Treatment Intensification with Chemotherapy: Does Volume Matter?

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- **Personal honoraria** for participation in *advisory boards* from Amgen, MSD, Orion; *other honoraria* from Radio-televisione Svizzera Italiana (RSI), German-speaking European School of Oncology (DESO); *invited speaker* for ESMO, Swiss group for Clinical Cancer Research (SAKK), Swiss Academy of Multidisciplinary oncology (SAMO), Orikata academy research group, China Anti-Cancer Association Genitourinary Oncology Committee (CACA-GU); *Speaker's bureau* for Janssen Cilag; *travel grant* from ProteoMEdiX.
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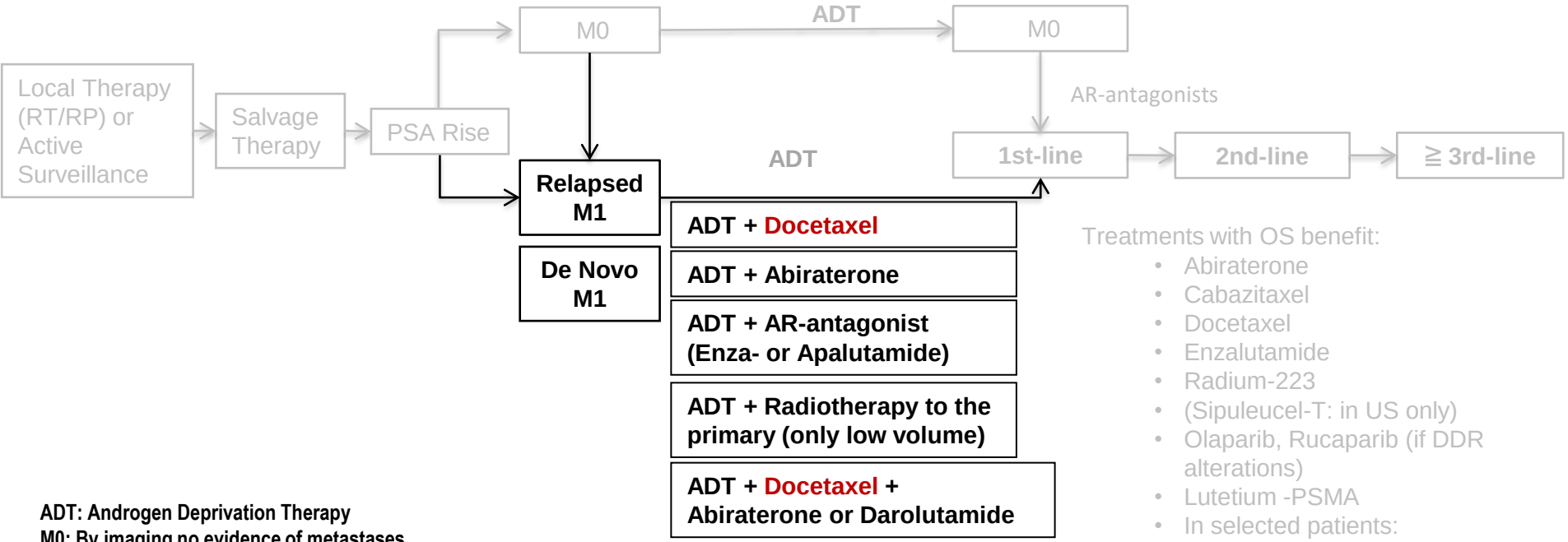
- **Non-financial interests:** Menarini Silicon Biosystems; Aranda
- Co-inventor on patent application (WO 2009138392 A1) for a method for biomarker discover (granted in China, Europe, Japan and the US)
- Deputy of the ESMO guidelines committee for GU cancers, member of the scientific committee of ESMO guidelines, member of the EAU guideline panel for prostate cancer, past chair of the EORTC GU group; Member of the STAMPEDE trial management group

Prostate Cancer: Hormone Sensitive (HSPC)

Localised Prostate Cancer

Advanced Prostate Cancer: *Castration-sensitive/naive*

Advanced Prostate Cancer: *Castration-resistant*

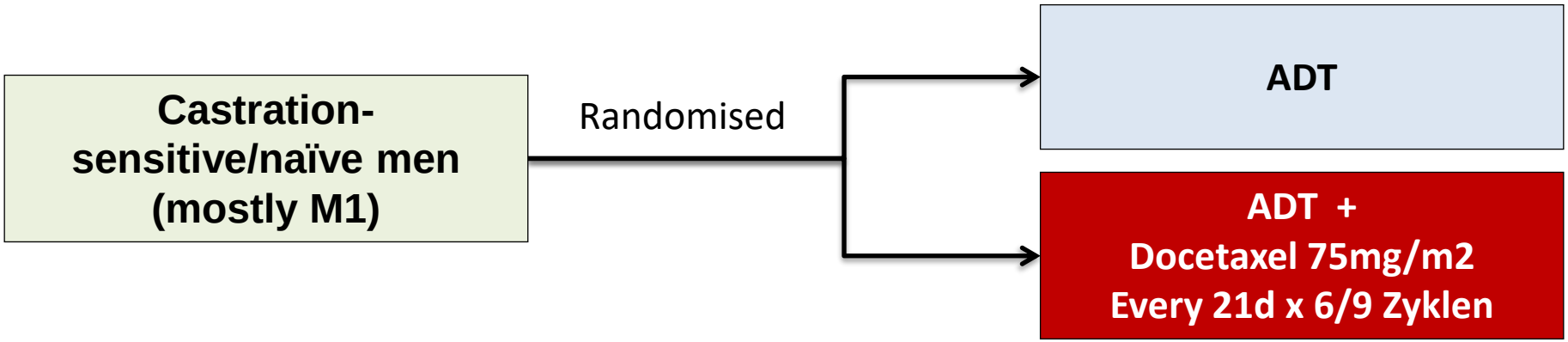


Treatments with OS benefit:

- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- (Sipuleucel-T: in US only)
- Olaparib, Rucaparib (if DDR alterations)
- Lutetium -PSMA
- In selected patients:
  - Pembrolizumab

ADT: Androgen Deprivation Therapy
M0: By imaging no evidence of metastases
M1: Metastases detected by imaging

ADT plus Docetaxel vs ADT alone



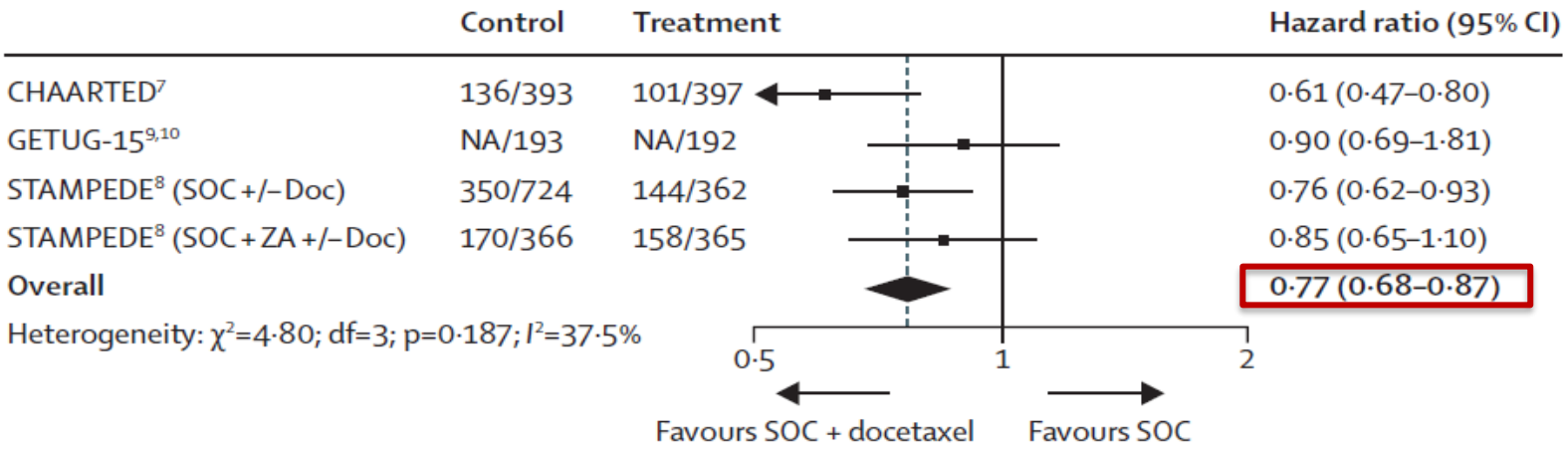
GETUG-15	n=385	Accrual: 2004-2008
CHAARTED	n=790	Accrual: 2006-2012
STAMPEDE	n= 2962	Accrual: 2005-2013

Gravis G Lancet Oncol. 2015; Sweeney CJ N Engl J Med. 2015;James ND Lancet. 2016

ADT + Docetaxel Overall Survival – Metaanalysis

M1 Patients

A



Median OS benefit: 14-16 months

Vale C et al. Lancet Oncol 2016

Some definitions for mHSPC

	High	Low
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or pelvis **OR/AND** Visceral metastasis	Not high Sweeney C et al. NEJM 2015
LATITUDE (risk)	≥ 2 high risk features of • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high Fizazi K et al. NEJM 2017

High metastatic burden (used in STAMPEDE) = high volume as above

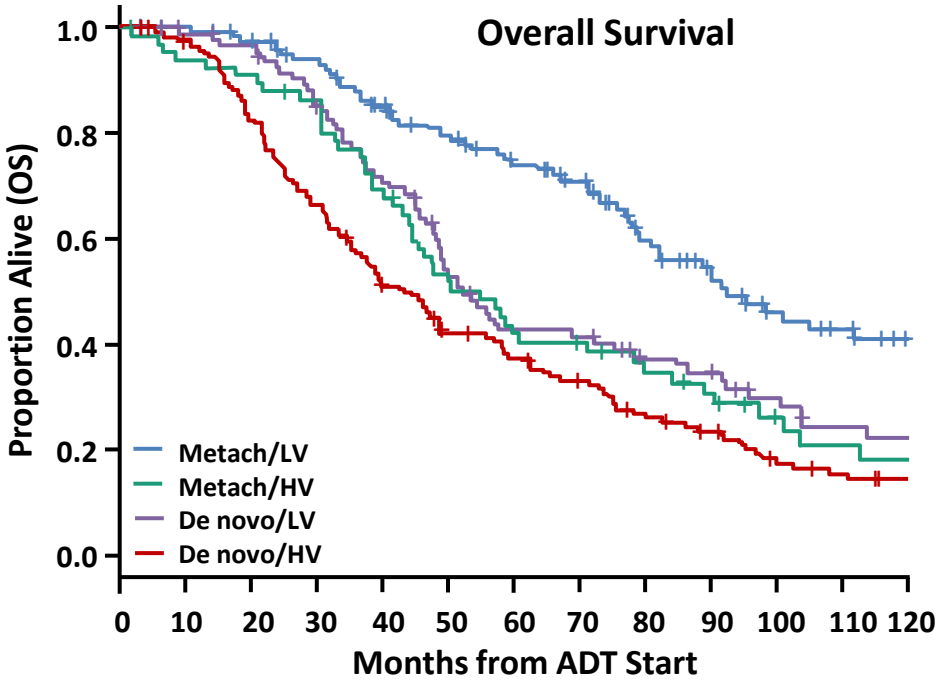
Parker C et al. Lancet 2018

De novo metastatic (synchronous): First diagnosis with metastases vs
Relapsed metastatic (metachronous). Diagnosis of metastases only after local radical therapy

Stratification of prognosis by type of presentation and by extend of metastases

Groups	N (% events)	mOS, years (95% CI)
Metach/LV	125 (50)	7.7 (6.7, 10.6)
Metach/HV	67 (75)	4.6 (3.7, 6.7)
De novo/LV	96 (70)	4.3 (4.0, 6.5)
De novo/HV	148 (84)	3.6 (3.1, 4.7)

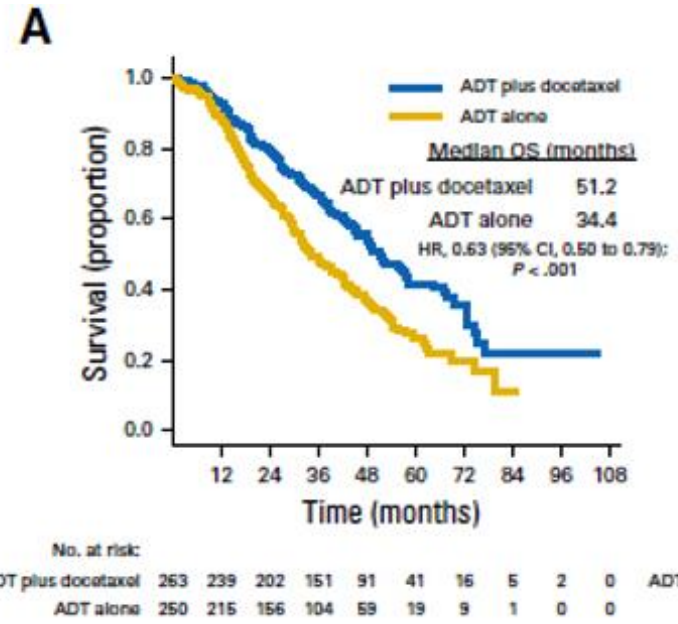
mOS, median overall survival



Francini E, et al. Prostate. 2018;78(12):889-895.; Gravis G, et al. Eur Urol. 2018;73(6):847-855.

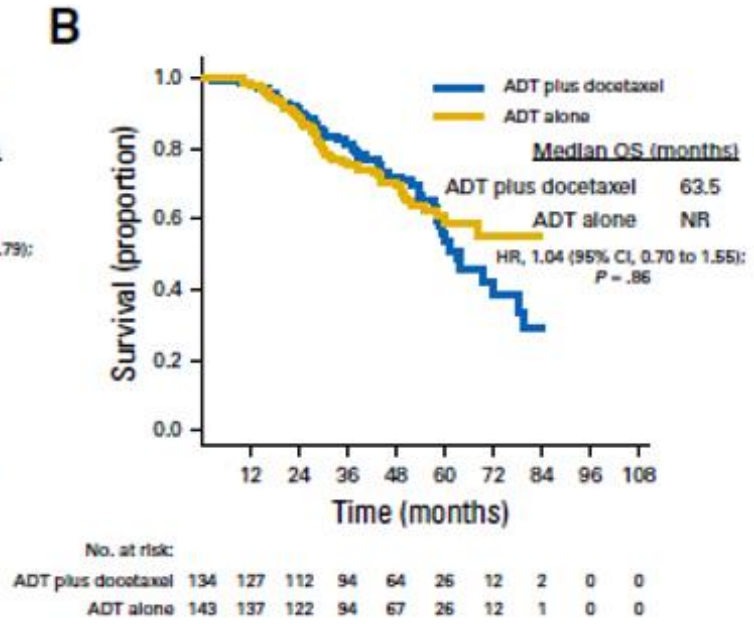
Subgroup-Analysis by volume in GETUG15 and CHAARTED

High volume



HR: 0.63
(0.5-0.79)

Low volume

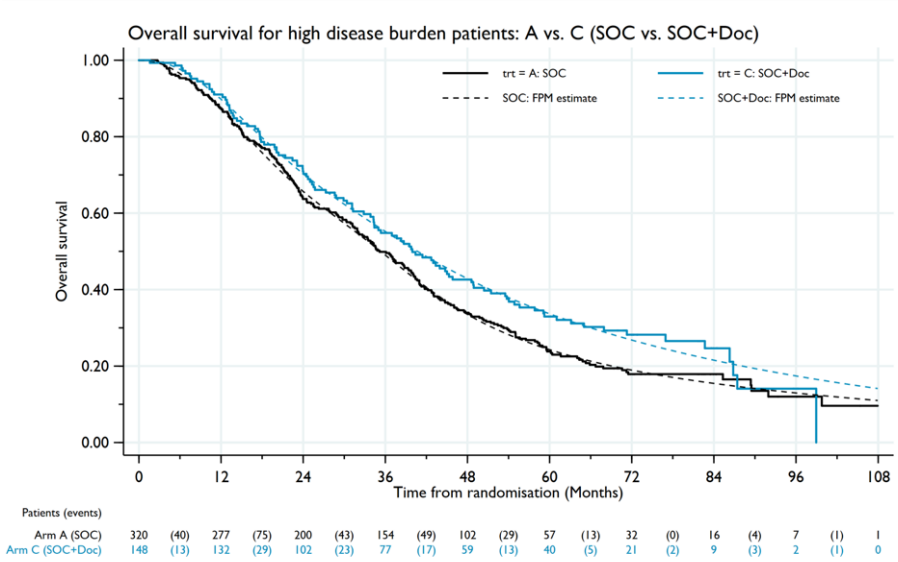


HR: 1.04
(0.7-0.1.55)

Gravis Eur Urol 2018
Kyriakopoulos JCO 2018

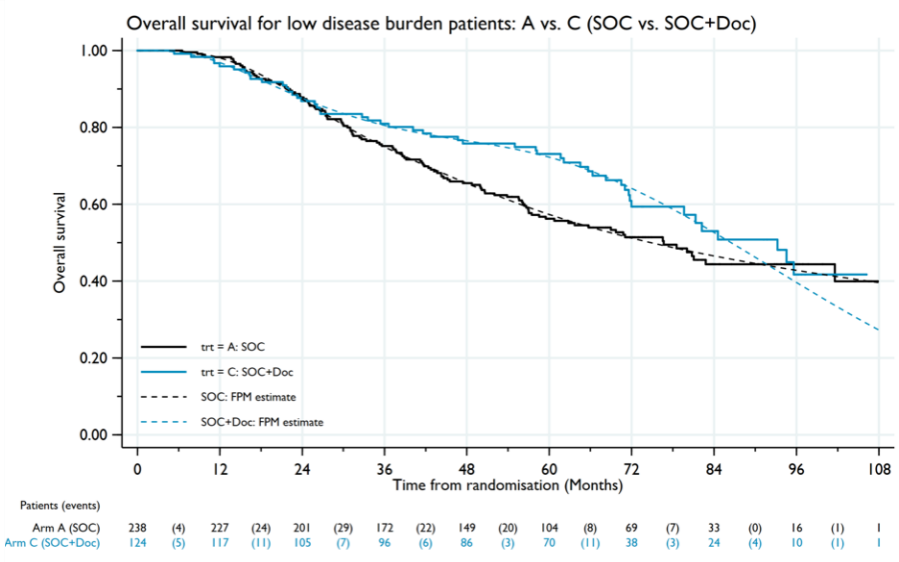
Subgroup-Analysis by volume in STAMPEDE

High volume



HR: 0.81
(0.64-1.02)

Low volume



HR: 0.76
(0.54-1.07)

No evidence that the beneficial effect varies by metastatic burden
interaction p-value = 0.827

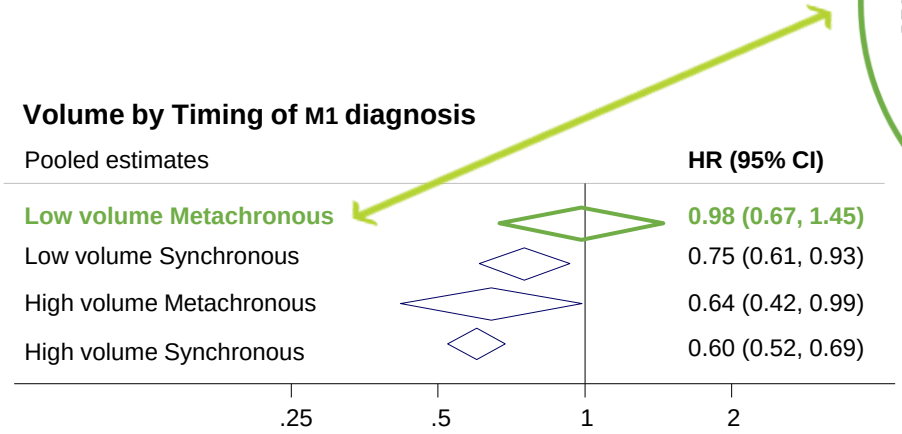
James ESMO 2019; Clarke Ann Oncol 2019; MRC-CTU

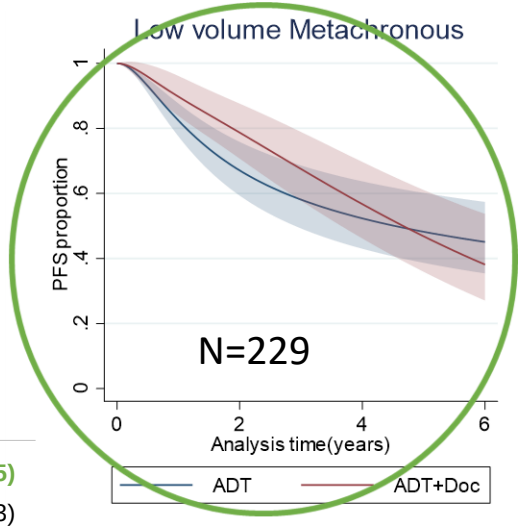
Differences in patient's characteristics in the trials

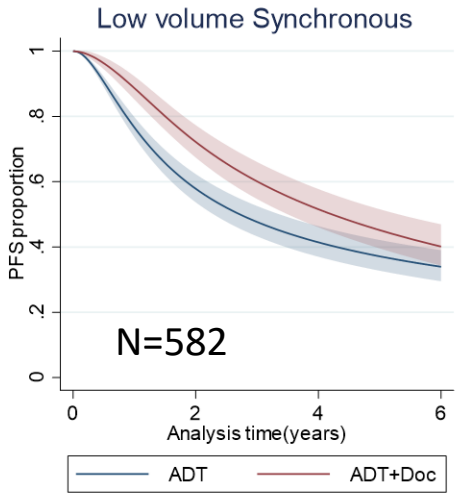
	STAMPEDE (1086 men)	CHAARTED (790 men)	GETUG-15 (385 men)
High Volume	~43%	**~65%**	~51%
Synchronous	**~95%**	~75%	~75%

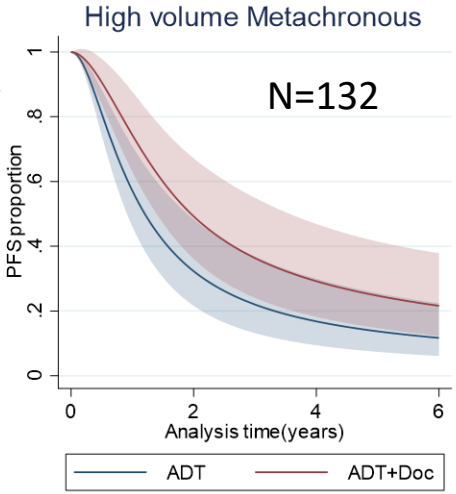
→ Meta-Analysis of individual patient data from all three trials: **STOPCAP**

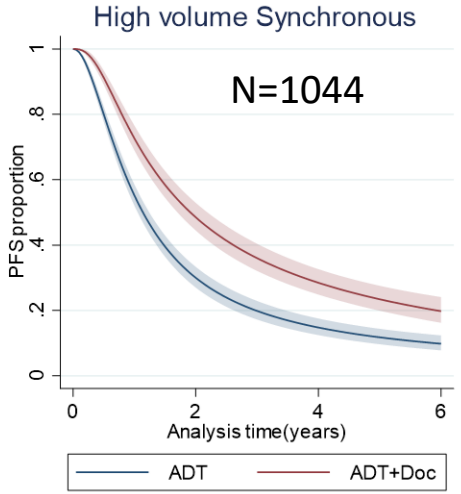
STOPCAP: Effect of docetaxel on PFS by volume & timing











Results were consistent for OS

Vale C et al. ASCO 2022

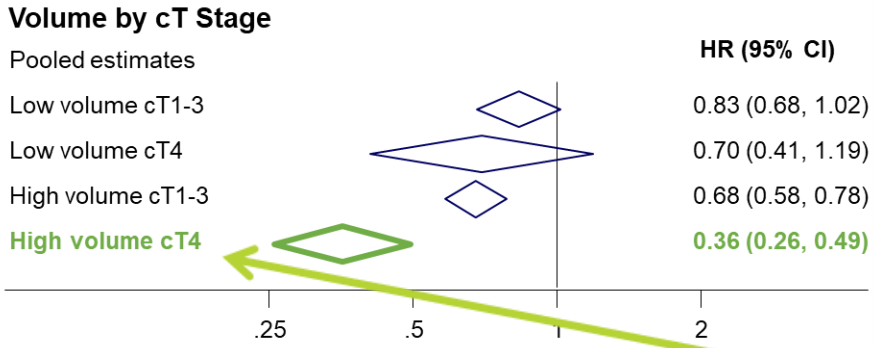
STOPCAP: Meta-analysis of individual participant data from randomized trials with docetaxel – overall survival

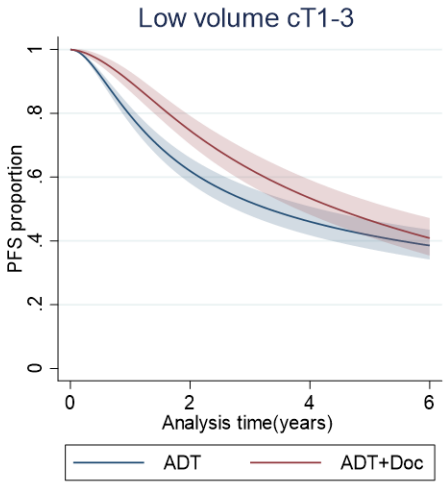
Subgroup	Absolute effect at 5 years			
	Progression free survival		Overall survival	
	% difference (95% CI)	Change from baseline	% difference (95% CI)	Change from baseline
Disease volume x timing of diagnosis				
Low volume, metachronous	-6% (-22 to 11%)	49% to 43%	0% (-13 to 13%)	73% to 73%
Low volume, synchronous	8% (0 to 15%)	38% to 45%	7% (-1 to 15%)	53% to 60%
High volume, metachronous	6% (-6 to 18%)	14% to 20%	4% (-16 to 24%)	29% to 33%
High volume, synchronous	12% (8 to 16%)	12% to 24%	12% (7 to 18%)	26% to 38%

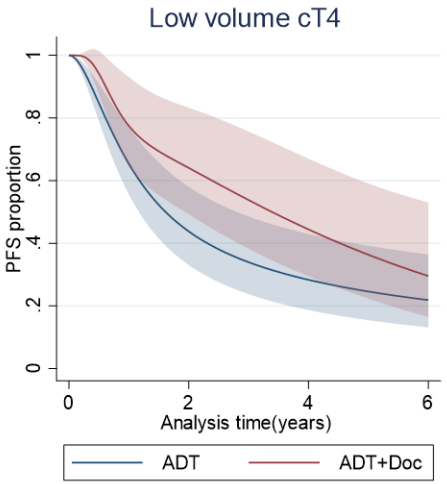
Abstract 5070: Defining more precisely the effects of docetaxel plus ADT for men with mHSPC: Meta-analysis of individual participant data from randomized trials. Claire L Vale, et al for the STOPCAP Collaboration. Proc ASCO 2022

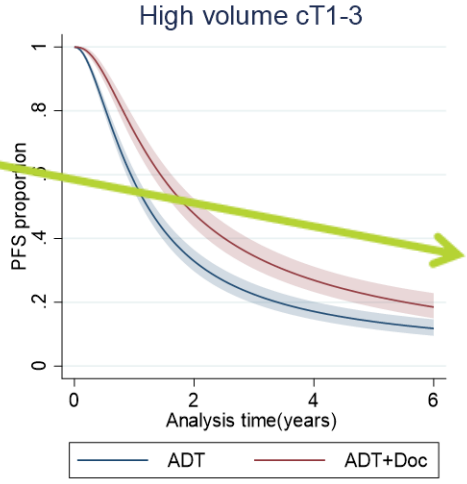
Courtesy N. James ***Vale C et al. ASCO 2022***

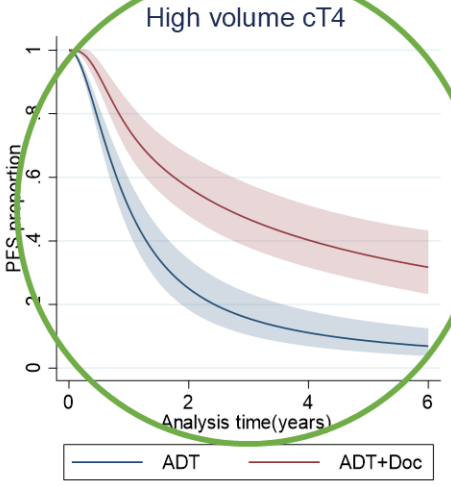
STOPCAP: Effect of docetaxel on PFS by volume & clinical T stage





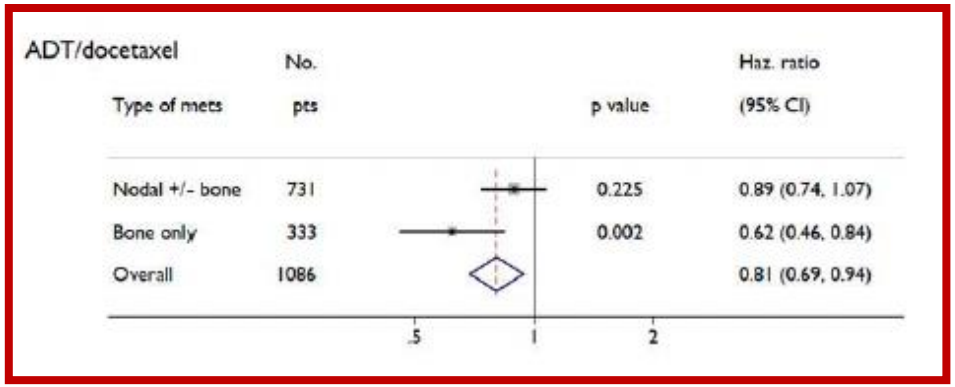


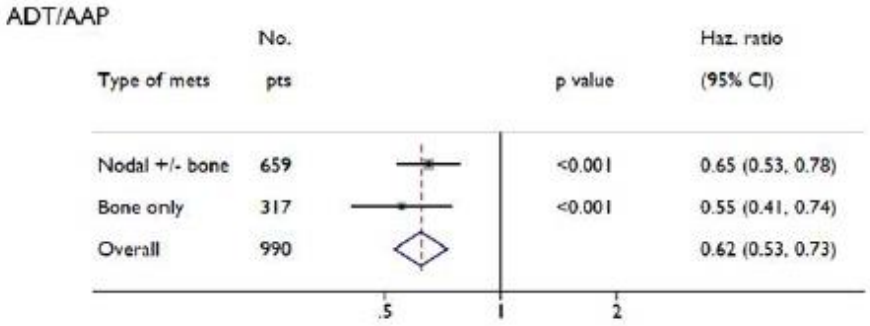




Vale C et al. ASCO 2022

Effect of docetaxel by other clinical parameters





- No significant treatment benefit with ADT/docetaxel in nodal subgroup
- Improved survival in patients with bone only metastases treated with ADT/docetaxel
- Nodal burden is prognostic for worse outcomes

PARIS 2022 ESMO congress

Haran AM et al, ESMO 2022

STAMPEDE

Conclusions I

- Patients with low volume, metachronous mHSPC seem not to benefit from addition of docetaxel to ADT
- Clear benefit of docetaxel added to ADT for patients with high volume mHSPC (specially when synchronous and/or cT4 stage)
- Treatment has to be individualised, “volume” definition helpful, can probably be refined by other clinical parameters (as long as we have no validated predictive molecular markers)
- Landscape changed again: ADT + ARSI vs ADT + docetaxel + ARSI

Triplet (systemic) therapy

Trial		rPFS (HR)	OS (HR)
Concurrent docetaxel + ARTA			
ADT + enzalutamide +/- docetaxel (amendment 11.2013) (> 4 weeks from start of enzalutamide, < 6 weeks randomization), 2 cycles completed at full dose tolerated allowed **ENZAMET**	503 patients concurrent docetaxel 178 previous docetaxel	0.48 (95% CI: 0.37-0.62)	0.9 (95% CI: 0.62 – 1.31) Docetaxel yes: High volume HR 0.87 (0.66;1.17) Low volume HR 0.61 (0.33-1.1)
ADT +/- docetaxel +/- abiraterone/prednisone **PEACE-1**	750 patients docetaxel CONCURRENT	0.5 (95% CI: 0.40 – 0.62)	0.75 (95% CI: 0.59 – 0.95)
ADT + docetaxel +/- darolutamide **ARASENS**	1306 patients CONCURRENT	n.r.	0.68 (95% CI: 0.57 – 0.8)
Docetaxel prior to ARTA			
ADT + enzalutamide prior docetaxel max. 6 cycles (completed > 2 months of enzalutamide start, confirmed non PD) **ARCHES**	205 patients **prior** docetaxel (90%: 6 cycles)	0.52 (95% CI: 0.3-0.89)	n.r.
ADT + apalutamide prior docetaxel max. 6 cycles (completed > 2 months of apalutamide start, confirmed non PD) **TITAN**	113 patients **prior** docetaxel	0.47 (95% CI: 0.22 – 1.01)	1.12 (95% CI: 0.59 – 2.12)

Adadpted from F. Turco

Chi, K *et al. New Engl J Med* 2019, Armstrong, AJ *et a. New Engl J Med*. 2019; Davis I *et al. New Engl J Med*. 2019; Fizazi, K *et al. The Lancet* 2022, Smith, MR *et al. New Engl J Med* 2022; ARTA= androgen-receptor targeted agent

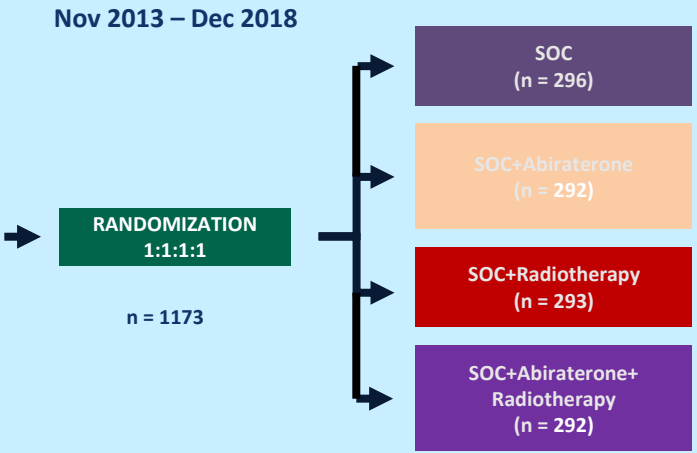
Design of PEACE-1 (2x2)

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

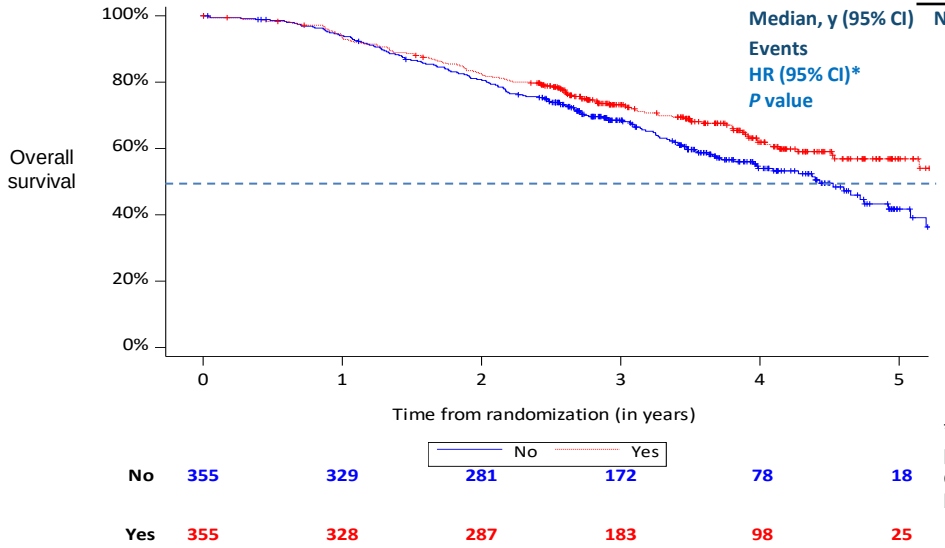
Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

Courtesy K. Fizazi

OS with Abiraterone in the ADT+docetaxel (+/-RXT) population



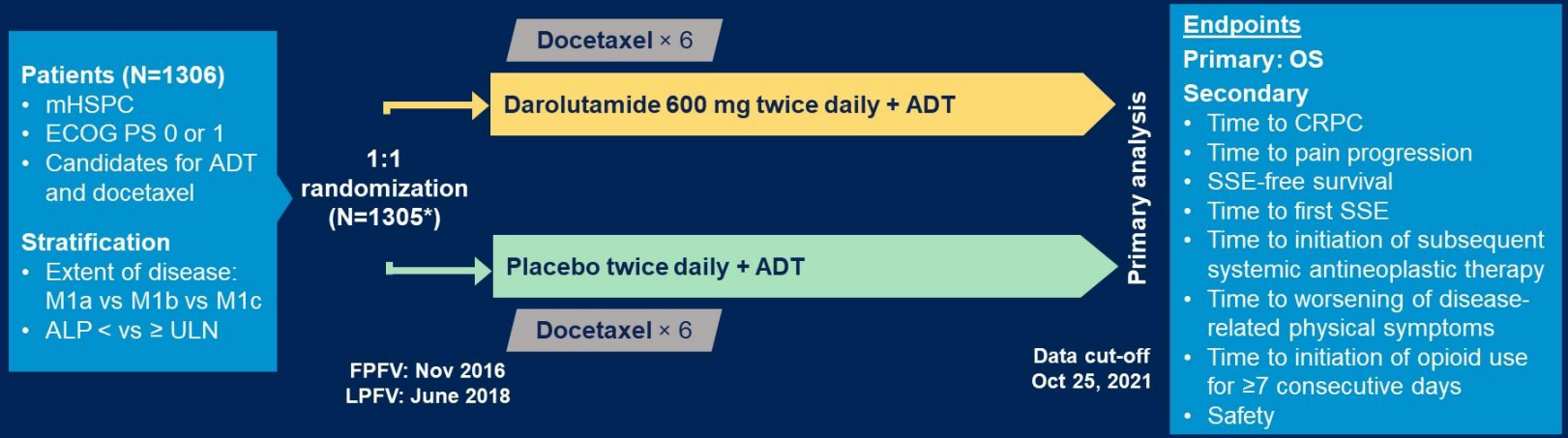
	SOC+Abi (n = 355)	SOC (n = 355)
Median, y (95% CI)	NE (4.5-NE)	4.4 (3.8-4.9)
Events	121	151
HR (95% CI)*	0.75 (0.59-0.95)	
P value	0.017	

*Adjusted on stratification parameters (RXT, type of castration, PS, metastatic burden)

Courtesy K. Fizazi

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

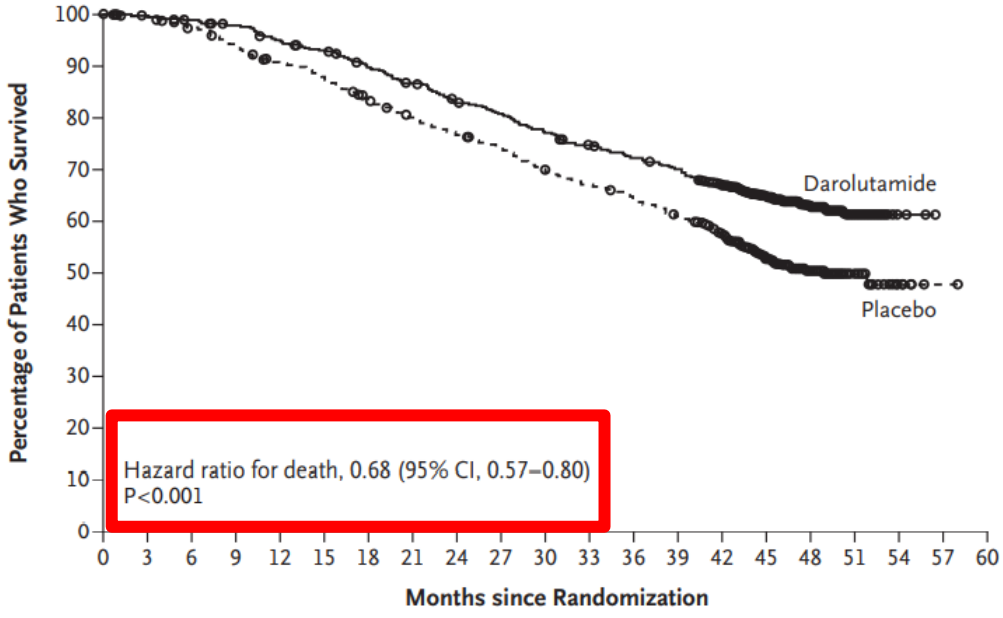


- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

Smith M et al, NEJM 2022

ARASENS: Overall Survival



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Figure 1. Overall Survival (Full Analysis Set).

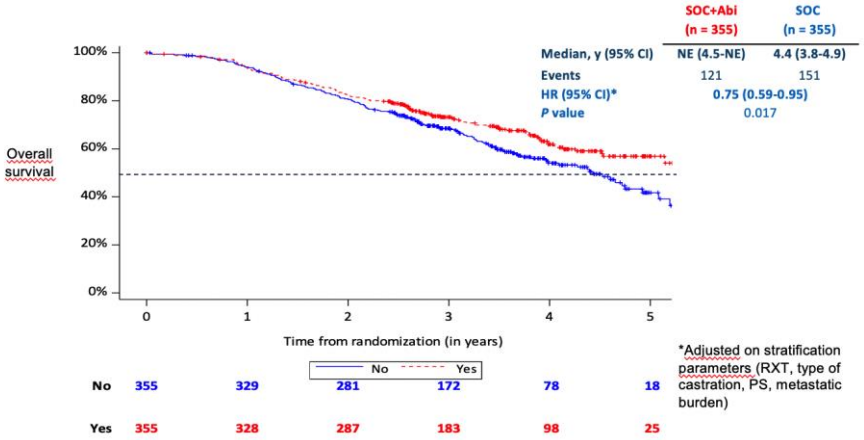
Kaplan–Meier estimates of overall survival are shown. For the analysis of overall survival, data were censored as of the last known date the patients were alive. One patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set. CI denotes confidence interval, and NE not estimable.

Smith M et al, NEJM 2022

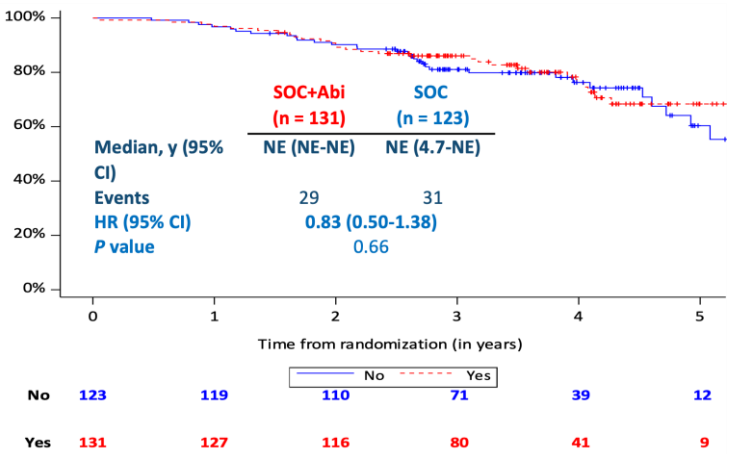
ADT + Doc + NHT vs ADT + Doc: Benefit also in the better prognosis patients?

PEACE-1: ALL patients de novo

high volume



low volume



Fizazi et al Lancet 2022

No trial (yet) asking ADT + NHT vs ADT + NHT + Doc!

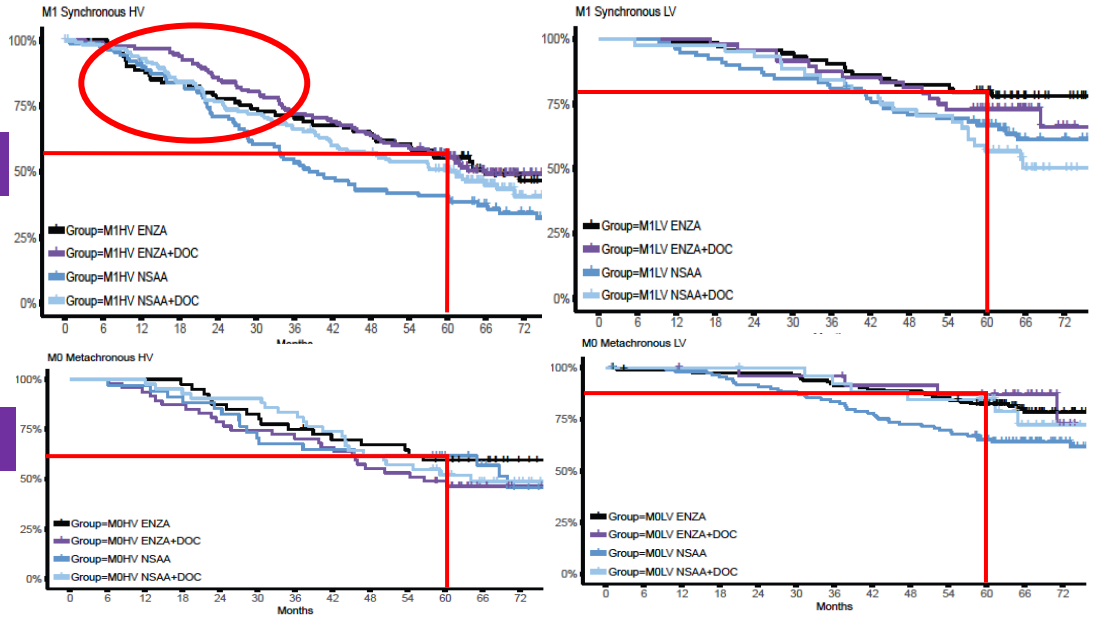
ENZAMET suggests the only subgroup who may benefit from adding docetaxel (purple) to ADT plus enzalutamide (black) is synchronous high volume

High Volume

Low Volume

Synchonous

Metachronous



ADT + docetaxel + enza (purple) better OS than ADT + doc (light blue) in synch mHSPC (like PEACE-1)

Courtesy C Sweeney

Davis I, ENZAMET ASCO 2022

Conclusions II

- After two trials showing an OS benefit for adding an ARSI to ADT and docetaxel I would not give docetaxel only with ADT in the majority of patients but doublet of ADT + ARSI (+/- RT to the primary in low volume) or triplet
- Added value of docetaxel in addition to ADT + ARSI formally not demonstrated
- Potential patients for triplet systemic therapy are the patients who profit from docetaxel in STOPCAP, in my opinion mostly for young(er) and fit patients with high volume disease
- **So, does volume matter? Yes, it does! However, not only volume matters**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