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EORTC GUCG 2238 “DE-ESCALATE”

INTERMITTENT ANDROGEN DEPRIVATION THERAPY IN THE ERA OF ANDROGEN RECEPTOR PATHWAY INHIBITORS; A PHASE 3 PRAGMATIC RANDOMISED TRIAL

An EORTC, UNICANCER, GETUG, CTI consortium Trial

Bertrand TOMBAL on March 26, 2024

Intermittent ADT as the standard of care treatment of metastatic PCa

- The historical standard of care treatment for metastatic hormone naïve prostate cancer (mHNPC) is androgen deprivation therapy (ADT)
- ADT increases OS with the price of chronic side effects, including a decreased libido, accelerated cognitive decline, increased bone loss leading to frailty fractures, and an increased risk of cardiovascular disease.
- Consensus and guidelines recognize that ADT can be administered intermittently (iADT) in patients with a significant PSA response after 6 to 8 months of treatment.
- The goal of iADT is to preserve OS benefits while improving QoL and reducing resource engagement.

ADT: androgen deprivation therapy;

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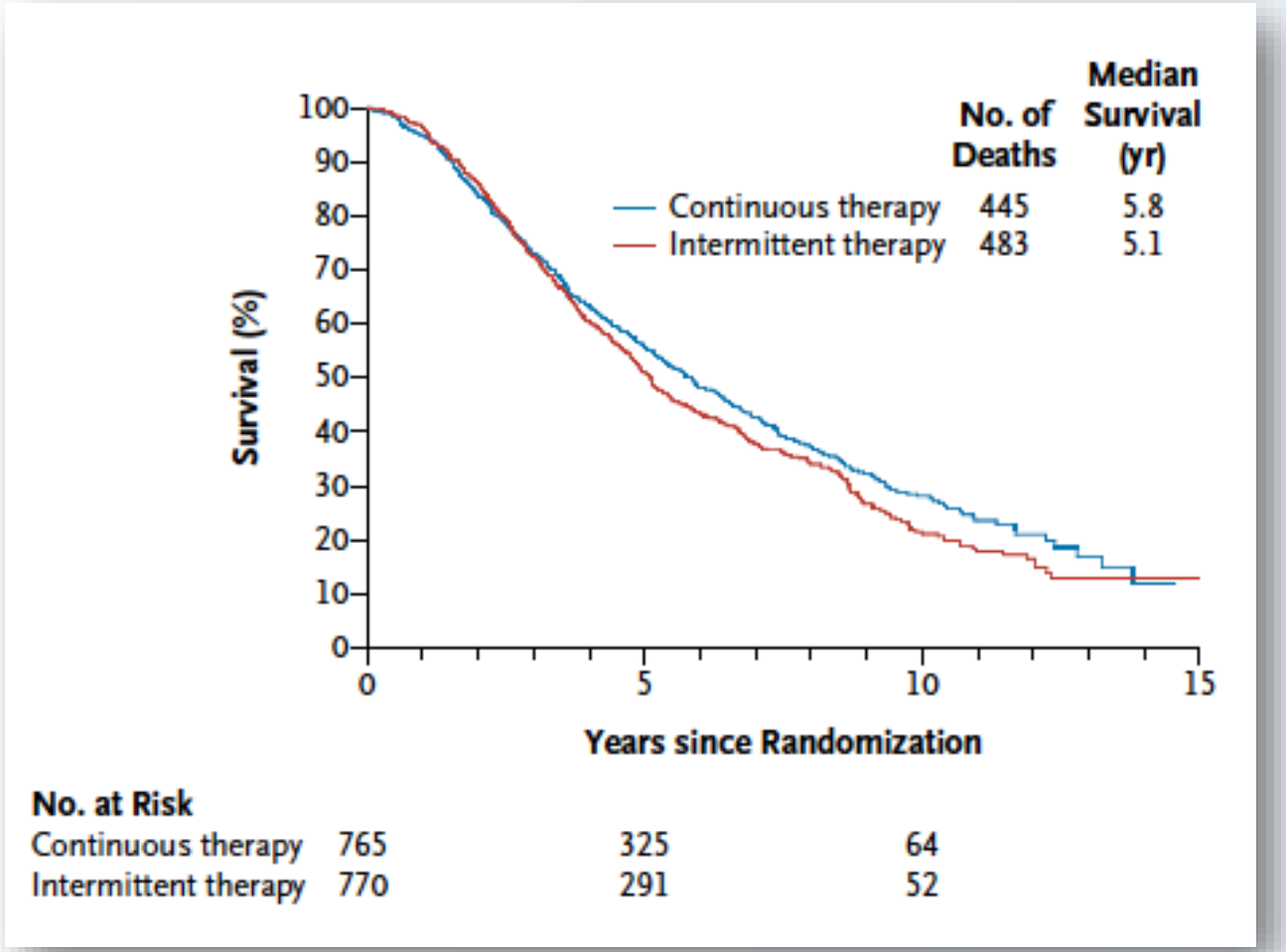
Intermittent versus Continuous Androgen Deprivation in Pca (SWOG-9346; EORTC 30985)

- 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



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

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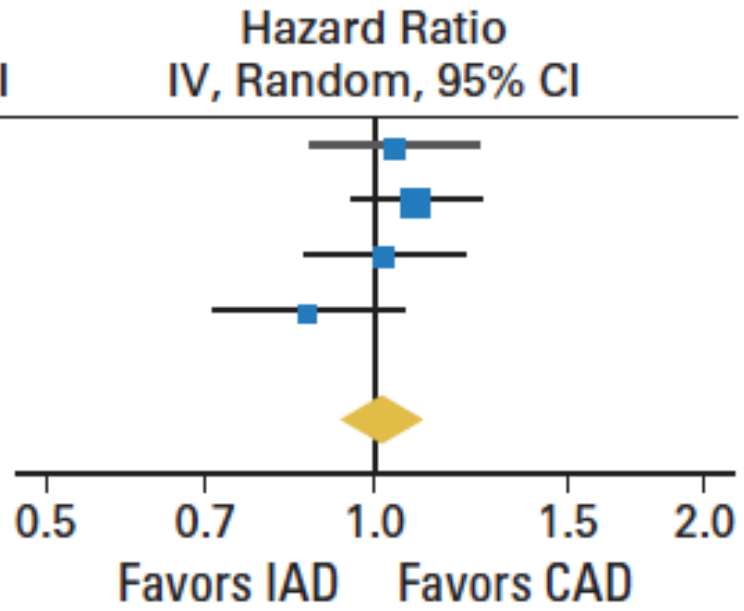
Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

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 ($P = .67$)



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

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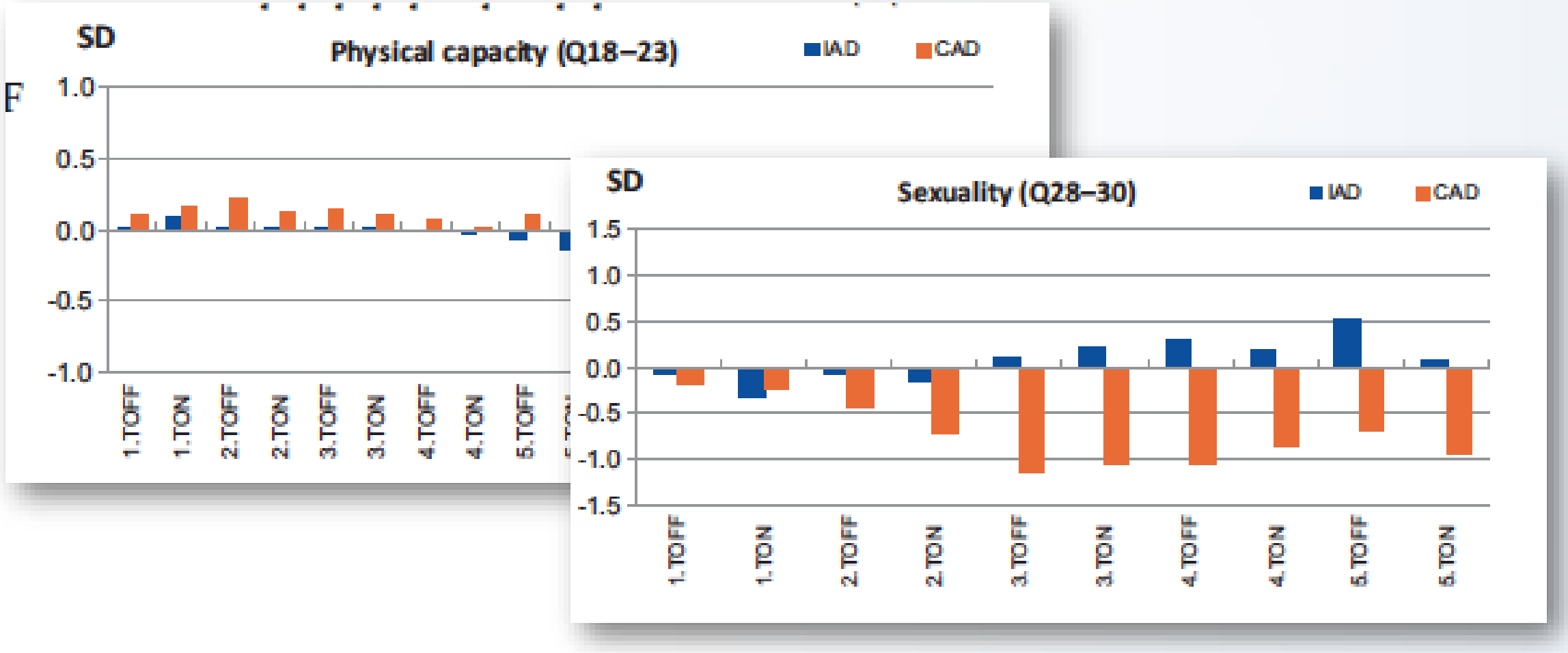
Advanced Prostate Cancer Treated with Intermittent or Continuous ADT in the Randomised FinnProstate Study VII: Quality of Life and Adverse Effect.



J. Salonen et al. Eur Urol. 2013 Jan;63(1):111-20Differences in QoL between IAD and CAD. Expressed by th 0.5 standard deviation rule in the domains of activity limitation, physical capacity, sexual functioning, and sexuality. Lower scores indicate better health in activity limitation, physical capacity, and sexuality; higher scores indicate better sexual functioning.

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ADT as the standard of care treatment of metastatic PCa

- Then came four AR pathway inhibitors (ARPI): abiraterone, apalutamide, enzalutamide, and darolutamide.
- Seven trials on 8921 patients have now established ADT + ARPI as the new standard of care…
- BUT, the concept of intermittent treatment was lost in the translation.

ADT: androgen deprivation therapy;

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Early intensification strategy in mHNPC

Agent	Study	n	HR (95%CI)	p
Abiraterone /P	LATITUDE[1]	1199	0.62 (0.51 - 0.76)	<0.001
	STAMPEDE ITT[2]	1917	0.63 (0.52 - 0.76)	<0.001
	PEACE 1 ITT[3]	1172	0.82 (0.69-0.98)	0.030
	PEACE 1 Docetaxel[3]	710	0.75 (0.59-0.95)	0.017
Apalutamide	Titan[4]	1052	0.65 (0.53 - 0.79)	<0.001
Enzalutamide	ENZAMET[5]	1125	0.67 (0.52 - 0.86)	0.002
	ARCHES[6]	1150	0.70 (0.58-0.84)	<0.0001
Darolutamide	ARASENS Docetaxel[7]	1306	0.68 (0.57-0.80)	<0.001

- Trials used continuous administration until progression, with no intermittent regimens.
- 20-30% long-term Grade 3-4 TEAE
- Cost increased from 15k to 150k per patient.
- No study so far has looked at a de-escalation, intermittent setting.

ITT: Intent to treat; HR: hazard ratio; CI: confidence interval

1) Fizazi, K. et al. Lancet Oncol. 2019 20(5):686-700; 2) James, N. D. et al.. NEJM 2017 27;377(4):338-351; 3) Fizazi K et al. Lancet . 2022 399(10336):1695-1707.4)Chi K. et al. JCO 2021 39(20):2294-2303, 4) Davis ID. Et al. NEJM 2019 381(2):121-131.5) Amstrong A. et al. JCO. 2019 Nov 10;37(32):2974-2986, 10) Smith et al. NEJM 2022 386(12):1132-1142.

ADT+ ARPI: long-term increase in side-effects

- significantly 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 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); and likely grade ≥ 3 fracture (RR, 1.71; 95% CI, 1.12-2.63; P = 0.01) [2].
- increased risk of cognitive toxic effects (risk ratio (RR) 2.10; 95%CI 1.30-3.38; P = 0.002) and fatigue (RR 1.34; 95%CI 1.16-1.54; P < .001)[3]

ADT: androgen deprivation therapy, ARpI: AR pathway inhibitors; CV: cardiovascular; HTA: hypertension

1) Rizzo A, Expert Opin Drug Metab Toxicol. . 2021 Oct;17(10):1237-1243; 2) Myint ZW JAMA Netw Open. 2020 Nov 2;3(11):e2025826; 3) Nowakowska MK, JAMA Oncol 2023 Jul 1;9(7):930-937.

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ADT as the standard of care treatment of metastatic PCa

- Then came four AR pathway inhibitors (ARPI): abiraterone, apalutamide, enzalutamide, and darolutamide.
- Seven trials on 8921 patients have now established ADT + ARPI as the new standard of care…
- However, the concept of intermittent treatment was lost in the translation
- Although:
  - There is an increased risk of side effects.
  - ADT+ ARpI significantly increases the proportion of patients with a profound PSA response, hence the proportion of patients that would be candidates for an intermittent approach.

ADT: androgen deprivation therapy;

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Absolute PSA value after ADT is a strong independent predictor of survival in new metastatic PCa: data from SWOG Trial 9346 (INT-0162).

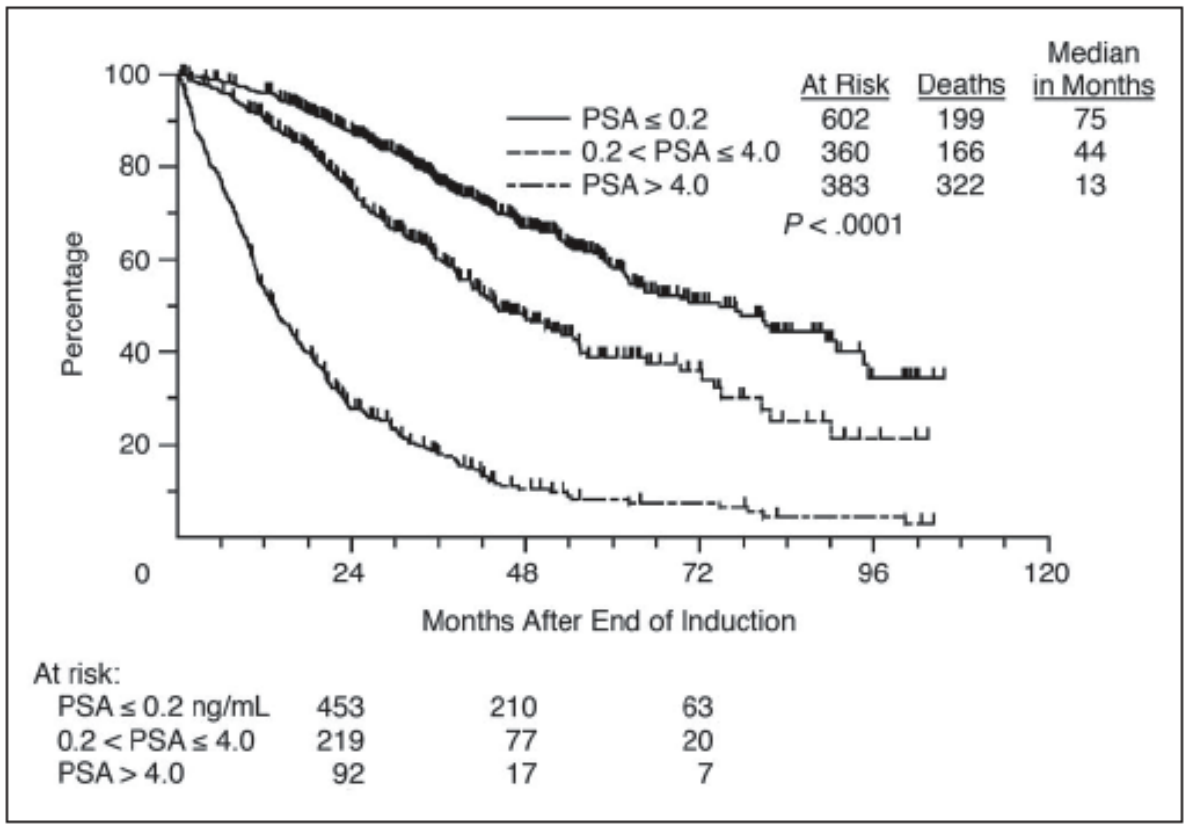

Fig 2. Overall survival by prostate-specific antigen (PSA, ng/mL) status at end of induction.

- 50% of the patients reached a PSA ≤ 0.2 ng/ml.
- Median OS 75 months.

Hussain M, J Clin Oncol. 2006 Aug 20;24(24):3984-90.

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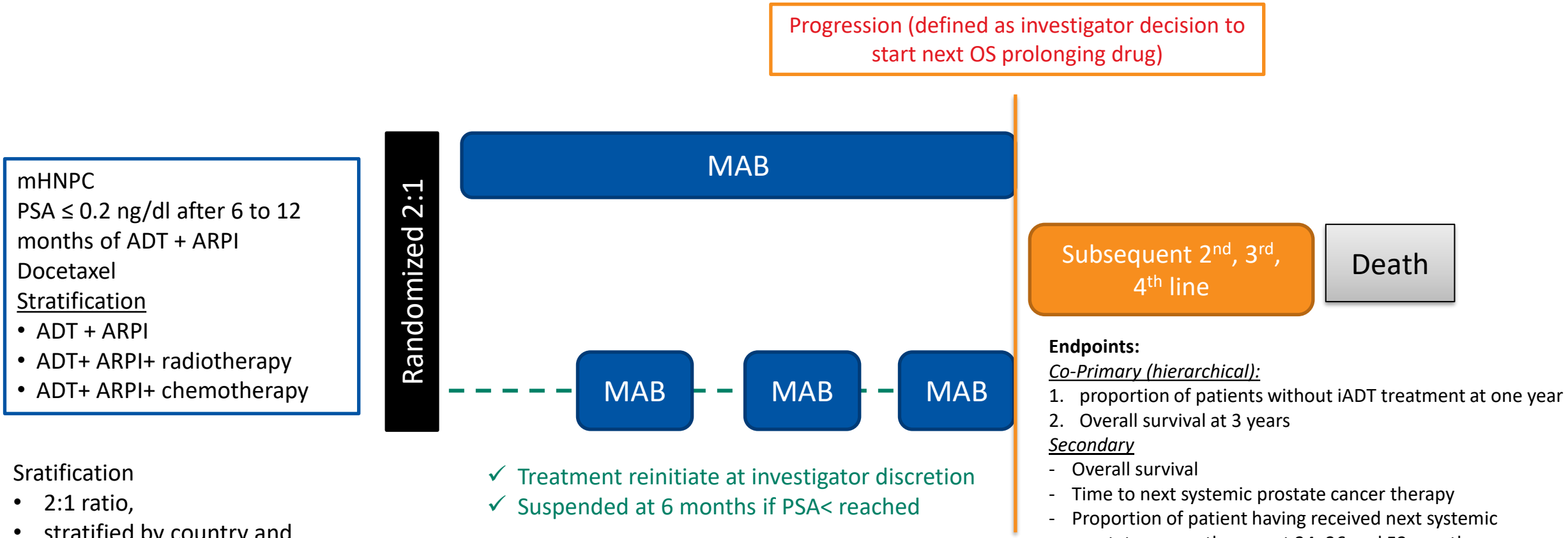
DE-ESCALATE Intermittent ADT in the era of AR pathway inhibitors; a phase 3 **pragmatic** randomized trial (EORTC 2238)

Funded by the European Union



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

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

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;

 This project has received funding from the European Union's HORIZON-MISS-CANCER-2022-01 under grant agreement Nº (101104574).

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The future of cancer therapy

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Study Objectives

Main objective

- The primary goal of de-escalation is to investigate whether using an intermittent regime results in a similar OS to continuous treatment.

Secondary objective(s)

- Assess Toxicity profile with iADT
- Assess the impact on QoL with iADT
- Assess the impact on treatment resources of using an intermittent schedule

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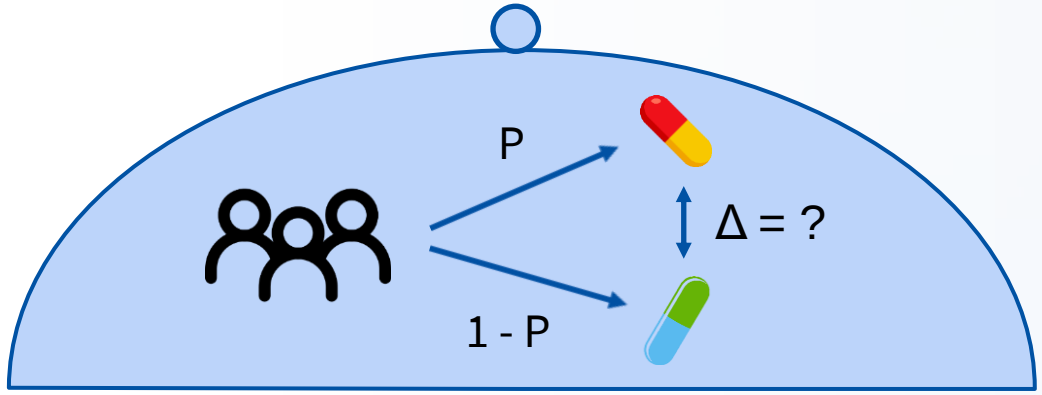
Explanatory *vs.* pragmatic trials

Explanatory trials

- Can the treatment work if it is applied under ideal circumstances?
- *Treatment efficacy*

Pragmatic trials

- Will the treatment work if it is applied in real-world clinical practice?
- *Treatment effectiveness*



Schwartz and Lellouch. J Chronic Dis (1967); Roland and Torgerson. BMJ (1998); Tunis et al. JAMA (2003); Patsopoulos. Dialogues Clin Neurosci (2011); Sedgwick. BMJ (2014); Ford and Norrie. N Engl J Med (2016)

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- Hurdles:
- There is no interest from a company, purely academic support (Horizon).
- The trial is feasible only in a pragmatic low-intervention scheme.
- Although it compares two historical SOCs, CTIS perceives the study as interventional, hence “killing” the pragmatism.
- Identical frameworks for developing a new drug and optimizing its use.

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