



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO
MEJOR DE **2023**

Madrid, 22 y 23 de noviembre de 2023

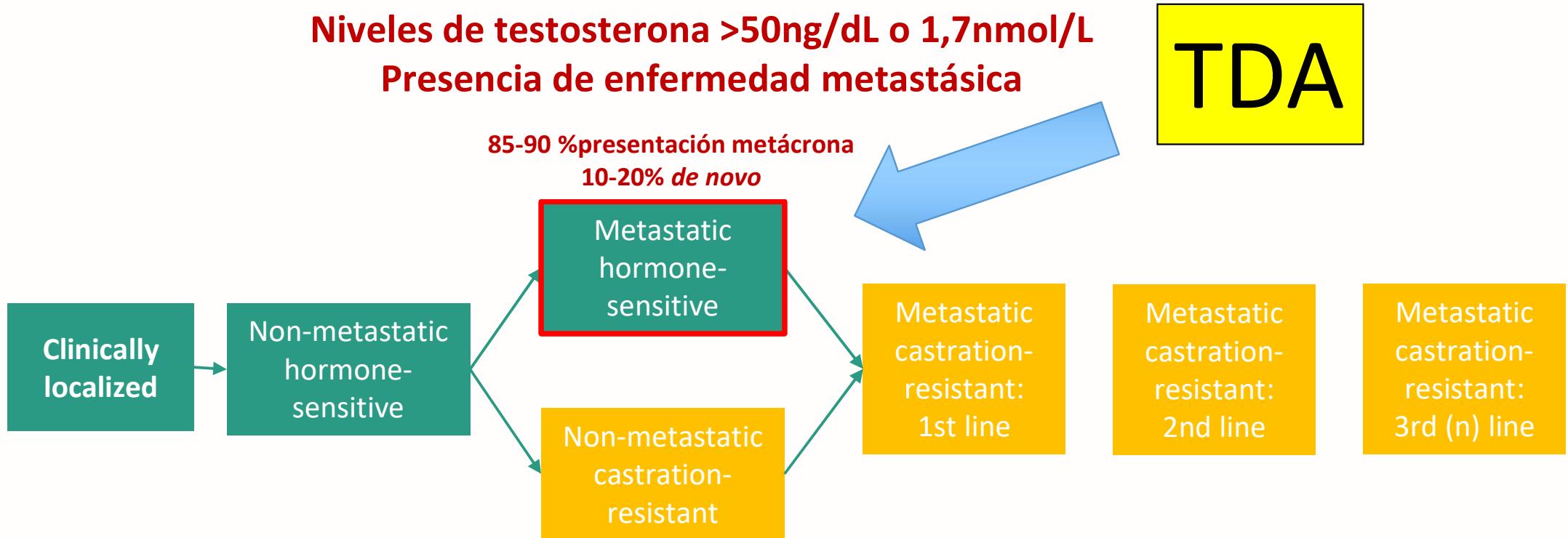
Cáncer de próstata hormonosensible metastásico: opciones terapéuticas

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Servicio de Oncología Médica
Hospital Universitario de Guadalajara

PROSTATE CANCER STAGES & THERAPEUTIC LANDSCAPE

Niveles de testosterona $>50\text{ng/dL}$ o $1,7\text{nmol/L}$
Presencia de enfermedad metastásica

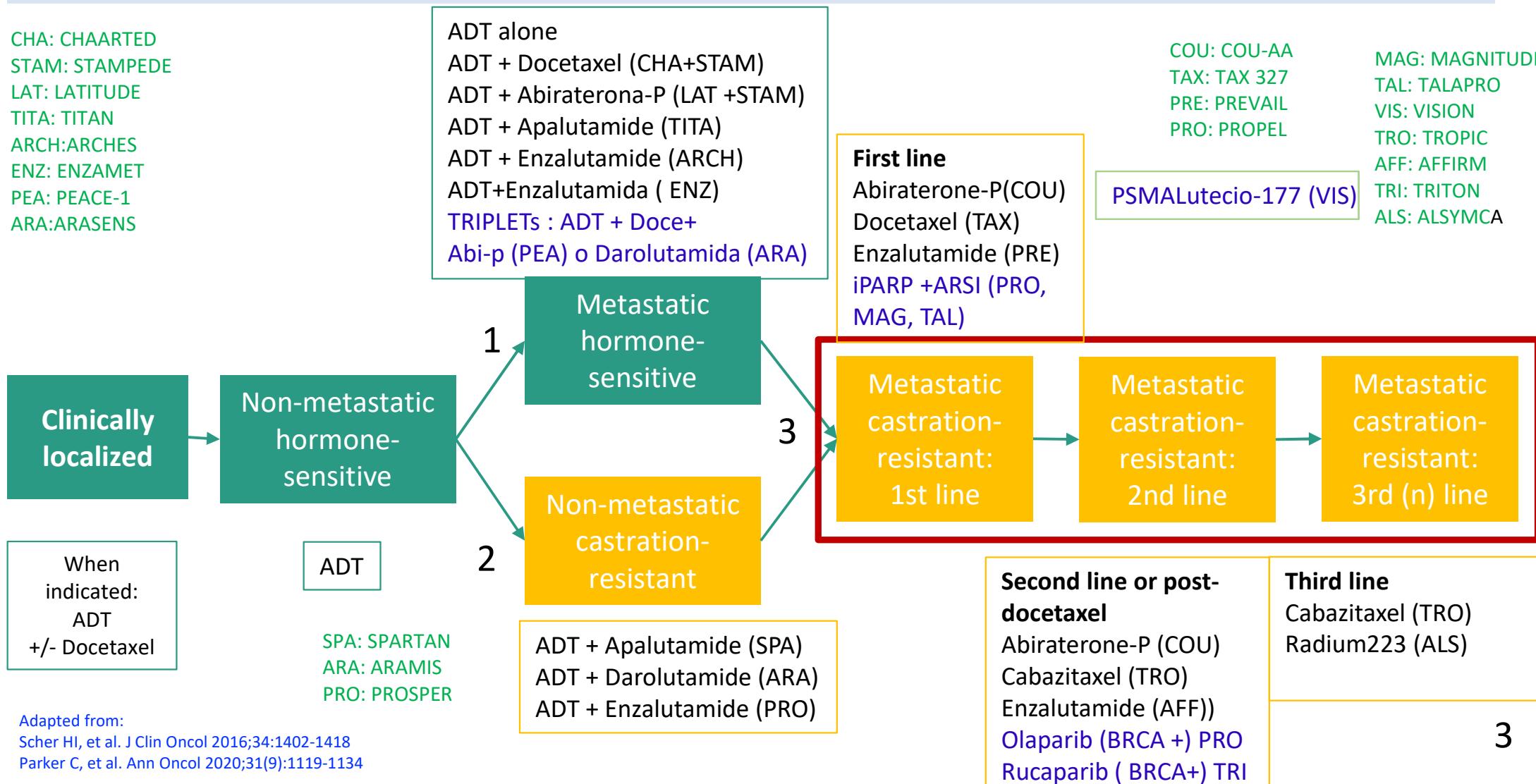


PROSTATE CANCER STAGES & THERAPEUTIC LANDSCAPE

CHA: CHARTED
 STAM: STAMPEDE
 LAT: LATITUDE
 TITA: TITAN
 ARCH: ARCHES
 ENZ: ENZAMET
 PEA: PEACE-1
 ARA: ARASENS

COU: COU-AA
 TAX: TAX 327
 PRE: PREVAIL
 PRO: PROPEL

MAG: MAGNITUDE
 TAL: TALAPRO
 VIS: VISION
 TRO: TROPIC
 AFF: AFFIRM
 TRI: TRITON
 ALS: ALSYMCA

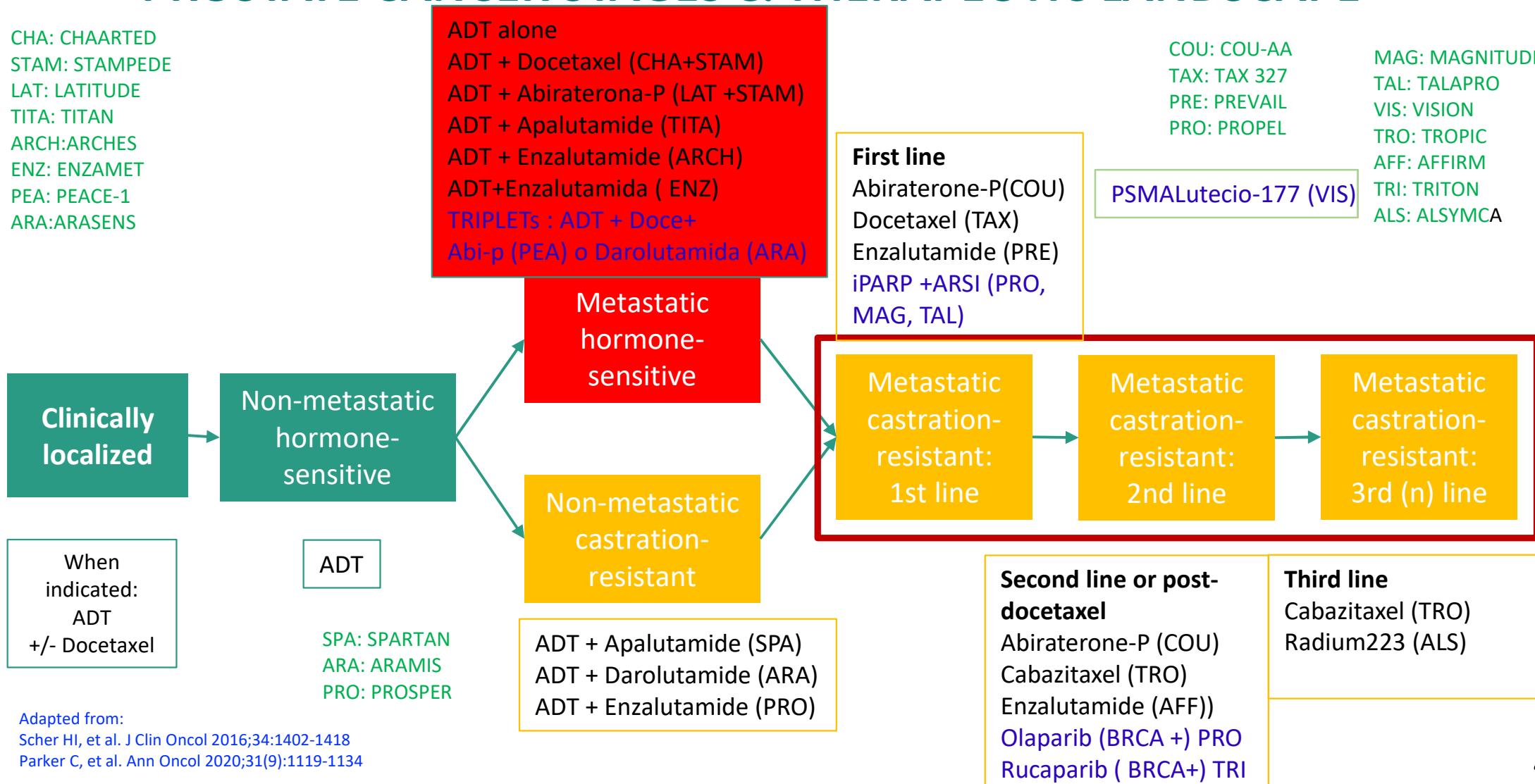


PROSTATE CANCER STAGES & THERAPEUTIC LANDSCAPE

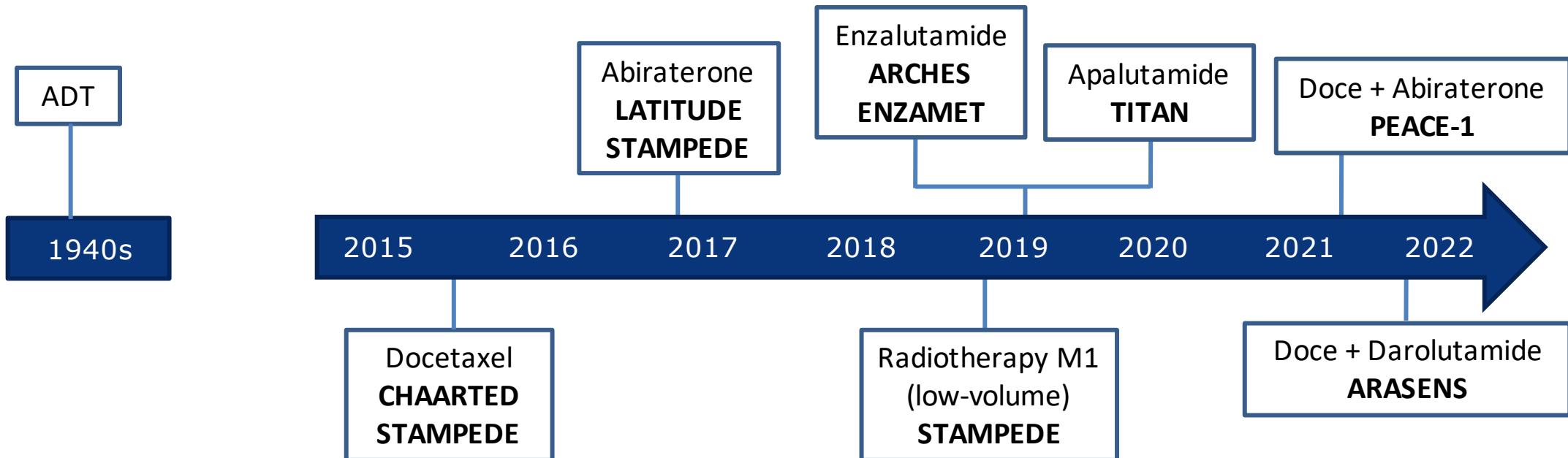
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Cáncer de Próstata Hormonosensible metastásico



mCPSC: cuestiones que importan

1. ¿Está indicado tratar sólo con ADT?
2. ¿Sigue siendo válidas la clasificaciones por volumen/riesgo y presentación *de novo*/metacróna de la enfermedad?
3. ¿Cuándo están indicados los tripletes de QT+ADT+ARSI vs dobletes QT+ADT o ARSI+ADT?
4. ¿Ayuda la biología molecular?

GU research consortium (GURC) national multicenter cohort study 2018 - 2021.



Treatment in mHSPC

Overall Patients (n= 189)

Treatment in mHSPC	Overall Patients (n= 189)
ADT alone	51 (27%)
Abiraterone	86 (45%)
Apalutamide	33 (17%)
Enzalutamide	6 (3%)
Docetaxel	15 (8%)

Yip et al. J Clin Oncol, 40, no. 6_suppl (February 20, 2022) 86-86.

RESULTADOS EN SUPERVIVENCIA GLOBAL COMPARADO ADT VERSUS INTENSIFICACIÓN CON ARSI O DOCETAXEL

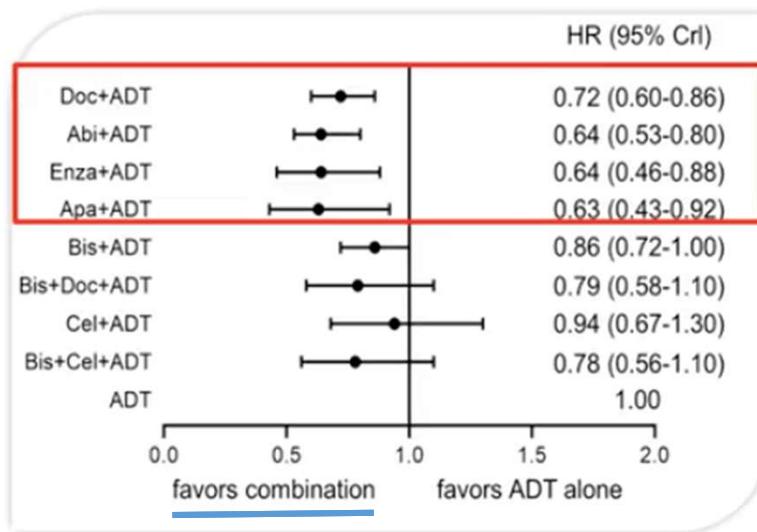
DOCETAXEL	CHAARTED	Median follow-up: 53.7 months, Median OS: 57.6 months vs 47.2 months	HR=0.72
	STAMPEDE-C	Median follow-up: 78.2 months, Median OS: 59.1months vs 43.1 months	HR=0.81
ABIRATERONE	LATITUDE	Median follow-up: 51.8 months, Median OS: 53.3 months vs 36.5 months	HR=0.66
	STAMPEDE-G	Median follow-up: 73.2 months, Median OS: 79.2 months vs 45.6 months	HR=0.60
ENZALUTAMIDE	ENZAMET	Median follow-up: 34.0 months, OS at 3 years 80% vs 72%	HR=0.67
	ARCHES	Median follow-up: 44.6 months, Median OS: NR vs NR	HR=0.66
APALUTAMIDE	TITAN	Median follow-up: 44.0 months, Median OS: NR vs 52.2 months	HR=0.65

Kyriakopoulos CE et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. Clarke NW et al. Annals of Oncology30:1992-2003, 2019. Fizazi K et al. Lancet Oncol 2019 May; 20(5):686-700. James N et al. 2020 ESMO. Davis IA et al. N Engl J Med 2019;381:121-131. Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25. Chi KN et al. J Clin Oncol. 2021 39:2294-2303.

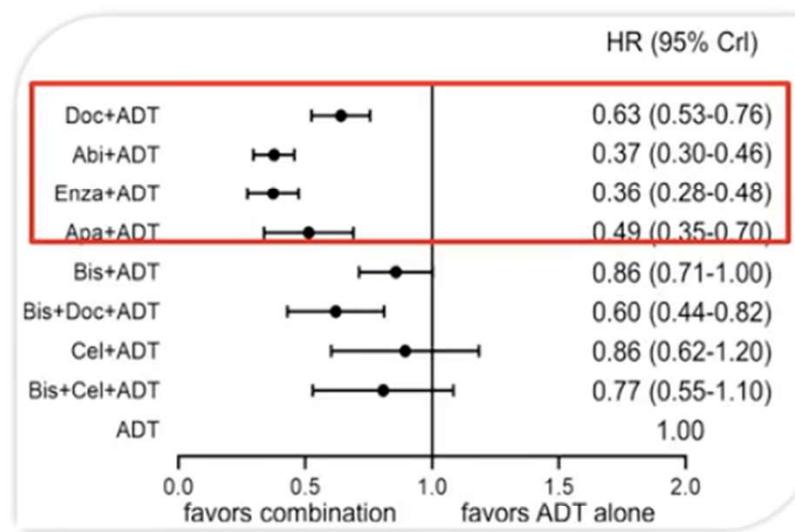
ARI: INHIBIDORES DE RECEPTOR ANDROGÉNICO/SÍNTESIS ANDROGÉNICA ÚLTIMA GENERACIÓN

Progress Report 2015-2020
Meta-Analysis: Combination Therapy Better Than ADT Alone :

Overall Survival



Failure free survival



Earlier ASI treatment seems Better stage-related increments in survival benefit with ASIs

Disease stage	Phase 3 trials	Median OS Active arm (months)	Median OS Control arm (months)	HR (95% CI)	Δ survival (months)
mCRPC post-taxanes	COU-AA-301 ¹	15.8	11.2	0.74 (0.64–0.86)	4.6
mCRPC post-taxanes	AFFIRM ²	18.4	13.6	0.63 (0.53–0.75)	4.8
mCRPC pre-taxanes	COU-AA-302 ³	34.7	30.3	0.81 (0.70–0.93)	4.4
mCRPC pre-taxanes	PREVAIL ⁴	35.5	31.4	0.83 (0.75–0.93)	4.1
mHSPC	LATITUDE⁵	53.3	36.5	0.66 (0.56–0.78)	16.8

CI, confidence interval; HR, hazard ratio; OS, overall survival.

A total of 16 positive and NO negative phase 3 trials reported to date
7 in mHNPC : LATITUDE, STAMPEDE, ARCHES, ENZAMET, TITAN, PEACE-1, ARASENS 10

mCPSC: cuestiones que importan

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4. ¿Ayuda la biología molecular?

CPSCM1

GRUPOS PRONÓSTICO

VOLUMEN-RIESGO-DE NOVO

GETUG 15

Criterios Glass
50% bueno
29% Int.
21% malo

CHAARTED

Alto volumen 65%
Bajo 35%
4 mets (1 fuera
axial)
Viscerales
pulmonares/hepát.

LATTITUDE

Al menos 2:
 ≥ 3 mets óseas
Gleason ≥ 8
Mets viscerales

STAMPEDE

M0 38%
M1 62% (59%
novo)
No
clasificación
de riesgo

ALTO VOLUMEN

ALTO RIESGO

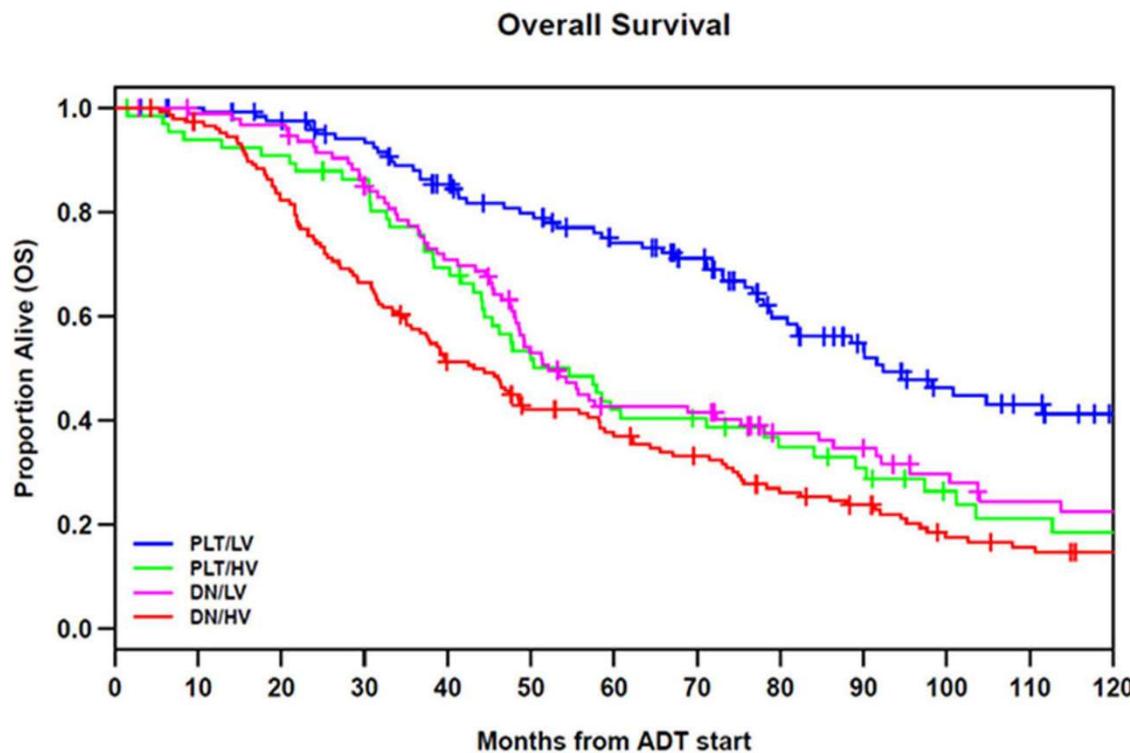
DE NOVO



BAJO

ALTO

Diferente pronóstico



Tto previo/Bajo Vol: 7,7 años

Tto previo/Alto Vol: 4,6 años

De Novo/Bajo Vol: 4,3 años

De Novo/Alto Vol: 3,6 años

Francini E, Prostate 2018

Cáncer de Próstata Hormonosensible metastásico

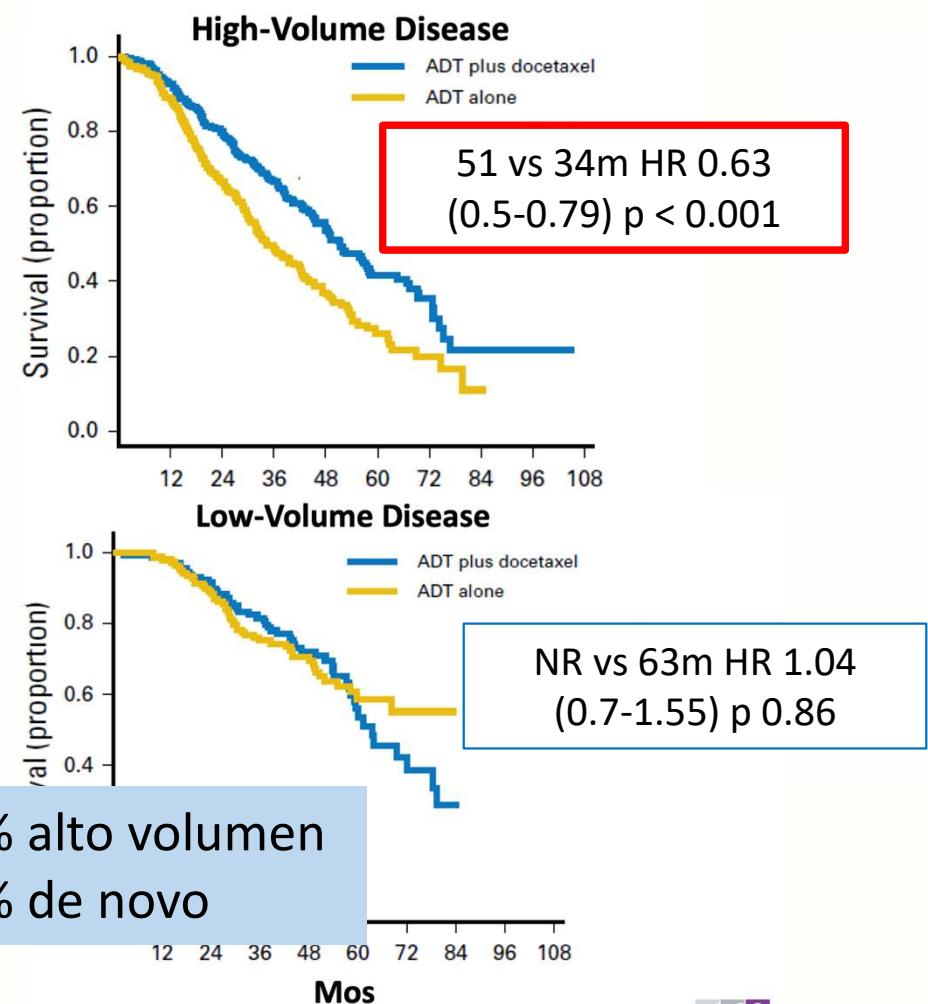
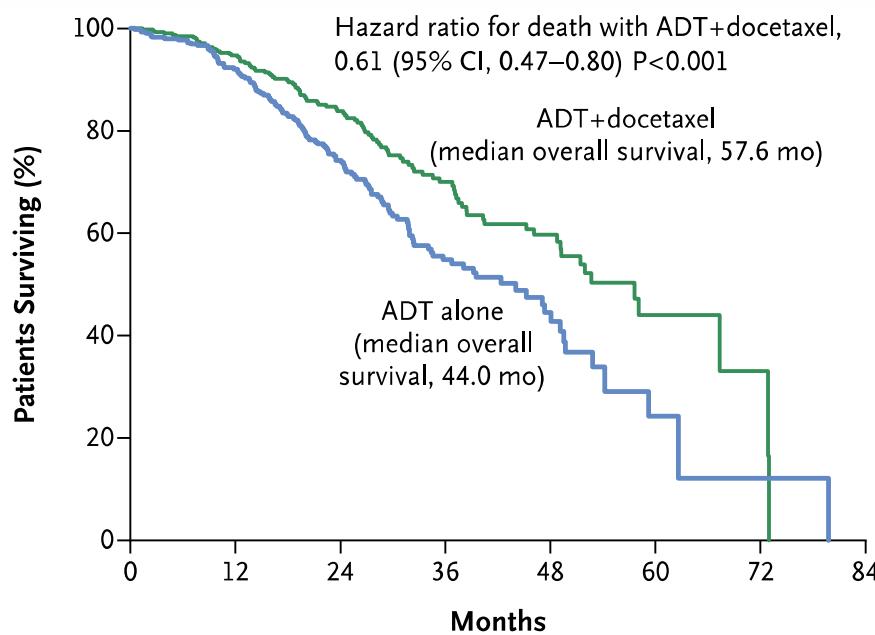
	Treatment		Docetaxel mHSPC	High volume	Visceral mts	Local treatment	<i>de novo</i> M1
	Experimental	Control					
CHAARTED	Docetaxel + ADT	ADT	--	64.9%	15%	27.2%	72.8%
STAMPEDE	Docetaxel + ADT	ADT	--	56%	6%	5%	95%*
STAMPEDE	Abiraterone +ADT	ADT	--	55%	6%	6%	95%†
LATITUDE	Abiraterone +ADT	ADT	--	79%	19%	--	100%
ARCHES	Enzalutamide + ADT	ADT +/- Doce	17.8%	63.2%	??	12-26%	66.6%
ENZAMET	Enzalutamide + ADT	ADT+AA +/-Doce	44%	52.3%	11.5%	42%	60.6%
TITAN	Apalutamide + ADT	ADT +/- Doce	10.7%	62.8%	12.1%	16.4%	80%

No ensayos clínicos que comparan diferentes esquemas

DOCETAXEL

CHAARTED

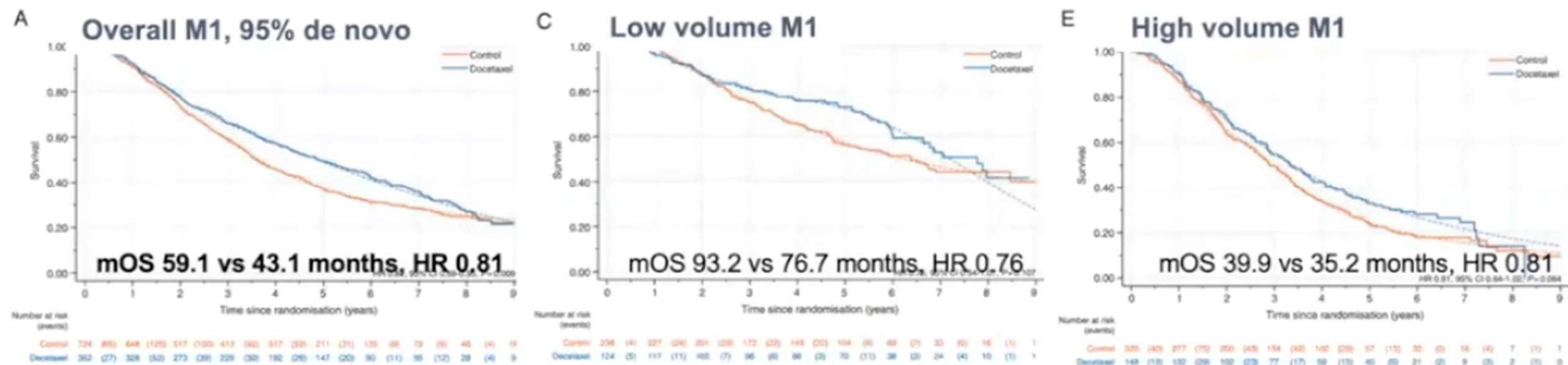
*Primary end point: OS
ITT*



ADT + Docetaxel

STAMPEDE 2018: updated OS analysis for M1 patients, median FU 78.2 months

Clarke et al. Annals of Oncology 30: 1992–2003, 2019



In STAMPEDE, benefit of docetaxel did not seem to differ by volume of disease

ADT + Docetaxel

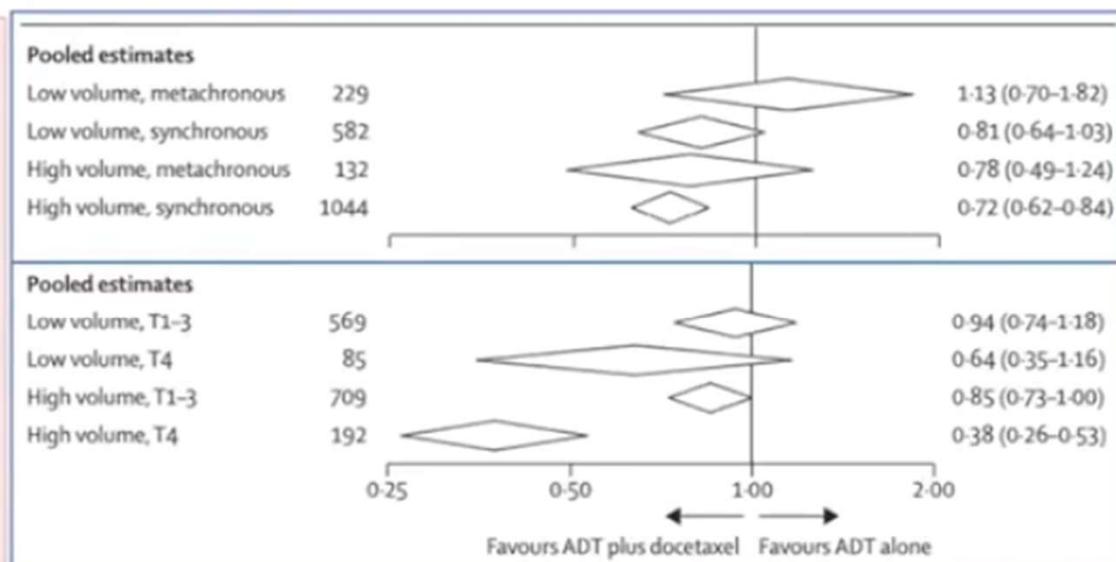
STOPCAP meta-analyses: GETUG, CHARTED, STAMPEDE

	GETUG-AFU15 ^a	CHAARTED ^b	STAMPEDE ^c
Accrual period	October, 2004, to December, 2008	July, 2006, to November, 2012	November, 2005, to March, 2013
Number of patients randomly assigned	385	790	1086
Control group treatment	ADT (LHRH agonist or LHRH antagonist plus anti-androgen therapy or surgical castration)	ADT (LHRH agonist or LHRH antagonist or surgical castration); oral calcium carbonate 500 mg daily; oral vitamin D 400 IU daily	ADT (GRH agonists or antagonists or orchidectomy)
Intervention group treatment	ADT (LHRH agonist or LHRH agonist plus antiandrogen therapy or surgical castration) plus docetaxel (75 mg/m ²) intravenously every 3 weeks for a maximum of nine cycles; premedication with an oral corticosteroid (8 mg dexamethasone or equivalent) the evening before, on the day of, and on the day after docetaxel infusion plus subcutaneous injection of G-CSF from day 5 for 5 days	ADT (LHRH agonist or LHRH antagonist or surgical castration) plus docetaxel (75 mg/m ²) intravenously every 3 weeks for six cycles; oral dexamethasone (8 mg approximately 12 h, 3 h, and 1 h before docetaxel); oral diphenhydramine optional; 500 mg oral calcium carbonate once daily; 400 IU oral vitamin D once daily	ADT (GRH agonists or antagonists or orchidectomy) plus docetaxel (75 mg/m ²) intravenously every 3 weeks for six cycles plus oral prednisolone (10 mg once daily)
Median follow-up for all participants (IQR, months)*	84 (79–89)	54 (42–67)	78 (63–96)

ADT=androgen deprivation therapy; G-CSF=granulocyte-colony stimulating factor; GRH=gonadotropin-releasing hormone; LHRH=luteinising hormone-releasing hormone.
*Data supplied for inclusion in the meta-analysis, and follow-up duration for each trial is in keeping with the most recent version of reported trial analysis, as cited.

Table 1: Trial design details and key participant characteristics

Overall survival

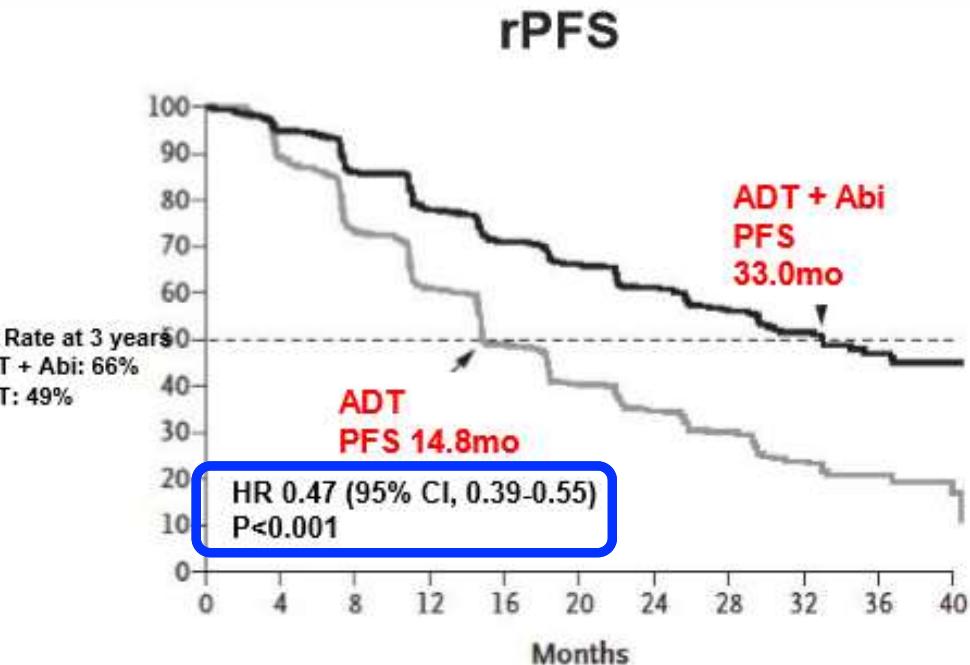
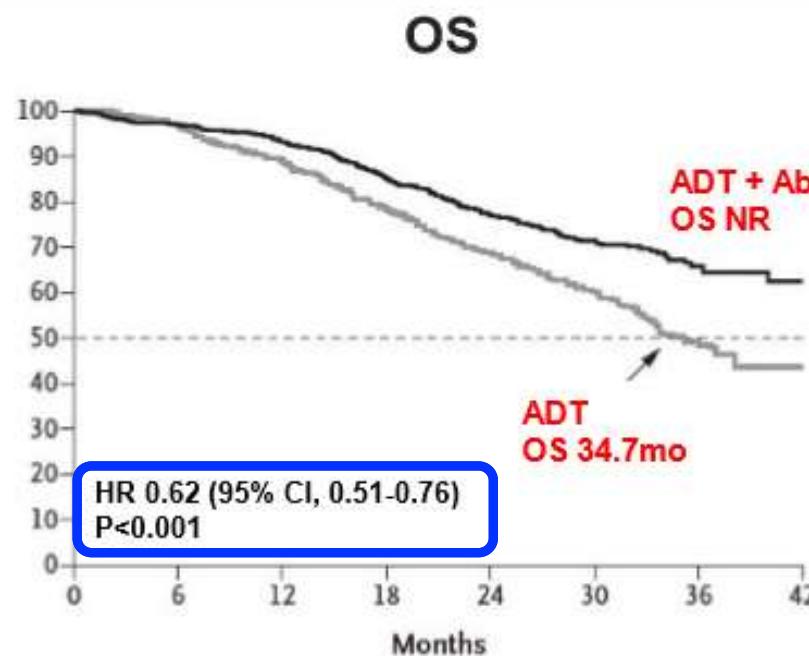


Vale et al. Lancet Oncol 2023; 24: 783–97

ADT + docetaxel benefit mostly in high volume disease and potentially patients with bulky primary tumours

ABIRATERONA

LATITUDE



Patient Reported Outcomes

- Improved pain
- Improved HRQoL

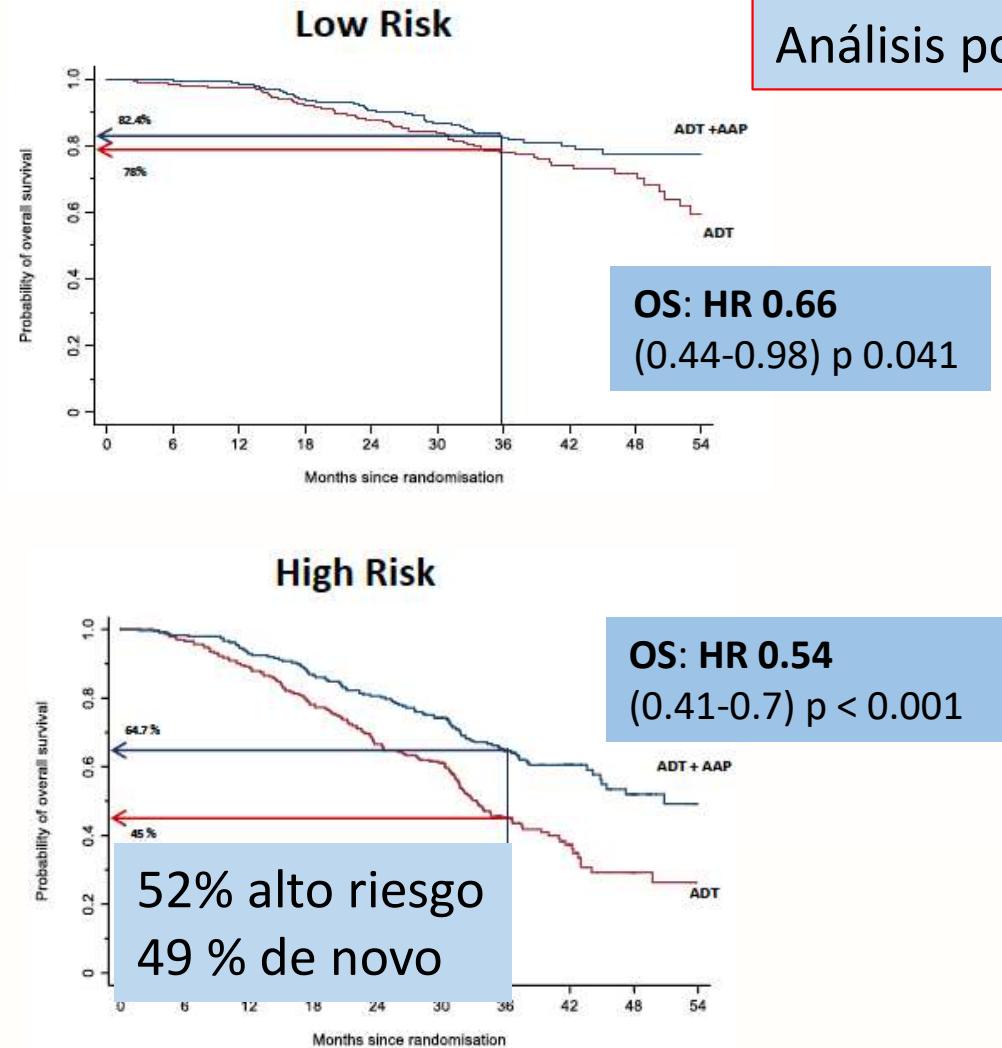
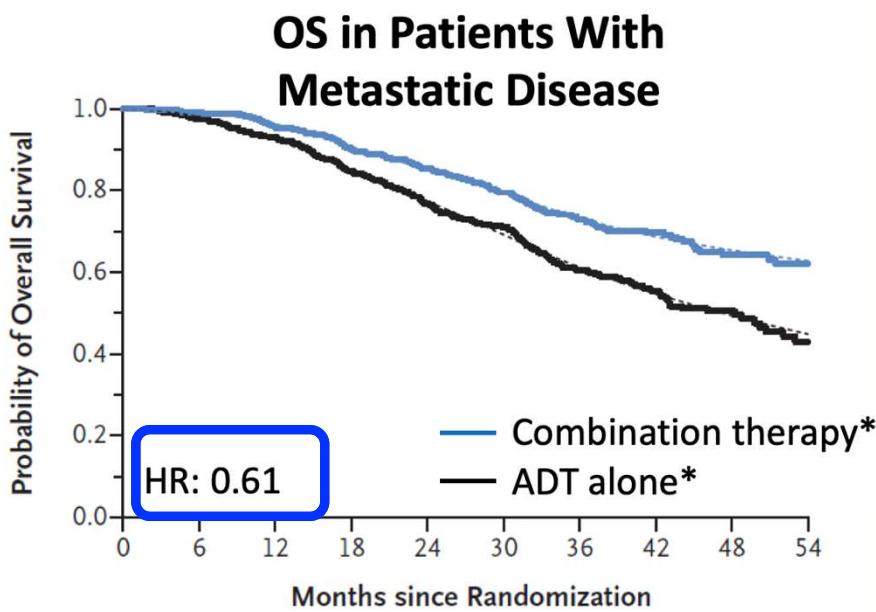
100% alto riesgo
100% de novo

Median follow-up: 30.4 months

1. Fizazi et al. ASCO 2017; 2. Fizazi et al. NEJM 2017

ABIRATERONA

STAMPEDE-G

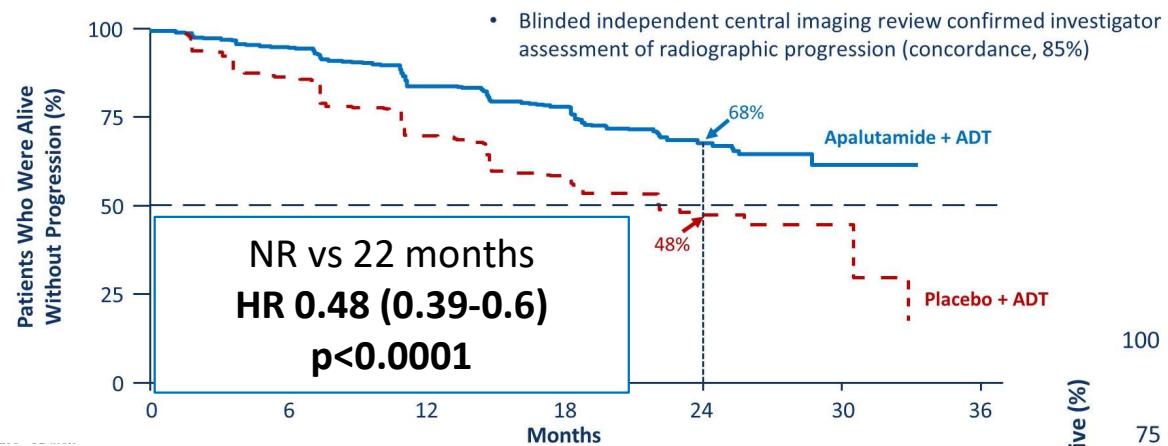


Análisis post HOC

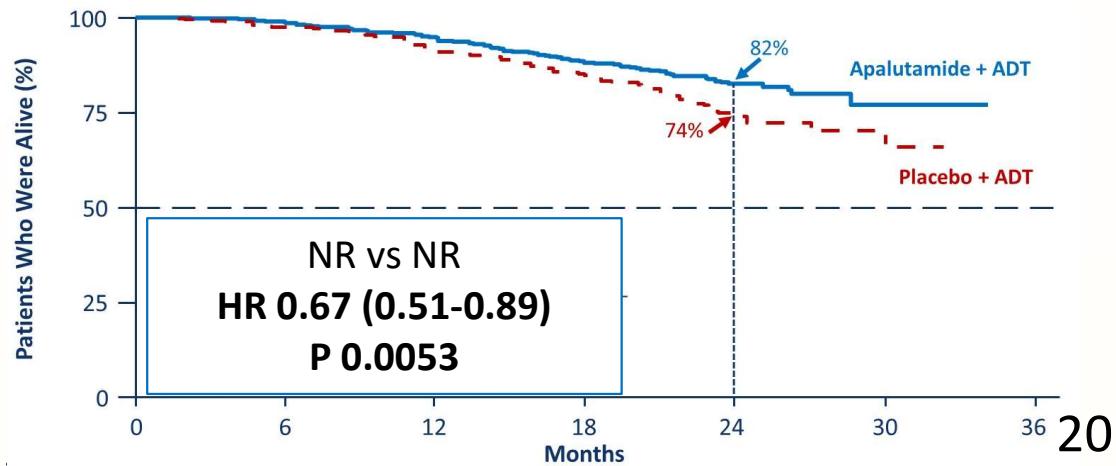
APALUTAMIDA

TITAN

Primary end-point: rPFS



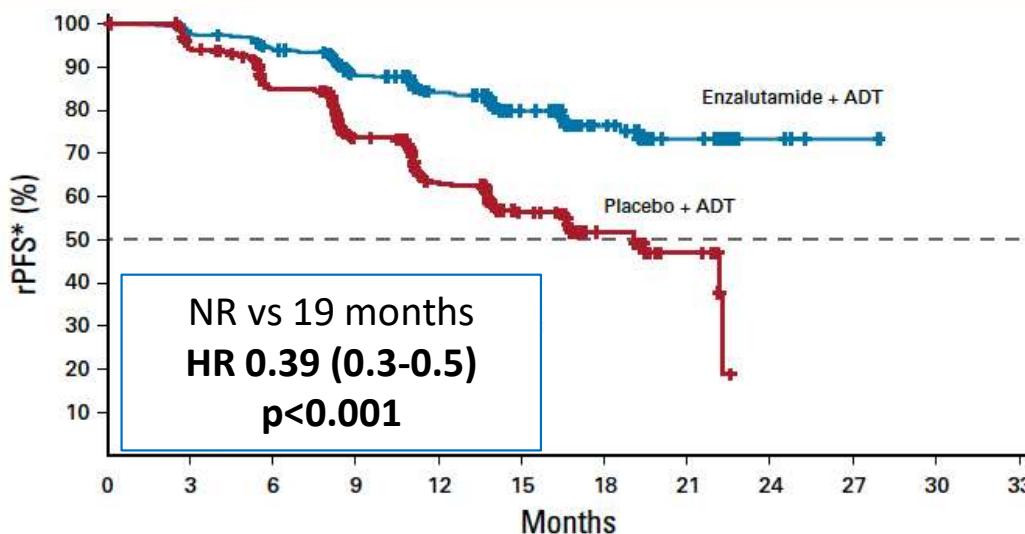
Primary end-point: OS



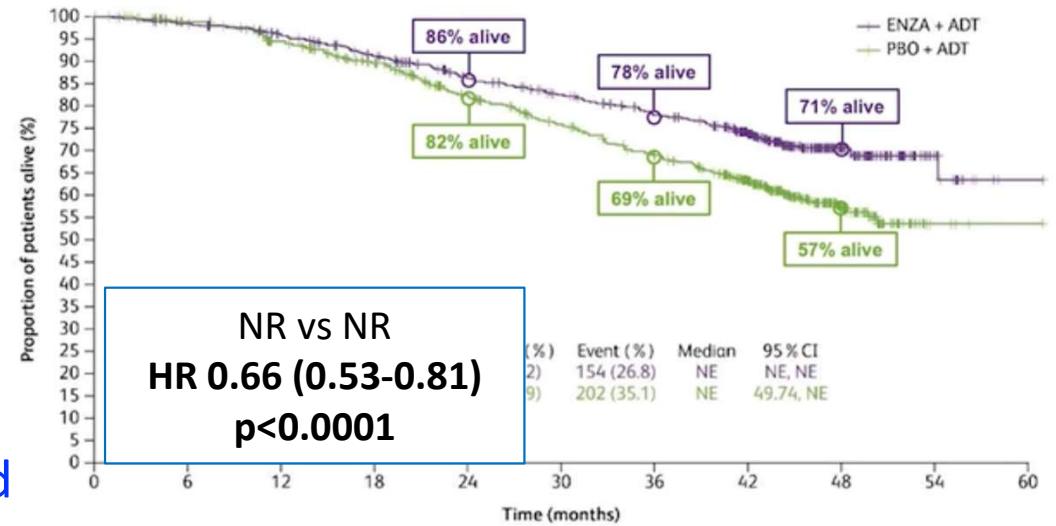
ENZALUTAMIDA

ARCHES

Primary end-point: rPFS



Secondary end-point: OS

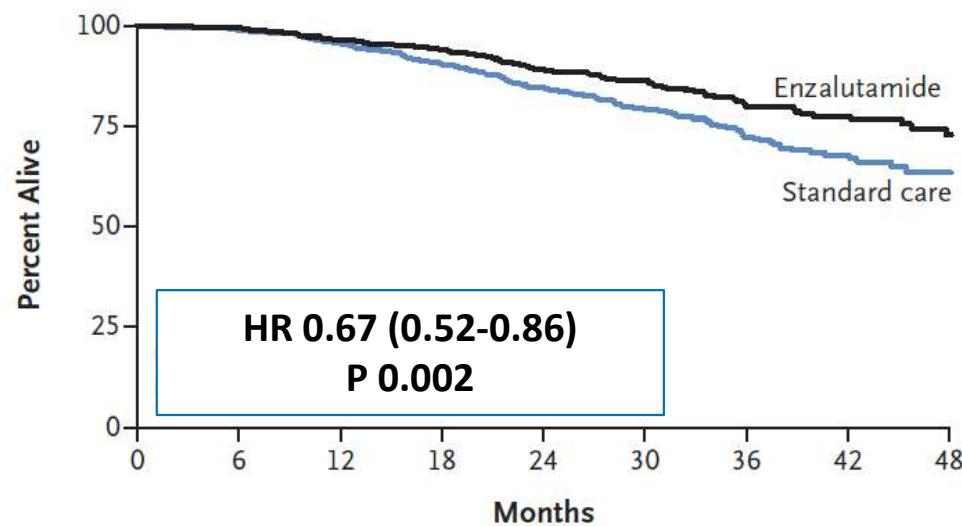


Armstrong A, et al. J Clin Oncol 2019; Presented by Armstrong A at ASCO 2021

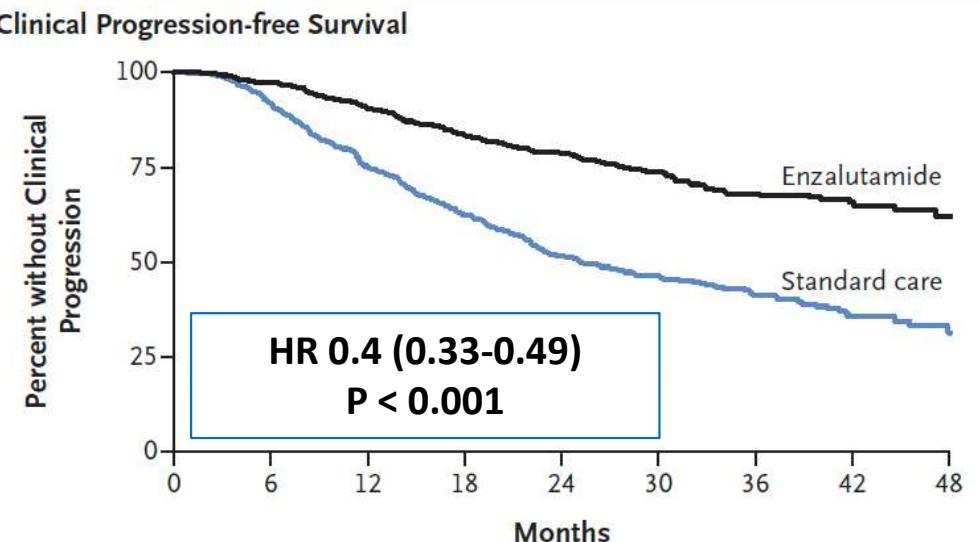
ENZALUTAMIDA

ENZAMET

Primary end-point: Overall Survival



Secondary end-point: PFS



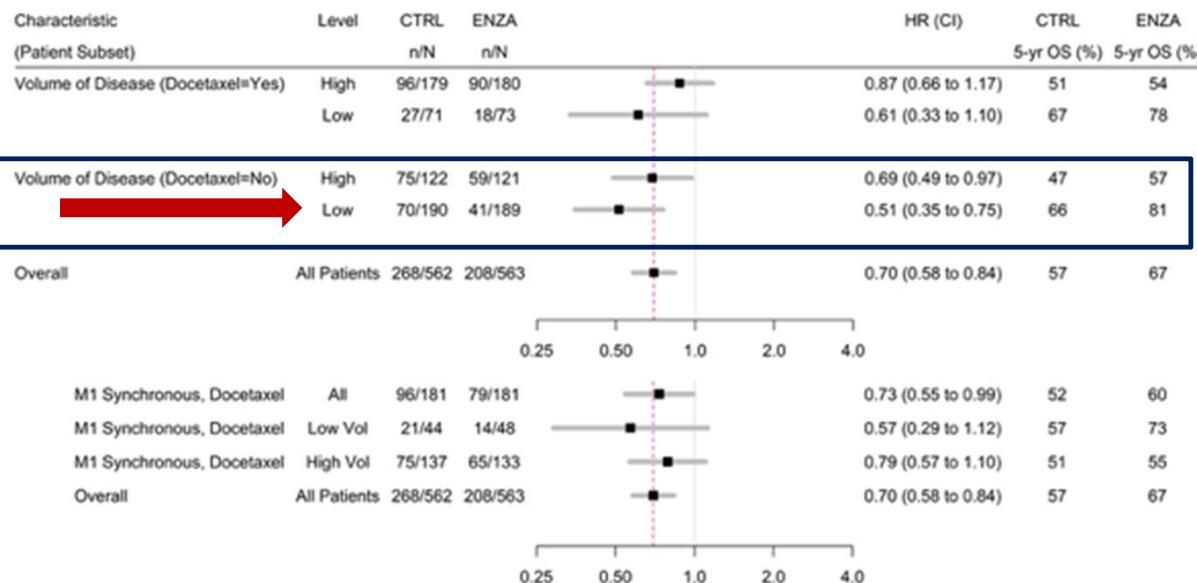
Davis ID, et al. NEJM 2019

Cáncer de Próstata Hormonosensible metastásico

ENZALUTAMIDA

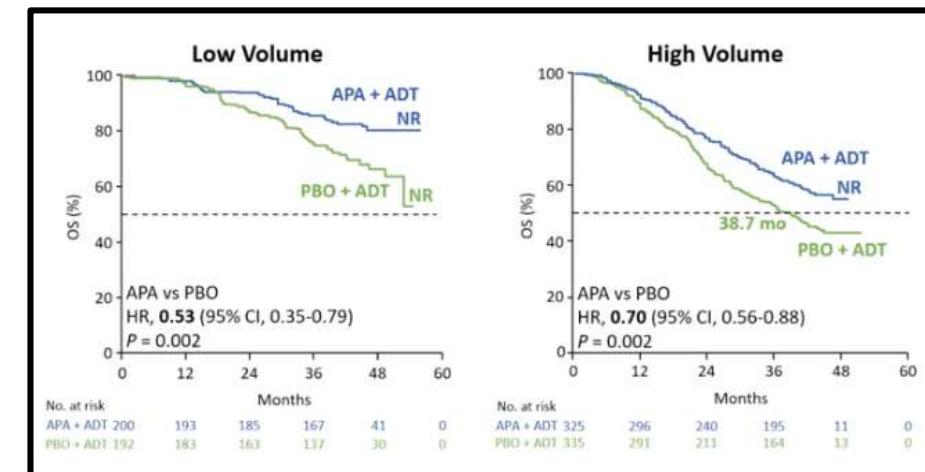
VOLUME OF DISEASE WITH ARSi

ENZAMET



APALUTAMIDA

TITAN



Trial	HR low-volume	HR high-volume
ENZAMET	0.54 (0.39-0.74)	0.79 (0.63-0.98)
ARCHES	0.66 (0.43-1.03)	0.66 (0.52-0.83)
TITAN	0.53 (0.35-0.79)	0.70 (0.56-0.88)

Armstrong AJ, JCO, 2022; Davis I, ASCO 2022, LBA 5004; Chowdhury S, EAU 2021

¿Determina el volumen de enfermedad la elección del tratamiento?

	ALTO VOLUMEN	BAJO VOLUMEN	
Docetaxel		(1)	
Abiraterona		(1)	
Enzalutamida		ENZAMET	
Apalutamida			

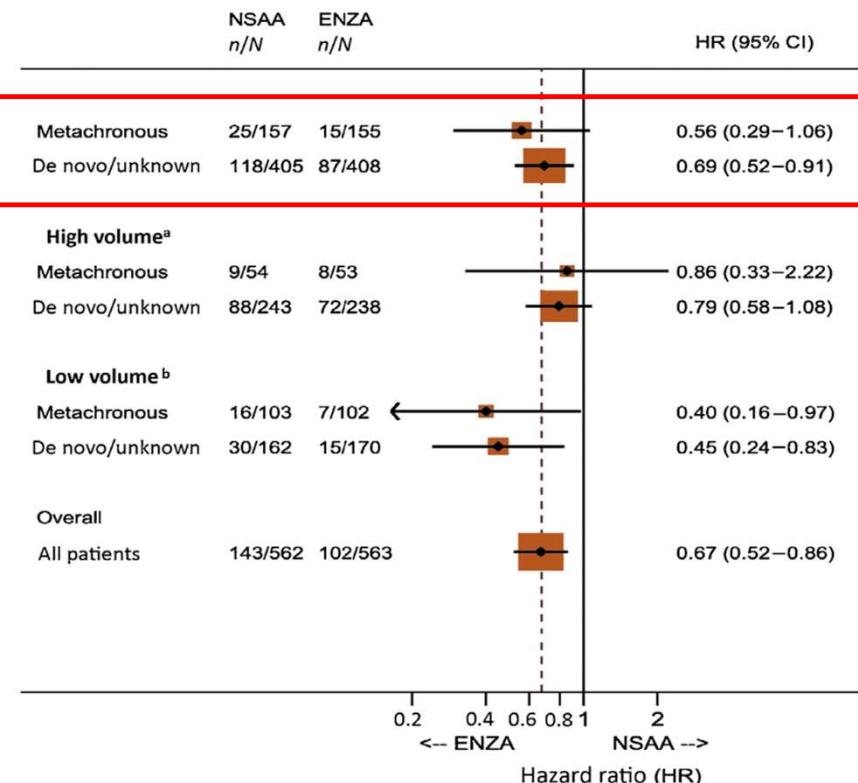
(1) *Post hoc, STAMPEDE TRIAL*

Armstrong AJ, JCO, 2022; Davis I, ASCO 2022; Armstrong AJ, ASCO GU 2022; Sweeney CJ, NEJM, 2015

PRESENTATION OF DISEASE

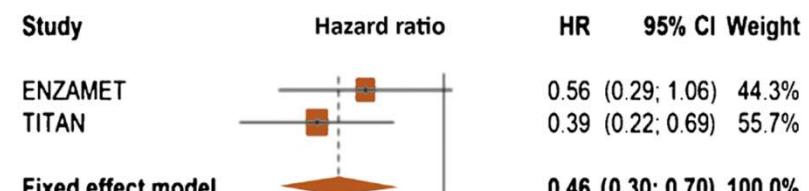
SYNCHRONOUS vs METACHRONOUS DISEASE: ENZAMET, ARCHES, TITAN trials

ENZAMET



Trial	<i>De novo</i>		Metachronous	
	N	HR	N	HR
ENZAMET	813	0.69 (0.29-0.91)	312	0.56 (0.29-1.06)
ARCHES	890	0.63 (0.50-0.79)	246	0.71 (0.41-1.21)
TITAN	852	0.72 (0.53-0.98)	144	0.40 (0.15-1.03)

Meta-analysis of OS in metachronous mHSPC



Armstrong AJ, JCO, 2022; Davis I, ASCO 2022; Armstrong AJ, ASCO GU 2022; Sweeney CJ, NEJM, 2015

¿Determina la presentación de la enfermedad la elección del tratamiento?

	<i>DE NOVO</i>	METÁCRONA
Docetaxel		
Abiraterona		
Enzalutamida		
Apalutamida		

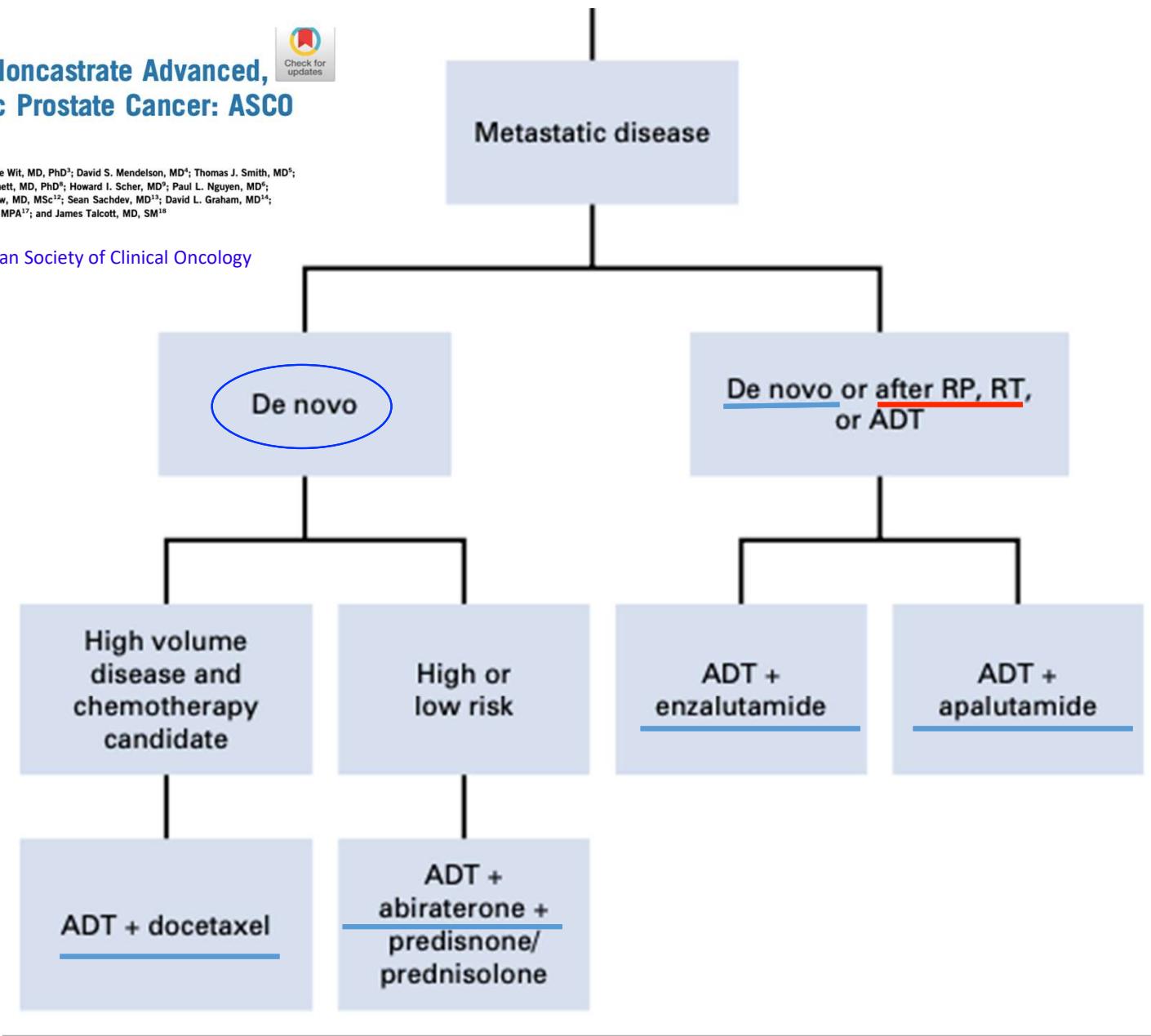
Armstrong AJ, JCO, 2022; Davis I, ASCO 2022; Armstrong AJ, ASCO GU 2022; Sweeney CJ, NEJM, 2015

Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update



Katherine S. Virgo, PhD, MBA¹; R. Bryan Rumble, MSc²; Ronald de Wit, MD, PhD³; David S. Mendelson, MD⁴; Thomas J. Smith, MD⁵; Mary-Ellen Taplin, MD⁶; James L. Wade III, MD⁷; Charles L. Bennett, MD, PhD⁸; Howard I. Scher, MD⁹; Paul L. Nguyen, MD¹⁰; Martin Gleave, MD¹¹; Scott C. Morgan, MD, MSc¹¹; Andrew Loblaw, MD, MSc¹²; Sean Sachdev, MD¹³; David L. Graham, MD¹⁴; Neha Vapiwala, MD¹⁵; Amy M. Sion, PharmD¹⁶; Virgil H. Simons, MPA¹⁷; and James Talcott, MD, SM¹⁸

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology



ADT + ARPI

Chemo

ARPI

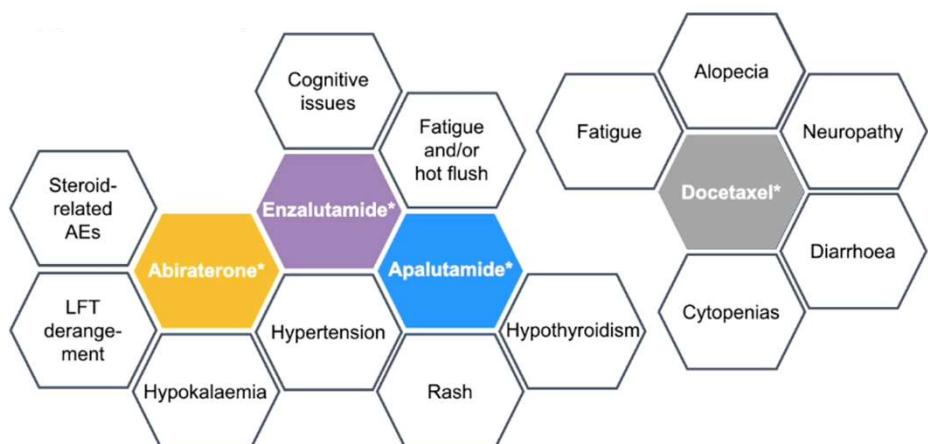
Trial	Regimen	OS Overall	OS high volume	OS low volume	
Chemotherapy	GETUG-AFU15	ADT +/- docetaxel	HR 0.88 (0.68 - 1.14)	HR: 0.78 (0.56-1.09)	HR 1.02 (0.67-1.55)
	CHAARTED	ADT +/- docetaxel	HR 0.72 (0.59 – 0.89)	HR 0.63 (0.50 – 0.79)	HR 1.04 (0.70 – 1.55)
	STAMPEDE	ADT +/- docetaxel	HR 0.78 (0.66 – 0.93)	HR 0.81 (0.64 – 1.02)	HR 0.76 (0.54 – 1.07)
	LATITUDE	ADT +/- abiraterone	HR 0.66 (0.56–0.78)	HR 0.58 (0.41 - 0.83)	HR 0.69 (0.58 – 0.82)
ARPI	STAMPEDE	ADT +/- abiraterone	HR 0.61 for M1	HR 0.54 (0.41 – 0.70)	HR 0.66 (0.44 – 0.98)
	TITAN	ADT +/- apalutamide	NR vs 52.2 mo, HR 0.65	HR 0.70 (0.56 – 0.88)	HR 0.53 (0.35-0.79)
	ARCHES	ADT +/- enzalutamide	NR vs NR HR 0.66	HR 0.66 (0.52-0.83)	HR 0.66 (0.43 – 1.02)
	ENZAMET	ADT (+/- docetaxel) +/- enzalutamide	HR 0.70 (0.58–0.84)	HR 0.79 (0.63–0.98)	HR 0.54 (0.39–0.74)

ADT + ARPI improves OS across disease spectrums in mCSPC

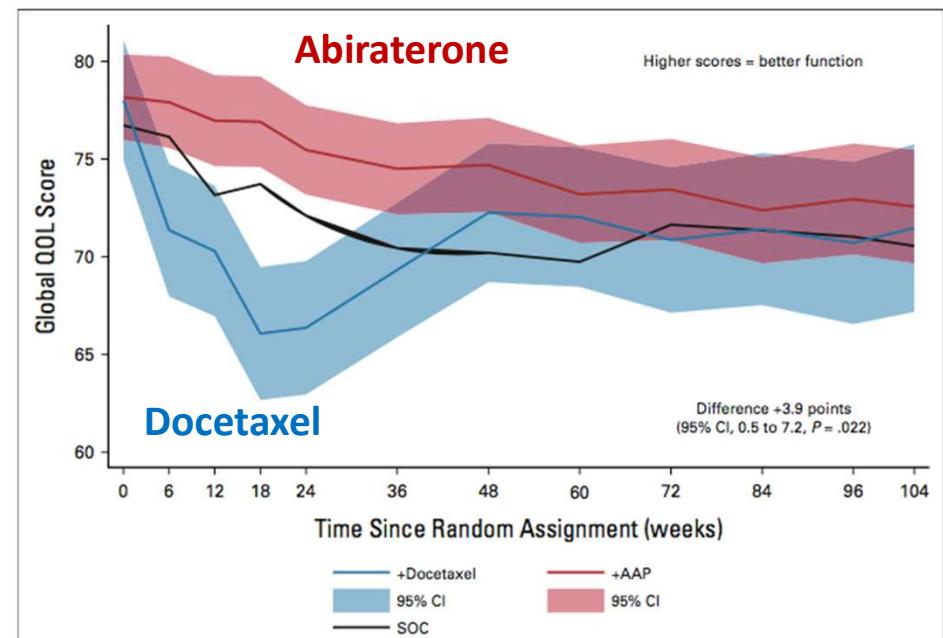
Cáncer de Próstata Hormonosensible metastásico

TOXICIDAD y CALIDAD DE VIDA comparativas

	CHAARTED		STAMPEDE		LATITUDE		STAMPEDE		ARCHEs		ENZAMET		TITAN	
	Doc	SOC	Doc	SOC	Abi	SOC	Abi	SOC	Enza	SOC	Enza	SOC	Apa	SOC
Any AE grade ≥ 3	29.6%	NR	52%	32%	63%	48%	47%	33%	24.3%	25.6%	57%	43%	42.2%	40.8%



1. Janssen-Cilag International NV. Abiraterone Summary of Product Characteristics. June 2022;
2. Astellas Pharma Europe BV. Enzalutamide Summary of Product Characteristics. July 2022;
3. Janssen-Cilag International NV. Apalutamide Summary of Product Characteristics. December 2022;
4. Sanofi Genzyme IP. Docetaxel Summary of Product Characteristics. December 2020;
5. Speaker's expert opinion.



Sweeney CJ, NEJM, 2015; James ND, Lancet, 2016; Fizazi K, NEJM, 2017; James ND, NEJM, 2017; Armstrong AJ, JCO, 2019

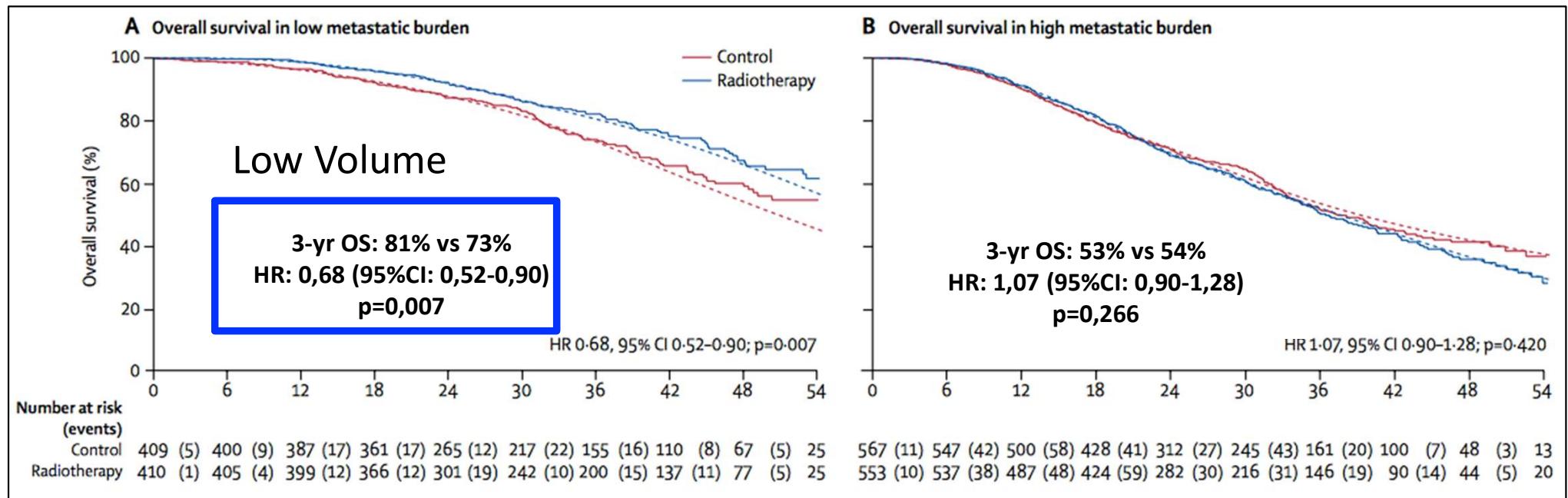
Davis ID, NEJM, 2019; Chi KN, NEJM, 2019; Chi K, JCO, 2021; Rush A, Ann Oncol, 2021

VALOR del Tratamiento local

TRATAMIENTO LOCAL (M1 de novo)

ESTUDIO STAMPEDE

Brazo H → Radioterapia en Cáncer Próstata Hormonosensible metastásico



James N. NEJM 2017

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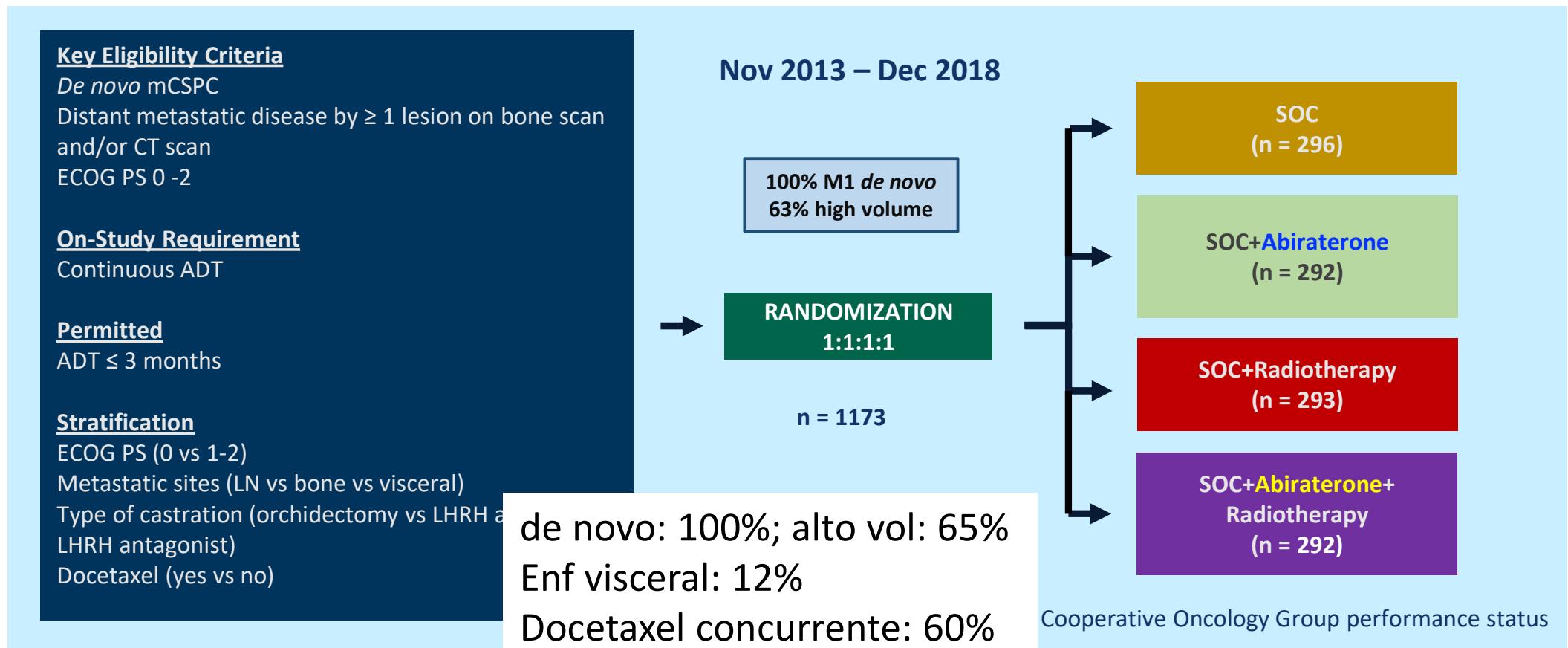
Cáncer de Próstata Hormonosensible metastásico

	Treatment		Docetaxel mHSPC	High volume	Visceral mts	Local treatment	<i>de novo</i> M1
	Experimental	Control					
CHAARTED	Docetaxel + ADT	ADT	--	64.9%	15%	27.2%	72.8%
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STAMPEDE	Abiraterone +ADT	ADT	--	55%	6%	6%	95%†
LATITUDE	Abiraterone +ADT	ADT	--	79%	19%	--	100%
ARCHES	Enzalutamide + ADT	ADT +/- Doce	17.8%	63.2%	??	12-26%	66.6%
ENZAMET	Enzalutamide + ADT	ADT+AA +/-Doce	44%	52.3%	11.5%	42%	60.6%
TITAN	Apalutamide + ADT	ADT +/- Doce	10.7%	62.8%	12.1%	16.4%	80%
PEACE-1	Abi + Doce + ADT	ADT + Doce	100%	64%	13%	--	100%
ARASENS	Daro + Doce + ADT	ADT + Doce	100%	77%	17.5%	13%	86%

Sweeney CJ, NEJM, 2015; James ND, Lancet, 2016; Fizazi K, NEJM, 2017; James ND, NEJM, 2017

Armstrong AJ, JCO, 2019; Davis ID, NEJM, 2019; Chi KN, NEJM, 2019; Chi K, JCO, 2021; Fizazi K, Lancet, 2022; Smith MR, NEJM, 2022

Design of PEACE-1 (2x2)

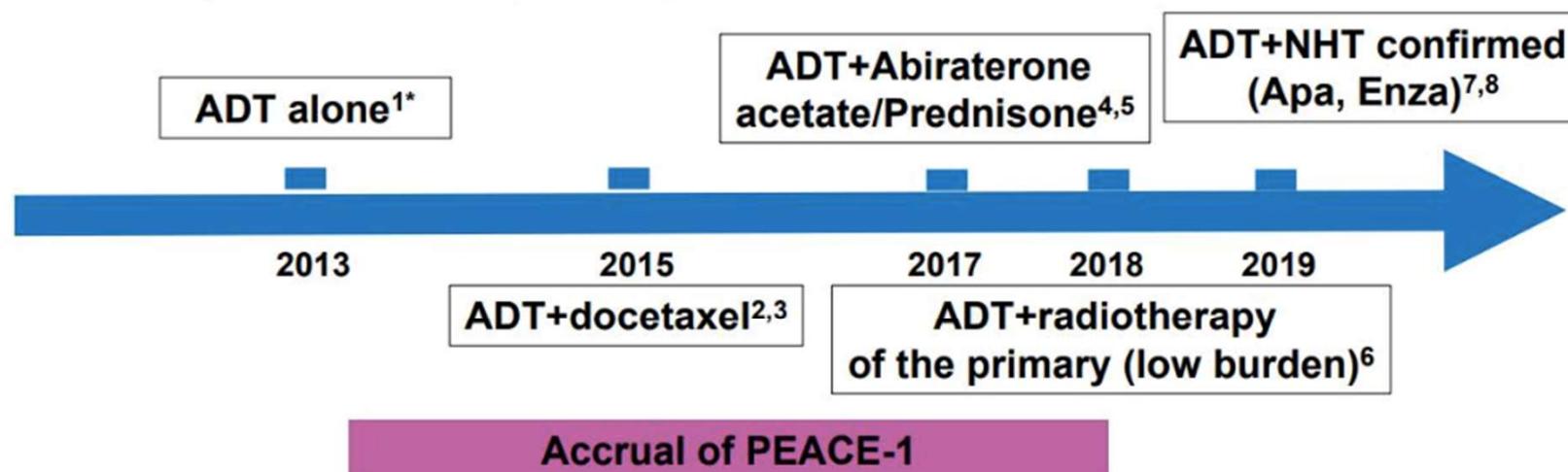




Background



Very rapidly evolving Standard of Care (SOC) for men with metastatic castration-sensitive prostate cancer (mCSPC)

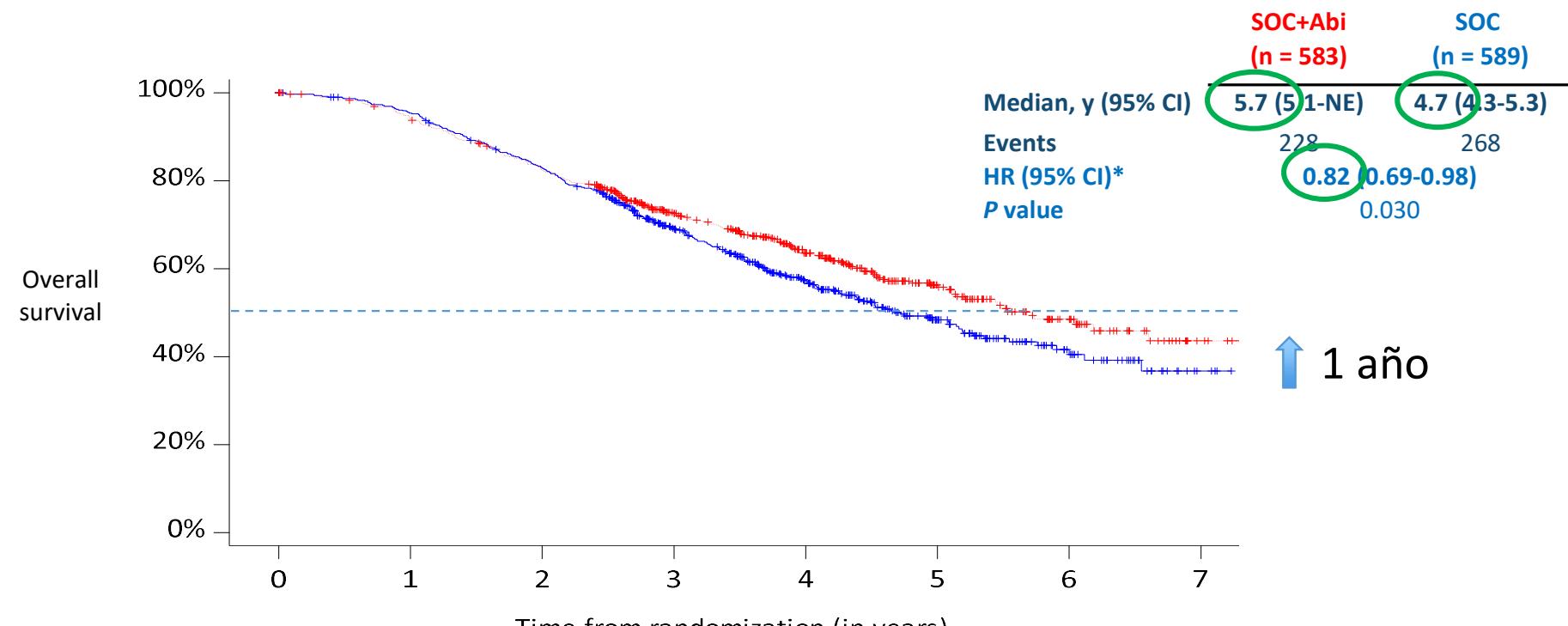


*ADT: Androgen Deprivation Thera

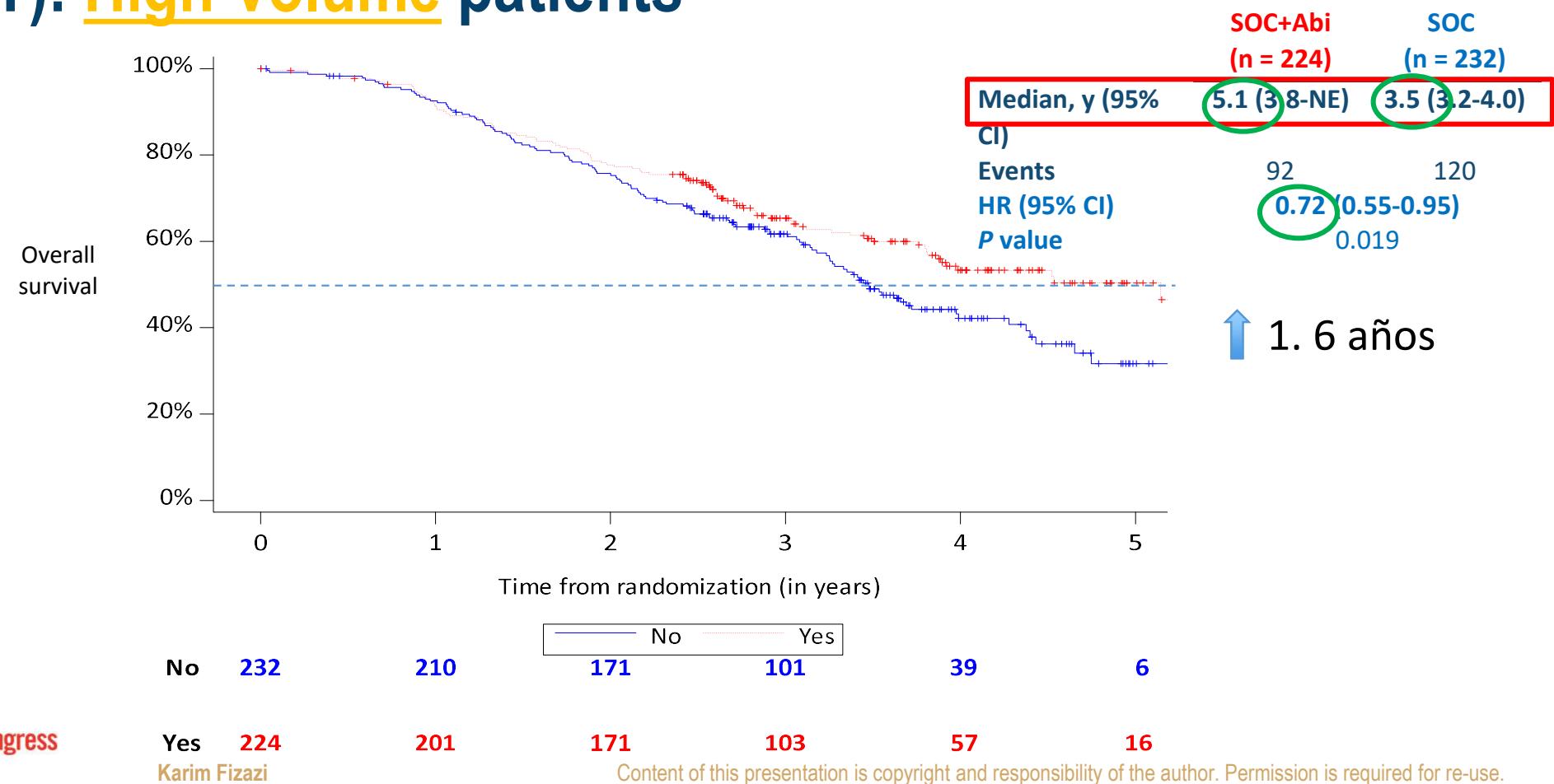


¹Gravis G, Lancet Oncol 2013, ²Sweeney C, NEJM 2015, ³James N, Lancet 2016, ⁴Fizazi K, NEJM 2017, ⁵James N, NEJM 2017, ⁶Parker C, Lancet 2018, ⁷Davis I, NEJM 2019, ⁸Chi K, NEJM 2019

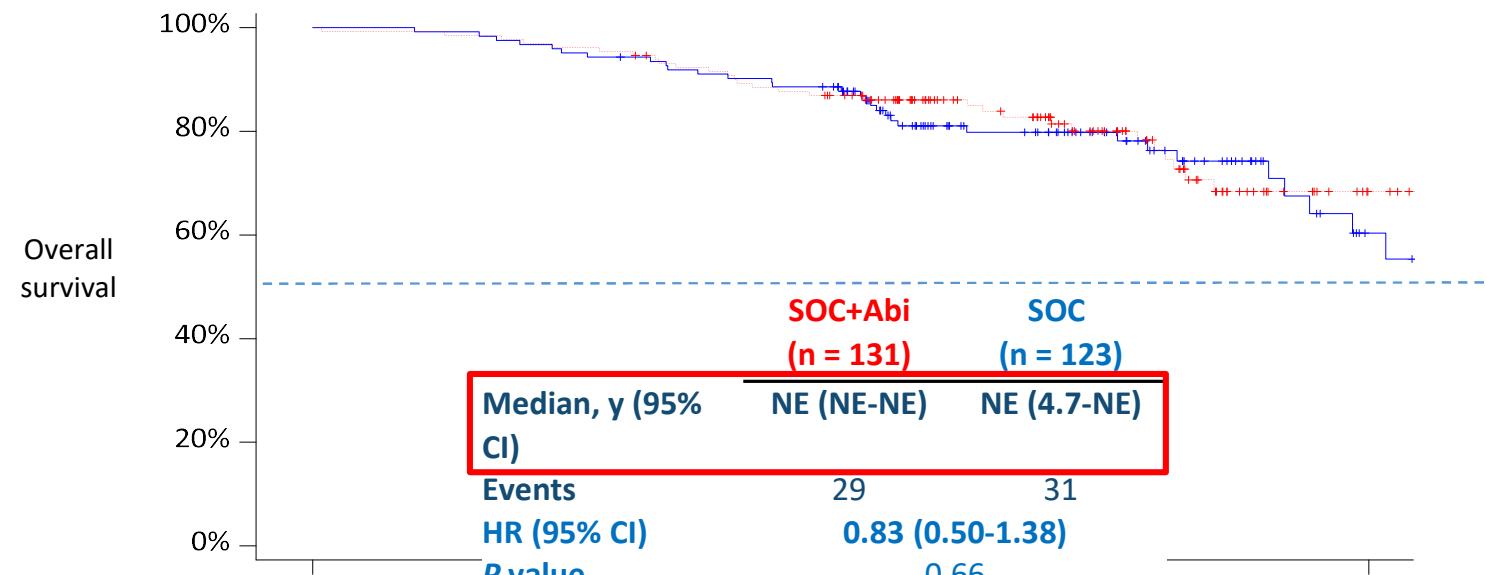
OS in the Overall population



OS with Abiraterone in the ADT+docetaxel (+/-RXT): High-volume patients



OS with Abiraterone in the ADT+docetaxel (+/-RXT): Low-volume patients



No	123	119	110	71	39	12
----	-----	-----	-----	----	----	----

No Yes

Yes	131	127	116	80	41	9
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ARASENS Study Design

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



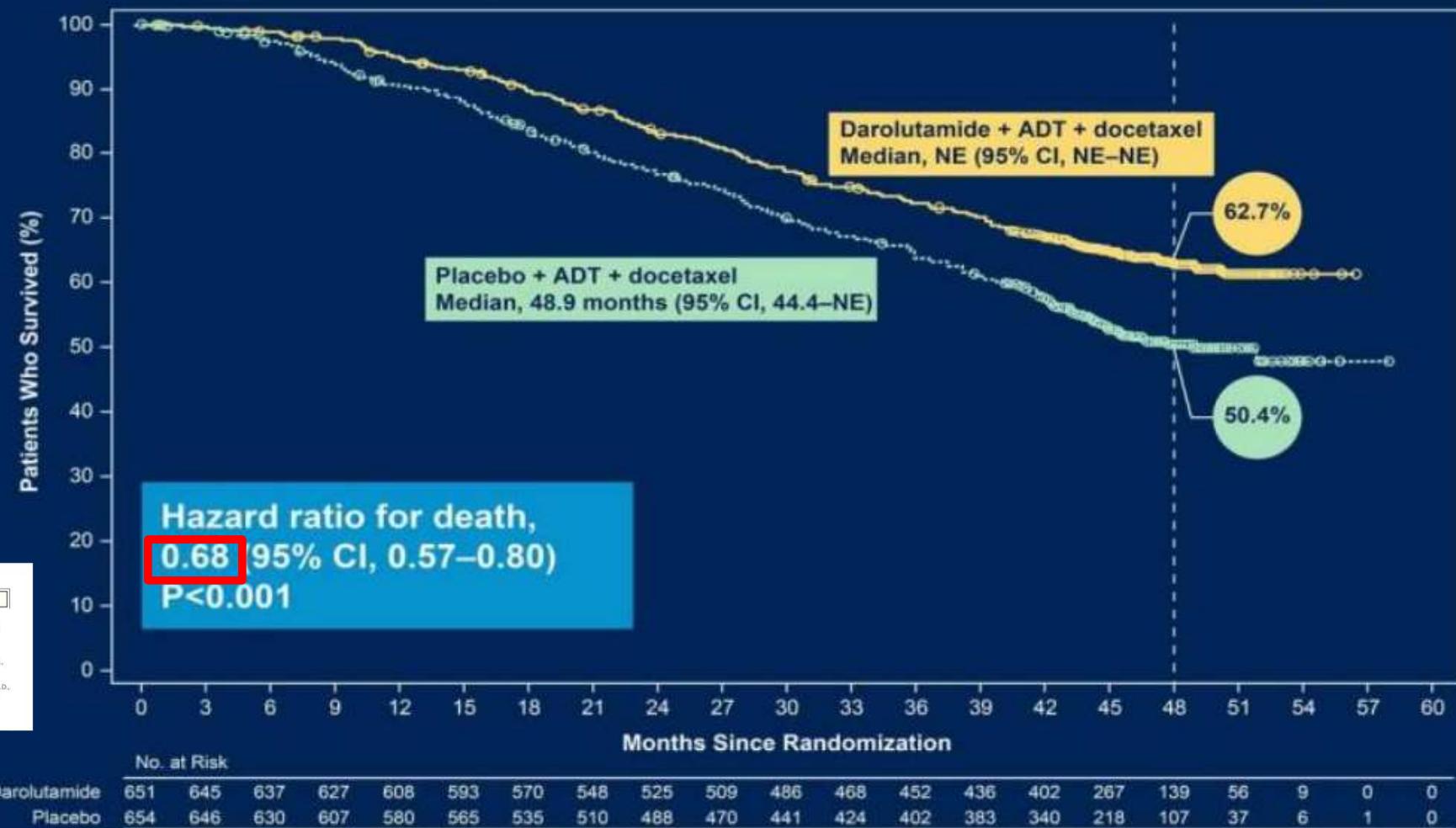
- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

Alto vol: 77%:de novo: 87%
Enf visceral: 17%
Docetaxel concurrente: 100%&

*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; FPPV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases \pm lymph node metastases; M1c, visceral metastases \pm lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

ARASENS Primary Endpoint*: Overall Survival

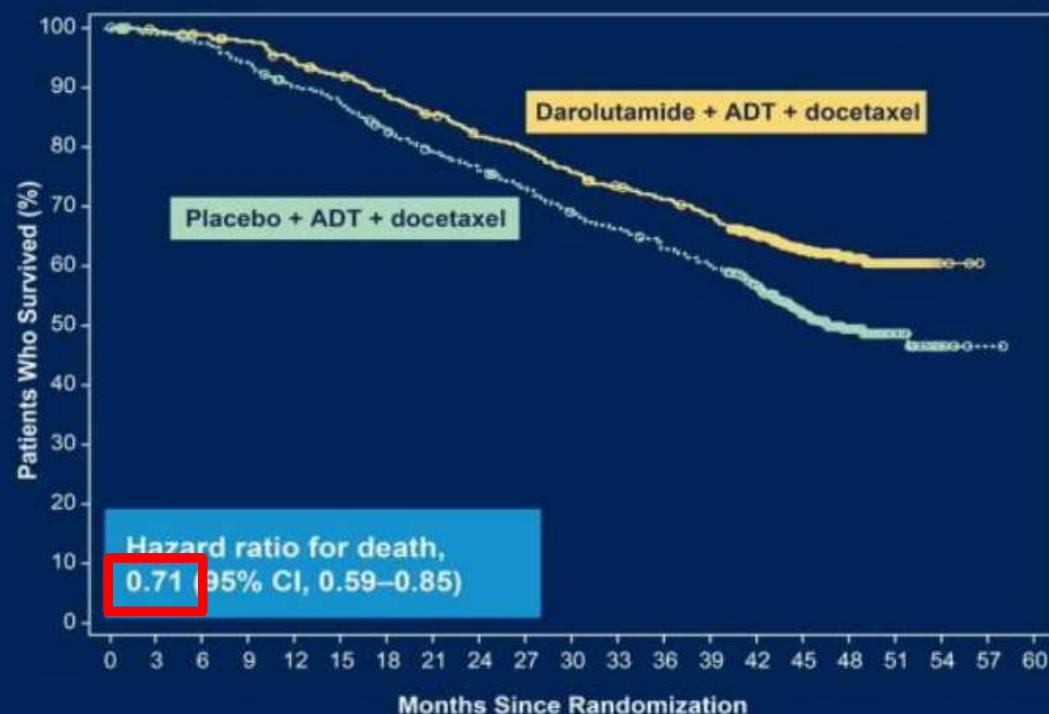
Darolutamide significantly reduced the risk of death by 32.5%



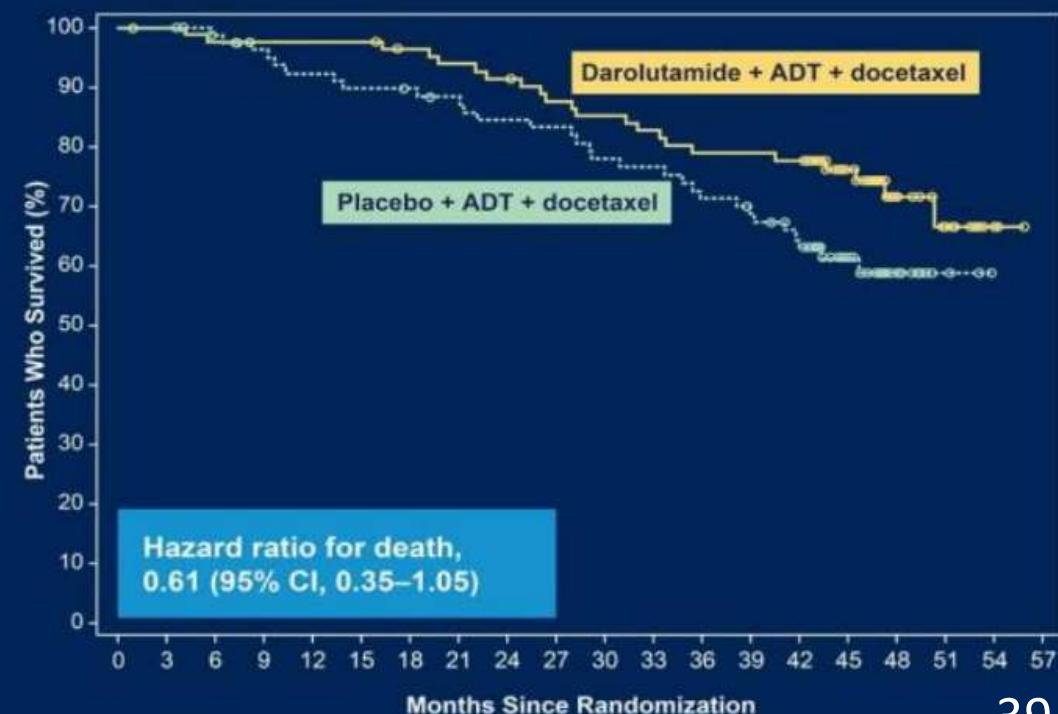
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Overall Survival By Metastatic Stage at Initial Diagnosis

De novo metastatic disease



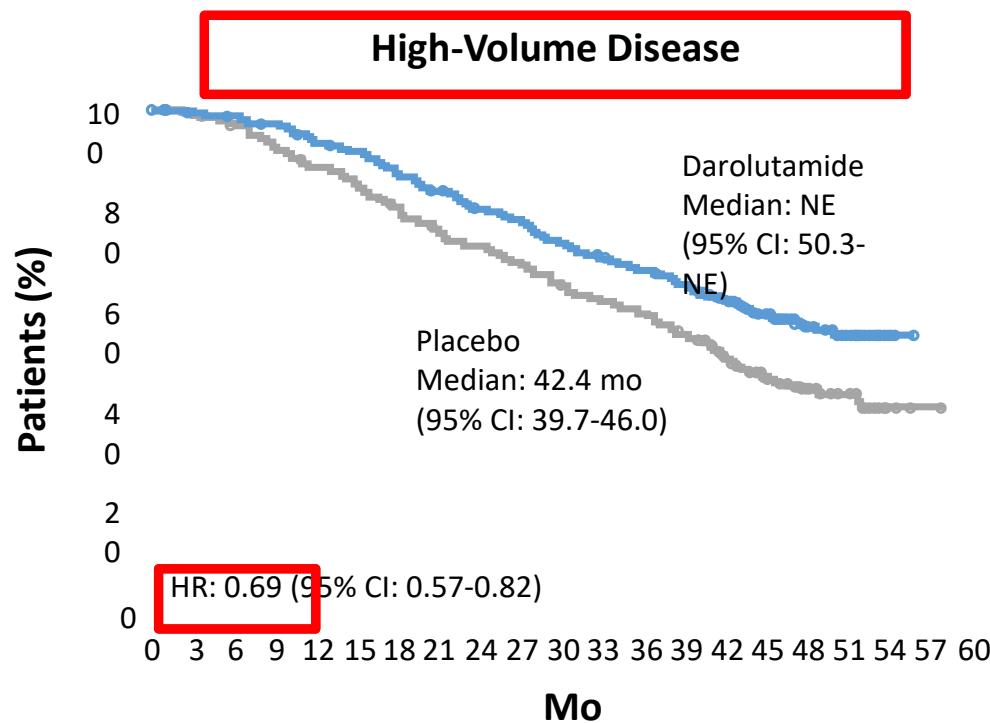
Recurrent metastatic disease



No. at Risk	
Darolutamide	558 553 547 539 520 505 485 466 445 433 412 396 383 367 334 220 116 45 7 0 0
Placebo	566 558 546 526 503 490 461 438 420 403 378 362 344 328 292 190 93 33 6 1 0

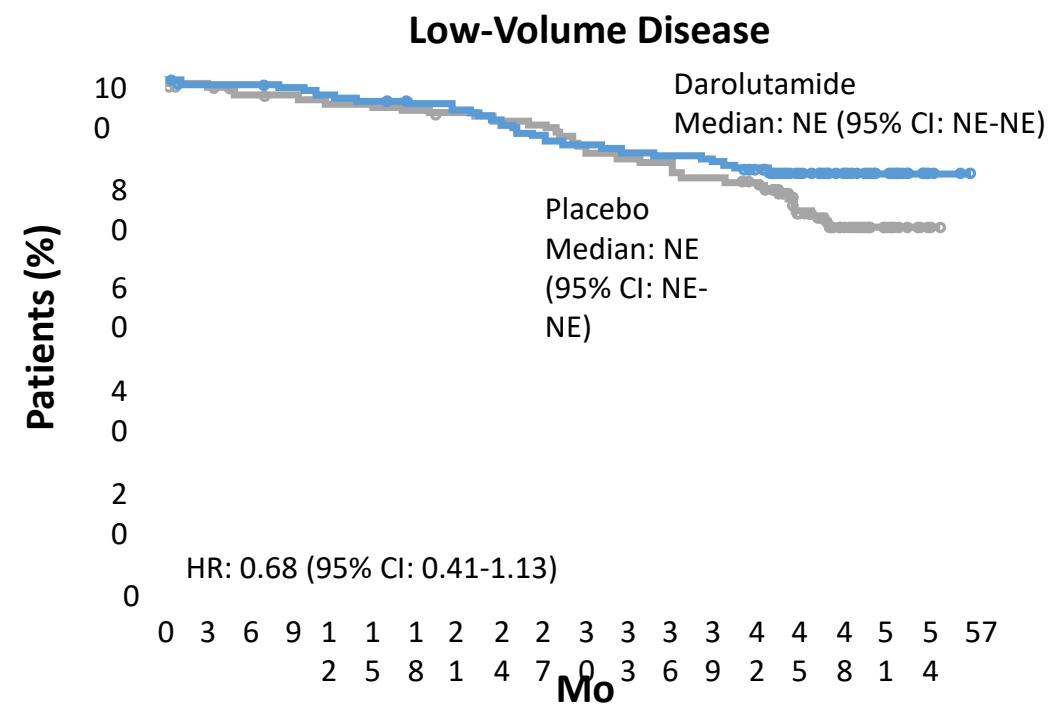
No. at Risk	
Darolutamide	86 85 83 81 81 78 76 74 70 68 66 63 63 62 43 20 11 2 0 0
Placebo	82 82 78 75 72 70 69 67 64 63 59 58 54 51 45 26 12 4 0 0

ARASENS: OS by Disease Volume



Patients at Risk, n

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0



Patients at Risk, n

Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

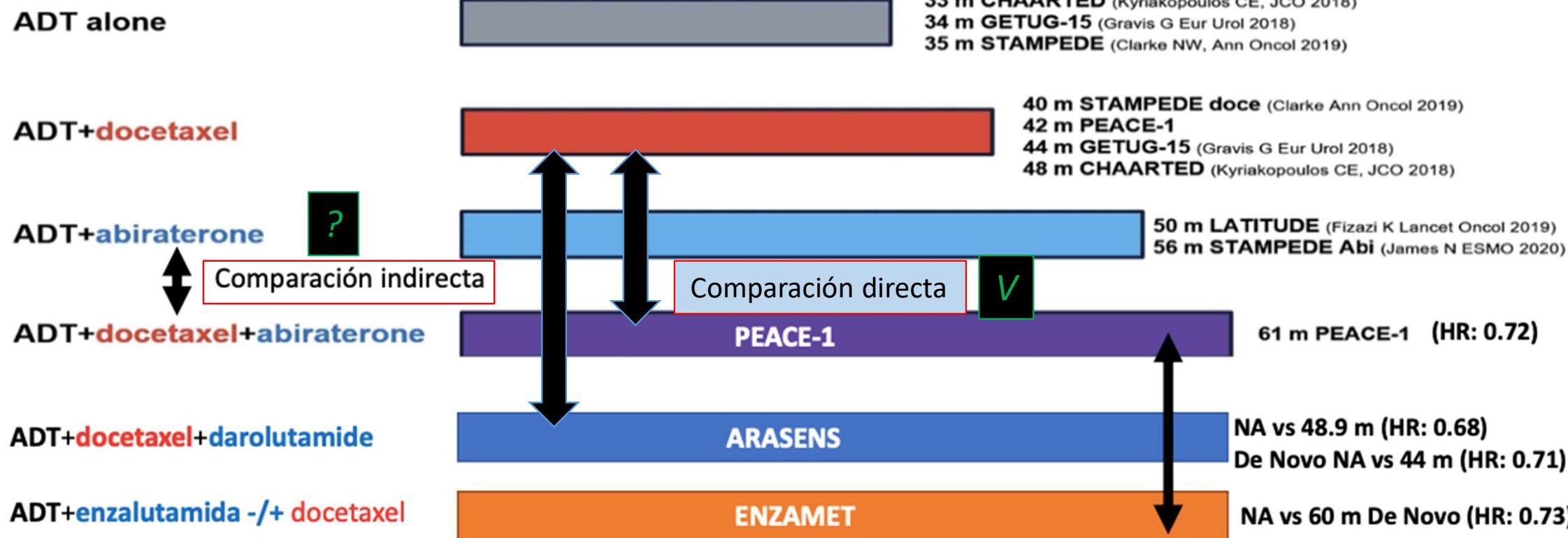
Table 2. Secondary Efficacy End Points (Full Analysis Set).*

End Point	Darolutamide–ADT–Docetaxel (N=651)†		Placebo–ADT–Docetaxel (N=654)†		Hazard Ratio (95% CI)	P Value
	Median	Patients with		Median	Patients with	
		mo	Event no. (%)		mo	Event no. (%)
Time to castration-resistant prostate cancer	NR	225 (35)	19.1	391 (60)	0.36 (0.30–0.42)	<0.001
Time to pain progression	NR	222 (34)	27.5	248 (38)	0.79 (0.66–0.95)	0.01
Symptomatic skeletal event–free survival	51.2	257 (40)	39.7	329 (50)	0.61 (0.52–0.72)	<0.001
Time to first symptomatic skeletal event	NR	95 (15)	NR	108 (17)	0.71 (0.54–0.94)	0.02
Time to initiation of subsequent systemic antineoplastic therapy	NR	219 (34)	25.3	395 (60)	0.39 (0.33–0.46)	<0.001
Time to worsening of disease-related physical symptoms	19.3	351 (54)	19.4	308 (47)	1.04 (0.89–1.22)	0.59
Time to initiation of opioid use for ≥7 consecutive days	NR	92 (14)	NR	117 (18)	0.69 (0.52–0.91)	NA

* NA denotes not applicable, and NR not reached.

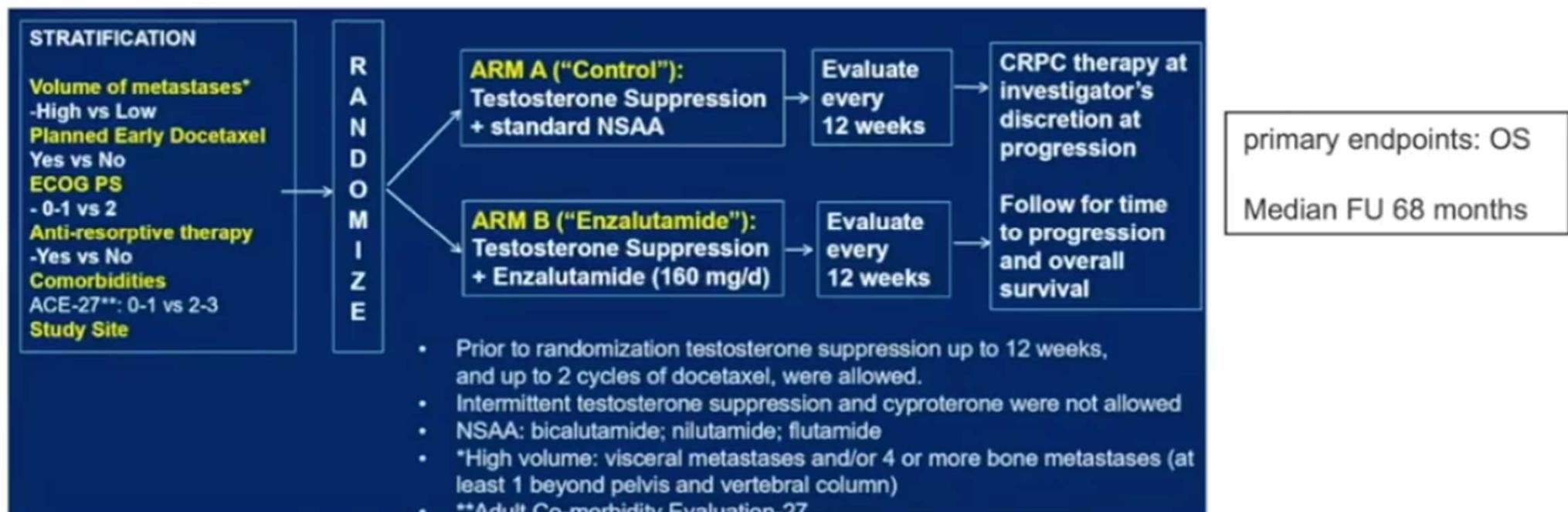
ESTUDIOS COMPARATIVOS CPSCM1

Mediana de Supervivencia Global De Novo-Alto Volumen



Triplet Therapy in mCSPC

ENZAMET



All comers, high-volume 57%, de novo 67%
Visceral disease 11%
Concurrent docetaxel 45%

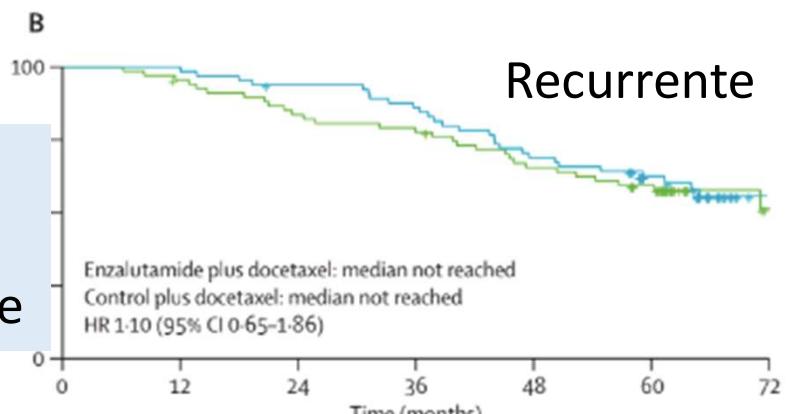
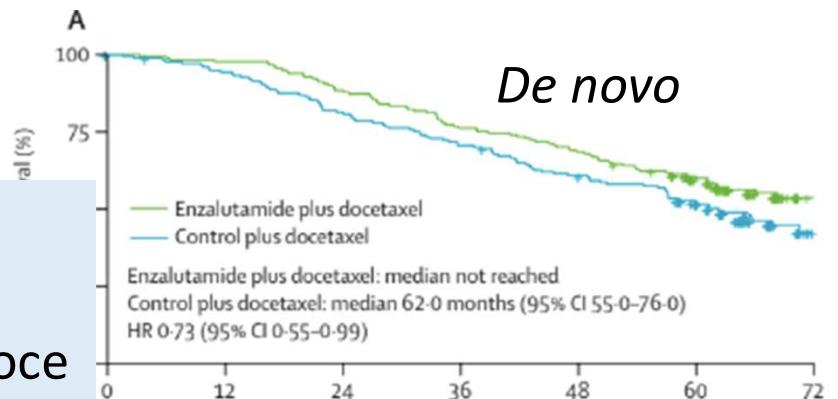
Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial



Christopher J Sweeney, Andrew J Martin, Martin R Stockler, Stephen Begbie, Leanna Cheung, Kim N Chi, Simon Chowdhury, Mark Frydenberg, Lisa G Horvath, Anthony M Joshua, Nicola J Lawrence, Gavin Marx, John McCaffrey, Ray McDermott, Margaret McJannett, Scott A North, Francis Parnis, Wendy Parulekar, David W Pook, Martin Neil Reaume, Shahneen K Sandhu, Alvin Tan, Thean Hsiang Tan, Alastair Thomson, Francisco Vera-Badillo, Scott G Williams, Diana Winter, Sonia Yip, Alison Y Zhang, Robert R Zielinski, Ian D Davis, for the ENZAMET trial investigators* and Australian and New Zealand Urogenital and Prostate Cancer Trials Group

Lancet Oncol 2023; 24: 323–34

Enza+doce
Vs
control + doce



C

A 68 m

Control (n/N)	Enzalutamide (n/N)	Hazard ratio (95% CI)	Control	Enzalutamide

Estudio no diseñado ni con potencia para analizar este subgrupo

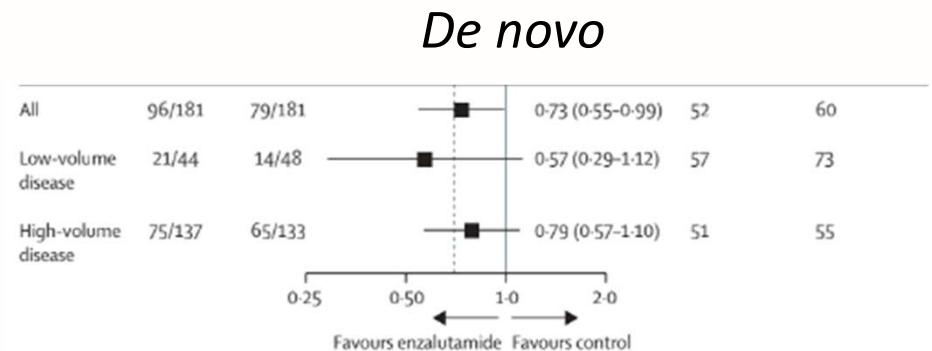
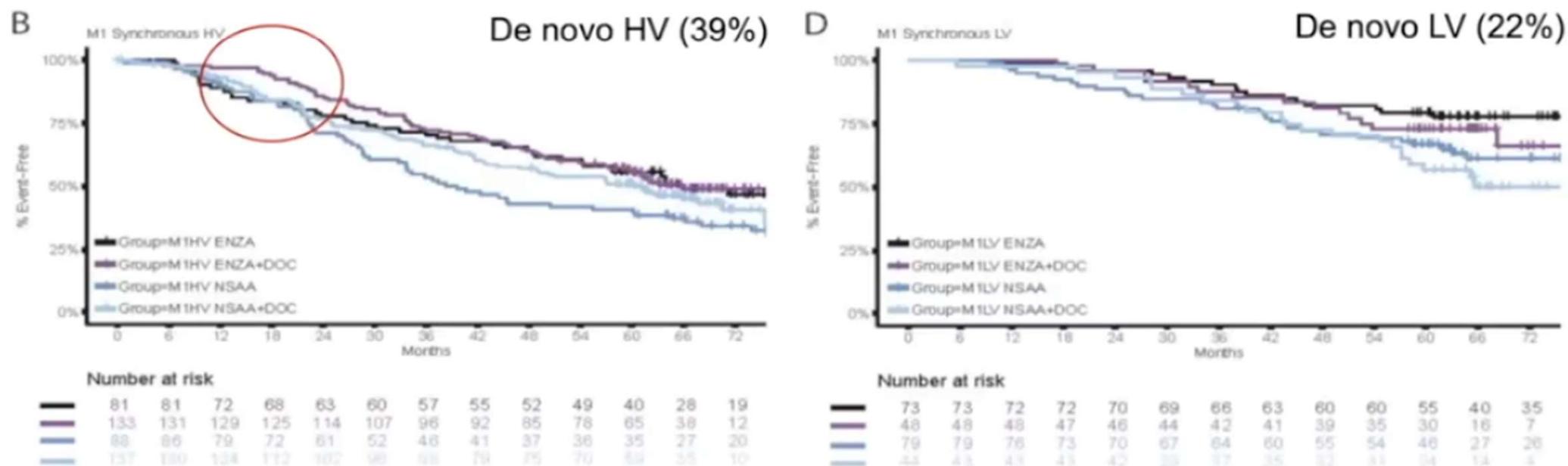


Figure 4: Prespecified overall survival analyses by prognostic subgroup
Overall survival in participants with synchronous metastatic disease (A) and metachronous metastatic disease (B) selected to receive docetaxel. (C) Overall survival in prognostic subgroups with synchronous metastatic disease selected to receive docetaxel. Dashed vertical line indicates the hazard ratio (overall survival) point estimate for enzalutamide treatment effect for the whole cohort. M1 synchronous defined as the first presentation of prostate cancer with metastatic disease and M0 metachronous defined as the first presentation of prostate cancer with non-metastatic disease.

Lancet Oncol 2023; 24: 323–34

Triplet Therapy in mCSPC

Davis et al. ASCO 2022



Group	Subset	Event/N	Overall Survival		HR (CI)	5y OS %
			Ref	HR (CI)		
M1HV	NSAA	58/88	■	Ref	41 (30 to 51)	
M1HV	NSAA+DOC	75/137	■	0.80 (0.57 to 1.13)	51 (42 to 59)	
M1HV	ENZA	43/81	■	0.69 (0.46 to 1.02)	56 (44 to 66)	
M1HV	ENZA+DOC	65/133	■	0.64 (0.45 to 0.91)	55 (47 to 63)	

Sweeney et al. Lancet Oncol 2023; 24: 323–34

Key limitations with PEACE1 and ENZAMET:

- Use of docetaxel was not randomized → confounding by indication
- Not powered for subgroup analyses

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



2022



Platinum Priority – Review – Prostate Cancer

Editorial by Hannah E. Dzimitrowicz, Andrew J. Armstrong on pp. 599–601 of this issue

Androgen Receptor Signaling Inhibitors in Addition to Docetaxel with Androgen Deprivation Therapy for Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Meta-analysis

Takafumi Yanagisawa ^{a,b}, Paweł Rajwa ^{a,c}, Constance Thibault ^d, Giorgio Gandaglia ^e, Keiichiro Mori ^b, Tatsushi Kawada ^{a,f}, Wataru Fukuokaya ^b, Sung Ryul Shim ^g, Hadi Mostafaei ^{a,h}, Reza Sari Motlagh ^{a,i}, Fahad Quhal ^{a,j}, Ekaterina Laukhtina ^{a,k}, Maximilian Pallauf ^{a,l}, Benjamin Pradere ^{a,m}, Takahiro Kimura ^b, Shin Egawa ^b, Shahrokh F. Shariat ^{a,k,n,o,p,q,r,*}



(A) OS

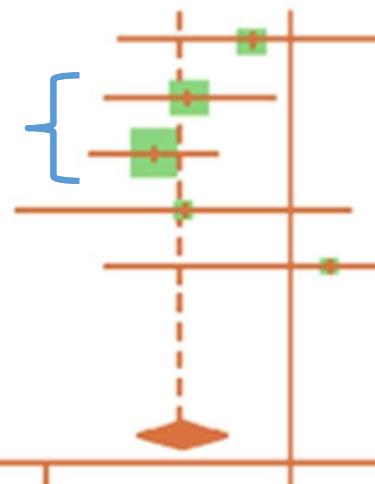
Study

ENZAMET
PEACE1
ARASENS
ARCHES
TITAN

Hazard ratio

HR

95% CI



Fixed-effect model

Heterogeneity: $\tau^2 = 0, p = 0.5$

Test for overall effect (fixed effect):
 $z = -4.72 (p < 0.001)$

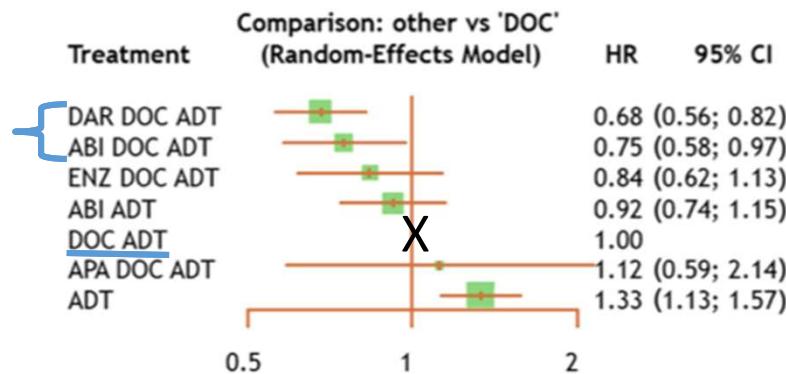


Favors [ARSI + DOC+ ADT] Favors [DOC + ADT]

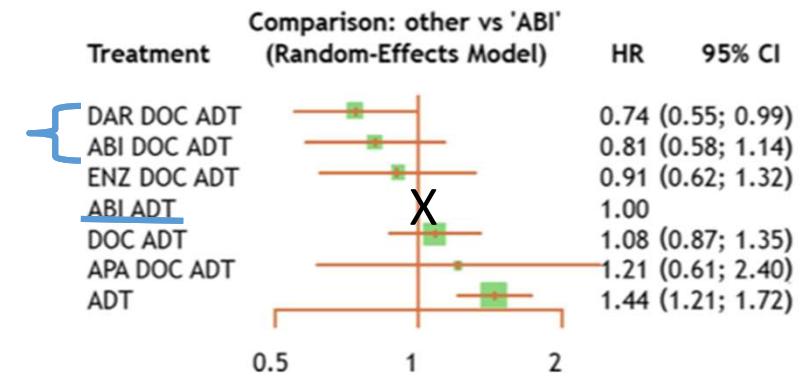
TRIPLETES > DOCETAXEL + ADT

SG

(B) Comparison to DOC + ADT



(C) Comparison to ARSI + ADT (ABI +ADT)



TRIPLETE > doblete de DOC

TRIPLETE ¿> doblete de ARSI?

Fig. 3 – Forest plots showing the association of systemic therapy for mHSPC with OS: (A) comparison with ADT alone, (B) comparison with DOC + ADT, and (C) comparison with ARSI (ABI) + ADT. ABI = abiraterone; ADT = androgen deprivation therapy; APA = apalutamide; ARSI = androgen receptor signaling inhibitors; CI = confidence interval; DAR = darolutamide; DOC = docetaxel; ENZ = enzalutamide; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; OS = overall survival.

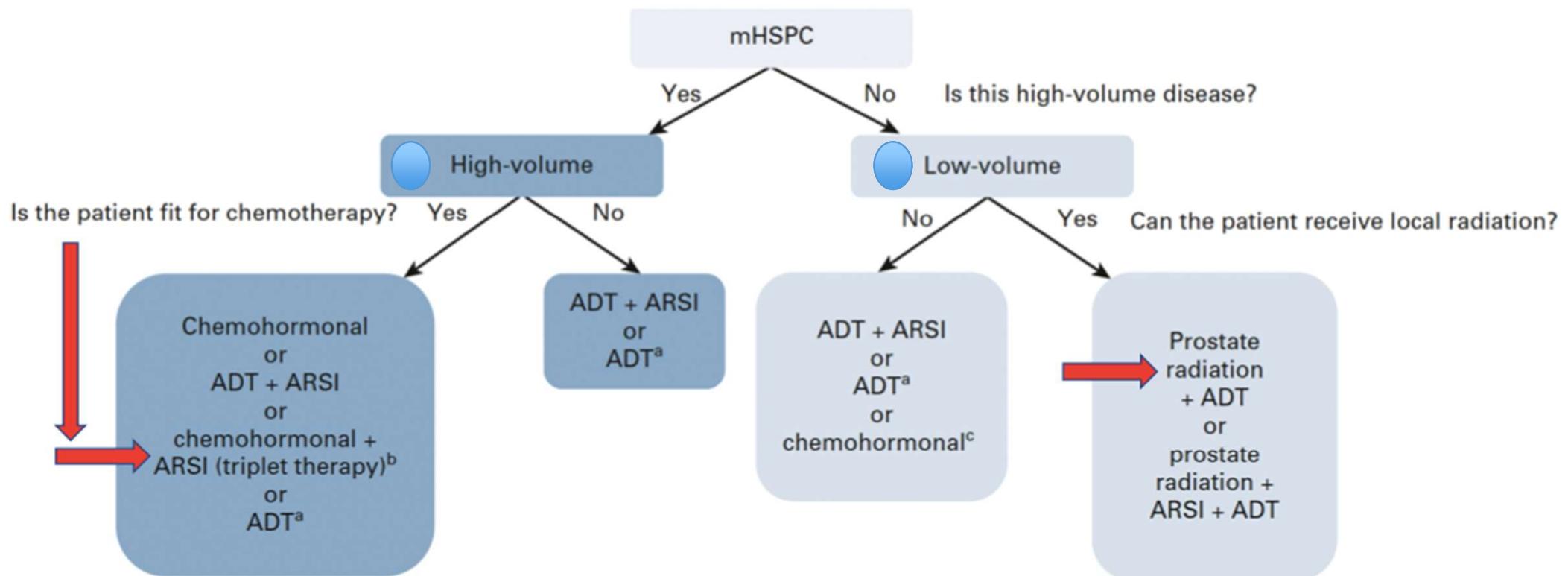
¿Qué nos dicen las guías?

Isn't Androgen Deprivation Enough? Optimal Treatment for Newly Diagnosed Metastatic Prostate Cancer

ASCO[®]

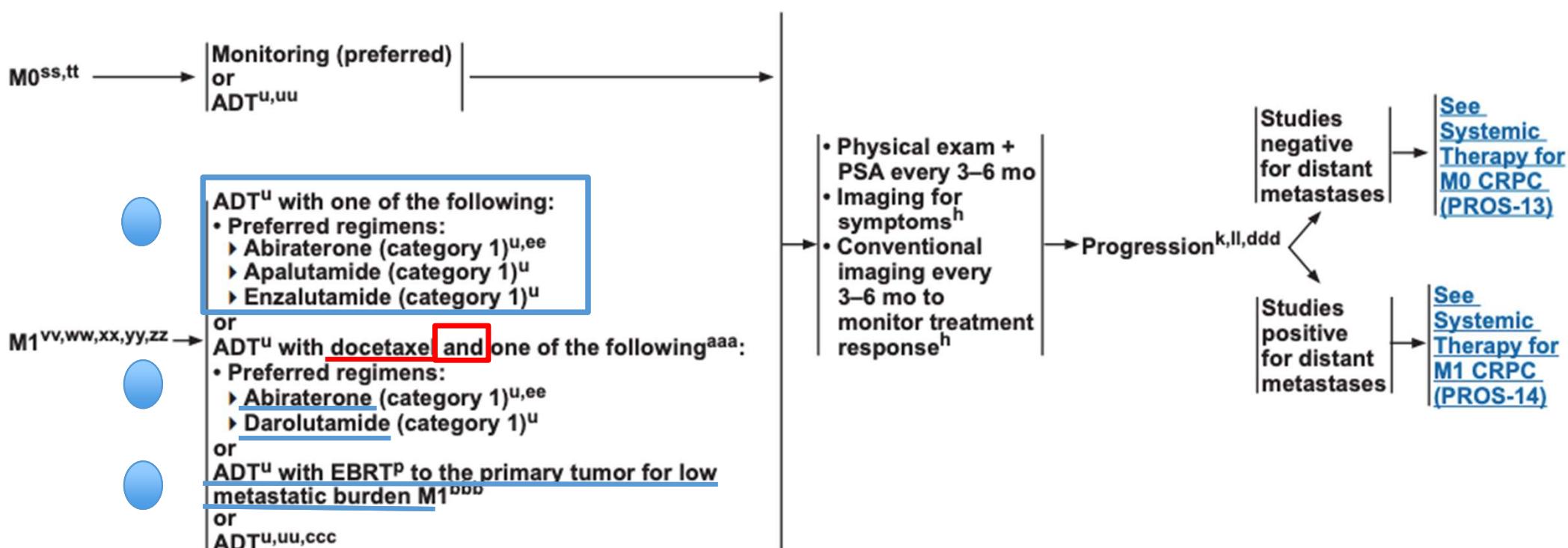
818 Volume 40, Issue 8

Alicia K. Morgans, MD, MPH¹; and Himisha Beltran, MD¹





SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER^{rr}



GUÍAS TERAPÉUTICAS EUROPEAS

Recommendation 9: Hormone-naïve metastatic prostate cancer

9a. ADT plus docetaxel and AAP is recommended as first-line treatment for fit patients with mHNPC, especially in those with *de novo* multiple bone metastases (≥ 3) or visceral metastases [I, B]. In other patients with mHNPC, ADT plus AAP

[ESMO-MCBS v1.1 score 4] or apalutamide [ESMO-MCBS v1.1 score 4 or 3] or docetaxel [ESMO-MCBS v1.1 score 4] or enzalutamide [ESMO-MCBS v1.1 score 4] is recommended as first-line treatment for mHNPC [I, A]. In patients with mHNPC, ADT alone should be used only in vulnerable patients who cannot tolerate treatment intensification [III, C].

9b. ADT plus radiation to the primary is recommended for patients with low volume mHNPC [I, A].

9c. ADT alone is recommended as first-line systemic treatment for mHNPC in patients who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A].

9d. For patients starting on ADT, management to prevent cancer treatment-induced bone loss (CTIBL) is recommended.

100%

100%

100%

100%



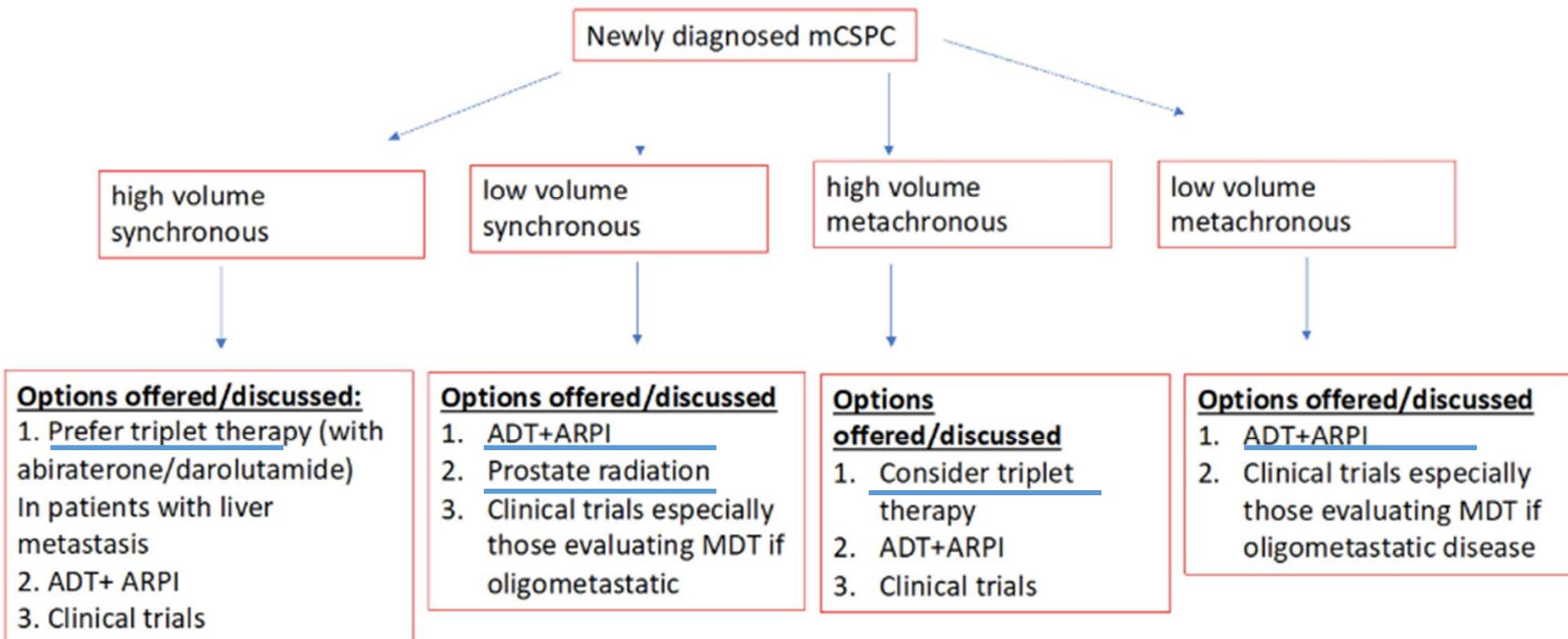
“Offer ADT plus docetaxel plus AAP as first treatment for fit patients with *de novo* and multiple bone or visceral mets”

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

Review

Triplet Therapy in Metastatic Castrate Sensitive Prostate Cancer (mCSPC)—A Potential New Standard of Care

Abhenil Mittal ¹ , Srikanth S. Sridhar ¹, Michael Ong ² and Di Maria Jiang ^{1,*} 

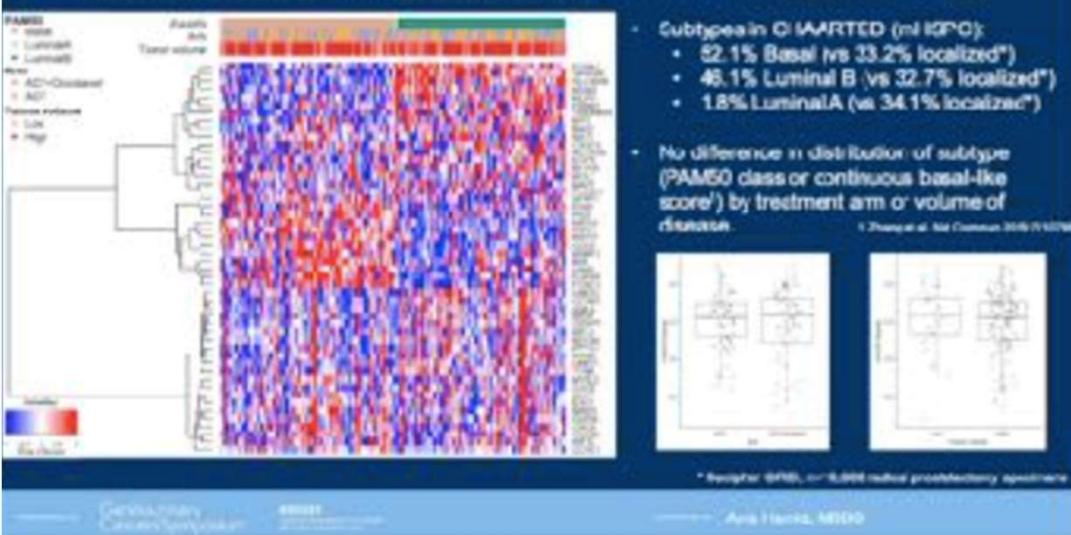


mCPSC: cuestiones que importan

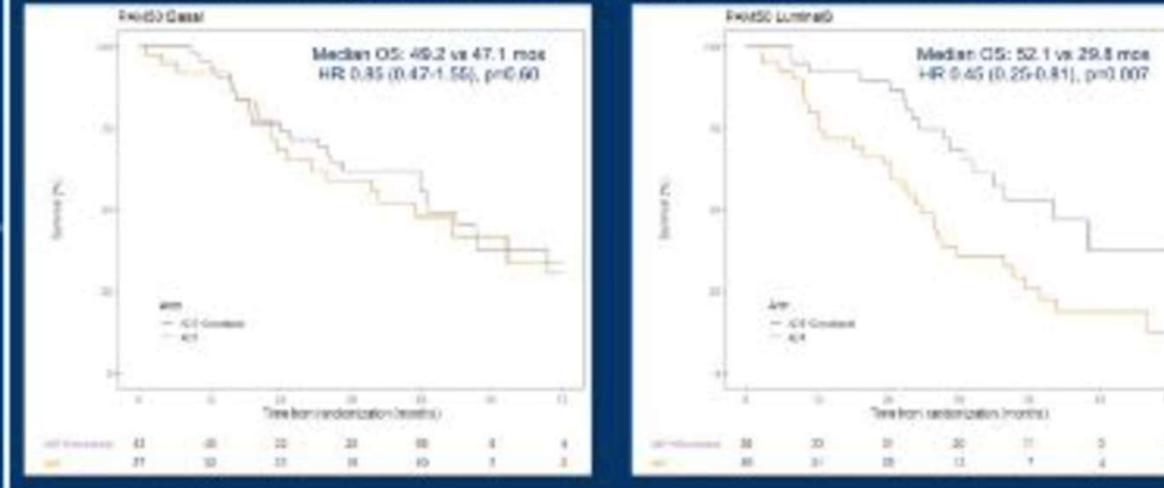
1. ¿Está indicado tratar sólo con ADT?
2. ¿Sigue siendo válidas la clasificaciones por volumen/riesgo y presentación *de novo*/metacróna de la enfermedad?
3. ¿Cuándo están indicados los tripletes de QT+ADT+ARSI vs dobletes QT+ADT o ARSI+ADT?
4. ¿Ayuda la biología molecular?

Luminal B Subtype as a Predictive Biomarker of Docetaxel Benefit for Newly Diagnosed Metastatic Hormone Sensitive Prostate Cancer: A Correlative Study of E3805 CHARTED

Distribution and features by luminal-basal subtype



OS: Differential benefit from addition of docetaxel



patients with luminal B subtype prostate cancer, those who received docetaxel had a much longer OS and time to onset of castration resistance



PAM 50
Luminal B 56

SPOP mutations (mtSPOP) are a treatment-selection biomarker in patients (pts) with de novo metastatic castration-sensitive prostate cancer (dn-mCSPC).

E-poster 1373

Umang Swami, et al. ESMO 2022

CLINICAL CANCER RESEARCH

ABOUT ▾ ARTICLES ▾ FOR AUTHORS ▾ ALERTS NEWS COVID-19 WEBINARS

RESEARCH ARTICLE | SEPTEMBER 11 2022

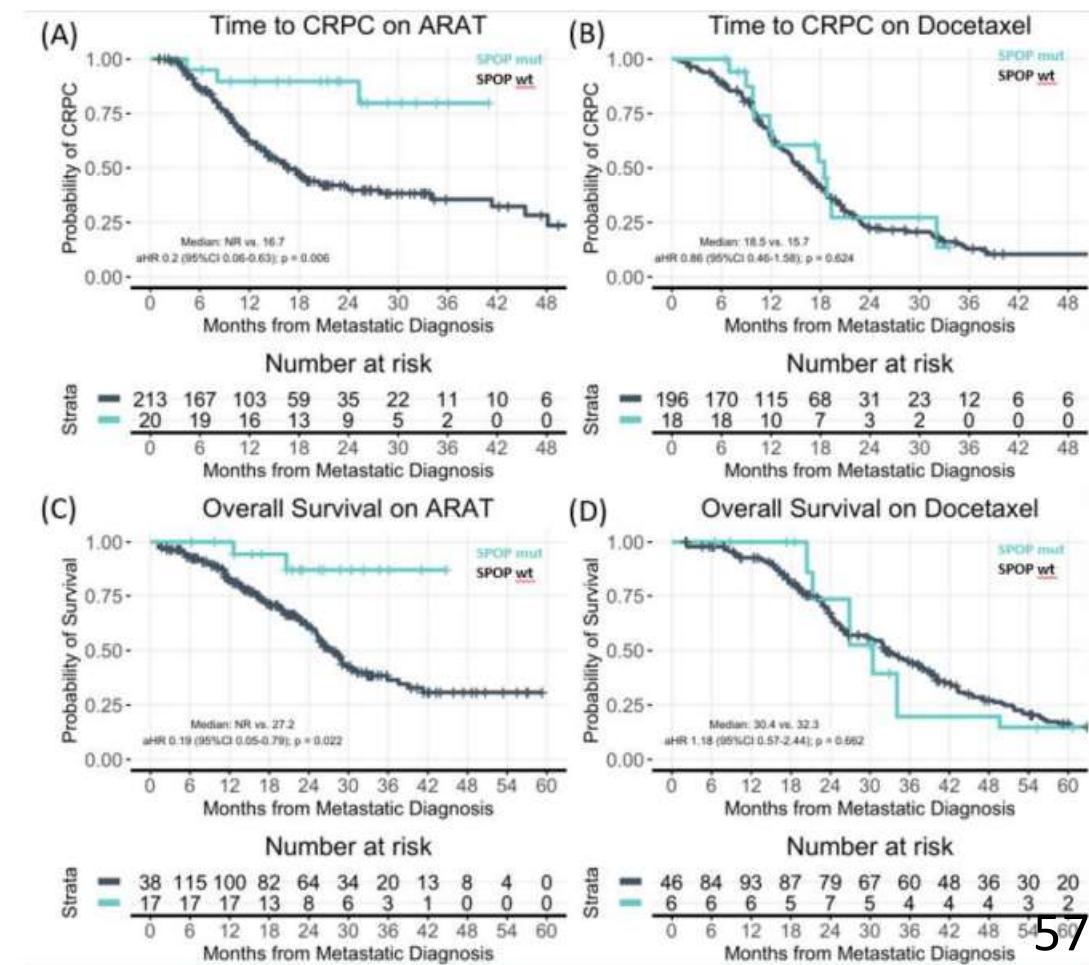
SPOP mutations as a Predictive Biomarker for Androgen Receptor-Axis-Targeted Therapy in De Novo Metastatic Castration-Sensitive Prostate Cancer

Uman Swami ; Ryon P. Graf ; Roberto H. Nussenzveig ; Virginia Fisher ; Hanna Tukachinsky ; Alexa B. Schrock ; Gerald Li ; Jeffrey S. Ross ; Nicolas Sayegh ; Nishita Tripathi ; Vinay Mathew Thomas ; Geoffrey R. Oxnard ; Emmanuel S. Antonarakis ; Neeraj Agarwal 



+ Author & Article Information
Clin Cancer Res CCR-22-2228

<https://doi.org/10.1158/1078-0432.CCR-22-2228> Article history 





(mis) CONCLUSIONES

1. ADT SÓLO NO DEBE UTILIZARSE (salvo en casos excepcionales, pacientes frágiles)
2. ADT CON DOCETAXEL ES ACTIVO EN ALTO VOLUMEN Y DE NOVO
3. TRIPLETES (ADT+DOCETAXEL+ABIRATERONA O DAROLUTAMIDA)
SON SUPERIORES A ADT+DOCETAXEL
-ADT+ docetaxel es tratamiento subóptimo



(mis) CONCLUSIONES

4. ADT CON DOCETAXEL Y ARSI, ¿SUPERIOR A ADT + ARSI?
(Probablemente, pero es comparación indirecta)
5. EN BAJO VOLUMEN (y DE NOVO) DEBE VALORARSE LA RT SOBRE EL PRIMARIO--->(Stampede)
6. NO DISPONEMOS (todavía) DE BIOMARCADORES PREDICTIVOS VALIDADOS

(mis) MENSAJES PRÁCTICOS en mCPSC

1. TRATAR CON ARSI + ADT

- Alto/bajo vol o de novo : abiraterona(post hoc en bajo) /enzalutamida/apalutamida
- Bajo volumen y metácrono : apalutamida o enzalutamida

2 VALORAR TRIPLETE, SI FIT PARA QT, EN ALTO VOL/RIESGO Y DE NOVO

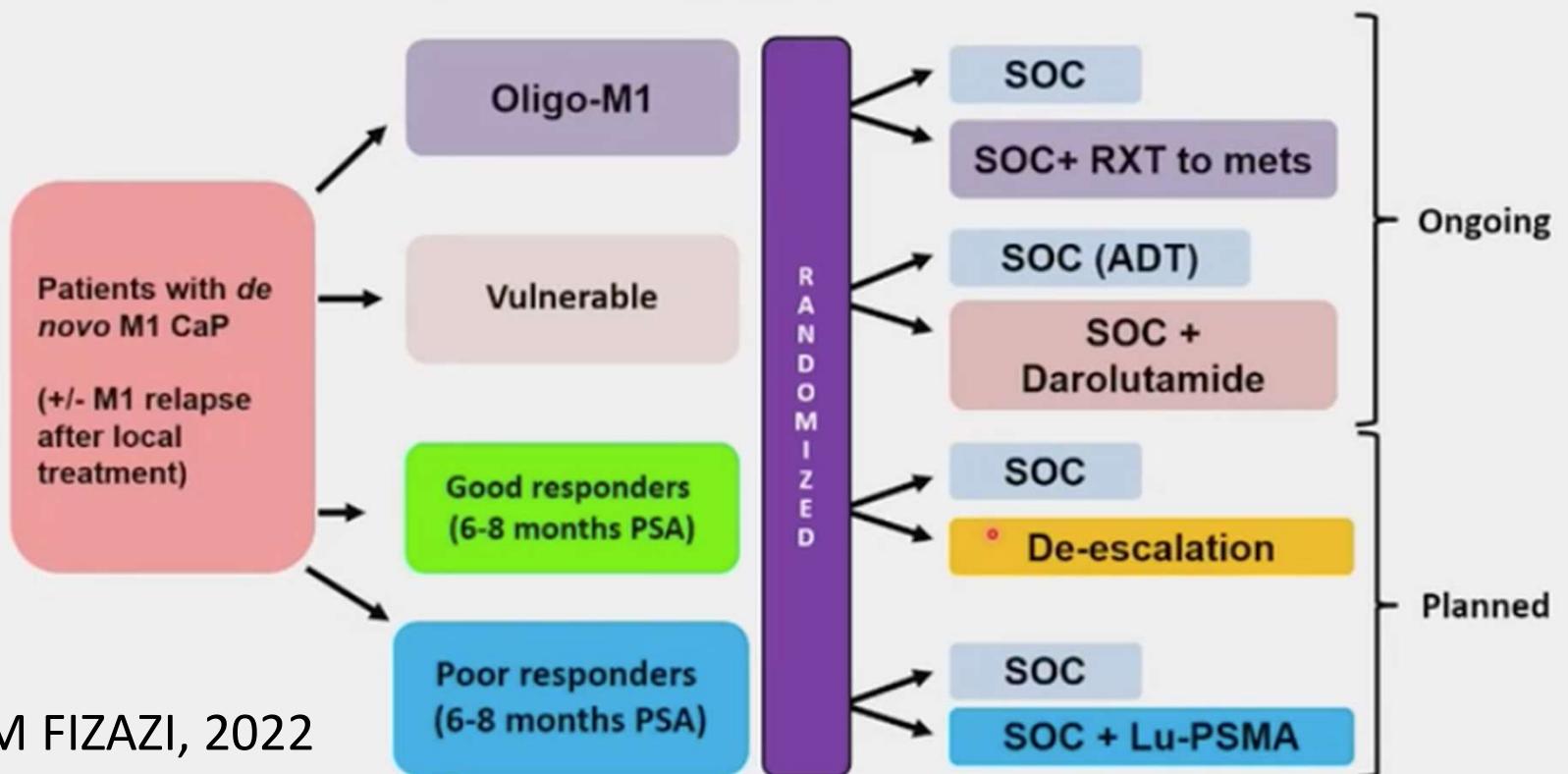
3. DOCETAXEL + ADT SÓLO ES YA SUBÓPTIMO, mejor en triplete

4. VALORAR RT SOBRE LA PRÓSTATA EN BAJO VOL (Stampede)

5. DEBE TENERSE EN CUENTA LA SITUACIÓN BASAL DEL PACIENTE Y LAS TOXICIDADES ESPERABLES ANTES DE ELEGIR EL TRATAMIENTO

02:49
TIME'S UP!
NICE WORK!

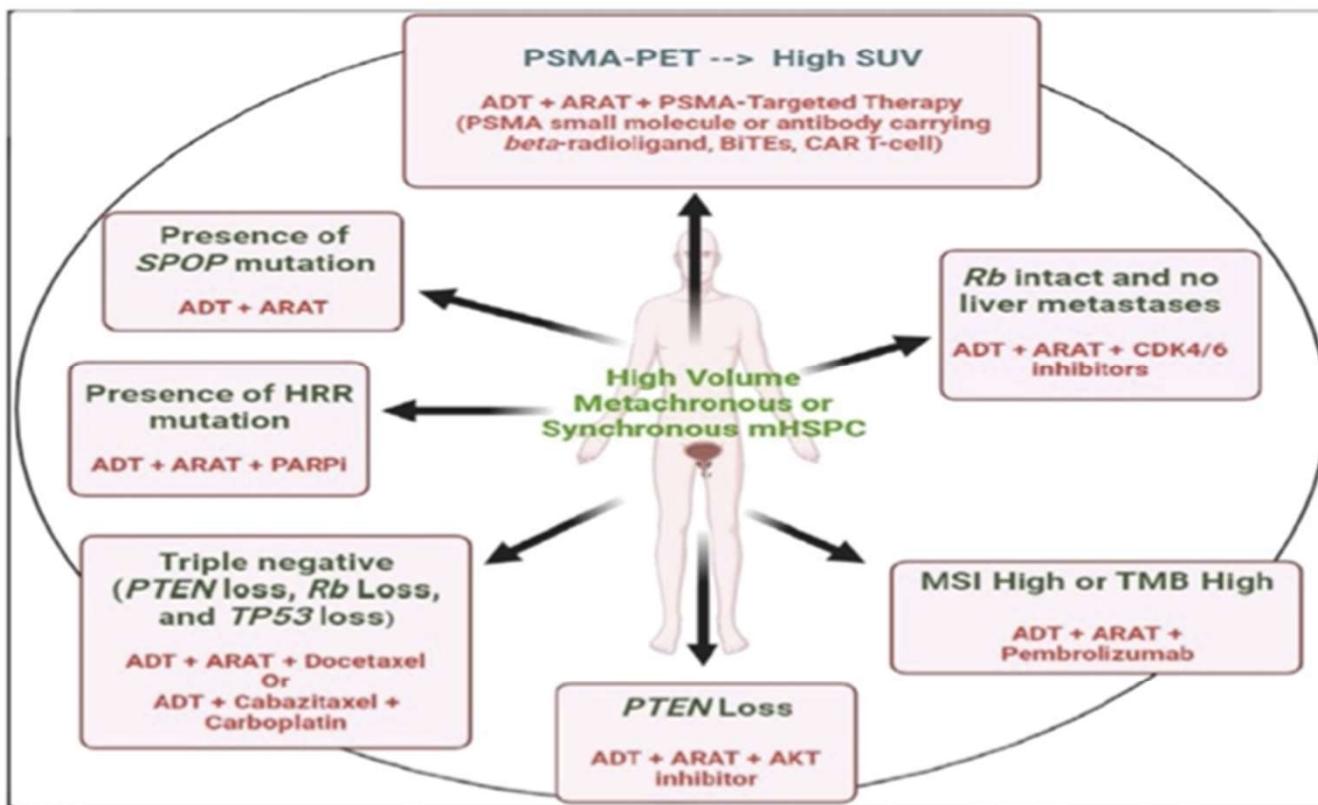
The PEACE-6 program: Current European trials in M1 CSPC



KARIM FIZAZI, 2022

Treatment of Metastatic Hormone-Sensitive Prostate Cancer in 2027

Neeraj Agarwal, MD | University of Utah | @neerajaiims



Low-volume mHSPC:
Metastases-directed therapy + treatment of primary if intact ± systemic therapy

ADT: androgen deprivation therapy; ARAT: androgen receptor axis targeted therapy; BiTEs: bispecific T cell engager; CAR T cell: chimeric antigen receptor T cell; CDK4/6: cyclin D Kinase 4/6; HRR: homologous recombination repair; mHSPC: metastatic hormone sensitive prostate cancer; MSI: microsatellite instability; PARPI: poly adenosine diphosphate-ribose polymerase inhibitor; PSMA: targeted therapy; PSMA small molecule or antibody carrying beta-radioligand; TMB: tumor mutation burden

Selected PHASE III ongoing trials in mCSPC

Table 3. Select ongoing trials in mCSPC.

	Keynote 991 [58]	PSMAdition [59]	AMPLITUDE [54]	TALAPRO-3 [55]	CAPITELLO-281 [56]	CYCLONE-3 [57]	SPARKLE [64]
NCT number	NCT04191096	NCT04720157	NCT04497844	NCT04821622	NCT04493853	NCT05288166	NCT05352178
Experimental arm	Pembrolizumab plus Enzalutamide plus ADT	Lu-177 plus SOC	Niraparib plus AAP plus ADT	Talazoparib plus enzalutamide plus ADT	Capivasertib plus AAP plus ADT	Abemaciclib plus AAP plus ADT	1 = MDT plus 1 month ADT 2 = MDT plus 6 months ADT + enzalutamide
Control arm	Enzalutamide plus ADT	SOC alone	AAP plus ADT	Enzalutamide plus ADT	AAP plus ADT	AAP plus ADT	MDT alone
Design	Randomised phase III double blind	Randomised phase III with cross over allowed	Randomised phase III double blind	Randomised phase III double blind	Randomised phase III double blind	Randomised phase III double blind	Randomised phase III open label
Number of patients	1232	1126	788	550	1000	900	873
Primary end point	rPFS and OS	rPFS	rPFS	rPFS	rPFS	rPFS	Poly metastatic free survival (PMFS)
Current status	Active, not recruiting	Recruiting	recruiting	Completed recruiting	Recruiting	recruiting	Recruiting

AAP—abiraterone; ADT—androgen deprivation therapy; rPFS—radiographic progression-free survival; OS—overall survival. Source: clinicaltrials.gov.

ENZA +/- PEMBRO

PSMAdition
(LU-177)

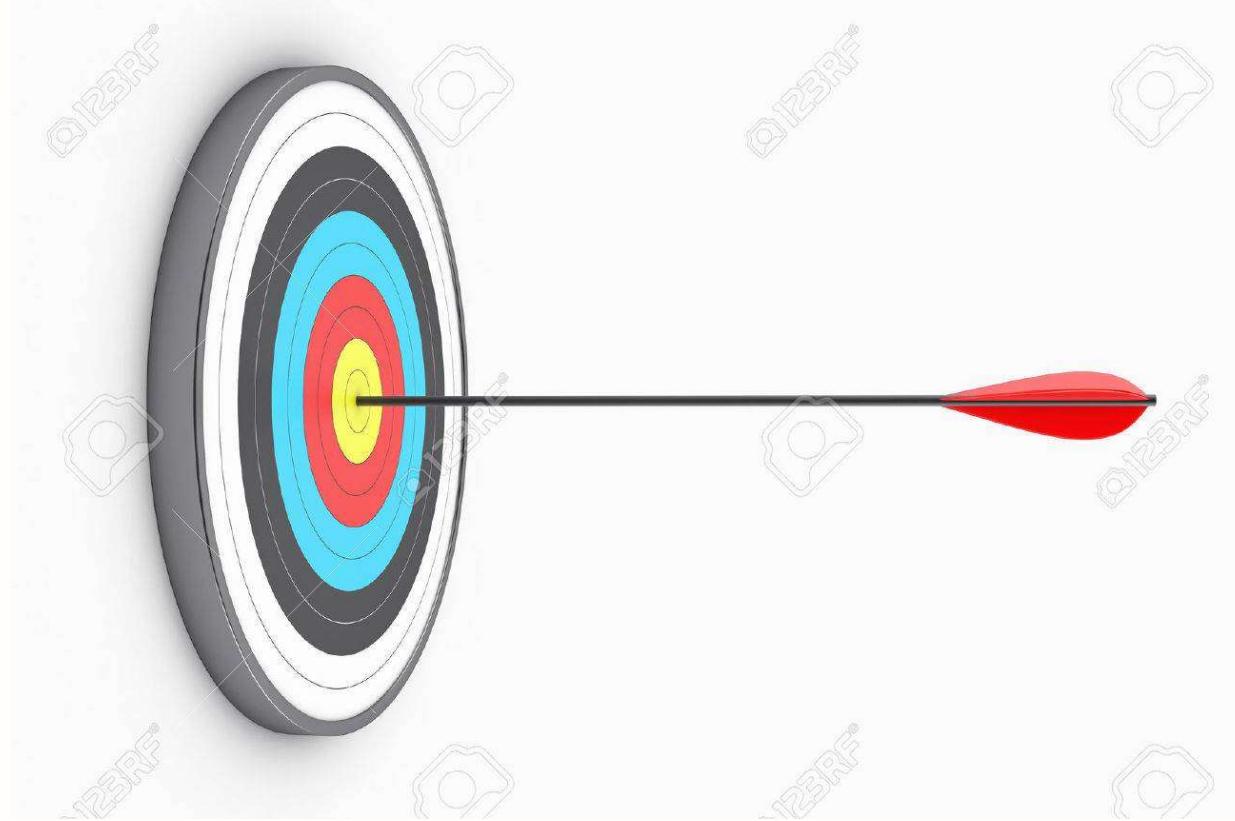
AMPLITUDE
(niraparib)

TALAPRO-3
(talazoparib)

CAPITELLO
(capivasertib)

CYCLONE
(abemaciclib)

SPARKLE
(ADT+RT EN M1+ENZA)



MUCHAS GRACIAS