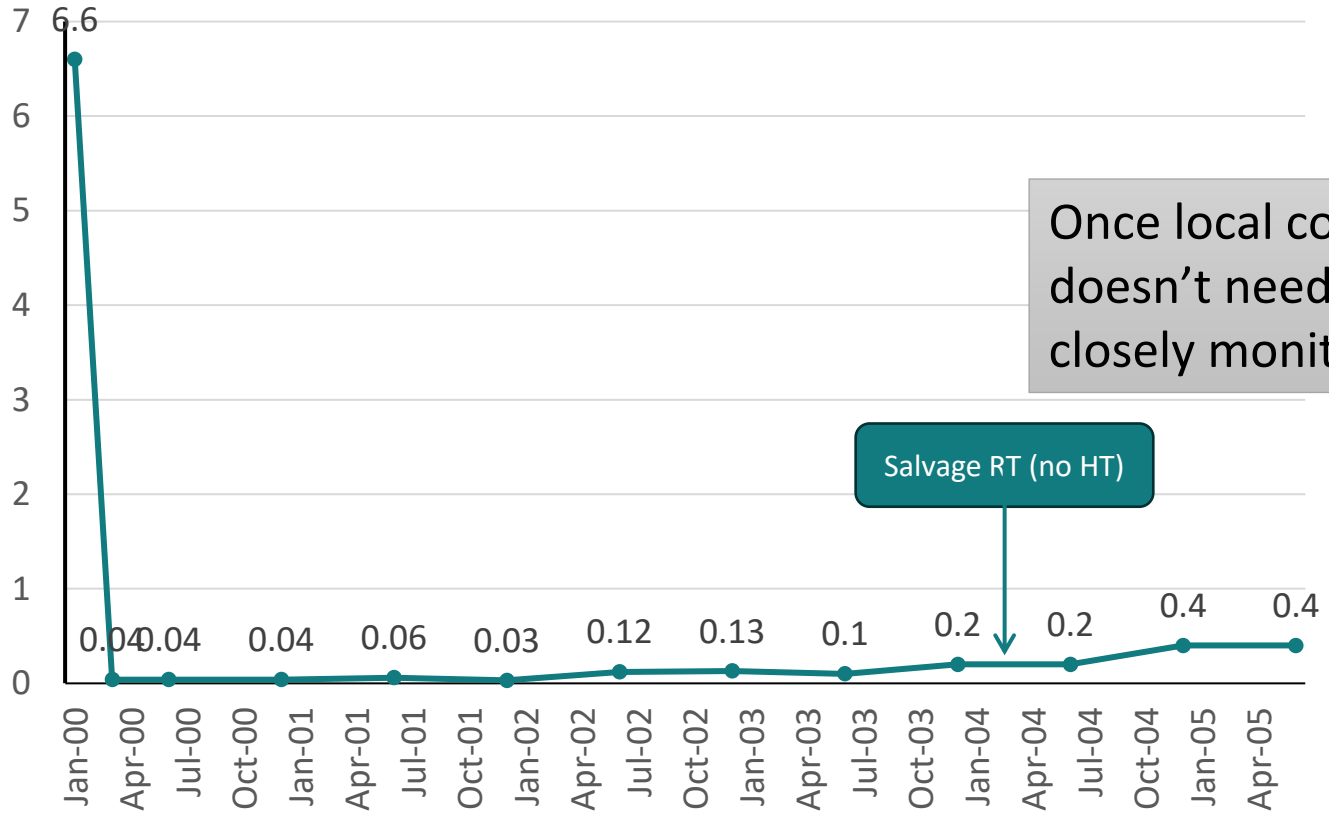
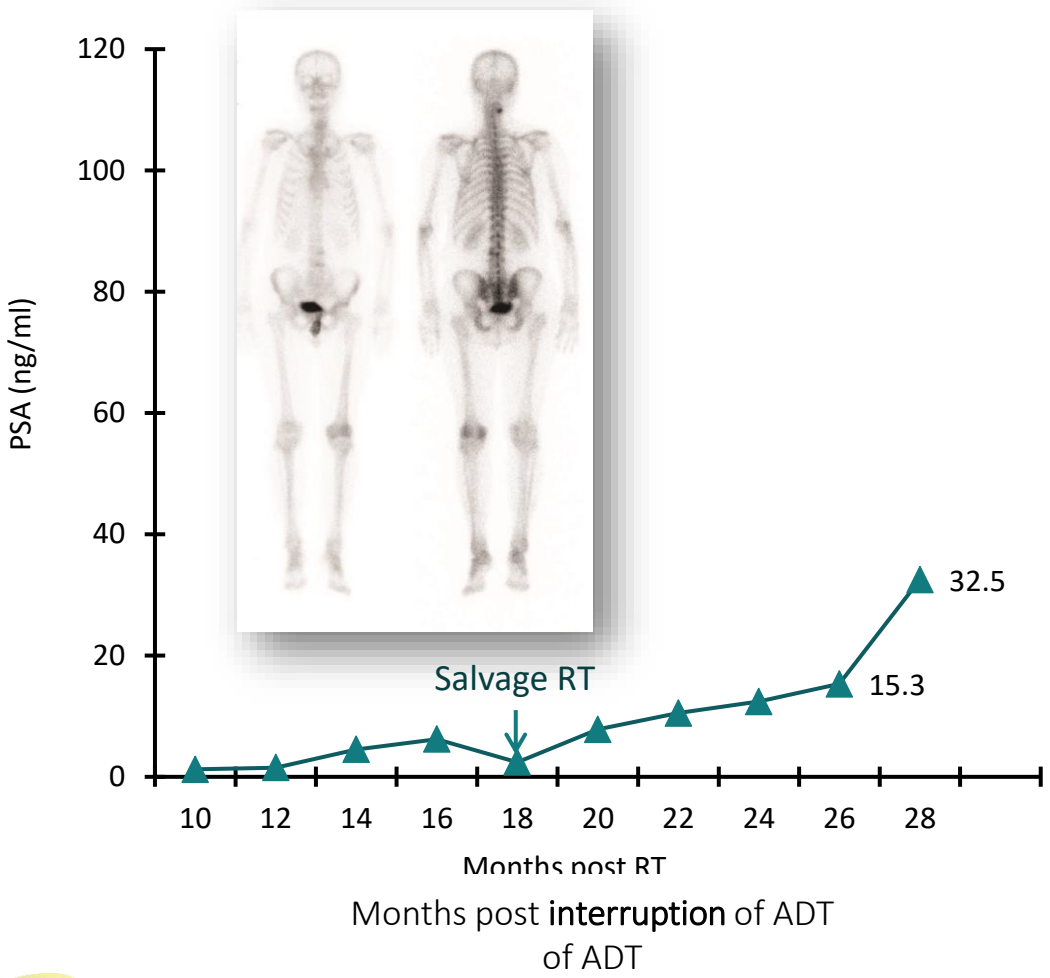


Once local control has been secured, that patient doesn't need treatment; he must be reassured and closely monitored.

Case and images courtesy of Bertrand Tombal and Frederic Lecouvet, CUSL, Brussels

- 71 y.o. EBRT + 2 years ADT for locally-advanced PCa (T3b, Gleason 8 (5+3), PSA 47 ng/ml, NO, MO), testosterone 43 ng/dl, PSA doubling time 7 months
- Salvage radiotherapy is applied, and no hormone therapy associated



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EBRT: external beam radiation therapy; ADT: androgen deprivation therapy, Images provided by B.Tombal & F.Lecouvet , Clinique Universitaires Saint-Luc, Belgium

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- The benefit of ADT is inconsequential, alone or adjuvant to RT, in an unselected patient population, while the side effects are significant.
- Because of that, delaying the initiation of ADT until a later stage was deemed acceptable.
  - ✓ This led to the extensive implementation of new imaging technologies and metastatic targeted therapies.

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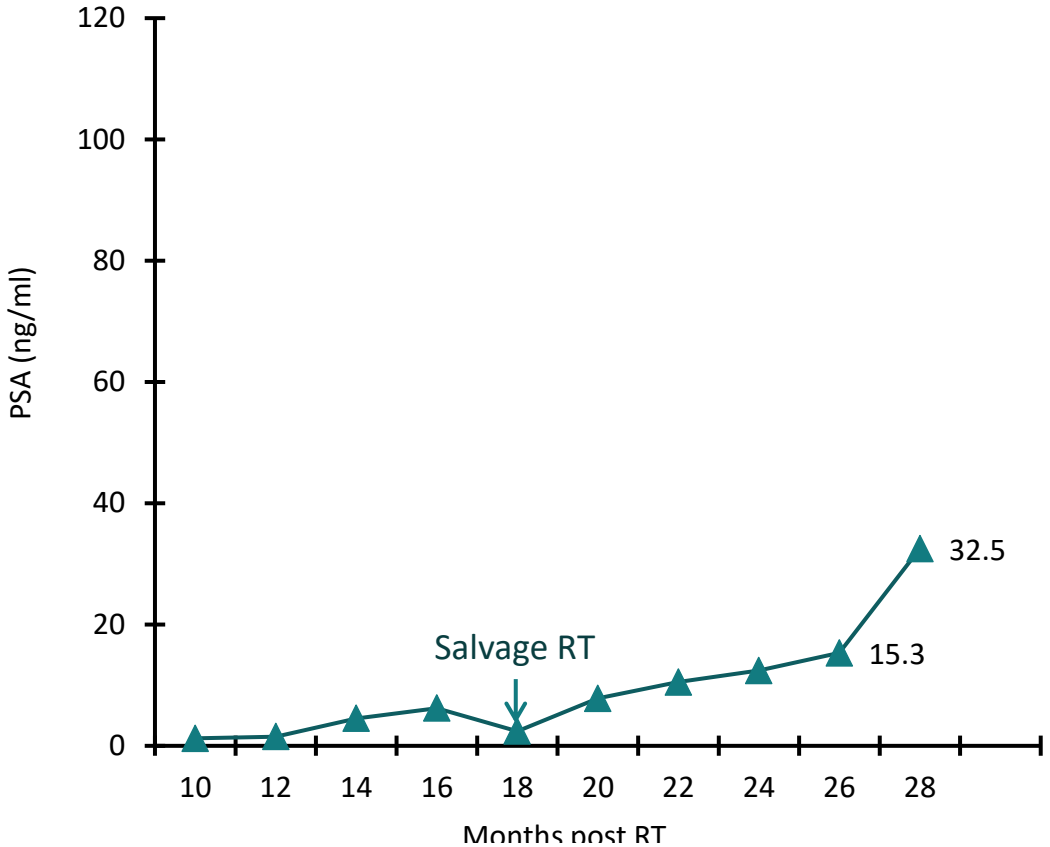
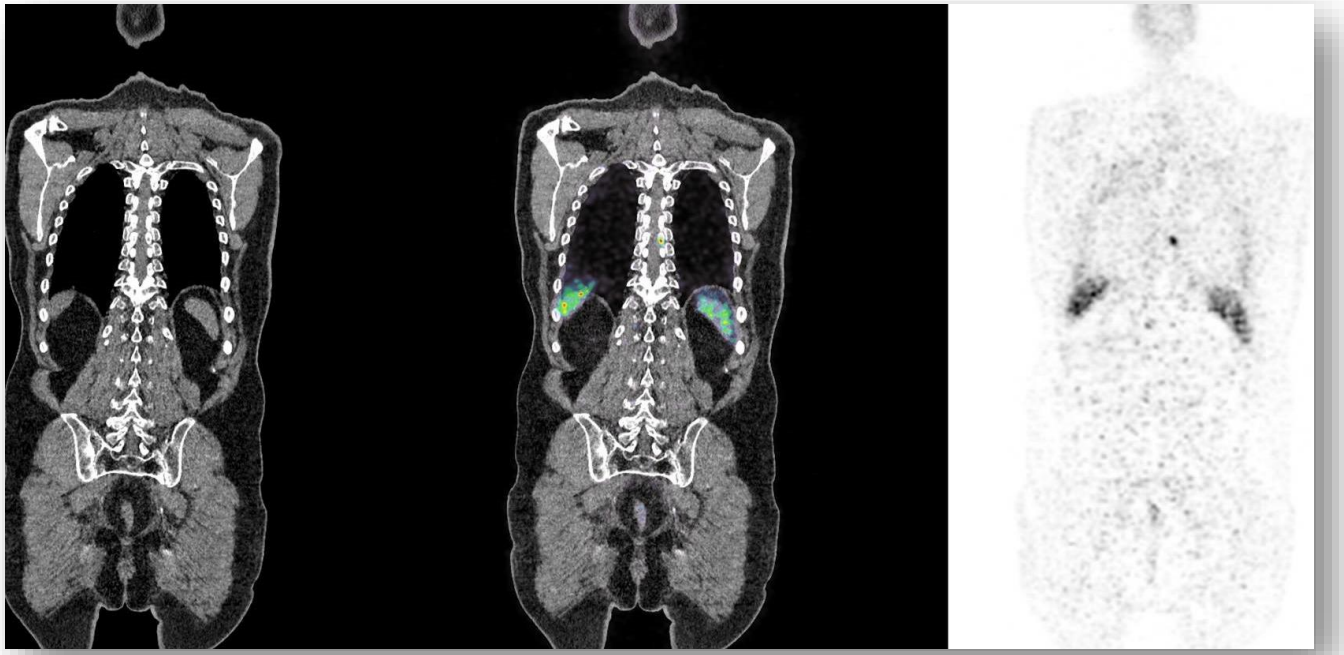


Months post **interruption** of ADT
of ADT



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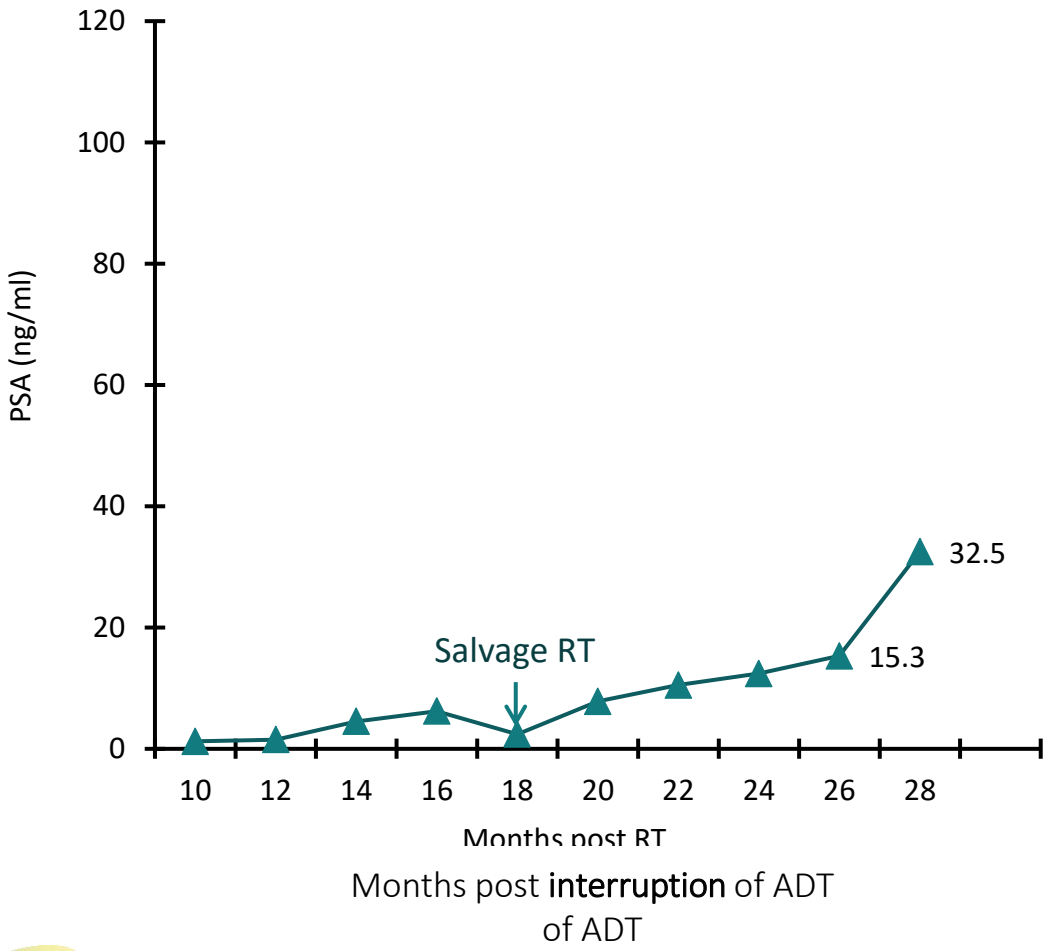

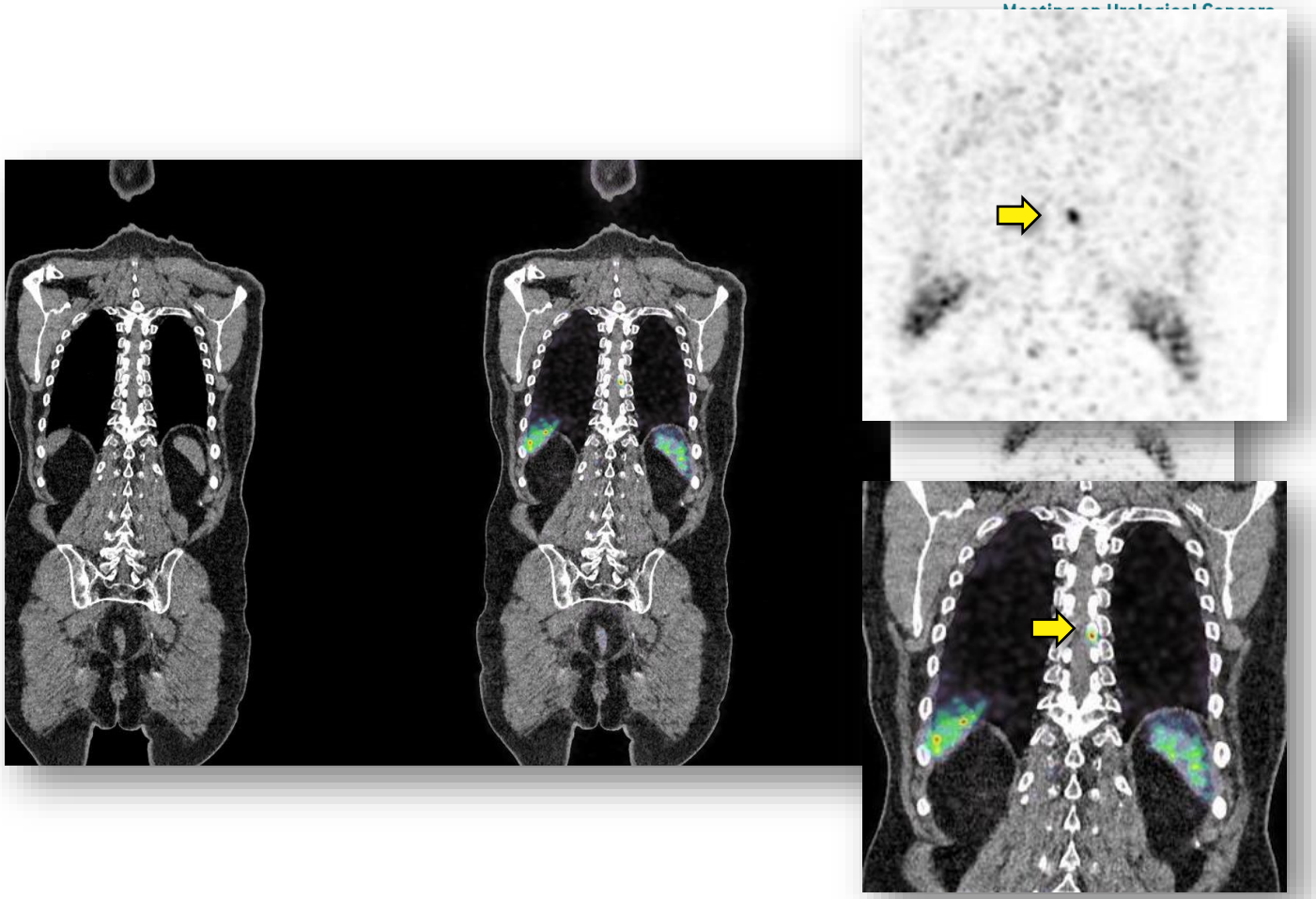

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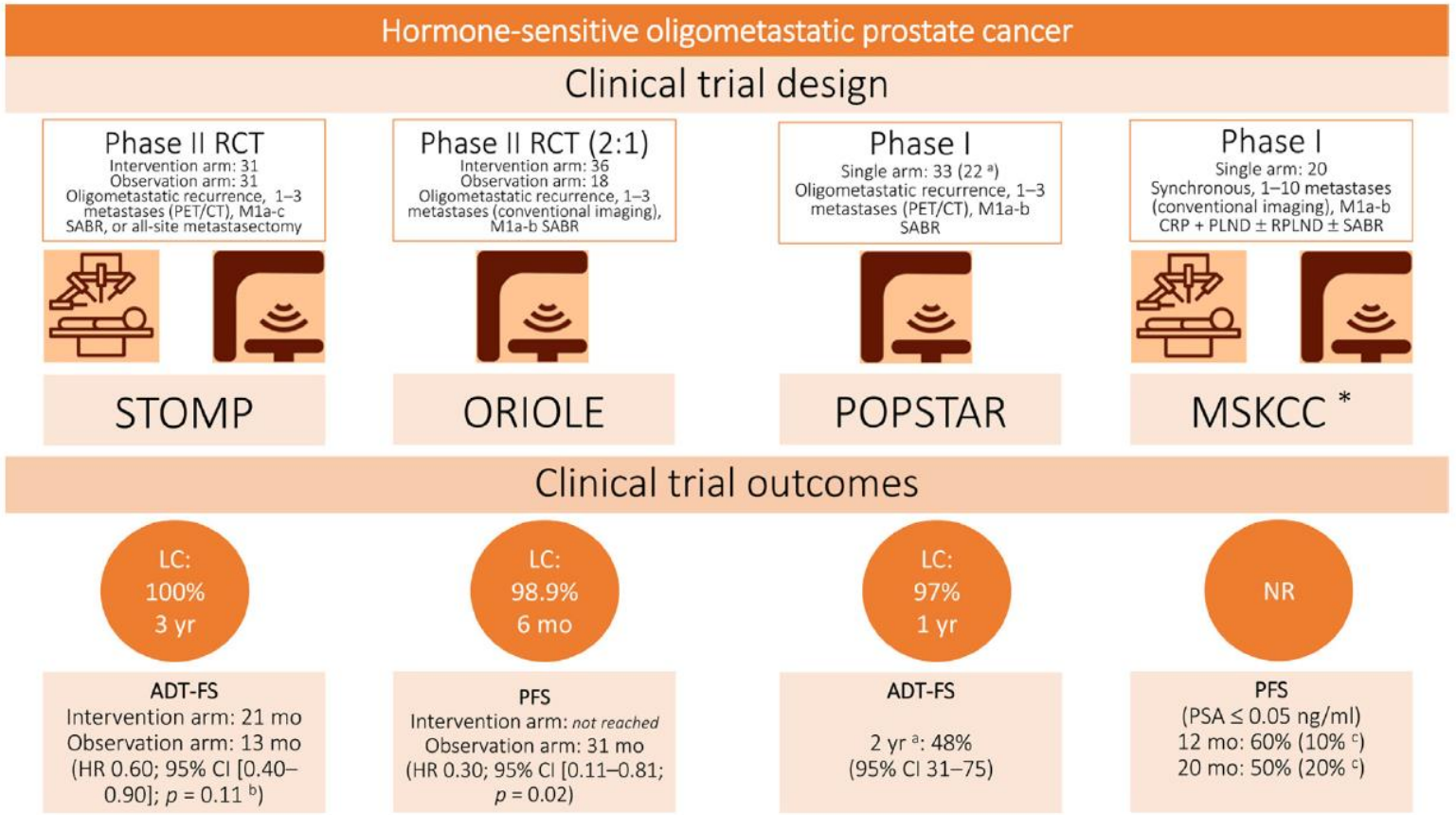
Targeting Oligometastasis with Stereotactic Ablative Radiation Therapy or Surgery in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review of Prospective Clinical Trials.

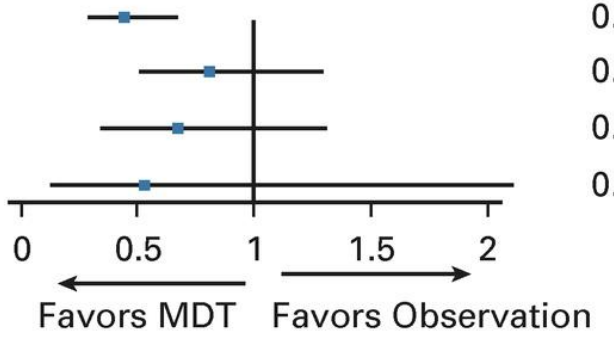


ADT-FS = ADT-free survival; CI = confidence interval; HR = hazard ratio; CRP = cytoreductive radical prostatectomy; LC = local control; MSKCC – Memorial Sloan Kettering Cancer Centre [22]; NR = not reported; PET/CT = positron emission tomography/computerised tomography; PFS = progression-free survival; PLND = pelvic lymph node dissection;; RCT = randomised controlled trial; RPLND = retroperitoneal lymph node dissection; SABR = stereotactic ablation radiotherapy.

MJ Connor et al. Eur Urol Oncol. 2020 Sep 2;S2588-9311(20)30095-X.

Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials.

Outcome	MDT Median Time to Event, months (95% CI)	Observation Median Time to Event, months (95% CI)	HR (95% CI)	*P*
PFS	11.9 (8 to 18.3)	5.9 (3.2 to 7.1)	0.44 (0.29 to 0.66)	< .001
rPFS	18.3 (12 to 36)	17 (13 to 22.8)	0.81 (0.50 to 1.29)	.37
CRPC	NR (62 to NR)	63 (53.9 to NR)	0.67 (0.34 to 1.31)	.24
OS	NR (84 to NR)	NR (73 to NR)	0.53 (0.13 to 2.11)	.36



Acceptability leads to Conventional Wisdom, not evidence…

John K. Galbraith, 1958

- The ideas which are esteemed at any time for their acceptability
- Important differences may exist between what is acceptable (the territory of the conventional wisdom) and what is true …

When recommending New imaging Technology to a rPSA patient,

- I take for granted that it is a poor prognostic marker and that this patient will die (which is not proven)
- I take for granted that applying metastatic-directed therapy will affect the disease trajectory (which is not proven).

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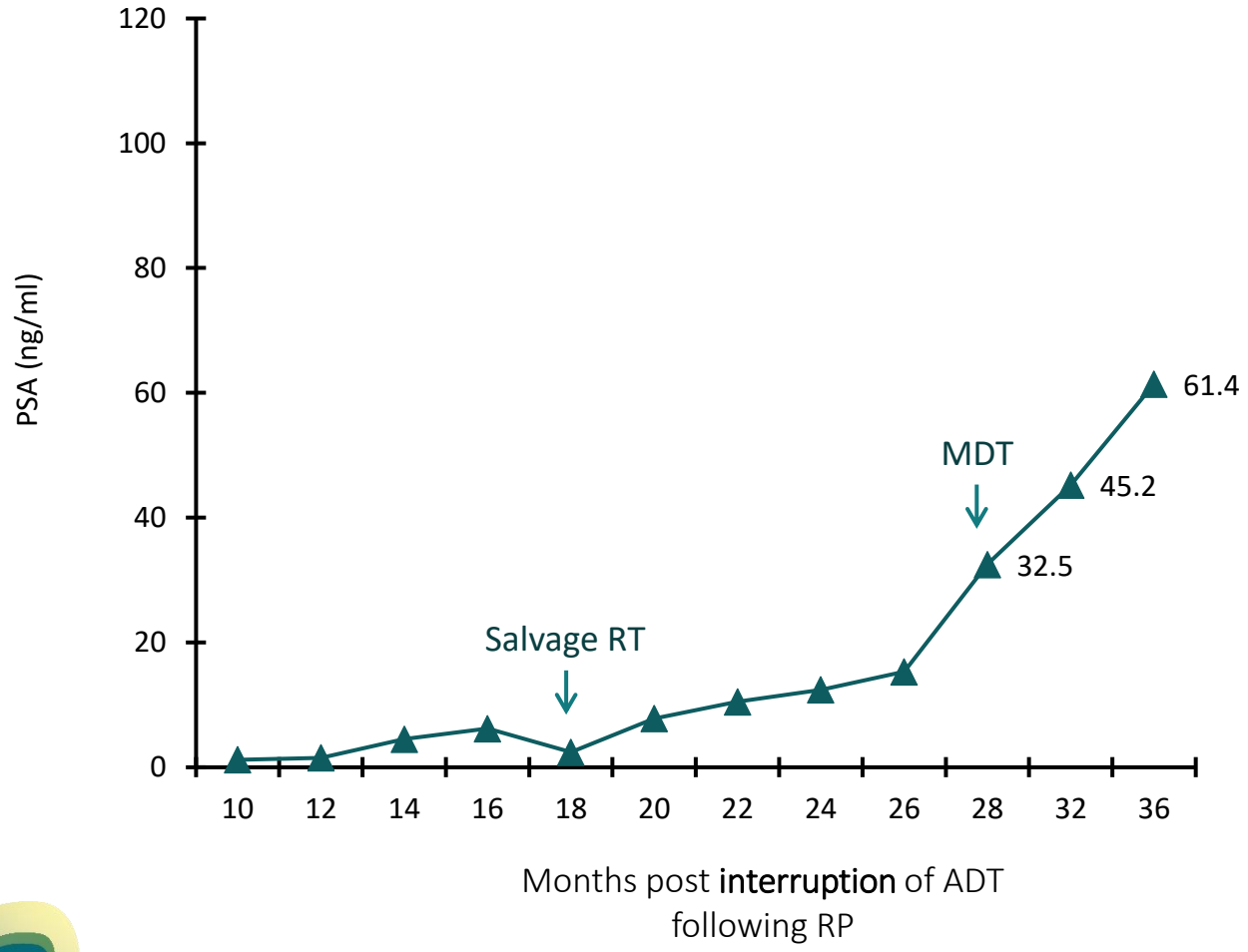

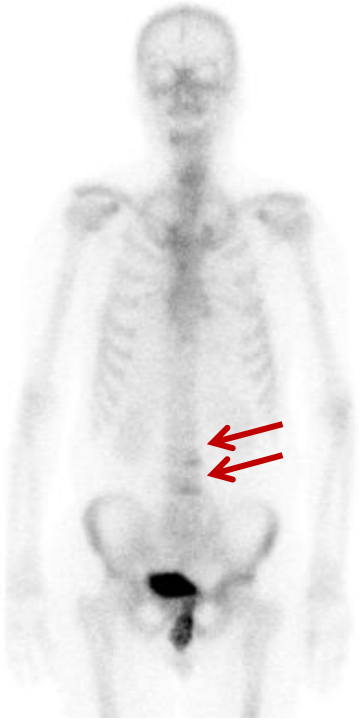

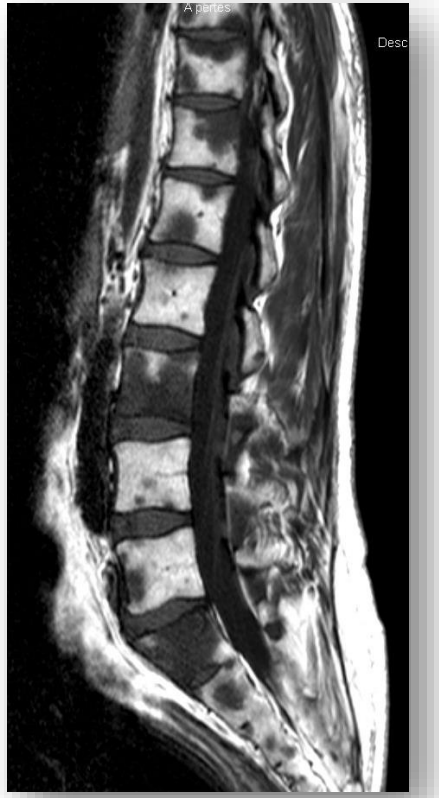

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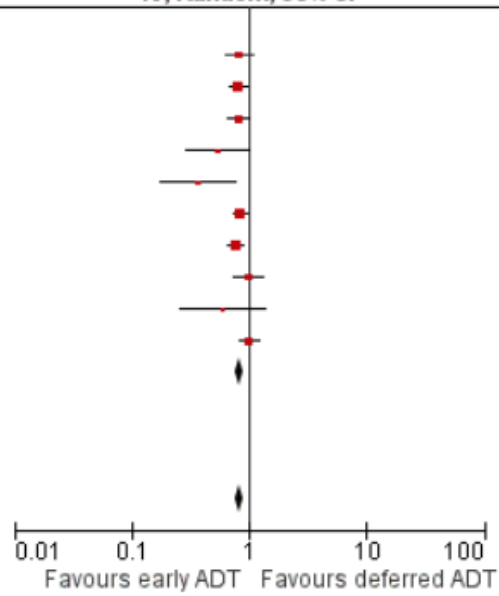
Early versus late hormonal treatment for advanced PCa

ultidisciplinary
ological Cancers

Study or Subgroup	log[Hazard Ratio]	SE	Early ADT Total	Deferred ADT Total	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Advanced disease (T2-4/N+ M0), metastatic disease (M1) and PSA relapse						
EORTC 30846	-0.1988	0.1448	119	115	8.3%	0.82 [0.62, 1.09]
EORTC 30891	-0.2231	0.0862	492	493	16.5%	0.80 [0.68, 0.95]
EPCP (1)	-0.2107	0.1123	335	322	12.0%	0.81 [0.65, 1.01]
EST 3886	-0.6162	0.3172	47	51	2.1%	0.54 [0.29, 1.01]
Granfors 2006 (2)	-1	0.38	20	19	1.5%	0.37 [0.17, 0.77]
MRC	-0.1758	0.0764	469	465	18.7%	0.84 [0.72, 0.97]
RTOG 85-31	-0.2624	0.0797	477	468	17.9%	0.77 [0.66, 0.90]
SAKK 08/88	-0.0101	0.1485	96	92	8.0%	0.99 [0.74, 1.32]
TROG 03.06/VCOG PR 0103	-0.5276	0.4181	124	137	1.3%	0.59 [0.26, 1.34]
VACURG (3)	0	0.1013	203	223	13.7%	1.00 [0.82, 1.22]
Subtotal (95% CI)			**2382**	**2385**	**100.0%**	**0.82 [0.75, 0.90]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.03$, df = 9 (P = 0.16); $I^2 = 31\%$						
Test for overall effect: Z = 4.07 (P < 0.0001)						
Total (95% CI)			**2382**	**2385**	**100.0%**	**0.82 [0.75, 0.90]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.03$, df = 9 (P = 0.16); $I^2 = 31\%$						
Test for overall effect: Z = 4.07 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Footnotes

(1) only participants included with locally advanced diseased receiving bicalutamide/placebo in combination with...
(2) only participants with lymph-node positive disease were included
(3) only patients with metastatic disease (M1) treated with orchiectomy+placebo vs placebo were included

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias):...
(**D**) Blinding of outcome assessment (detection bias): Time to...
(**E**) Incomplete outcome data (attrition bias): Oncological...
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Kunath F, Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD003506.

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Then came the ARpIs….

https://uroweb.org/guidelines/prostate-cancer/chapter/treatment, accessed on 1/03/2024

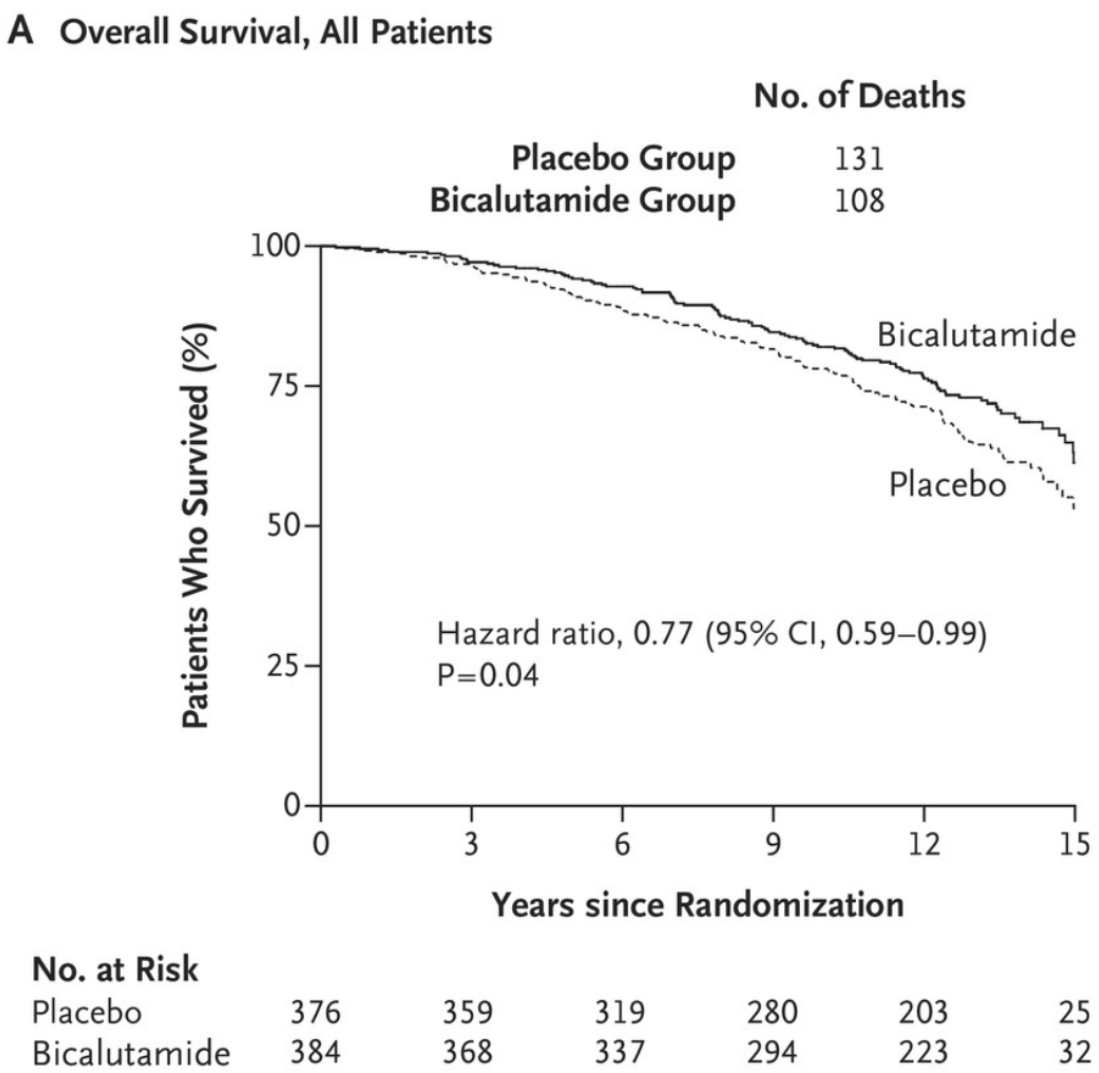
Early intensification strategy in mHSPC

Trial	Intervention	Patients, No.	OS, HR (95% CI)
GETUG-AFU15	ADT ± docetaxel	385	0.88 (0.68 to 1.14)
CHAARTED	ADT ± docetaxel	790	0.72 (0.59 to 0.89)
STAMPEDE[a]	ADT ± docetaxel	1,086	0.81 (0.69 to 0.95)
LATITUDE	ADT ± abiraterone	1,199	0.66 (0.56 to 0.78)
STAMPEDE[a]	ADT ± abiraterone	901	0.66 (0.44 to 0.98)
TITAN	ADT ± apalutamide	1,052	0.65 (0.53 to 0.79)
ARCHES	ADT ± enzalutamide	1,150	0.66 (0.53 to 0.81)
ENZAMET (all patients)	ADT ± enzalutamide	1,125	0.70 (0.58 to 0.84)
ENZAMET (docetaxel = yes)	ADT ± enzalutamide	503	
ENZAMET (docetaxel = no)	ADT ± enzalutamide	622	
PEACE-1	ADT + docetaxel ± abiraterone	710	0.75 (0.59 to 0.95)
ARASENS	ADT + docetaxel ± darolutamide	1,305	0.68 (0.57 to 0.80)
HORRAD	ADT ± prostate RT	432	0.90 (0.70 to 1.14)
STAMPEDE	ADT (docetaxel allowed) ± prostate RT	2061	0.90 (0.81 to 1.01)

Wala J, et al. J Clin Oncol 2023;41(20):3584-3590.

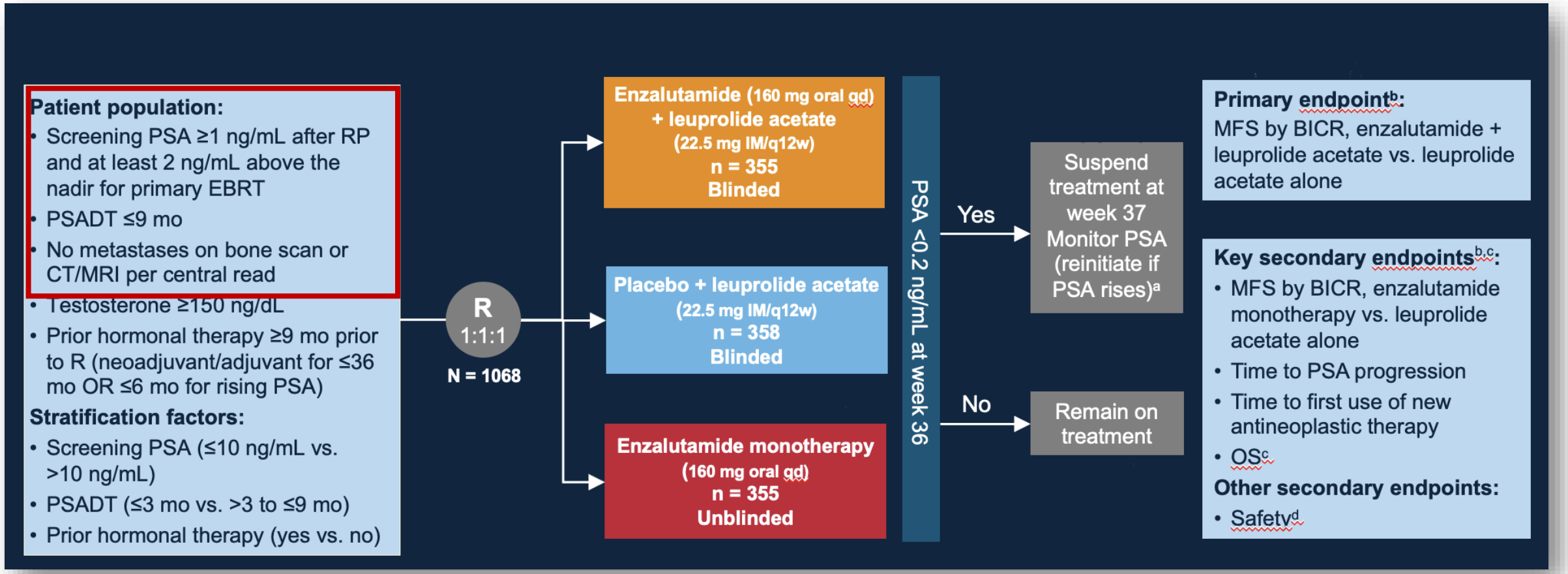
Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer (RTOG 9601)

- 760 patients
- PSA level of 0.2 to 4.0 ng/ml
- 24 months of bicalutamide at 150 mg daily or daily placebo tablets during and after radiation therapy.



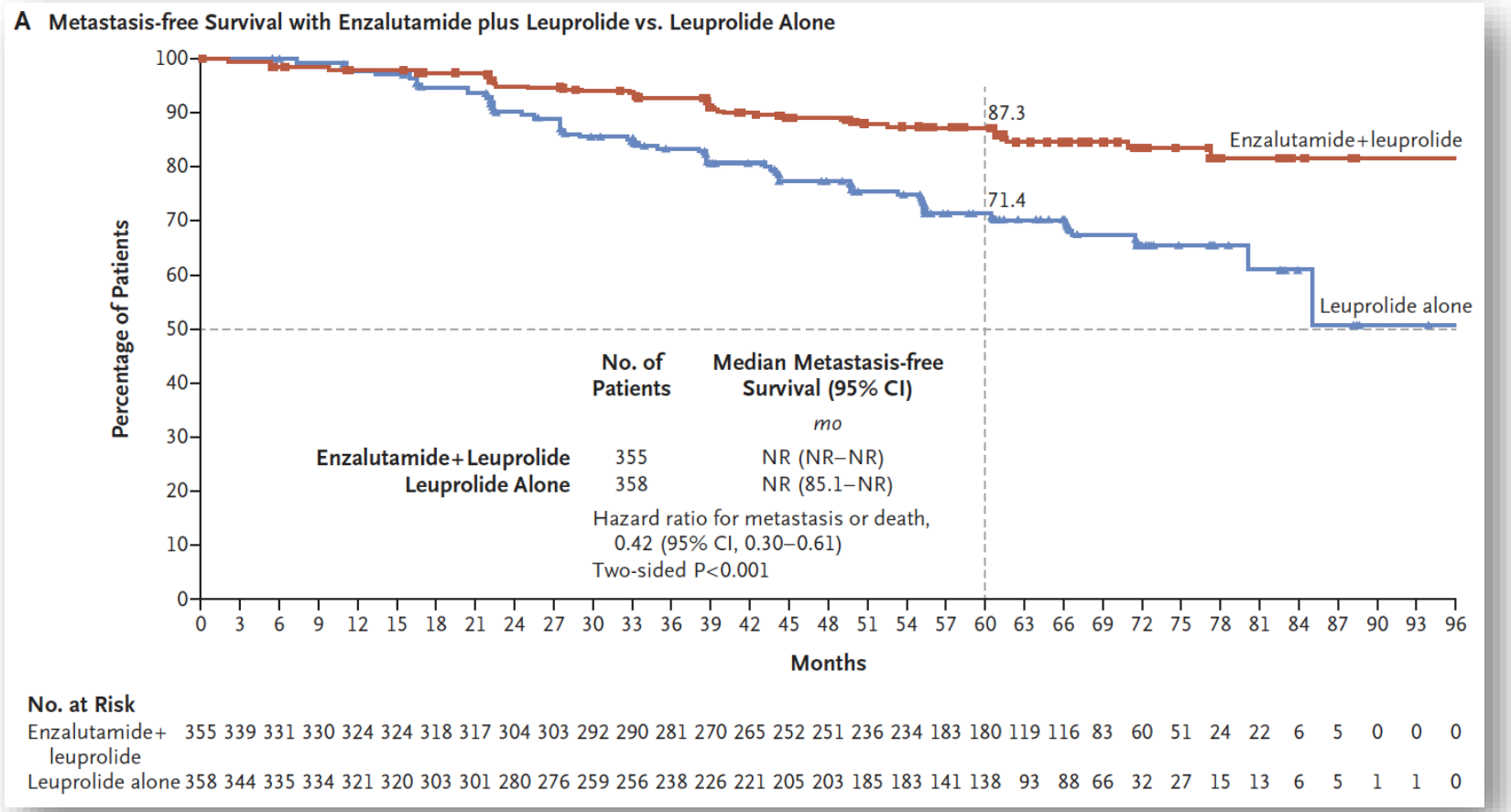
Shipley W. et al. NEJM. 2017 Feb 2;376(5):417-428.

Improved Outcomes with Enzalutamide in High-risk Biochemically Recurrent PCa



Freedland SJ, NEJM. 2023 Oct 19;389(16):1453-1465.

Improved Outcomes with Enzalutamide in High-risk Biochemically Recurrent PCa

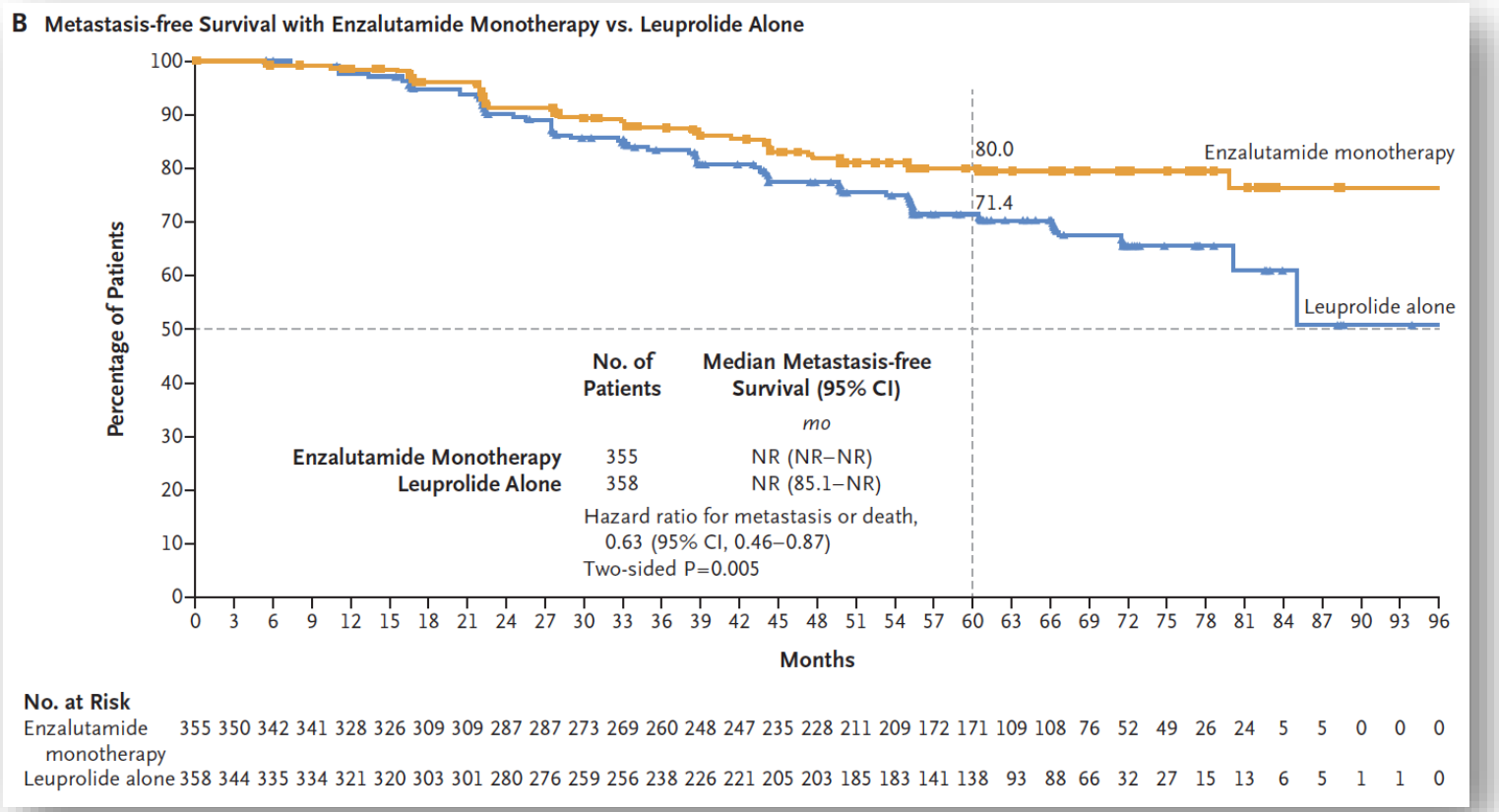


ADT + enzalutamide improve MFS (and OS) over ADT

Not a surprised….

Freedland SJ, NEJM. 2023 Oct 19;389(16):1453-1465.

Improved Outcomes with Enzalutamide in High-risk Biochemically Recurrent PCa

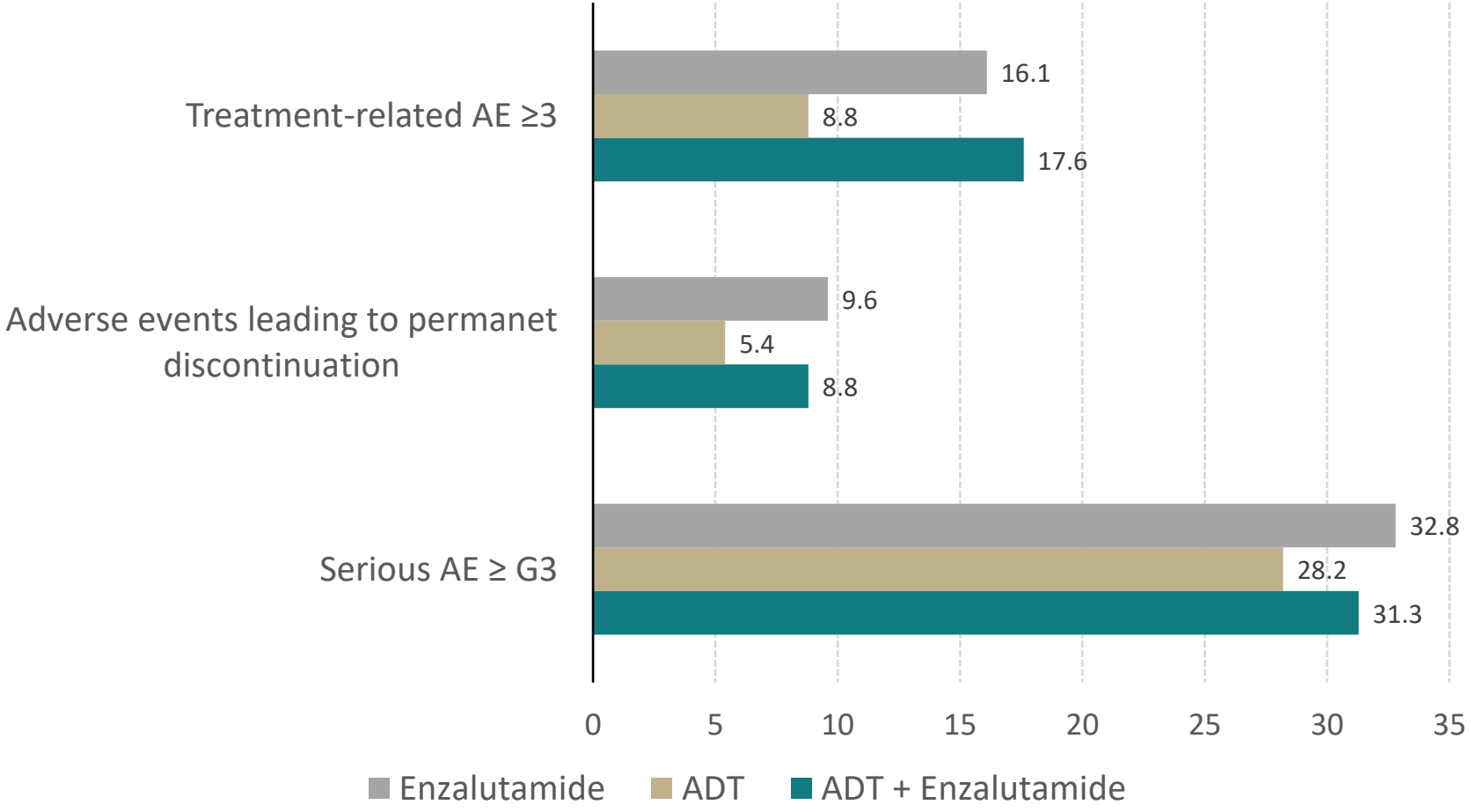


Enza alone improve MFS over ADT alone…

Who is the backbone now?

Freedland SJ, NEJM. 2023 Oct 19;389(16):1453-1465.

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

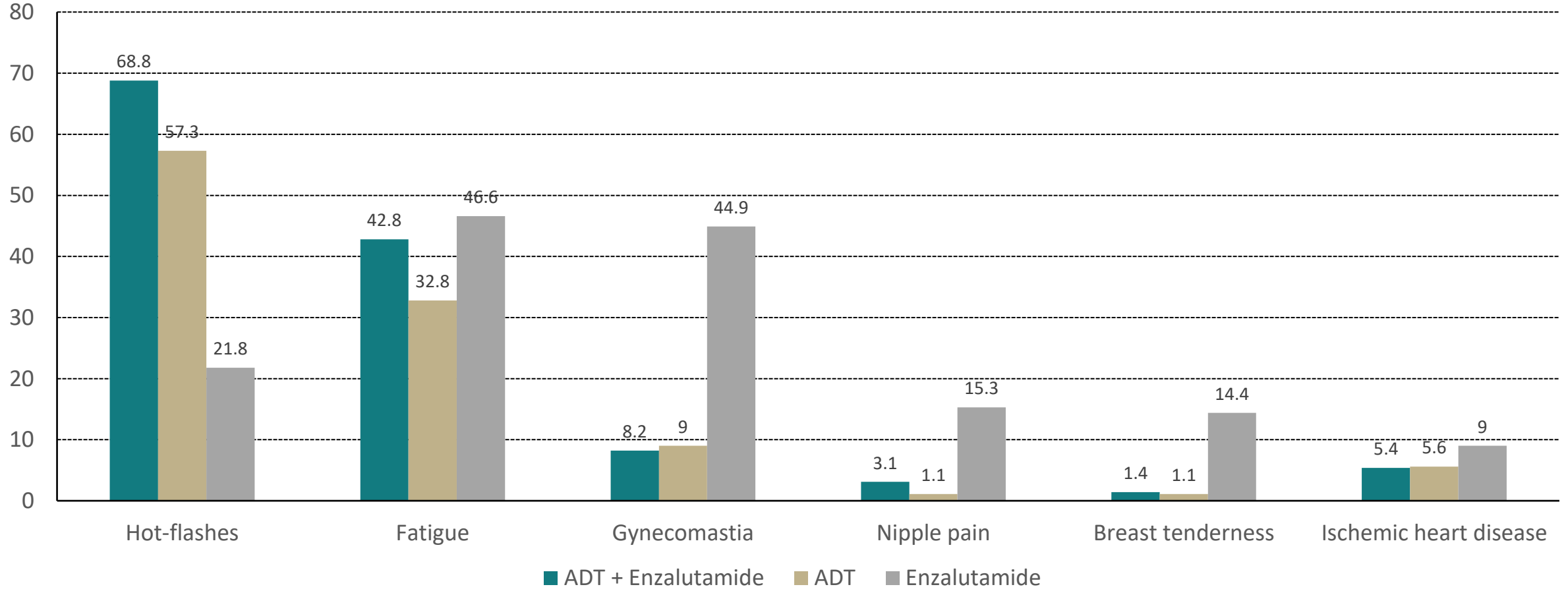


Side effects are **not** numerically inferior with enzalutamide monotherapy.

Freedland SJ, NEJM. 2023 Oct 19;389(16):1453-1465.

Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

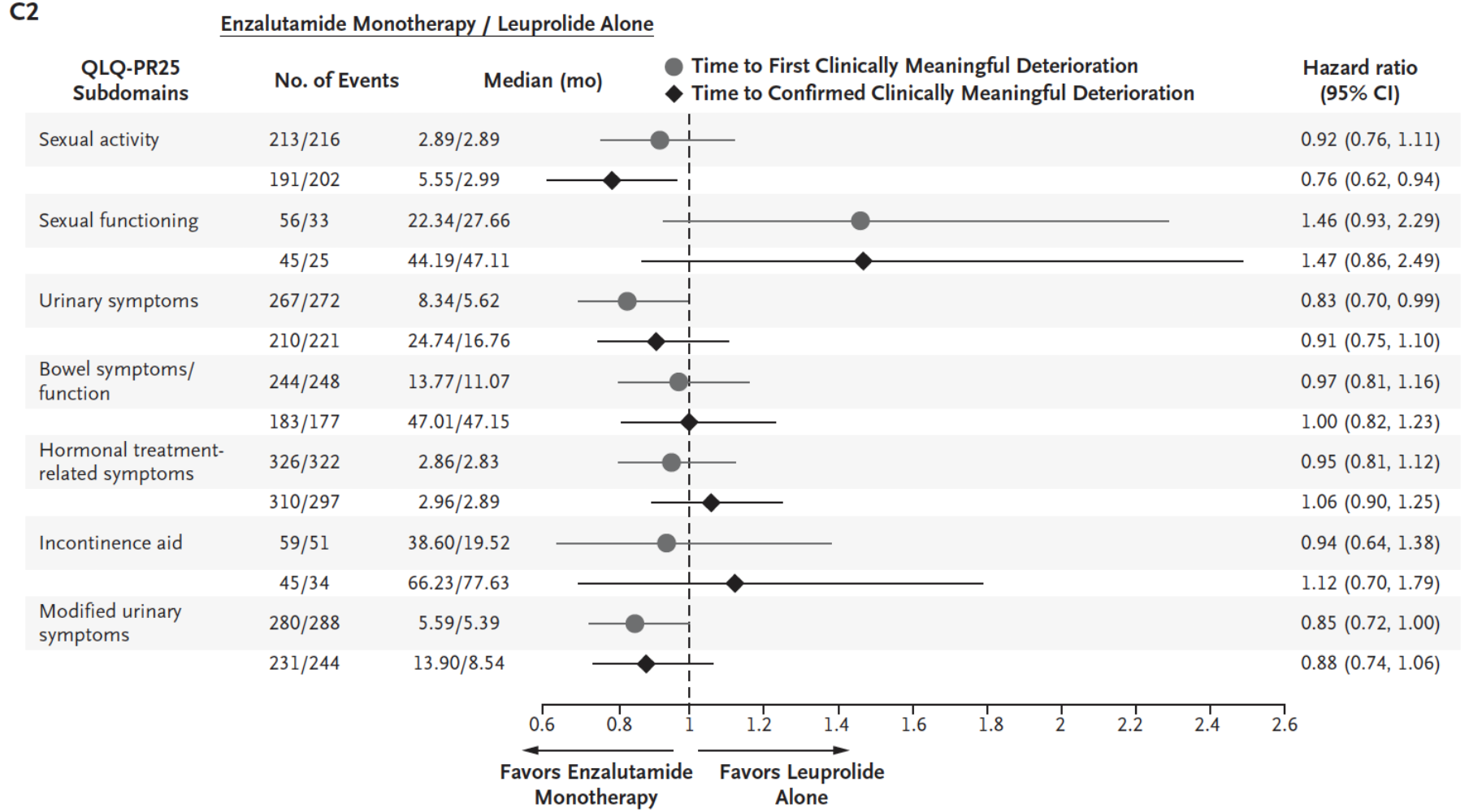
BMUC
UROLOGY - RADIATION ONCOLOGY - MEDICAL ONCOLOGY
11th Belgian Multidisciplinary Meeting on Urological Cancers



Freedland SJ, NEJM. 2023 Oct 19;389(16):1453-1465.

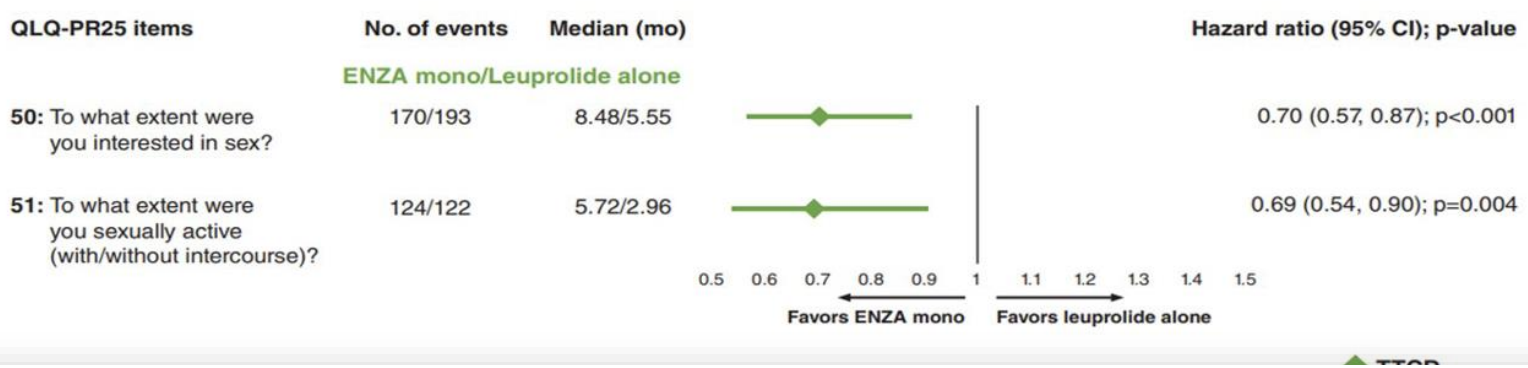
Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer

C2

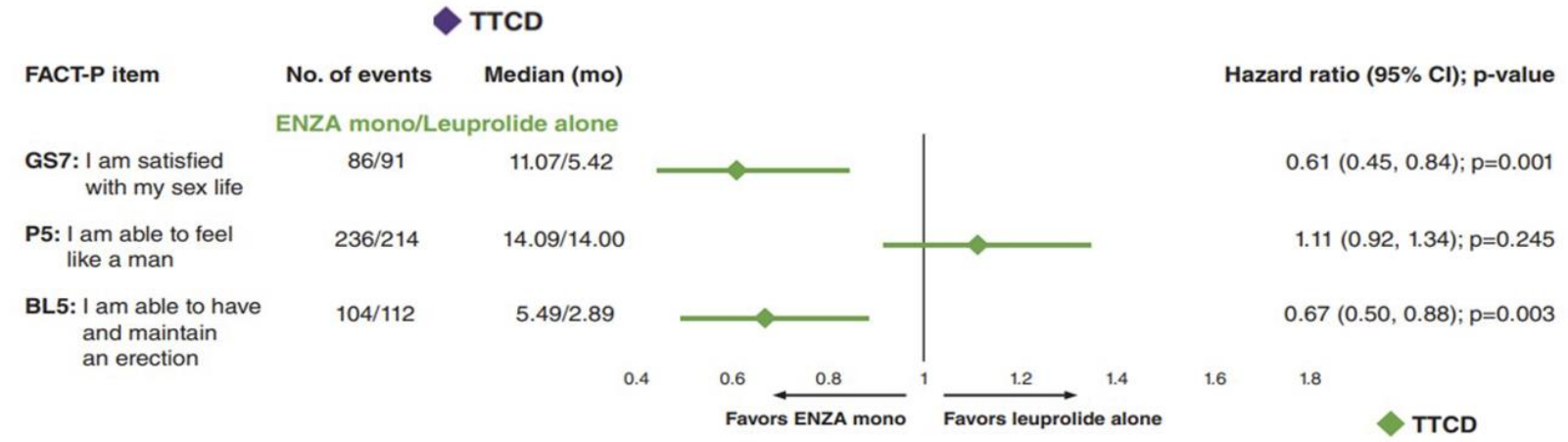


EMBARK post hoc analysis of sexual activity patient-reported outcome measures.

- TTCD was delayed in ENZA mono vs leuprolide alone for:
  - QLQ-PR25 item 50 (interest)
  - QLQ-PR25 item 51 (activity)



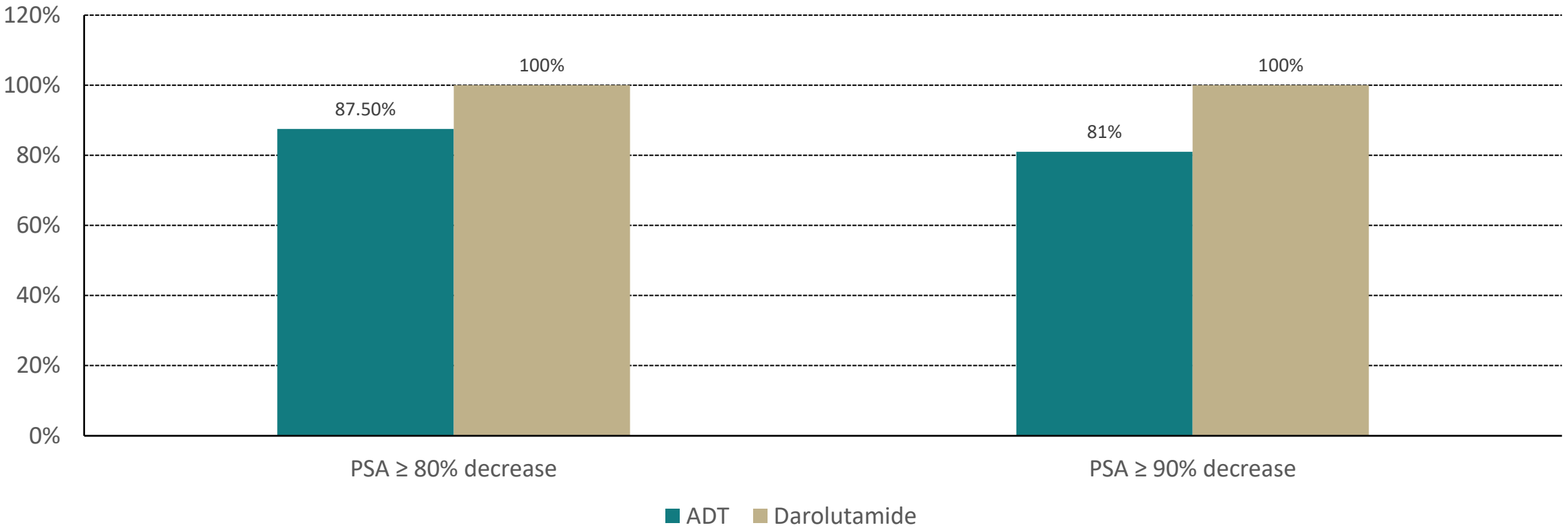
- TTCD was delayed in ENZA mono vs leuprolide alone for:
  - FACT-P item GS7 (satisfaction)
  - FACT-P item BL5 (erectile function)



Freedland et al. J Clin Oncol 42, 2024 (suppl 4; abstr 313)

A Phase 2 Randomized Open-label Study of Oral Darolutamide Monotherapy vs. ADT in Men with HSPC (EORTC-GUCG 1532)

PSA decrease at 24 weeks of treatment



Tombal et al. Eur.Urol.Onc, online.

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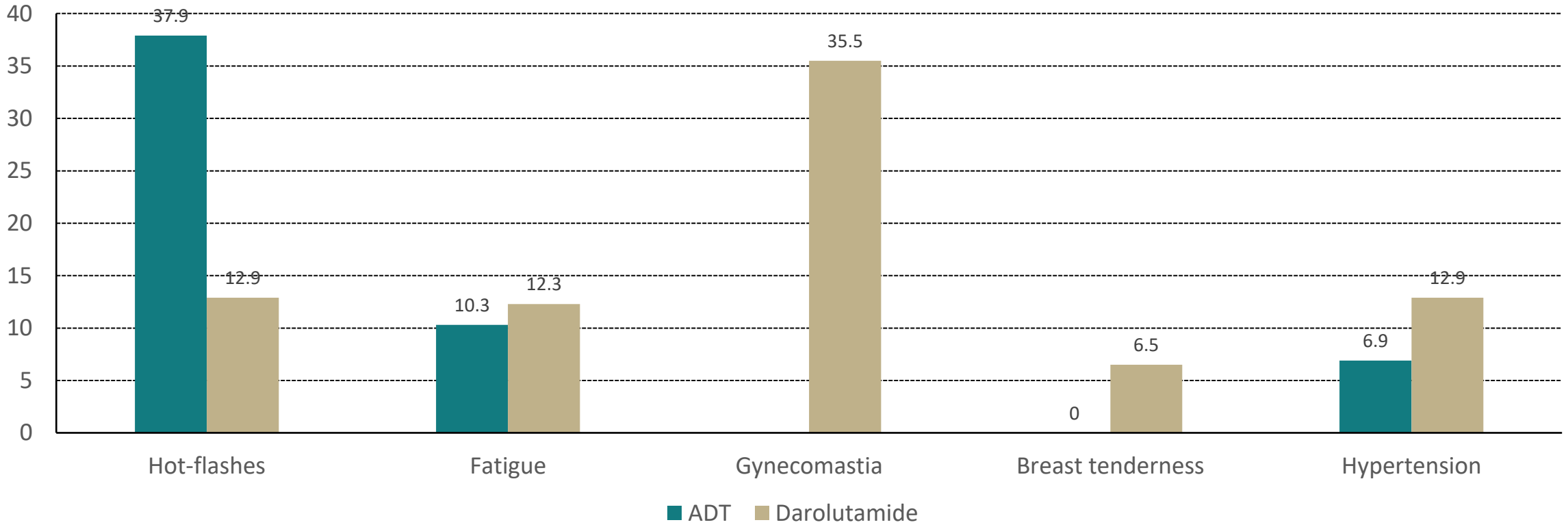

Tombal et al. Eur.Urol.Onc, online.

Systemic therapy optimisation

EAU Low-Risk BCR

- PSA-DT > 1 year AND pathological ISUP grade < 4 for RP; interval to biochemical failure > 18 months AND biopsy ISUP grade < 4 for RT)

EAU High-Risk BCR

- PSA-DT < 1 year OR pathological ISUP grade 4–5 for RP, interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5 for RT

- The benefit of ADT is inconsequential, alone or adjuvant to RT, in an unselected patient population, while the side effects are significant.
- Because of that, delaying the initiation of ADT until a later stage was deemed acceptable.
- Enzalutamide (±ADT) significantly increases OS.
- Hence, is it still acceptable to delay the ARpI ?

But then, what about MDT?

https://uroweb.org/guidelines/prostate-cancer/chapter/treatment, accessed on 1/03/2024

Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic CRPC: A Randomized Phase II Trial (ARTO).

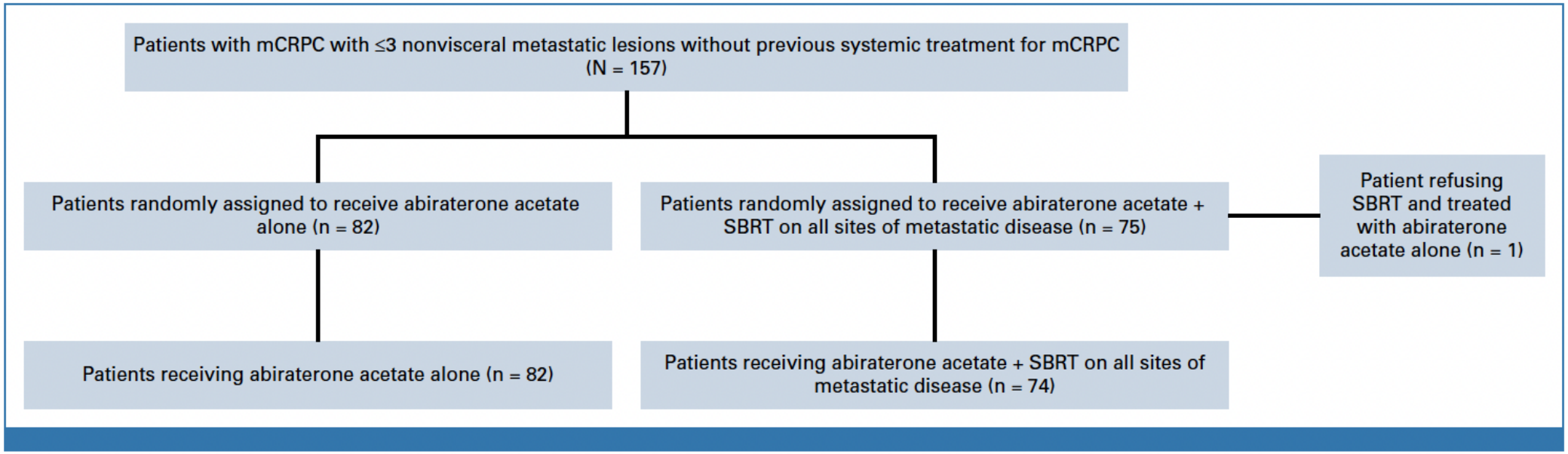

FIG 1. Flow diagram summarizing enrollment and treatment allocation. mCRPC, metastatic castration-resistant prostate cancer; SBRT, stereotactic body radiation therapy.

Francolini, J Clin Oncol. 2023 Sep 21;JCO2300985.

Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic CRPC: A Randomized Phase II Trial (ARTO).

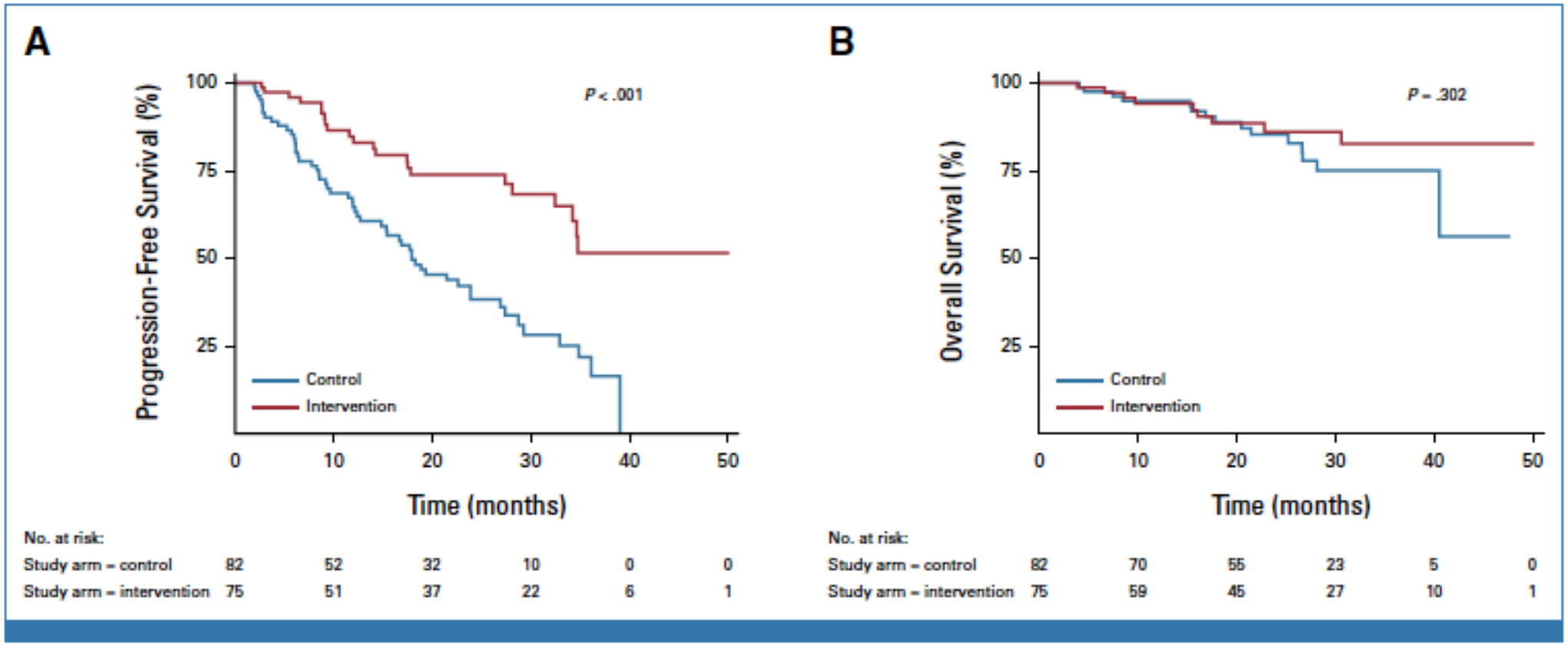

FIG 2. Cox regression analysis for (A) progression-free survival and (B) overall survival in the experimental versus control arm.

Francolini, J Clin Oncol. 2023 Sep 21;JCO2300985.

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- Enzalutamide (±ADT) significantly increases OS.
- Hence, is it still acceptable to delay the ARpI ?
- But then, there is the perspective of overtreatment and increased toxicity.

https://uroweb.org/guidelines/prostate-cancer/chapter/treatment, accessed on 1/03/2024

Safety of ARPIs

Increased PFS
Increased OS

Increased long-term toxicity

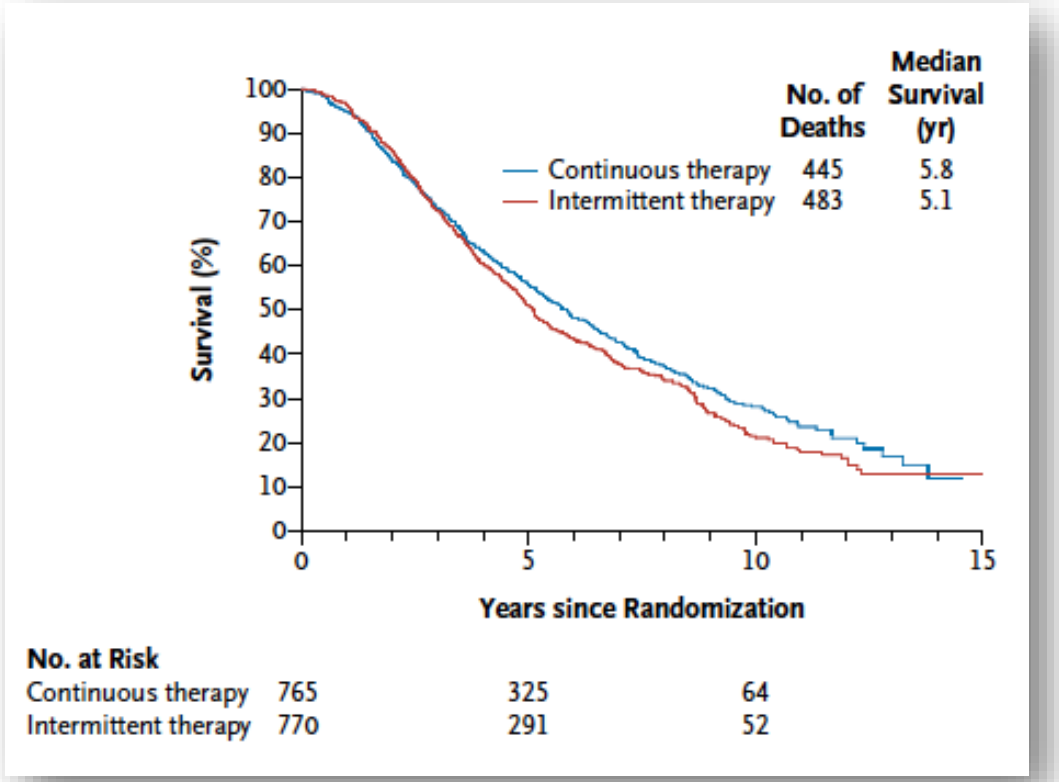
- Increased risk of CV events
  - ✓ (RR 1.71 [95% CI: 1.29–2.27]) and grade 3–4 HTA (RR 1.53 [95% CI: 1.19–1.97])[1]
- Increased risk of falls and fractures[2]:
  - ✓ Grade ≥3 fall (RR 1.6 [95% CI: 1.27–2.08; p<0.001])
  - ✓ All-grade fracture (RR 1.59 [95% CI: 1.35–1.89; p<0.001])
  - ✓ Likely grade ≥3 fracture (RR 1.71 [95% CI: 1.1–2.63; p=0.01])
- Increased risk of cognitive toxic effects[3]
  - ✓ (RR 2.10 [95% CI: 1.30–3.38; p=0.002]) and fatigue (RR 1.34 [95% CI: 1.16–1.54; p<0.001])

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; CV, cardiovascular; HTA, hypertension; OS, overall survival; PFS, progression-free survival; RR, relative risk. 1. Rizzo A. *Expert Opin Drug Metab Toxicol* 2021;17:1237–1243; 2. Myint ZW, et al. *JAMA Netw Open* 2020;3:e2025826; 3. Nowakowska MK, et al. *JAMA Oncol* 2023;9:930–937.

Intermittent *vs.* Continuous Androgen Deprivation in PCa (SWOG-9346; EORTC 30985)

- 3,040 patients with HSM1PC pts with performance status (PS) 0-2, PSA ≥ 5 ng/ml were treated with 7 months (m) of goserelin + bicalutamide.
- After 7 m of CAD, 1535 eligible pts achieved PSA ≤4.0
- HR for death IAD 1.10, 90% CI: 0.99 to 1.23

- Our findings were statistically inconclusive.
- In patients with mHNPC, the CI for survival exceeded the upper boundary for noninferiority, suggesting that we cannot rule out a 20% greater risk of death with iADT. Still, too few events occurred to rule out the significant inferiority of intermittent therapy.
- iADT resulted in small improvements in quality of life.



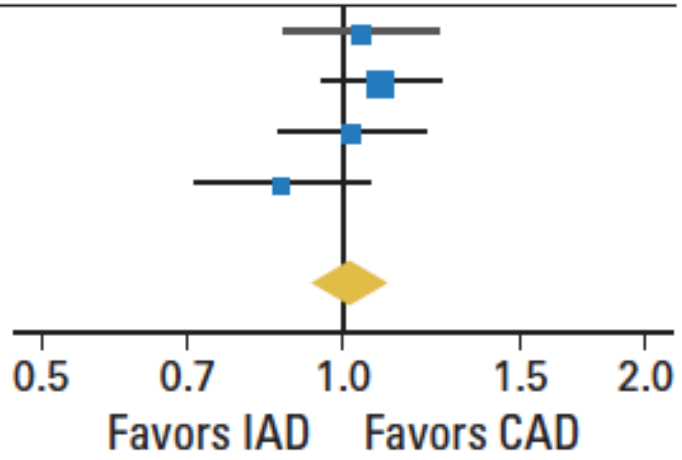
M. Hussain et al. N Engl J Med 2013;368:1314-25.

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

A

Study or Subgroup	Sample Size	Weight, %	Hazard Ratio IV, Random, 95% CI
daSilva (2011)	626	22.4	1.04 (0.87 to 1.24)
Hussain (2012)	1,535	35.5	1.09 (0.95 to 1.25)
Crook (2012)	1,386	24.3	1.02 (0.86 to 1.21)
Salonen (2012)	554	17.9	0.87 (0.71 to 1.06)
Total (95% CI)		100.0	1.02 (0.93 to 1.11)

Heterogeneity: $\chi^2 = 3.35$, df = 3 ($P = .34$); $I^2 = 10\%$
Test for overall effect: $Z = 0.42$ ($P = .67$)

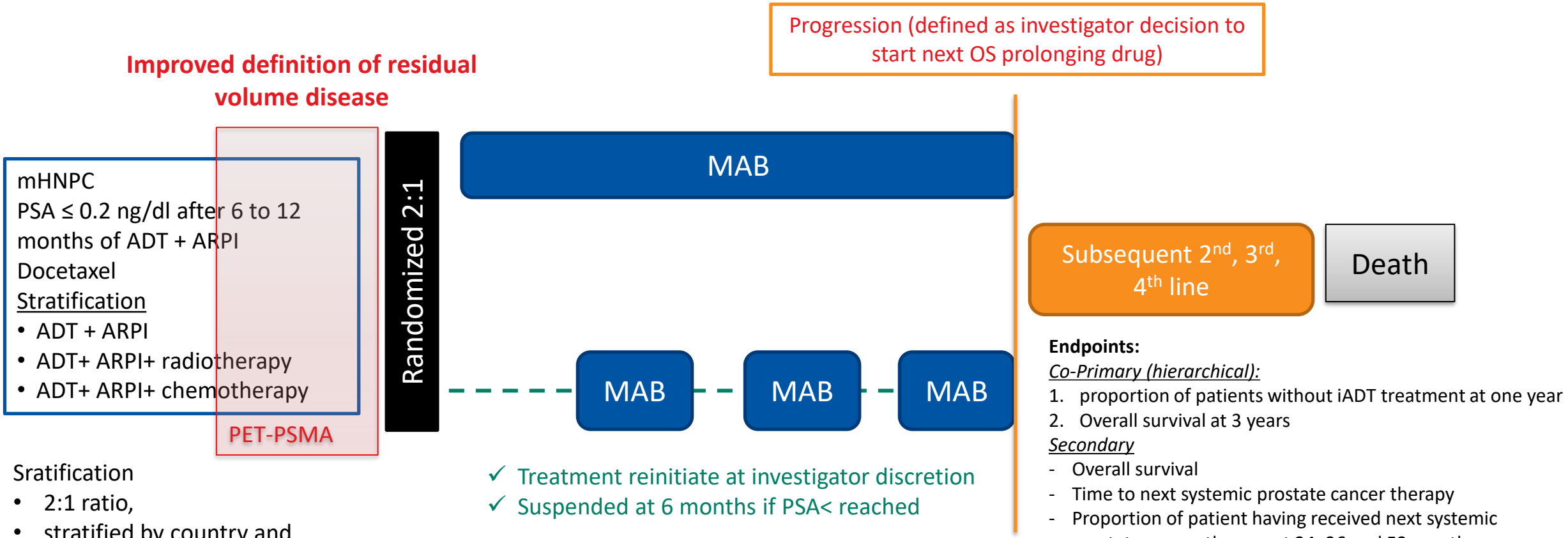


- There is fair evidence to recommend the use of IAD instead of CAD for the treatment of men with relapsing, locally advanced, or metastatic PCa who achieve a good initial response to ADT.
- This recommendation is based on evidence against superiority of either strategy for time-to-event outcomes and substantial decrease with IAD in exposure to ADT , resulting in less cost, inconvenience, and potential toxicity.

Niraula. J Clin Oncol. 2013 Jun 1;31(16):2029-36.

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

✓ Treatment reinitiate at investigator discretion
✓ Suspended at 6 months if PSA< reached

Endpoints:

Co-Primary (hierarchical):

1. proportion of patients without iADT treatment at one year
2. Overall survival at 3 years

Secondary

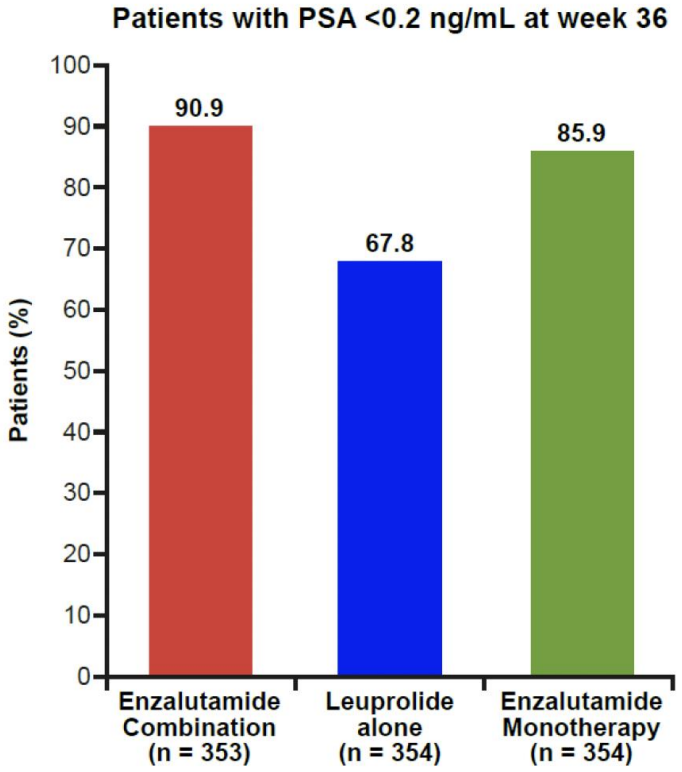
- Overall survival
- Time to next systemic prostate cancer therapy
- Proportion of patient having received next systemic prostate cancer therapy at 24, 36 and 52 months.
- Toxicity with CTCAE v5
- Quality of life with QLQ-C30/PR-25
- Health economics parameters (e.g. Incremental cost effectiveness ratio)

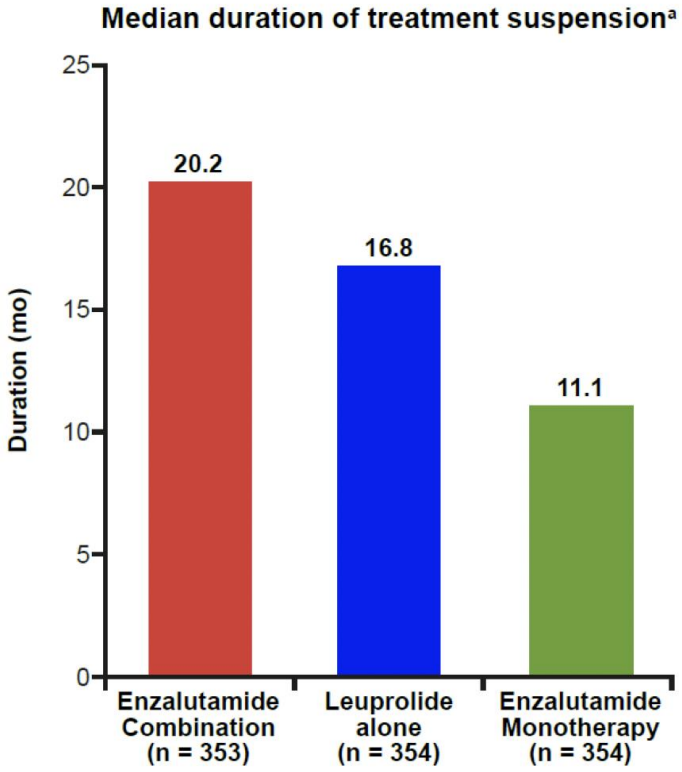
mHNPC: metastatic hormone naïve prostate cancer patients;

EORTC

The future of cancer therapy

Percentage of Patients who Achieved Undetectable PSA and duration of treatment suspension in EMBARK.



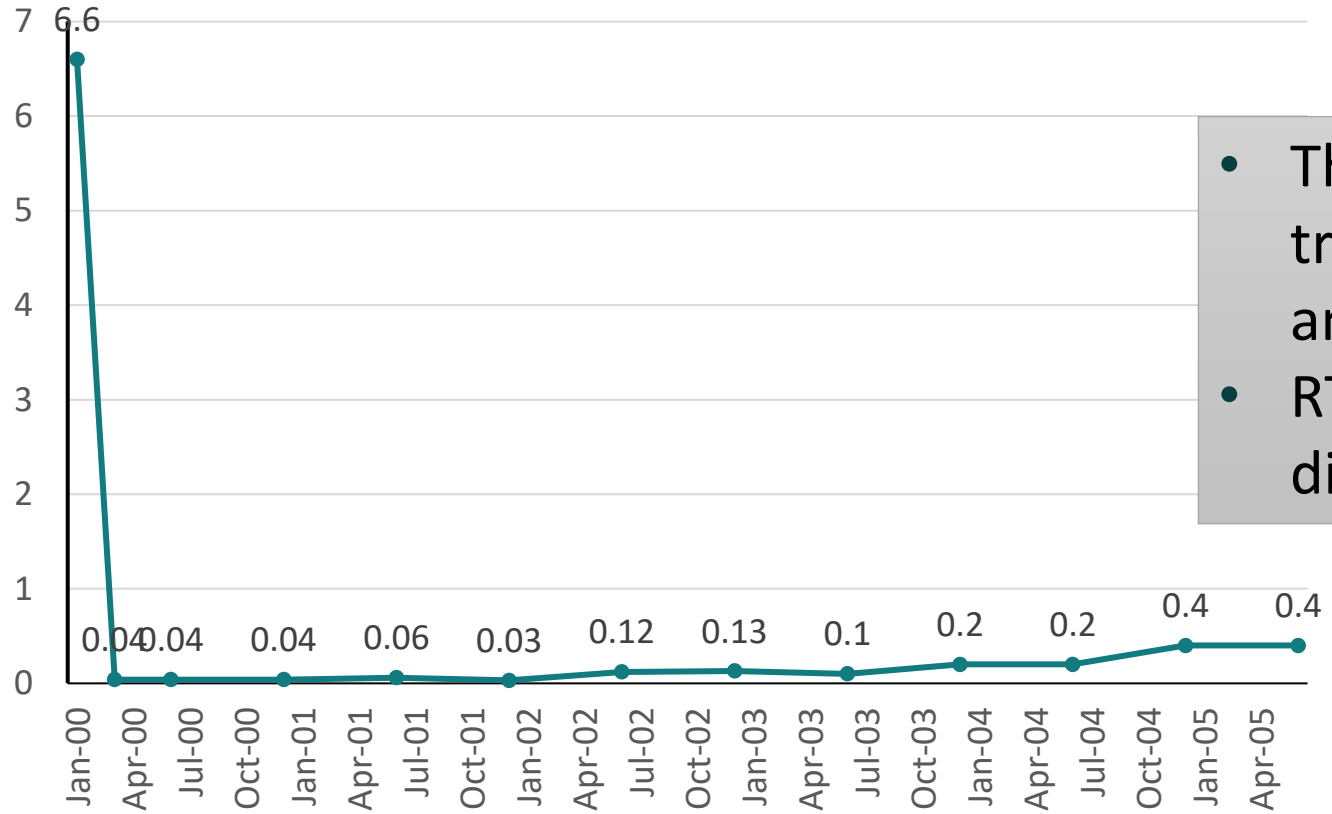


Can we prolong the duration of the "OFF" period?

Freedland et al. N Engl J Med 2023;389:1453-65.

Low-risk BCR

- 61-y.o. intermediate risk localized (PSA 7 ng/ml, T1c, 3/12 Bx Gleason 7 (4+3), mpMRI T2c)
- RP + limited LND 01/2000: T2b Gleason 7 (4+3), R0, N0 (8 Ln), M0

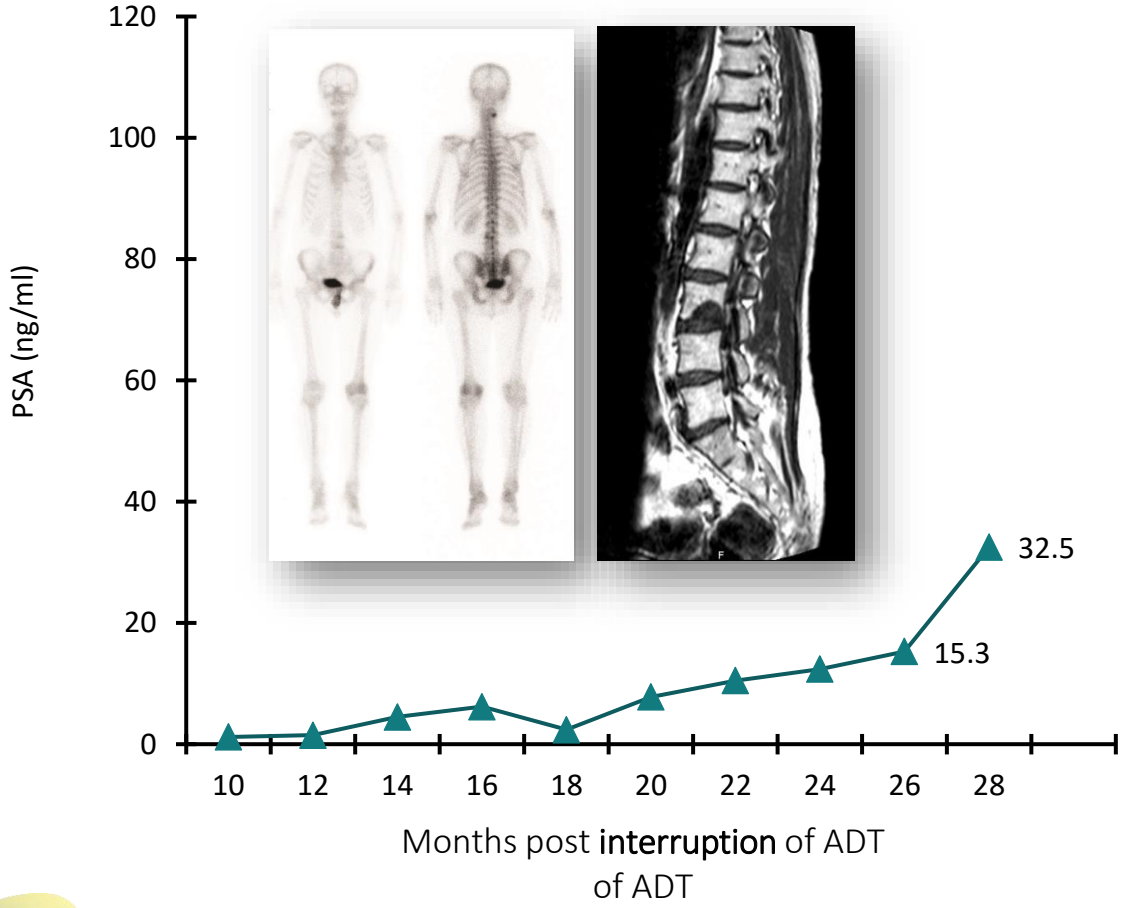


- That patient probably doesn't need treatment; he must be reassured and closely monitored.
- RT without hormone can be discussed

Case and images courtesy of Bertrand Tombal and Frederic Lecouvet, CUSL, Brussels

High-risk BCR

- 71 y.o. EBRT + 2 years ADT for locally-advanced PCa (T3b, Gleason 8 (5+3), PSA 47 ng/ml, NO, MO), testosterone 43 ng/dl, PSA doubling time 7 months



- It was acceptable to delay ADT
- I don't believe it is still acceptable delaying treatment with an ARPI
- Intermittent treatment remains central
- New imaging technology and MDT will remain crucial to enhance the benefit of systemic treatment

EBRT: external beam radiation therapy; ADT: androgen deprivation therapy, Images provided by B.Tombal & F.Lecouvet , Clinique Universitaires Saint-Luc, Belgium