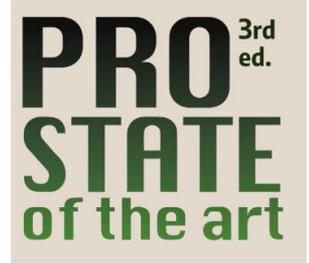


Metastatic Castration-Sensitive Landscape

Clinical Case and Evidence from Literature



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Clinical case

Clinical case

66 yo, no comorbidities

09/2021 PSA 11,7 ng/ml

8/10/2021 Prostate MR: PIRADS 5 nodule

22/10/2021 Fusion biopsy: prostate adenocarcinoma GS 8 (4+4) in the targeted sampling and in 6/12 bilateral samplings

25/11/2021 CT t/a w ce: left ovoid iliac-obturator lymph node of 17 x 11 mm, suspected for metastasis. Negative bone, except island of compact bone at right iliac crest.

05/12/2021 Bone scan: negative

30/11/2021 robot-assisted radical prostatectomy + bilateral pelvic lymphadenectomy:
Prostate acinar adenocarcinoma, GS 9 (4+5), pT4 pN1 (2/26)

Clinical case

28/12/2021 post-surgery PSA: 2.94 ng/ml.

14/01/2022 PSMA PET: intense focal accumulation in prostatic lodge, suggestive of residual disease. Focal anomalous accumulation in a common left iliac node. Circumscribed intense anomalous accumulations in the left supra-acetabular region, bilateral iliac bone, right iliac wing, left hemi-sacrum and lateral portion of the VIII left rib, suspected for secondary lesions. Further irregularities in the remaining skeletal area, particularly at the level of the pelvis, of the posterior arch of D7 and of the right humeral head, of non-univocal interpretation worthy of monitoring.

Table 2 – Definition of high and low volume, and risk in CHARTED [54–56] and LATITUDE [57] based upon imaging with bone scan and CT scan.

	High	Low
CHAARTED (volume)	≥4 Bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis	Not high
LATITUDE (risk)	≥2 High-risk features of: ≥3 Bone metastasis Visceral metastasis ≥ISUP grade 4	Not high
CT=computed tomography; ISUP=International Society of Urological Pathology.		

Conventional imaging:

- Low risk
- Low volume

PSMA PET

- High-risk
- High-volume

Clinical case

30/01/2022 Start **Leuproreline Acetate + Bicalutamide 50 mg** (flare-up)

01/04/2022 CT t/a w ce: No lymphadenopathies in abdomen. At the bone level, roundish lesions with clear, bluntly thickening edges of about 10 mm at the level of the left sacral flap and about 6-7 mm at the level of the right and left iliac wing, of unclear pathological significance are. The alteration reported at D7 in the previous PET is not evident.

20/04/2022 **Bone scan:** Appearance of tracer accumulation area on the VIII left coast. This finding has non-univocal interpretation: unacknowledged post-traumatic outcomes? dyskaryokinetic lesion?. No accumulation in sacrum or iliac wings.

21/04/2022 **Molecular analysis in AMPLITUDE:** Negative (BRCA1/2 included).

Clinical case

27/06/2022 EE: PSA 0.14, TST 0.17 ng/ml

05/07/2022 Start **Apalutamide 240 mg die**

02/08/2022 PSA 0.08 test 0.16

30/08/2022 PSA 0.07 test 0.23

07/09/2022 TC torace addome con mdc: Not variations. Note and unchanged small rounded hypodense lesions at the level of the left sacral wing, the right and left iliac wing, and the left supracetabular region.

07/09/2022 SOTB: Reduction of tracer accumulation at the level of the VIII left rib.

14/10/2022 PSA 0.12 test 0.17

15/12/2022 PSA 0.45

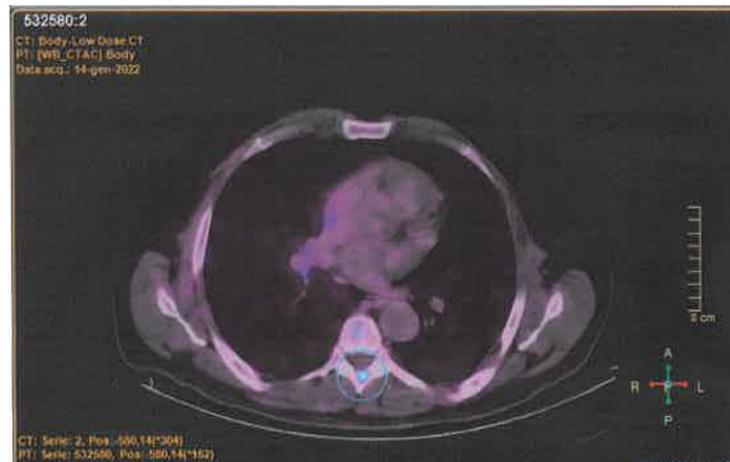
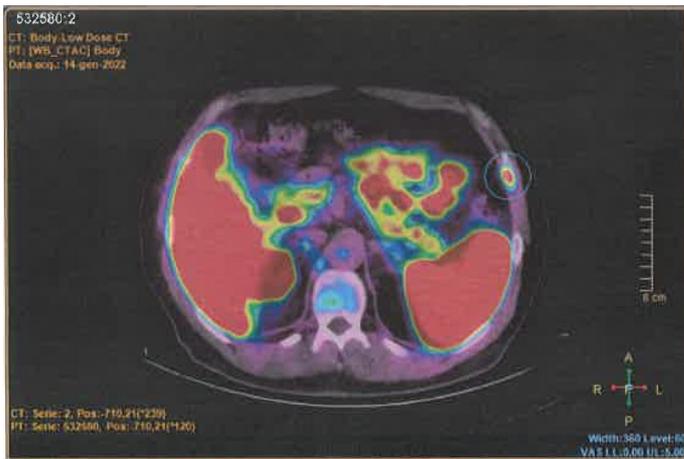
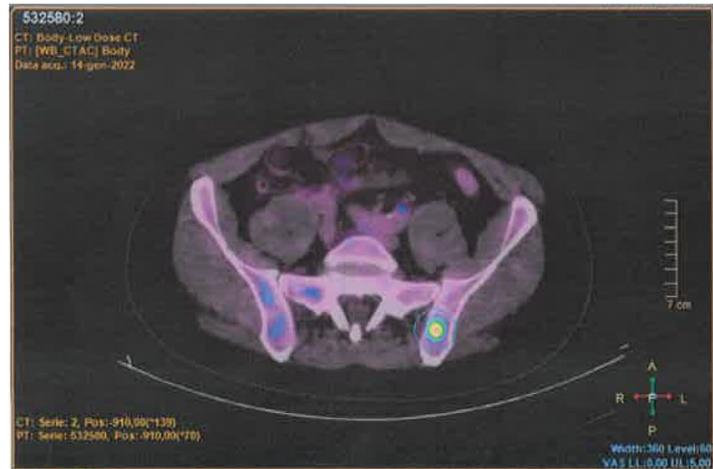
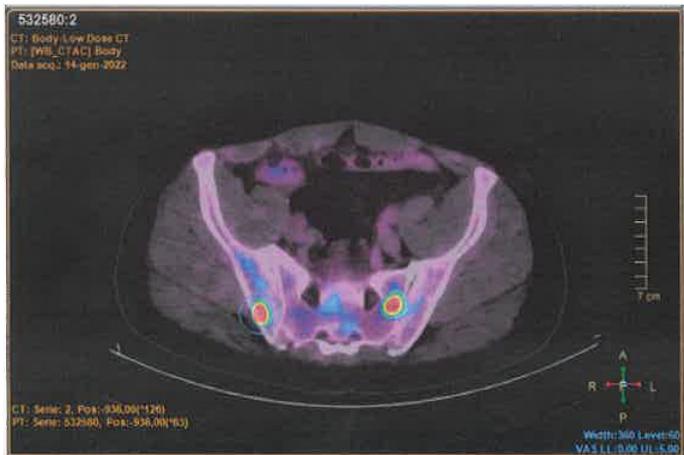
05/01/23 PSA 0.85 Test 0.24

OPEN ISSUES

- Need to follow-up this patient with PSMA-PET ?
- What to do if PET and conventional imaging disagree?
- Was intensification of therapy appropriate for this patient?
 - Only ADT?
 - ADT plus docetaxel?
 - ADT+ARSi?
 - Triplet?
- Would this patient have undergone surgery if he had had PET imaging done immediately? Was it helpful to him?

1.

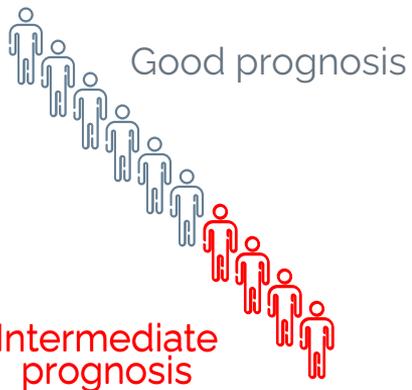
PET vs CIM



Conventional imaging

Low volume

PSMA/choline PET



OS 60 mo → OS 70 mo



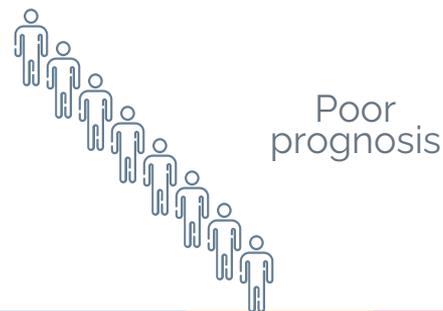
Conventional imaging

High volume

PSMA/choline PET

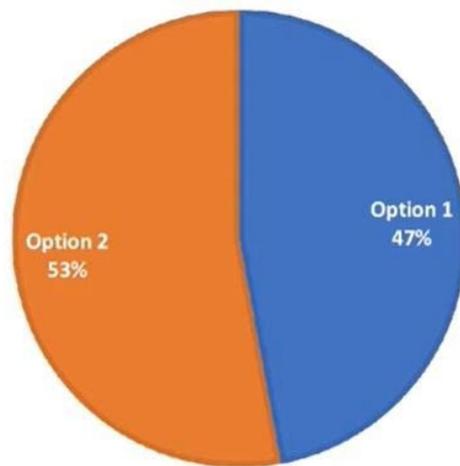


OS 40 mo → OS 45 mo



79. What is your recommended treatment strategy, in the majority of patients with mHSPC that have low-volume disease by conventional imaging but high-volume by next-generation imaging?

1. Treat as per high-volume
2. Treat as per low-volume
3. Abstain/unqualified to answer



Option	Votes
Option 1	48
Option 2	54
Option 3	3
Total votes	105

Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2022

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2.

Choice in mHSPC

OPZIONI PAZIENTE mHSPC

- ▷ Sola ADT
- ▷ ADT + docetaxel
- ▷ ADT + apalutamide
- ▷ ADT + enzalutamide
- ▷ ADT + abiraterone
- ▷ ADT + docetaxel + abiraterone
- ▷ ADT + docetaxel + darolutamide
- ▷ RT su primitivo

Figure 1: FDA approvals in mHSPC



*Level 1 evidence, but not FDA approved

Comparator ADT

**ADT
+
DOCETAXEL**

GETUG-AFU15 (n 385)

ADT +/- docetaxel

OS 0.88 (0.68-1.14)

Median not reached in
low-volume patients

CHAARTED (n 790)

ADT +/- docetaxel

OS 0.72 (0.59-0.89)

In high-volume disease: OS 0.63 (0.50-0.79)

In low-volume disease: OS 1.04 (0.70-1.55)

STAMPEDE (n 1086)

ADT +/- docetaxel

OS 0.81 (0.69-0.95)

PFS 0.69 (0.59-0.81)

No differences on high/low metastatic burden

**ANDROGEN DEPRIVATION (ADT)
+
ADVANCED ANDROGEN
BLOCKAGE (AAB)**

LATITUDE (n 1199)
ADT + **abiraterone** +
prednisone/placebo
OS 0.66 (0.56-0.78)
PFS 0.47(0.39-0.55)
100% high risk patients

STAMPEDE (n 1917)
ADT + **abiraterone** +
prednisone/placebo
OS 0.63 (0.52-0.76)
**Volume disease unknown
(48% M0)**

ENZAMET (n 1125)
ADT+**enzalutamide**/antiandrogen
OS 0.67 (0.52-0.86)
53% high volume / 47% low
45% concurrent docetaxel
67% synchronous M1

ARCHES (n 1150)
ADT+**enzalutamide**/placebo
PFS 0.39 (0.30-0.50)
63% high volume / 37% low
18% prior docetaxel
67% synchronous M1

TITAN (n 1052)
ADT+**apalutamide**/placebo
OS 0.65 (0.53-0.79)
63% high volume / 37% low
11% prior docetaxel
81% synchronous M1

Comparator ADT

Comparator ADT + docetaxel

Comparator ADT or ADT + docetaxel

ARASENS (n 1306)

ADT+ docetaxel + darolutamide/placebo

OS 0.68 (0.57-0.80)

100% concurrent docetaxel

Volume disease not evaluated

86% synchronous M1

17% visceral metastases

TRIPLT THERAPY (TT)

PEACE-1 (n 1173)

(ADT +/- docetaxel) +/- abiraterone

OS 0.82 (0.69-0.98)

PFS 0.54(0.46-0.64)

60% concurrent docetaxel

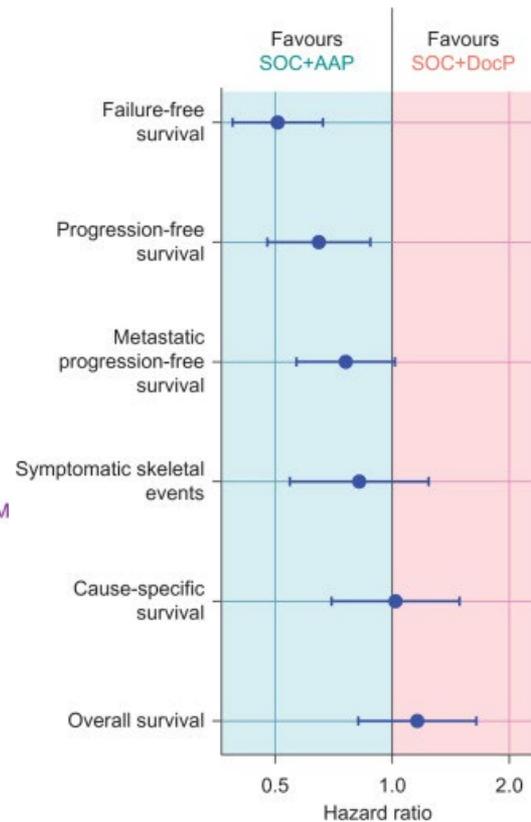
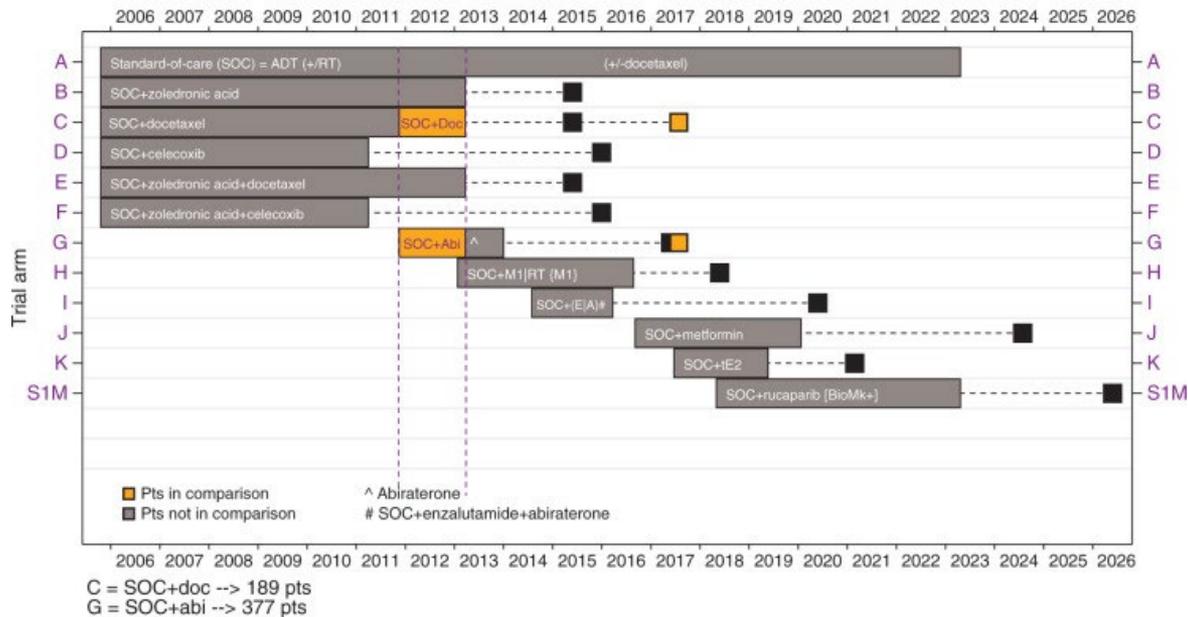
57% high volume / 43% low volume

100% synchronous M1

11% visceral metastases

Abiraterone vs. docetaxel

STAMPEDE: Docetaxel vs abiraterone -- direct comparison



STAMPEDE

Directly randomized data

Sydes M, Ann Oncol, 2018

Safety

		GETUG-AFU 15	CHAARTE D	STAMPEDE	LATITUDE	STAMPEDE	ARCHES	ENZAMET	TITAN
		Docetaxel	Docetaxel	Docetaxel	Abiraterone	Abiraterone	Enzalutamide	Enzalutamide	Apalutamide
SAFETY	Most frequent ≥ 3 AEs in experimental arm	Neutropenia (32%), febrile neutropenia (7%), fatigue (7%)	Neutropenia (12%), febrile neutropenia (6%), fatigue (4%)	Neutropenia (12%), febrile neutropenia (15%), general (7%) and GI disorder (8%)	Hypertension (21%), hypokalemia (12%), ALT (5%) AST (4%) increase	Hypertension (5%), CV disorder (10%), hepatic disorder (7%)	Hypertension (3%)	Hypertension (8%), neutropenia (6%), fatigue (6%), syncope (4%)	Rash (6%), asthenia (2%)

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Decision factors

- ▷ Efficacy is likely to be similar among different ARSi
- ▷ Tolerability profile of drugs is different
- ▷ Oral vs. EV agent
- ▷ Comorbidities (diabetes, mental impairment, cardiovascular disease, gastric ulcer)
- ▷ Duration of treatment
- ▷ Costs
- ▷ Drug interactions
- ▷ Patients' preference and comfort

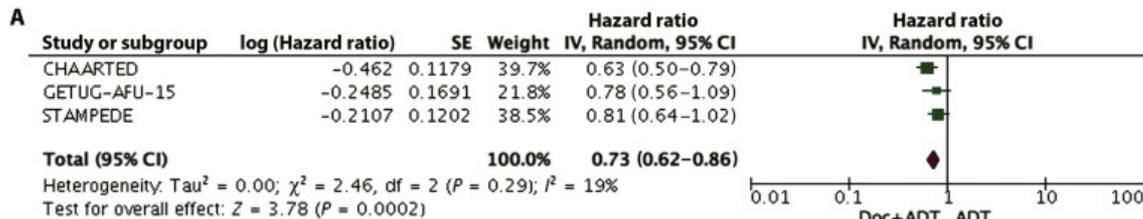
3.

Disease volume

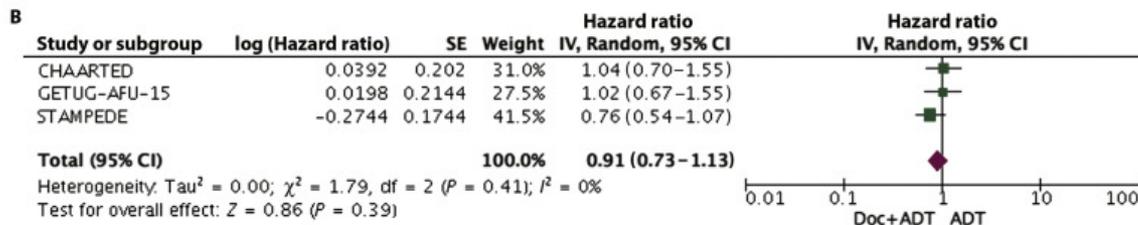
Does it matter?

Docetaxel

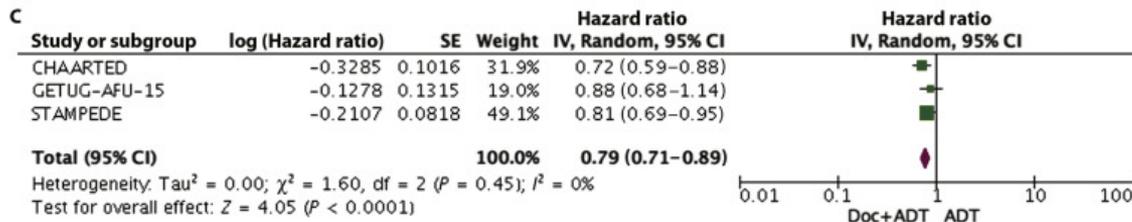
High-volume



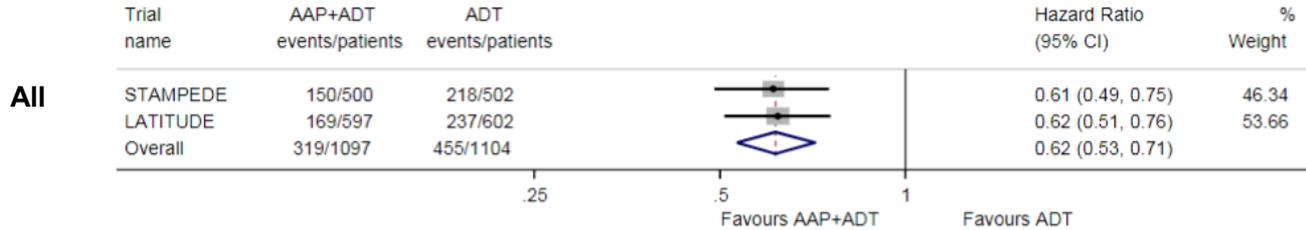
Low-volume



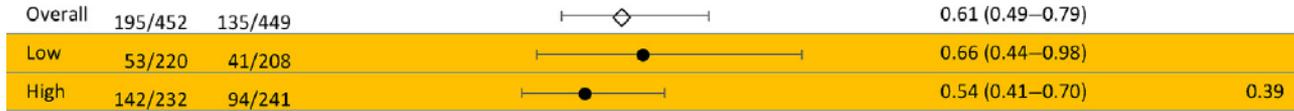
All



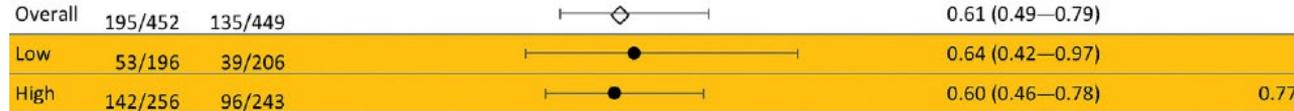
Abiraterone acetato



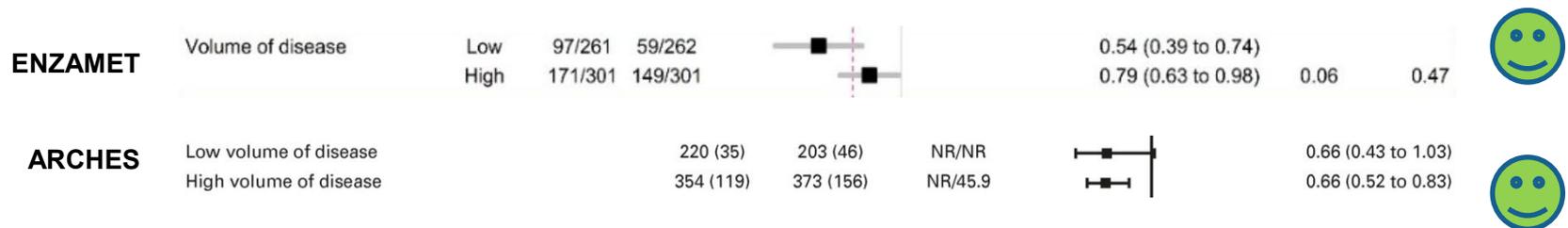
**STAMPEDE
Risk sec Latitude**



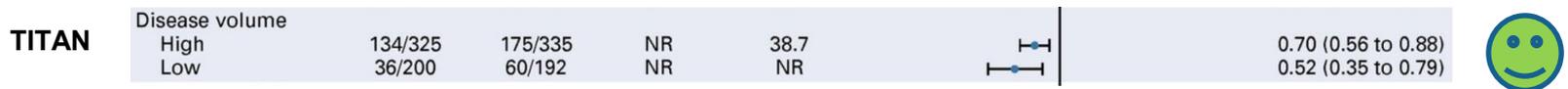
**STAMPEDE
Volume sec Chaarted**



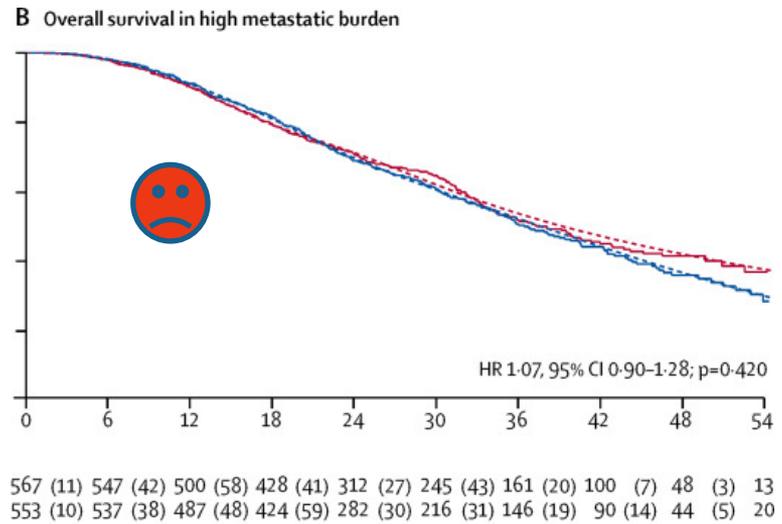
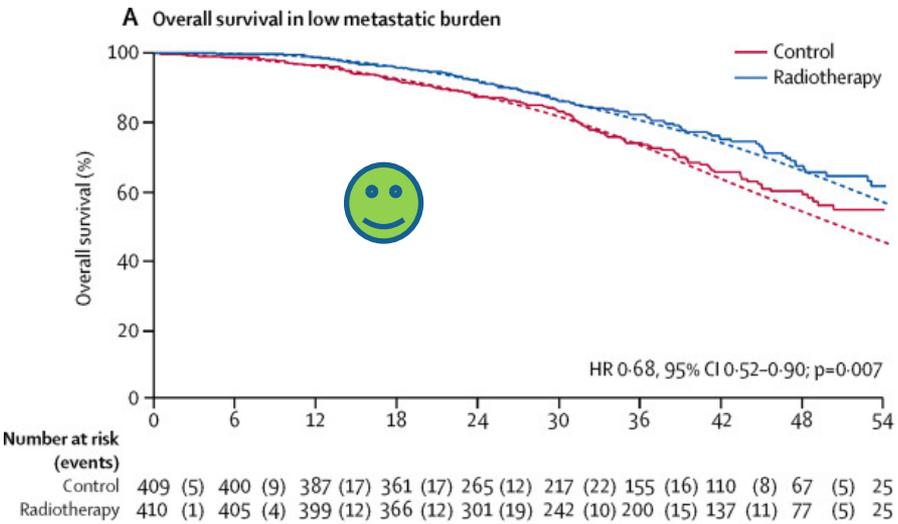
Enzalutamide



Apalutamide



RT su primitivo



STAMPEDE

4.

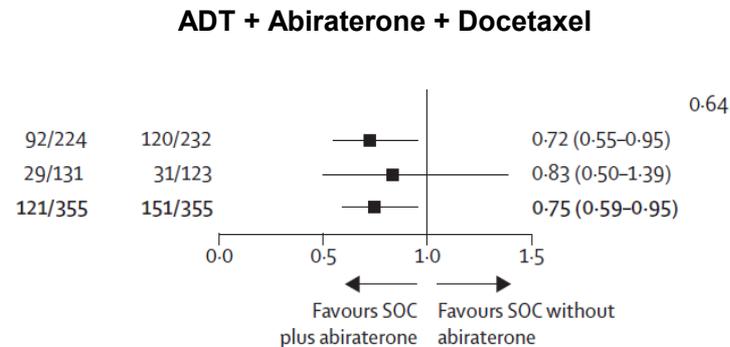
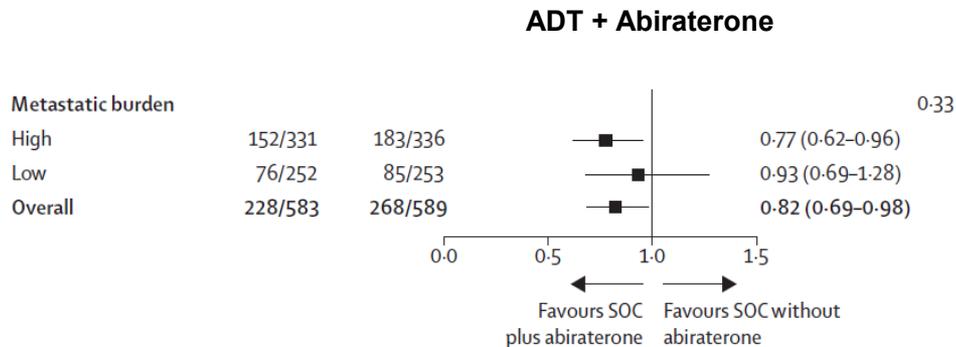
Visceral metastases

Metastasi viscerali

ENZAMET	Visceral metastases	Yes	34/70	33/69		0.94 (0.58 to 1.51)	0.2	0.65
		No	234/492	175/494		0.66 (0.55 to 0.81)		
ARCHES	Disease localization at baseline—bone only		268 (64)	245 (84)	NR/NR	0.59 (0.43 to 0.82)		
	Disease localization at baseline—soft tissue only		51 (12)	45 (9)	NR/NR	1.13 (0.48 to 2.69)		
	Disease localization at baseline—bone and soft tissue		217 (72)	241 (106)	NR/44.3	0.62 (0.46 to 0.84)		
TITAN	Visceral disease at baseline							
	Yes	27/56	43/72	40.8	30.1	0.76 (0.47 to 1.23)		
	No	143/469	192/455	NR	52.2	0.65 (0.52 to 0.80)		
LATITUDE	Visceral disease							
	Yes		52/114	70/114		0.58 (0.41-0.83)		
	No		223/483	273/488		0.69 (0.58-0.82)		
CHAARTED	Type of metastases							
	Visceral metastases with or without bone metastases			123		0.52 (0.25-1.07)		
	High-volume disease with bone metastases alone			389		0.64 (0.46-0.89)		
ARASENS	Extent of disease (eCRF)							
	Non-regional lymph node metastasis		5/23	5/16		0.65 (0.19-2.25)		
	Bone metastasis		171/517	237/520		0.67 (0.55-0.81)		
	Visceral metastasis		53/111	62/118		0.79 (0.55-1.14)		

5. Triplets

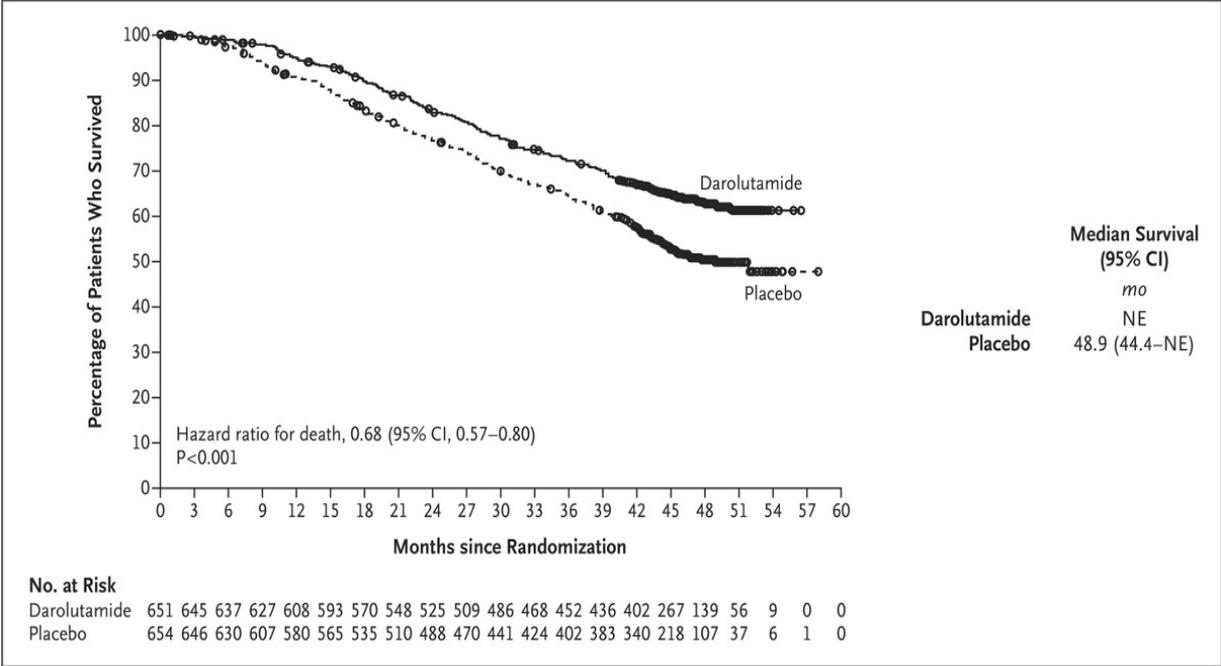
Abiraterone + Docetaxel



PEACE-1

No info on Abi + Doce vs Abi

Darolutamide + Docetaxel

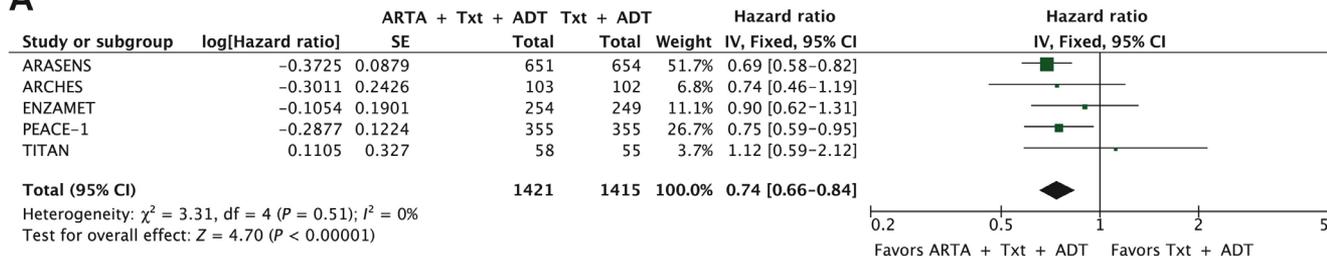


No data on disease volume

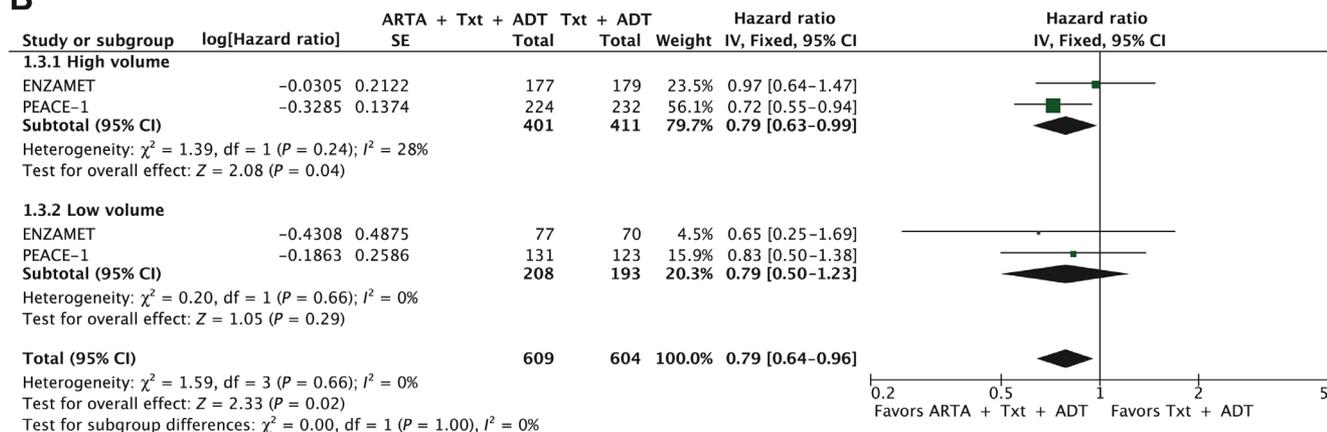
Triplets subgroups



A



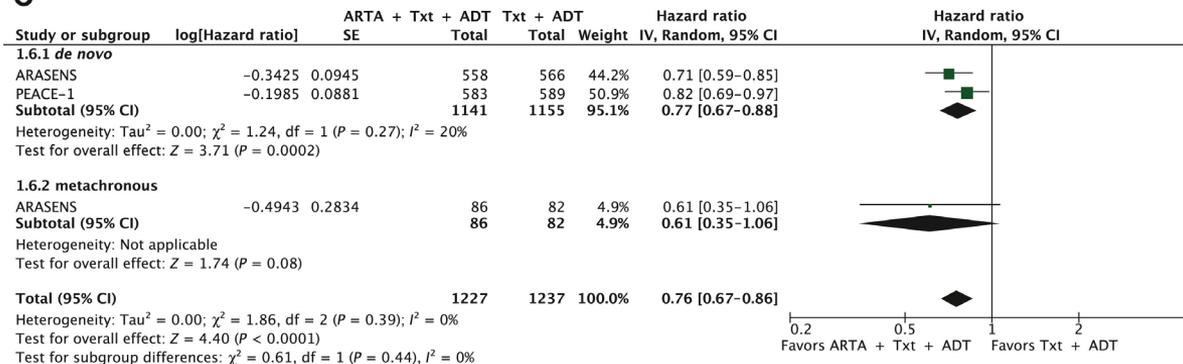
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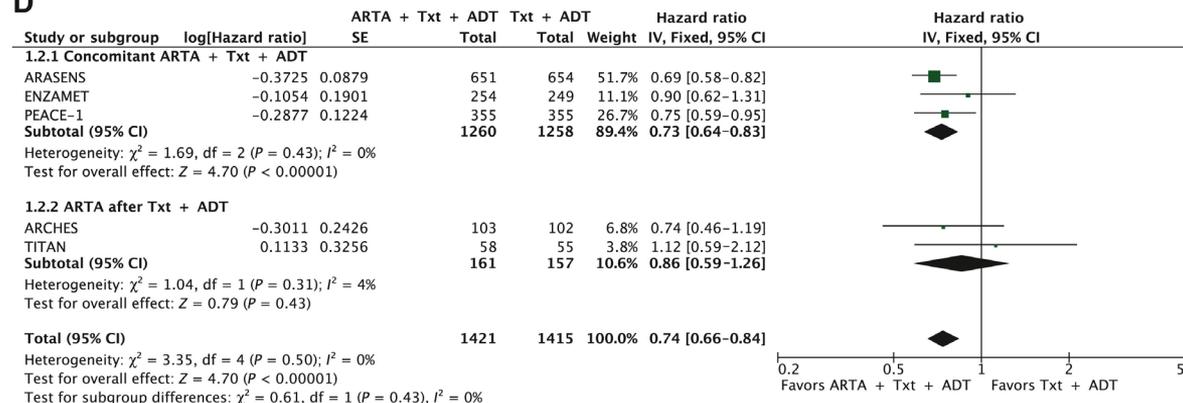
Triplets subgroups



C



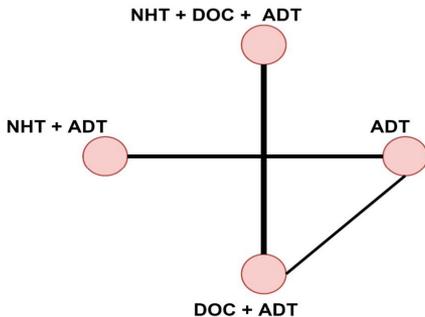
D



Role of docetaxel?

Figure. Network meta-analysis

Network plot



League Table

Overall survival				
	ADT	DOC+ADT	NHT+ADT	NHT+DOC+ADT
ADT		0.79 (0.70-0.88)	0.61 (0.53-0.70)	0.59 (0.50-0.69)
DOC+ADT	1.27 (1.13-1.42)		0.77 (0.64-0.92)	0.74 (0.66-0.84)
NHT+ADT	1.65 (1.43-1.90)	1.30 (1.09-1.56)		0.97 (0.78-1.20)
NHT+DOC+ADT	1.70 (1.44-2.02)	1.35 (1.19-1.52)	1.03 (0.83-1.29)	

Radiographic progression free survival				
	ADT	DOC+ADT	NHT+ADT	NHT+DOC+ADT
ADT		0.67 (0.60-0.75)	0.40 (0.35-0.47)	0.33 (0.26-0.41)
DOC+ADT	1.49 (1.34-1.66)		0.60 (0.50-0.72)	0.49 (0.40-0.59)
NHT+ADT	2.48 (2.14-2.87)	1.66 (1.38-1.99)		0.81 (0.63-1.05)
NHT+DOC+ADT	3.03 (2.51-3.66)	2.03 (1.74-2.37)	1.23 (0.95-1.60)	

CLINICAL CASE OPEN ISSUES (my opinion)

- **Need to follow-up this patient with PSMA-PET ?**
 - my personal answer is no, I have no evidence and no reason at this time to restage patients with PET
- **What to do if PET and conventional imaging disagree?**
 - what gives more benefit to the patient, offering him more therapeutic options (not less), but avoiding overtreatment
- **Was intensification of therapy appropriate for this patient?**
 - Yes, I would do ADT+ARSi again, but I do not regret not having done chemotherapy
- **Would this patient have undergone surgery if he had had PET imaging done immediately? Was it helpful to him?**
 - I think that treatment of the primary tumor (surgery or RT) is useful in a patient with low volume disease per CIM, regardless of PSMA PET

Thanks



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