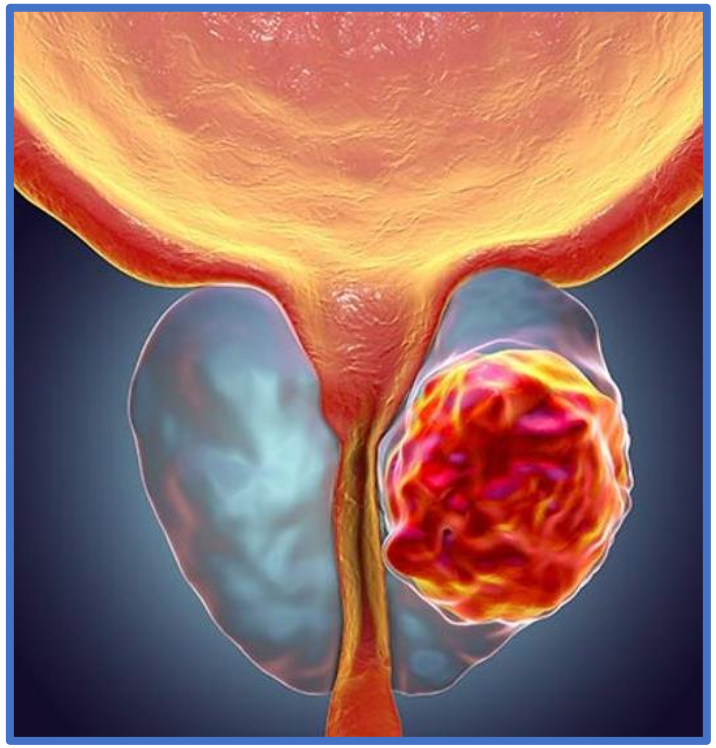
Cáncer de próstata metastásico

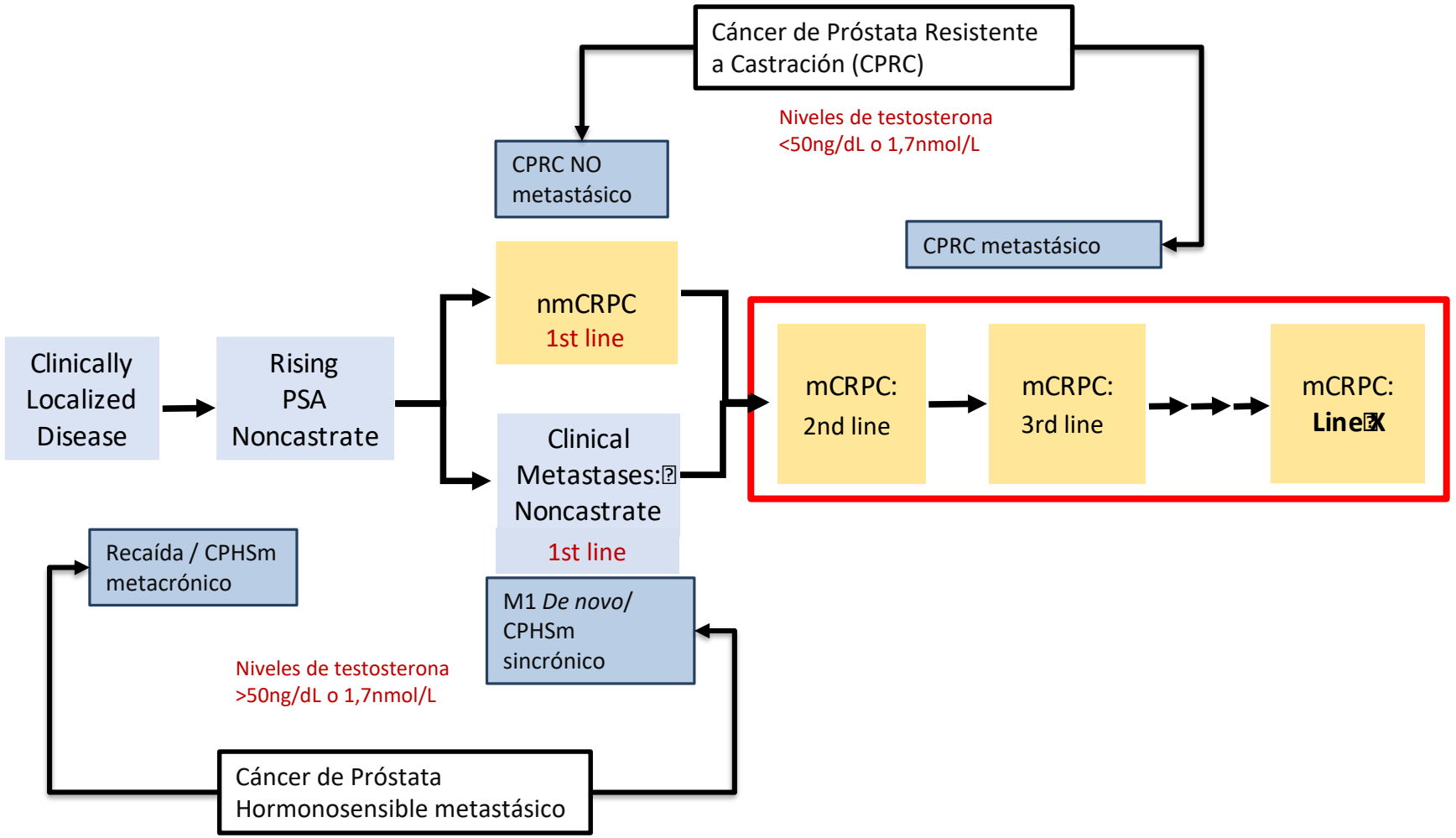
Aránzazu González del Alba Baamonde
H.U. Puerta de Hierro-Majadahonda (Madrid)

Webinar SEOM OPE

22 de enero de 2024



Escenarios clínicos en cáncer de próstata

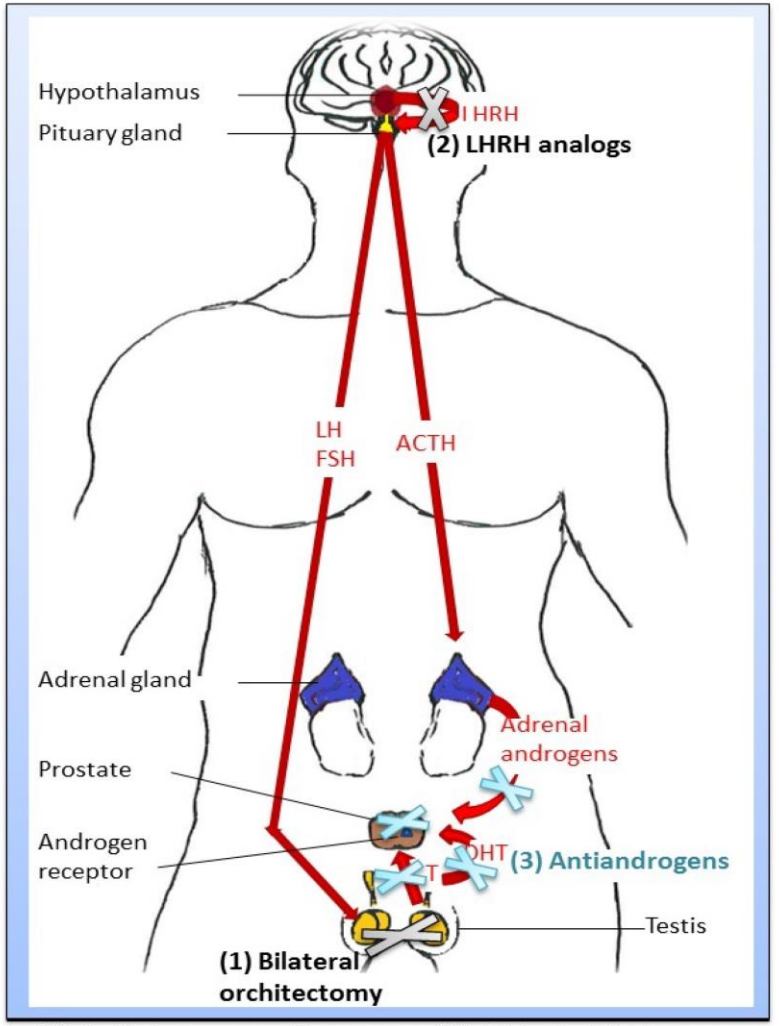


Cortesía de Rebeca Lozano

Figura modificada de Scher et al, J Clin Oncol 2016

Androgen deprivation therapy (ADT)

- **ADT has been the cornerstone of the systemic treatment for metastatic hormone-sensitive prostate cáncer (mHSPC)** during the past 8 decades
  - Orchiectomy → Huggins 1941
  - **LHRHa/GnRHa → Standard of care until recently**
  - Alternatives:
    - Maximun Androgen Blockage (MAB)
    - Intermitent blockage
- **ADT may induce responses >90% of patients, but after a median of 24-36 months progression to CRPC occurs**



DHT, 5α-dihydrotestosterone; T, testosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LHRH, Luteinizing hormone-releasing hormone

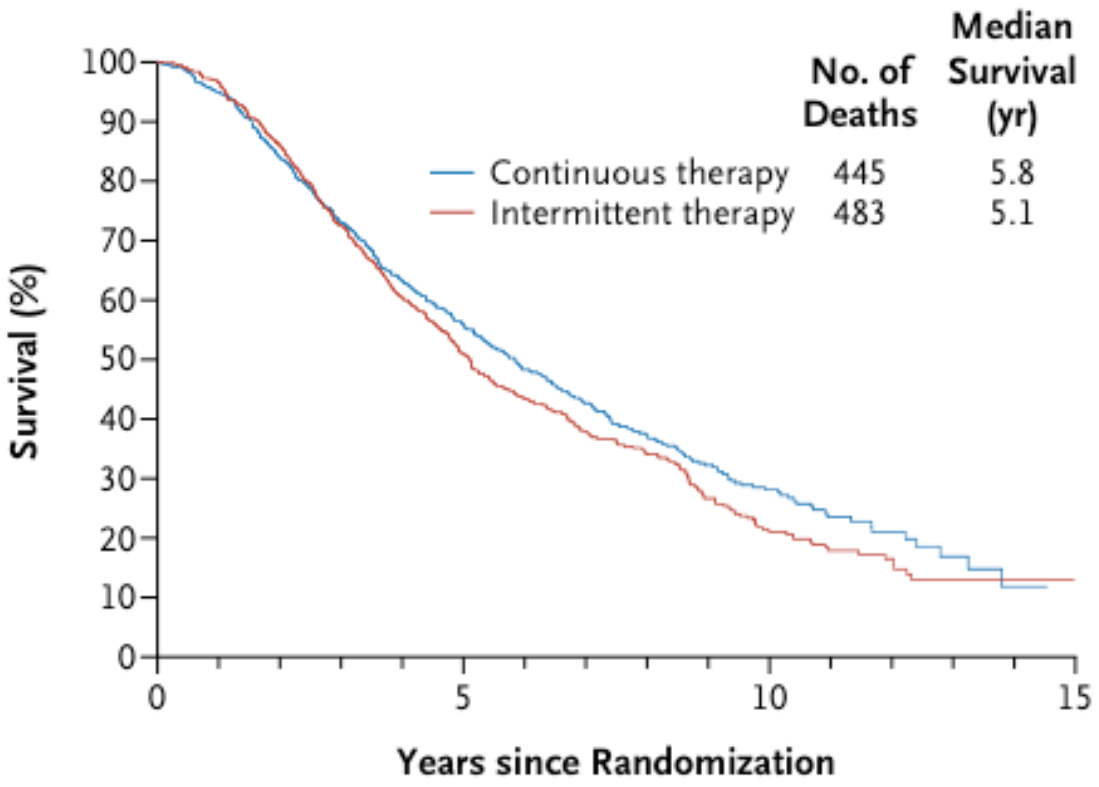
Huggins C, Can Res, 1941;2 Messing EM, N Eng J Med, 1999;
Prostate cancer trialists collaborative group, Lancet,2000; 4. Hussain, N Eng J Med, 2013;

Survival for ADT in SWOG 9346 trial

The NEW ENGLAND JOURNAL of MEDICINE

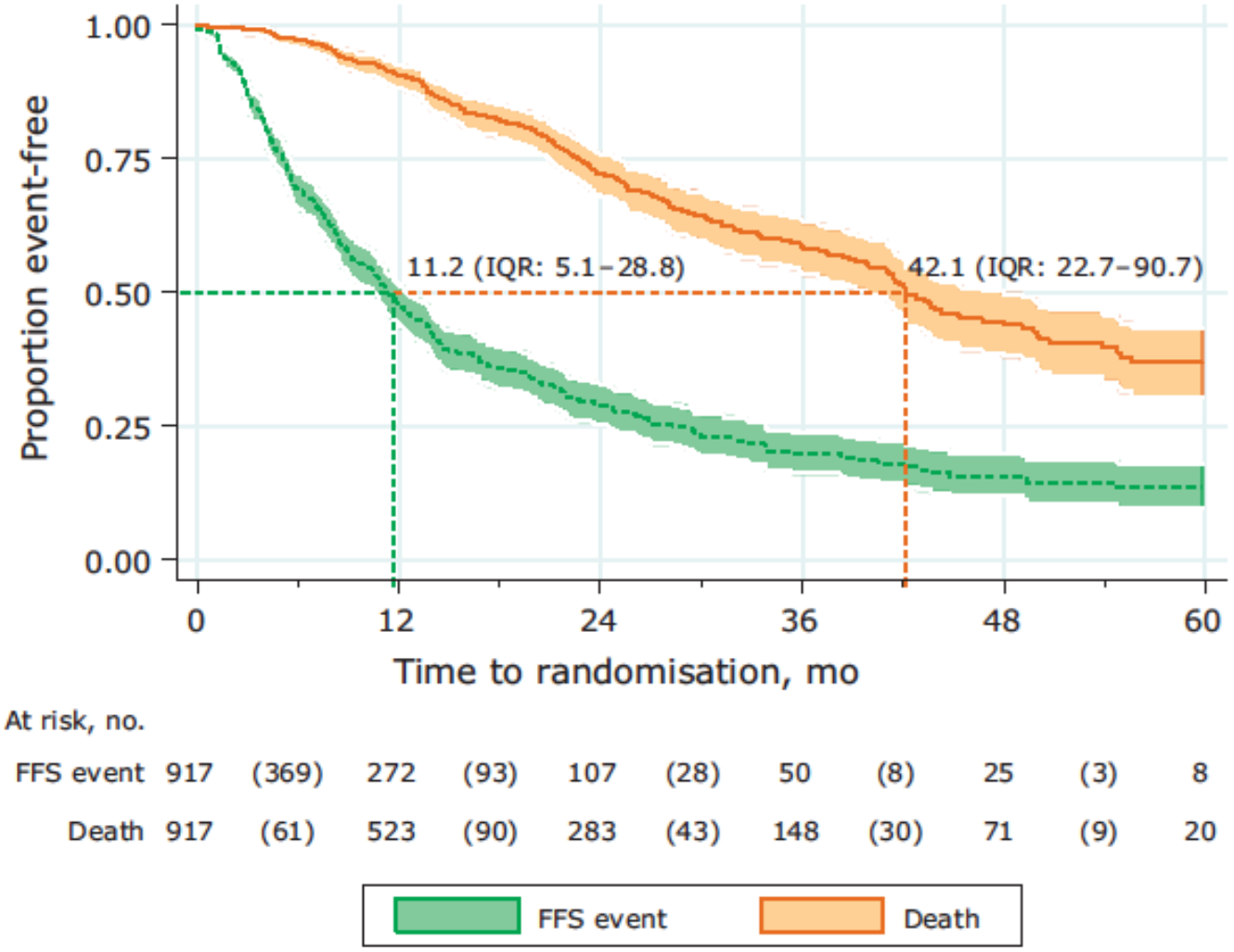
ORIGINAL ARTICLE

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer



Hussain M, et al. N Engl J Med 2013;368:1314-1325

2015: PFS with newly diagnosed metastatic prostate cancer: Data from 917 patients in the control arm of the STAMPEDE trial



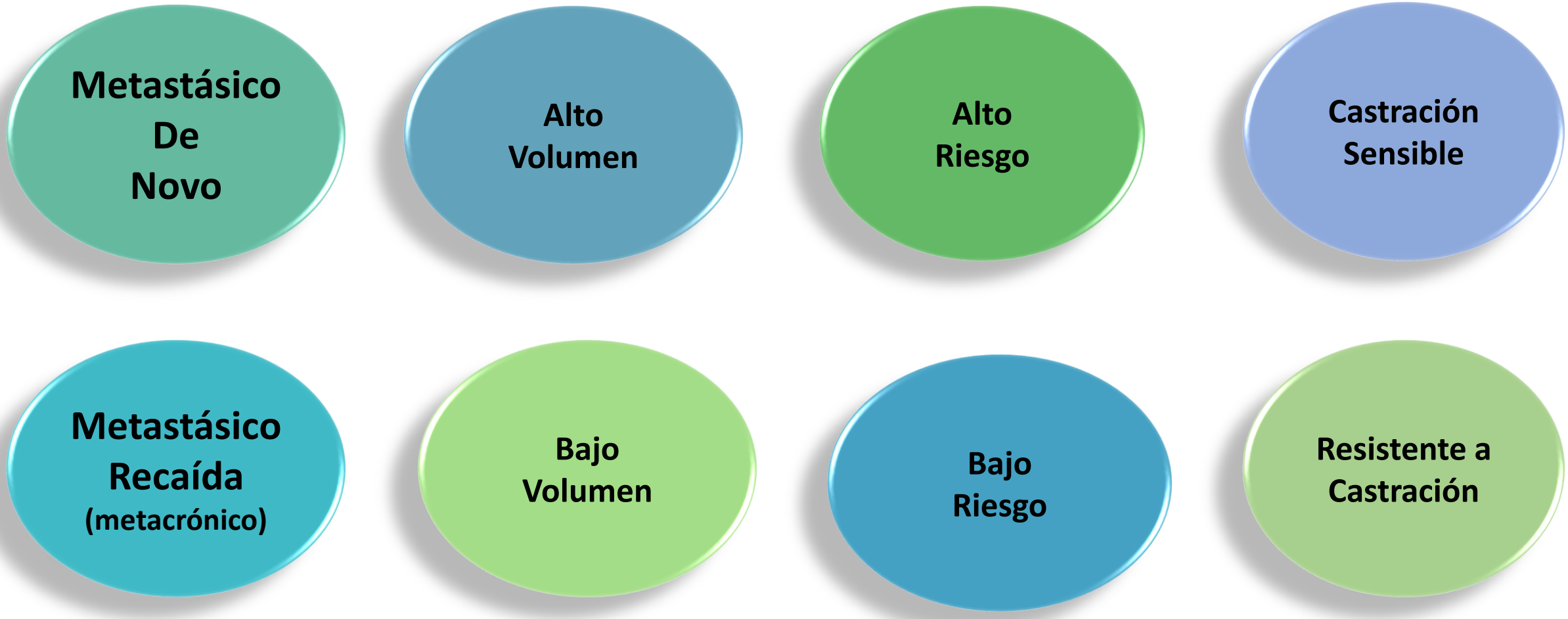
James ND, et al. Eur Urol 2015;67:1028-1038

Overall survival with ADT

Trial	Nº of patients	Median OS (mo)
SWOG 9346	765	68.4
GETUG 15	193	48.6
STAMPEDE	917	42.1
CHAARTED	393	47.2
LATITUDE	602	36.5

Hussain M, et al. N Engl J Med 2013;368:1314-1325
Gravis G, et al. Eur Urol 2016;70:256-262
James ND, et al. Eur Urol 2015;67(6):1028-1038
Kyriakopoulos CE, et al. J Clin Oncol 2018;36:1080-1087
Fizazi K, et al. Lancet Oncol 2019;20:686-700

CaP metastásico. Enfermedad Heterogénea



CRITERIOS CHAARTED

ALTO VOLUMEN

≥ 4 mets óseas (incluyendo ≥ 1 fuera columna vertebral o pelvis)
+/-
Metástasis visceral

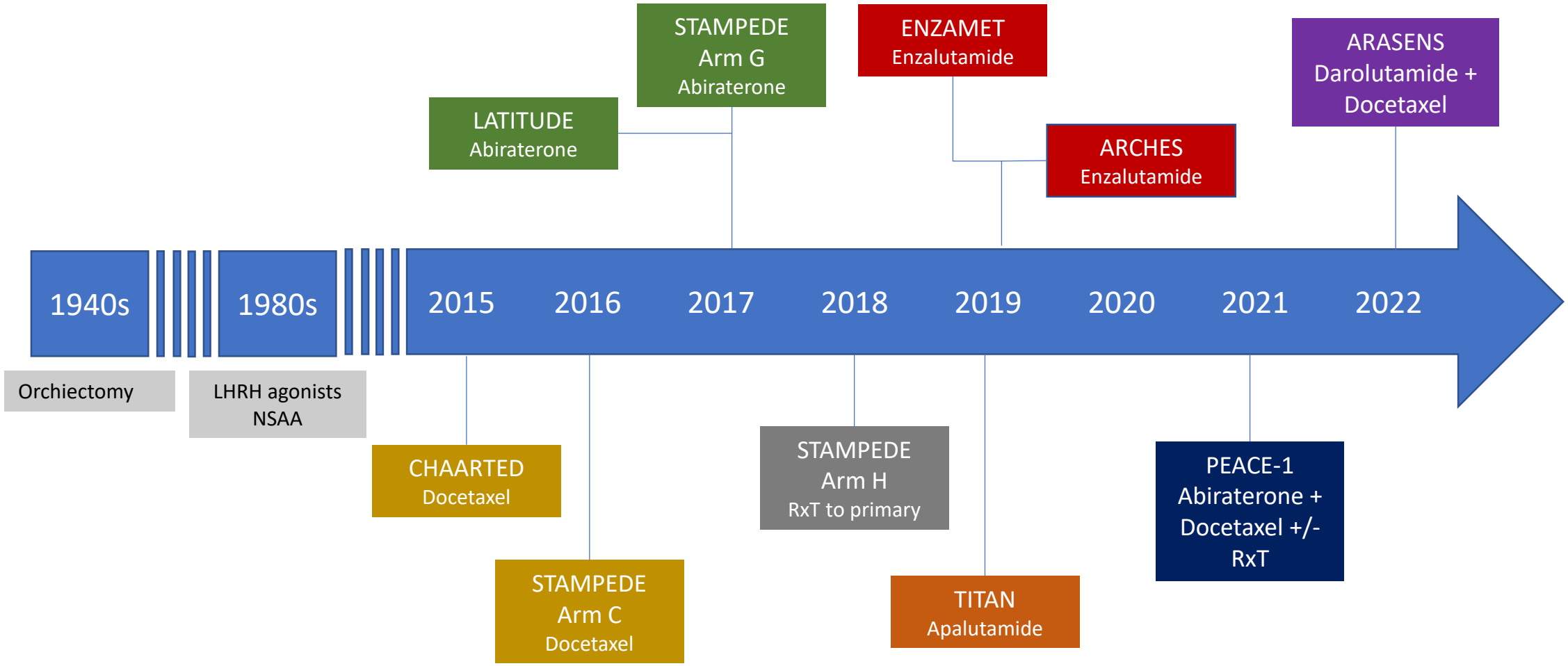
CRITERIOS LATITUDE

ALTO RIESGO

≥ 2 criterios:
≥ 3 mts óseas
Metástasis visceral
≥ ISUP grado 4

Silke Gillessen at ESMO 2022 Congress Paris

ENSAYOS PIVOTALES EN CÁNCER DE PRÓSTATA HORMONOSENSIBLE METASTÁSICO



Sweeney CJ, et al. N Engl J Med. 2015;373:737-746. James ND, et al. Lancet. 2016;387:1163-1177. Fizazi K, et al. N Engl J Med. 2017;377:352-360.
James ND, et al. N Engl J Med. 2017;377:338-351. Armstrong AJ, et al. J Clin Oncol 2019;37:2974-2986. Davis, ID, et al. N Engl J Med. 2019;381:121-131.
Chi K, et al. N Engl J Med. 2019 381:13-24. Fizazi K, et al Lancet 399:1695-1707. Smith MR, et al. N Engl J Med. 2022;386:1132-1142.

	Treatment		Docetaxel mHSPC	High volume	Visceral mts	Local treatment	*de novo* 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%
PEACE-1	Abi + Doce + ADT	ADT + Doce	100%	64%	13%	--	100%
ARASENS	Daro + Doce + ADT	ADT + Doce	100%	??	17.5%	13%	86%

**95% of patients with M1 disease at randomization (61% of entire population); †95% of patients with metastatic disease at randomization (50% of entire population)*

DOCETAXEL TRIALS IN METASTATIC HSPC

GETUG-15

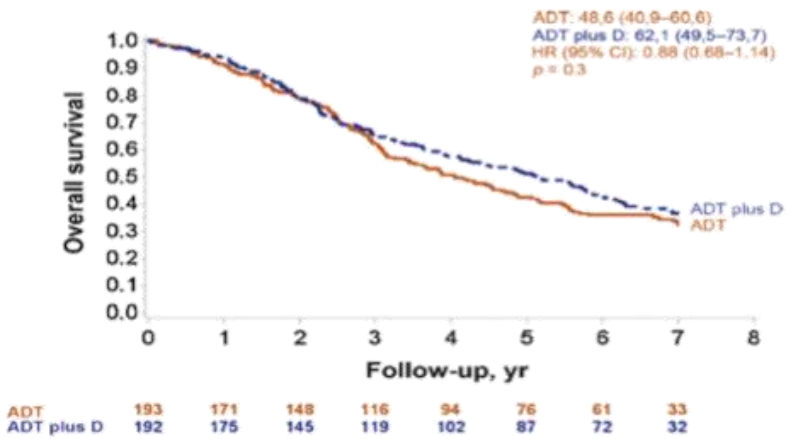
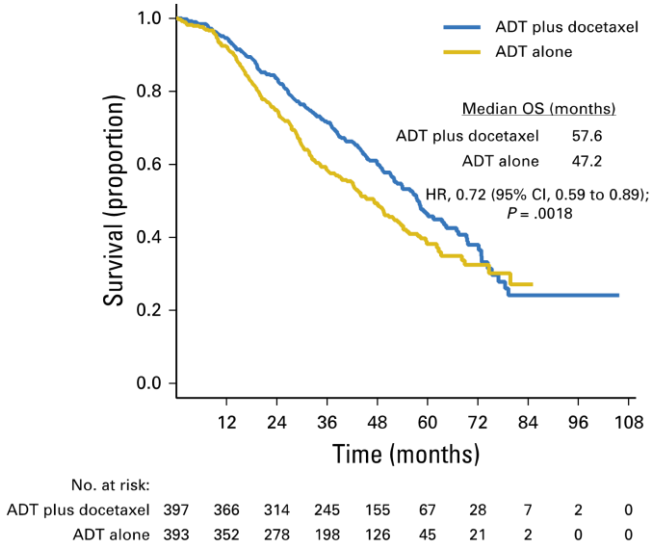
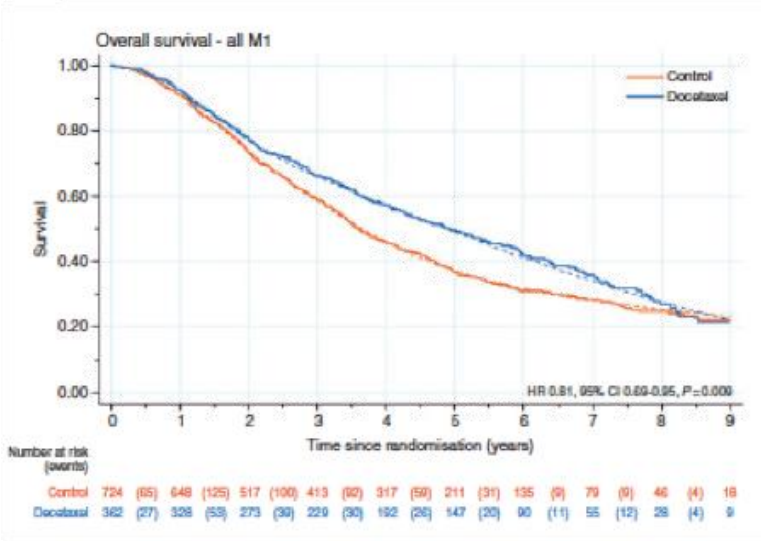


Fig. 1 – Overall survival in the overall population.
ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.

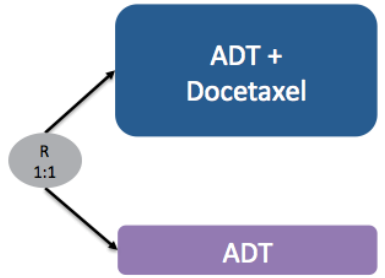
CHAARTED



STAMPEDE



Study	N	Follow up	OS docetaxel	HR OS	95% CI
GETUG-15	385	84 mo	62.1 mo	0.88	0.68-1-14
CHAARTED	790	54 mo	57.6 mo	0.72	0.59-0.89
STAMPEDE M1	2962/1817 M1	78 mo	60 mo	0.76	0.62-0.92

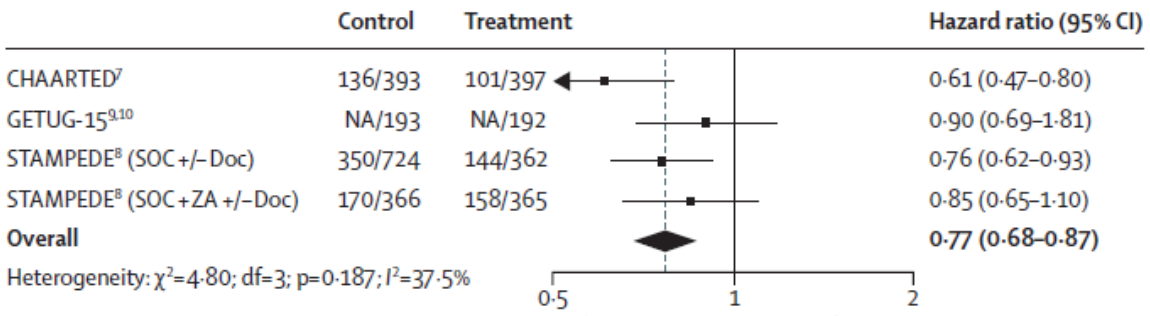


Gravis G, et al. Eur Urol 2016;70:256-262
Kyriakopoulos CE, et al. J Clin Oncol 2018;36:1080-1087
Clarke NW, et al. Ann Oncol 2019;30:1992-2003

mHSPC: Meta-analysis of ADT + docetaxel trials

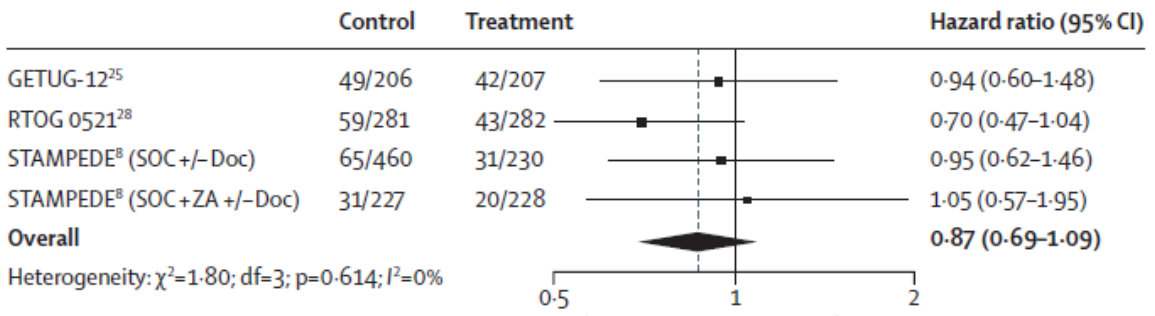
M1 overall survival

A



M0 overall survival

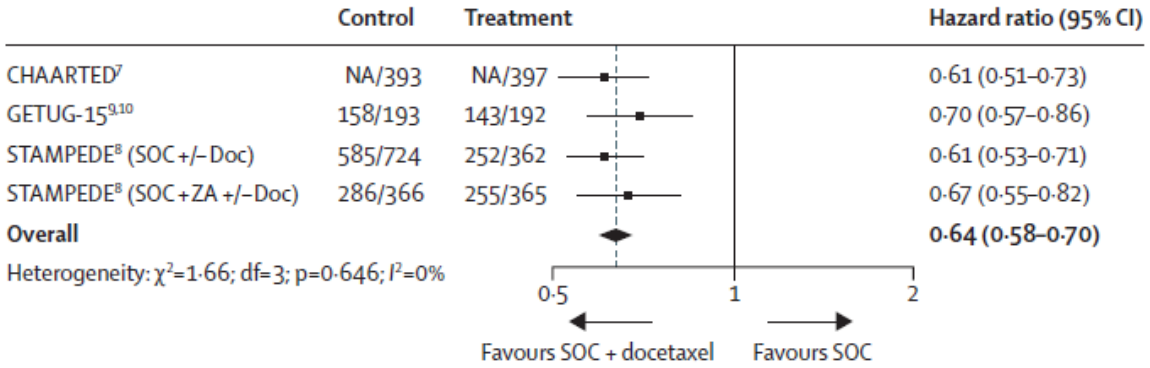
C



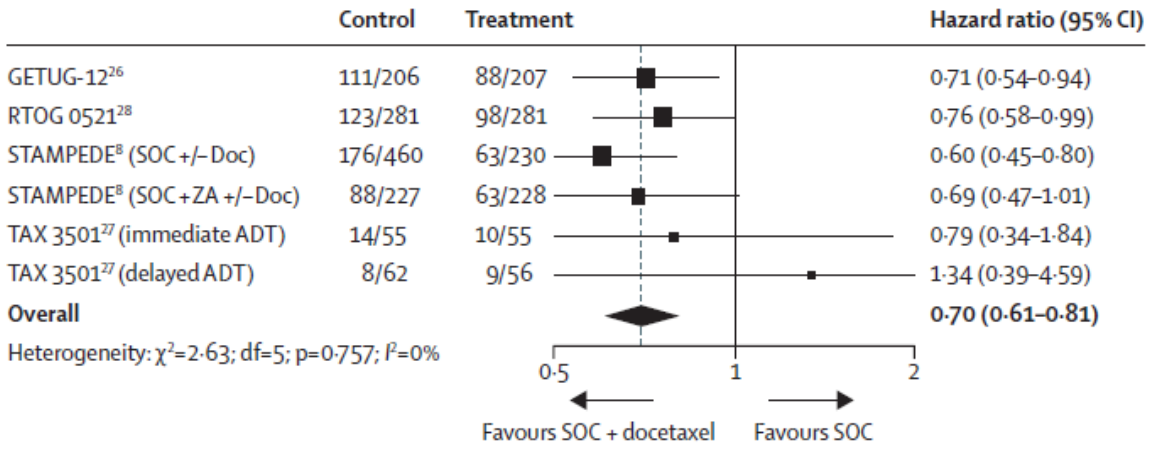
Adding docetaxel to SOC improves survival of men with M1 disease with an absolute improvement of around 9% at 4 years

M1 failure-free survival

B



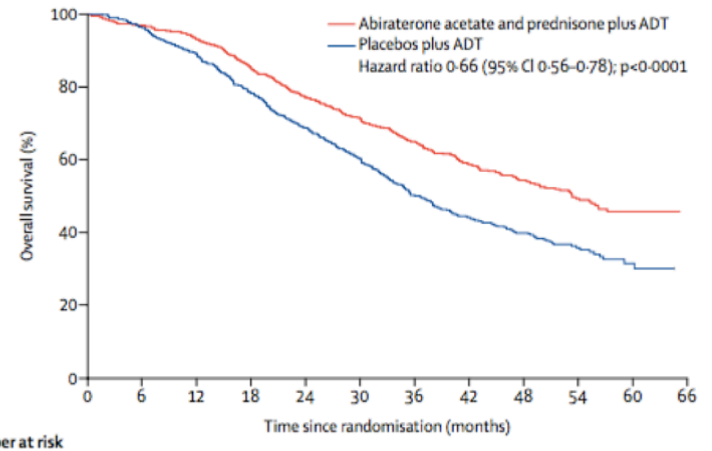
D



Vale CL et al. Lancet Oncol 16: 243-256, 2016

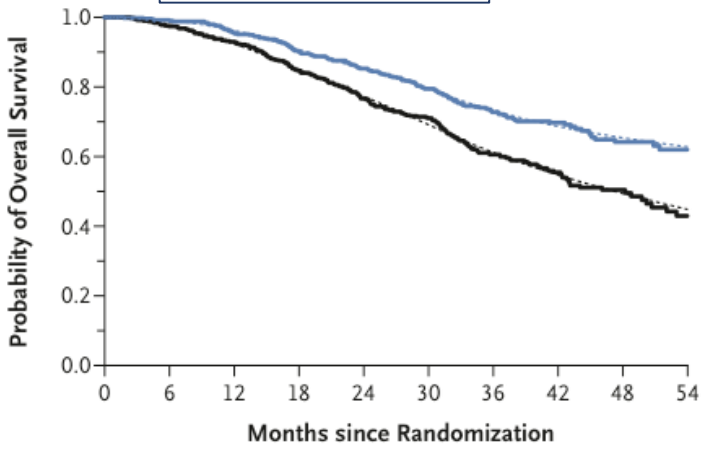
ABIRATERONE TRIALS IN METASTATIC HSPC

LATITUDE



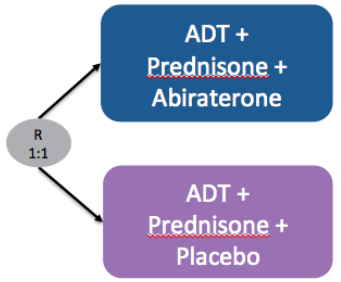
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

STAMPEDE



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

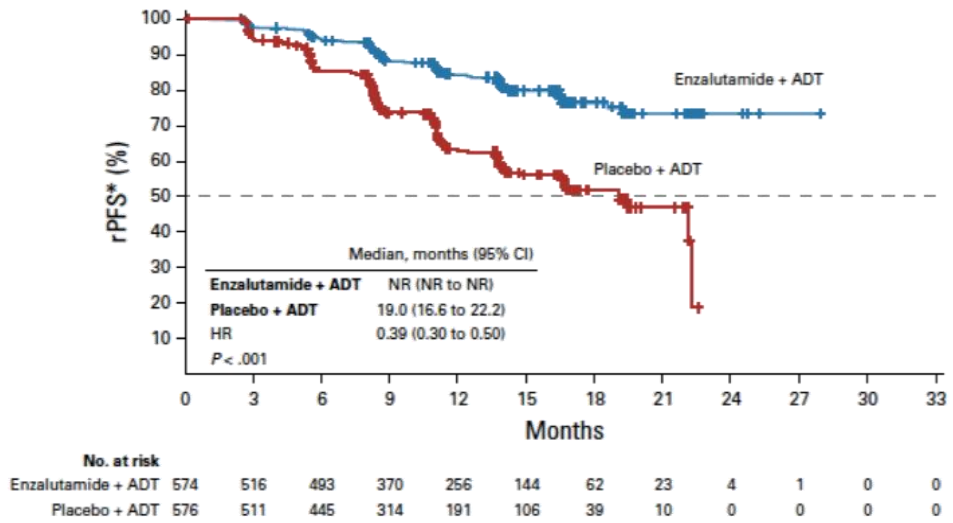
Study	N	Follow up	OS abiraterone	HR OS	95% CI
LATITUDE	1199	52 mo	53.3 mo	0.66	0.56-0.78
STAMPEDE	1917	40 mo	NR	0.63	0.52-0.73



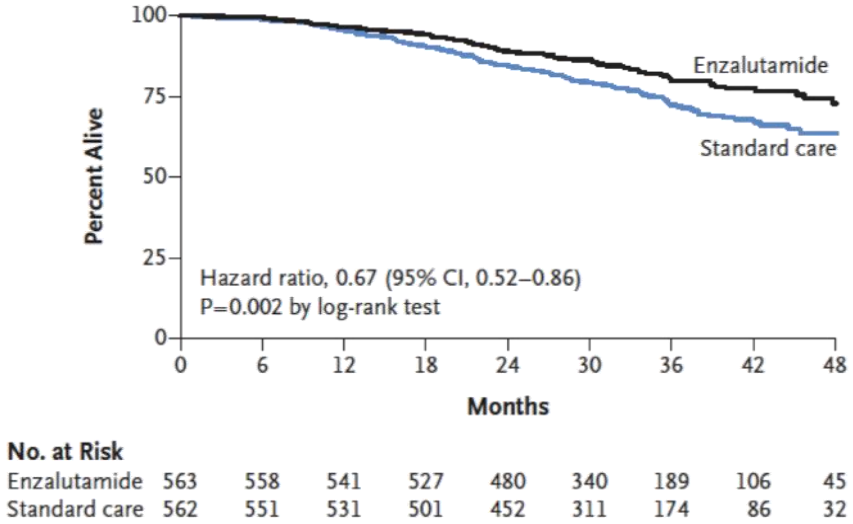
James ND, et al, N Engl J Med 2017;377(4):338-351
Fizazi K, et al. Lancet Oncol 2019; 20: 686-700

ENZALUTAMIDE TRIALS IN MET HSPC

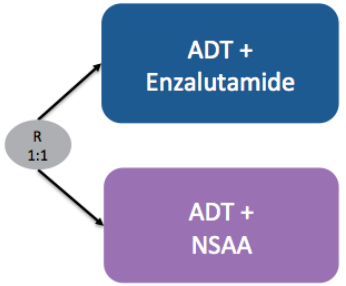
ARCHES



ENZAMET



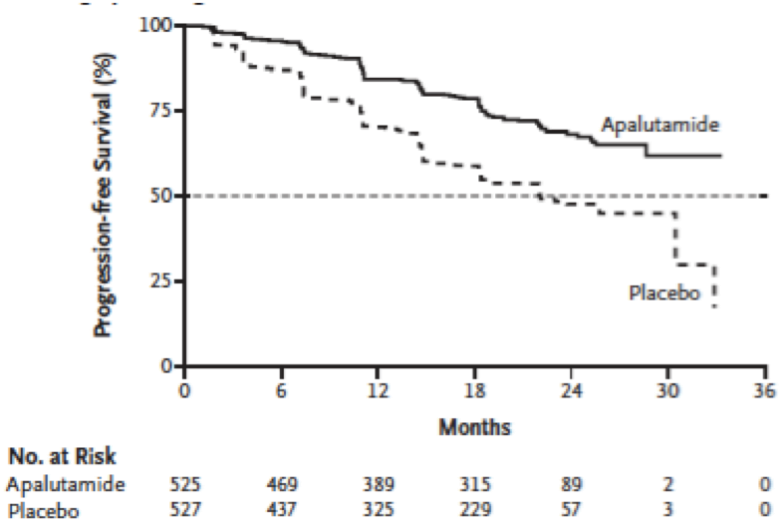
Study	N	Follow up	HR OS (95% CI)	HR PFS (Rx/Clinical)
ARCHES	1150	52 mo	*Immature data* 0.52 (0.33-0.80)	0.39 (0.30-0.50)
ENZAMET	1125	40 mo	**0.67 (0.52-0.86)**	0.40 (0.33-0.49)



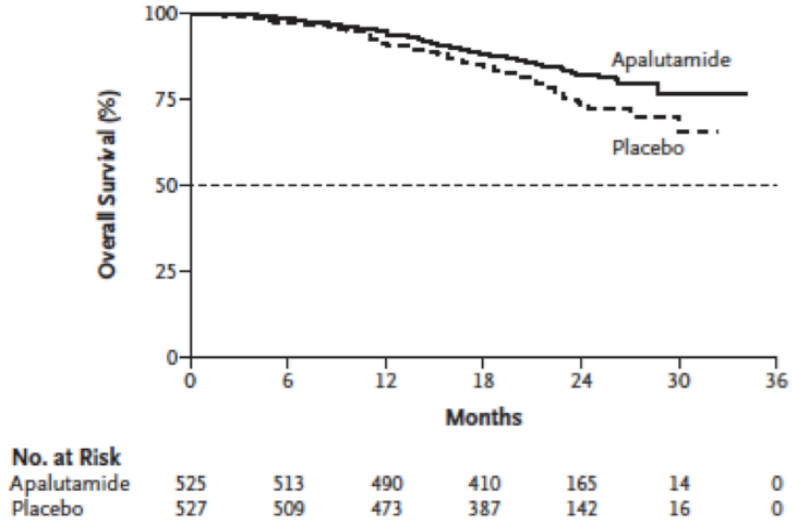
Armstrong AJ, et al. J Clin Oncol 2019;37:2974-2986
Davis ID, et al. N Engl J Med 2019;381:121-131

APALUTAMIDE TRIAL IN MET HSPC

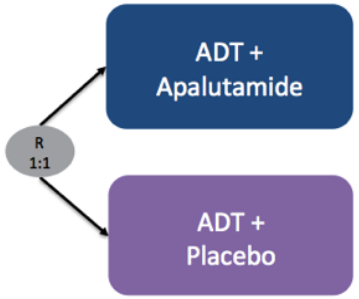
TITAN - rPFS



TITAN - OS



Study	N	Follow up	HR OS (95% CI)	HR rPFS (95% CI)
TITAN	1052	40 mo	0.67 (0.51-0.89)	0.48 (0.39-0.60)



Chi KN, et al. N Engl J Med 2019;381:13-24

Radiotherapy to the primary tumor +ADT in mHSPC

HORRAD study

No OS benefit

only PSA-PFS

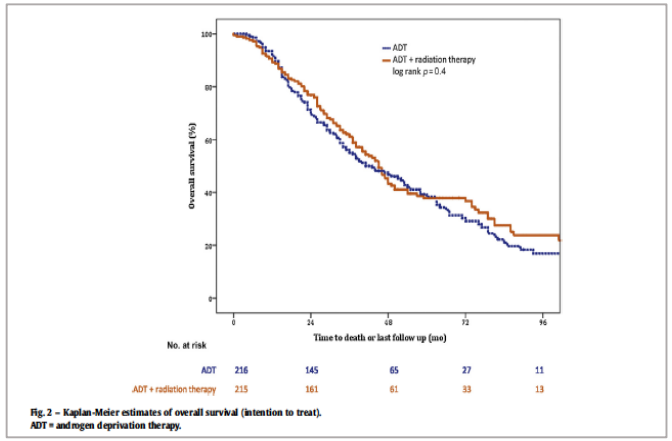


Fig. 2 – Kaplan-Meier estimates of overall survival (intention to treat).
ADT = androgen deprivation therapy.

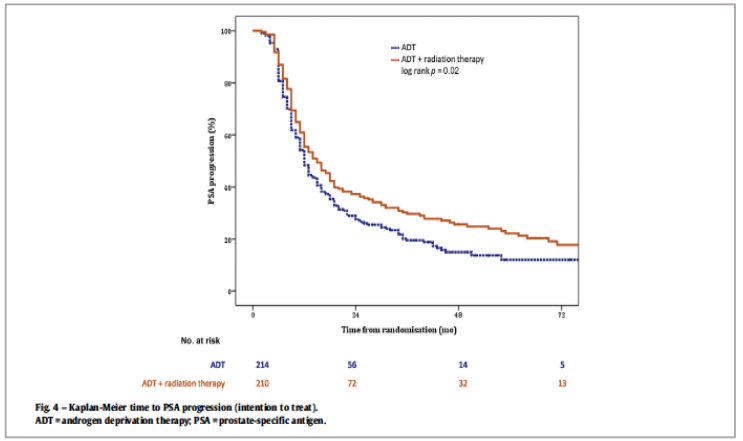
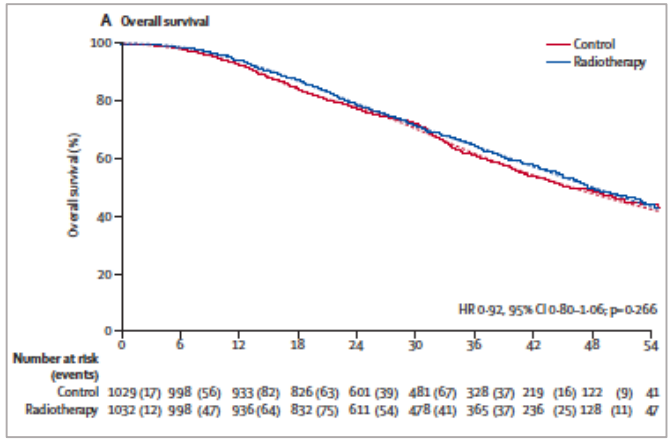


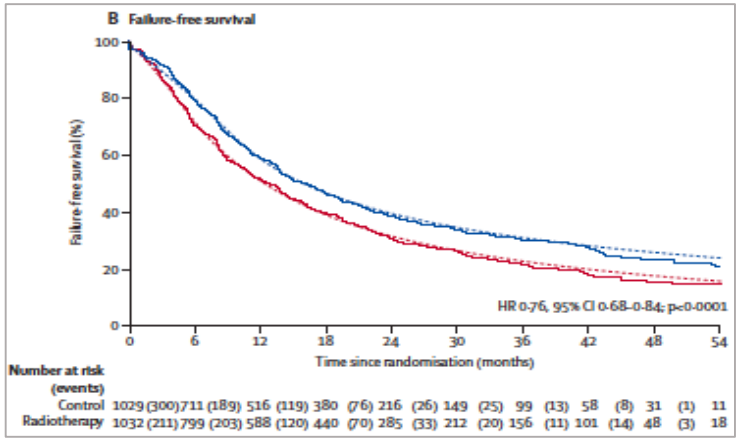
Fig. 4 – Kaplan-Meier time to PSA progression (intention to treat).
ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

STAMPEDE study

OS benefit in

low-volumen disease

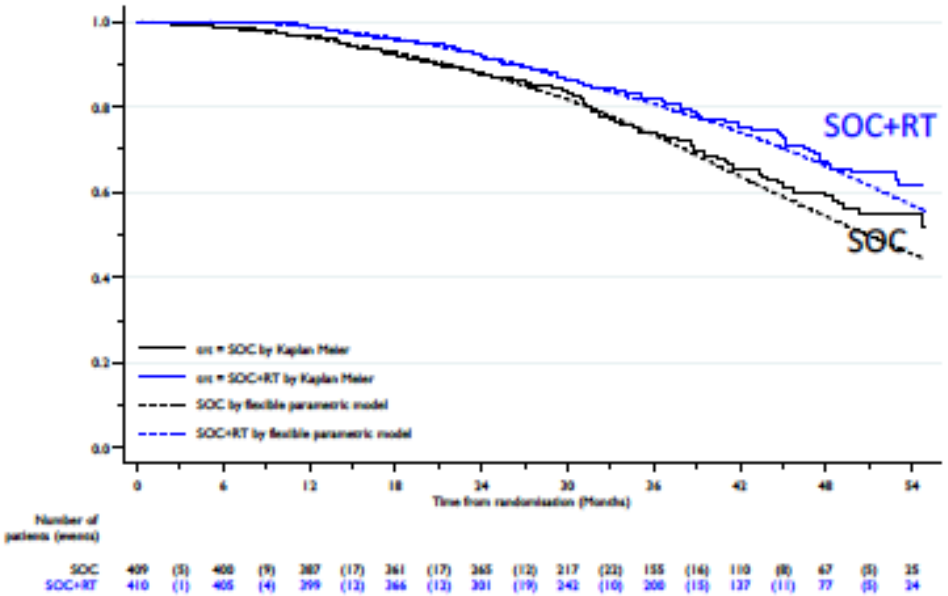




Radioterapia sobre el tumor primario

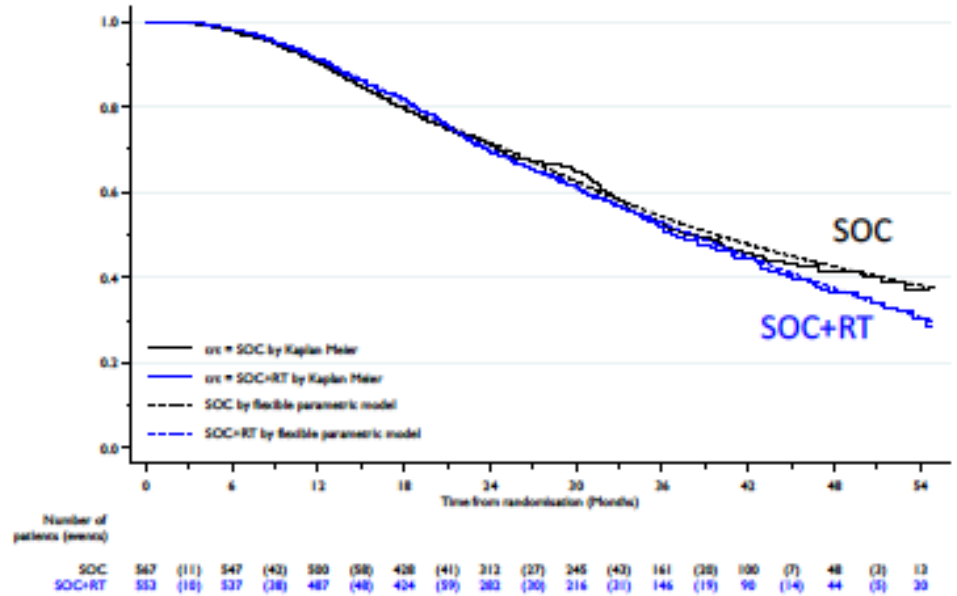
SG

Low burden



HR: 0.68 (95% CI 0.52-0.90); p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

High burden

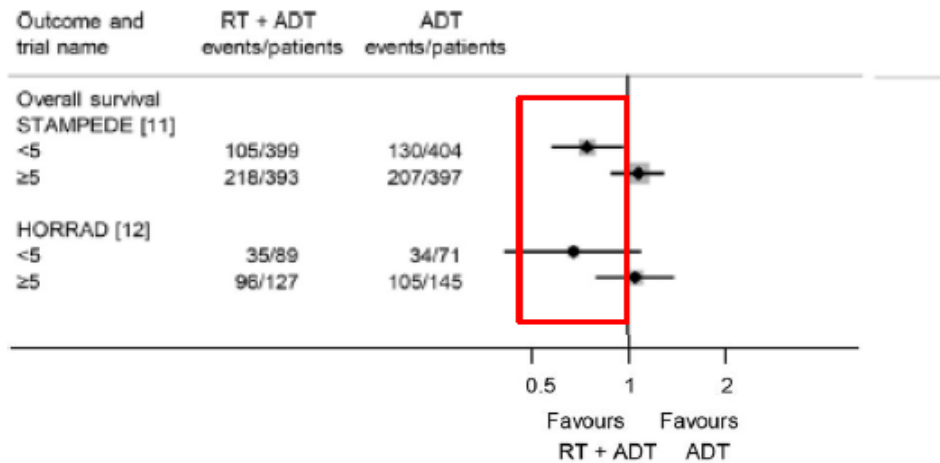


HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%

Parker CC. ESMO 2018

Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Sarah Burdett[a,], Liselotte M. Boevé[b,c,†], Fiona C. Ingleby[d,†], David J. Fisher[a], Larysa H. Rydzewska[a], Claire L. Vale[a], George van Andel[c], Noel W. Clarke[e], Maarten C. Hulshof[f], Nicholas D. James[g], Christopher C. Parker[h], Mahesh K. Parmar[d], Christopher J. Sweeney[i], Matthew R. Sydes[d], Bertrand Tombal[j], Paul C. Verhagen[k], Jayne F. Tierney[a], the STOPCAP M1 Radiotherapy Collaborators*



For patients with 4 or less bone metastasis: 7% improvement in 3-year OS; HR 0.73
Clear treatment effect for low volume patients across two trials (more than docetaxel)

Burdett et al, European Urol 2019

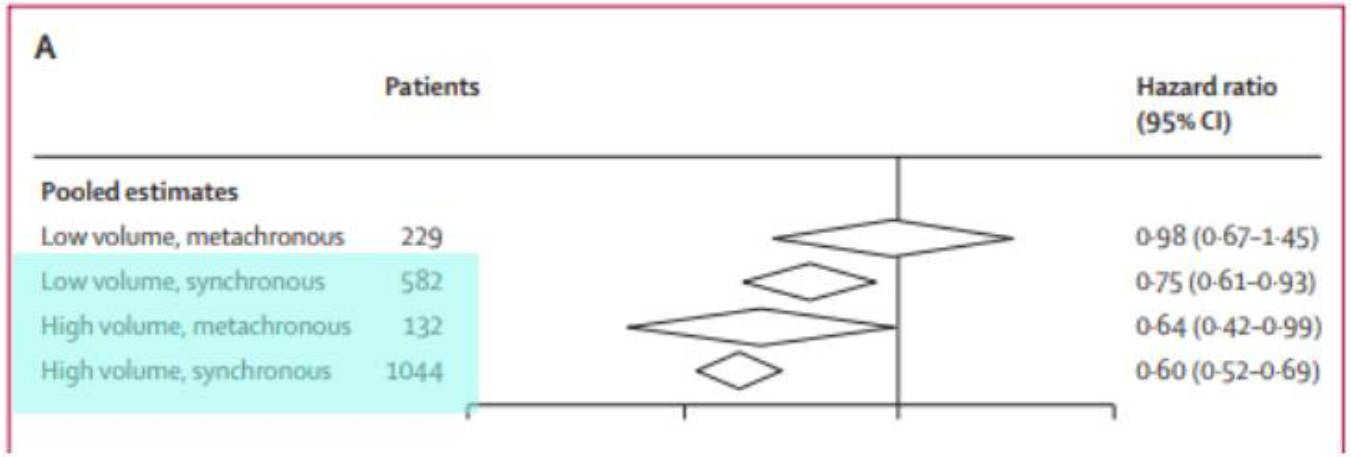
HETEROGENEIDAD EN INTRA E INTER PACIENTE

- Identificación del riesgo individual del paciente

Alto y Bajo volumen
Metacrónico vs sincrónico
Debut complicación aguda

Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials

2261 patients from 3 trials (GETUG-AFU15, CHAARTED, and STAMPEDE trials),



- **Beneficio de QT** en alto volumen
- **Beneficio de QT** en debut m1 (independiente de la carga)

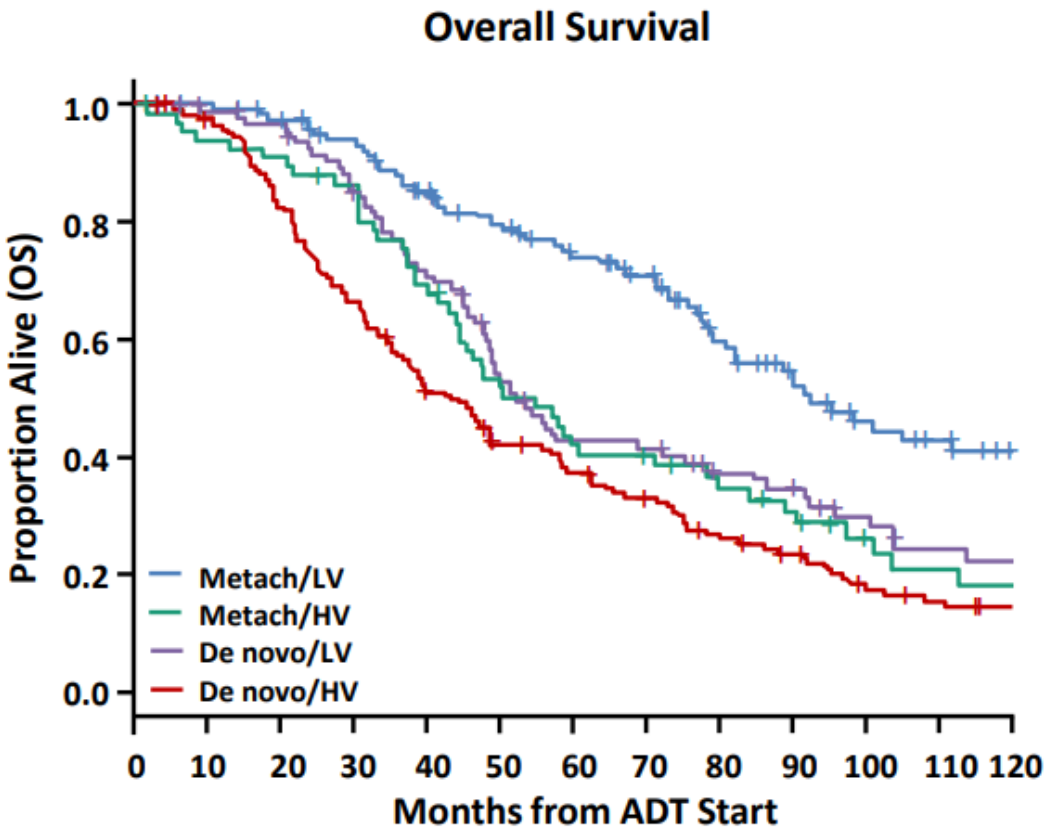
Prognoses Stratification by Type of Presentation & Extent of Metastases

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)

ADT: LHRHa therapy of choice or orchiectomy

Metachronous metastases: relapse after radical local therapy

High volume: visceral metastases and/or 4 or more bone metastases, at least one beyond vertebra and pelvis



LHRHa, luteinizing hormone releasing hormone analogue; 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.

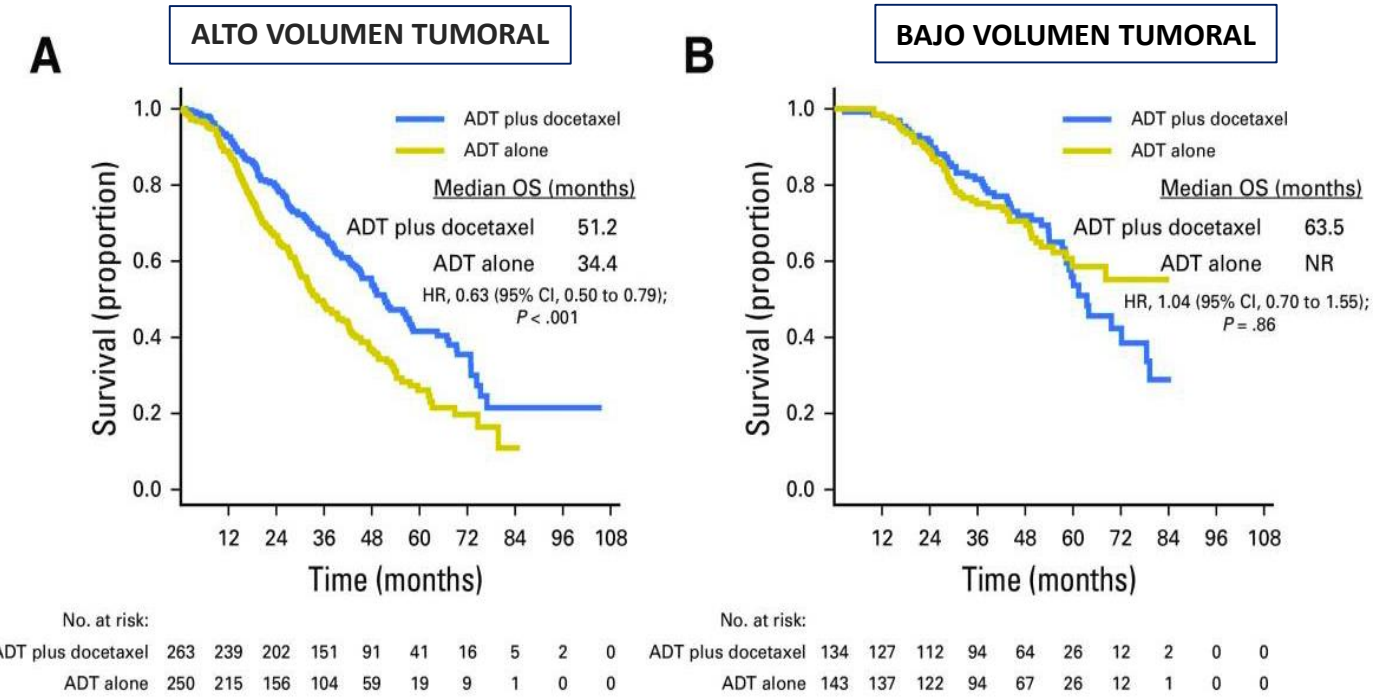
Courtesy C. Sweeney, B. Rini, S. Gillessen

INTEGRITY CONTINUING EDUCATION

Silke Gillessen at Prostate Perceptorship 2021 LUGANO

CHAARTED long follow up

8-year survival rates



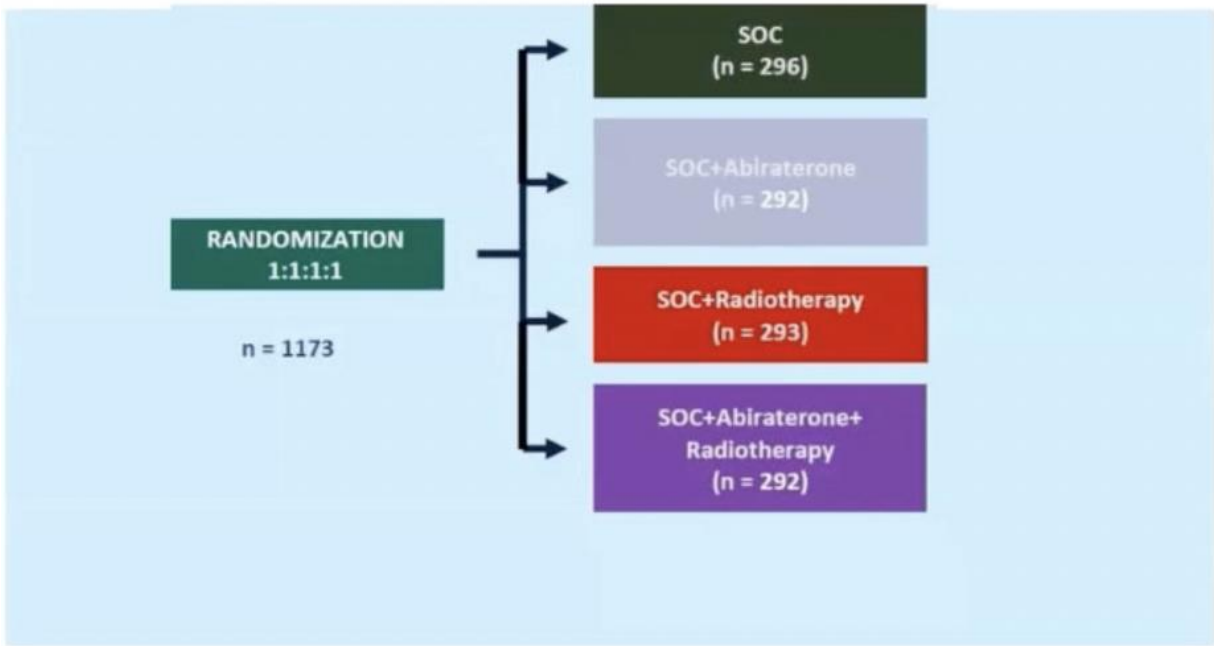
	ADT+D		ADT Alone		HR[3] (95% CI; p-value)
	# Death/N	8-year OS rate (95% CI)	# Death/N	8-year OS rate (95% CI)	
Overall	266/397	34.9% (30.0, 39.8)	286/393	28.9% (24.3, 33.5)	0.77 (0.65, 0.92; p=0.004)
De novo[1] High Volume	157/214	28.5% (22.2, 35.1)	174/207	15.4% (10.7, 20.8)	0.67 (0.53, 0.84; p=0.0005)
De novo[1] Low Volume	42/75	44.6% (32.9, 55.6)	52/79	40.9% (29.6, 51.9)	0.77 (0.51, 1.18; p=0.23)
Metach[2] High Volume	32/49	37.1% (23.6, 50.6)	34/42	19.8% (9.3, 33.1)	0.84 (0.49, 1.46; p=0.54)
Metach[2] Low Volume	35/59	43.4% (30.1, 55.9)	25/64	64.2% (50.9, 74.8)	1.65 (0.95, 2.87; p=0.07)
High Volume	189/263	30.2% (24.4, 36.1)	209/250	16.0% (11.7, 21.0)	0.67 (0.55, 0.82; p<.0001)

Median OS in the overall population was 60.4 and 47.2 months in the ADT + docetaxel and ADT arms respectively (HR 0.77, 95% CI 0.65, 0.92; p=0.004);

Tripathi ASCO 22

Abiraterone + prednisone added to ADT + docetaxel in de novo mHSPC (PEACE-1): a multicentre, openlabel, randomised, phase 3 study with a 2 × 2 factorial design

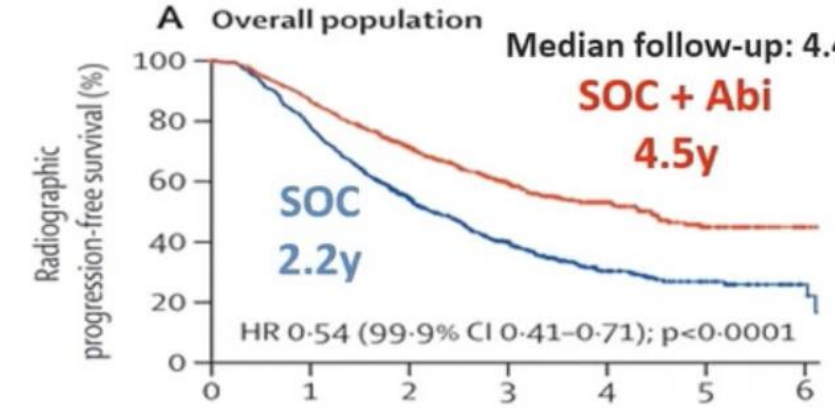
≥ 1 distant lesion on bone and/or CT scan), ECOG PS 0-2



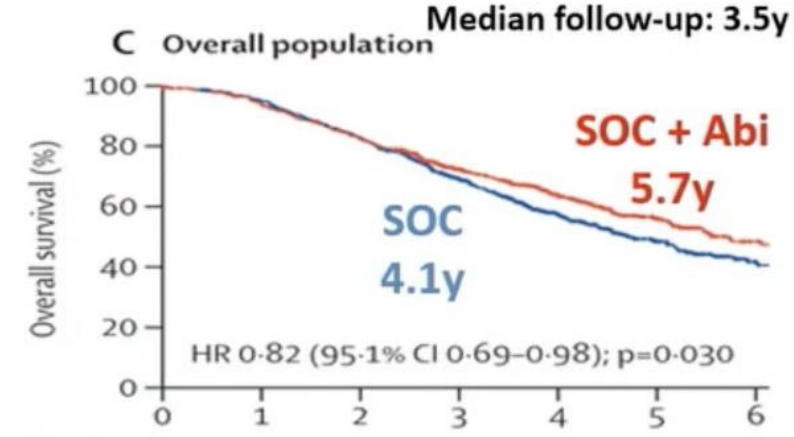
Grade 3-5 AEs (>5%, ABI vs control):
neutropenic fever (5% vs 5%), neutropenia (10% vs 9%), liver toxicity (6% vs 1%) and HTN (21% vs 13%)

SOC, ADT + docetaxel.
Fizazi K, et al. *Lancet*. April 8, 2022.

Coprimary Endpoints (Overall Population)

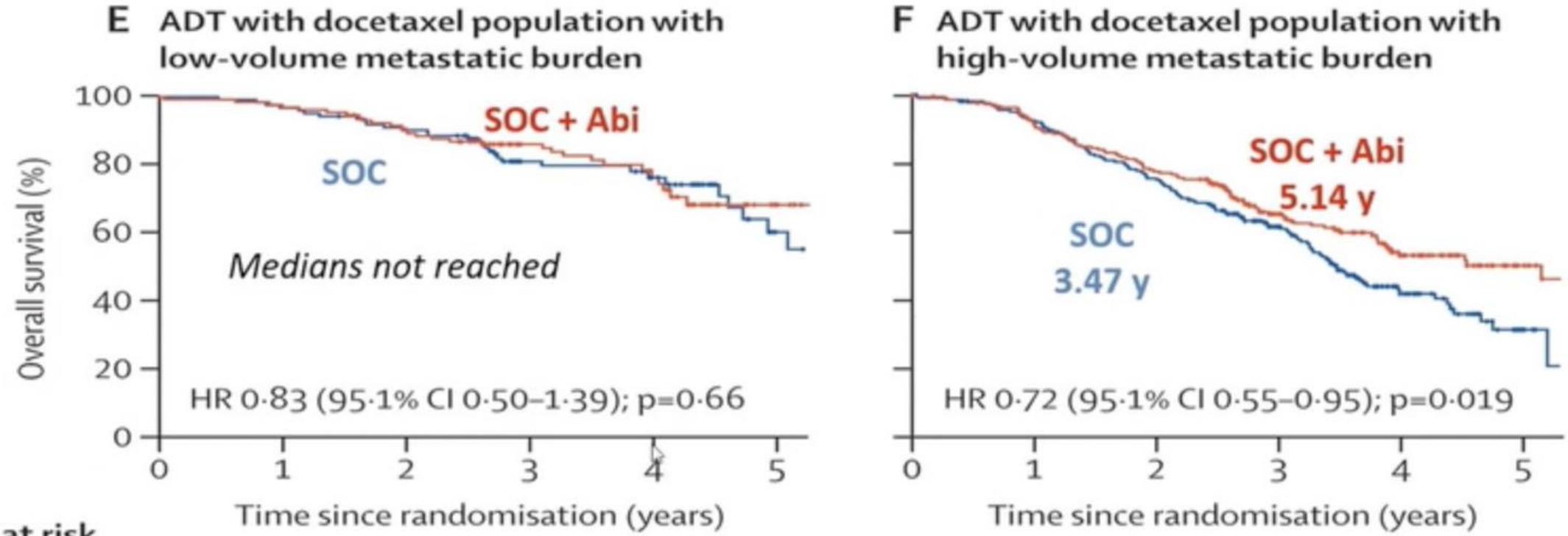


Number at risk							
SOC without abiraterone groups	589	453	274	158	72	31	7
SOC plus abiraterone groups	583	495	355	230	119	47	12



Number at risk							
SOC without abiraterone groups	589	556	480	334	207	101	37
SOC plus abiraterone groups	583	541	470	340	230	111	47

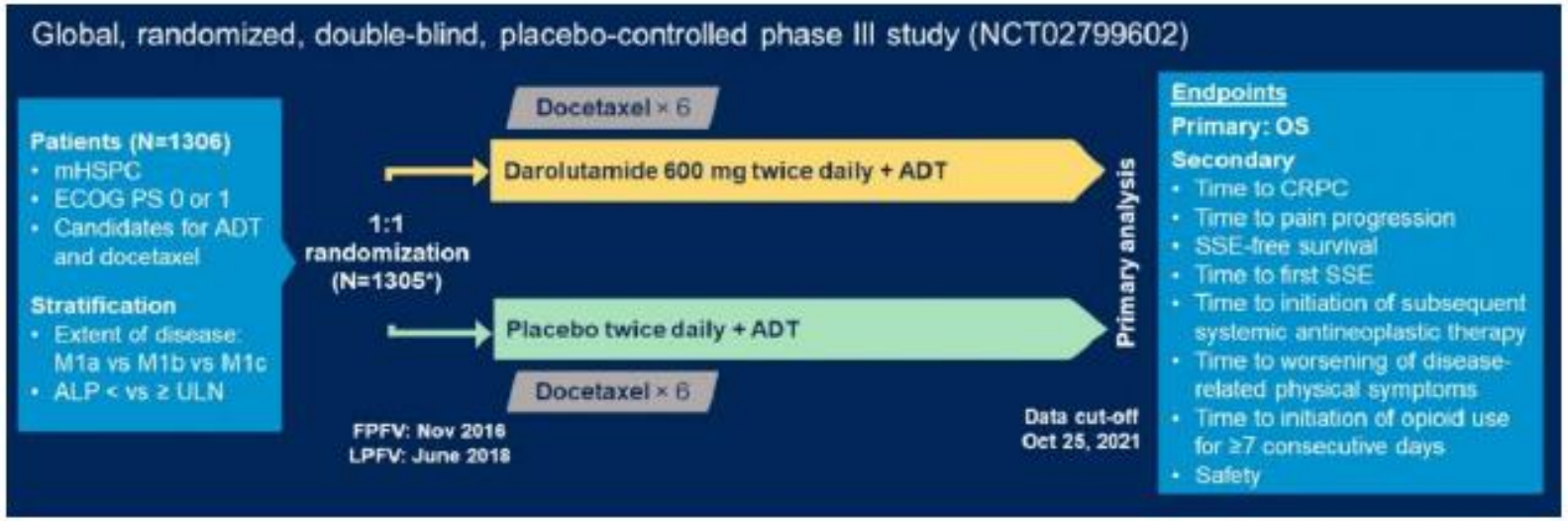
Phase 3 PEACE-1 Study (2x2): Abiraterone + ADT + Docetaxel ± RT for mHSPC—Outcomes by Tumor Burden



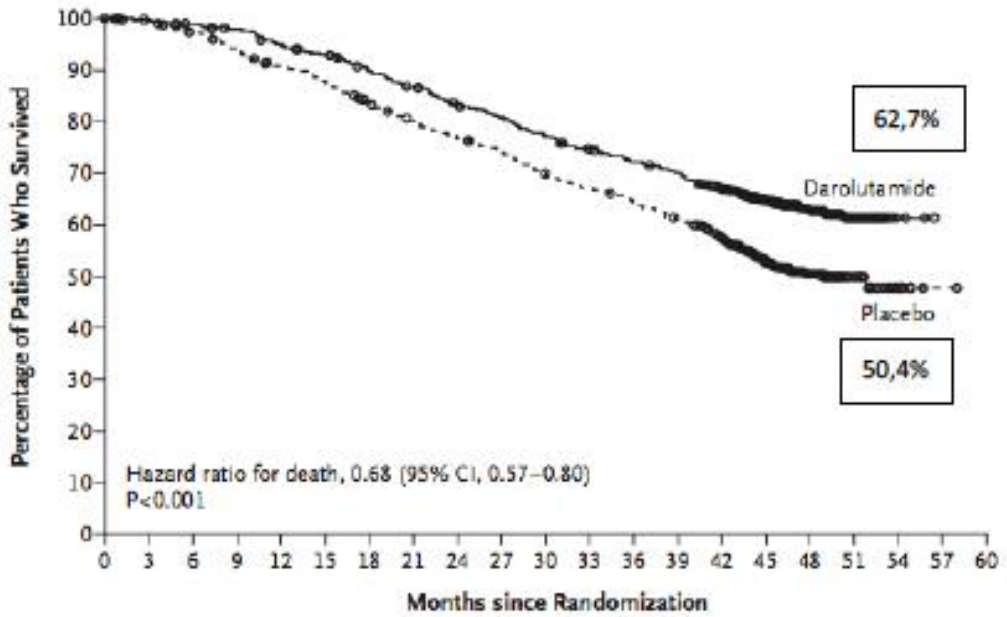
Number at risk												
SOC without abiraterone groups	123	119	110	71	39	12	232	210	171	101	39	6
SOC plus abiraterone groups	131	127	116	80	41	9	224	201	171	103	57	16

	Low-volume	High-volume
Median rPFS, y (HR; 99.9% CI; P)	**NR vs 2.7 years (0.58; 0.29–1.15; .0061)**	**4.1 vs 1.6 (0.47; 0.30-0.72; <.0001)**

ARASENS TRIAL



86% *de novo* metastatic



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

Fizazi K, Lancet, 2022

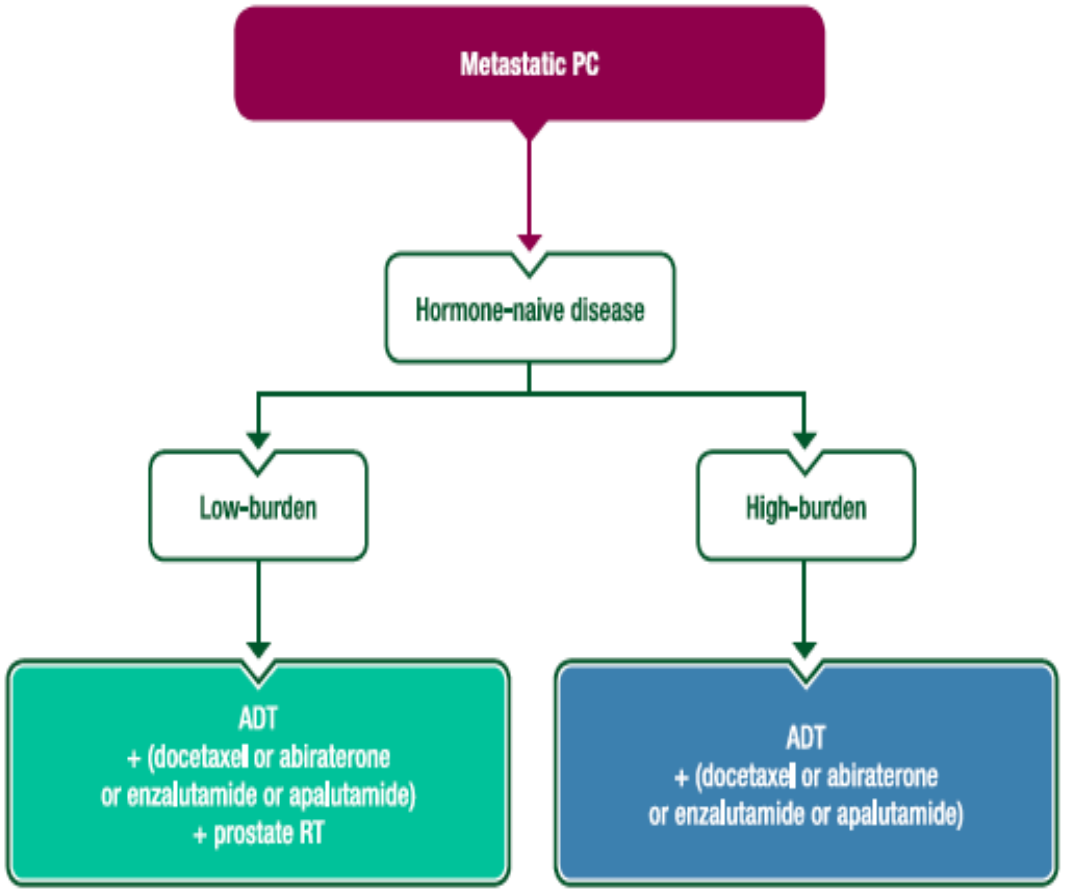
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker[1], E. Castro[2], K. Fizazi[3], A. Heidenreich[4], P. Ost[5], G. Procopio[6], B. Tombal[7] & S. Gillessen[8,9,10], on behalf of the ESMO Guidelines Committee*



Recommendation	Level of recommendation
ADT is recommended as first-line treatment of mHNPC in combination with • abiraterone/prednisone (ESMO-MCBS) v1.1 score: 4] or apalutamide [ESMO-MCBS v1.1 score: 4] or • docetaxel [ESMO-MCBS v1.1 score: 4] or • enzalutamide [ESMO-MCBS v1.1 score: 4].	I, A
RT to the primary tumour combined with the systemic treatment is recommended for patients with low volume mHNPC.	I, A
ADT alone is recommended as first-line systemic treatment of mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel	III, A

SEOM clinical guidelines for the treatment of advanced prostate cancer (2020)

A. González del Alba[1] · M. J. Méndez-Vidal[2] · S. Vazquez[3] · E. Castro[4] · M. A. Climent[5] · E. Gallardo[6] · E. Gonzalez-Billalabeitia[7,8] · D. Lorente[9] · J. P. Maroto[10] · J. A. Arranz[11]

Recommendation	Level of recommendation
In high-risk or high-volume mHNPC patients, ADT should be combined with docetaxel, abiraterone, enzalutamide or apalutamide, rather than using ADT alone.	I, A
In low-volume mHNPC patients, RT to the primary tumor combined with systemic therapy is recommended	I, B
In symptomatic metastatic patients, ADT should be offered immediately to palliate symptoms and prolong survival.	I, A
Deferred ADT could be considered in selected wellinformed asymptomatic patients to minimize longterm adverse effects	II, A
Combination of LHRH with first generation antiandrogens for longer than one month to avoid androgen flare, does not offer clinical benefit	I, D

González del Alba A, et al. Clin Transl Oncol 2021;23:969-979

EAU22 | AMSTERDAM 1-4 July 2022

Proposed mHSPC Treatment Plans

AKA: @ChrisSweens1 approach

Prognosis ADT alone	Presentation of Metastases (prostate intact Y/N)	Metastases Distribution	Main Plan Testo suppression +	Trials
Good ~ 8yrs	Metachronous	3 or less bone mets (+/- NRLN)	Abi/Enza/Apa	Add on SBRT New Agents
Intermediate ~ 4.5 yrs	Metachronous	4 or more bone mets (visc mets: rare)	Abi/Enza/Apa	New Agent (Consider docetaxel#)
Intermediate ~ 4.5 yrs	Synchronous	3 or less bone mets (+/- NRLN)	Abi/Enza/Apa plus Radiate Prostate^	SBRT as MDT if "oligometastatic"
Poor ~ 3 yrs	Synchronous	4 or more bone mets &/or visceral mets	Abi/Daro/Enza + docetaxel# or Abi/Enza/Apa	Trials with New Agents

#If chemofit; ^Await PEACE-1

(i.e. potent hormonal therapy is back-bone for ALL patients
→ add in docetaxel and prostate radiation for select patients)

Cáncer de próstata resistente a castración. CPRC.

❑ Definición.

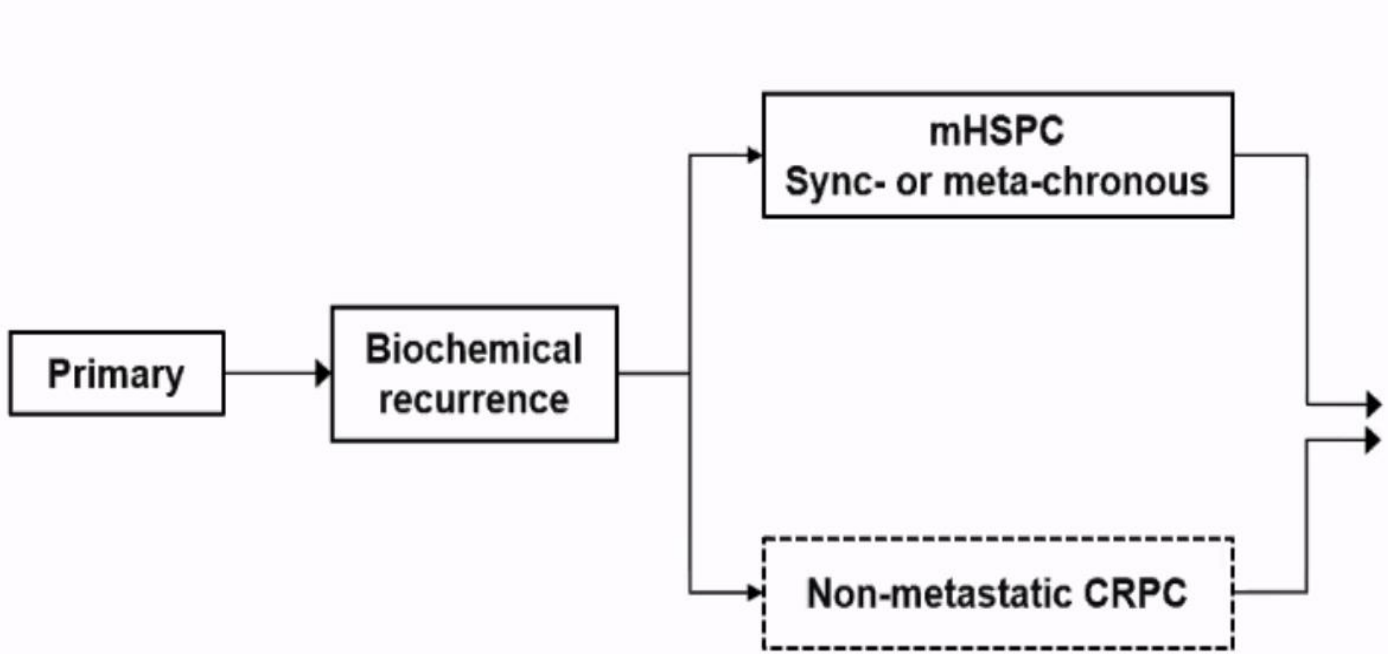
Tres elevaciones consecutivas de PSA, separadas por al menos una semana, con dos incrementos del 50% sobre el nadir y con una cifra de PSA mayor de 2 ng/ml
Niveles de testosterona inferiores a 50 ng/dl o 1,7 nmol/l.
Progresión de lesiones óseas ≥ 2 en gammagrafía ósea o progresión de lesiones de tejidos blandos según los criterios RECIST

- ◉ Mal pronóstico

  - Se asocia a **deterioro rápido de la calidad de vida.**
  - **Más del 80% de los pacientes presentan dolor óseo asociado a metástasis ósea** con disminución de la calidad de vida y mayor riesgo de muerte.
  - El **20-30% presentan metástasis visceral** (pulmón y/o hígado), que se asocia con peor pronóstico
  - Mediana desde la progresión hasta la muerte ≈30 meses

Sandford M et al. Drugs 2013;73:1723.
Evans CP, et al. Eur Urol 2016;70(4):675.
Shore ND, et al. Lancet Oncol 2016;17(2):153.

Treatment landscape in mCRPC



1L mCRPC	2L mCRPC	3+L mCRPC	
Docetaxel 2004	Cabazitaxel 2010	Cabazitaxel 2010	Radium-223 2013
Abiraterone 2012	Abiraterone 2011	Abiraterone 2011	
Enzalutamide 2014	Enzalutamide 2012	Enzalutamide 2012	

US FDA only:
Radium-223 (1/2/XL)
sipuleucel-T (1/2/XL)
Pembrolizumab[e] (>2L)

Olaparib[a,b] (post-ARPI) 2020

^{177}Lu-PSMA-617[c] (post-ARPI, post-docetaxel) 2022

Olaparib[d] + abiraterone 2022

Niraparib[a] + abiraterone 2023

US FDA only:
Talazoparib[a] + enzalutamide (2023)

If not otherwise indicated, approval lines and dates reflect treatment approvals in the EU (as of August 2023).
Please refer to treatment guidelines (e.g. ESMO) for specific advice on treatment sequencing.

What are the goals of treatment?

Prolonging survival

In **symptomatic** patients: improving symptoms → response to treatment

Improving symptoms, QoL measures, delaying time to clinical progression, SREs

In **asymptomatic** patients: preserving quality of life → delaying progression

Preventing clinical progression, SREs, time to QoL deterioration, preventing toxicity

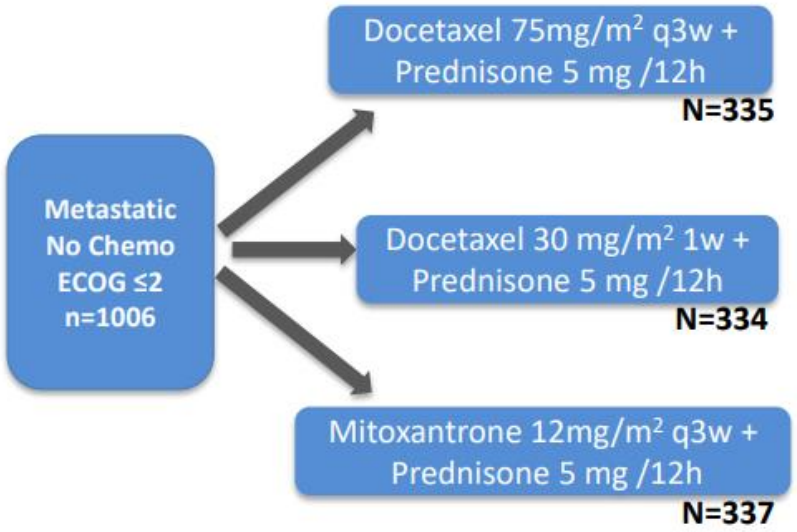
PSA response has been associated with OS but is not a proven surrogate

Different agents may have different effects on PSA response or progression

Scher et al. J Clin Oncol 2016;34:1402-1418.

Docetaxel

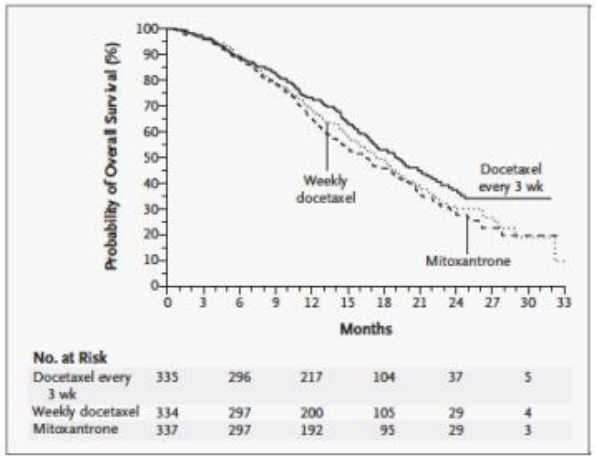
TAX-327



Study end points:

- Primary: **OS**
- Secondary: **Pain reduction, QoL, ≥50% PSA decline, tumor response**

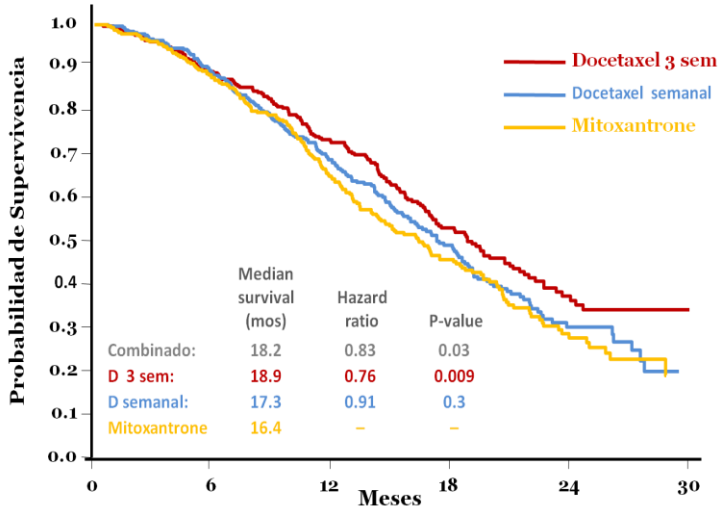
Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer



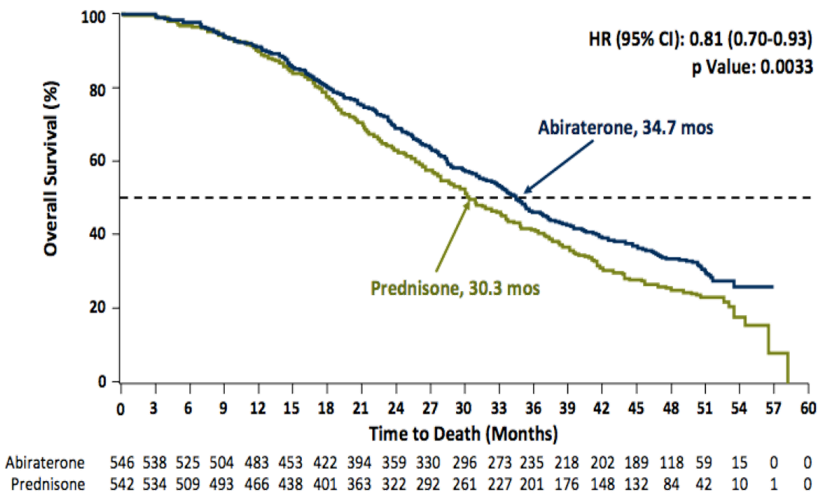
	Docetaxel 75mg/m² q3w	Docetaxel 1Wk 30 mg/m² 1w	Mitoxantrone 12mg/m² q3w
OS 95%CI; P-value	**18.9** (17.7-21.2) P=0.009	**17.4** (15.7-19) P=0.36	**16.5** (14.4-18.6)
Pain reduction 95%CI; P-value	**35** (27-43) P=0.01	**31** (24-39) P=0.08	**22** (16-29)
%≥50 PSA decrease 95%CI P-value	**45** (40-51) P<0.001	**48** (42-54) P<0.001	**32** (26-37)
ORR 95%CI; P-value	**12** (7-19) 0.11	**8** (4-14) 0.59	**7** (3-12)
QoL 95%CI; P-value	**22** (17-27) P=0.009	**23** (18-28) P=0.005	**13** (9-18)

PRIMERA LÍNEA DE TRATAMIENTO EN CPRCm. BENEFICIO DE SUPERVIVENCIA

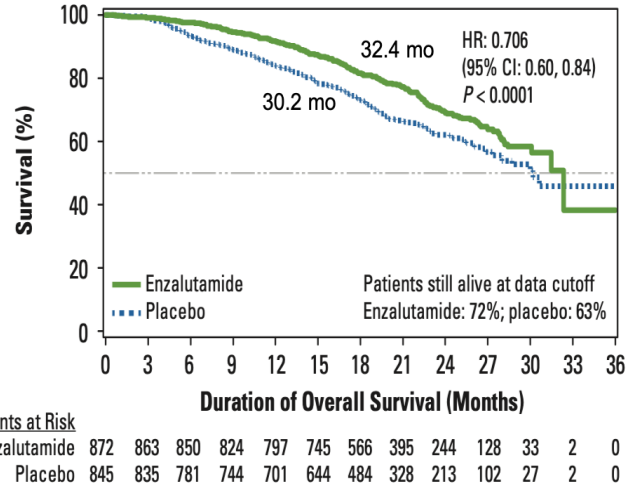
Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer



Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy



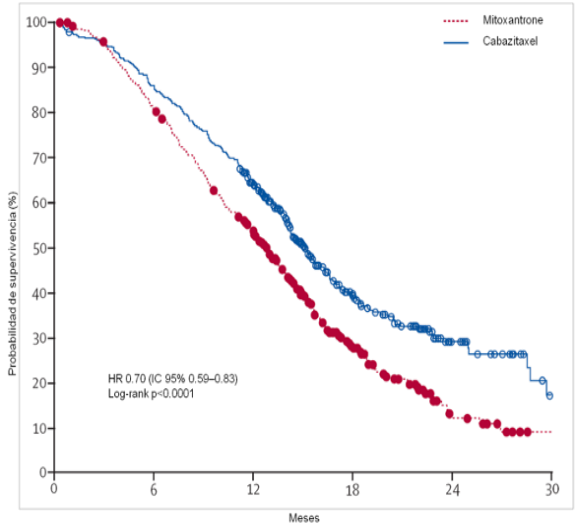
Enzalutamide in Metastatic Prostate Cancer before Chemotherapy



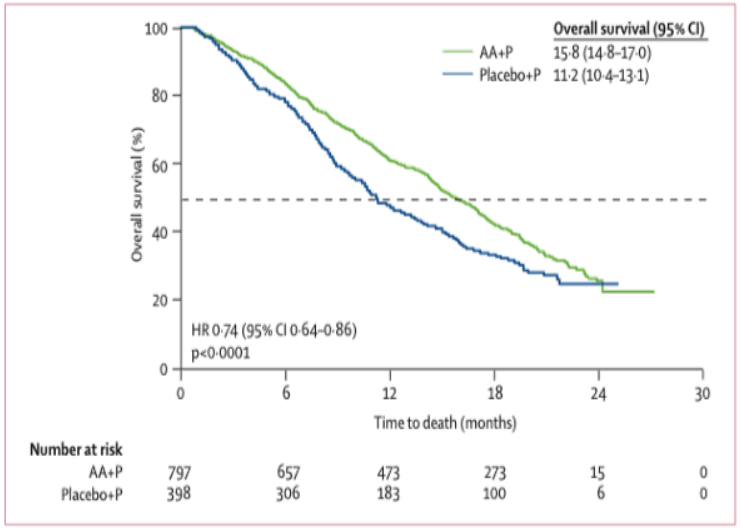
Tannock IF, et al. N Engl J Med 2004;351(15):1502-1512
Ryan CJ, et al. N Engl J Med 2013;368:138-148
Beer TM, et al. N Engl J Med 2014;371:424-433

SEGUNDA LÍNEA DE TRATAMIENTO EN CPRCm. BENEFICIO DE SUPERVIVENCIA

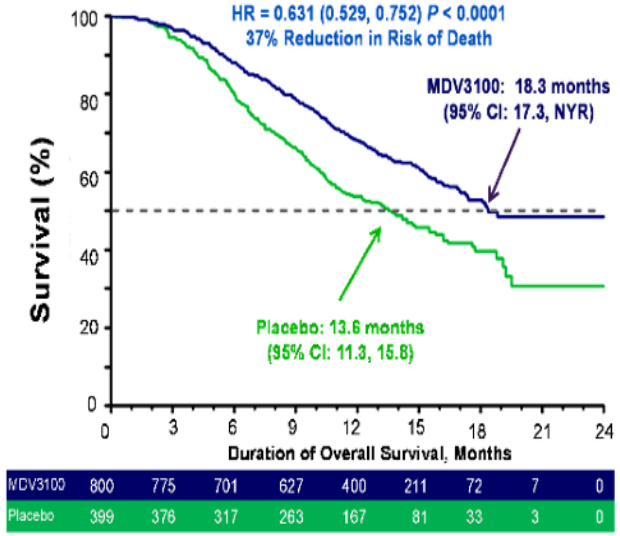
Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial



Abiraterone and Increased Survival in Metastatic Prostate Cancer



Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy



de Bono JS, et al. Lancet 2010;376:1147-1154
de Bono JS, et al. N Engl J Med 2011;364:1995-2005
Scher HI, et al. N Engl J Med 2012;367(13):1187-1197

Therapeutic options in mCRPC: Wich trials support the use of an agent in 1st line?

Study	Agents	N	Indication	HR	Δ OS
TAX-327	Docetaxel/P vs mito/P	1006	mCRPC	0.76	+2.9
IMPACT	Sipuleucel-T vs pbo	512	mCRPC (pre-Doc)	0.78	+4.1
COU-AA-302 COU-AA-301	Abiraterone/P vs P Abiraterone/P vs P	1088 1195	mCRPC (pre-Doc) mCRPC (post-Doc)	0.81 0.74	+4.4 +4.6
PREVAIL AFFIRM	Enzalutamide vs pbo Enzalutamide vs pbo (or P)	1717 1199	mCRPC (pre-Doc) mCRPC (post-Doc)	0.71 0.63	+4.0 +4.8
TROPIC	Cabazitaxel/P vs mito/P	755	mCRPC (post-Doc)	0.70	+2.4
ALSYMCPA	Radium-223 vs pbo	921	mCRPC	0.70	+2.8

THIRD LINE IN mRPC – CARD TRIAL

mCRPC
progressing ≤ 12 months on ABI or ENZA

before or after Docetaxel

RANDOMIZE 1:1

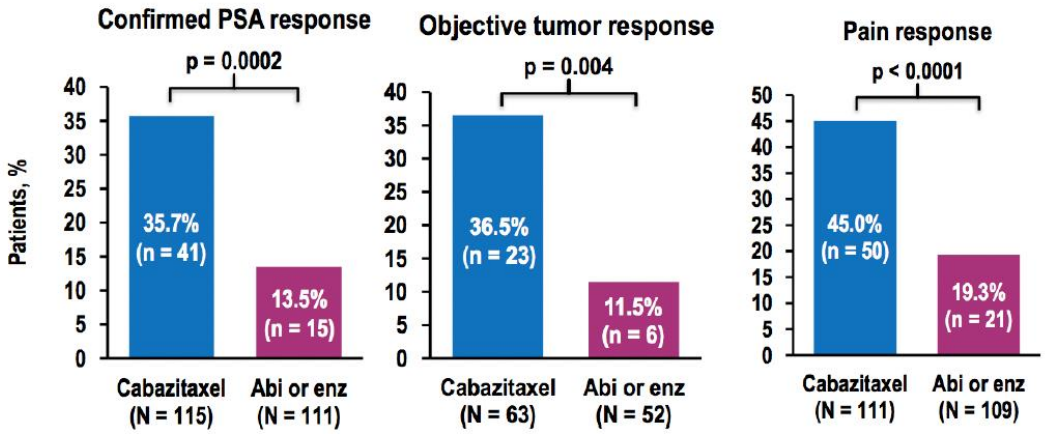
CABAZITAXEL
n=162

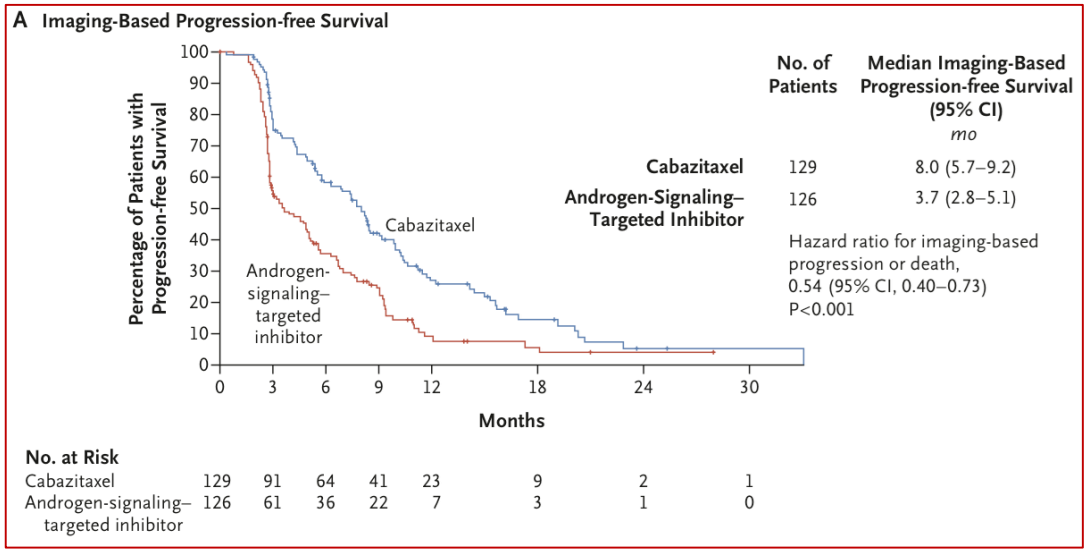
Switch to another AR-targeted agent (ABI or ENZA depending of first therapy)
n=162

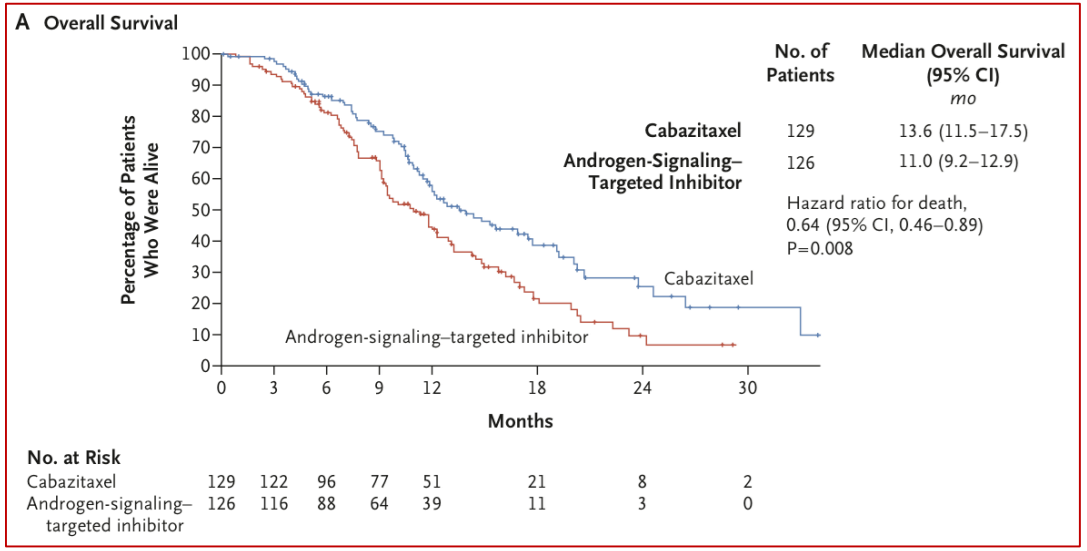
Stratification factors:
ECOG (0-1 vs 2),
time to progression (≤6 vs 6-12 mths),
timing of AR-targeted agent (before or after docetaxel)

Primary endpoint: radiological PFS

Secondary end-points: PSA response, ECOG, PFS (clinical or radiological), objective tumor response, pain, (QoL), time to SREs, OS, safety, biomarkers







de Wit R, et al. N Engl J Med 2019 Dec 26;381(26):2506-2518

¿Donde posicionar Radium 223?

Pacientes sintomáticos
sin metástasis viscerales
Con/sin Docetaxel previo

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

Estudio ALSYMPCA

Pacientes con CPRCm en progresión
Metástasis óseas
Chemo-naïve o post-docetaxel
(N = 921)

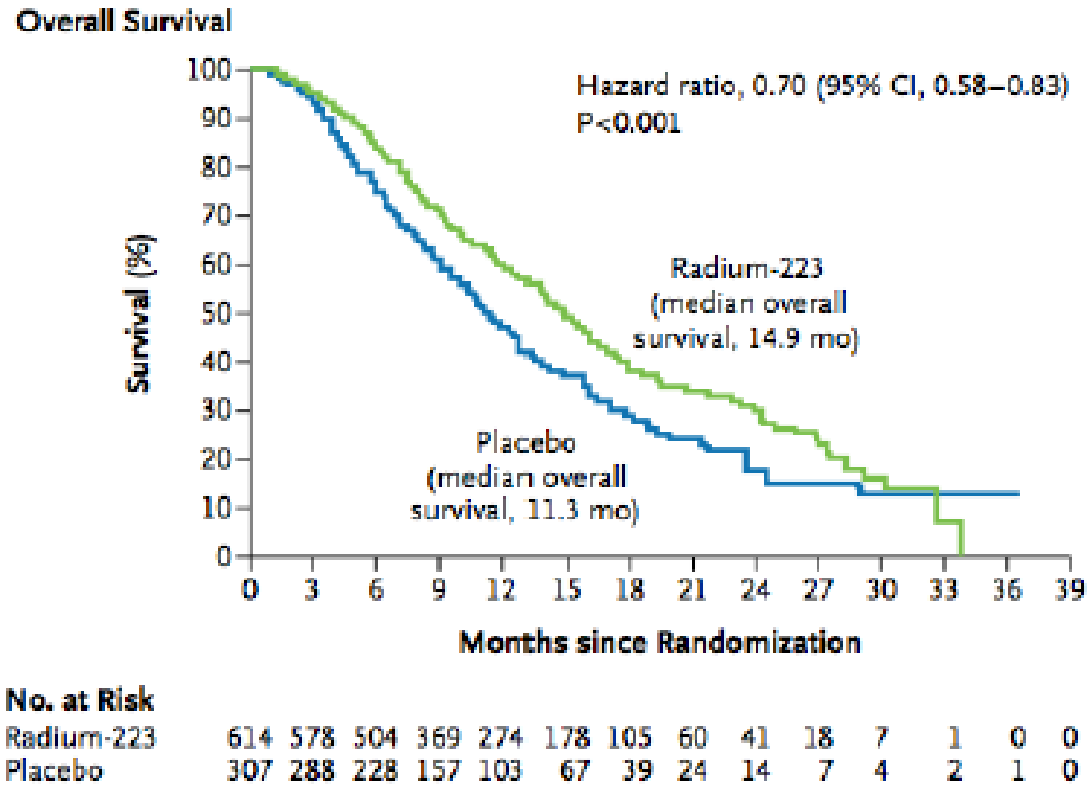
R
2:1

Radium-223 50 kBq/kg
(n = 614)

Placebo
(n = 307)

OBJETIVO PRIMARIO: OS

OBJETIVOS SECUNDARIOS: Tiempo hasta el primer ERE, tiempo hasta elevación de FAlc, normalización de FAlc, tiempo hasta elevación del PSA, otros



'EAN MEDICINES AGENCY
CE MEDICINES HEALTH

18
21/2018

PRAC recommends restricting use of prostate cancer medicine Xofigo

Medicine should only be used after two previous treatments or when other treatments cannot be taken

EMA's safety committee PRAC has recommended restricting the use of the cancer medicine Xofigo (radium-223 dichloride) to patients who have had two previous treatments for metastatic prostate cancer (prostate cancer that has spread to the bone) or who cannot receive other treatments.

These restrictions follow a review of data from a study suggesting that patients given Xofigo seemed t be at risk of dying earlier and had more fractures than patients given placebo (a dummy treatment). The study included patients with no or only mild symptoms, whereas Xofigo is only authorised in patients with symptoms. In the study, patients given Xofigo with Zytiga (abiraterone acetate) and prednisone/prednisolone died on average 2.6 months earlier than those given placebo with Zytiga and prednisone/prednisolone. In addition, 29% of patients who received the Xofigo combination had fractures, compared with 11% of patients given placebo.

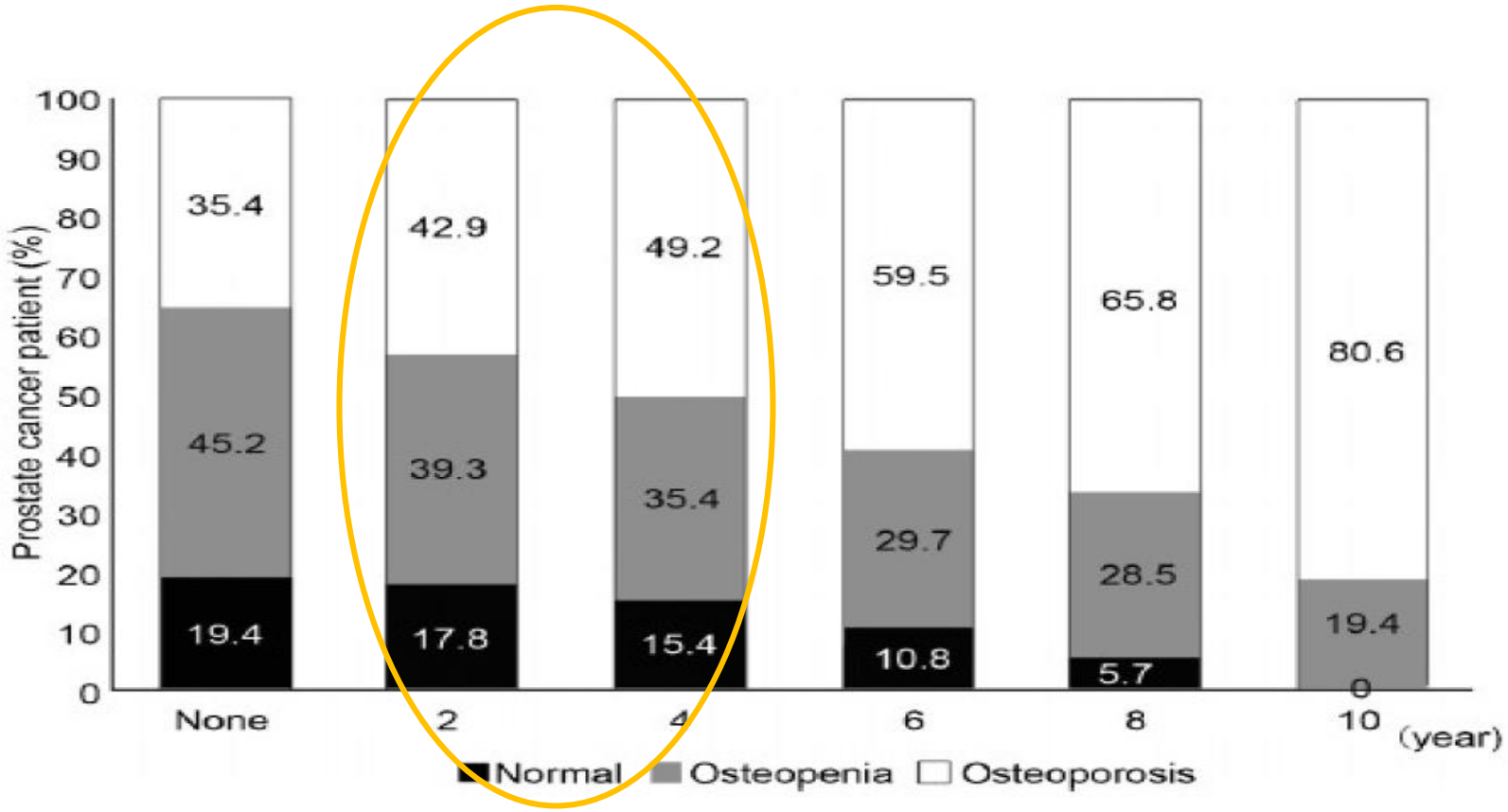
It is thought that Xofigo, which is taken up by the bone, accumulates at sites where the bone is already damaged, for example by osteoporosis or micro-fractures, increasing the risk of fracture. However, the reasons for a possible earlier death in this study are not fully understood.

The PRAC also confirmed its previous interim recommendation that the medicine must not be used wit Zytiga and prednisone/prednisolone.

https://www.ema.europa.eu/documents/referral/xofigo-article-20-procedure-prac-recommends-restricting-use-prostate-cancer-medicine

IMPORTANCIA DE LA SALUD ÓSEA

Pérdida progresiva de DMO en pacientes tratados con TDA

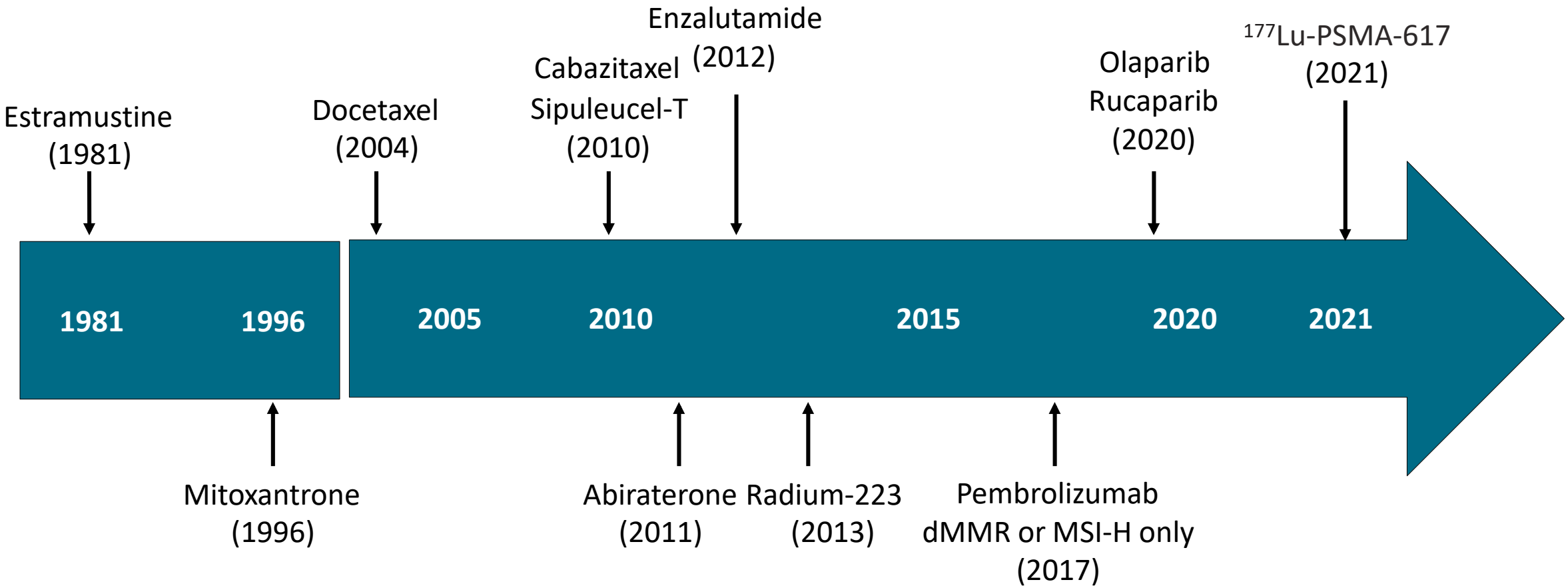


El riesgo de fractura debido a pérdida de DMO es un problema clínico importante en los pacientes de mayor edad con cáncer de próstata.

Las fracturas patológicas o por fragilidad son factores de riesgo para disminución de supervivencia en CaP.

1. Guise TA. Oncologist. 2006 Nov-Dec;11(10):1121-31
2. Morin JP. et al. Asian J Androl 2012; 14:670-5.
3. Oefelein MG, Ret al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol. 2002;168:1005-7
4. Roghmann F, et al. The burden of skeletal-related events in patients with prostate cancer and bone metastasis. Urol Oncol. 2015;33:17 e9-e18

FDA-Approved Agents for mCRPC



- Dates are for initial approvals

Abiraterone PI. Enzalutamide PI, Docetaxel PI. Cabazitaxel PI. Mitoxantrone PI. Estramustine PI. Sipuleucel-T PI. Pembrolizumab PI. Radium-223 PI. Olaparib PI. Rucaparib PI.

Cáncer de próstata avanzado

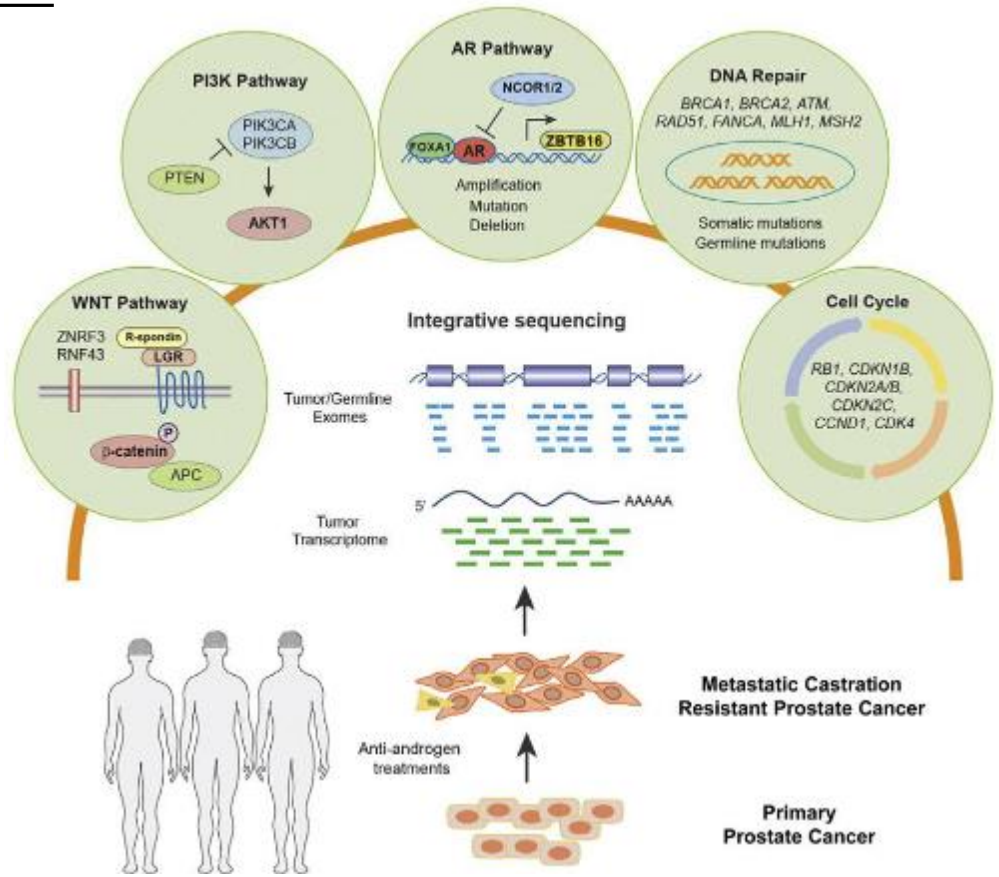
HETEROGENEIDAD EN INTRA E INTER PACIENTE

Caracterización molecular

Many genomic subtypes

Key druggable genotypes

- **Mismatch repair defective**: PD-1/PD-L1i
- *CDK12* biallelic alterations: PD-1/PD-L1i?
- ***BRCA2* biallelic loss:** PARPi or platinum
- ***PALB2* biallelic loss:** PARPi or platinum
- Other key PARPi sensitising DNA repair gene **biallelic loss, including *ATM***
- *PTEN* loss: PI3K/AKT blockade
- AR mutations: 3rd generation AR blockers?

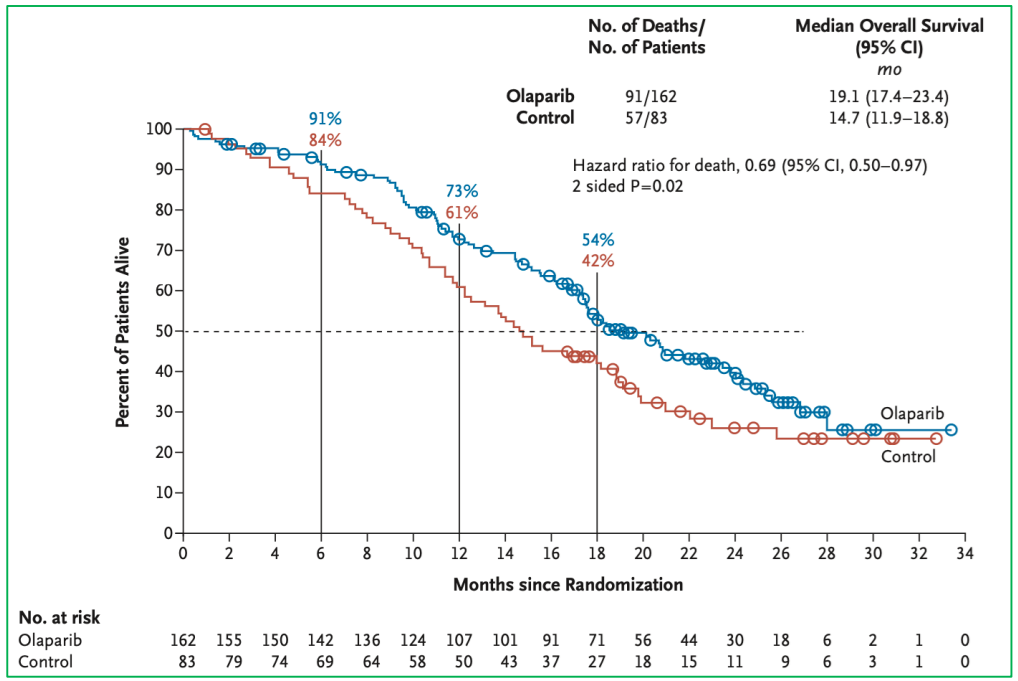


iPARP 2L CPRCm HRR mutados

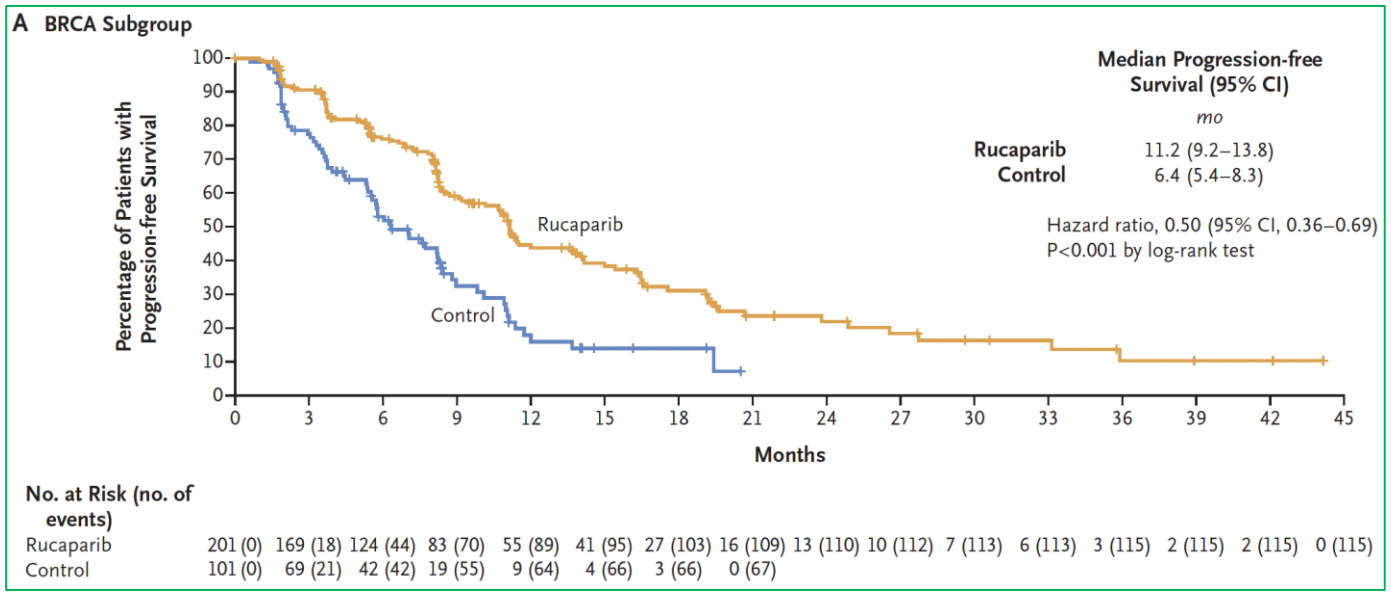
PROFOUND
HRR alterations
Previous Tx with 1 ARTA +/- docetaxel

TRITON-3
HRR alterations
Previous Tx with 1 ARTA

PROFOUND trial
Cohort A: BRCA1/BRCA2/ATM – Overall survival

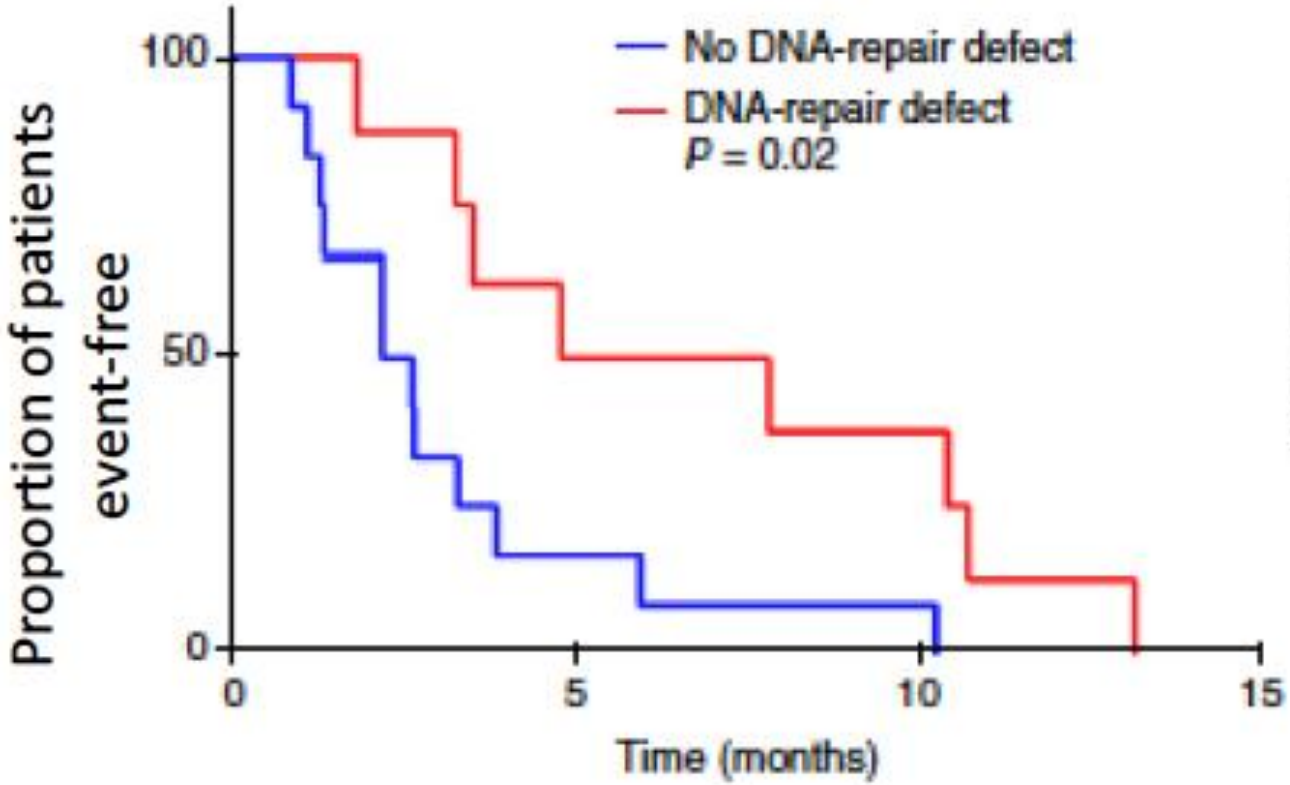


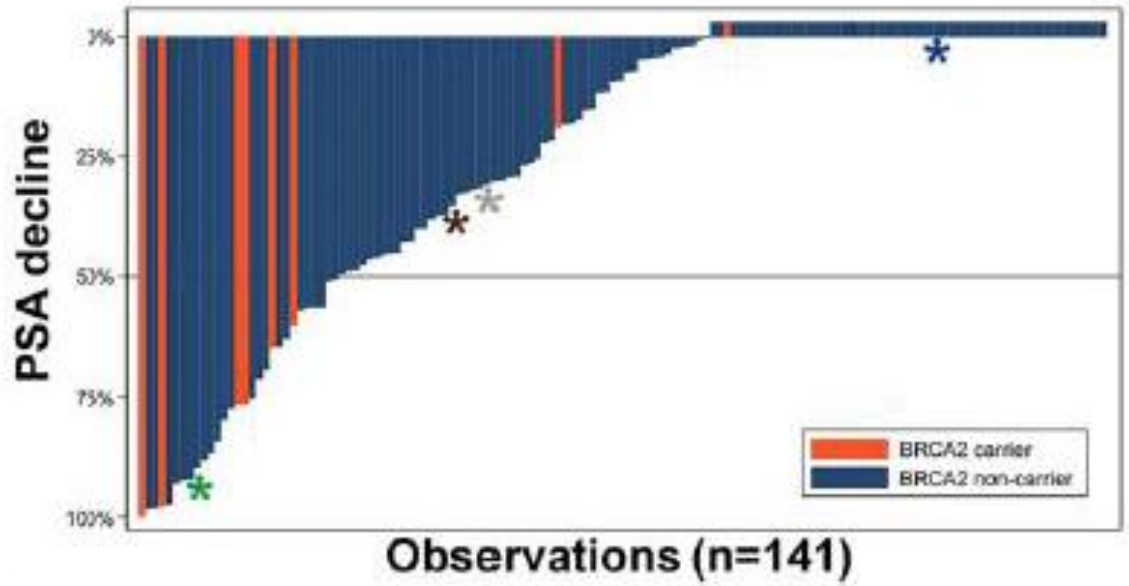
TRITON-3 trial
Cohort BRCA1/BRCA2 – Progression-free survival



Hussain MA, et al. N Engl J Med 2020;383:2345-2357
Fizazi K, et al. N Engl J Med 2023;388:719-732

HRD can predict sensitivity to platinum therapy





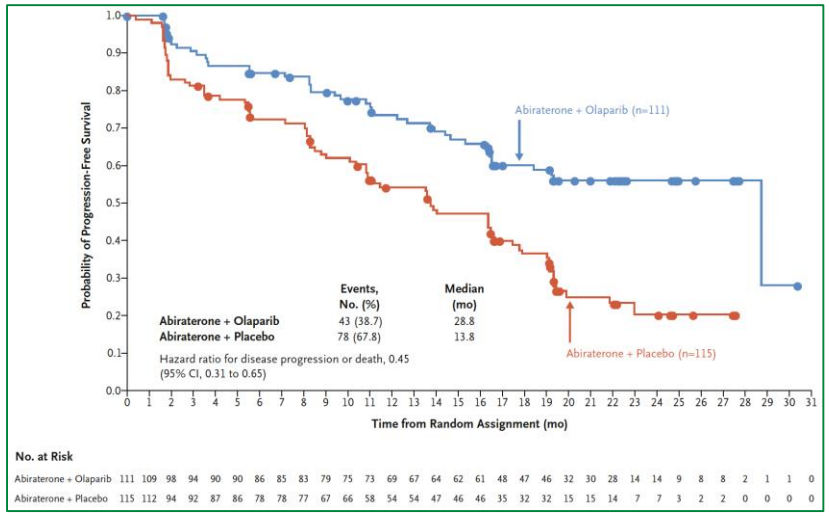
Kumar A. Nat Med 2016
Cheng HH. Eur Urol 2016

Pomerantz MM . Cancer 2017

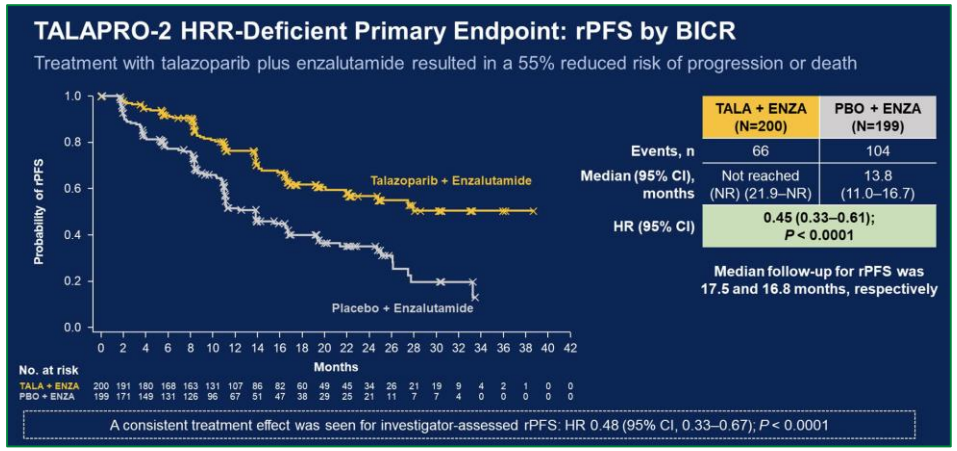
iPARP en 1ª línea en CPRCm HRR mutados

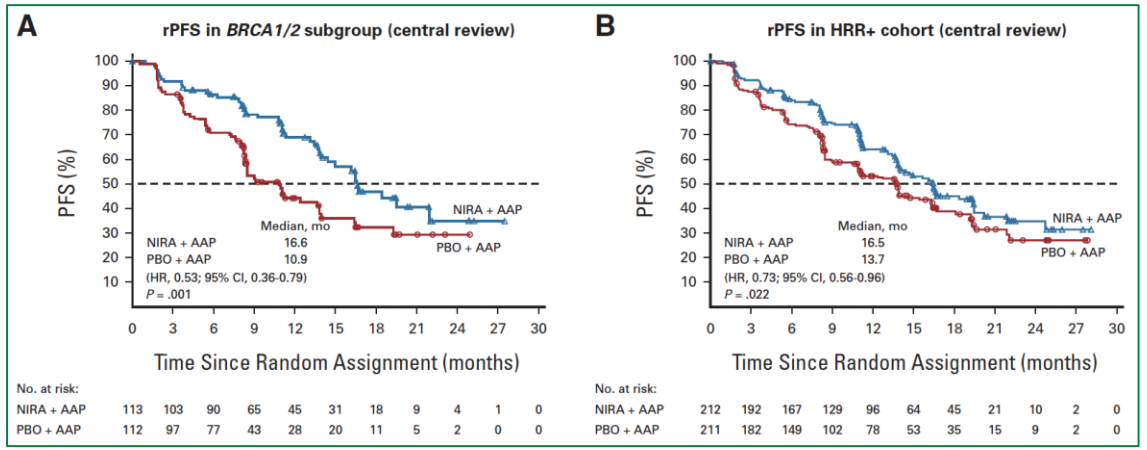
PARPi + ARTA demonstrate better PFS than ARTA alone in 1st line in HRR-mutated mCRPC patients

PROPEL



TALAPRO-2



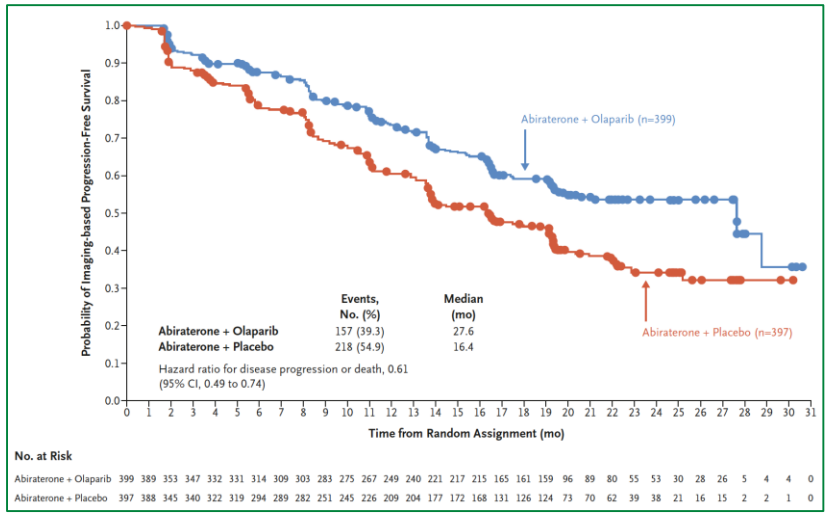


MAGNITUDE

Clarke NW, et al. NEJM Evid 2022; 1 (9). DOI: 10.1056/EVIDoa2200043
Chi KN, et al. J Clin Oncol 2023;41:3339-3351
Fizazi K, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 5004)

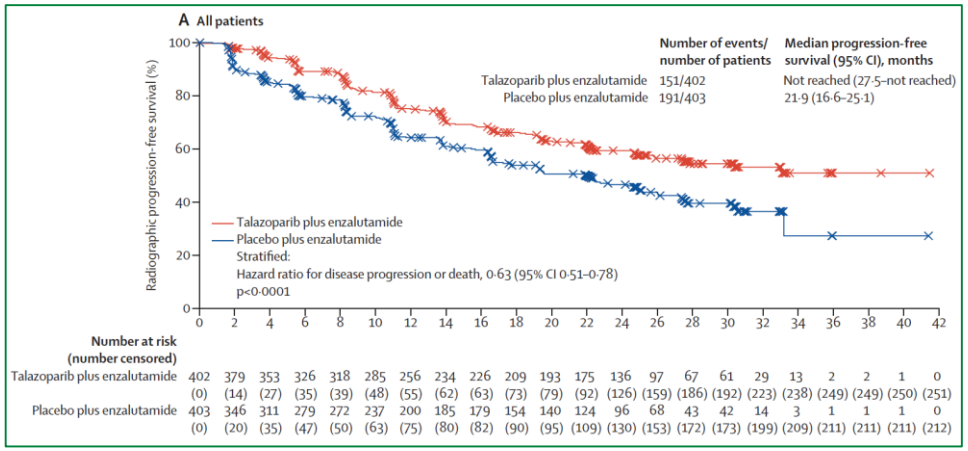
iPARP en 1ª línea en CPRCm. All comers

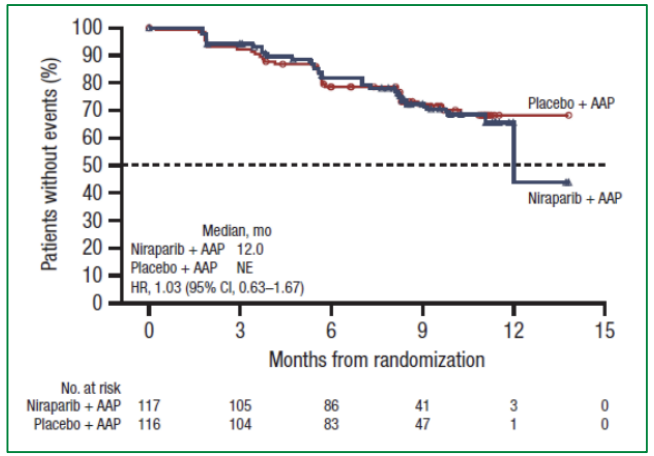
PROPEL



PARPi + ARTA demonstrate better PFS than ARTA alone in 1st line in all-comers mCRPC patients in PROpel and TALAPRO-2, but controversial.
No benefit for HRRwt patients in MAGNITUDE.

TALAPRO-2





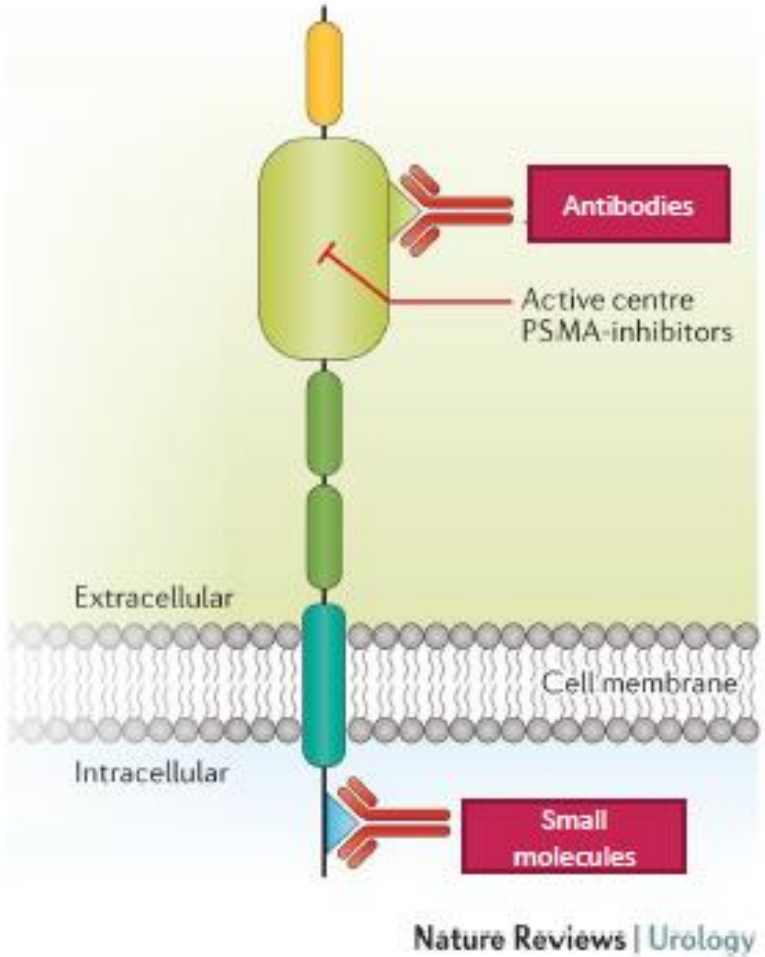
MAGNITUDE

Clarke NW, et al. NEJM Evid 2022; 1 (9). DOI: 10.1056/EVIDoa2200043
Chi KN, et al. J Clin Oncol 2023; 41:3339-3351
Agarwal N, et al. Lancet 2023 Jun 2;S0140-6736(23)01055-3. doi: 10.1016/S0140-6736(23)01055-3

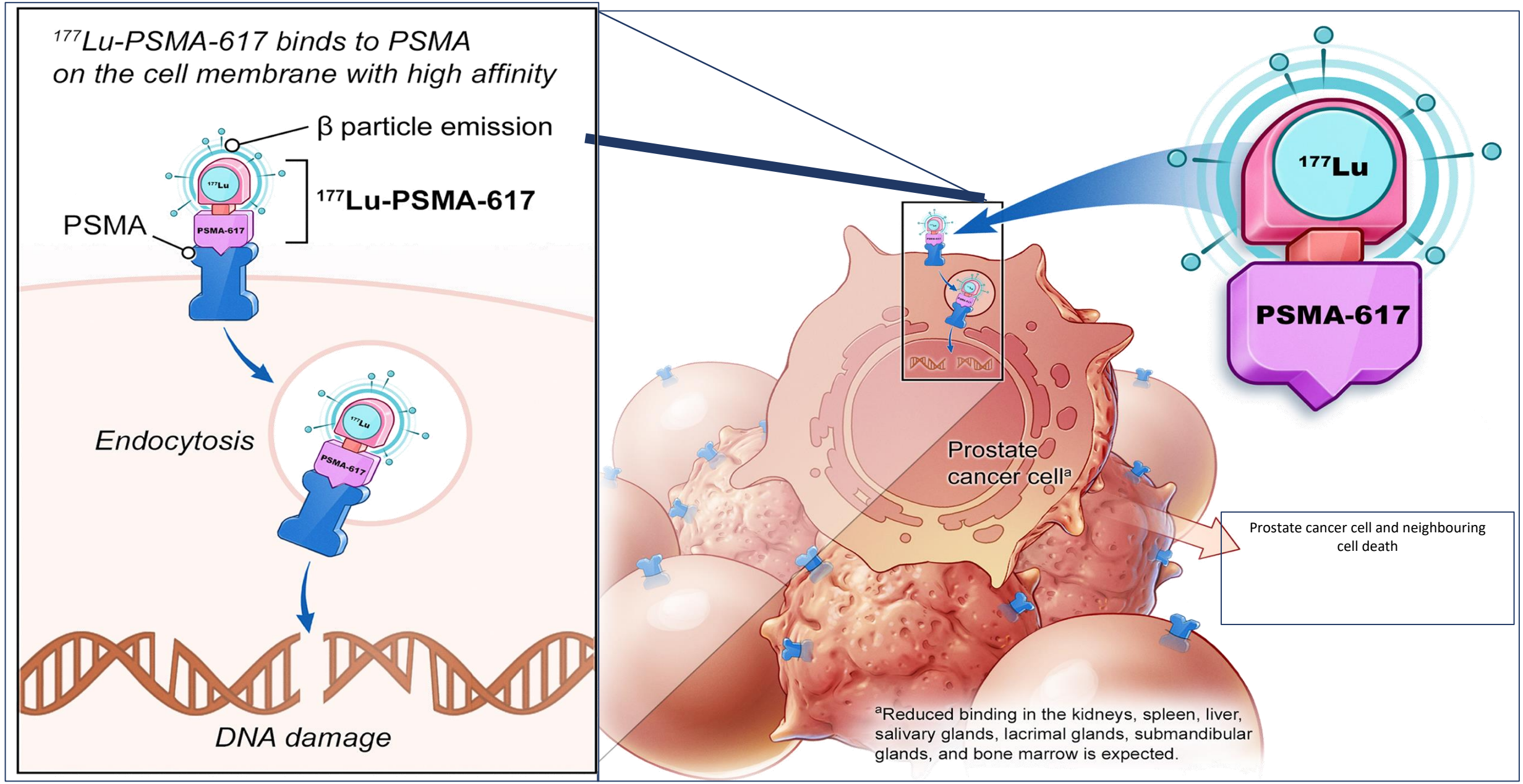
PSMA: Therapeutic target

- Type II transmembrane glycoprotein
- 90-95% of prostate cancer have an increased PSMA expression
- Expression correlates with cancer agressiveness
- Targeted by extracellular antibodies and small molecules

PSA	PSMA
Secretory protein	Integral membrane protein
Known function—liquefaction of semen	Several enzymatic functions
Measured in serum as a cancer marker	Upregulated with androgen deprivation
Decreased with androgen deprivation	RT-PCR used to detect in serum; not verified as screening tool/ marker
	Expression correlates with cancer aggressiveness and represents an independent indicator of poor prognosis



Chang D, Rev Urol 2014; Maurer T, Nat Rev Urol 2016. Haberkorn U, et al. Clin Cancer Res 2016


177Lu-PSMA-617 binds to PSMA on the cell membrane with high affinity
β particle emission
177Lu-PSMA-617
PSMA
177Lu
PSMA-617
Endocytosis
DNA damage
Prostate cancer cell[a]
[a]Reduced binding in the kidneys, spleen, liver, salivary glands, lacrimal glands, submandibular glands, and bone marrow is expected.
Prostate cancer cell and neighbouring cell death

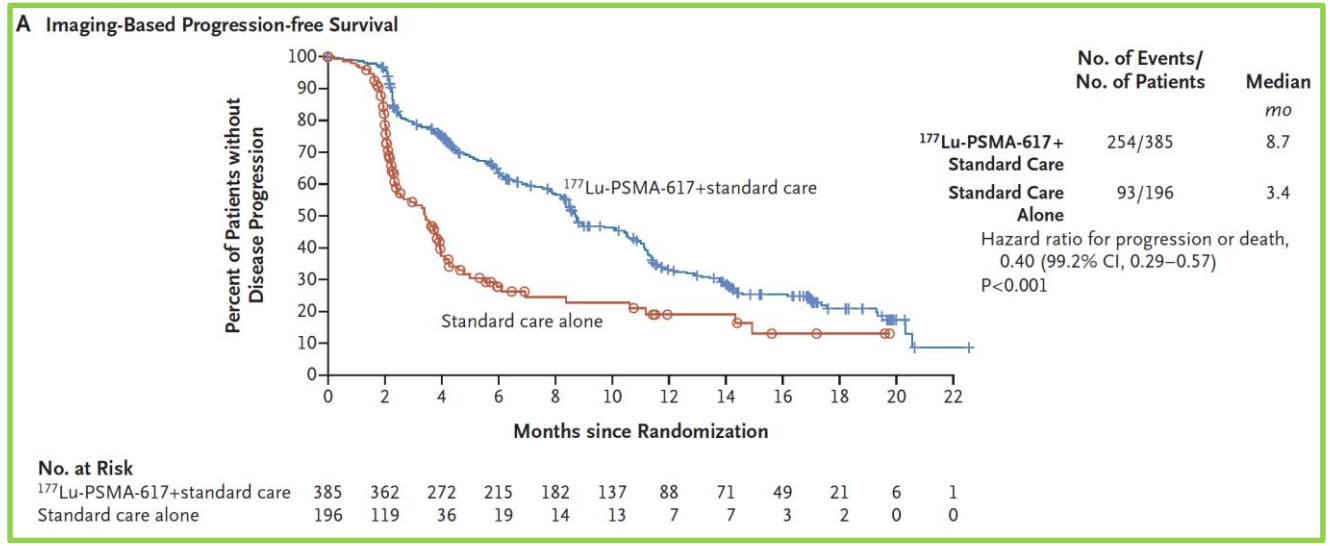
VISION trial – 177Lu-PSMA-617

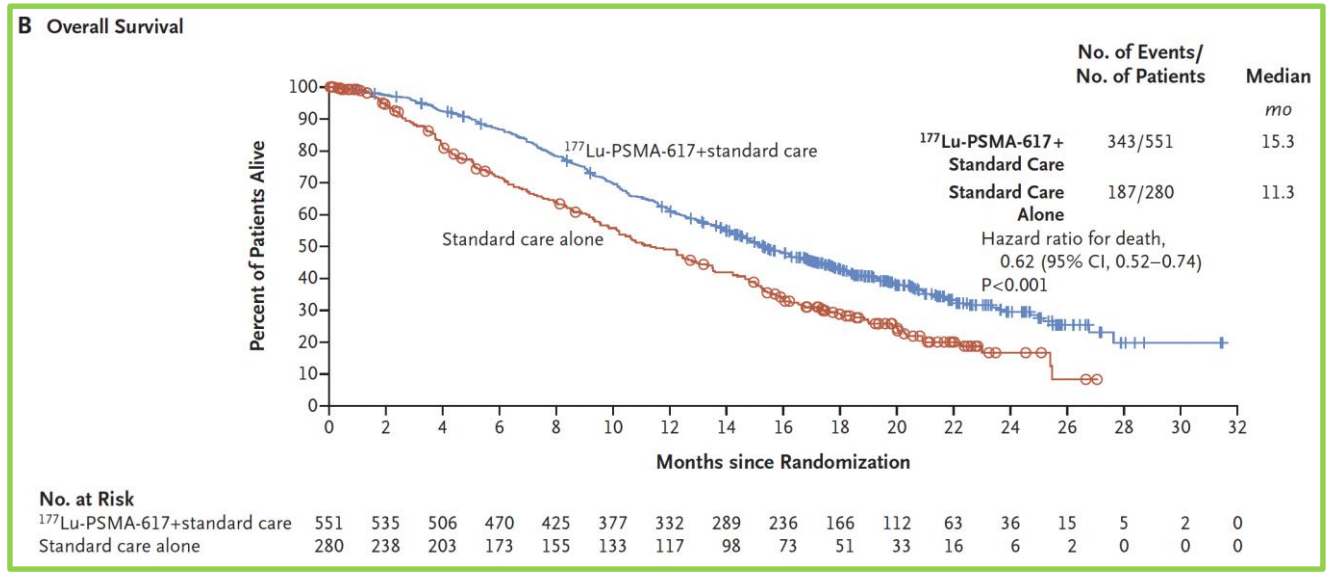
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (N=831)	
	^{177}Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)	^{177}Lu-PSMA-617 plus Standard Care (N=551)	Standard Care Alone (N=280)
Median age (range) — yr	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG performance-status score of 0 or 1 — no. (%)†	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease — no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Previous androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)





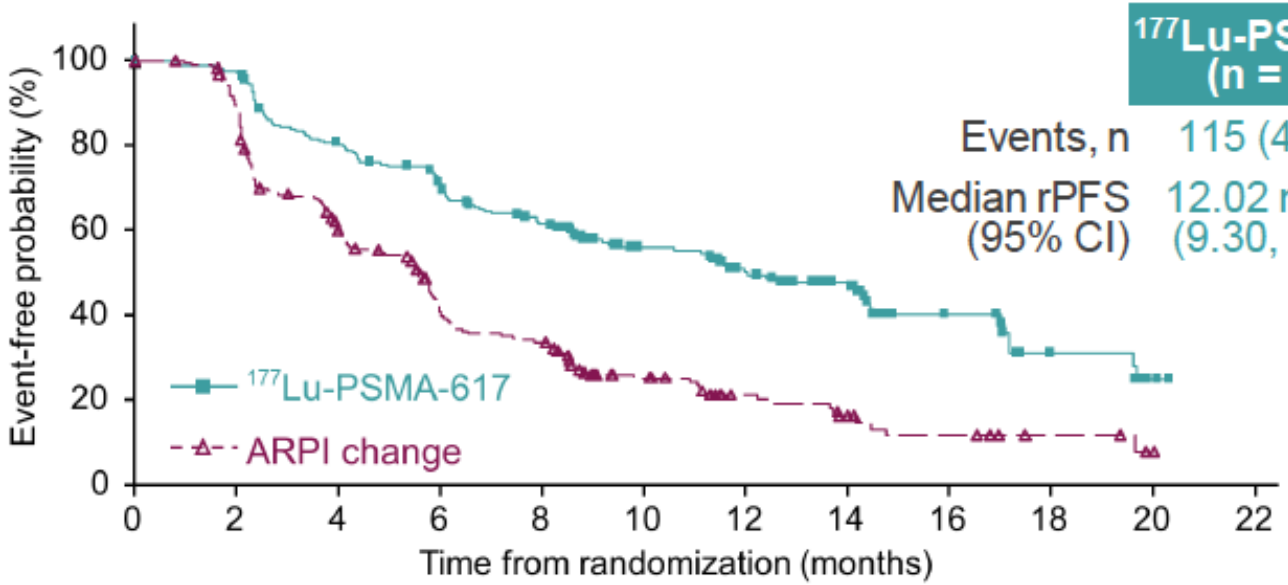
Sartor O, et al. N Engl J Med 2021;385(12):1091-1103

PSMAfore Phase 3 Trial of [177Lu]Lu-PSMA-617 in Taxane-Naive Patients with mCRPC

rPFS: primary endpoint was met

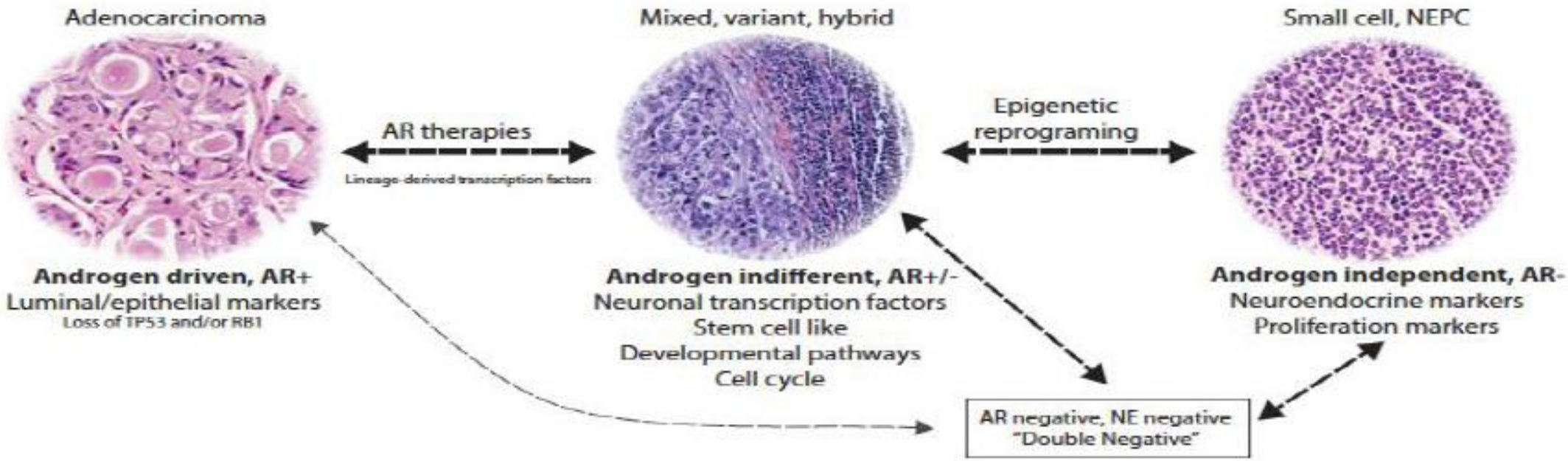
Primary HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Updated HR: 0.43 (95% CI: 0.33, 0.54)



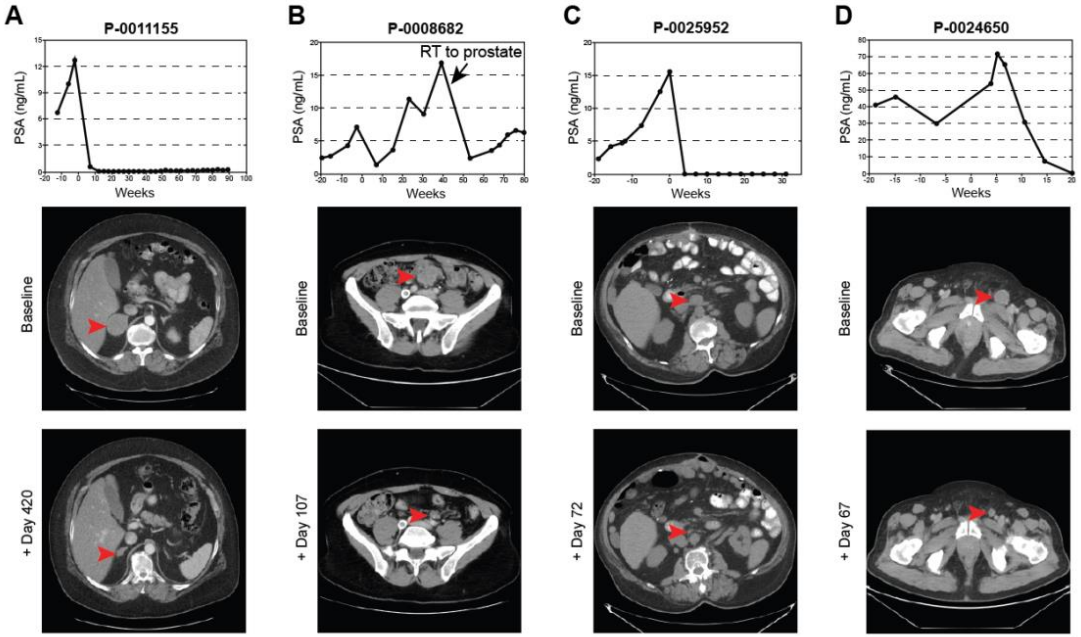
	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

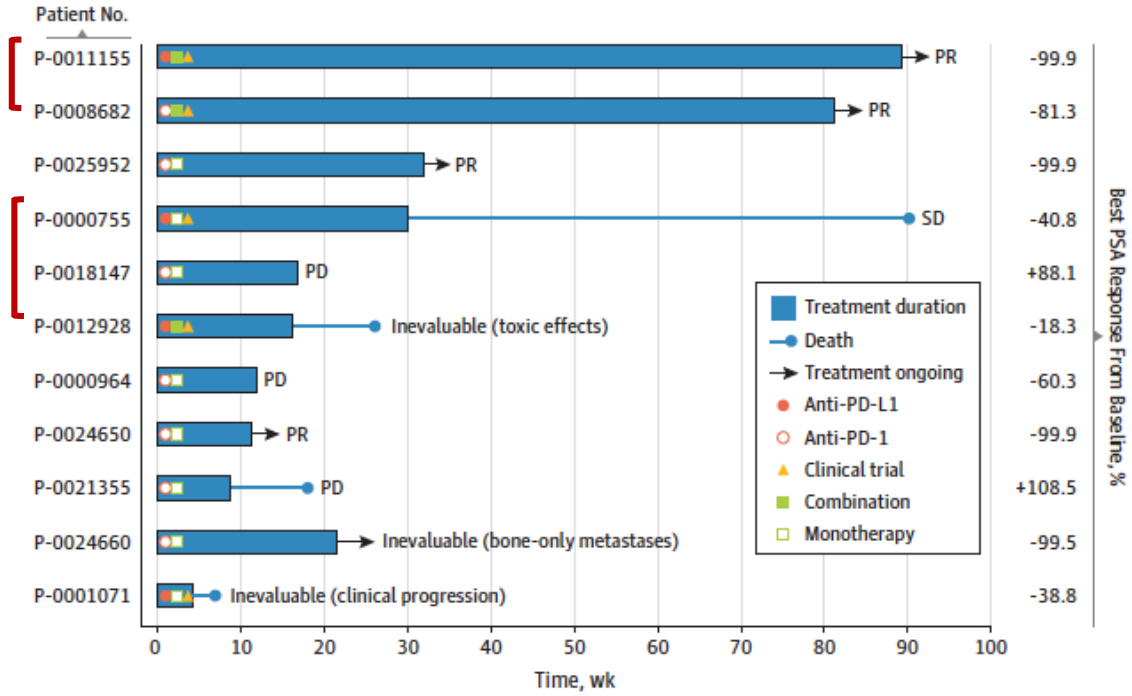
Desdiferenciación Neuroendocrina



H. Beltran. Clin Cancer Res 2019

MSI-H/dMMR may predict response to anti PD1/PD-L1 therapy





Abida et al, JAMA Oncol 2019

Mensajes para casa

- El CaP avanzado es una muy **enfermedad heterogénea.** Imprescindible adecuada estratificación del riesgo.
- **La intensificación de tratamiento (ADT+ARTA+QT docetaxel)** ha cambiado la supervivencia del CaP avanzado.
- **La caracterización genético-molecular del CaP** tiene utilidad terapéutica y pronóstica
- Garantizar que el paciente reciba la **secuencia terapéutica adecuada** con una monitorización estrecha que precisa un abordaje multidisciplinar en donde la oncología médica es clave