

¿Estrategia de intensificación o desescalada en CPHSm de primera línea (1L)?

Intensification or de-escalation strategy in 1L
mHSPC?

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Disclosures

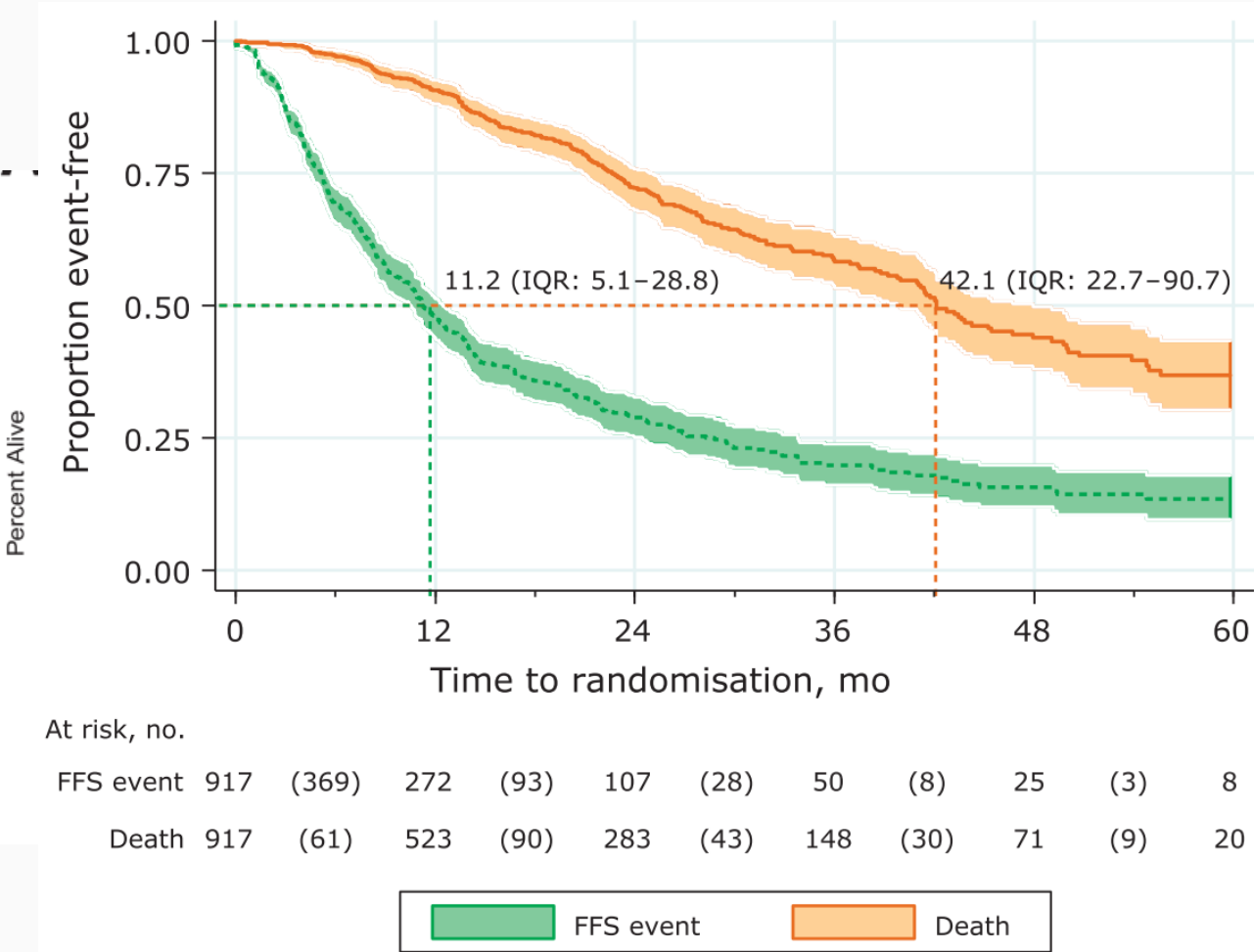
- Employment: None
- Consultant or Advisory Role: Janssen, Astellas, MSD, Bayer
- Stock Ownership: None
- Research Funding: None
- Grant support: None
- Other (Speaking and travel grants): Janssen, Astellas, Pfizer, Ipsen, Bristol, Astra-Zeneca, Roche, MSD

Intensification or de-escalation strategies in 1L mHSPC

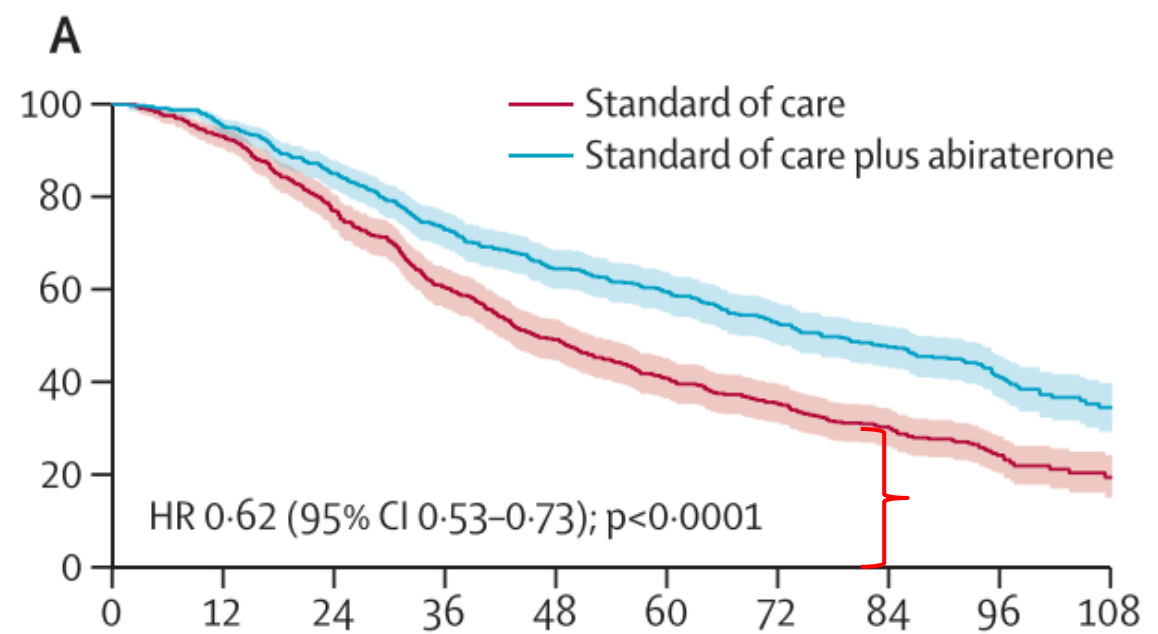
- Assessing heterogeneity in prostate cancer
- Who needs intensified therapy?
- Who can do with less?

Recent advances in drug development have dramatically increased survival

Survival with **ADT alone in STAMPEDE** (2015): median OS 42 months



of patients in the **STAMPEDE-Abiraterone** treatment arm
alive at 7 years



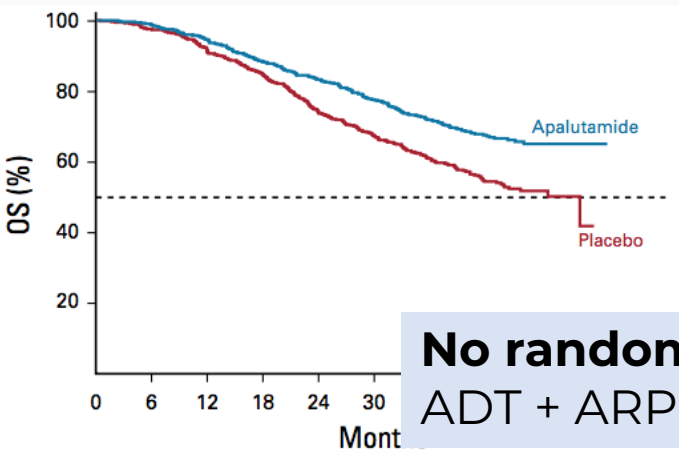
30% of patients initially treated with **ADT alone** (+SOC) arm are **alive at 7 years**

ADT alone is not standard any more

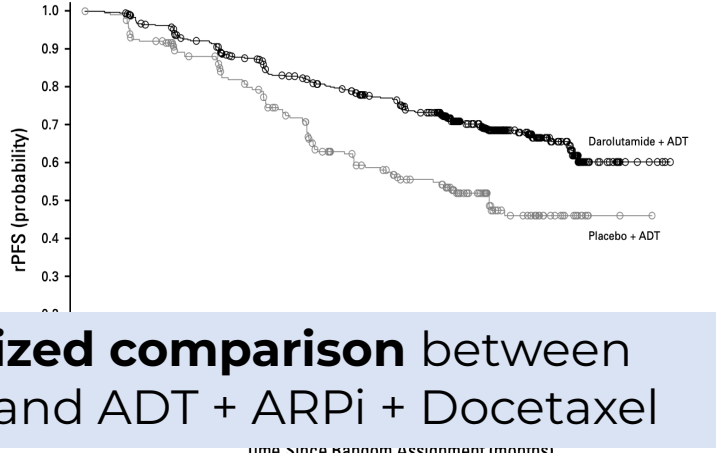
Neither is ADT + Docetaxel

ARPi doublets are better than ADT alone (or ADT + 1st gen AR antagonists)

TITAN: ADT+Apalutamide

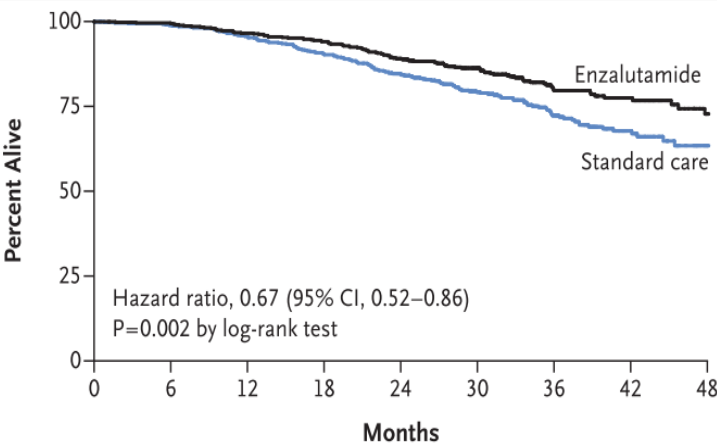


ARANOTE: ADT + Darolutamide

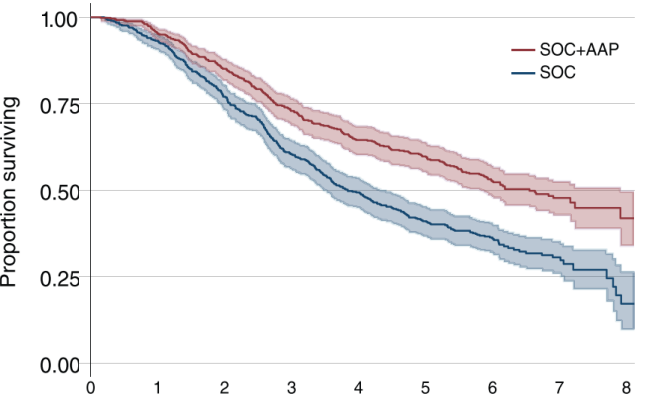


No randomized comparison between ADT + ARPi and ADT + ARPi + Docetaxel

ENZAMET: ADT + Enzalutamide

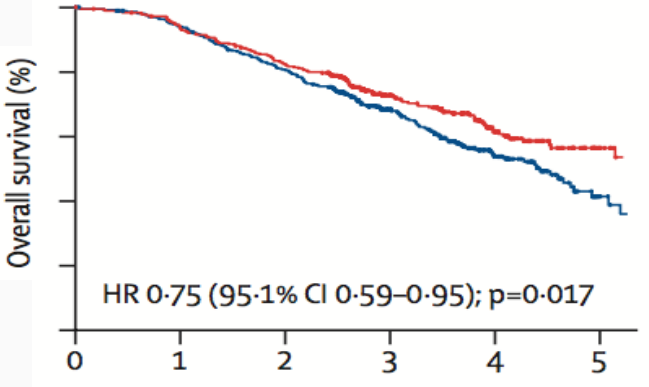


STAMPEDE: ADT + Abiraterone

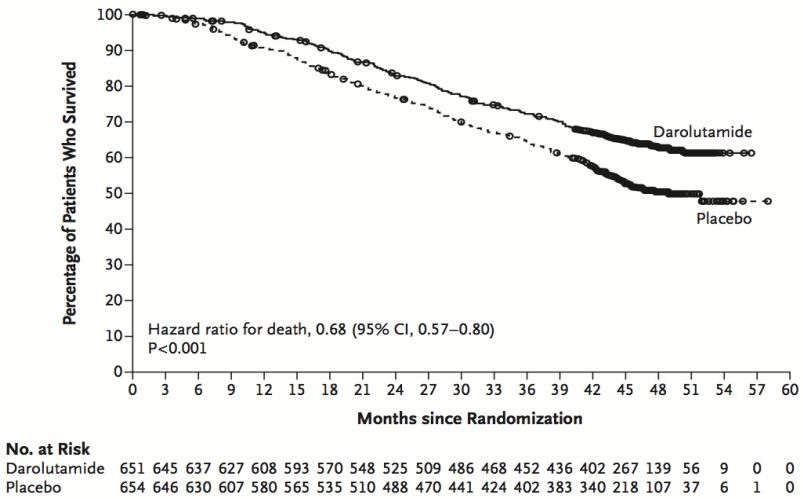


ARPi + Docetaxel triplets are better than ADT + Docetaxel doublets

PEACE-1: ADT + Docetaxel + Abiraterone



ARASENS: ADT + Docetaxel + Darolutamide



James et al. Lancet 2015. Fizazi et al N Eng J Med 2017. James et al. N Eng J Med 2017. Davis et al N Eng J Med 2019.. Chi et al. N Eng J Med 2019. Smith et al. N Eng J Med 2022. Saad et al. Eur Urol 2024.

All patients receive ADT + ARPi. Who needs chemotherapy?

No randomized comparison between ADT + ARPi +/- Docetaxel

Large, randomized phase III trials were designed for an **all-comers population**
Sugroup analyses based mainly on impact of **disease volume** are available
These **do not assess the heterogeneity** of advanced prostate cancer adequately

	CHAARTED	STAMPEDE		LATITUDE	ENZAMET	ARCHES	TITAN	PEACE-1 (Docetaxel)	ARASENS
		Docetaxel	Abiraterone						
Patients	mHSPC	mHSPC & high risk nmHSPC		High risk mHSPC	mHSPC	mHSPC	mHSPC	mHSPC	mHSPC
High volume	64.9%	56%	52%	-	52.3%	63.2%	62.8%	63%	77%
Prior local therapy	27.2%	5%	7%	4%	-	12-26%	16.4%	0	14%
Docetaxel for mHSPC	0	0	0	0	45%	15.5%	10.7%	100%	100%
Visceral metastases	15%	5%	6%	12-17%	11.5%	?	12.1%	12%	17%

Prostate cancer is clinically heterogeneous

80 years of age. Ischemic cardiopathy.
Prostatectomy in 2015. PSA relapse with PSADT 16 months. PET-PSMA with oligorecurrence (two single lymph node SUV 12). Asymptomatic.



54 years of age. No significant comorbidity.
De novo metastatic prostate cancer with multiple bone and lymph node metastases.
Pain requiring opioid analgesia.



Should the approach be similar based on a pooled benefit on overall survival in phase III clinical trials?

Are the goals the same?

Intensification or de-escalation strategies in 1L mHSPC

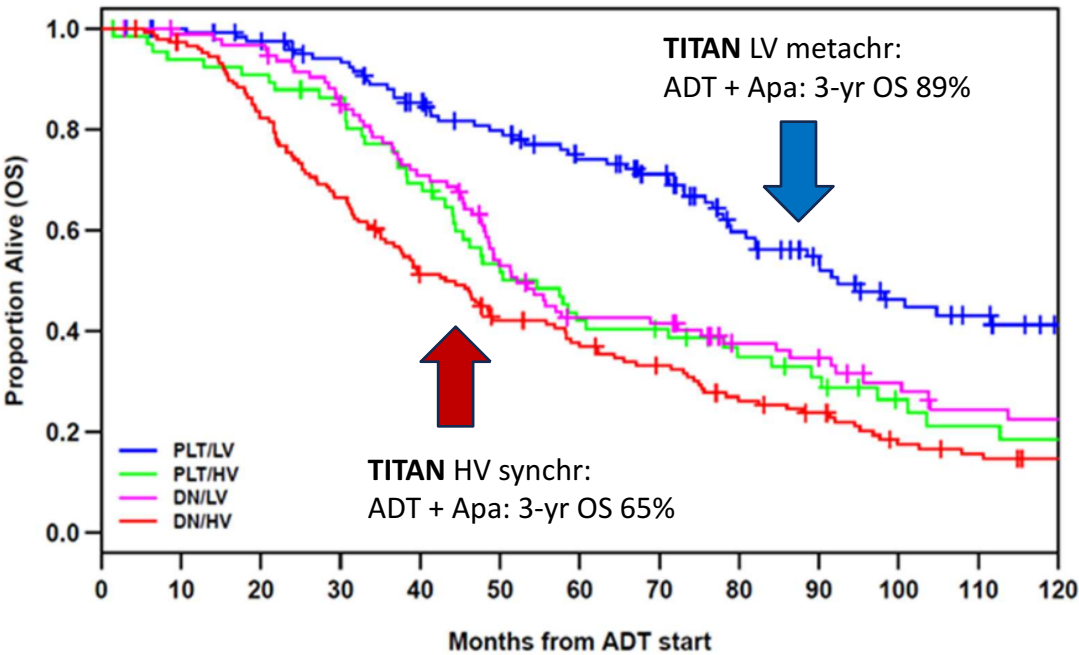
- **Assessing heterogeneity in prostate cancer**
- Who needs intensified therapy?
- Who can do with less?

Prognostic factors – Volume / timing of presentation

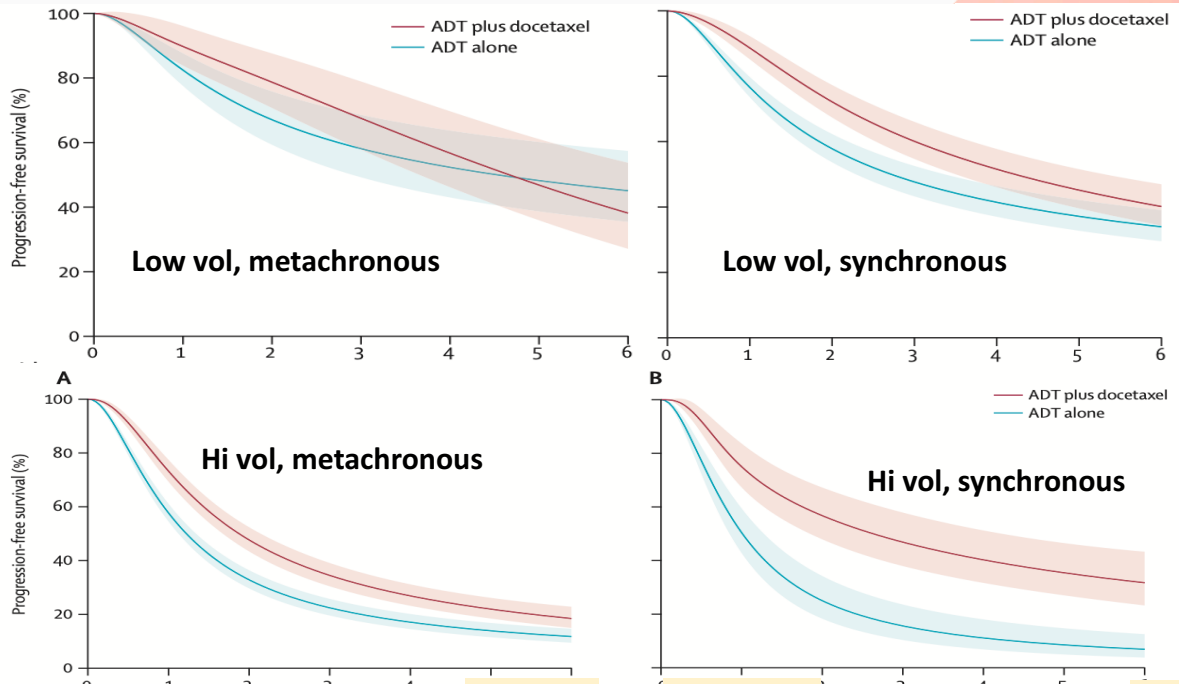
What is the risk of an event?

Disease volume (CHAARTED criteria) and **timing of presentation** (synchronous vs metachronous) are the main prognostic factors
Volume criteria are **assessed by conventional imaging**

Overall Survival



STAMPEDE Metaanalysis: Chemotherapy no benefit in low volume metachronous



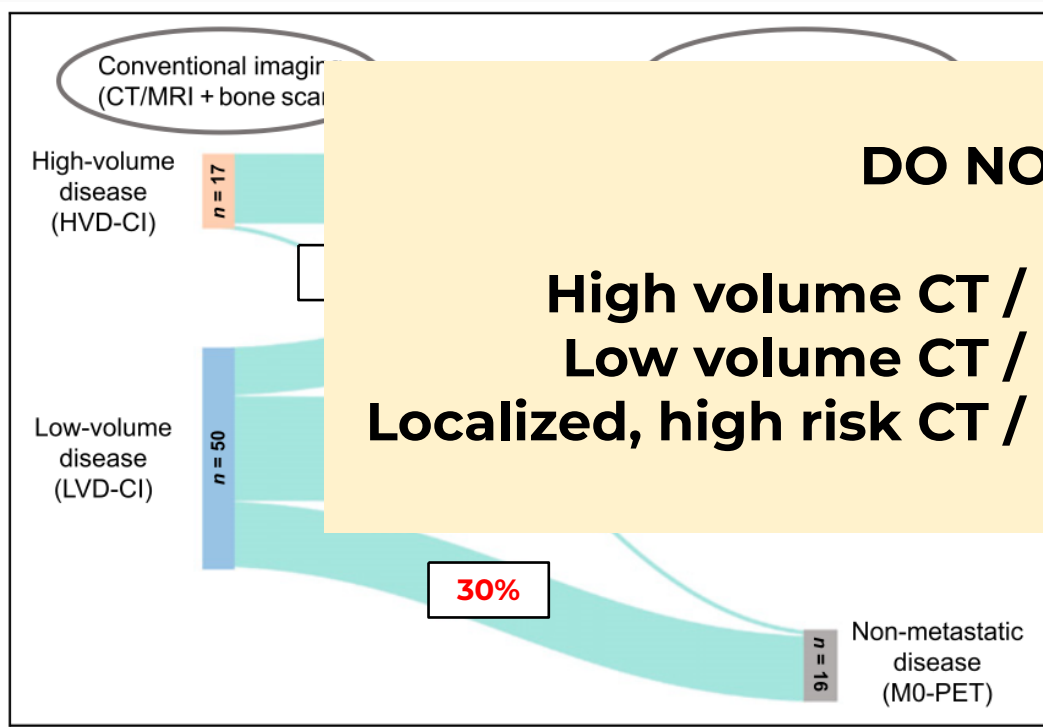
	N events/pts	Absolute effect at 5 yrs	5-yr OS ADT	5-yr OS ADT + Docetaxel
Low volume, metachronous†	70/229	0% (-10 to 12)	72% (63 to 82)	73% (63 to 83)
Low volume, synchronous	267/582	8% (0 to 16)	52% (47 to 57)	60% (54 to 66)
High volume, metachronous	78/132	10% (-6 to 26)	28% (18 to 43)	38% (25 to 57)
High volume, synchronous	736/1044	12% (7 to 18)	26% (23 to 30)	39% (34 to 43)

Are criteria for disease volume valid in the PET-PSMA era?

High and low volumen disease by PSMA-PET and conventional imaging have different prognostic meaning
These are not the same patients!!!

N=67. Conventional imaging & PSMA PET

Stage migration in 27 of 67 patients (40.3%)



Pro-PSMA trial

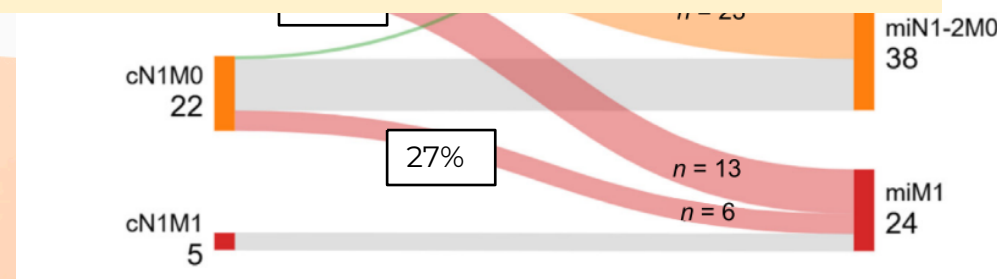
High risk localized prostate cancer
Increased sensibility and specificity with PET-PSMA vs conventional imaging

THUNDER trial

High risk localized prostate cancer. CT/BS & PET-PSMA

DO NOT EXTRAPOLATE:

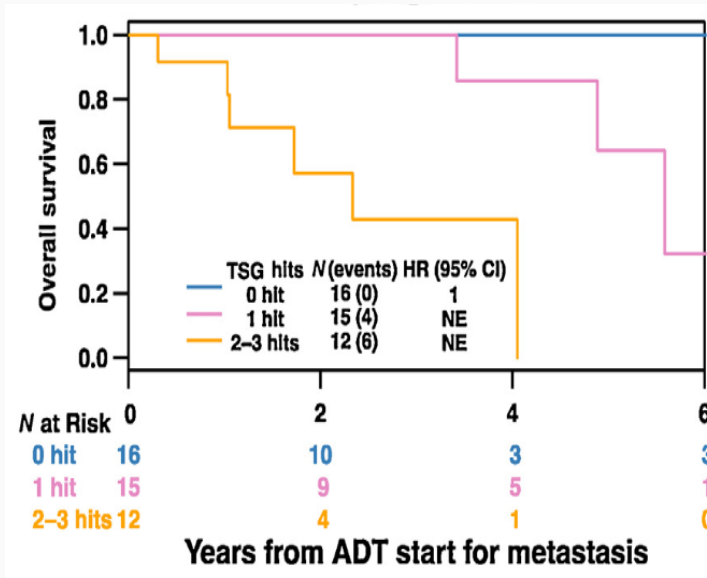
High volume CT / BS $\neq$ High volume PET-PSMA
Low volume CT / BS $\neq$ Low volume PET-PSMA
Localized, high risk CT / BS $\neq$ Localized, high risk PET-PSMA



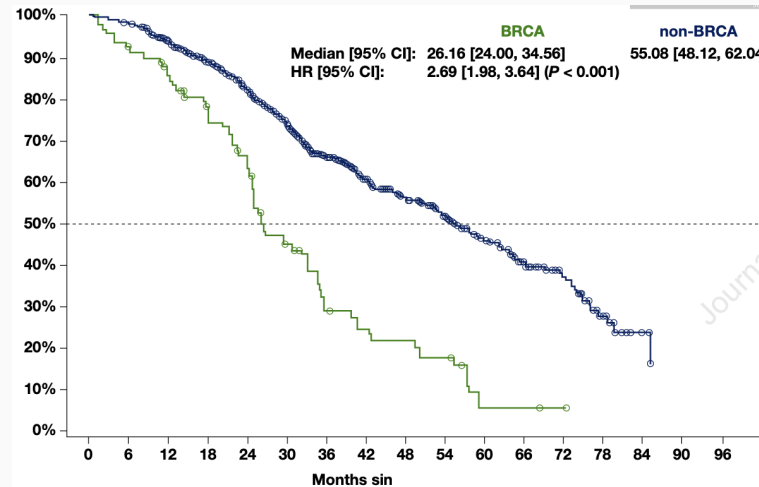
Prognostic factors – Molecular alterations

Loss of function of **tumor suppressors** is associated with adverse prognosis

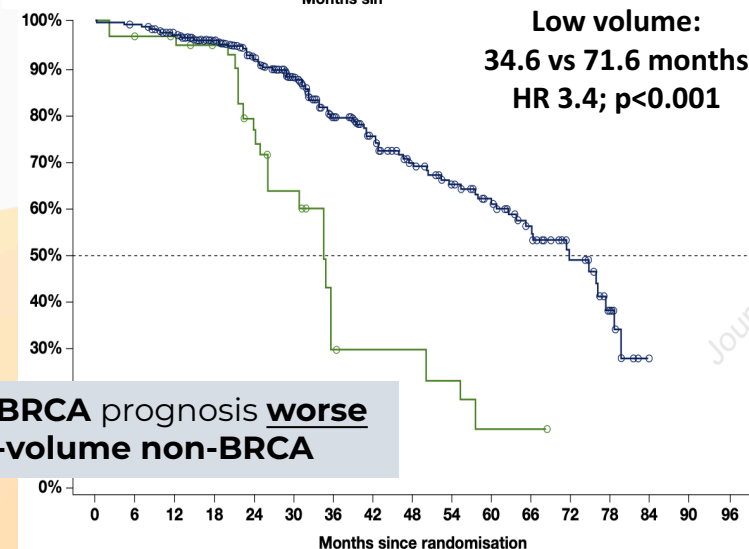
Mutations in the TP53, RB1 and PTEN suppressor genes associated with adverse outcome



BRCA alterations identify aggressive disease (high and low volume)

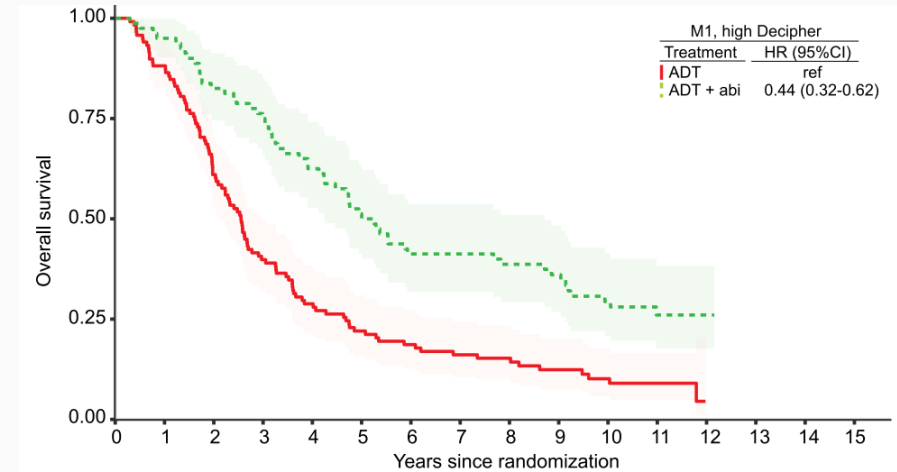


Low volume:
34.6 vs 71.6 months
HR 3.4; $p < 0.001$

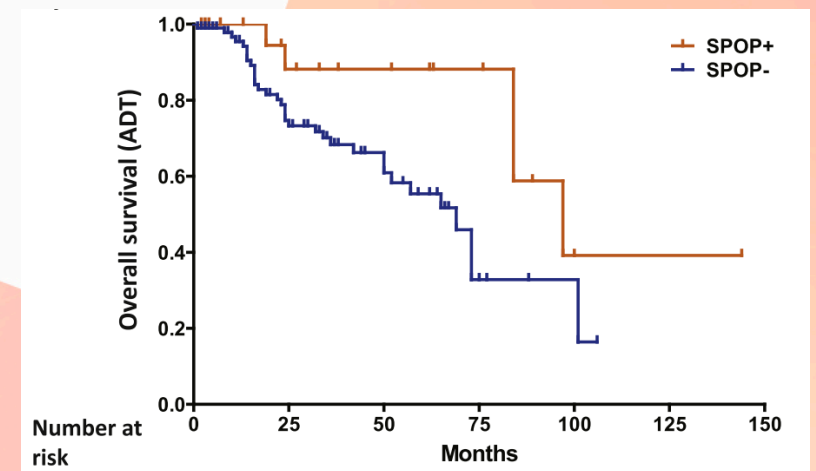


Low-volume BRCA prognosis worse than high-volume non-BRCA

Decipher-high scores associated with adverse outcome



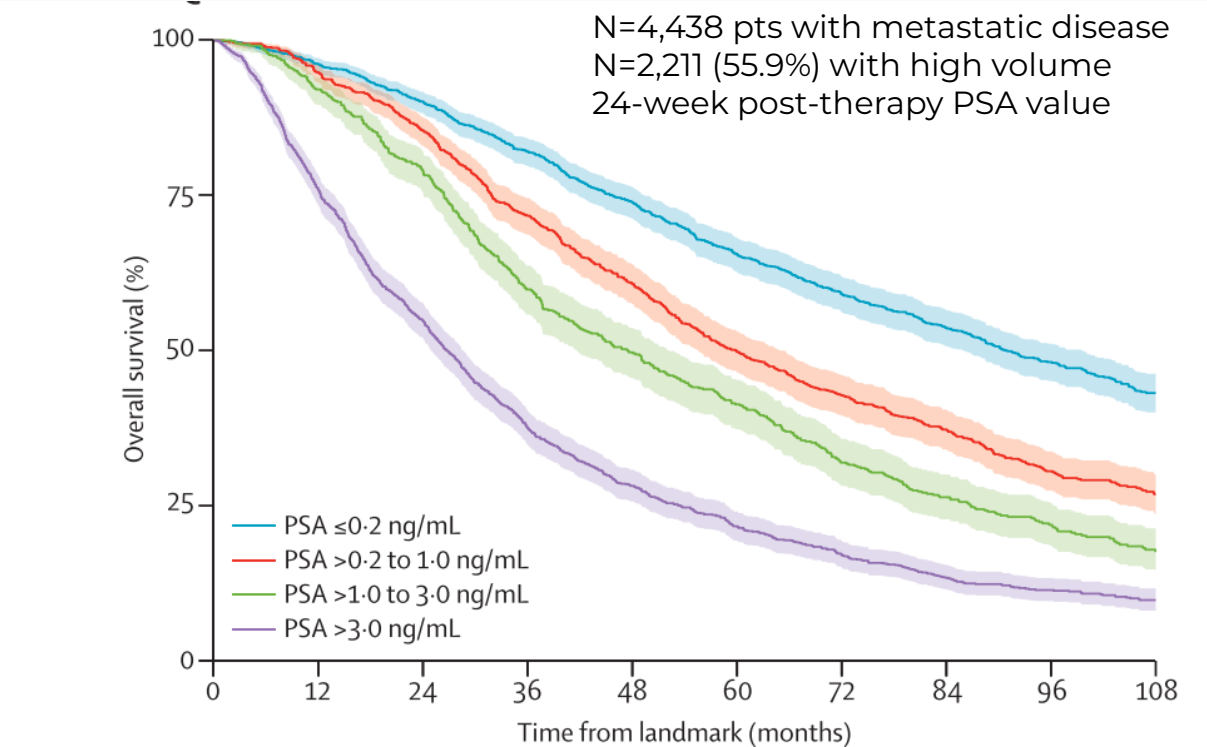
SPOP alterations associated with favorable prognosis



Prognostic factors – post-therapy PSA

What is the risk of an event?

STAMPEDE trial: PSA vaules after 24 wks of therapy



Number at risk (censored)

PSA ≤0.2 ng/mL	1164 (0)	1113 (7)	1041 (9)	945 (12)	837 (27)	726 (44)	635 (65)	560 (82)	400 (191)	247 (309)
PSA >0.2 to 1.0 ng/mL	910 (0)	861 (2)	770 (8)	644 (11)	536 (21)	432 (30)	361 (41)	299 (57)	196 (112)	131 (156)
PSA >1.0 to 3.0 ng/mL	594 (0)	547 (0)	469 (1)	355 (1)	293 (3)	238 (9)	179 (15)	142 (21)	102 (39)	64 (59)
PSA >3.0 ng/mL	1206 (0)	910 (6)	656 (9)	447 (12)	333 (15)	251 (21)	193 (28)	145 (34)	102 (57)	71 (75)

PSA response after 6-9 months of therapy is a strong prognostic factor

Prognosis is not independent of tumor volume

8-year overall survival
ADT + Abiraterone

PSA level at 24 weeks	High volume	Low volume
≤ 0.02 ng/mL	44.6%	64.1%
>0.2 – 1 ng/mL	28.4%	42.9%
>1 – 3 ng/mL	9.1%	28.1%
> 3 ng/mL	7.7%	21.7%

Intensification or de-escalation strategies in 1L mHSPC

- Assessing heterogeneity in prostate cancer
- **Who needs intensified therapy?**
- Who can do with less?

ADT + ARPi is the backbone of therapy

Who?

Who needs **intensified therapy**?

Patients with **biologically aggressive disease**:
(high volume, visceral mets, symptomatic disease)

What for?

Goals of therapy: induce response, control symptoms, prolong survival

Why?

Patients may not receive all life-prolonging options at progression

Trade toxicity for **response / disease control**

Intensify **with what**?

Docetaxel
Targeted therapies
Radioligands

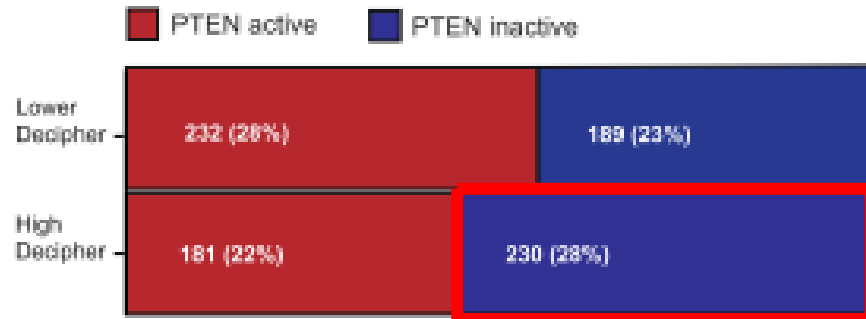
Intensify **when**?

- **Upfront** (predictive biomarkers)?
- Based on **initial response** to ADT + ARPi?

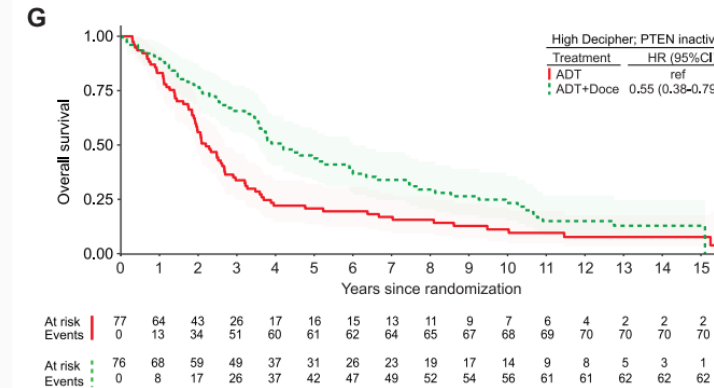
Upfront intensification based on DECIPHER and PTEN

Benefit from Docetaxel in STAMPEDE restricted to patients with high Decipher (+ PTEN loss)

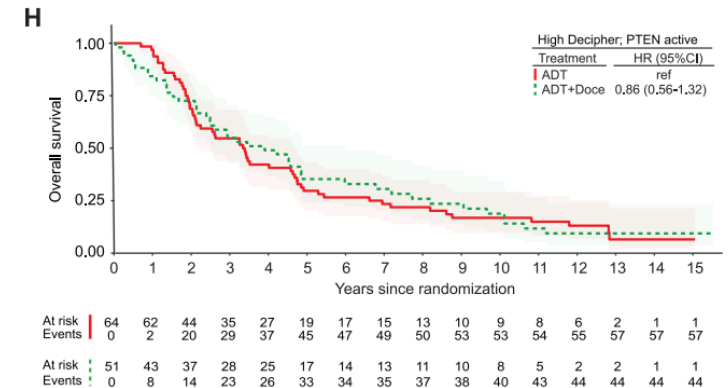
Adding docetaxel for tumors classified as both **high Decipher** and **PTEN inactive** reduced the hazard of death by 45% (HR 0.55, 99% CI 0.34–0.89)



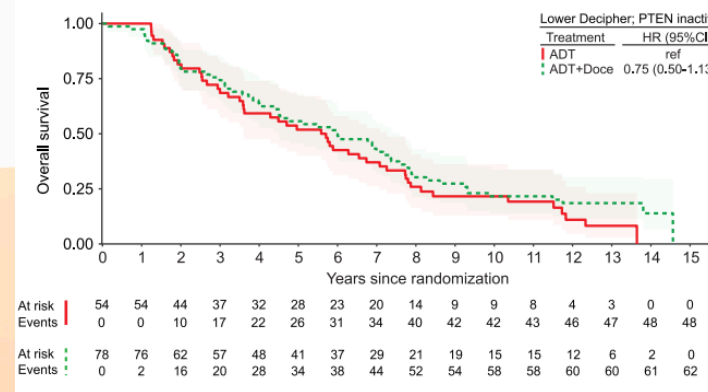
High Decipher PTEN-loss: HR 0.55 (0.38-0.79)



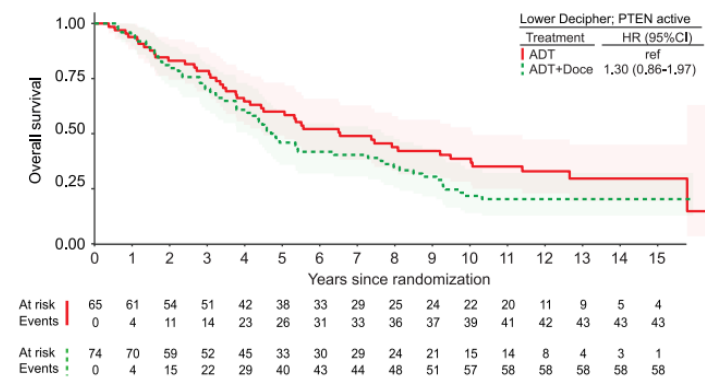
High Decipher PTEN-normal: HR 0.86 (0.56-1.32)



Low Decipher PTEN-loss: HR 0.75 (0.5-1.13)



Low Decipher PTEN-normal: HR 1.3 (0.88-1.97)



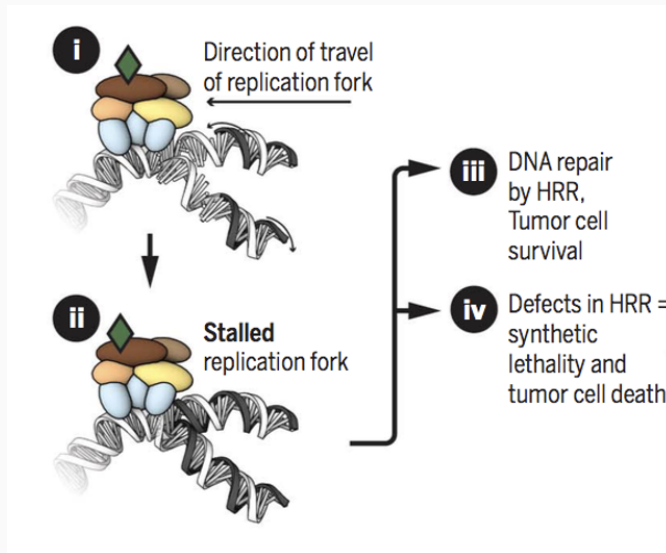
Upfront intensification with targeted agents / radioligands

Intensification with targeted therapies in biomarker-selected patients

PARP inhibitors

Homologous recombination repair defects (BRCA)

Synthetic lethality

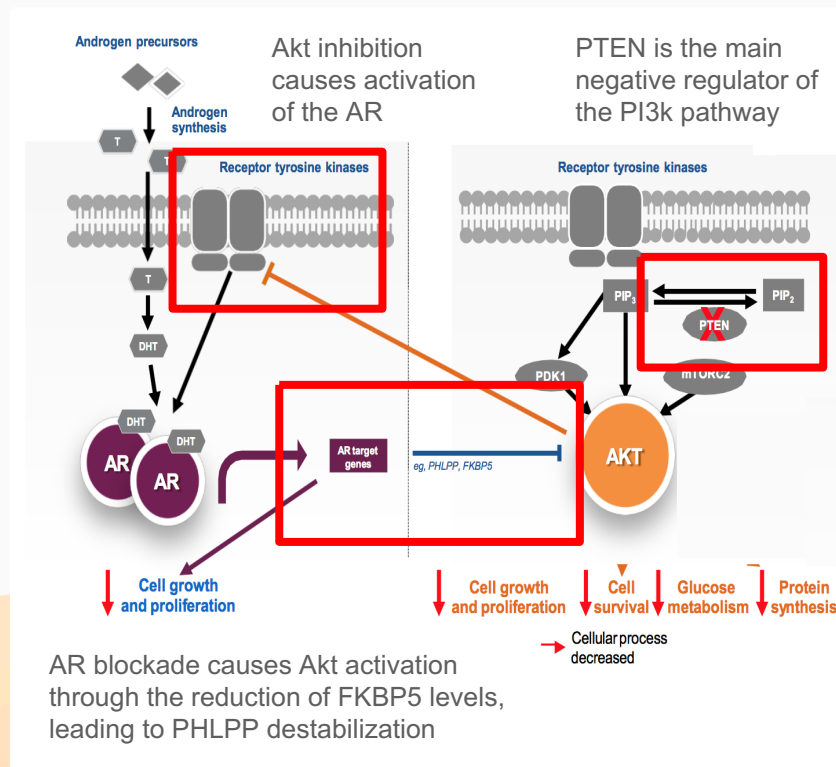


Niraparib + Abi

Talazoparib + Enza

Akt Inhibitors

PTEN loss

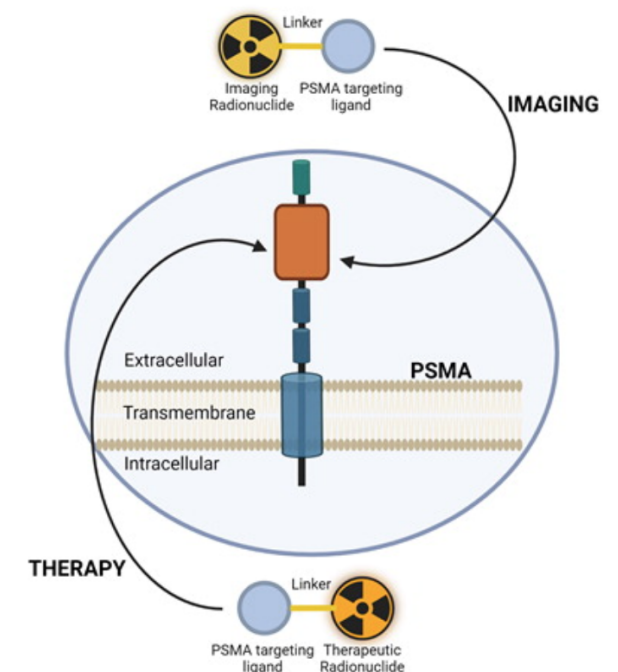


AR blockade causes Akt activation through the reduction of FKBP5 levels, leading to PHLPP destabilization

Capivasertib + Abi

Radioligands

PSMA uptake on PET-CT



177-Lu-PSMA-617



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PARPi – ARPi combinations improve rPFS in HRR mutant mHSPC

The AMPLITUDE trial: Niraparib + Abiraterone

Randomised phase III trial. N=796.

Eligibility:

mCRPC
HRR alterations
ECOG PS 0-2
No prior PARPi or ARPi
ADT ≤ 6 months
Docetaxel ≤ 6 cycles allowed

Niraparib 200 mg/24h
+ Abiraterone 1000 mg/24h

Placebo
+ Abiraterone 1000 mg/24h

Primary endpoint:
rPFS

Stratification:
BRCA2 vs CDK12 vs other
Prior docetaxel
Disease volume

Alteration in ≥1 HRR gene: BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, RAD54L

5,903 pts
prescreened



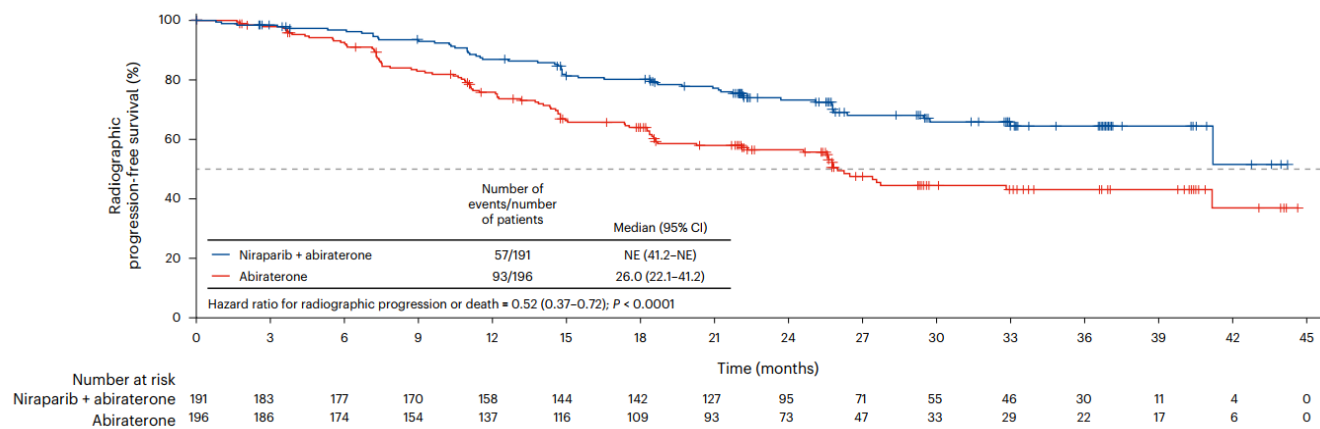
1,054 pts
positive



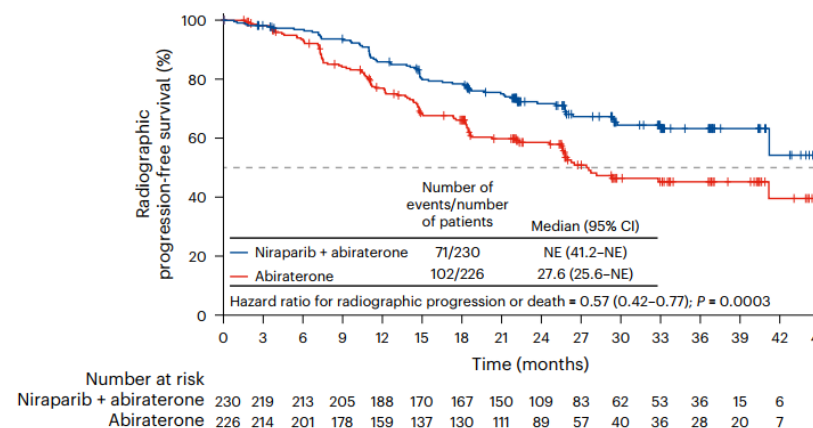
665 pts
screened

@GuardConsortium

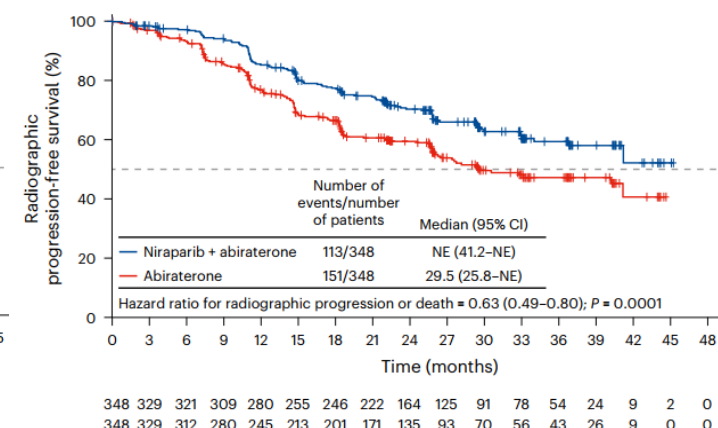
BRCA: NR vs 26 months (HR 0.52; 95%CI: 0.37-0.72; p<0.001)



Overall: NR vs 27.6 months
(HR 0.57; 95%CI: 0.42-0.77; p<0.001)



HRR non-BRCA: NR vs 29.5m
(HR 0.63; 95%CI: 0.49-0.8; p<0.001)



PARPi – ARPi combinations improve rPFS in HRR mutant mHSPC

The TALAPRO-3 trial: Talazoparib + Enzalutamide

Randomised phase III trial. N=599.

Eligibility:
mCRPC
HRR alterations
ECOG PS 0-2
No prior PARPi or ARPi
ADT ≤ 3 months
Previous docetaxel not allowed

Talazoparib 0.5 mg/24h + Enzalutamide 160 mg/24h

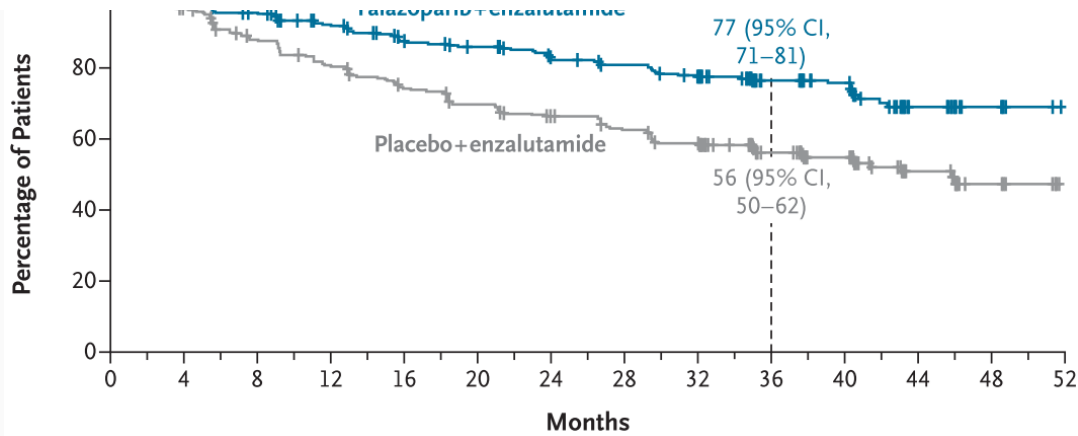
Placebo/24h + Enzalutamide 160 mg/24h

Primary endpoint: rPFS

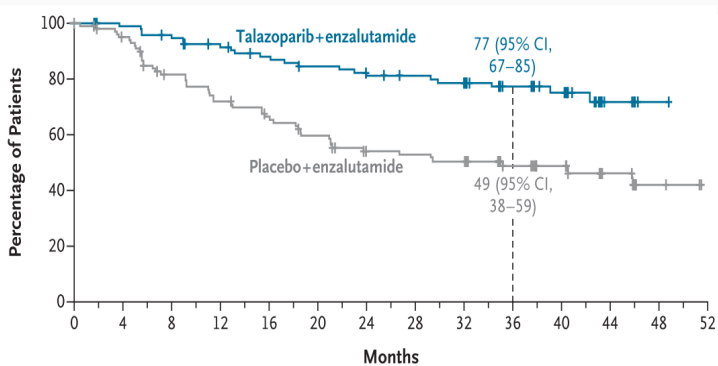
Stratification:
De novo vs metachronic
High vs low volume
BRCA vs non-BRCA

Alteration in ≥1 HRR gene: **ATM**, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C
Tissue or liquid biopsy

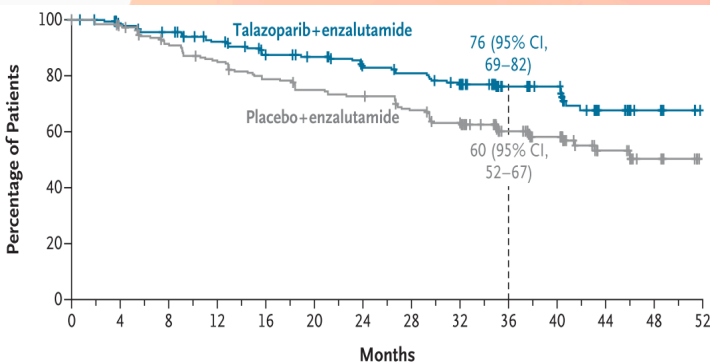
rPFS Overall: NR vs 45.8 months (HR 0.48; 95%CI: 0.36-0.65; p<0.001)



rPFS BRCA: NR vs 27.6 months (HR 0.57; 95%CI: 0.42-0.77; p<0.001)



rPFS HRR non-BRCA: NR vs 29.5m (HR 0.63; 95%CI: 0.49-0.8; p<0.001)



No. at Risk

Talazoparib+enzalutamide	104	93	89	82	77	73	69	66	64	46	35	10	4
Placebo+enzalutamide	103	93	76	67	60	53	44	43	41	29	23	12	4

No. at Risk

Talazoparib+enzalutamide	196	178	171	159	145	140	127	123	114	80	61	22	10	0
Placebo+enzalutamide	196	183	167	155	143	135	131	120	110	69	51	20	8	0

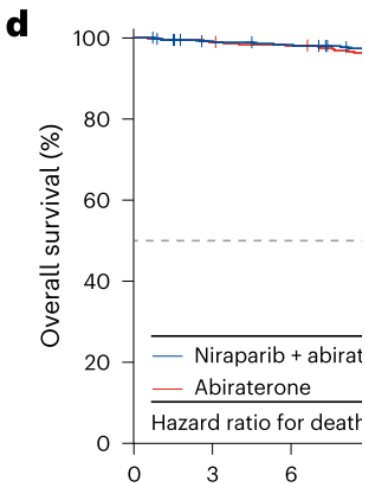
3,201 pts prescreened → 599 pts randomized

AMPLITUDE and TALAPRO-3: Overall Survival

Immature results – more follow-up needed

Niraparib + Abiraterone

HRR: HR 0.7
BRCA: HR 0.



Number at risk

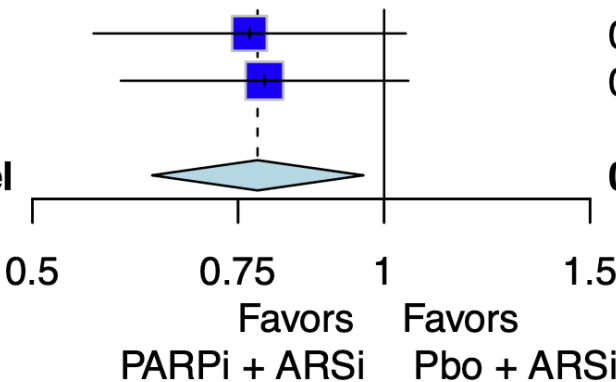
Niraparib + abiraterone	348	339	335	3
Abiraterone	348	344	340	3

Study

TALAPRO-3
AMPLITUDE

Fixed Effects Model

Overall Survival HRR positive

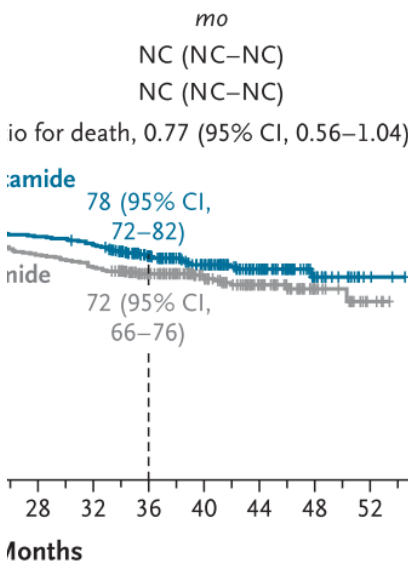


Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.8899$
Test for overall effect: $z = -2.34$ ($p = 0.0191$)

Talazoparib + Enzalutamide

0.56-1.04)

HR	95%-CI	Weight
0.77	[0.56; 1.04]	45.9%
0.79	[0.60; 1.05]	54.1%
0.78	[0.63; 0.96]	100.0%



248	239	183	121	69	24	3	0
228	215	166	113	64	21	5	0

AKT inhibitors in patients with PTEN protein loss

The Capitello-281 trial

Randomised phase III trial

Eligibility

mHSPC
PTEN deficient

Stratification

M1 volume
(CHAARTED)
Visceral mets
Geography

Primary endpoint

rPFS

Secondary endpoints

OS, time to first subsequent therapy,
SSE-free survival, time to PSA
progression

PTEN loss (IHC):

No detectable PTEN in $\geq 90\%$ of cells

Randomization
1:1

Abiraterone 1000 mg
c/24h
+ Capiwasertib 400
mg c/12h 4d on, 3d
off

Abiraterone 1000 mg
c/24h
+ Placebo c/12 4d on,
3d off

6,566 pts
prescreened

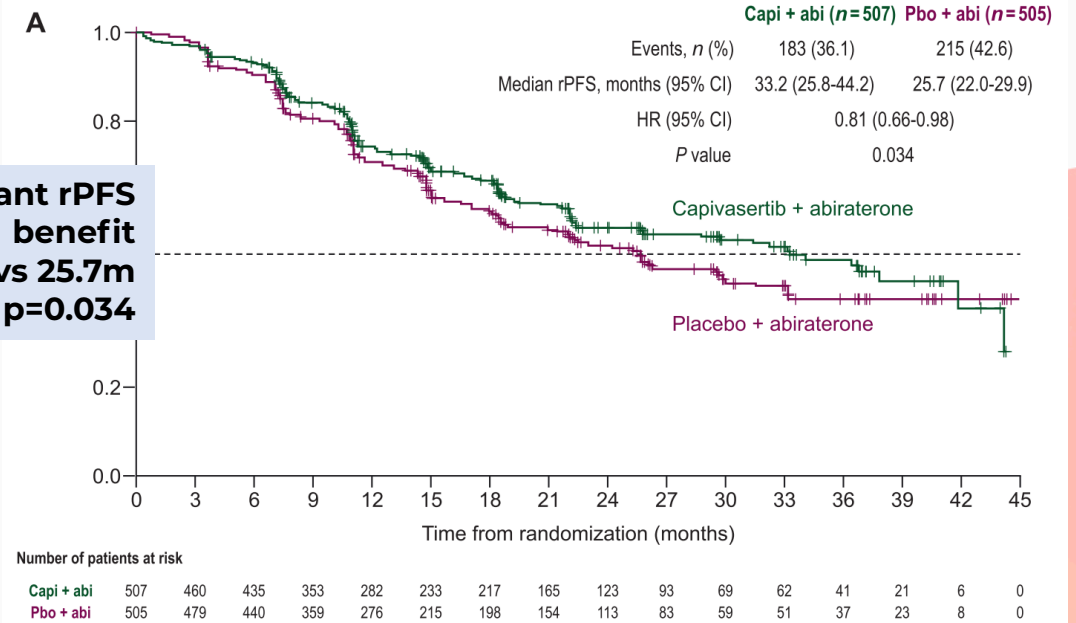


1,012 pts
randomized

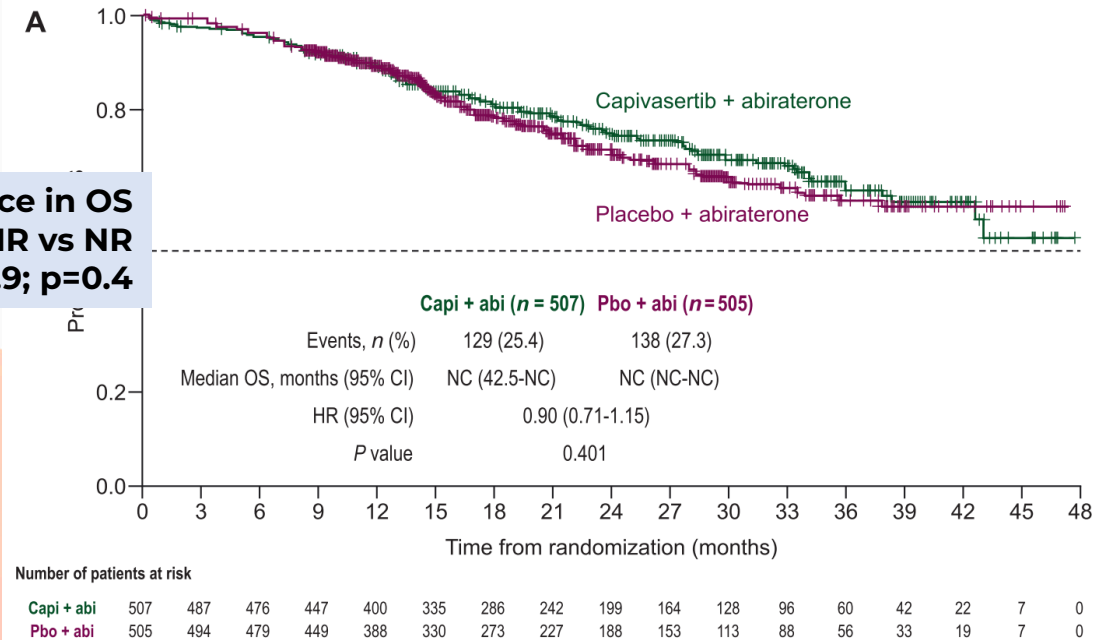
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X @GuardConsortium

Fizazi et al. Ann Oncol 2026

**Significant rPFS
benefit
33.2 vs 25.7m
HR 0.81; p=0.034**



**No difference in OS
NR vs NR
HR 0.9; p=0.4**



177-Lu-PSMA-617 in PSMA+ patients

The PSMA-Addition trial

Randomised phase III trial

Eligibility

mHSPC
≥1 PSMA+ metastatic lesion
on 68Ga-PSMA-11 PET/CT

Stratification

M1 volume (CHAARTED)
Age > 70 y
Prior local therapy

Randomization
1:1

177-Lu-PSMA-617 x
6 cycles +
ADT + ARPi
(abi/enz/apa/daro)

Crossover at
progression

ADT + ARPi
(abi/enz/apa/daro)

Primary endpoint

Radiographic
progression-free survival

PSMA+

Uptake greater than liver, no
PSMA negative lesions

Secondary endpoints

OS, time to first subsequent therapy,
SSE-free survival, time to PSA
progression

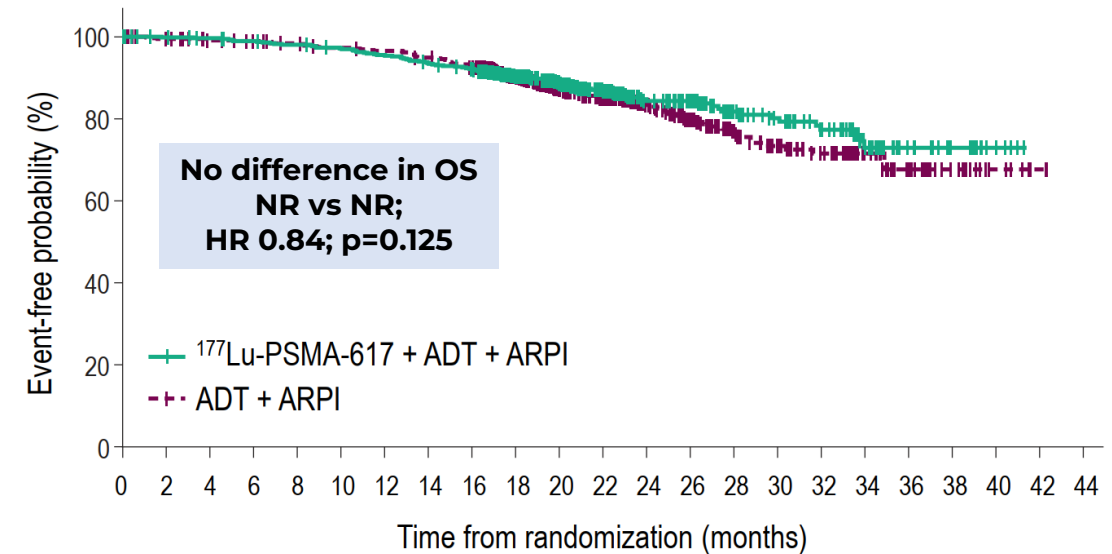
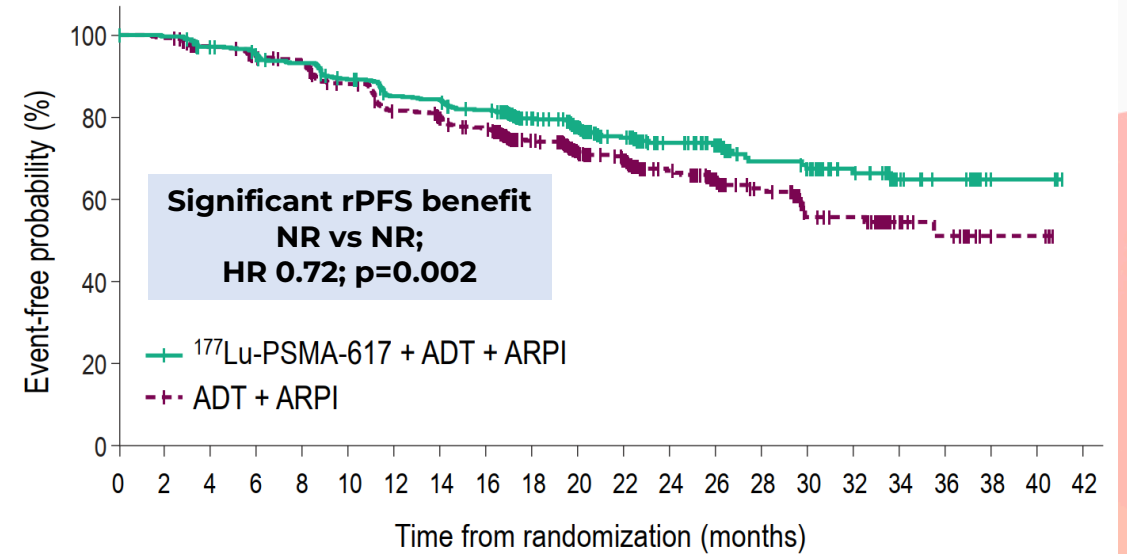
1,529 pts
screened
1,420 PSMA-PET
n



1,232 pts
positive



1,144 pts
included



Number of patients still at risk

572	566	562	556	550	543	533	521	512	424	336	267	195	174	109	94	78	45	27	12	5	0	0
572	561	551	547	539	531	526	516	501	432	315	268	196	159	118	91	72	46	28	16	7	2	0

Intensification has been tested mainly in patients with aggressive disease

High volume, synchronous disease

	Amplitude	Talapro-3	Capitello	PSMA-Addition
Hi volume	77.5%	71%	74%	68%
Synchronous	86.5%	85%	Not reported	50%
Biomarker +	17.8%	18.8%	15.4%	86.7%
HR rPFS	0.57 (p<0.001)	0.48 (p<0.001)	0.81 (p=0.034)	0.72 (p=0.002)
HR OS	0.79 (p=0.1)	0.77 (p=NS)	0.9 (p=0.4)	0.84 (p=0.125)
Dose interruption	67%	69%	62.8%	12%
Dose reduction	21.9%	60%	-	4%
Dose discontinuation	14.7%	19%	18.3%	8%

Higher efficacy comes at the price of greater toxicity

Hematologic toxicity (anemia), fatigue, GI tox (nausea)
Anemia must be treated aggressively and early
Balance toxicity vs quality of life (baseline risk)

AMPLITUDE

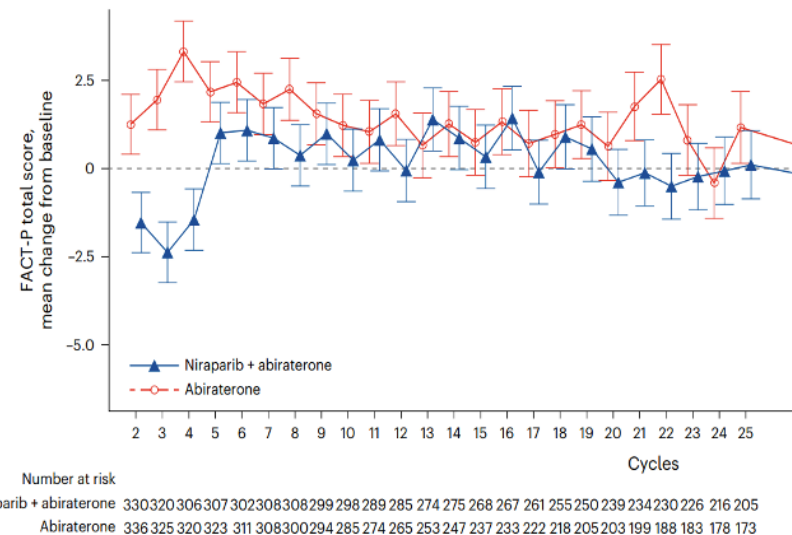
	Niraparib plus abiraterone (n=347)		Abiraterone (n=348)	
	All grades	Grade ≥3	All grades	Grade ≥3
Events reported in ≥15% of patients in either group, n (%)				
Anemia ^b	179 (51.6)	101 (29.1)	83 (23.9)	16 (4.6)
Hypertension ^b	152 (43.8)	92 (26.5)	113 (32.5)	64 (18.4)
Constipation	122 (35.2)	0	57 (16.4)	1 (0.3)
Nausea	107 (30.8)	0	50 (14.4)	0
Fatigue	91 (26.2)	7 (2.0)	64 (18.4)	4 (1.1)
Hypokalemia ^b	90 (25.9)	40 (11.5)	70 (20.1)	38 (10.9)
Neutropenia ^b	76 (21.9)	33 (9.5)	28 (8.0)	7 (2.0)
Arthralgia	73 (21.0)	2 (0.6)	74 (21.3)	6 (1.7)
Back pain	68 (19.6)	12 (3.5)	77 (22.1)	5 (1.4)
Thrombocytopenia ^b	66 (19.0)	24 (6.9)	20 (5.7)	1 (0.3)
COVID-19	65 (18.7)	3 (0.9)	71 (20.4)	4 (1.1)
Hot flush	63 (18.2)	0	48 (13.8)	0
Leukopenia	58 (16.7)	16 (4.6)	18 (5.2)	1 (0.3)
Vomiting	56 (16.1)	3 (0.9)	30 (8.6)	0
Peripheral edema ^b	55 (15.9)	1 (0.3)	42 (12.1)	0
Weight decreased	53 (15.3)	4 (1.2)	18 (5.2)	0
Alanine aminotransferase increased ^b	22 (6.3)	6 (1.7)	54 (15.5)	17 (4.9)

TALAPRO-3

Event of any grade occurring in ≥10% of patients¶

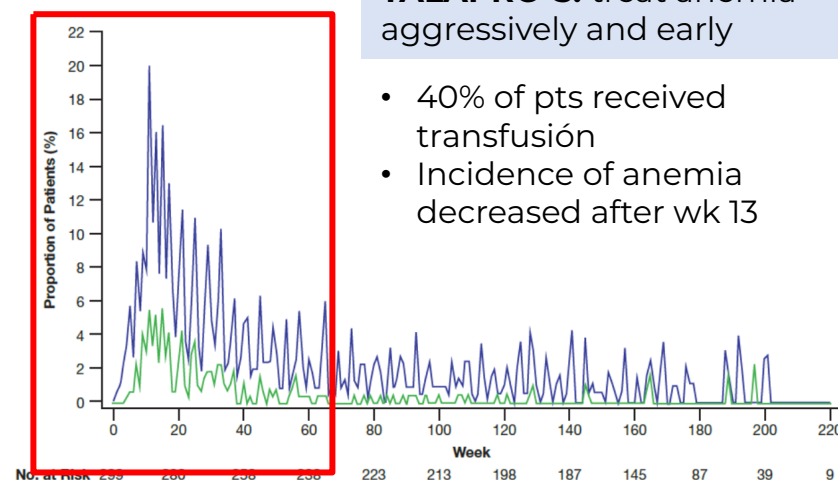
	Talazoparib + Enzalutamide (N = 299)	
	All Grades	Grade ≥3
Anemia	213 (71)	152 (51)
Fatigue	85 (28)	9 (3)
Neutrophil count decreased	81 (27)	34 (11)
Neutropenia	66 (22)	26 (9)
Asthenia	64 (21)	17 (6)
White-cell count decreased	64 (21)	17 (6)
Hot flash	60 (20)	0
Decreased appetite	59 (20)	6 (2)
Back pain	56 (19)	4 (1)
Constipation	54 (18)	0
Nausea	51 (17)	0
Platelet count decreased	49 (16)	14 (5)
Arthralgia	45 (15)	0
Diarrhea	40 (13)	5 (2)
Fall	40 (13)	1 (<1)

AMPLITUDE:
worsened QoL at initial stages of treatment



TALAPRO-3: treat anemia aggressively and early

- 40% of pts received transfusión
- Incidence of anemia decreased after wk 13



Higher efficacy comes at the price of greater toxicity

Capivasertib (Capitello-281)

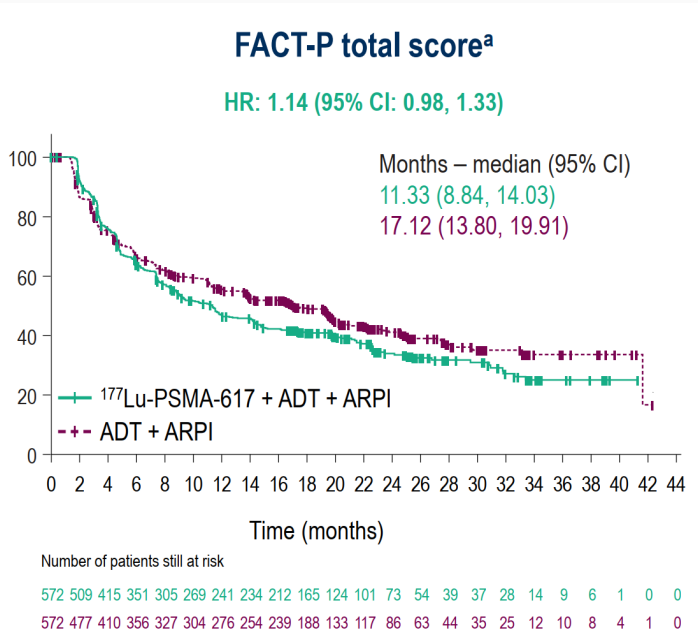
Diarrea, hyperglycemia, rash, anemia, hypertension
Dose reduction 62%, discontinuation 18%

Adverse event	Capivasertib plus abiraterone (n = 503)	
	All grades	Grade ≥3
Any adverse event, n (%)	497 (98.8)	337 (67.0)
Diarrhea	261 (51.9)	31 (6.2)
Hyperglycemia ^a	191 (38.0)	52 (10.3)
Rash ^b	178 (35.4)	62 (12.3)
Anemia	120 (23.9)	26 (5.2)
Hypokalemia	111 (22.1)	44 (8.7)
Hypertension	100 (19.9)	29 (5.8)
Fatigue	80 (15.9)	2 (0.4)
ALT increased	71 (14.1)	22 (4.4)
Urinary tract infection	69 (13.7)	21 (4.2)
AST increased	65 (12.9)	13 (2.6)
Nausea		
COVID-19		
Asthenia		
Pyrexia		
Hot flush		
Pruritus		
Back pain		
Constipation		
Arthralgia		

Time from randomization to discontinuation due to any adverse event			
	Capivasertib + Abiraterone (N=503)	Placebo + Abiraterone (N=503)	
Total	92 (18.3%)	24 (4.8%)	
≤ 3 months	58 (11.5%)	4 (0.8%)	
> 3 months	34 (6.8%)	20 (4%)	

¹⁷⁷Lu-PSMA (PSMA Addition)

- Better toxicity profile
 - Hematologic
 - Dry eye
 - Dry mouth
- No difference in quality of life



Patients with AE in grouping – n (%)	¹⁷⁷ Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dry mouth ^a	262 (46.5)	0	22 (3.9)	0
Cytopenias	248 (44.0)	81 (14.4)	115 (20.4)	28 (5.0)
Anaemia ^b	158 (28.0)	28 (5.0)	79 (14.0)	16 (2.8)
Neutropenia ^c	83 (14.7)	21 (3.7)	24 (4.2)	5 (0.9)
Thrombocytopenia ^d	63 (11.2)	10 (1.8)	19 (3.4)	3 (0.5)
Fractures	52 (9.2)	16 (2.8)	43 (7.6)	15 (2.7)
Renal events ^e	40 (7.1)	9 (1.6)	26 (4.6)	5 (0.9)
Second primary malignancies	37 (6.6)	24 (4.3)	31 (5.5)	14 (2.5)
Dry eye	33 (5.9)	0	3 (0.5)	0
Intracranial haemorrhage	6 (1.1)	4 (0.7)	4 (0.7)	2 (0.4)

Can we use post-therapy PSA to guide treatment intensification with Docetaxel?

REINFORCE

No deep PSA response after 24–30 weeks of apalutamide + ADT, without progression. Deep response is PSA ≤ 0.2 ng/mL OR $\geq 90\%$ decline with PSA ≤ 4 ng/mL.

Key inclusion criteria

- mHSPC
- ECOG PS 0-1
- Apalutamide as first line mHSPC¹
- **Not achieving deep PSA response at 6 months²**

Exclusion Criteria

- Tumor progression to first line³
- Prior docetaxel

Stratification factors

- *Synchronous vs Metachronous*
- *Tumor volume*

Randomization 1:1

Apalutamide + ADT
+ Docetaxel x 6 cycles

Apalutamide + ADT

Multi-EMEA country: 6-7 countries

Multi-centers: ~70 sites

Total study duration: ~48 mo (from FPI)

PRIMARY ENDPOINT

- Event-Free Survival $\uparrow$

SECONDARY ENDPOINTS

- PSA progression-free survival
- Time to Castration Resistance
- Time to Subsequent treatment
- Overall Survival
- Symptomatic Skeletal event free survival (SSE-FS)
- Time to initiation of opioid use (≥ 7 days)
- Safety and Security

Triple-SWITCH

PSA ≥ 0.2 ng/mL after 6–12 months of ADT, with ≥ 4 months of ARPI.

Study Population

- mCSPC (any volume/risk)
- Received 6-12 months ADT
- Received ≥ 4 months ARPI: *abiraterone enzalutamide apalutamide OR darolutamide*
- PSA ≥ 5 prior to ADT
- **PSA ≥ 0.2 at enrolment**
- Docetaxel naïve / eligible

1:1 Randomization*

Continue Standard of Care
ADT + ARPI
plus
Docetaxel 75mg/m² IV q3wk x6

Continue Standard of Care
ADT + ARPI

Primary Objective

- Overall Survival

Secondary Objectives

- PSA 50/90
- PSA < 0.2 , < 0.02
- Clinical progression-free survival
- ctDNA and archived tissue (exploratory)

ITENSIFY

PSA ≥ 0.2 ng/mL after 5-8 months of ADT + ARPI.

Study Population

- mHSPC
- Received 5–8 months of ADT + ARPI
- PSA ≥ 0.2 ng/mL after initial doublet therapy

Assessment centred on 6 months

1:1 Randomisation

Continue Standard of Care
ADT + ARPI
plus
**Docetaxel IV every 3 weeks
for up to 6 cycles**

Continue Standard of Care
ADT + ARPI

Primary Objective

- Overall survival

Secondary Objectives

- PSA progression-free survival
- Clinical progression-free survival
- Adverse events
- Health-related quality of life
- Cost-effectiveness

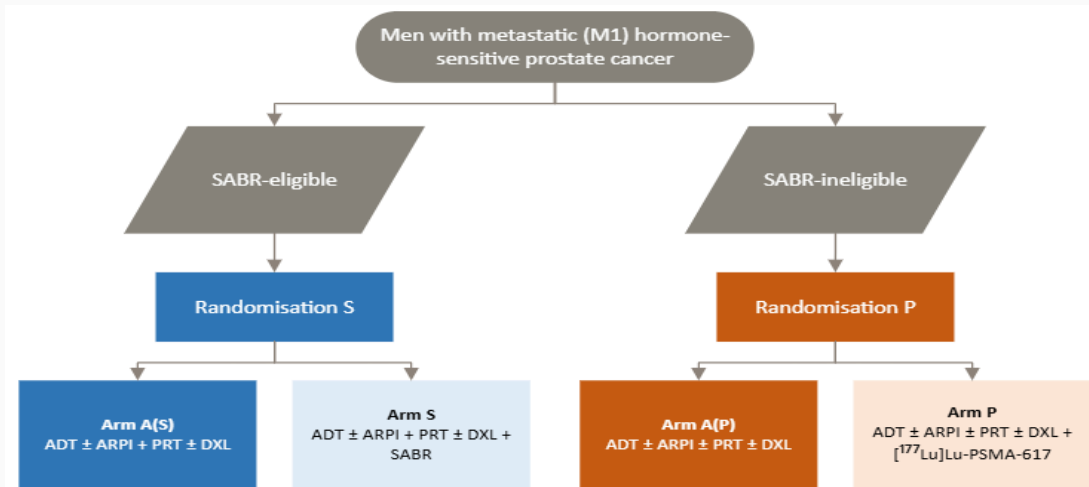
Translational objectives: Decipher Prostate Score and PTEN Inactivity Score as predictors of docetaxel benefit.

Source: University of Southampton ITENSIFY trial overview; HRA • ISRCTN17215075

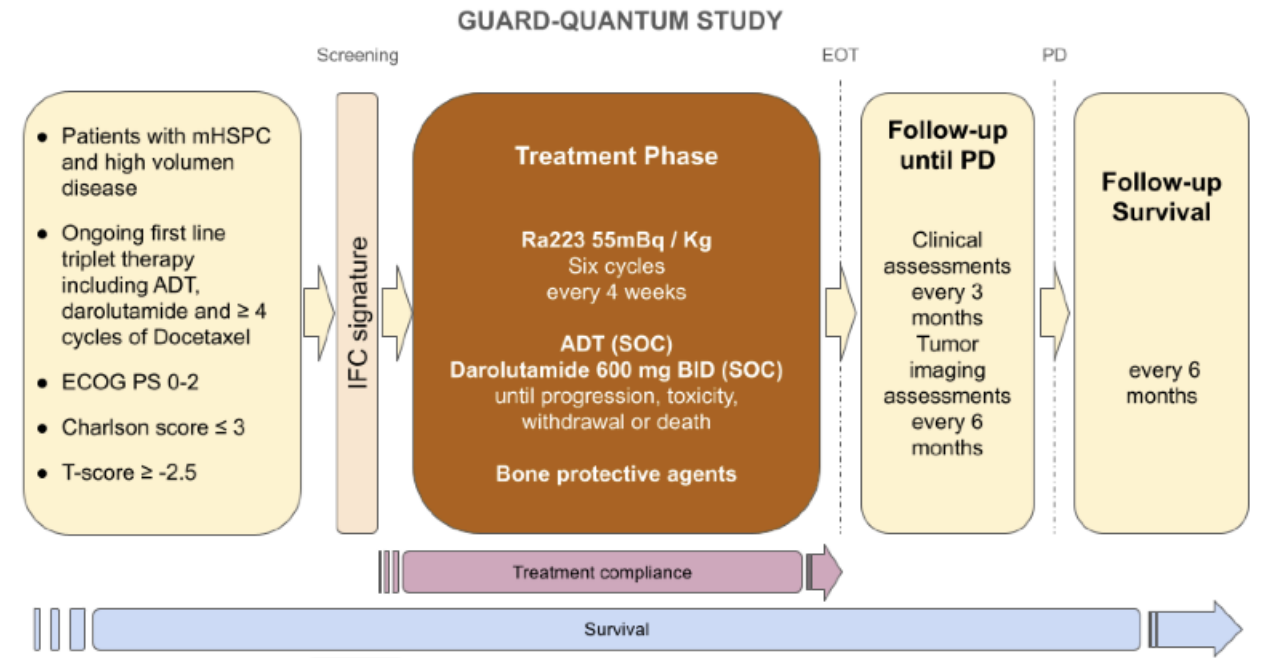
*Stratification Factors: PSA 0.2-4 vs > 4 ; ARPI class (CYP17 vs AR antagonist); Liver mets; Timing of mets; ADT 6-9 vs 9-12 mo

Other ongoing intensification studies

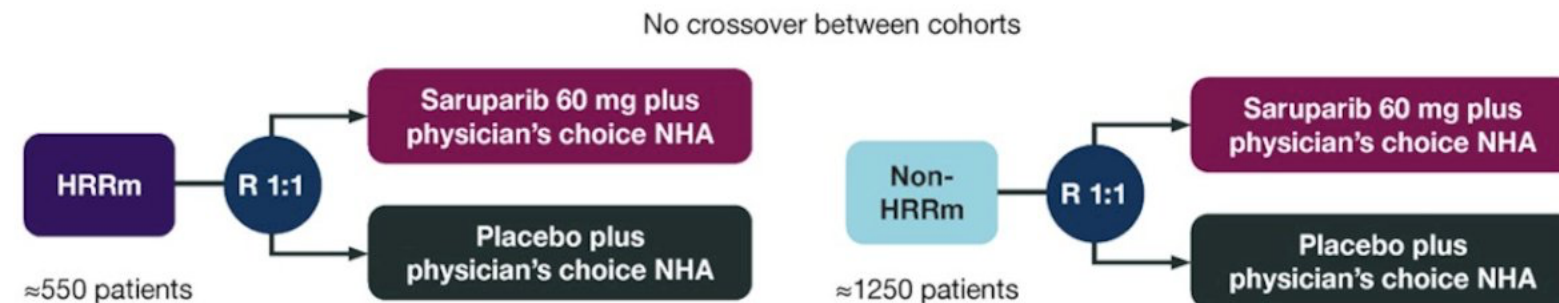
STAMPEDE-2



QUANTUM-223: Ra-223 after triplet therapy



EVOPAR-03



Treatment will continue until disease progression, unacceptable toxicity, or participant-initiated withdrawal

Intensification or de-escalation strategies in 1L mHSPC

- Assessing heterogeneity in prostate cancer
- Who needs intensified therapy?
- **Who can do with less?**

ADT + ARPi is the backbone of therapy

Who?

Who could **do with less therapy?**

Patients with **indolent disease** (low volume, metachronous)
Oligometastatic disease candidates for **ablative therapy** (SBRT)

What for?

Avoid toxicity in the absence of disease related symptoms

Why?

Patients able to receive **treatments in sequence** with (potentially) no detriment to the overall outcome

Maintain **quality of life**

De-escalate **what?**

ADT
ARPi
ADT & ARPi

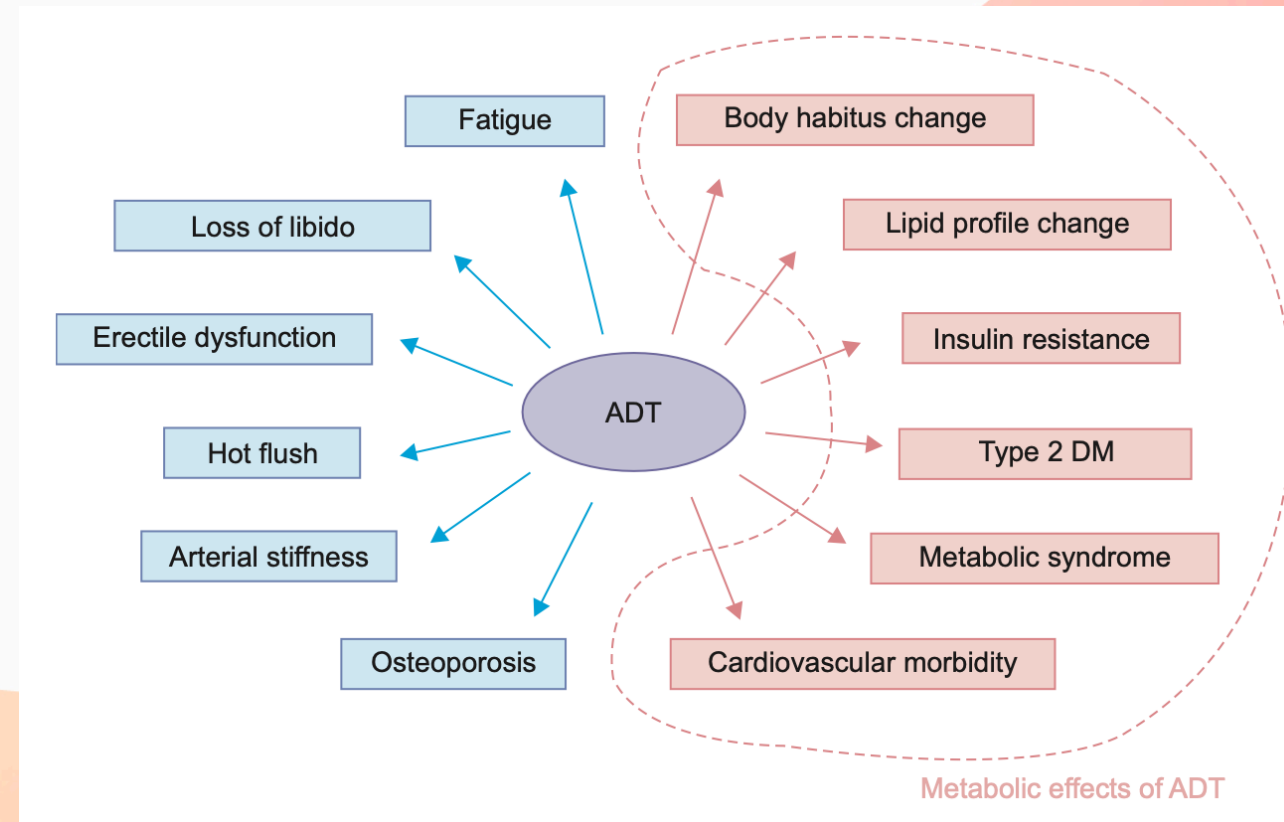
Re-start **when?**

PSA threshold
Symptoms
Radiographic progression

Treatment toxicity can affect quality of life

Androgen deprivation therapy

- **Hot flashes**
- **Sexual dysfunction:** loss of libido, impotence
- Gynecomastia, decreased penile and testicular size, and thinning of body hair
- **Osteoporosis** and risk of bone fractures
 - Vitamin D & calcium supplementation mandatory
 - Consider denosumab / bisphosphonates if risk of fracture
- Metabolic syndrome, **cardiovascular disease**, diabetes
- Decreased muscle and increased fat
- **Cognitive dysfunction**



Treatment toxicity can affect quality of life

Androgen pathway inhibitors (+ ADT)

All-grade toxicity

Abiraterone (LATITUDE)

	ADT + Abi	ADT only
Hypertension	37%	22%
Hypokalemia	20%	4%
AST/ALT increase	16%	12%
Hyperglycemia	13%	11%
Cardiac disorder	12%	8%
Fatigue	13%	14%

Enzalutamide (ARCHES)

	ADT + Enz	ADT only
Seizures	0.3%	0.3%
Hypertension	8.6%	6.3%
Cognitive/memory	4.5%	2.1%
Fatigue	24.1%	19.5%
Fall	3.7%	2.6%
CV events	4%	3%

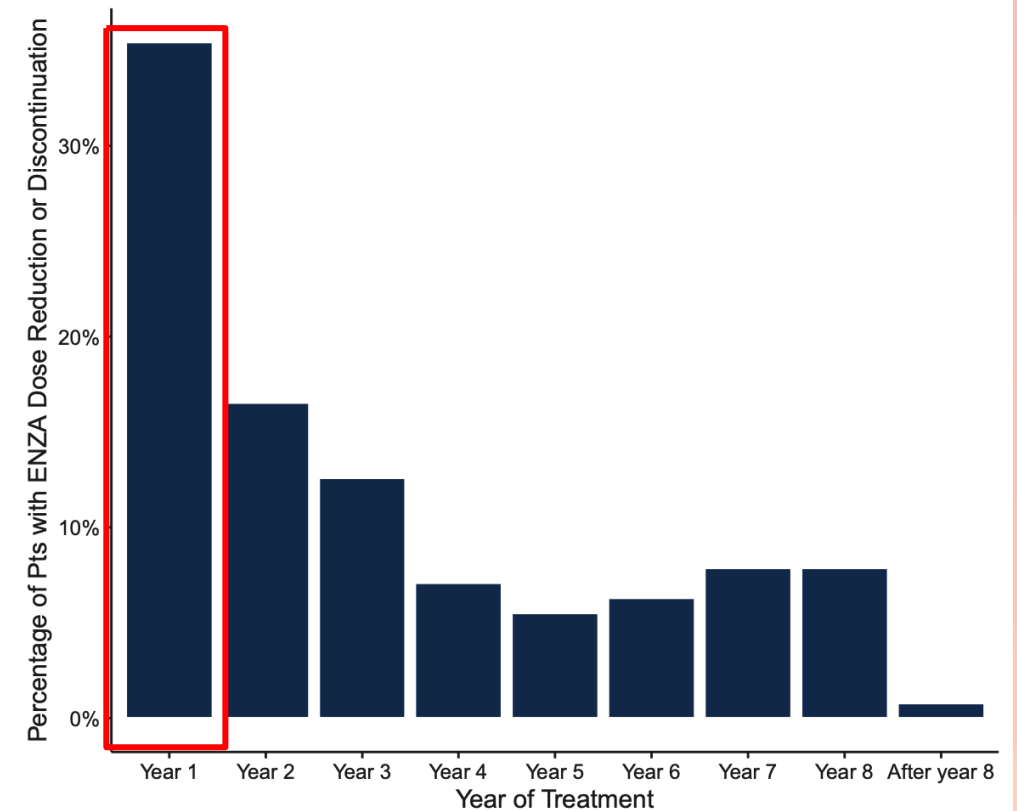
Apalutamide (TITAN)

	ADT + Apa	ADT only
Rash	27.1%	8.5%
Fatigue	19.7%	16.7%
Fall	7.4%	7%
Hypothyroidism	6.5%	1.1%
Fracture	6.3%	4.5%
Seizure	0.6%	0.4%

Darolutamide (ARANOTE)

	ADT + Daro	ADT only
Hot flashes	9.2%	7.2%
Fatigue	5.6%	8.1%
Insomnia	6.3%	2.7%
Hypertension	8.5%	8.6%
Hyperglycemia	6.1%	3.6%

>30% of patients in the treatment arm of Enzamet required dose reduction or discontinuation in the first year



Treatment toxicity can affect quality of life

Androgen pathway inhibitor monotherapy in EMBARK

AEs with leuprolide or enza monotherapy in **EMBARK**

Table 2. Adverse Events (Safety Population).*

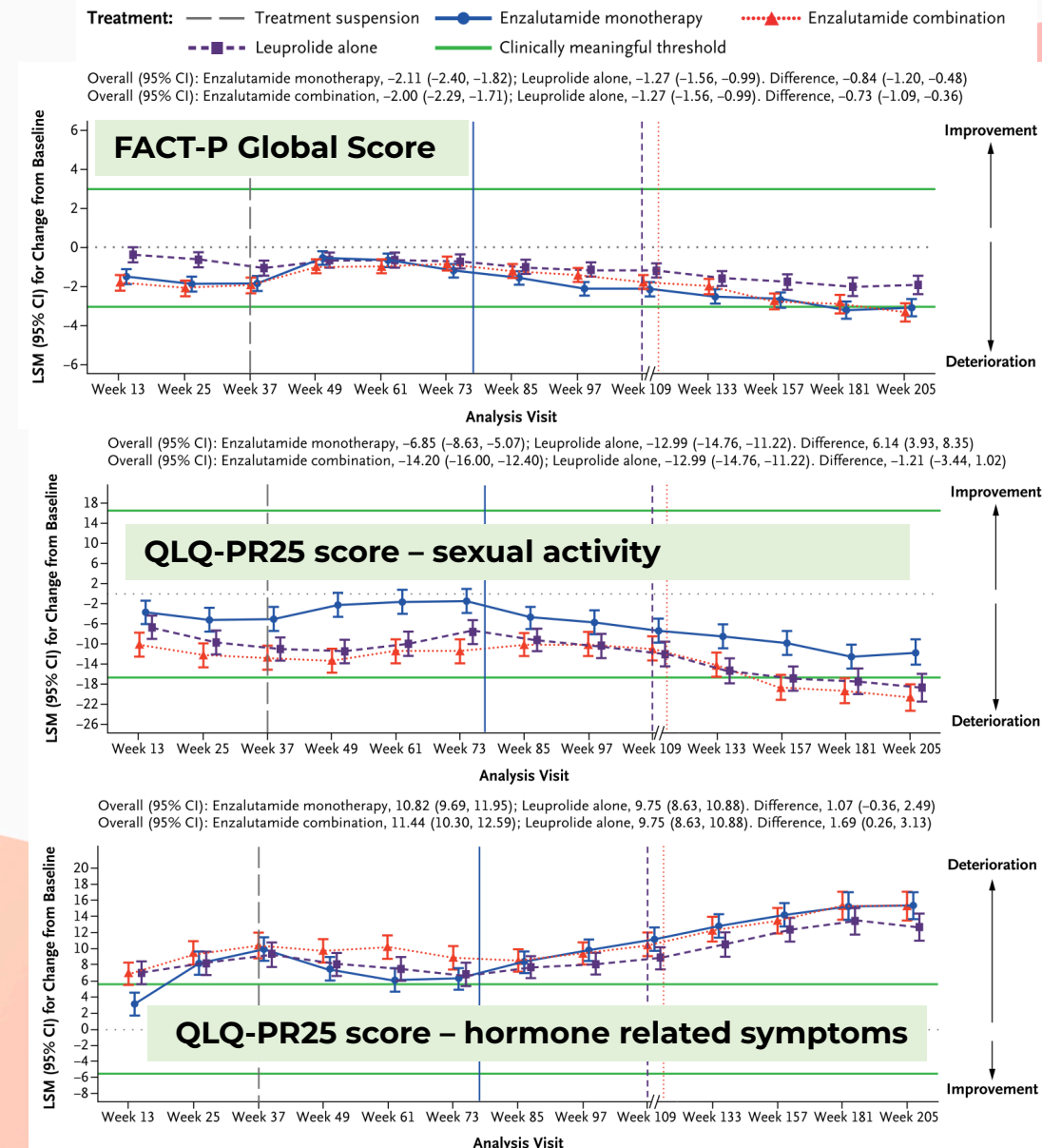
Event	Enzalutamide + Leuprolide (N = 353)		Leuprolide Alone (N = 354)		Enzalutamide Monotherapy (N = 354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
			<i>number (percent)</i>			
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)

Leuprolide had more frequent **hot flashes** (57.3% vs 21.8%)

Enzalutamide had more frequent **fatigue** (46.6% vs 32.8%)
gynecomastia (44.9% vs 9.1%)
nipple pain (15.3% vs 1.1%)
breast tenderness (14.4% vs 1.1%)

#guardsymposium2026
 X @GuardConsortium

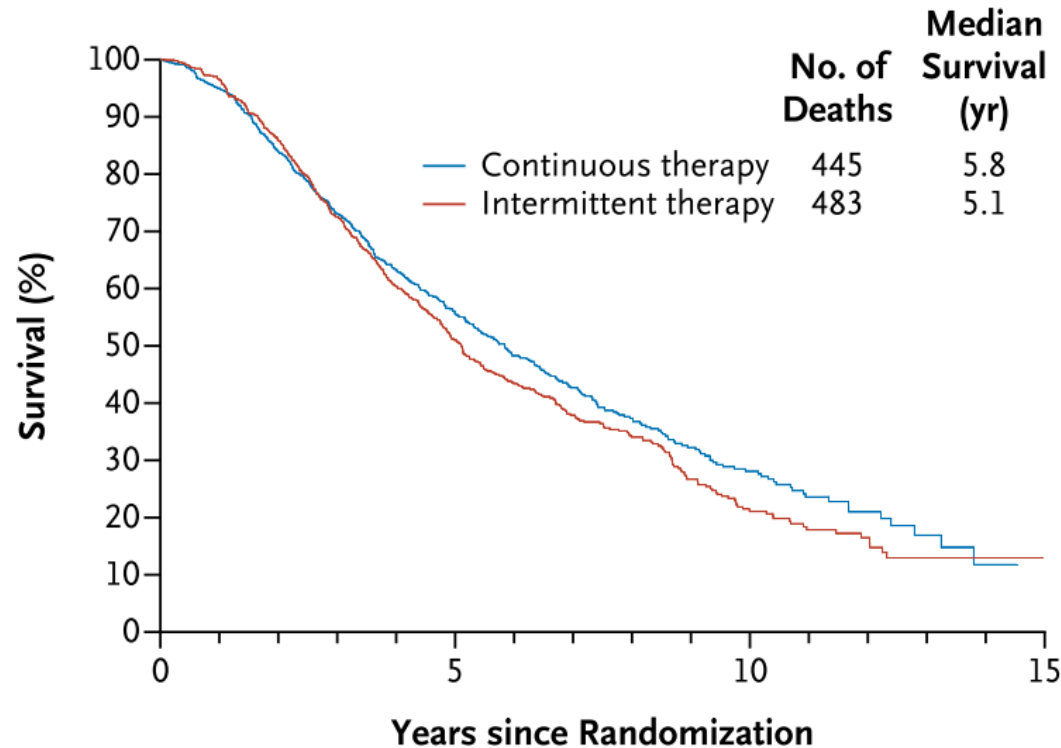
Freedland et al. N Eng J Med 2023. Freedland et al. NEJM Evid 2023



Treatment de-escalation is not new to mHSPC

Intermittent ADT: the SWOG 9346 trial

Intermittent ADT not non-inferior to continuous ADT
5.8 vs 5.1 yr (HR 1.1; 90%CI 0.99-1.23)



No. at Risk

Continuous therapy	765	325	64
Intermittent therapy	770	291	52

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But...

- High and low volume disease
- **PSA threshold** to stop **4 ng/mL**
- **Restart** not until **PSA 20 ng/mL** or baseline level or 10 ng/mL + symptoms

Improvement in quality of life
Change from baseline at 9 months

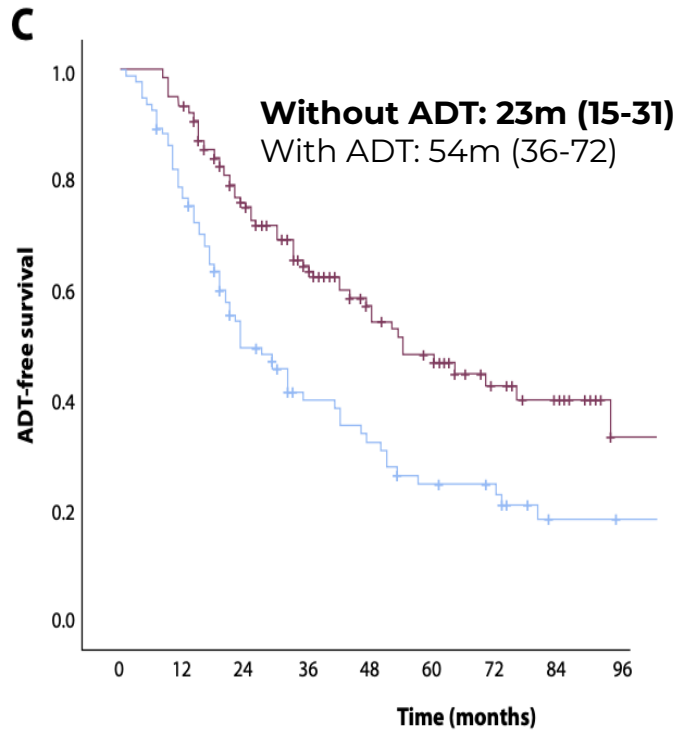
	Intermittent	Continuous	p-value
Erectile dysfunction	-8%	2%	<0.001
High libido	+20%	-11%	0.01
Vitality	-0.36	-3.07	0.03
Mental health	0.08	-1.94	0.07
Physical functioning	-0.66	-3.67	0.02

Oligometastatic patients may have very prolonged survival

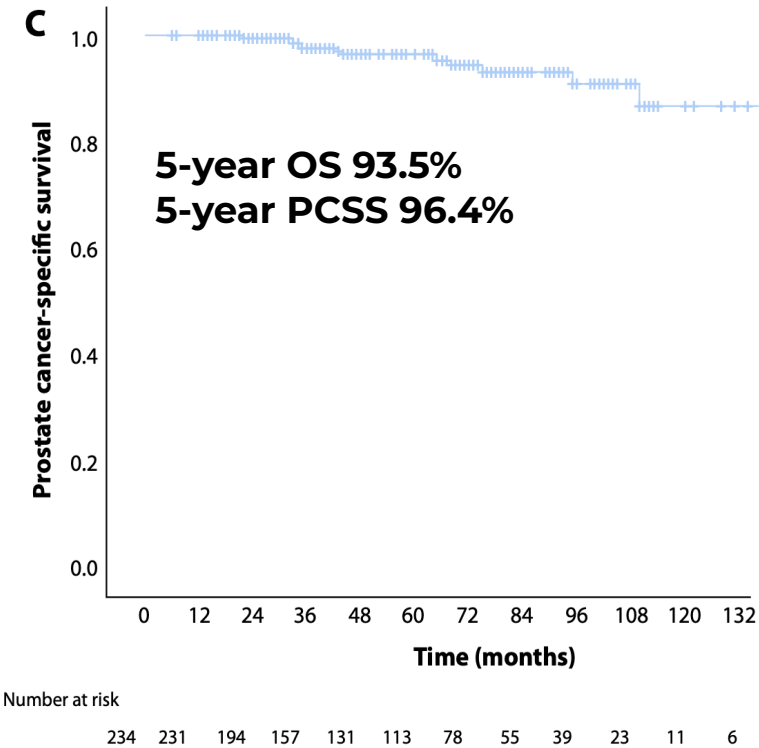
Patient selection is key

234 patients. **Metachronous oligometastatic (≤ 3 , PET-CT) mHSPC**
SBRT alone (+ short course ADT in 104 pts)

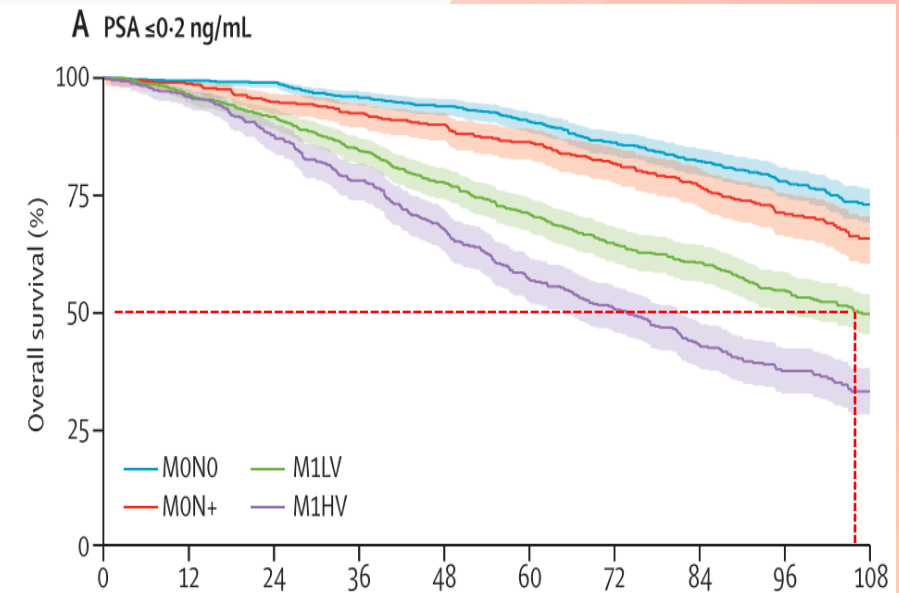
Time to ADT start



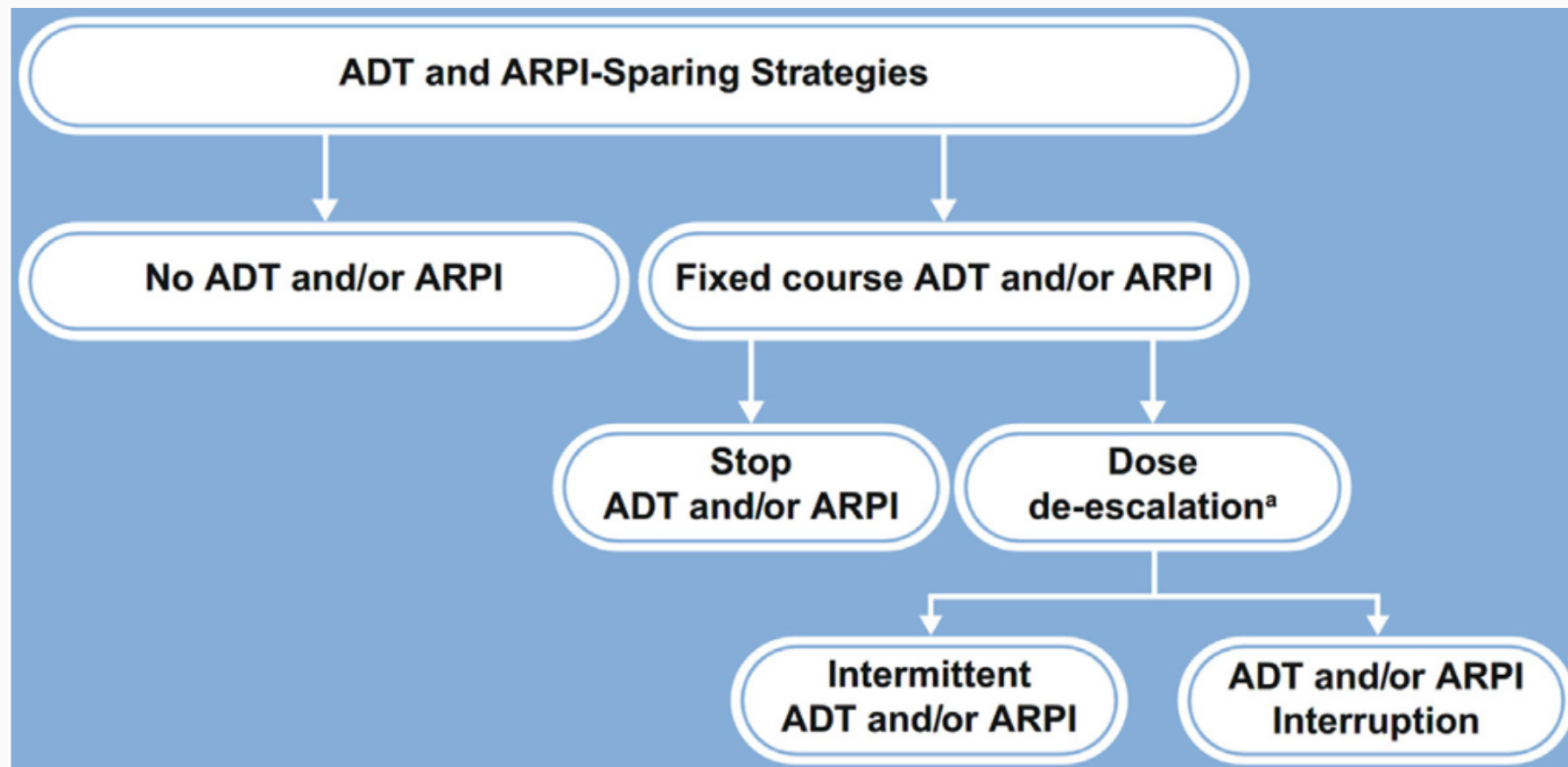
Overall survival



PSA response in low volume disease is associated with very prolonged survival



De-escalation strategies



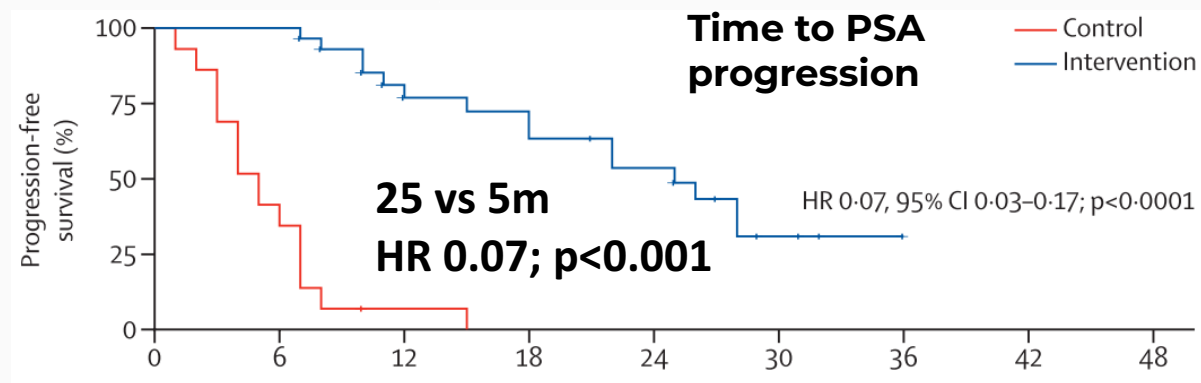
No ADT-No ARPi

Bullseye trial

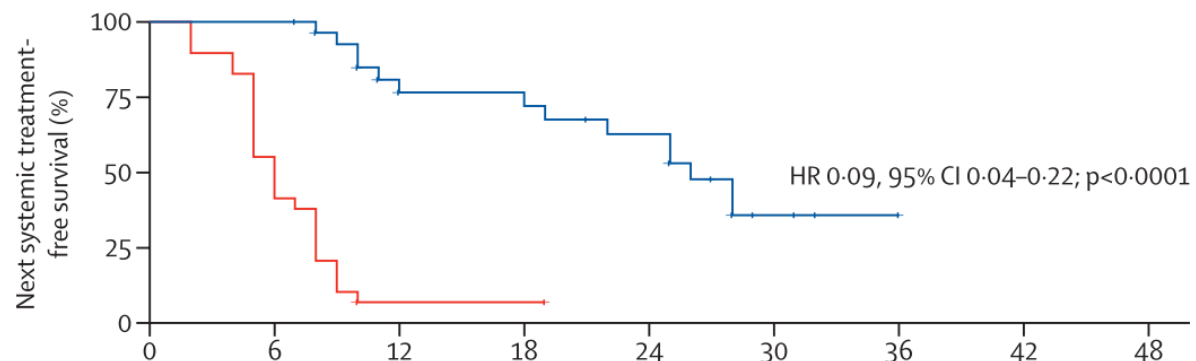
N=58 pts
Recurrent oligometastatic PC
PSADT < 6 monts

¹⁷⁷Lu-PSMA x 2 → 2 additional
cycles if persitent disease
vs
Deferred ADT at progression

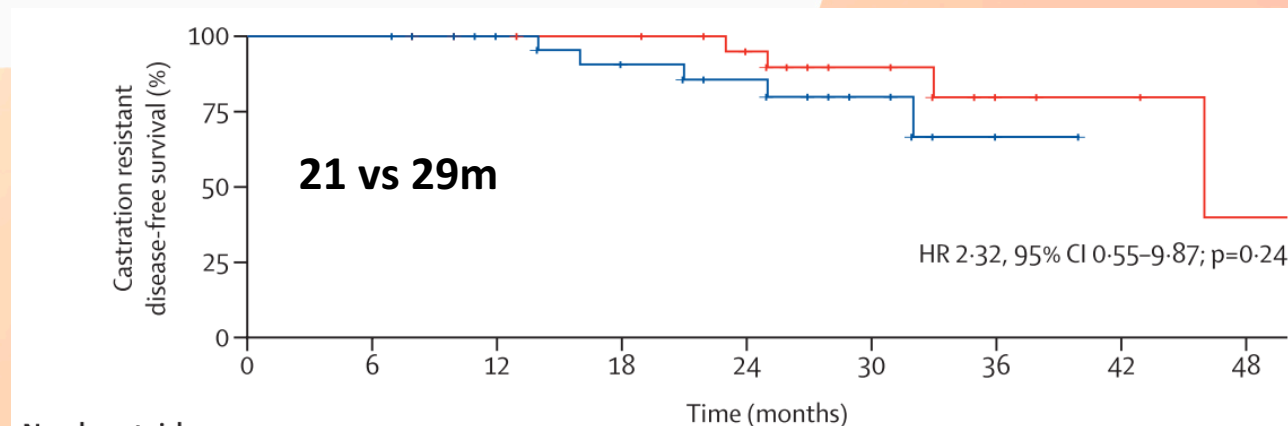
77% progression-free at **12 months**
54% progression-free at **24 months**



Time to next therapy



Time to castration resistance



De-escalating therapy in favorable PSA responders

A-DREAM (Alliance A032101)

N=75

mHSPC on ADT (>18m) & ARPi (at least 12m)

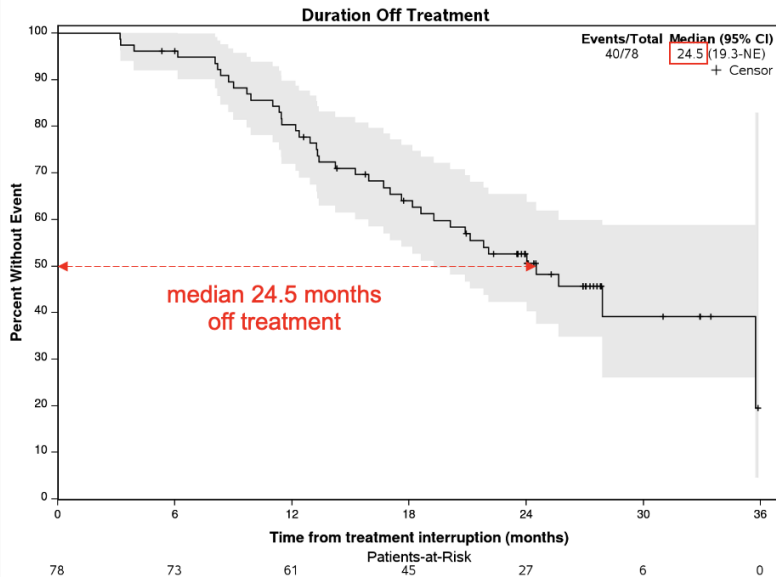
PSA < 0.2 ng/mL

Stop ADT + ARPi. Restart if PSA > 5 ng/mL

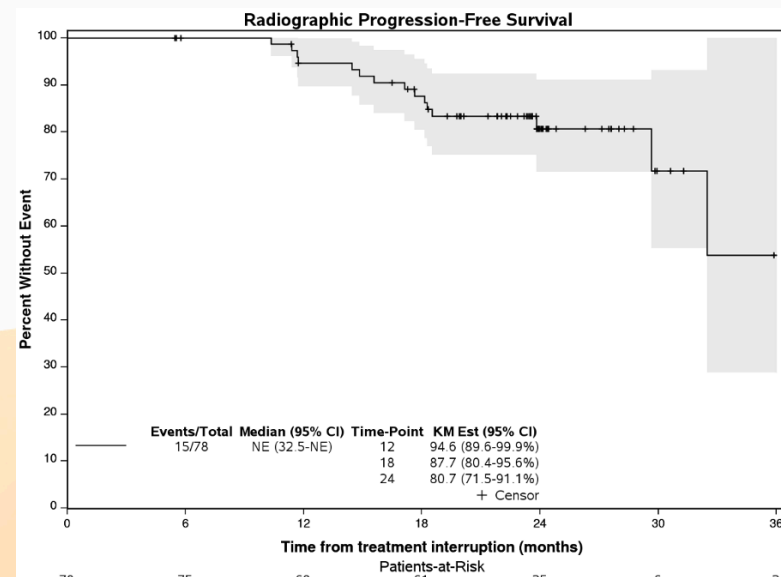
35% high volume. 30% RT to metastatic sites

57.7% treatment free for 18 months
41% treatment-free for 18 months with
testosterone recovery

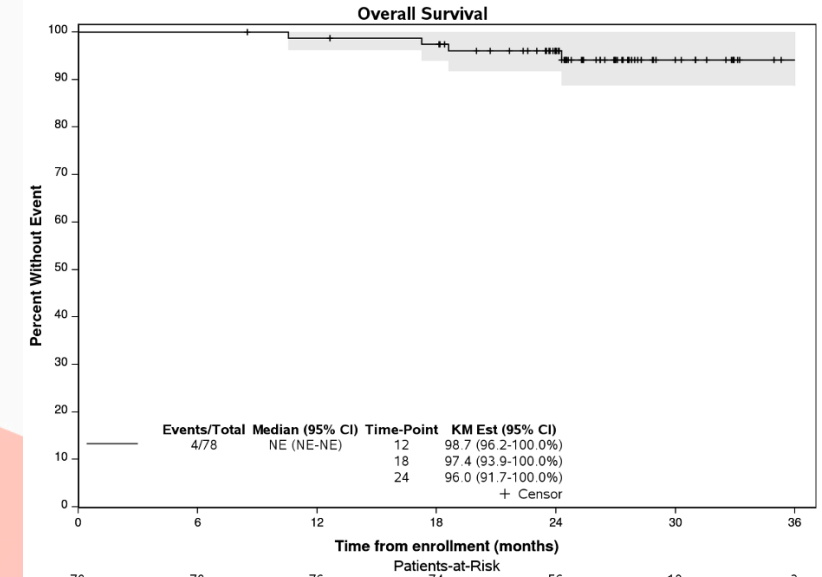
Pts with low volume and RT to mets
had longer time off



2-year rPFS 80%



2-year OS 96%



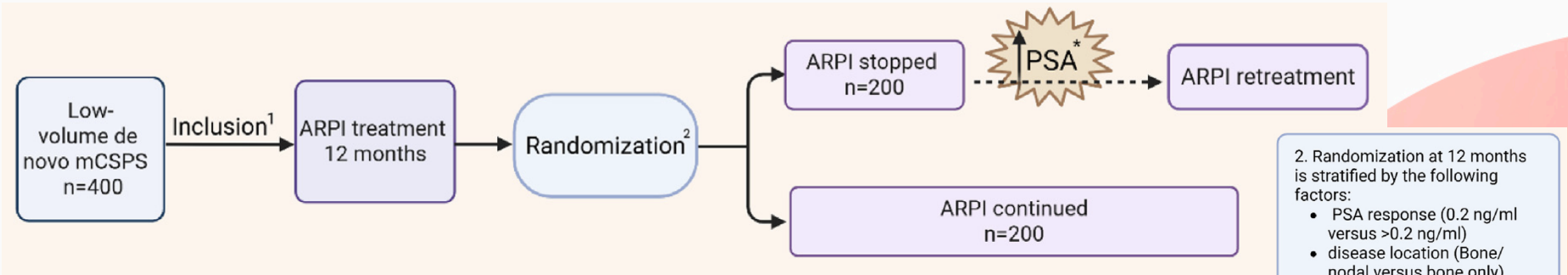
@GuardConsortium

Choudhury et al. ASCO 2026

De-escalating in PSA responders: strategies under evaluation

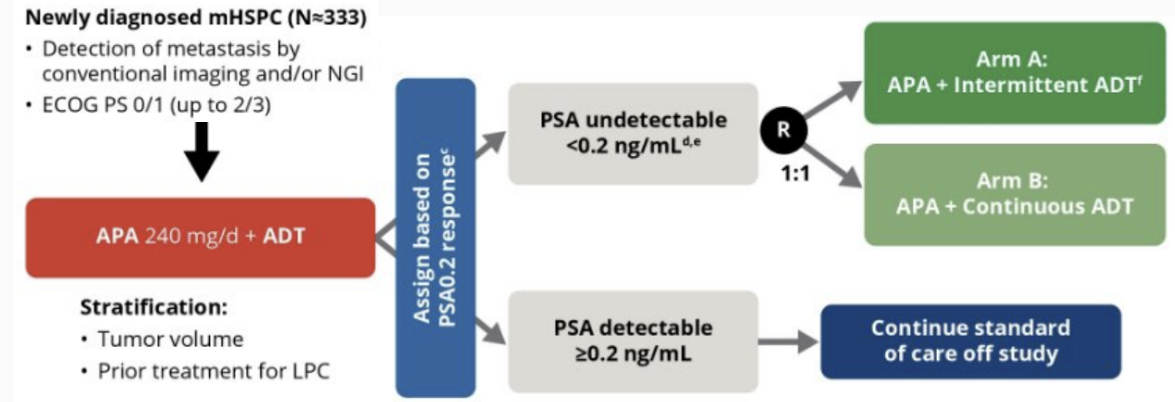
Stop ARPi, continue ADT

Apa-Enza SHORT
NCT07260435



Stop ADT, continue ARPi

LIBERTAS
NCT07260435

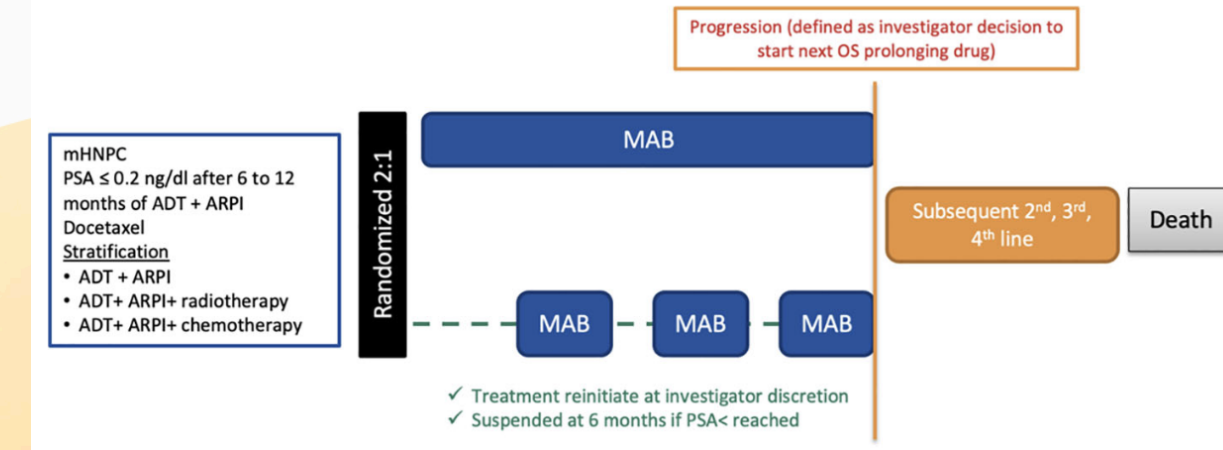


Restart

PSA ↑ to ≥10 ng/mL (or return to baseline if <10 ng/mL before ADT), PSADT <6 months, or new or worsening cancer symptoms

Stop ADT and ARPi

EORTC De-Escalate
NCT07260435



Restart

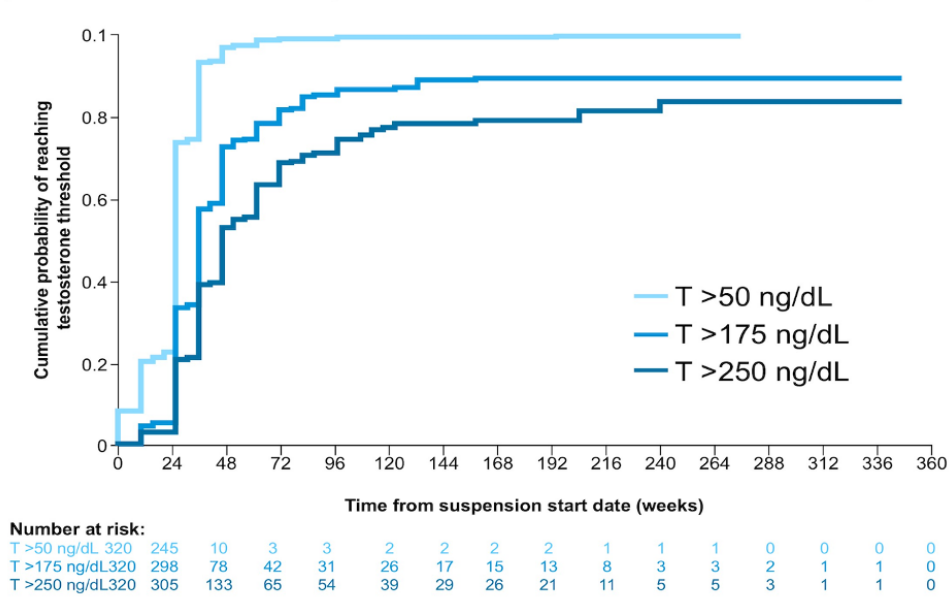
PSA ↑ to ≥50% of diagnostic value (max 5 ng/mL) or clinical or radiological progression-related symptoms

What benefit can we expect from de-escalating therapy?

Testosterone recovery after treatment suspension in EMBARK

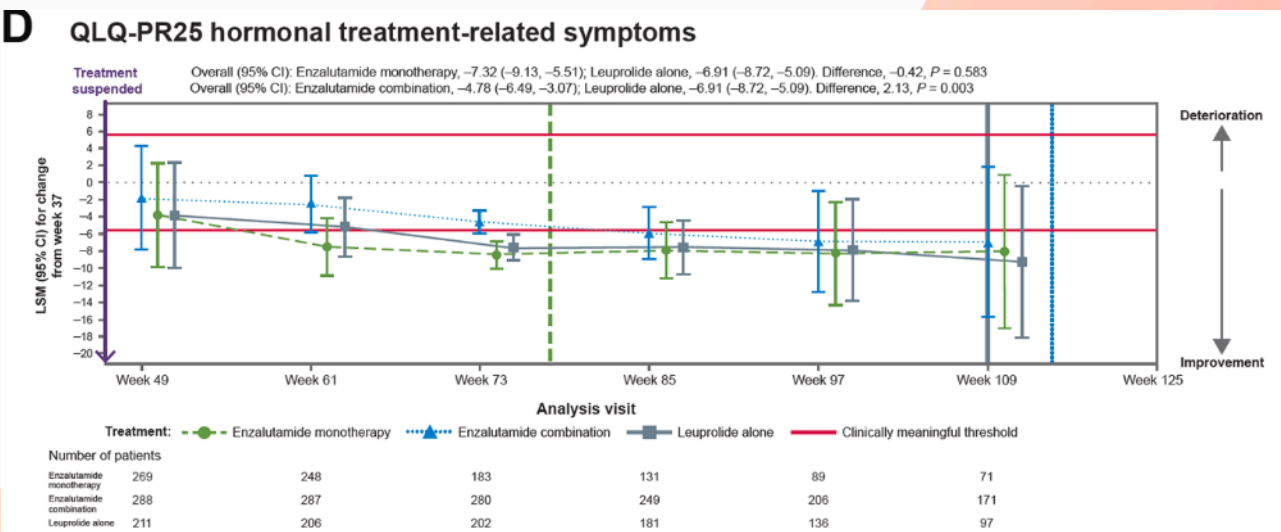
Hormonal symptoms may improve after discontinuation, often over several months, while a large improvement in global quality of life is not assured

Figure 2. Cumulative probability of reaching testosterone thresholds among patients with treatment suspension after 37 weeks of enzalutamide + leuprolide



	Enzalutamide combination (n=320)
Patients who reached T recovery (>250 ng/dL), n (%)	108 (33.8)
Time to T recovery (>250 ng/dL), months†	
Median (range)	5.6 (0.0–22.1)
Mean (SD)	6.8 (2.87)

Gradual improvement in hormonal treatment-related symptoms—hot flashes, breast enlargement, swelling, weight changes, feeling less masculine



Change in overall quality of life, physical well-being, pain, sexual activity, and urinary and bowel symptoms **do not exceed the threshold for clinical significance**

Intensification or de-escalation strategies in 1L mHSPC

- **ADT + ARPi doublets are the backbone** of systemic therapy for mHSPC
- Most patients should receive this as initial therapy
- A **one-size fits all** approach is **no longer acceptable** → not aligned with the needs of specific patients
- Some patients **need intensified therapy** because their disease is aggressive
 - Induce response and maintain it for as long as possible
 - Potential toxicity generally offset by the better disease control
 - Use of clinical criteria (volume) now hindered by the advent of next-generation imaging (PSMA)
 - **Molecular biomarkers** will help us guide the decision of **what to intensify** therapy **with (Docetaxel, PARPi, AKTi, radioligands)**
- Some patients may afford to receive **less toxic therapy**
 - Preserve quality of life if it is satisfactory
 - Avoid unnecessary worsening in patients with declining baseline status / comorbidities
 - **Different strategies** (what & when to de-escalate) may provide **different benefits / risk**
 - Combination with **ablative techniques (SBRT)** will likely increase long-term control
 - **Evidence is still lacking** that **long-term efficacy is equivalent** (trials ongoing)

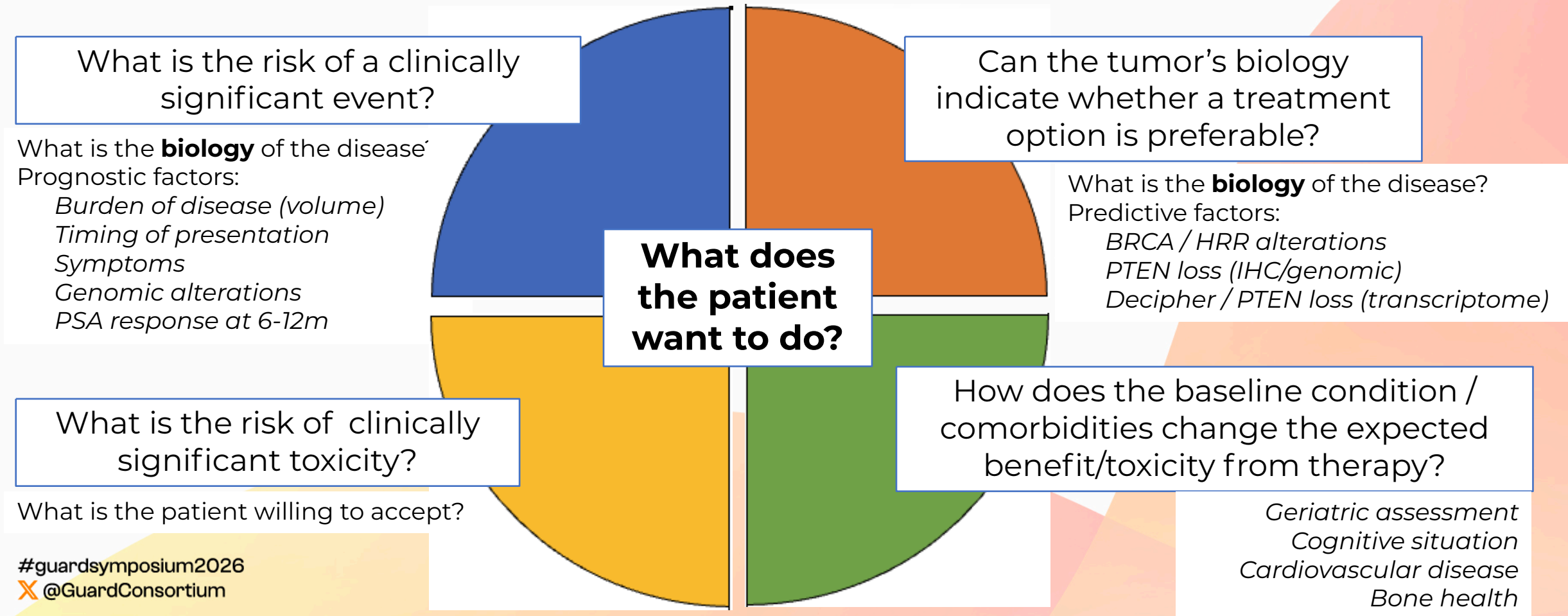
Intensification or de-escalation strategies in 1L mHSPC

	Who needs intensified therapy ?	Who could do with less therapy ?
Who?	Patients with biologically aggressive disease: (high volume, visceral mets, symptomatic disease)	Patients with indolent disease (low volume, metachronous) Oligometastatic disease candidates for ablative therapy (SBRT)
What for?	Induce response , control symptoms, prolong survival	Avoid toxicity in the absence of disease related symptoms
Why?	Patients may not receive all life-prolonging options at progression	Patients able to receive treatments in sequence with (potentially) no detriment to the overall outcome
	Trade toxicity for disease control	Maintain quality of life

Intensification or de-escalation strategies in 1L mHSPC

Personalizing therapy means **focusing on what a patient needs**

What is the patient's **clinical situation**? What are the **goals of therapy**?



Thank you

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FUNDACIÓN
INSTITUTO VALENCIANO DE ONCOLOGÍA

