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Management of metastatic CSPC

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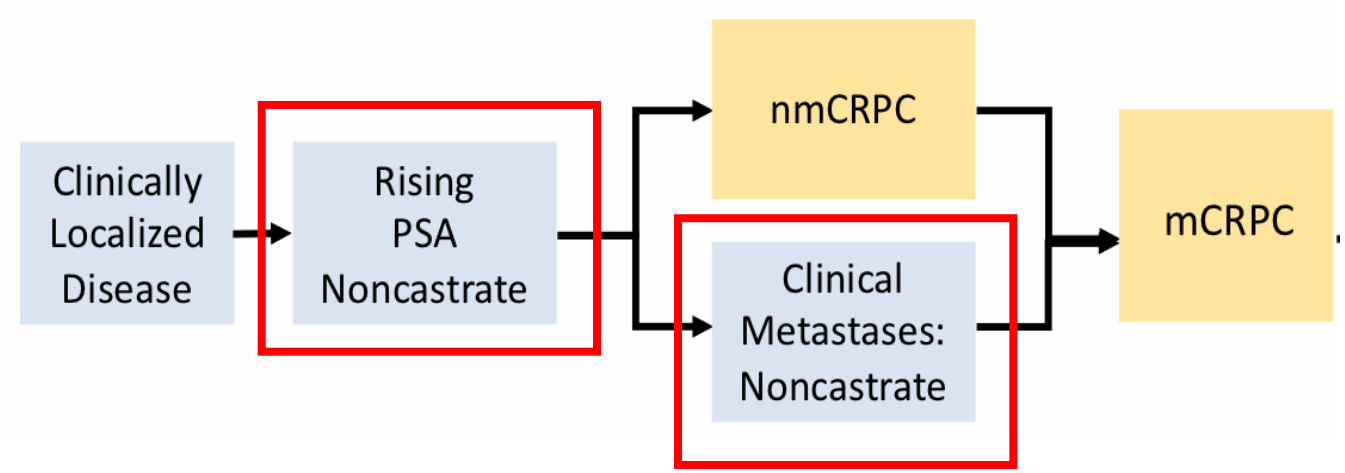
Management of metastatic CSPC

- **Systemic therapy options**
- Risk stratification based on clinical biomarkers
- Radiotherapy to the primary tumor
- What is the right treatment strategy?
- Therapy intensification / deintensification
- Molecular biomarkers

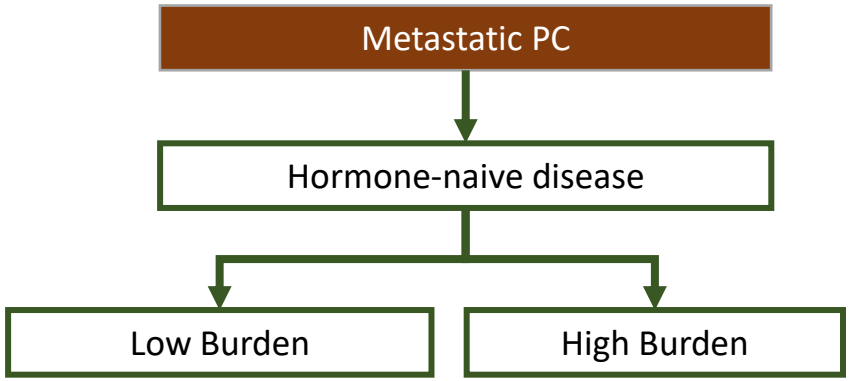
What is mCSPC?

- Detection of **distant metastases**
  - Traditionally by CT scan/bone scan
  - Novel imaging techniques (PSMA-PET CT)
- **Testosterone** in the non-castrate range (> 50 ng/dL)



What treatment options are available?

2020 ESMO guidelines



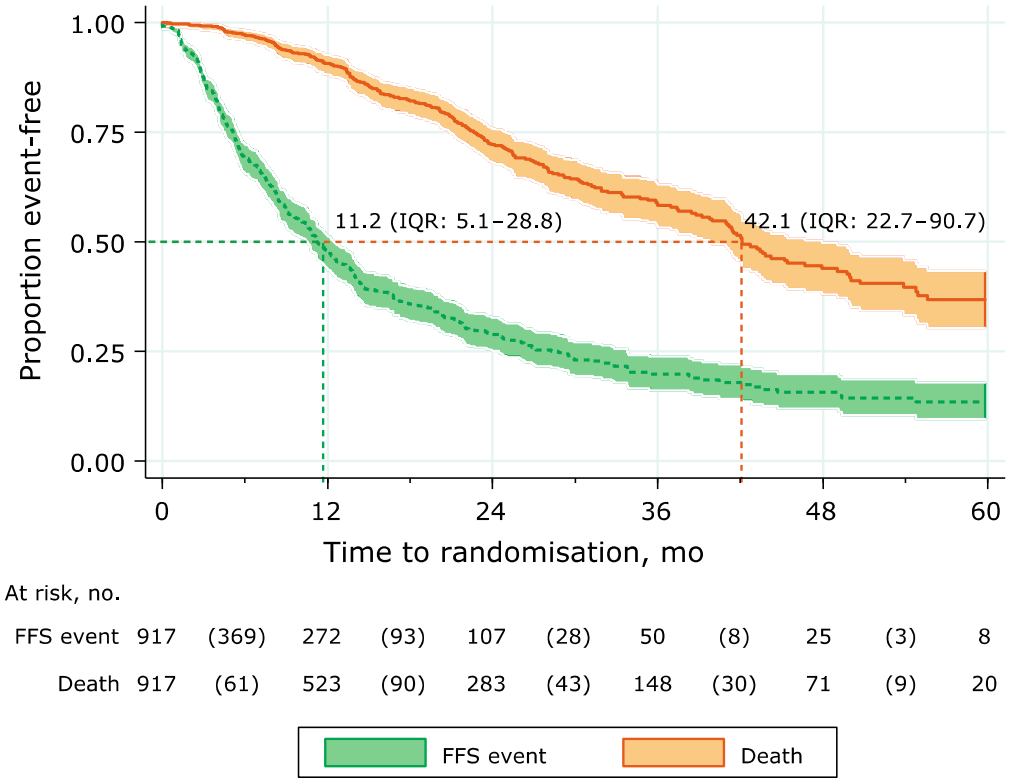
RT to the primary (prostate)	ADT + Docetaxel
	ADT + Abiraterone
	ADT + Apalutamide
	ADT + Enzalutamide

But now, also…

- ADT + Docetaxel + Abiraterone
- ADT + Docetaxel + Darolutamide

Scher et al. J Clin Oncol 2016. Parker et al. Ann Oncol 2020

Androgen deprivation therapy (ADT) is the main therapeutic approach in metastatic prostate cancer and **must be continued throughout the disease**



STAMPEDE trial: control group

917 mHSPC patients treated in the contrl group of the STAMPEDE trial
GnRH analogues +/- bicalutamide with/without prior radiotherapy

FFS (median)	11.2 m
OS (median)	42.1 m
2-yr OS	72%

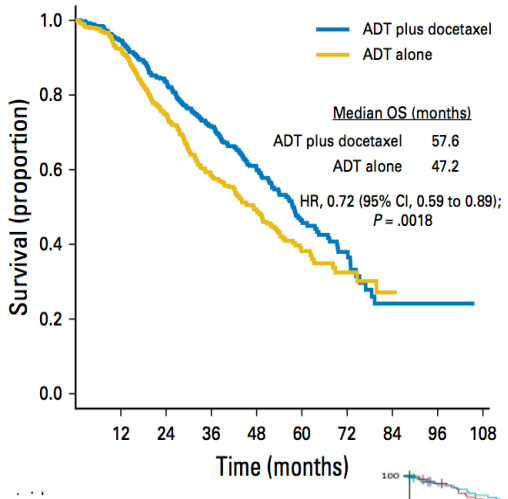
7-month PSA response with ADT + bicalutamide
(control group SWOG 1216 trial)
PSA < 0,2 ng/mL: 44%
PSA < 4 ng/mL: 75%

James et al. Eur Urol 2015;67(6):1028-38

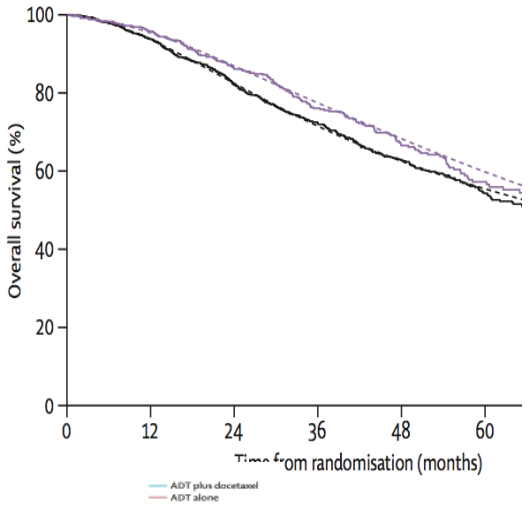
ADT alone is inferior to ADT + Docetaxel

Phase III trials: ADT + Docetaxel vs ADT alone

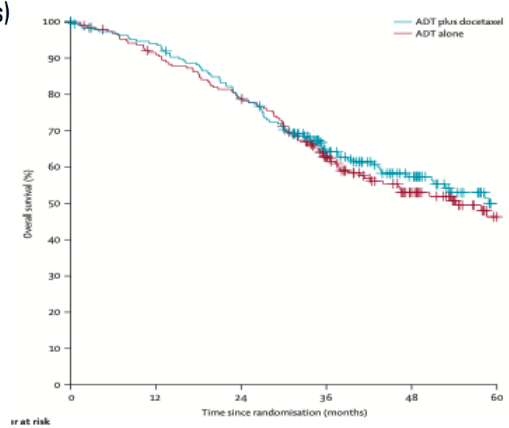
CHAARTED trial



STAMPEDE trial



GETUG-AFU-15 trial



STOPCAP Metaanalysis

Metastatic disease

	Control	Treatment	Hazard ratio (95% CI)
CHAARTED[7]	136/393	101/397	0·61 (0·47–0·80)
GETUG-15[9,10]	NA/193	NA/192	0·90 (0·69–1·81)
STAMPEDE[8] (SOC +/– Doc)	350/724	144/362	0·76 (0·62–0·93)
STAMPEDE[8] (SOC + ZA +/– Doc)	170/366	158/365	0·85 (0·65–1·10)
Overal			·77 (0·68–0·87

Heterogeneity: χ^2=4·80; df=3; p=0·187; I^2=37·5%

0·5 1 2

Favours SOC + docetaxel Favours SOC

Non-metastatic disease

	Control	Treatment	Hazard ratio (95% CI)
GETUG-12[25]	49/206	42/207	0·94 (0·60–1·48)
RTOG 0521[28]	59/281	43/282	0·70 (0·47–1·04)
STAMPEDE[8] (SOC +/– Doc)	65/460	31/230	0·95 (0·62–1·46)
STAMPEDE[8] (SOC + ZA +/– Doc)	31/227	20/228	1·05 (0·57–1·95)
Overall			**0·87 (0·69–1·09)**

Heterogeneity: χ^2=1·80; df=3; p=0·614; I^2=0%

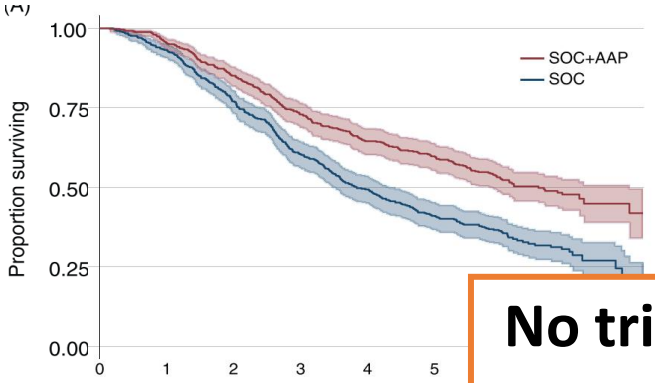
0·5 1 2

Favours SOC + docetaxel Favours SOC

Sweeney et al. NEJM 2015. James et al. Lancet 2015. Gravis et al. Lancet Oncol 2013.Vale et al. Lancet Oncol 2016.

ADT (+/- bicalutamide) is inferior to ADT + novel hormonal agents

STAMPEDE: ADT + Abiraterone



LATITUDE: ADT + Abiraterone

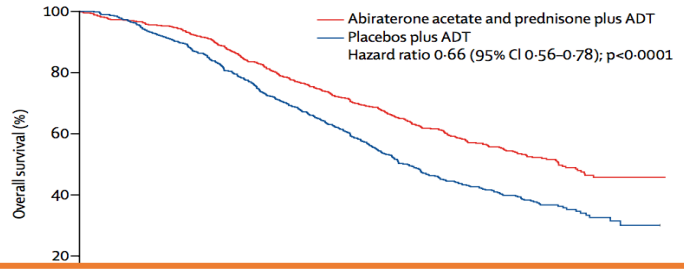
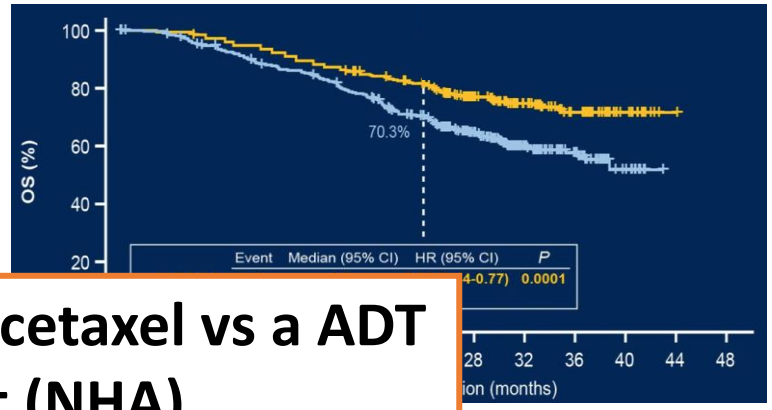
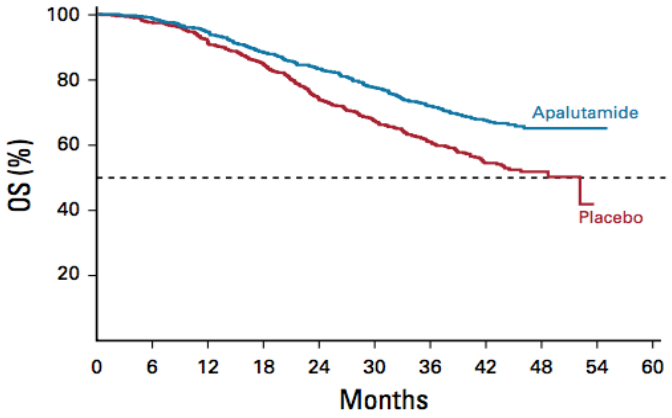


CHART: ADT + SHR3680 (Rezvilutamide)



No trials have compared ADT + Docetaxel vs a ADT + a novel hormonal agent (NHA)

TITAN: ADT+Apalutamide



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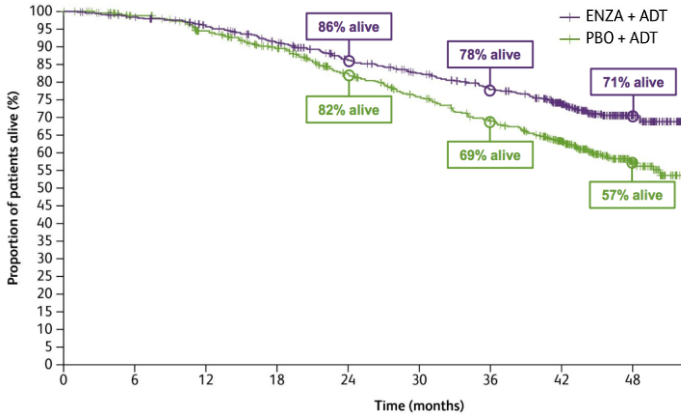
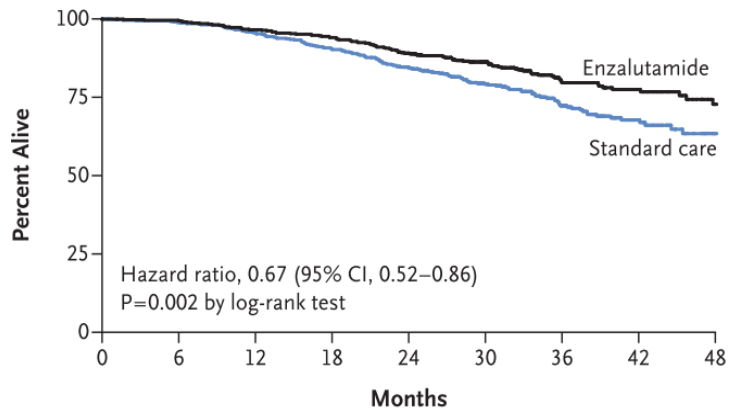




Kyriakopoulos J Clin Oncol 2018; Fizazi et al. Lancet Oncol 2019; Clarke et al. Ann Oncol 2019; James et al. ESMO 2020. Abs 611O. Davis et al N Eng J Med 2019. Armstrong et al J Clin Oncol 2019. Chi et al. N Eng J Med 2019

What is the best option? ADT + ARSIs or ADT + Docetaxel?

No direct comparison between treatment strategies to date

	FUP	OS tto		OS control		HR (95%CI)	Δ 3yr OS	p-value
		Median	3-yr	Median	3-yr			
CHAARTED	53.7 m	57.6 m	~71%*	47.2 m	~58%*	0.72 (0.59-0.89)	~13%	p=0.0018
STAMPEDE (Docetaxel)	78.2 m	59.1 m	~66%*	43.1 m	~59%*	0.81 (0.69-0.95)	~7%	p=0.003
LATITUDE	51.8 m	53.3 m	~65%*	36.5 m	~51%**	0.66 (0.56-0.78)	~14%	p<0.001
STAMPEDE (Abiraterone)	73 m	79.2 m	~73%*	45.6	~60%*	0.60 (0.50-0.71)	~13%	p<0.001
ENZAMET	68 m	NR	80%	73.2 m	72%	0.67 (0.52-0.86)	8%	p=0.002
ARCHES	44.6 m	NR	78%	NR	69%	0.66 (0.53-0.81)	9%	p<0.001
TITAN	44 m	NR	-	52.2 m	-	0.67 (0.51-0.89)	-	p=0.005
CHART	30.5 m	NR	~71%*	NR	~58%*	0.58 (0.44-0.77)	~13%	p<0.001

**Estimation based on KM curve inspection*

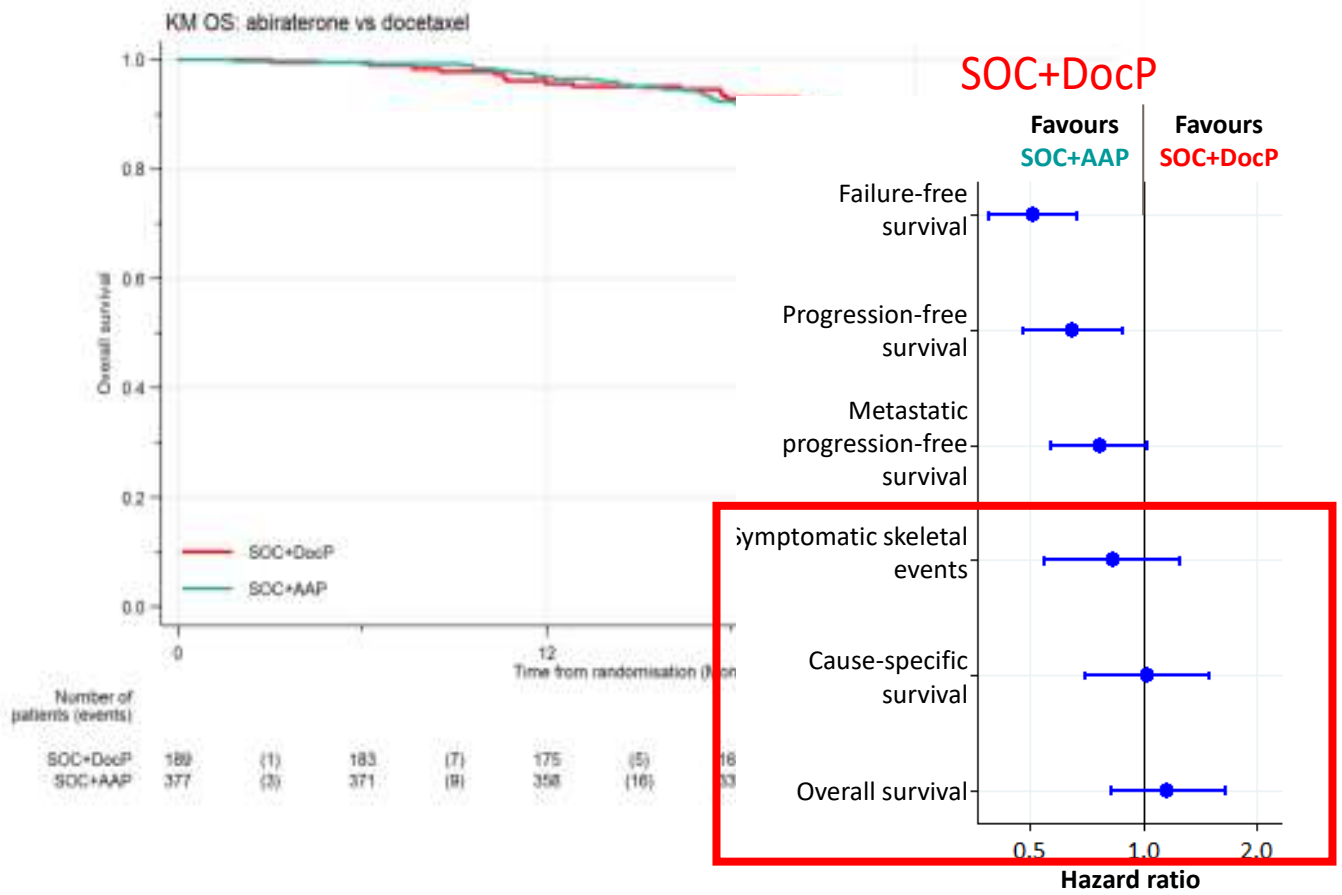
Kyriakopoulos J Clin Oncol 2018; Fizazi et al. Lancet Oncol 2019; Clarke et al. Ann Oncol 2019; James et al. ESMO 2020. Abs 611O. Davis et al N Eng J Med 2019. Armstrong et al J Clin Oncol 2022. Chi et al. N Eng J Med 2019. Ye et al. ASCO 2022. Abs 5005

Beware of indirect comparisons and network meta-analyses!!

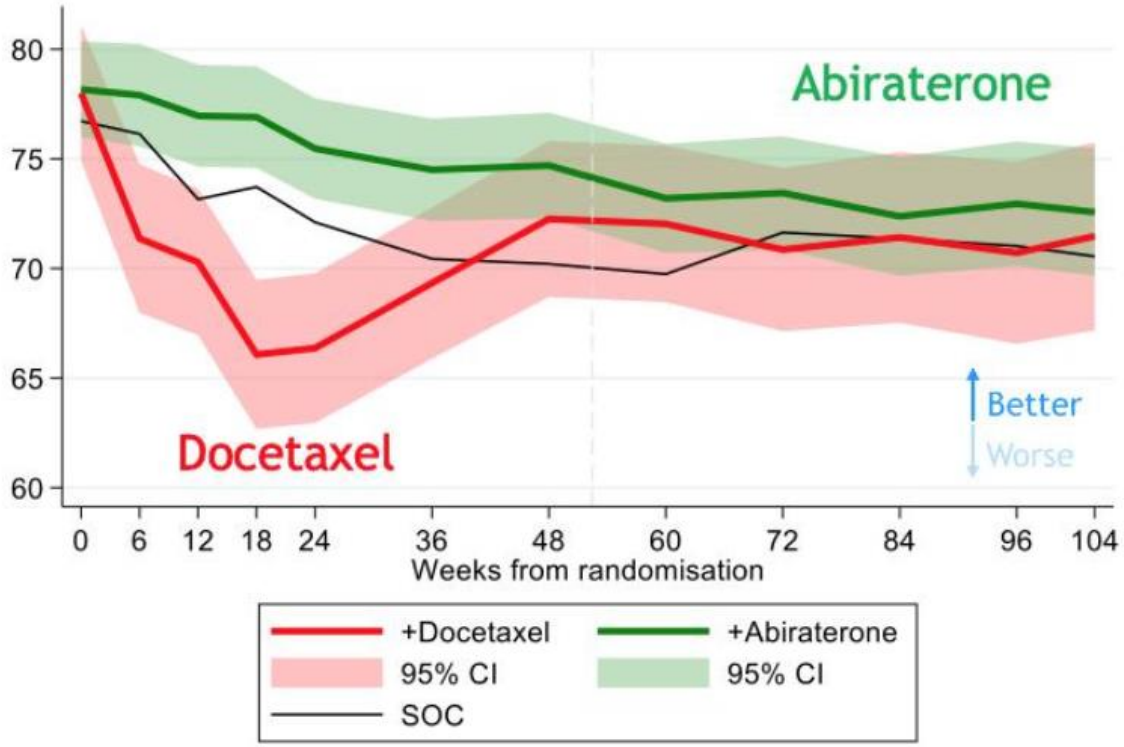
	CHAARTED	STAMPEDE		LATITUDE	ENZAMET	ARCHES	TITAN	CHART
		Docetaxel	Abiraterone					
Patients	mHSPC	mHSPC & high risk nmHSPC		High risk mHSPC	mHSPC	mHSPC	mHSPC	mHSPC
Primary endpoint	OS	OS		OS & rPFS	OS	rPFS	OS	OS & rPFS
Comparator arm	ADT	SOC	SOC	ADT	ADT +/- Doce	ADT + AA +/- Doce	ADT +/- Doce	ADT + AA
Follow-up	53.7 m	78.2 m	73 m	51.8 m	68 m	44.6 m	44 m	30.4 m
High volume	64.9%	56%	52%	-	52.3%	63.2%	62.8%	100%
Prior local therapy	27.2%	5%	7%	4%	-	12-26%	16.4%	~10%
Docetaxel for mHSPC	0	0	0	0	45%	15.5%	10.7%	0
ECOG PS 2	1.5%	NR	NR	?	0	0	0	0
Age	64 a	66 a	66 a	67 a	69 a	70 a	69 a	69 a
Gleason ≥ 8	60.7%	67.5%	77.3%	97.6%	58.3%	66%	67.4%	81.5%
Visceral metastases	15%	5%	6%	12-17%	11.5%	?	12.1%	20%

Sweeney et al. NEJM 2015. 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. Armstrong et al J Clin Oncol 2019. Chi et al. N Eng J Med 2019.

No difference in OS between ADT + Abi & ADT + Docetaxel in a post-hoc, indirect, non-randomised comparison of contemporaneous patients of the STAMPEDE trial



Better quality of life for patients treated with ADT + Abiraterone than those treated with ADT + Docetaxel in the STAMPEDE trial



Sydes et al. Ann Oncol 2018. Rush et al. J Clin Oncol 2022

ADT + novel hormonal agents have a better toxicity profile

NHAs are easy to use, with manageable toxicity profiles

Docetaxel (CHAARTED)

	Grade ≥ 3
Fatigue	0.3%
Allergic reaction	3.3%
Neuropathy	0.7%
Fatigue	1.7%
Anemia	0.3%
Thrombopenia	0.3%
Neutropenia	12.1%
Febrile neutropenia	6.1%

CHAARTED: 86% of the patients in the combination group completed six cycles of docetaxel therapy

ADT + NHA doublets have been the prefered treatment option based on oral administration & a more favorable toxicity profile

Abiraterone (LATITUDE)

	All Grades	G ≥ 3
Hypertension	37%	20%
Hypokalemia	20%	11%
AST/ALT increase	16%	6%
Hyperglycemia	13%	4%
Cardiac disorder	12%	4%
Fatigue	13%	2%

Apalutamide (TITAN)

	All Grades	Grade ≥ 3
Rash	27.1%	6.3%
Fatigue	19.7%	1.5%
Fall	7.4%	0.8%
Hypothiroidism	6.5%	0
Fracture	6.3%	1.3%
Seizure	0.6%	0.2%

Enzalutamide (ARCHES)

	All Grades	Grade ≥ 3
Seizures	0.3%	0.3%
Hypertension	8.6%	3.3%
Cognitive/memory	4.5%	0.7%
Fatigue	24.1%	1.7%
Fall	3.7%	0.3%
CV events	4%	1.5%

Sweeney et al. N Eng J Med 2015. Fizazi et al. N Eng J Med 2017. Davis et al N Eng J Med 2019. Chi et al. N Eng J Med 2019. Rush et al. J Clin Oncol 2022

Is more better? Triplet therapy

The ARASENS trial

Elegibility:
Prostate adenocarcinoma
Evidence of metastatic disease (CT/BS)
ADT < 12 weeks

Induction (6 cycles)

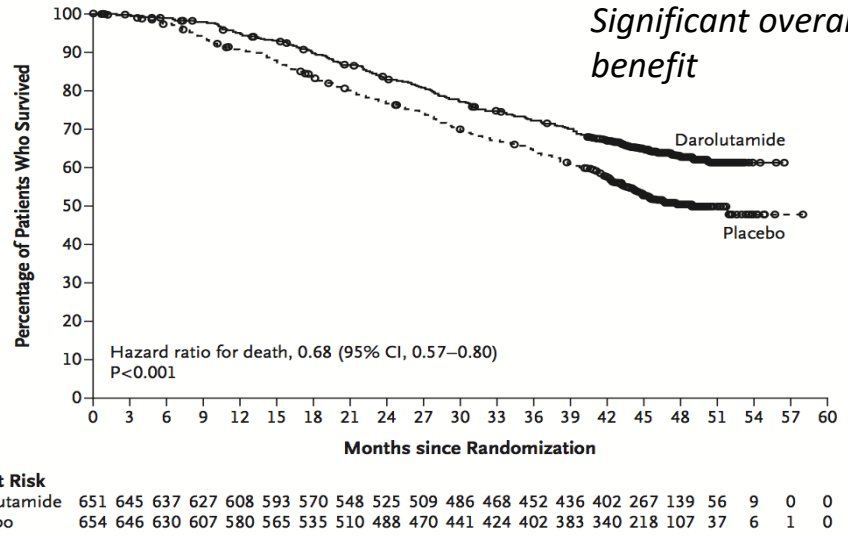
- ADT + Docetaxel 75 mg/m² + Darolutamide 600 mg/12h (N=574) → *Maintenance until PD*: ADT + Darolutamide 600 mg/12h
- ADT + Docetaxel 75 mg/m² + Placebo (N=574) → *Maintenance until PD*: ADT + Placebo

Primary endpoint
Overall survival

Secondary endpoints
Time to CRPC
Time to pain progression
Time to skeletal related event
Time to clinial progression

Stratification:
Stage IVa vs IVb vs IVc
Alkaline Phosphatase > or < LSN

Significant overall survival benefit



Results with a median follow-up of 43.7 months (overall survival)

	ADT+D+Daro	ADT+D	HR (IC95%);p-val
OS (median)	NA	48.9 m	0.68 (0.57-0.80); p<0.001
4-yr OS	62.7%	50.4%	
TTCRPC	NA	19.1 m	0.36 (0.30-0.42); p<0.001
T to pain prog	NA	27.5 m	0.79 (0.66-0.95); p=0.01
SRE-PFS	51.2 m	39.7 m	0.61 (0.52-0.72); p <0.001

Smith et al. N Eng J Med 2022;6736(15):1-24

The PEACE-1 trial

Elegibility:
De novo mHSPC
≥1 lesion in bone scan
ECOG PS 0-2

Randomization 1:1:1:1

- SOC (n=296)
- SOC + RT (n=293)
- SOC + Abiraterone (n=292)
- SOC + Abiraterone + RT (n=293)

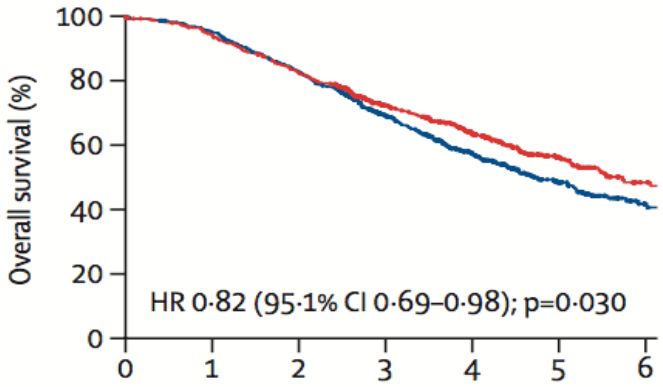
→ SOC (n=589) / SOC + Abiraterone (n=583)

→ ADT + Docetaxel (n=296) / ADT + Docetaxel + Abiraterone (n=296)

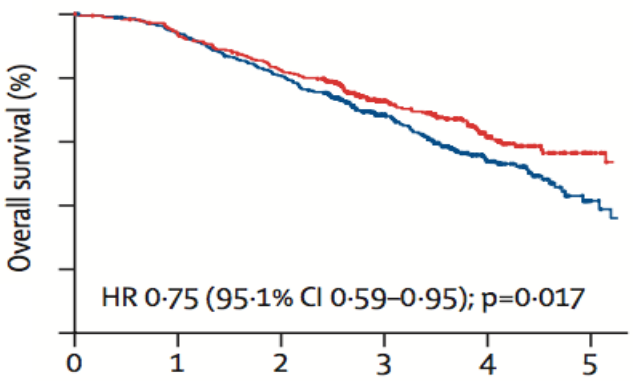
Primary endpoint
Radiographic progression-free survival
Overall survival

Stratification:
ECOG PS
Type of ADT (GnRH vs orquiect)
Disease volume
Treatment with Docetaxel

*Significant OS benefit in the **overall population***



*Significant OS benefit in the **Docetaxel-treated population***



Fizazi et al. Lancet 2022

	ADT+D+ Abi	ADT+D	HR (IC95%);p-val	
OS	NA	52.8 m	0.75 (0.59-0.95); p=0.017	**Arasens: HR 0.68**
PCSM	NA	56.4 m	0.50 (0.34-0.71); p=0.006	
rPFS	54 m	36 m	0.36 (0.30-0.42); p<0.001	
TT mCRPC	45.6 m	18 m	0.38 (0.66-0.95); p=0.01	**Arasens: HR 0.36**

Management of metastatic CSPC

- Systemic therapy options
- **Risk stratification based on clinical biomarkers**
- Radiotherapy to the primary tumor
- What is the right treatment strategy?
- Therapy intensification / deintensification
- Molecular biomarkers

Doublet (ADT + NHA) and triplet (ADT + Docetaxel + NHA) are the main systemic therapy options in fit patients.

Can we use <u>biomarkers</u> to decide what option to recommend? What questions can these biomarkers answer?

Do I need a more intensive treatment or can I spare toxicity?

Can an improved **<u>prognostic</u>** assessment guide therapy decisions?

- **Avoiding overtreatment** (= toxicity) in patients with **indolent disease** that will be candidates for sequential treatment
- **Intensifying therapy** in patients with **aggressive disease** that may otherwise not receive all therapeutic options (higher risk of progression & death)

Can we develop **<u>predictive biomarkers</u>** to improve decision-making?

- Identification of subsets based on clinical biomarkers that are **more likely to benefit** from a particular treatment option (ADT + NHAs vs ADT + Docetaxel + NHAs)

Advanced prostate cancer is a clinically heterogeneous disease

Burden of metastatic disease and **timing** of presentation **define clinically relevant subgroups**

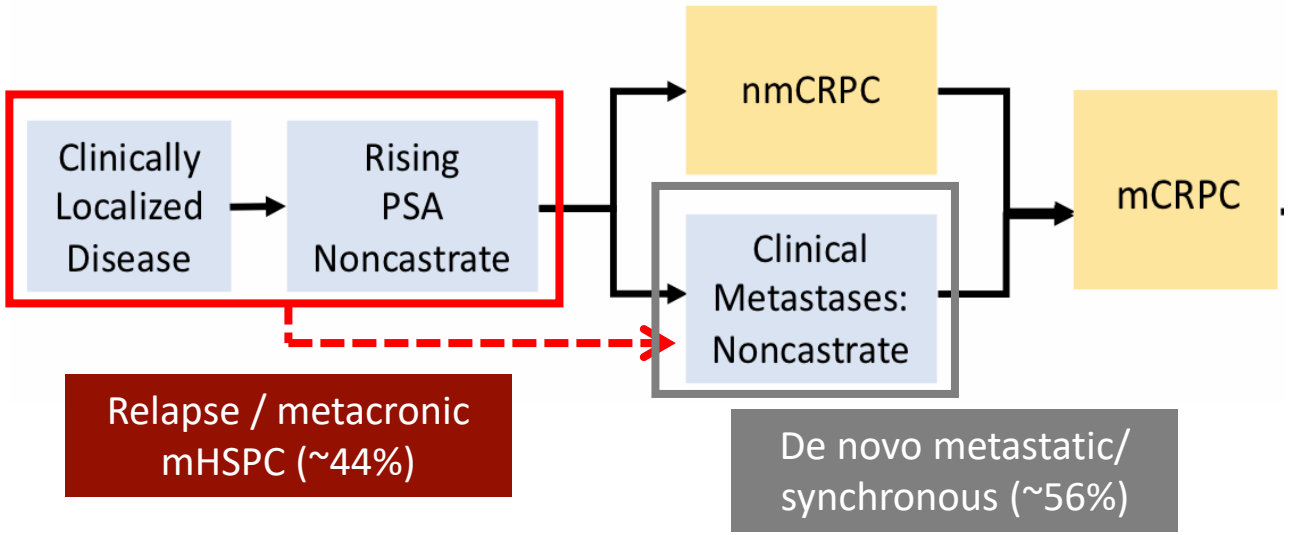
Volume / risk

Defined by CT and bone scintigraphy

Low volume/risk = everything that is not high volume/risk

	High volume/risk
GLASS	Visceral metastases or in the appendicular skeleton.
CHAARTED	≥ 4 bone mets with ≥ 1 outside the spine or bone mets in pelvis or visceral mets
LATITUDE	Two or more of the following: > 3 bone mets, visceral mets, Gleason ≥ 8

Prior Therapy



Sweeney et al. N Eng J Med 2015. Gravis et al. Lancet Oncol 2013. Fizazi et al. N Eng J Med 2017. Patridikou et al Pros Can Pros Dis 2014. Scher et al. J Clin Oncol 2016.

Advanced prostate cancer is a clinically heterogeneous disease

Burden of metastatic disease and **timing** of presentation have a **clear prognostic value**

Volume / risk

Overall survival in pts treated with ADT alone (control arm)

	Median		5 yr OS	
	Hi vol	Low vol	Hi vol	Low vol
CHAARTED	34,4m	NR	~27%*	~54%*
STAMPEDE (Docetaxel)	35,2m	76,7m	~23%*	~56%*
STAMPEDE (Abi)**	~34m*	NR	28%	55%

**Estimation based on the inspection of the Kaplan Meier curves*
***Using LATITUDE high/low risk criteria*

Prior Therapy

Overall survival in pts treated with ADT alone (control arm)
GETUG-AFU-16, STAMPEDE, CHAARTED trials

Overall survival		5-yr OS
High volume	Synchronous (n=1044)	26%
	Metachronic (n=132)	28%
Low volume	Synchronous (n=582)	52%
	Metachronic (n=229)	72%

5-year overall survival rates on ADT alone can range from 26% (high volume, synchronous) to 72% (low volume metachronic)

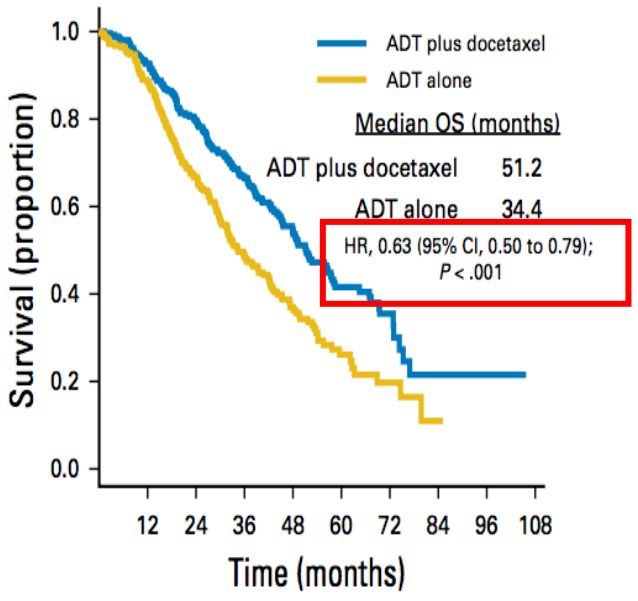
→ Should the treatment strategy be the same for all patients?

Sweeney et al. N Eng J Med 2015 . James et al. Lancet 2015. James et al. N Eng J Med 2017.

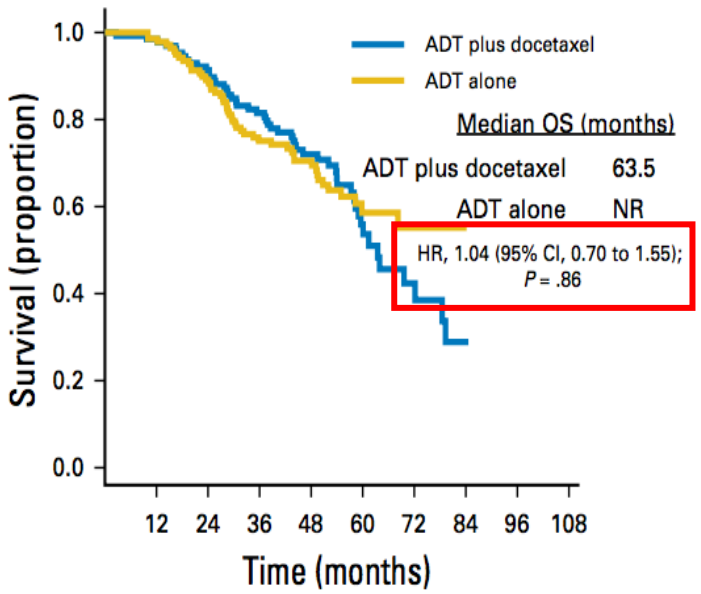
Is burden of disease a predictive factor?

CHAARTED TRIAL:
Benefit of ADT + Docetaxel restricted to high-volume patients

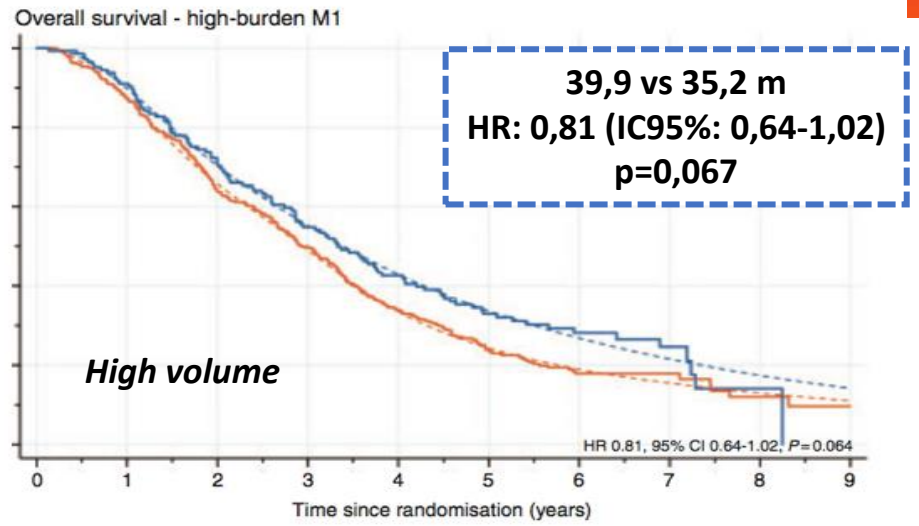
High volume

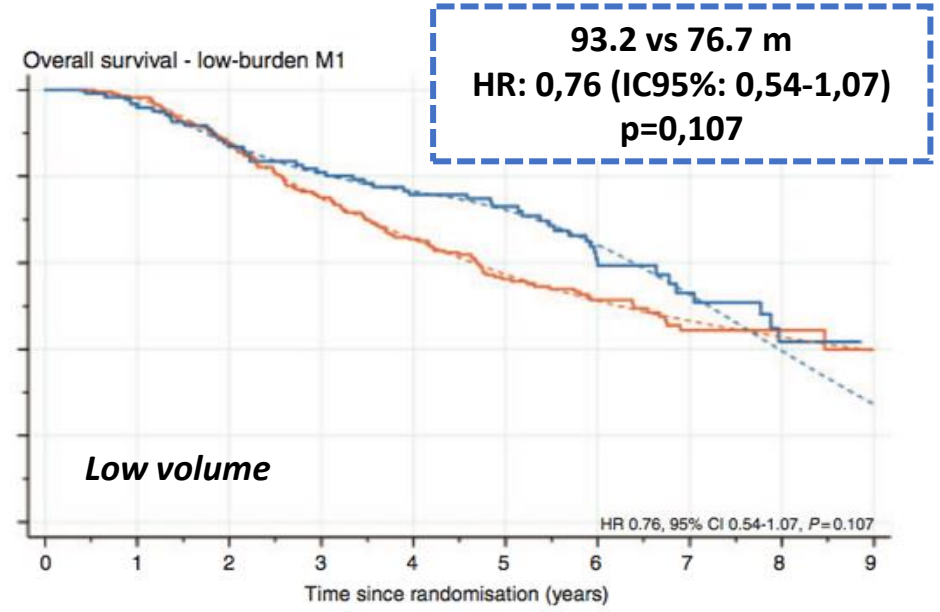


Low volume



STAMPEDE trial:
Benefit from ADT + Docetaxel is similar in high and low-volume pts

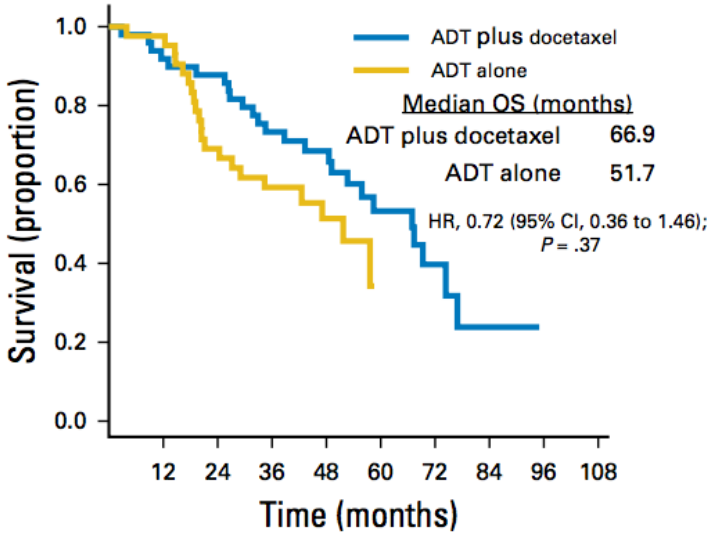


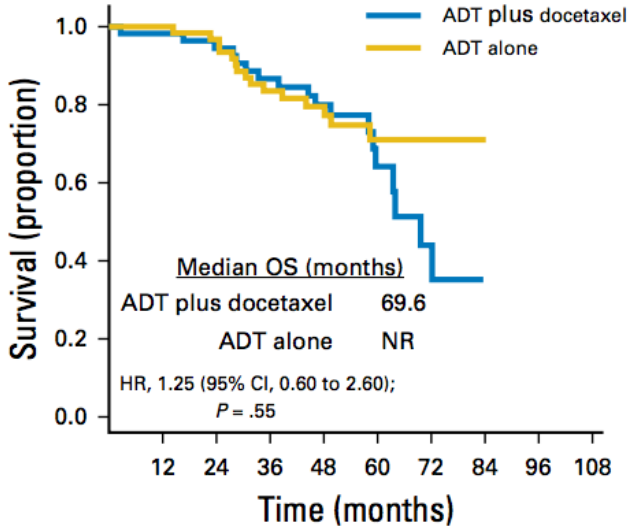


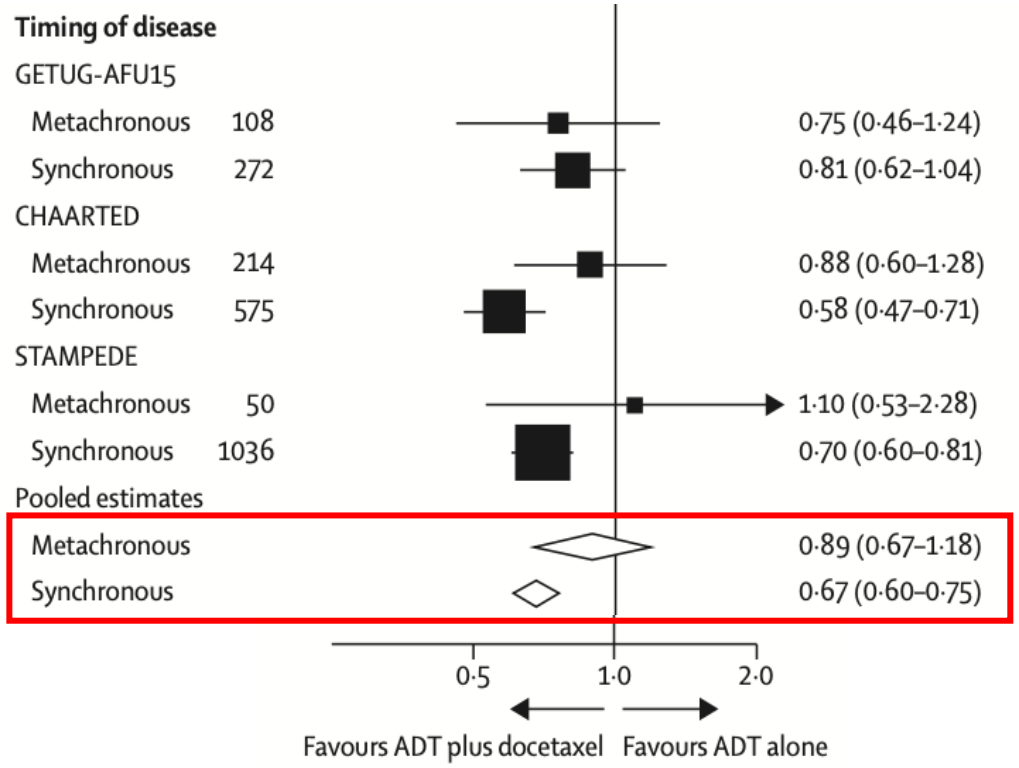
Kyriakopoulos J Clin Oncol 2018; Hoyle et al. Eur Urol 2019;

What about timing of presentation?

CHAARTED trial: 575 patients (72,8%) did not receive local therapy, and were considered “de novo metastatatic”





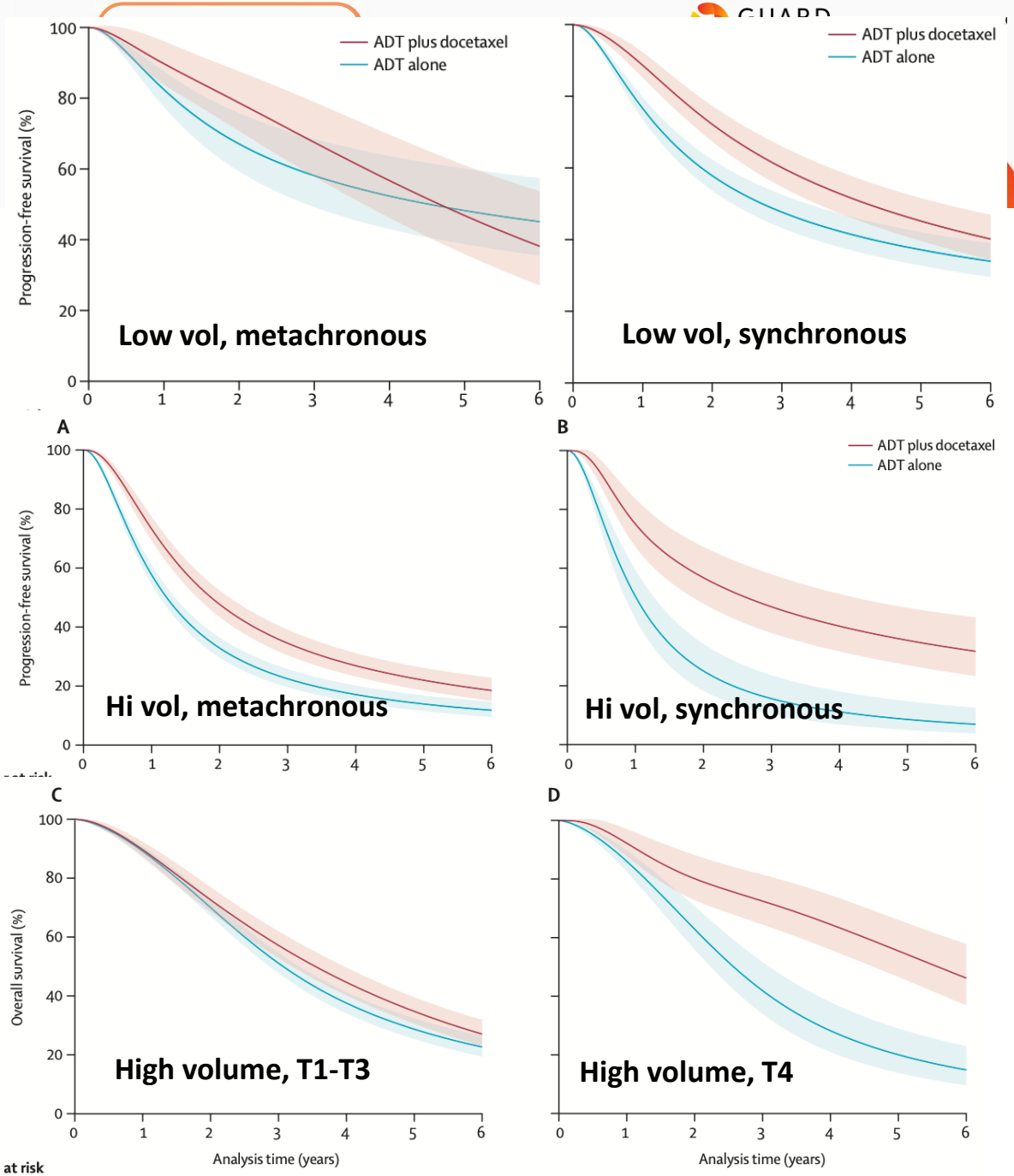


Kyriakopoulos et al. J Clin Oncol 2018. Vale et al. Lancet Oncol 2023

Who benefits from chemotherapy?

CHAARTED, STAMPEDE, GETUG trial metaanalysis
Patients with **low volume metachronic mHSPC do not benefit** from ADT + Docetaxel

	Overall survival			
	Number of events/ patients	Absolute effect at 5 years (95% CI)	5-year survival (95% CI), ADT alone	5-year survival (95% CI), ADT plus docetaxel
Disease volume and timing of diagnosis				
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)
Disease volume and clinical T stage				
Low volume, T stage 1–3	225/569	4% (−3 to 11)	58% (53 to 63)	62% (57 to 68)
Low volume, T stage 4	51/85	16% (−3 to 36)	38% (26 to 54)	54% (39 to 74)
High volume, T stage 1–3	484/709	6% (0 to 12)	29% (25 to 32)	35% (31 to 37)
High volume, T stage 4‡	136/192	35% (24 to 47)	20% (14 to 29)	55% (47 to 66)



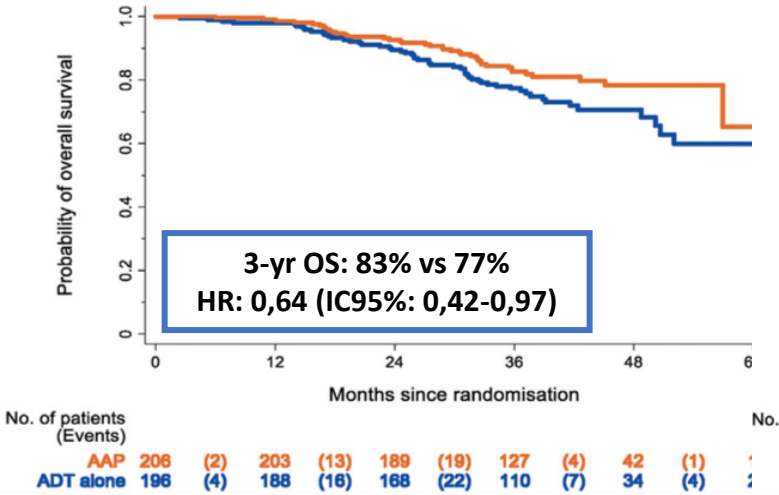
Vale et al. Lancet Oncol 2023

Volume & Timing in ADT + NHA-treated patients

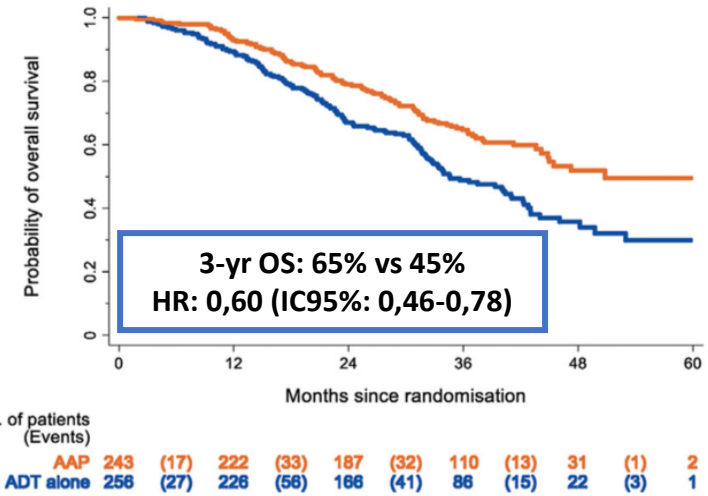
STAMPEDE trial (abiraterone)

Interaction treatment-volume (OS): p=0,77

OS in high-volume pts



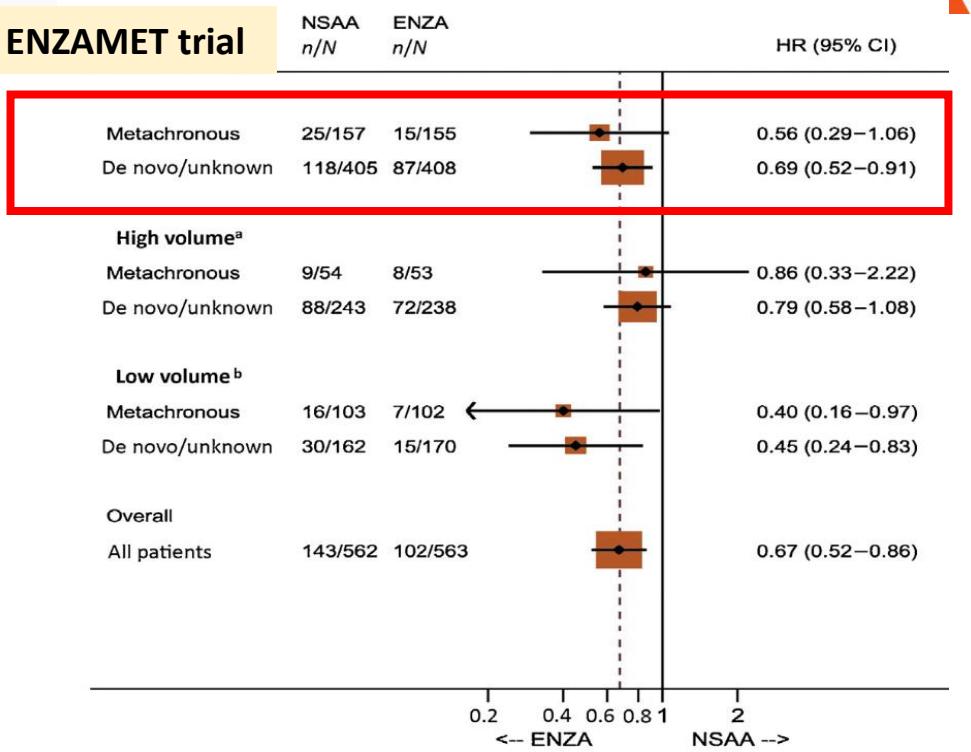
OS in low-volume pts

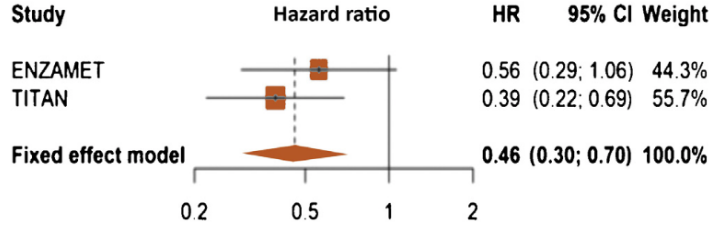


Disease volume and impact of treatment with enzalutamide and apalutamide

Trial	HR low volume	HR high volume
ENZAMET	0.43 (0.26-0.72)	0.80 (0.59-1.07)
ARCHES	0.66 (0.43-1.03)	0.66 (0.52-0.83)
TITAN	0.36 (0.22-0.57)	0.53 (0.41-0.67)

ENZAMET trial



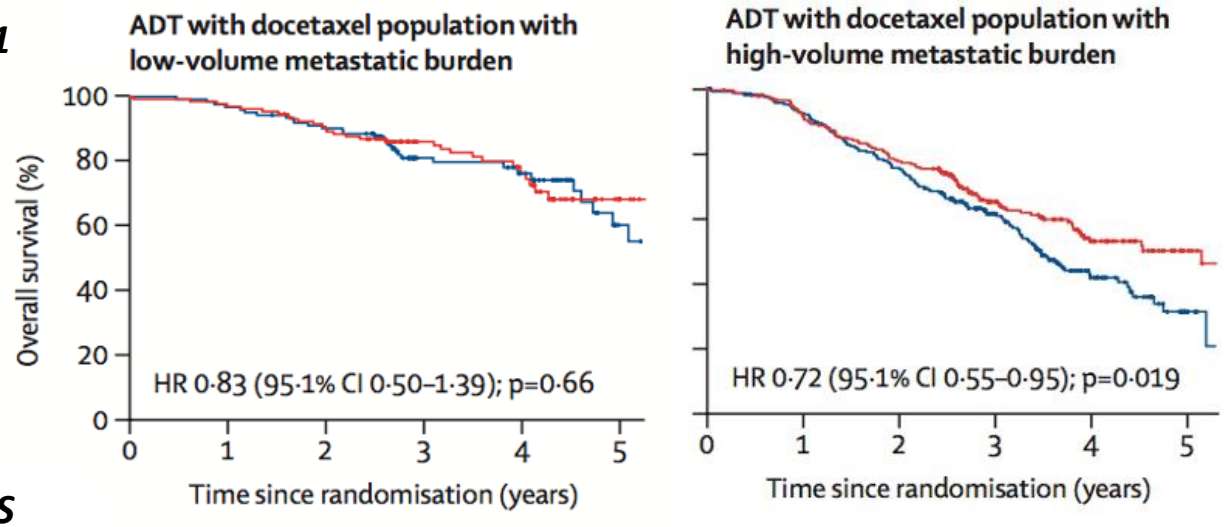


Hoyle et al. Eur Urol 2019; Sweeney et al. Eur Urol 2021

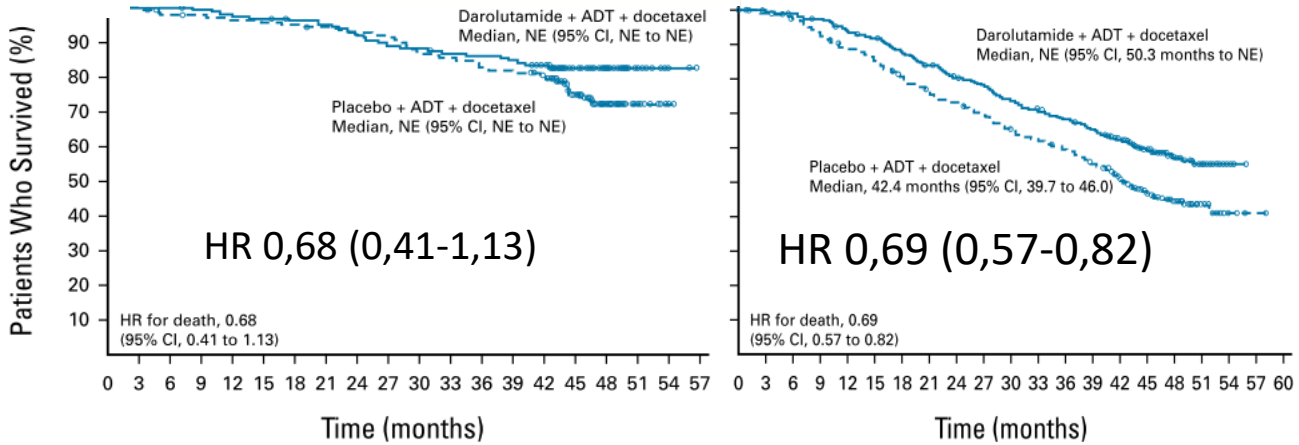
What about triplet therapy?

Only the impact of adding NHA to Docetaxel is assessed
Estimating the impact of Docetaxel is not possible in ARASENS or PEACE-1

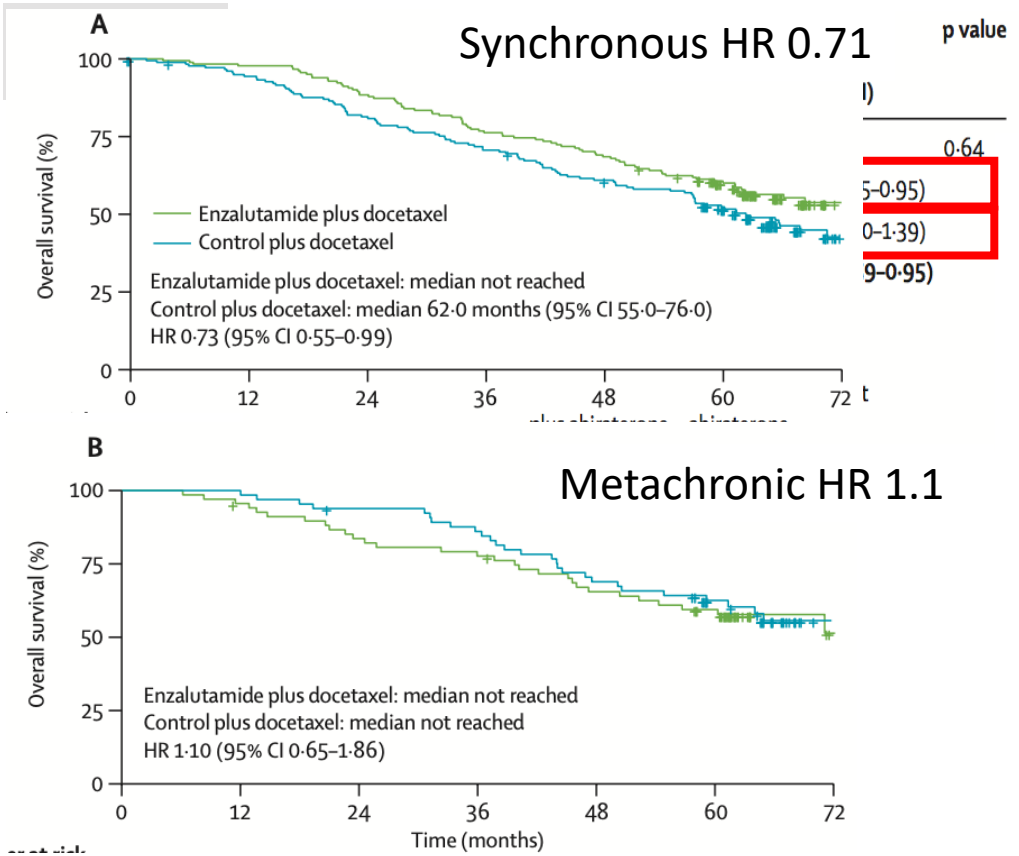
PEACE-1



ARASENS



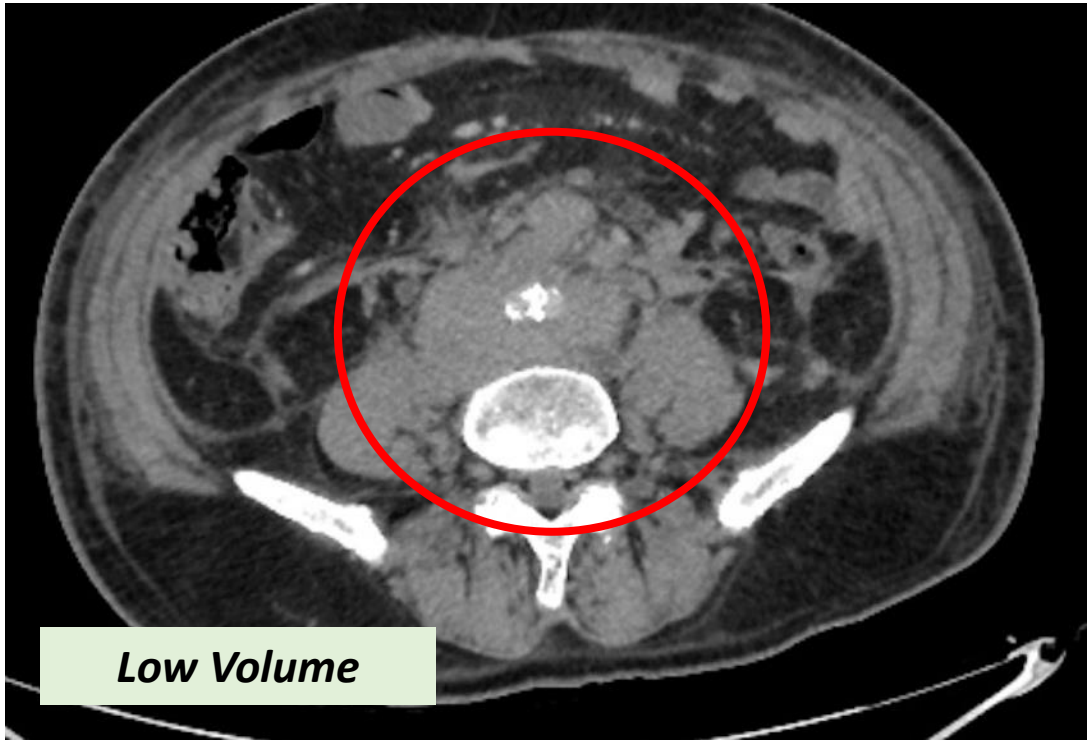
ENZAMET: lower benefit from the addition of enzalutamide in metachronic patients
But we know that NHAs benefit all patients!!



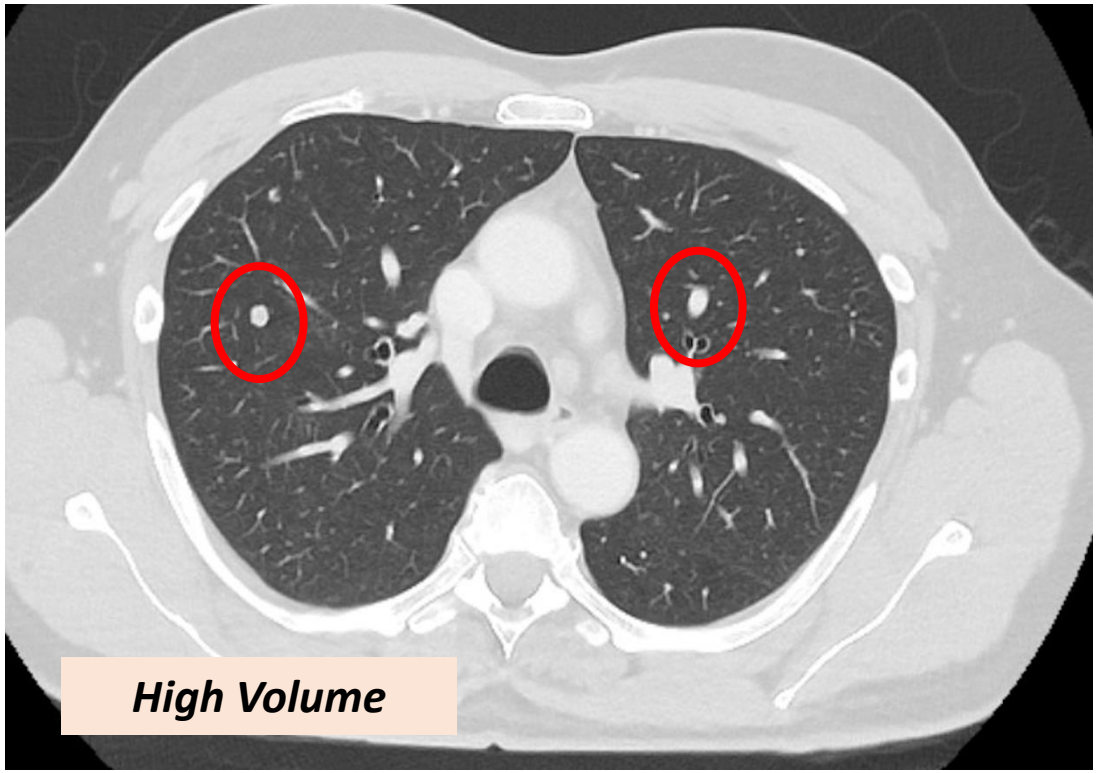
Fizazi et al. Lancet 2022. Smith et al. N Eng J Med 2022. James et al N Eng J Med 2019
Hussain et al. J Clin Oncol 2023 Sweeney et al. Lancet Oncol 2023.

Are all high and low volume the same?

60 yrs. Prostate Adenocarcinoma Gleason 10.
PSA 5 ng/mL. LDH 700 IU/L. Large **retroperitoneal lymph node mass** causing bilateral leg compressive oedema and pain. No bone disease.



60 yrs. Prostate Adenocarcinoma Gleason 8.
Asymptomatic. PSA 60 ng/mL.
Small **lung metastases** with no bone disease.



Management of metastatic CSPC

- Systemic therapy options
- Risk stratification based on clinical biomarkers
- **Radiotherapy to the primary tumor**
- What is the right treatment strategy?
- Therapy intensification / deintensification
- Molecular biomarkers

Radiotherapy to the primary tumor

STAMPEDE (H)

Elegibility:
Metastatic prostate cancer (de novo) by CT/BS
ECOG PS 0-2
Prior ADT up to 90 days

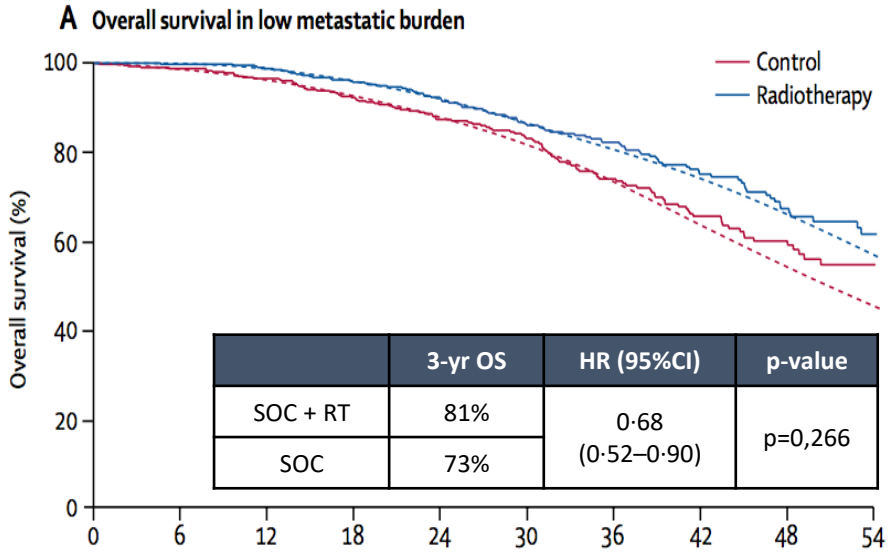
Primary endpoint
Overall survival

- Standard therapy (N=1029)
- Daily RT (55 Gy 20 fx during 4 weeks) N=535
- Weekly RT (36 Gy 6 fx during 6 weeks) N=497

Global population: no difference in overall survival

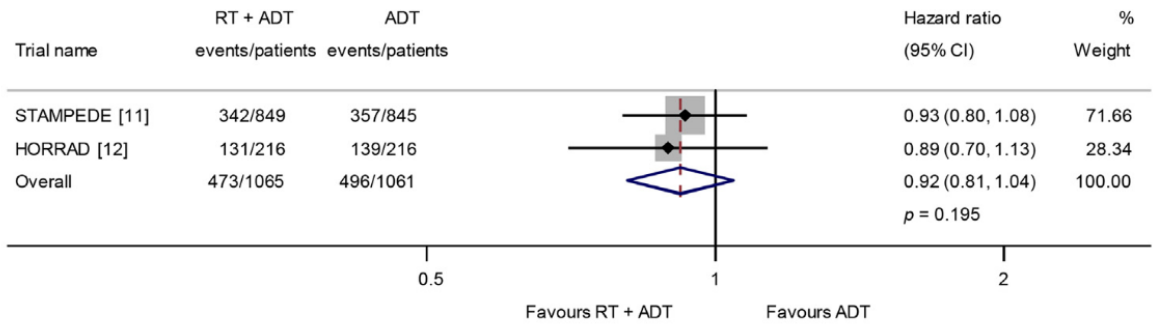
	SOC	SOC + RT
3-yr OS	62%	65%
HR	0.92 (0.8-1.06)	
p-avl	p=0.266	

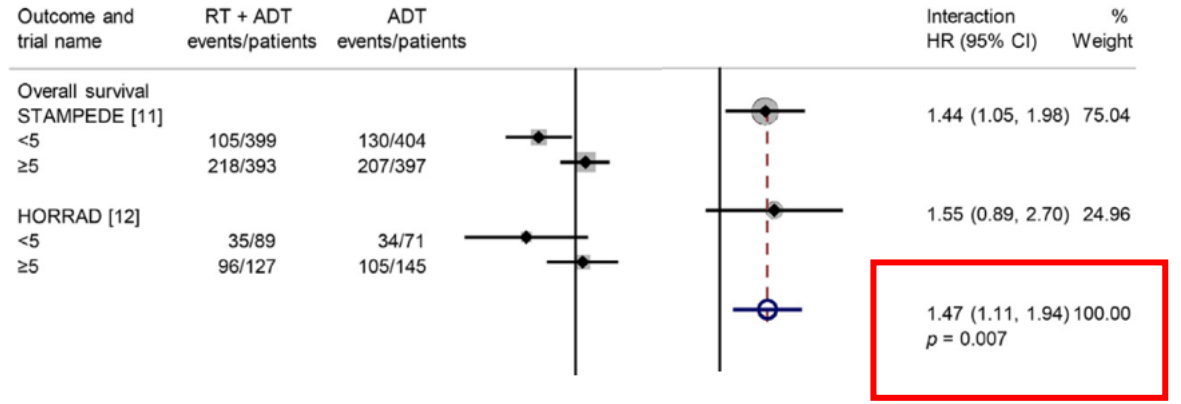
Significant survival benefit in low-volume patients



	3-yr OS	HR (95%CI)	p-value
SOC + RT	81%	0·68 (0·52–0·90)	p=0,266
SOC	73%		

STOPCAP Metaanalysis (STAMPEDE + HORRAD): significant interaction between volume and OS





Parker et al. Lancet 2018;392:2353-2366. Boevé et al. Eur Urol 2019;75(3):410-18

Radiotherapy to the primary tumor

Radiotherapy: 74 Gy in 37 fractions, after docetaxel completed

The PEACE-1 trial

Elegibility:
De novo mHSPC
≥1 lesion in bone scan
ECOG PS 0-2

Randomization 1:1:1:1

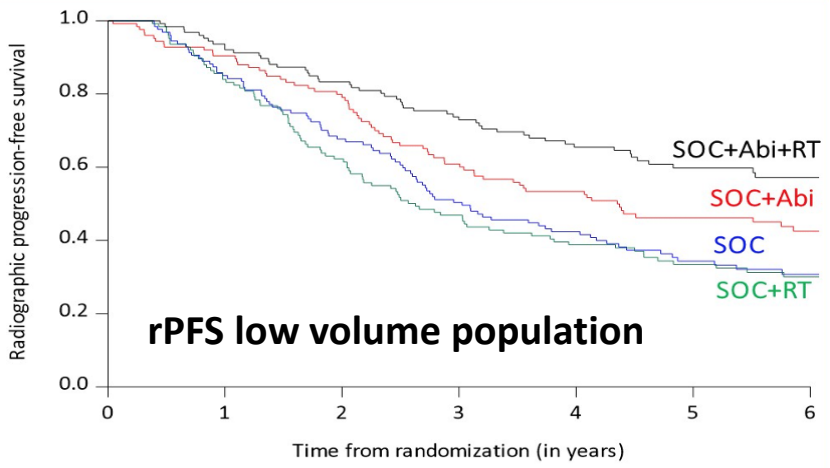
- SOC (n=296)
- SOC + Abiraterone (n=292)
- SOC + RT (n=293)
- SOC + Abiraterone + RT (n=293)

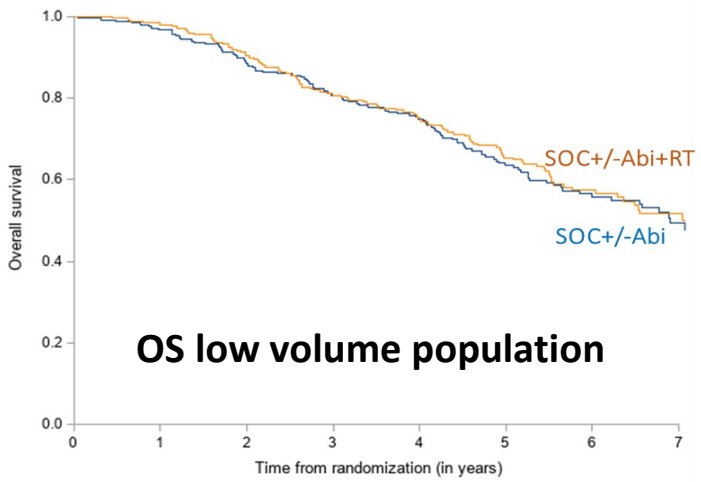
→ SOC +/- Abi (n=589)
→ SOC +/- Abi + Radiotherapy (n=583)

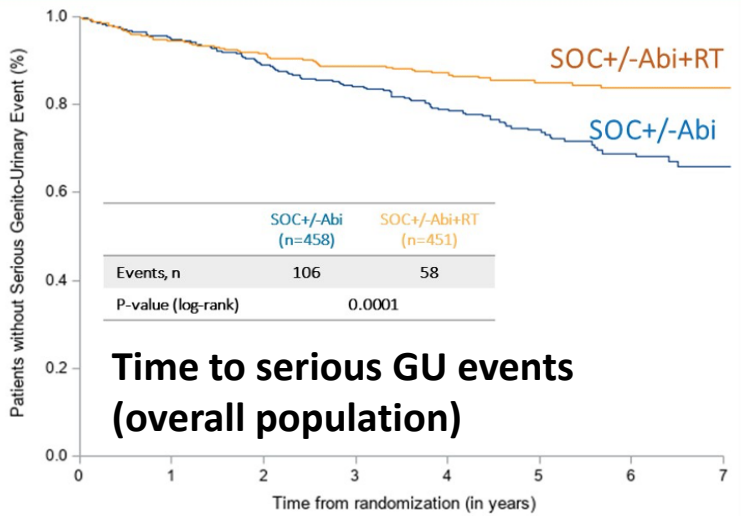
Primary endpoint
Radiographic progression-free survival
Overall survival

Stratification:
ECOG PS
Type of ADT (GnRH vs orquiect)
Disease volume
Treatment with Docetaxel

	SOC +/- Abi	SOC +/- Abi + RT
Low Vol	253 (43%)	252 (43%)
High Vol	335 (57%)	332 (57%)







Bossi et al. ASCO 2023

Radiotherapy to the primary tumor

The PEACE-1 trial

		SOC	SOC + RT	SOC + Abi	SOC + Abi + RT
rPFS (low vol)	Median (yr)	3	2.6	4.4	7.5
	HR	-	1.1 (0.67-1.84)	0.76 (0.45-1.28)	0.50 (0.28-0.88)
OS (low vol)	Median (yr)	7.1	5.8	6.9	NR
	HR	-	1.19 (0.82-1.72)	1.05 (0.72-1.54)	0.81 (0.55-1.22)
Time to serious GU events (low V)	Events	32	18	20	6
	p-val	0.048		0.003	
Time to serious GU events (all)	Events	61	34	45	24
	p-val	0.003		0.018	
Time to CRPC (all)	Median (yr)	1.3	1.6	3.1	4.3
	HR	-	0.79 (0.66-0.94)	0.41 (0.34-0.50)	0.33 (0.27-0.40)

Bossi et al. ASCO 2023

Management of metastatic CSPC

- Systemic therapy options
- Risk stratification based on clinical biomarkers
- Radiotherapy to the primary tumor
- **What is the right treatment strategy?**
- Therapy intensification / deintensification
- Molecular biomarkers

What do we know?

- mHSPC is a **highly heterogeneous disease**: great difference in survival from high volume synchronic to low volume metachronic

What are the goals of treatment?

We want to:
control the disease (symptoms - efficacy)
prolong survival
with the **best quality of life possible (toxicity)**
for as long as possible

etaxel (inferior to triplet ADT + Docetaxel + ARSI) are

***Balance** to find the greatest efficacy (risk of **overtreatment**) with the least toxicity (risk of **undertreatment**)*

ed

+

e, time to GU symptoms in all patients

  - No evidence of OS benefit in the PEACE-1 trial

- In fit patients, **we assume** that receiving **all life-prolonging therapies available** (ARSIs, docetaxel, cabazitaxel, Ra-223, PARPi) at some point during the disease will result in longer overall survival

There is no direct comparison between ADT + ARSIs & ADT + ARSIs + Docetaxel

- Is the patient **fit for chemotherapy** (Docetaxel 75 mg/m^2 every 3 wks x 6 cycles)?
  - Blood counts, renal, liver function, contraindications for chemotherapy
- If elderly, what is the **risk of toxicity**? Geriatric assessment. Only **fit elderly patients** are eligible for triplet therapy.

- What about **volume and timing** of disease? Balance **toxicity and efficacy**
  - Chemotherapy not indicated in low volume, metachronous disease → ADT + hormonal agent
  - For all other patients, **volume and timing are prognostic**
    - Give **less toxic treatment (ADT + NHA) to pts with better prognosis** that will be able to receive all available therapies in sequence --> reduce overtreatment
    - Give **more intensive (& toxic) treatment to pts with worse prognosis**, that may not be able to receive all life-prolonging therapies during the course of the disease

- What does the patient want? How will therapy impact his life?
- What is the proposed **therapy sequence**? What are the second & further-line therapy options?

When should the primary be irradiated?

- A discussion on the **risk/benefit of radiotherapy** to the primary must be held with the **patient and at the MDT**

- Low volume patients: rPFS & delay/prevention of GU sypmtoms
  - STAMPEDE arm H: increased OS vs ADT alone
  - PEACE-1: no difference in OS (vs ADT +/- Docetaxel +/- Abiraterone)

  → All patients except if contraindication to radiotherapy?

- High volume patients: delay/prevention of GU symptoms
  - No survival (rPFS, OS) benefit expected

  → Large primary tumors?
  Urinary symptoms at diagnosis?

Management of metastatic CSPC

- Systemic therapy options
- Choice of systemic therapy
- Radiotherapy to the primary tumor
- **Therapy Intensification / Deintensification**
- Molecular biomarkers

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

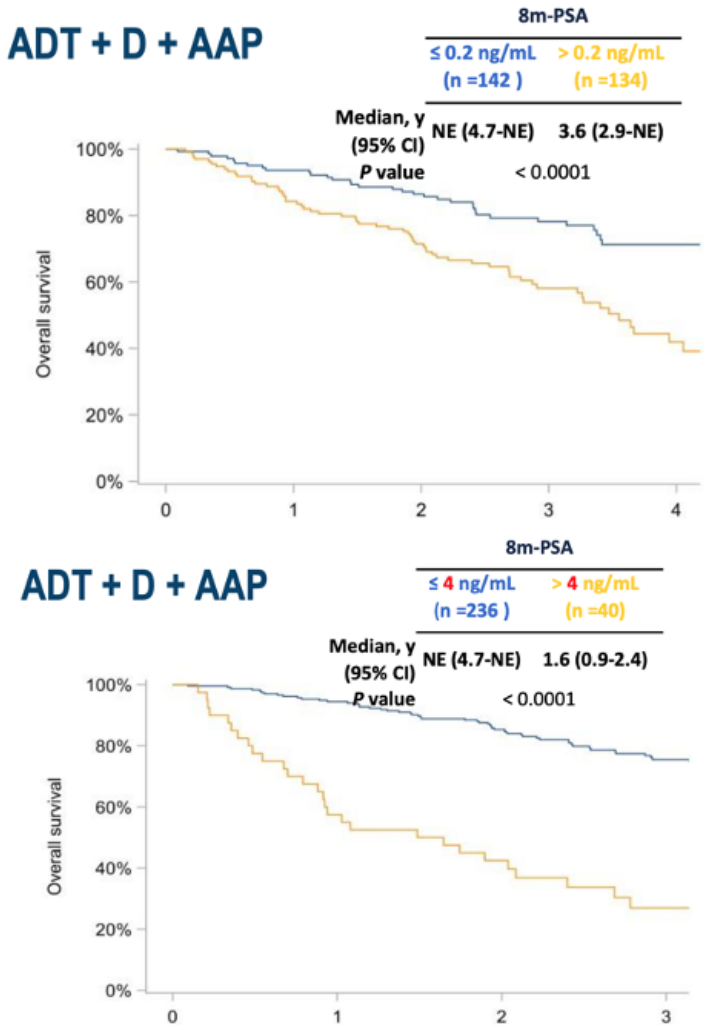
The prognostic value of PSA at 7-8 months has already been reported in the LATITUDE, SWOG 9346, CHAARTED trials

PSA < 0.2 ng/mL @ 9 months

	PSA 8-m	N (%)	OS	p-val
ADT + D	≤0,2 ng/mL	74 (25%)	NR	0,0007
	>0,2 ng/mL	223 (75%)	3,5 yrs	
ADT + D + AAP	≤0,2 ng/mL	142 (51%)	NR	<0,0001
	>0,2 ng/mL	134 (49%)	3,6 yrs	

PSA < 4 ng/mL @ 9 months

	PSA 8-m	N (%)	OS	p-val
ADT + D	≤4 ng/mL	213 (72%)	4,5 yrs	<0,0001
	>4 ng/mL	84 (28%)	2,1 yrs	
ADT + D + AAP	≤4 ng/mL	236 (86%)	NR	<0,0001
	>4 ng/mL	40 (14%)	1,6 yrs	



SWOG 9346:
PSA ≥ 4 ng/mL after 6-7 months of ADT alone associated with worse OS

CHAARTED:
improved OS with PSA ≤ 0.2 ng/mL at 7 months

LATITUDE:
PSA < 0.1 ng/mL associated with improved rPFS & OS

ARASENS:
undetectable PSA @ 24 & 36 wks associated with improved outcome

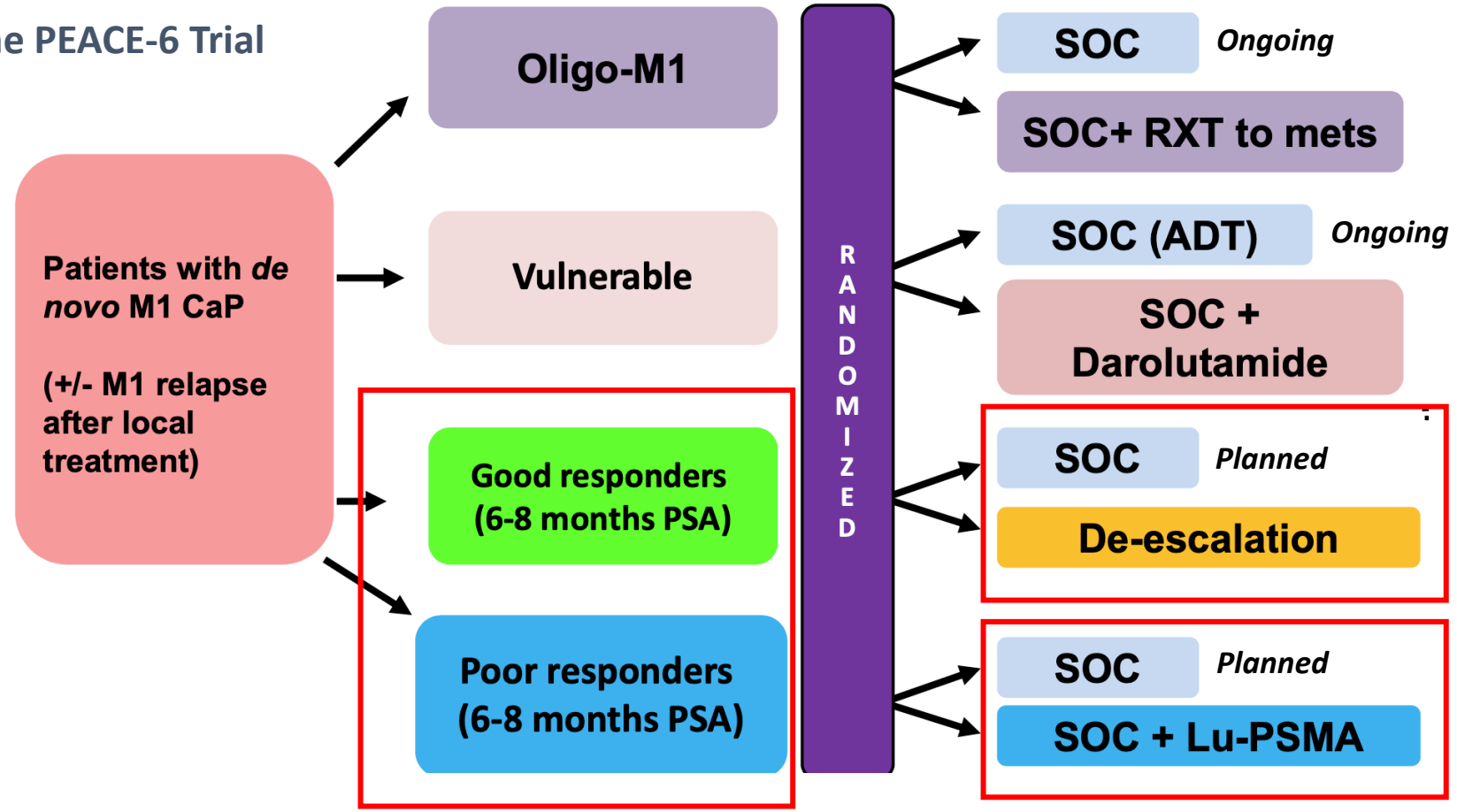
TITAN:
PSA ≤ 0.2 ng/mL at landmark 3 months of Apa associated with increased OS

Gravis et al. ESMO 2022.

Can we use PSA response to guide therapy?

Can we intensify or de-escalate therapy based on 9-month PSA values?

The PEACE-6 Trial



Can we avoid side effects without compromising efficacy in low-risk patients?

Will treatment intensification improve outcome in high-risk patients?

K. Fizazi. SOGUG Symposium 2022

SWOG 9346 Trial (RPIII, non-inferiority)

Elegibility:
mCSPC
PSA < 4 ng/mL after 7 months of ADT + Antiandrogen

- Continuous ADT + antiandrogen (N=765)
- Intermittent therapy (N=770)

Primary endpoint
Non-inferiority in OS (upper boundary HR 1.20)
QoL 3 months after randomization

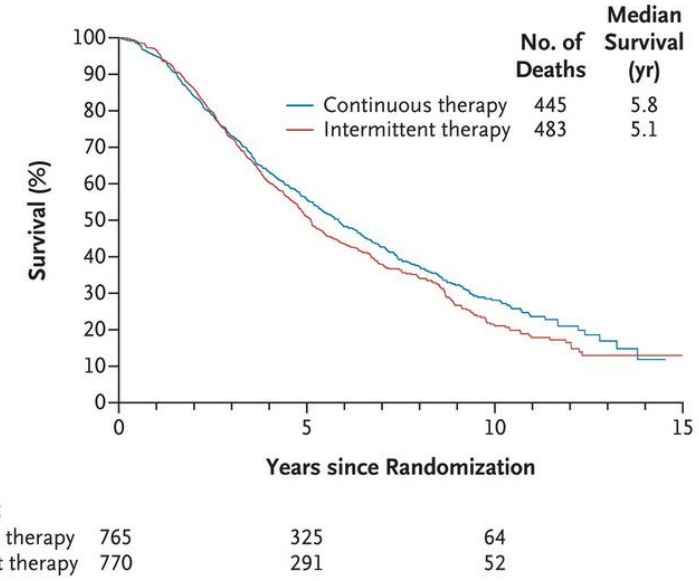
Changes in QoL at 3 months

	Intermittent	Continuous	Difference; p-val
Erectile dysf	-7%	2%	-10%; p<0.001
High libido	16%	-2%	+18%; p=0.02
Vitality	-0.11	-1.42	+1.32; p=0.23

Grade 3-4 AEs were similar in both groups

Hussain et al. N Eng J Med 2013

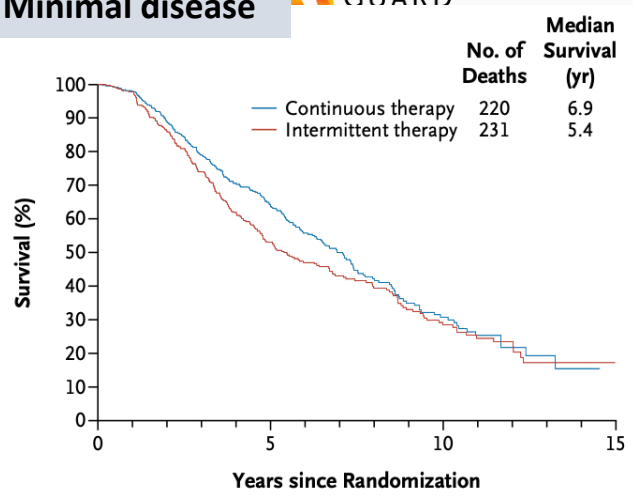
Hazard ratio for death: 1.10 (95%CI 0.99-1.23)



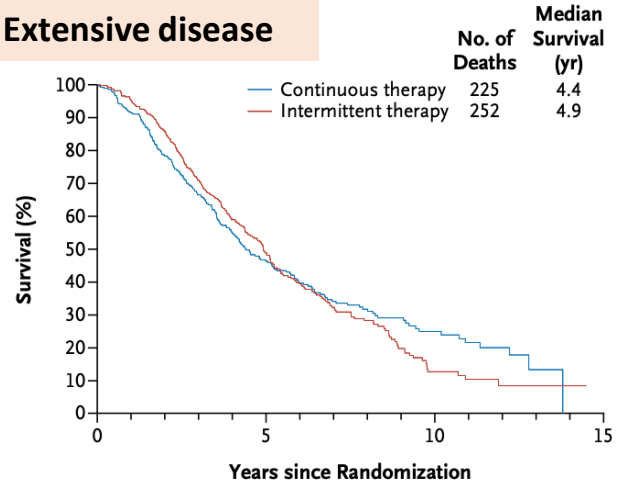
No. at Risk

Continuous therapy	765	325	64
Intermittent therapy	770	291	52

Minimal disease



Extensive disease



CONCLUSIONS

Our findings were statistically inconclusive. In patients with metastatic hormone-sensitive prostate cancer, the confidence interval for survival exceeded the upper boundary for noninferiority, suggesting that we cannot rule out a 20% greater risk of death with intermittent therapy than with continuous therapy, but too few events occurred to rule out significant inferiority of intermittent therapy. Intermittent therapy resulted in small improvements in quality of life. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT00002651.)

GUARD SYMPOSIUM

6-7 JULIO 2023

GU-Alliance for Research and Development

GUARD CONSORTIUM

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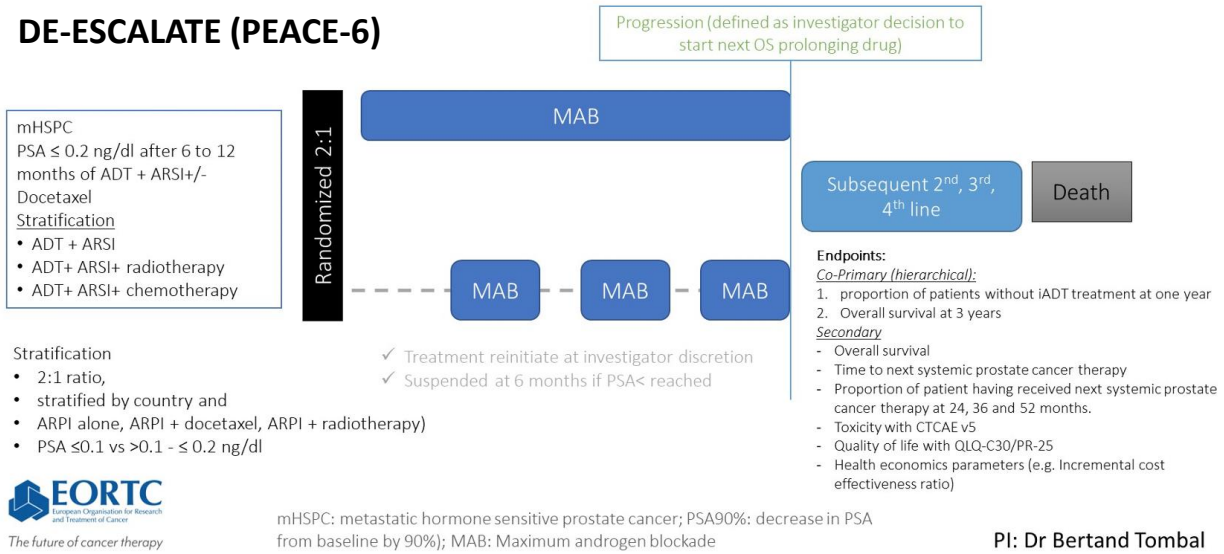
DE-ESCALATE (PEACE-6)



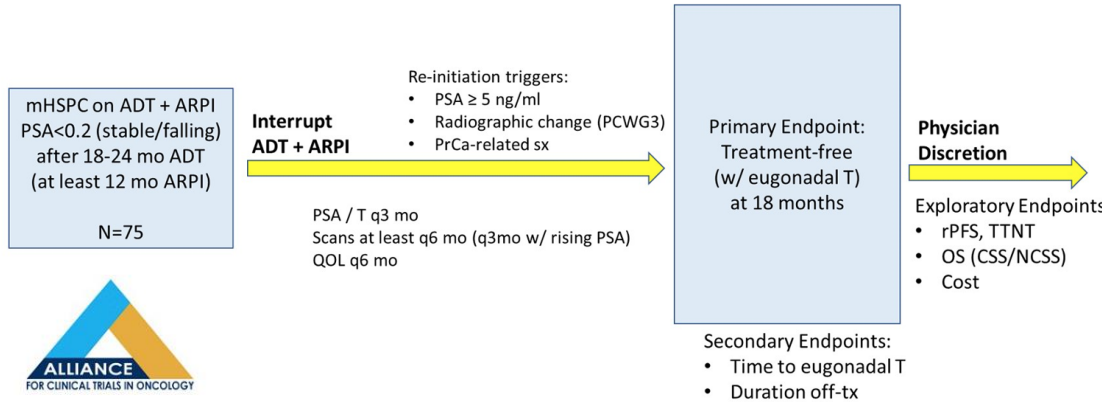
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

mHSPC: metastatic hormone sensitive prostate cancer; PSA90%: decrease in PSA from baseline by 90%); MAB: Maximum androgen blockade

PI: Dr Bertand Tombal

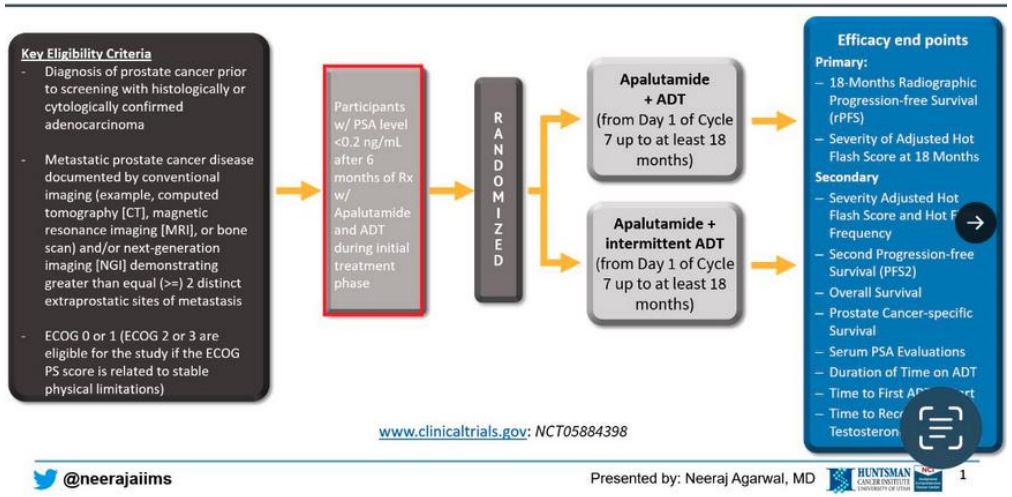
A-DREAM

A Phase 2 Trial of ADT Interruption in Patients Responding Exceptionally to AR-pathway Inhibitor In mHSPC



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

LIBERTAS Trial: Phase 3 Trial Design



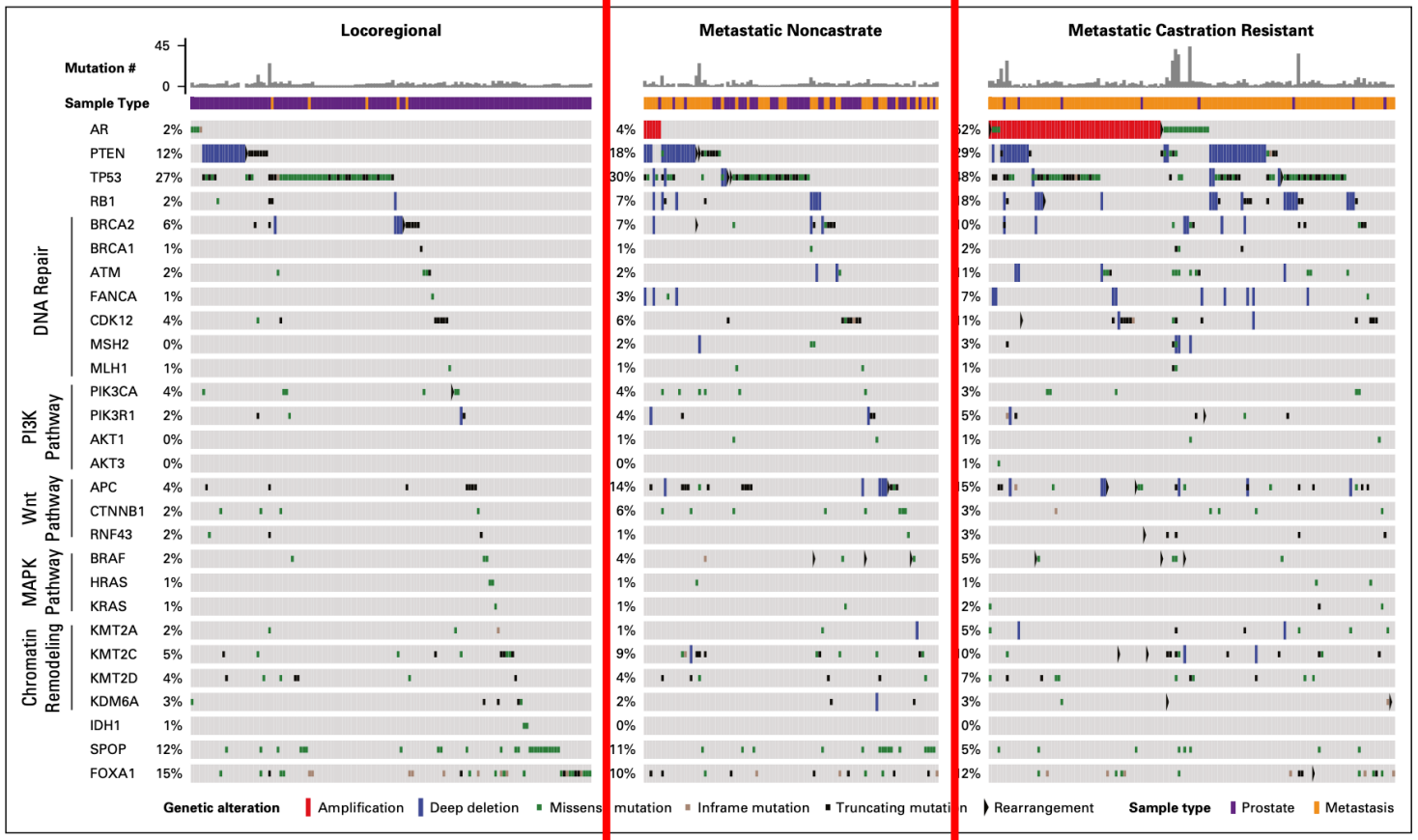
- **How do we design trials** to prove that de-escalation is not actually harming our patients?
- How do we **measure the benefit** of de-escalation?
- **Non-inferiority trials** are hard to design and recruit
- Will the **number of events** be enough (especially in low-risk patients)? What are the conclusions if a study is under-powered?
- Are endpoints **not based on overall survival** acceptable?

Management of metastatic CSPC

- Systemic therapy options
- Choice of systemic therapy
- Radiotherapy to the primary tumor
- Intensifying / Deintensifying treatment
- **Molecular biomarkers**

Genomic alterations in mHSPC

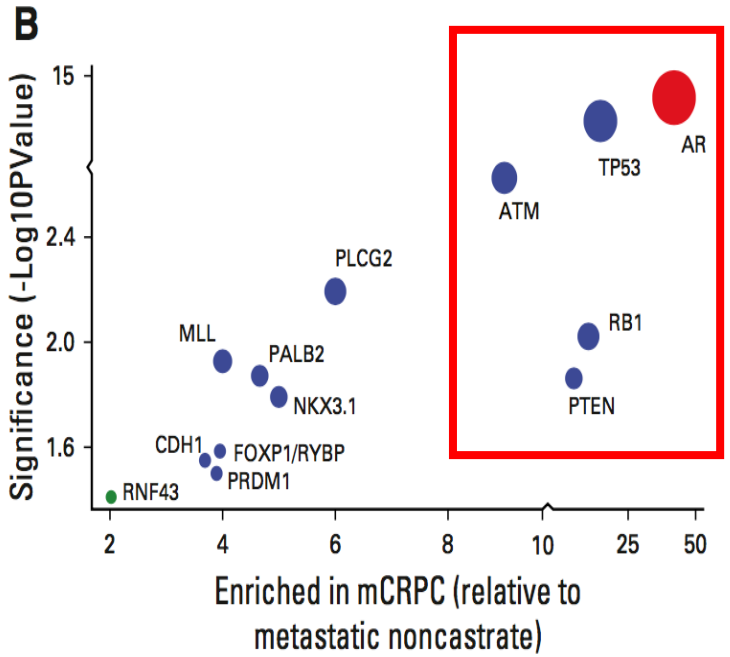
How does the landscape evolve?



Abida et al. JCO Precis Oncol 2017

Greater mutational burden in mCRPC than mHSPC & locoregional disease

- **AR** is the **most enriched gene in mCRPC,** absent in mHSPC
- **TP53, RB1, PTEN, ATM** enriched in **mCRPC**
- **SPOP enriched in** locoregional & **mHSPC**
- No differences in BRCA2



What do we want molecular biomarkers for?

- Assessment of **prognosis**
  - Is the disease indolent or aggressive?
  - Can I wait and give less intensive treatment (sparing toxicity), or will the disease progress rapidly & maybe deteriorate before all life-prolonging therapies can be administered?
  - Prognostic value is **independent of the specific benefit** (i.e. will the patient live more with treatment A than he would have with treatment B or with no treatment?) **from therapy**

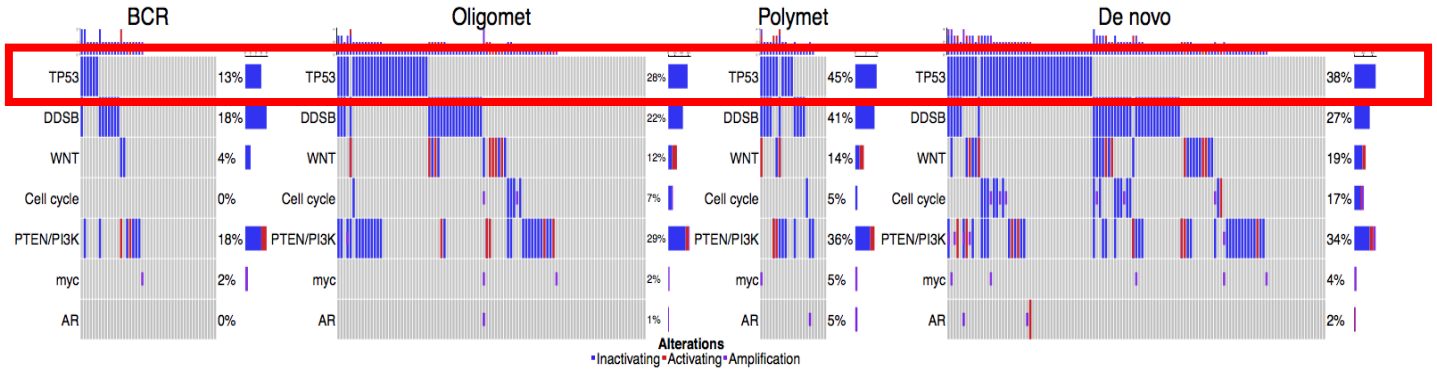
- **Predictive** biomarkers
  - Can I estimate the relative benefit of therapy options that are already approved?
  - Can I guide my choice of treatment A over treatment B based on the likelihood of an **improvement in outcome**?

- Development of **Targeted** therapies
  - Can I idenfity molecular targets that are sensitive to specific drugs?
  - Can I treat the tumor based on its biology?

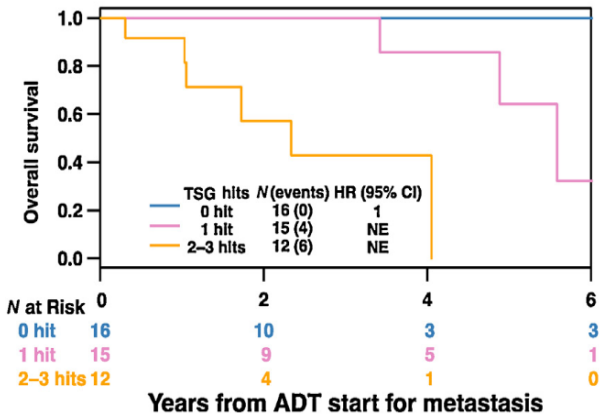
Genomic alterations and prognosis in mHSPC

Loss of function of tumor supressors is associated with adverse prognosis

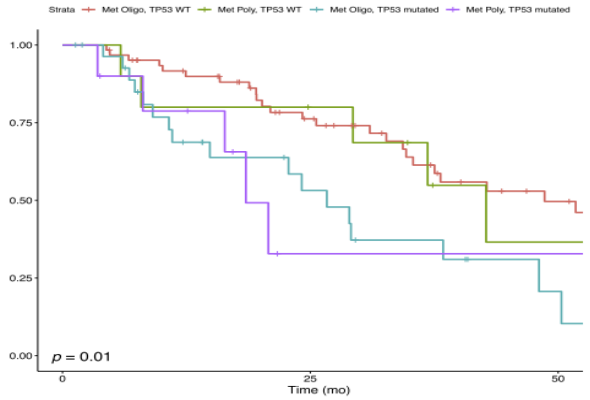
Increased TP53 alterations with higher volume of metastatic disease



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

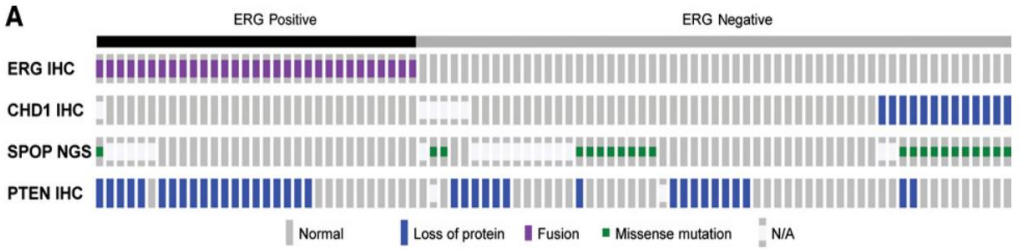


TP53 mutations associated with adverse prognosis in both oligo- and polymetastatic disease

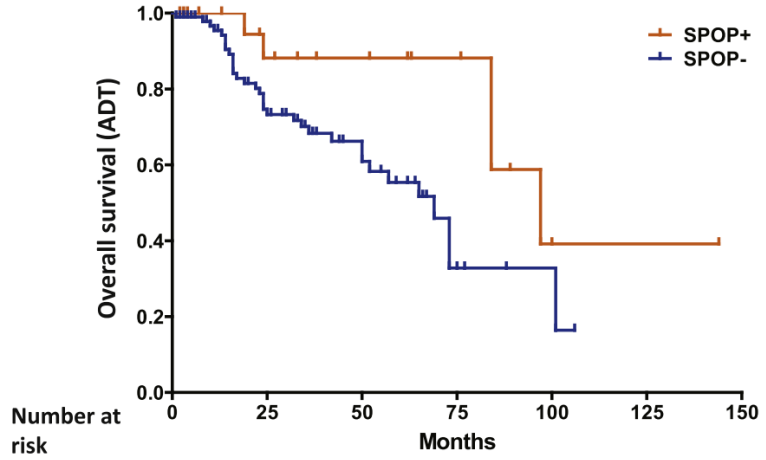


SPOP mutations associated with favorable prognosis

Most frequently mutated gene in prostate cancer
Mutations in the MATH domain



SPOP mutation associated with higher response rate and time on abiraterone in mCRPC

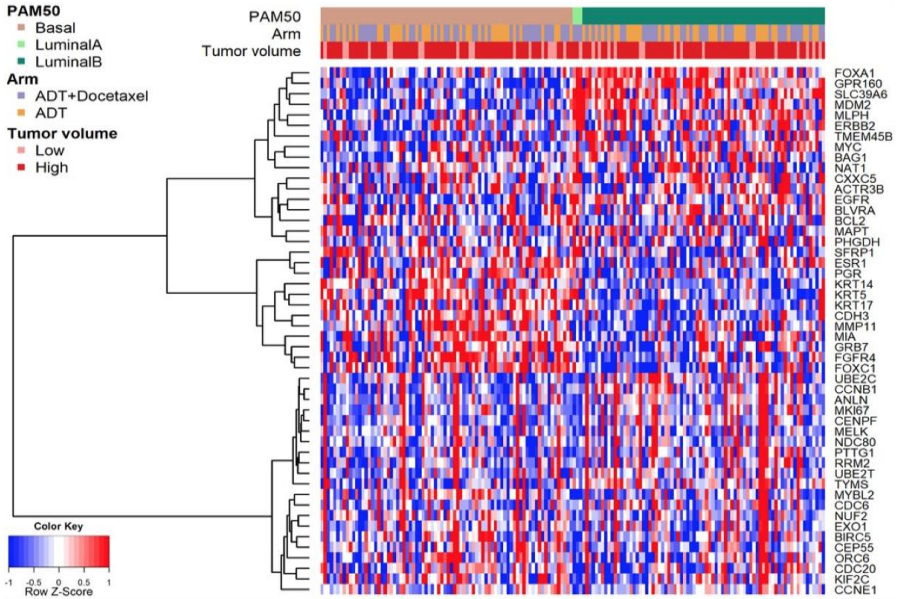


Abida et. PNAS 2019;166(23):11428-11436. Hamid et al. Eur Urol 2019;76(1):89-97. Deek et al. Eur Urol 2021;80(5)632-640.

Gene Expression Profiles and Outcome

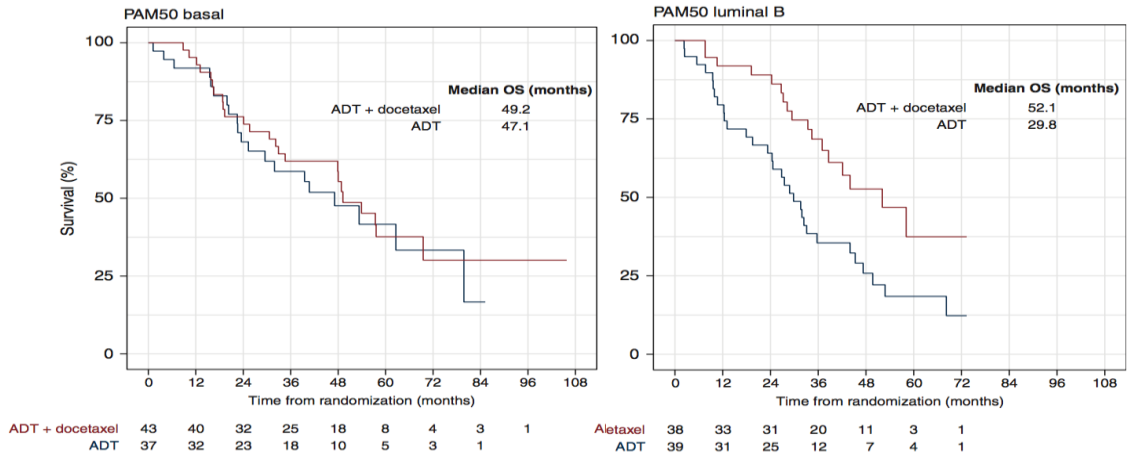
In prostate cancer, luminal B and basal subtipes are associated with the highest and lowest AR activity, respectively

	mHSPC	Localized
Basal	52.1%	33.2%
Luminal B	46.1%	32.7%
Luminal A	1.8%	34.1%

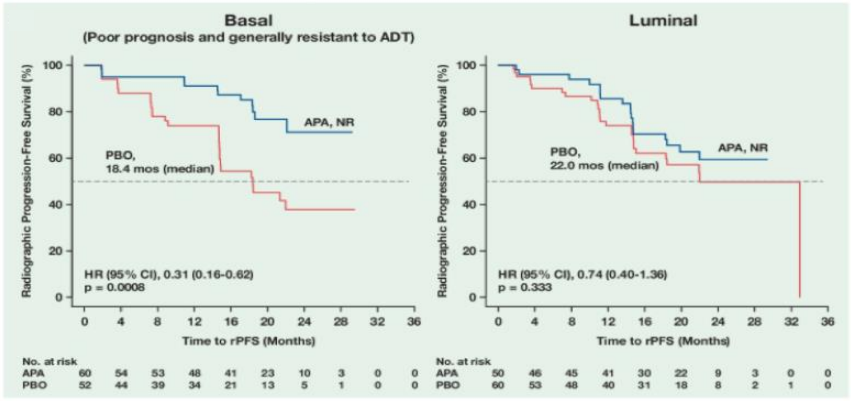


Hamid et al. Ann Oncol 2021;23(9):157-1166. Feng et al. ASCO 2020; Abstract #5521
Parry et al. ESMO 2022; Abstract #1358º.

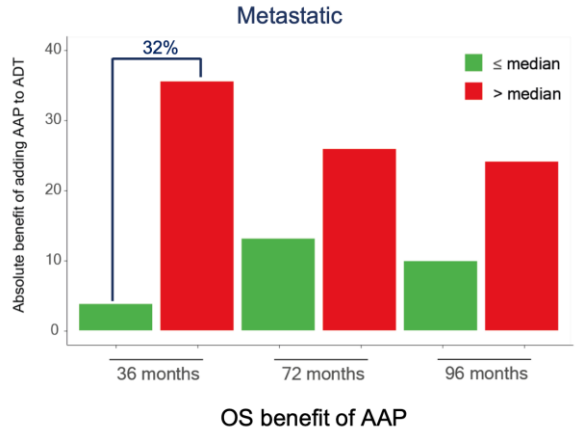
CHAARTED trial: benefit from ADT + Docetaxel Luminal B patients



Ensayo TITAN: greater benefit in patients with basal subtype

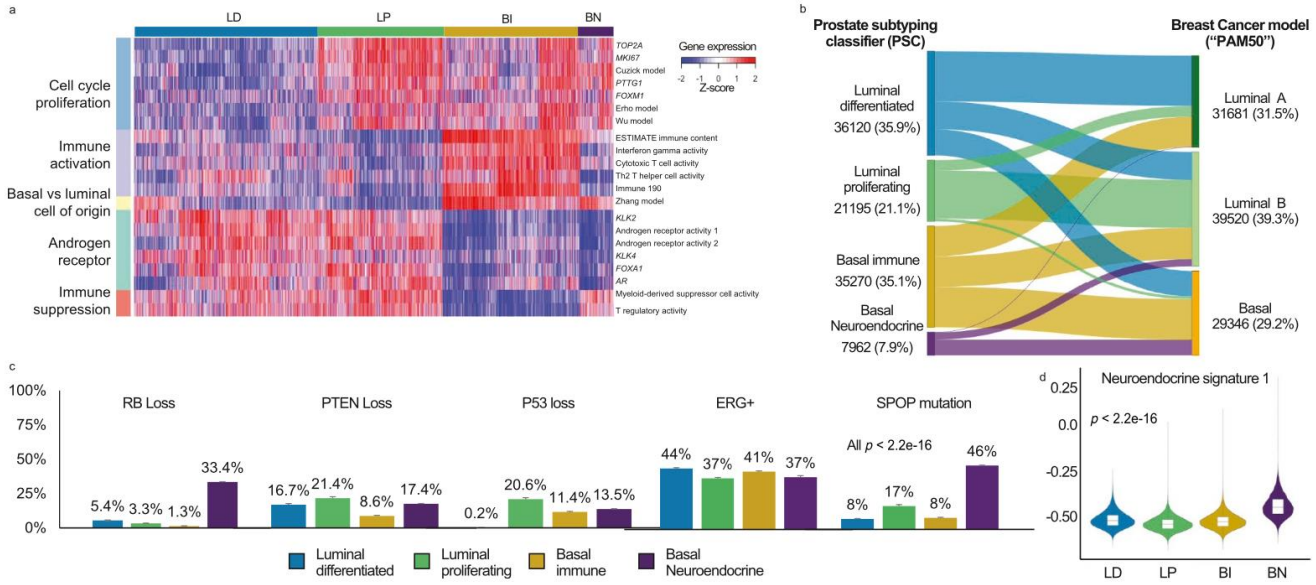


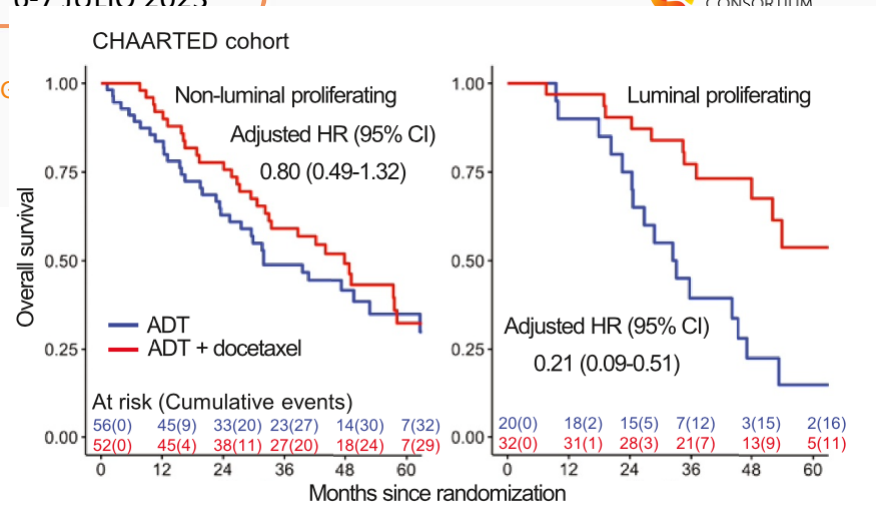
STAMPEDE: high risk (DECIPHER) associated with greater absolute benefit

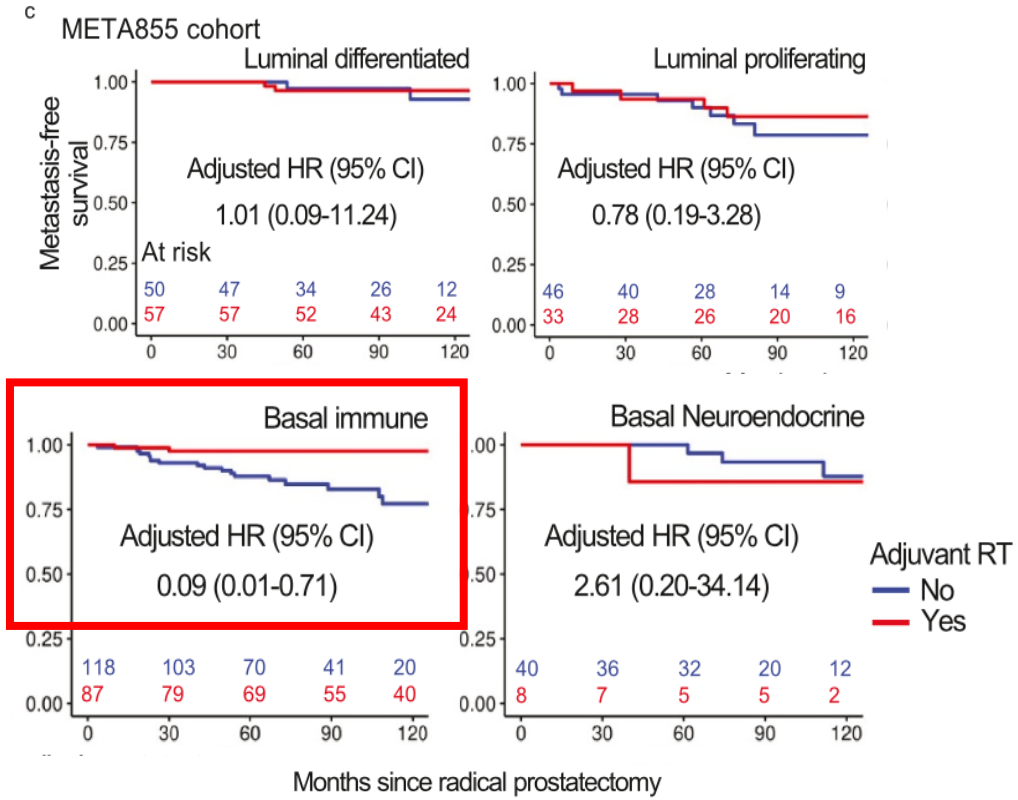


Luminal/Basal Phenotypes in Prostate Cancer

- Novel PSC classification based on transcriptomic analysis of PC samples
- Better performance than PAM50 (derived from breast cancer)
- Model training cohort (*n* = 32,000) and an evaluation cohort (*n* = 68,547)
- 4 groups: luminal differentiated, luminal proliferating, basal immune, basal neuroendocrine
- Potential implications for therapy



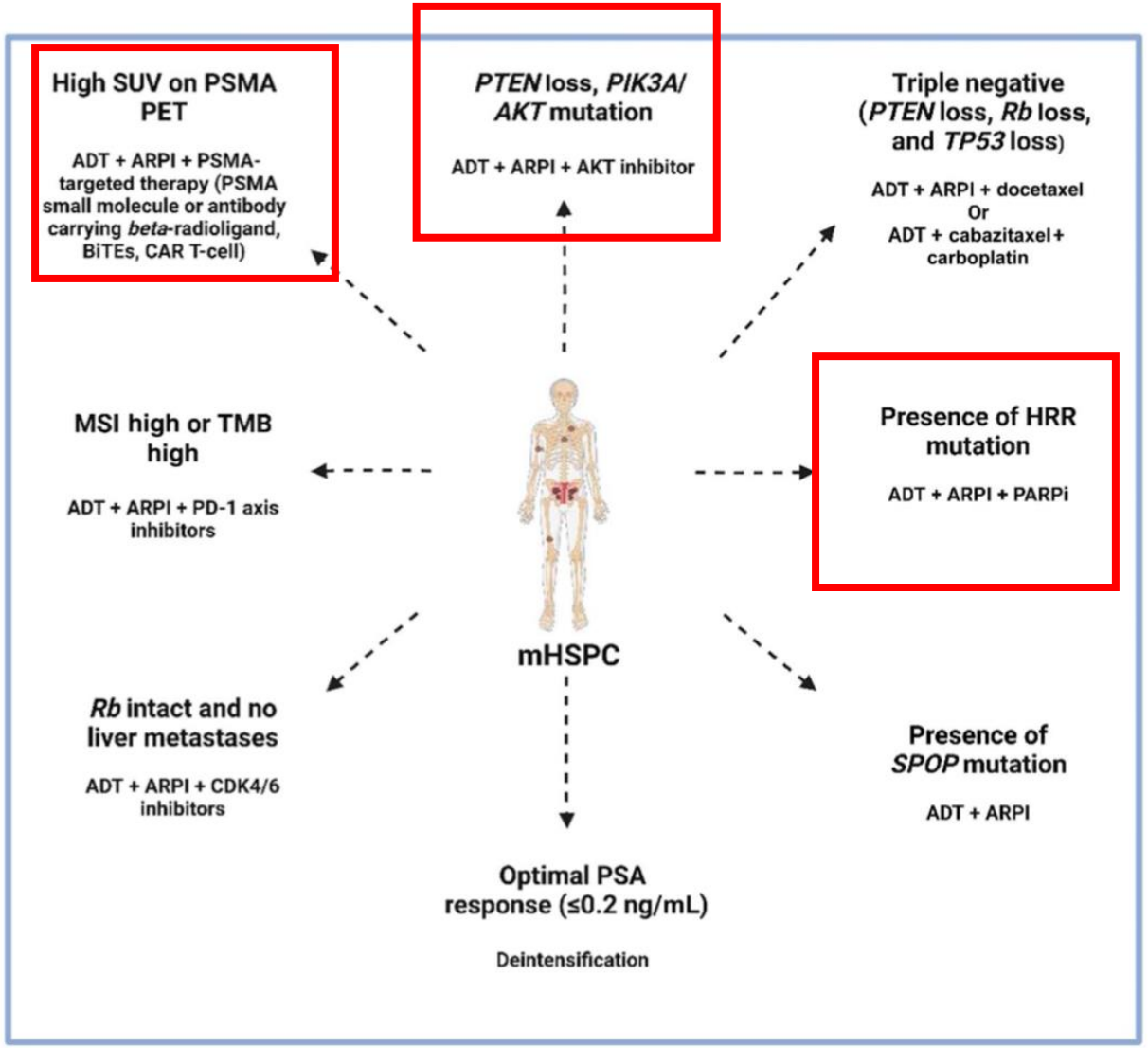




Weiner et al, Cancer 2023

Targeted therapies in mCSPC

Some potential biomarker-guided strategies for the treatment of mCSPC



Hamid et al. ASCO Educational Book 2023

Ongoing clinical trials of targeted therapy in mCSPC

Trial	Phase	Target Enrollment	Inclusion Criteria	Previous Docetaxel Therapy in the Metastatic Hormone-Sensitive Setting	Intervention Arm	Control Arm	Primary End Point
PSMAddition (NCT04720157)	III	1,126	PSMA-positive disease on a ^{68}Ga-PSMA-11 PET/CT scan Treatment-naïve or up to 45 days of ADT before inclusion or up to 45 days of ARSI	Not allowed	^{177}Lu-PSMA-617 intravenously once every 6 weeks for six cycles plus standard of care (ADT plus ARSI)	Standard of care (ADT plus ARSI)	rPFS
AMPLITUDE (NCT04497844)	III	788	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Radiation with curative intent or previous treatment with PARPi not allowed Up to 6 months of ADT or 45 days of abiraterone acetate and prednisone allowed before random assignment	Allowed	Niraparib 200 mg orally once daily plus abiraterone acetate 1,000 mg orally once daily plus prednisone 5 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg once daily plus prednisone 5 mg once daily	rPFS
TALAPRO-3 (NCT04821622)	III	550	Positive for deleterious germline or somatic homologous recombination repair gene mutations Ongoing ADT Previous docetaxel for mHSPC or previous treatment with a PARPi not allowed ≤3 months of ADT with or without ARSI for mHSPC allowed before random assignment	Not allowed	Talazoparib 0.5 mg orally once daily plus open-label enzalutamide 160 mg orally once daily	Placebo plus open-label enzalutamide 160 mg orally once daily	rPFS
CAPItello-281 (NCT04493853)	III	1,000	Synchronous mHSPC PTEN deficiency on tissue immunohistochemistry Ongoing ADT Previous surgery or radiation with curative intent not allowed	Not allowed within 3 weeks of first dose of study treatment	Capivasertib 400 mg orally twice daily (intermittent weekly dosing schedule) plus abiraterone acetate 1,000 mg orally once daily	Placebo plus abiraterone acetate 1,000 mg orally once daily	rPFS
CYCLONE-03 (NCT05288166)	III	900	High-risk mHSPC (≥4 bone metastases and/or ≥1 visceral metastasis) Ongoing ADT Previous systemic treatment for metastatic prostate cancer not allowed except ADT with or without ARSI up to 3 months before random assignment	Allowed	Abemaciclib plus abiraterone acetate plus prednisone	Placebo plus abiraterone acetate plus prednisone	rPFS

Hamid et al. ASCO Educational Book 2023

Management of metastatic CSPC

- Metastatic hormone-sensitive prostate cancer is a **clinically heterogeneous disease**
  - **Volume of disease and timing of presentation** define **prognostic subgroups**
  - 5-yr OS with ADT alone ranges from 72% (low volume, metachronic) to 26% (hi volume, synchronous)

- Systemic therapy is based on combinations of ADT + novel hormonal agents +/- Docetaxel

- What do we know about the efficacy of systemic therapy?
  - **ADT alone and ADT + Docetaxel are not recommended** (inferior to ADT doublets and ADT triplets, respectively)
  - No direct comparison between triplet & doublet therapy
  - **ADT + NHA + Docetaxel** is **not recommended in metachronic low volume disease** based on lack of efficacy of Docetaxel in this subpopulation

Management of metastatic CSPC

- Triplet or doublet therapy?
  - Only pts fit for chemotherapy are elgible for upfront triplet therapy
  - **ADT + NHA alone** is favored **in pts with good prognosis (low volume)** → maximize benefit/toxicity ratio
  - Consider **ADT + NHA + Docetaxel in pts with adverse prognosis (hi volume, synchronous, T4)** → may not receive all available therapies
  - Not all low volume are good & not all high volume are bad!
  - **Patient preference** (conocomitant vs sequential treatment) must be taken into consideration

- Radiotherapy to the primary tumor
  - Low volume: **rPFS benefit & delay/prevention of GU sypmtoms**. Conflicting results on OS (STAMPEDE, PEACE-1)
  - High volume: delay/prevention of GU sypmtoms. No OS or rPFS benefit
  - Discuss in MDT → favor RT in low volume & hi volume if large primary tumor or urinary symptoms?

Management of metastatic CSPC

- De-intensification strategies
  - A significant proportion of our patients are likely over-treated. Reducing toxicity in them is highly appealing
  - Proving that a de-intensification approach does not impact negatively and has significant benefits in prospective trials is challenging

- Molecular biomarkers
  - Genomic biomarkers have mostly prognostic value (adverse: PTEN, Rb1, TP53 or favorable: SPOP)
  - Burden of genomic alterations is associated with aggressiveness
  - Gene expression profiling may help identify patients that derive greater benefit from chemotherapy combinations (luminal B) or hormone agents alone.
  - **Clinical validation** in well designed, prospective trials is **needed before** any of the potential biomarkers can be **used in the clinic**

Thank you!

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INSTITUTO VALENCIANO DE ONCOLOGÍA