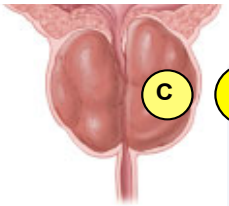
Systemic treatment in metastatic prostate cancer

A brief review…

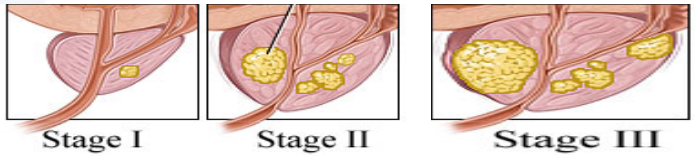
Emmanuel Seront, MD PhD
Oncologue médical

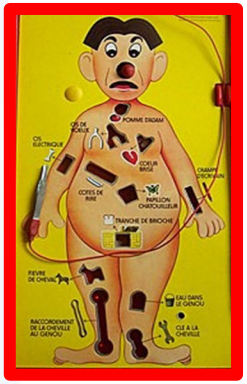
Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

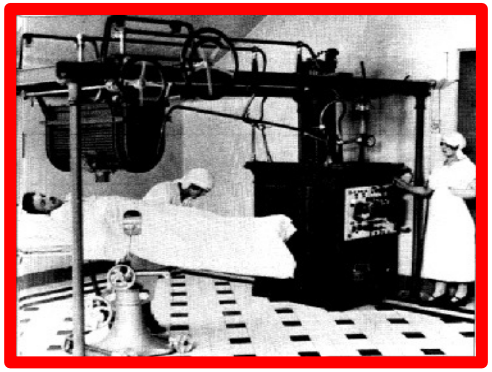


C A N C E R

Localized ou Locally advanced

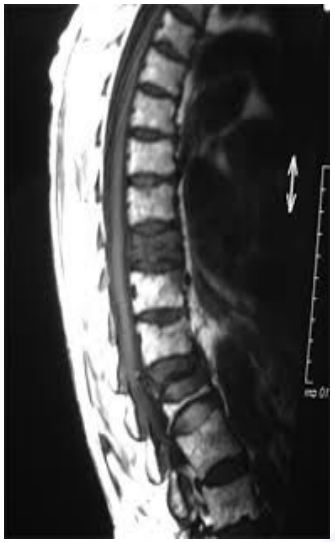


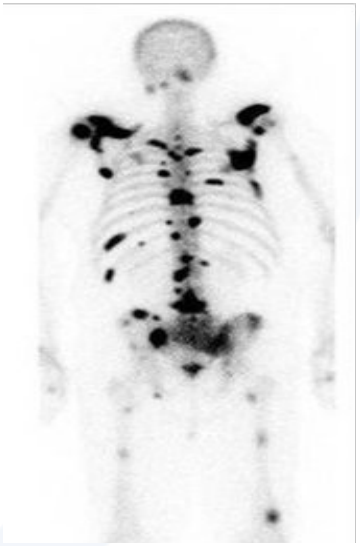


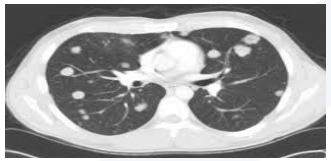


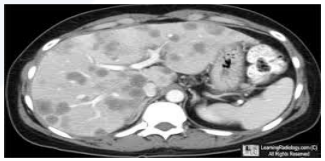
5-year survival = 95-100%

Metastatic







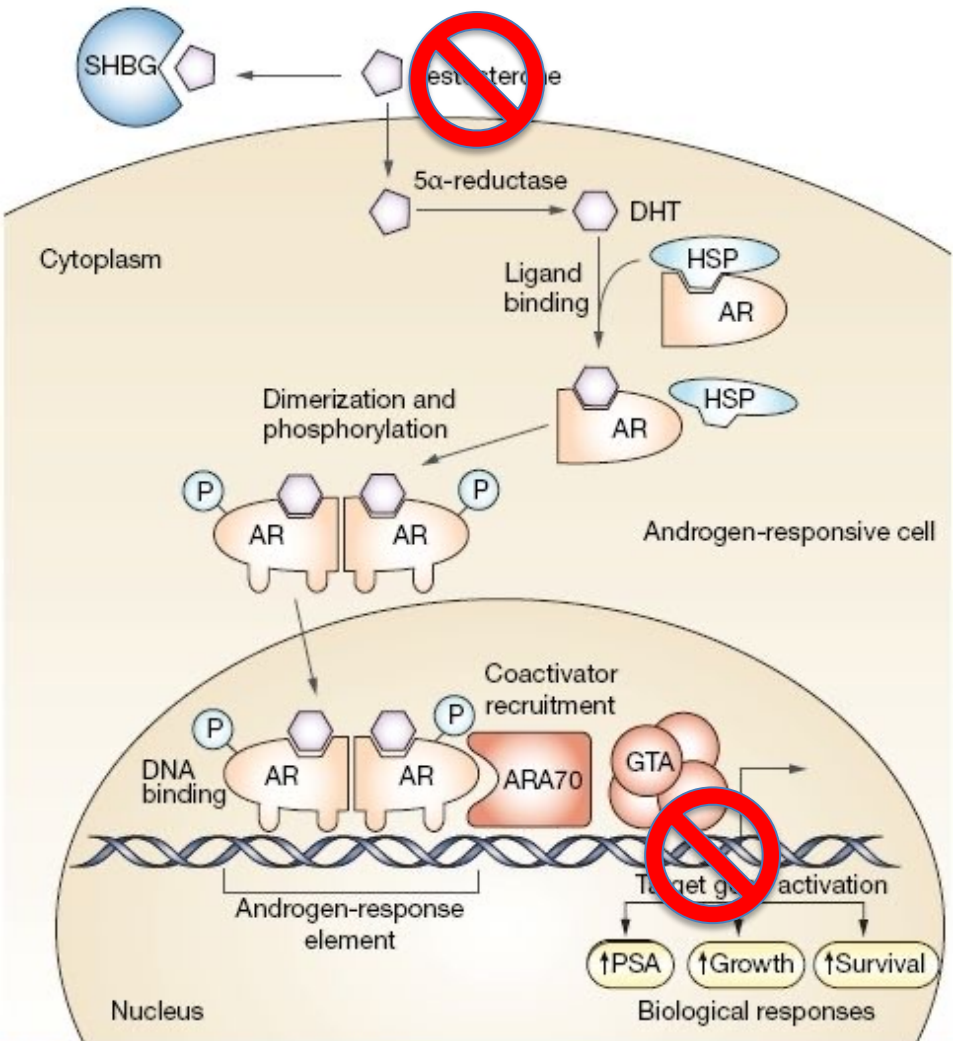


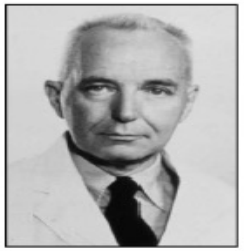
Systemic treatment

5-year survival = 25%

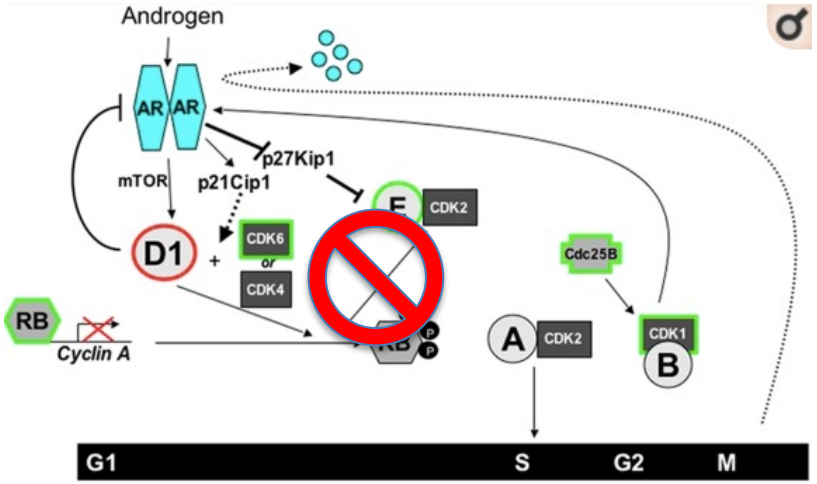
Androgen deprivation therapy : cornerstone

Androgen deprivation therapy (ADT)





Charles HUGGINS
1901–1997
1966 Nobel Prize



Nature 2009

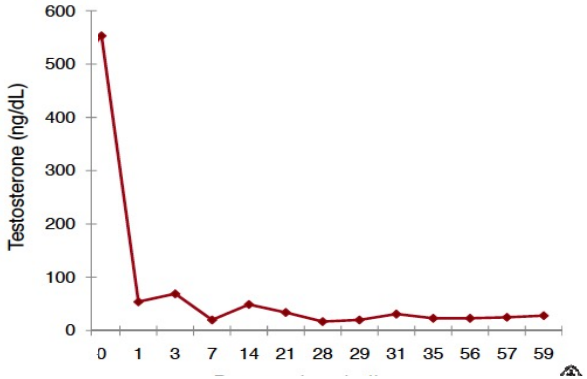
Balk et al; 2008

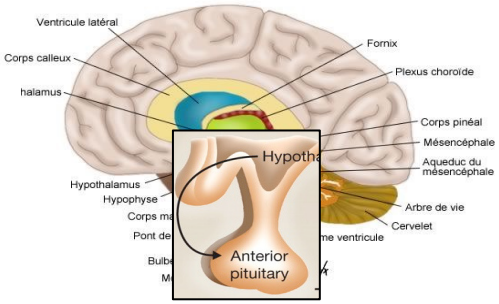
ANTAGONISTE LH-RH

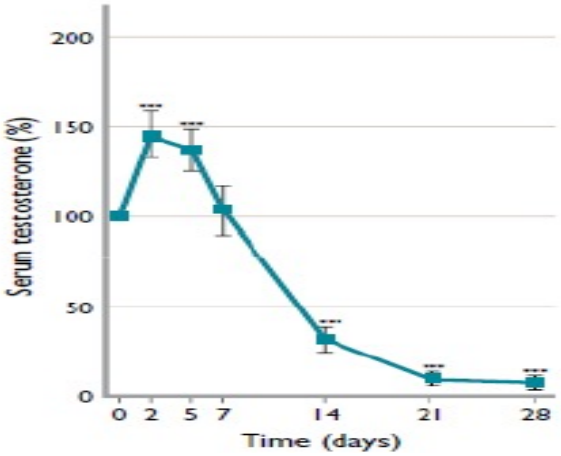
Degarelix (Firmagon®)
2x 120mg for the 1st injection
and then 80mg monthly

AGONISTE LH-RH

- Triptoreline (Decapeptyl®)
- Leuproreline (DepoEligard®
- Gosereline (Zoladex®)







Immediate effect

No Flare Up

LH, FSH

Orchidectomie

Testicule

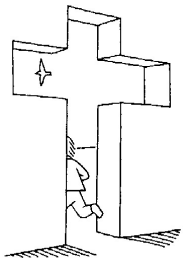
Testostérone

Flare Up

castrated after 2 weeks

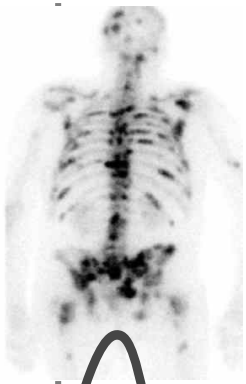
+/- antiandrogen

ADT



80-90% of response

- ➔ **Pain improvement**
- ➔ **PSA decrease**
- ➔ **Radiological response**
- ➔ **QoL improvement**



PSA

Table 6.4.2: Prognostic factors based on the SWOG 9346 study [1049]

PSA after 7 months of castration	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 months
> 4 ng/mL	13 months

Castration sensitive

Castration resistant

18-24 months

Hussain, M., *et al.* J Clin Oncol, 2006. 24: 3984.

Identify right diagnosis with criteria "CRPC"

Serum testosterone

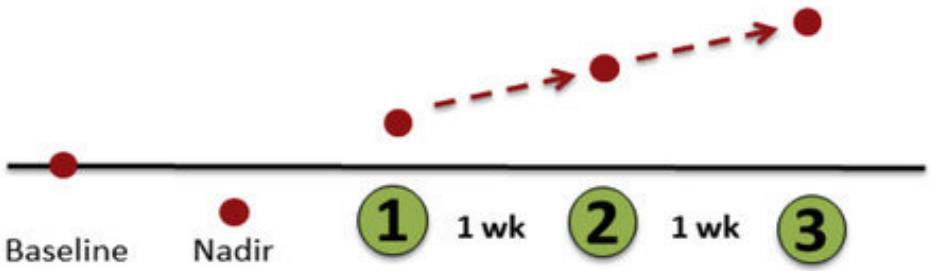
< 50 ng/dL (1.7 nmol/L)

using androgen deprivation therapy

One or any in combination

Biochemical progression

Three consecutive rises in PSA



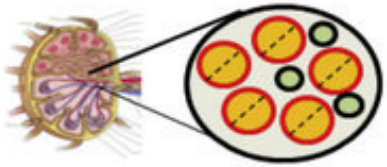
PSA increases ≥ 50% and ≥ 2 ng/mL above nadir

PSA increases ≥ 50% and ≥ 2 ng/mL above nadir

Confirm the trend of PSA increase

Radiological progression

Or

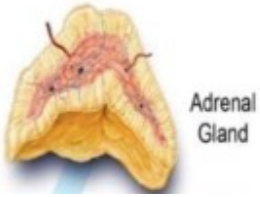


Presence ≥ 2 bone lesions

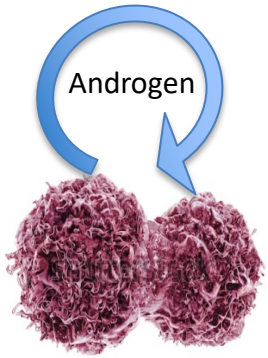
Presence soft tissue lesions with nodes >2 cm in diameter

EAU guideline 2015; PCWG2; RECIST 1.1

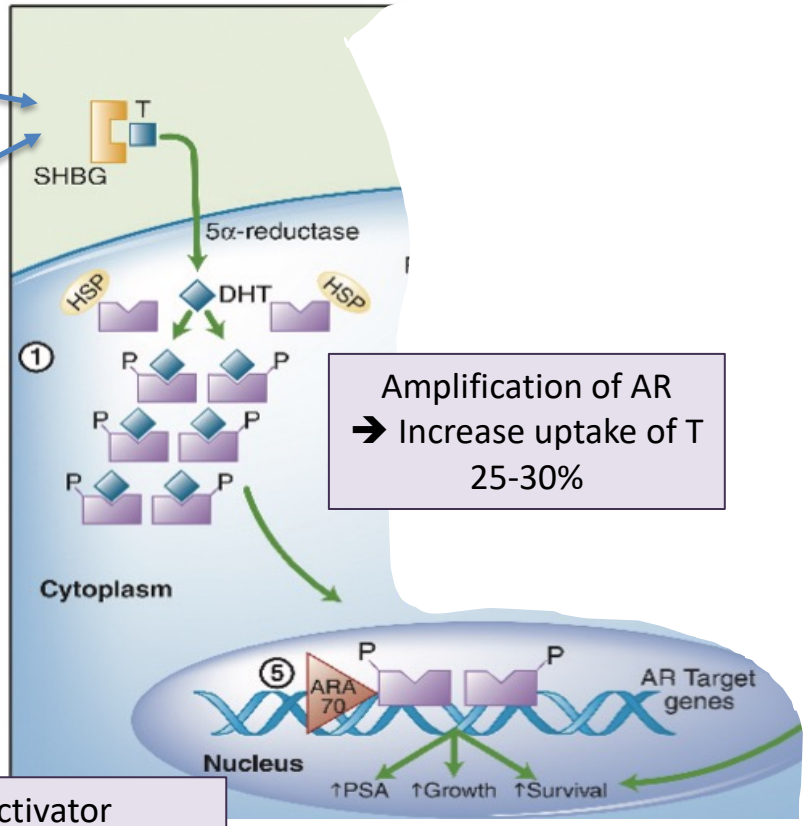
AR-related resistance mechanisms (1)



Surrenale
➔ 10% of residual DHT



DHT secretion by cancer cells
➔ Intratumoral T level >>> serum

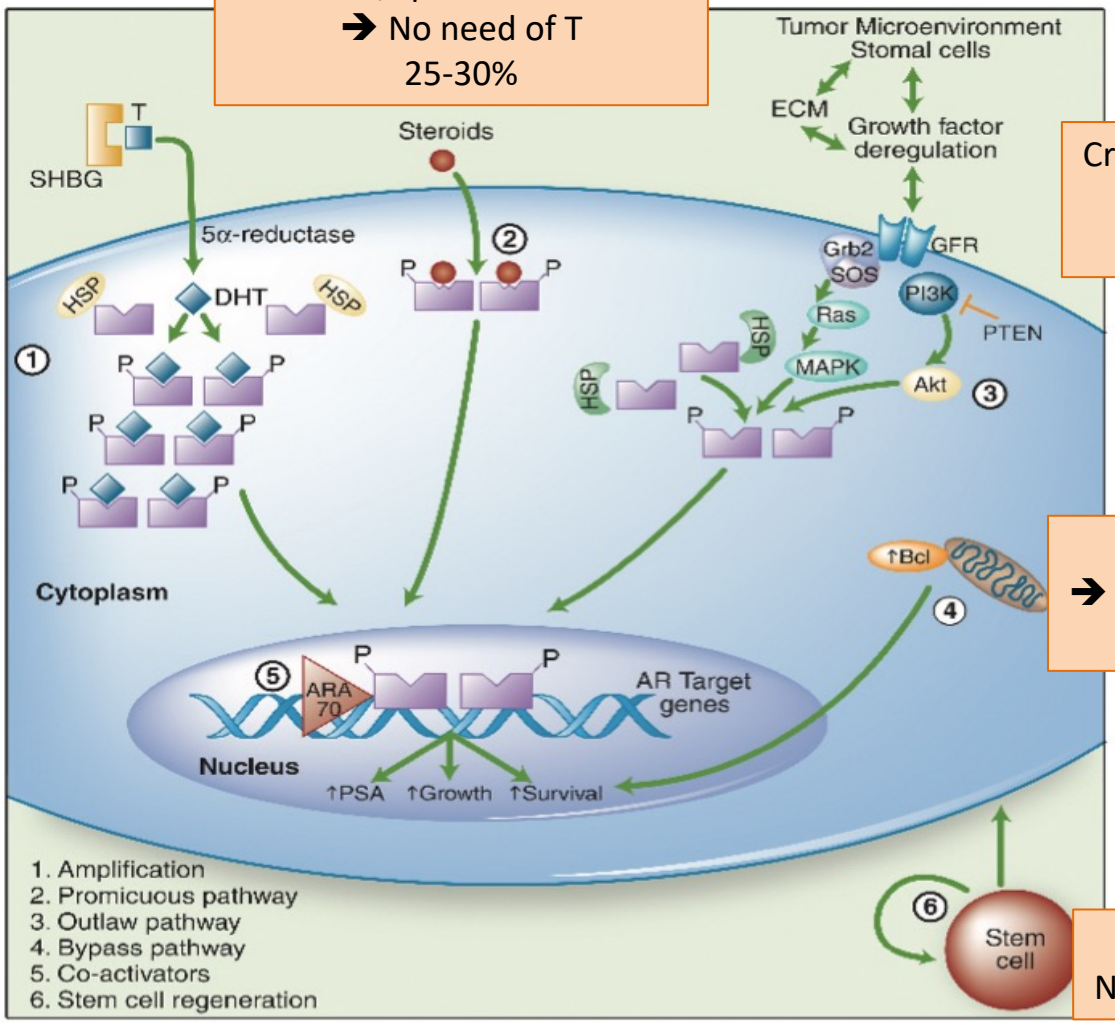


Amplification of AR
➔ Increase uptake of T
25-30%

Co-Activator
➔ Increase activity AR-T
25-30%

AR-related resistance mechanisms (2)

Mutation, splice variant of AR
➔ No need of T
25-30%



Crosstalk activating AR
➔ No need of T
15-20%

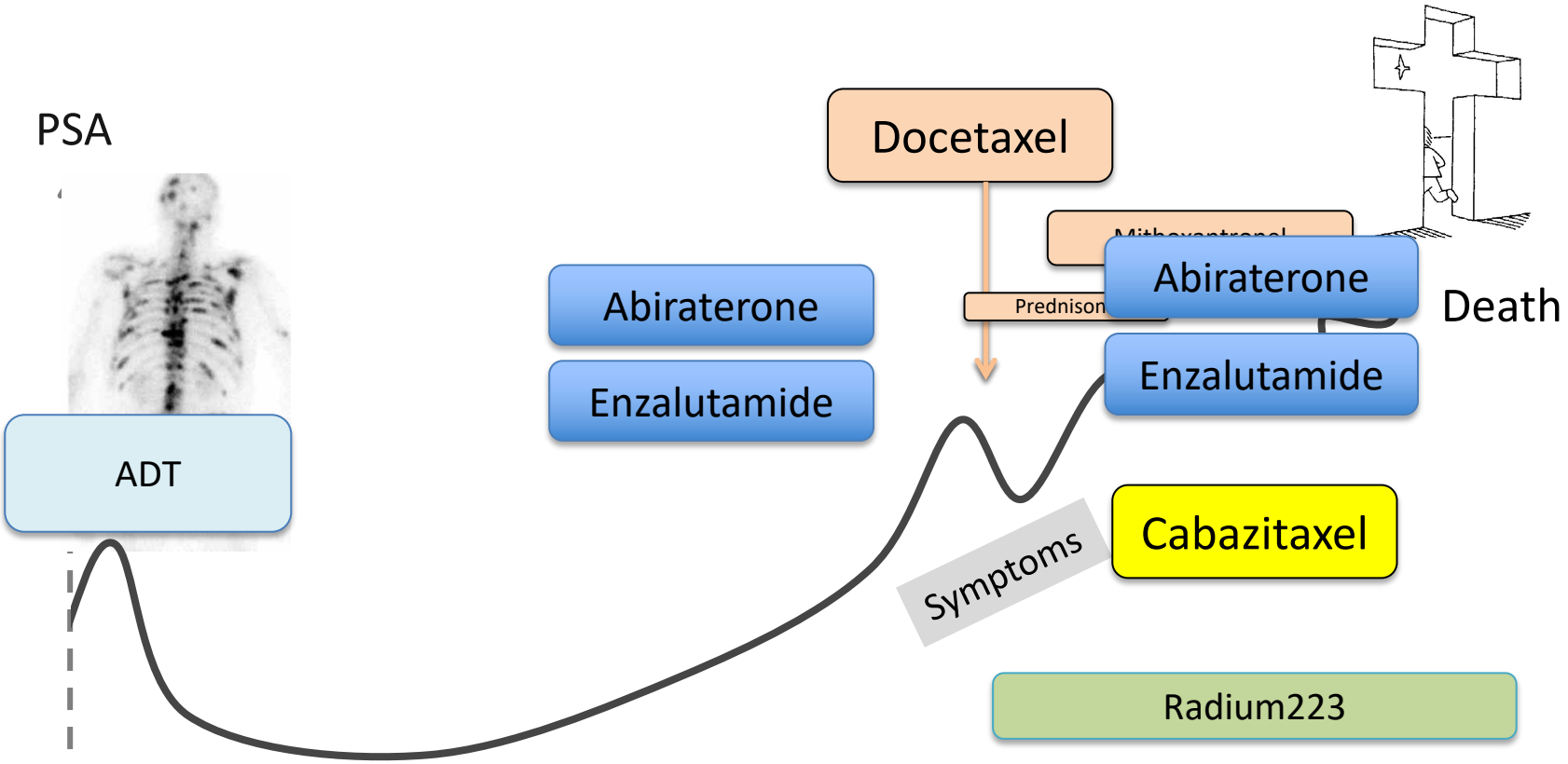
Bypass
➔ No need of AR
15-20%

Stem Cell Prostate
Not dependent of AR

Arsenal therapies for Advanced Prostate Cancer

mCRPC

Historical way to treat advanced PC = the mCRPC



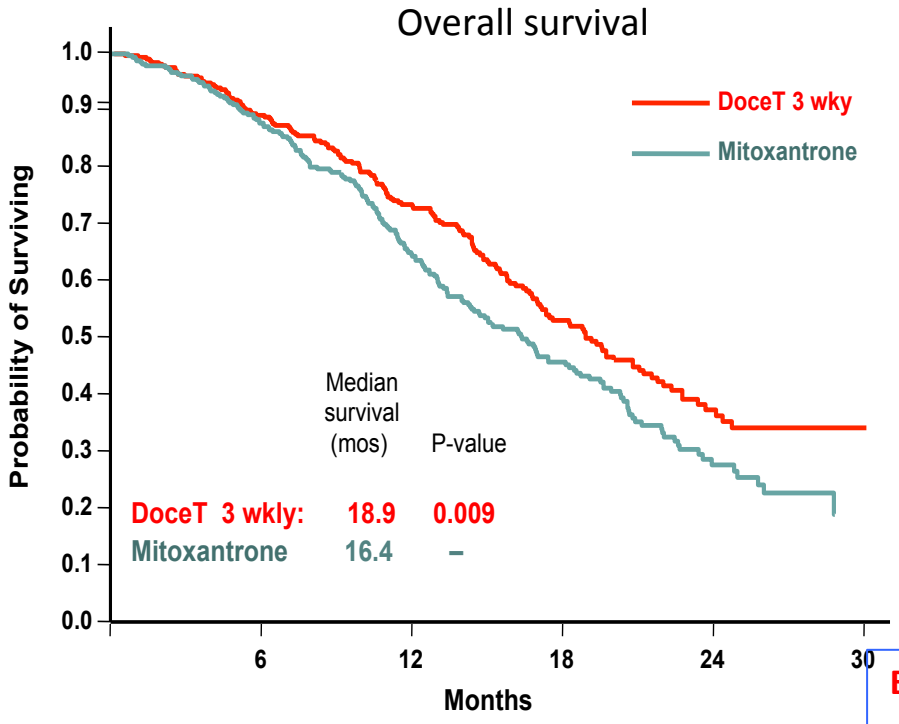
The NEW ENGLAND JOURNAL of MEDICINE

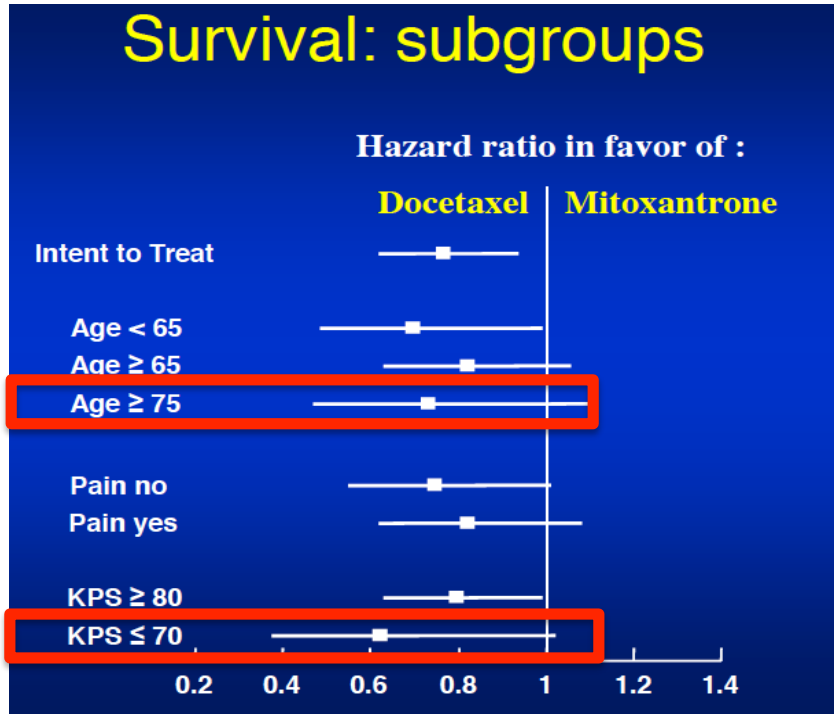
Oct 7,2004

ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

Etude TAX 327





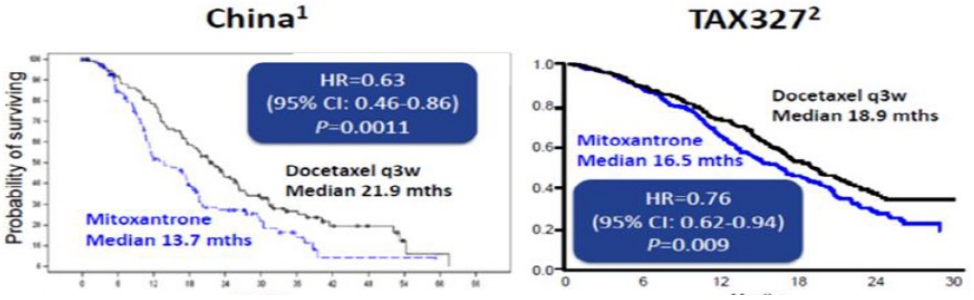
Effective in all subgroups of patients (elderly and frail patients)

Improvement in quality of life

Consideration with Docetaxel

1) Different pharmacokinetic in population

Phase 2 trial in China



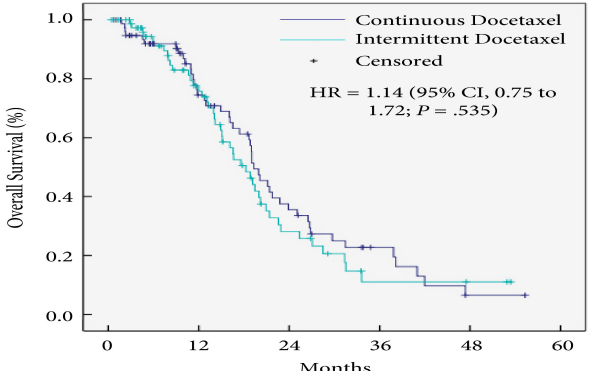
2) Association of Survival Benefit With Docetaxel and Total Number of Cycles Administered

JAMA oncology 2017

	No. of Participants	Event	Censored	Median Survival Time, mo	Survival (95% CI)
1:DPL ≥8 cycle	275	221 (80%)	54 (20%)	25.0	(23.0-27.9)
2:DP ≥8 cycle	332	264 (80%)	68 (20%)	29.8	(27.8-32.1)
3:DPL <8 cycle	258	213 (83%)	45 (17%)	14.2	(12.7-16.8)
4:DP <8 cycle	194	159 (82%)	35 (18%)	15.0	(11.5-18.3)

3) Intermittent vs continuous administration

PRINCE trial (BJU 2018)



4) 2-week Doce 50mg/m2 = 3-week Doce 75mg/m2

But with better tolerance

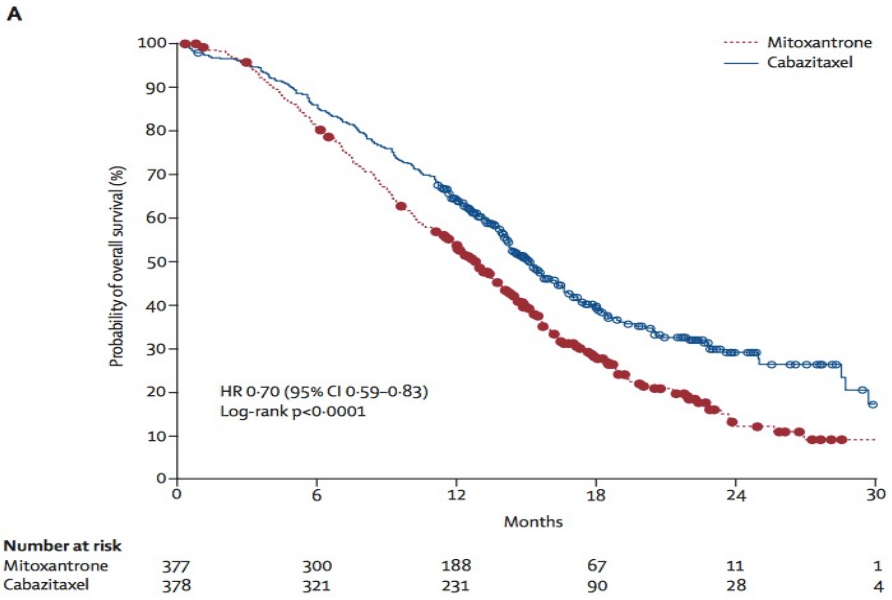
Lancet oncology 2013

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)	Hazard ratio (95% CI)	p value
Median (95% CI) TTTF (months)	5·6 (5·0–6·2)	4·9 (4·5–5·4)	1·3 (1·1–1·6)	0·014
Median (95% CI) TTP or death (months)	15·8 (13·6–18·1)	14·6 (13·2–16·0)	1·3 (1·0–1·6)	0·047
Median (95% CI) overall survival (months)	19·5 (15·9–23·1)	17·0 (15·0–19·1)	1·4 (1·1–1·8)	0·021
PSA response	84 (49%)	74 (42%)	..	0·486

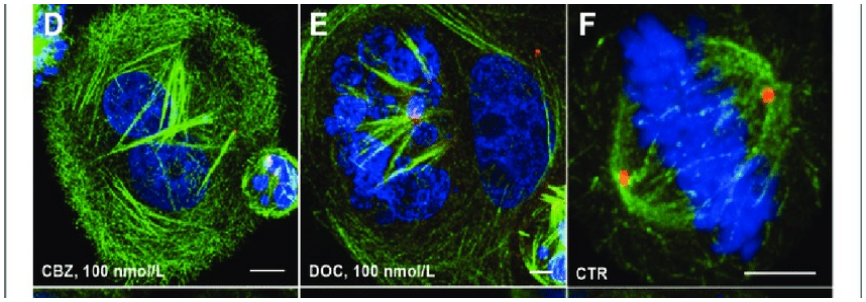
Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

Lancet 2010

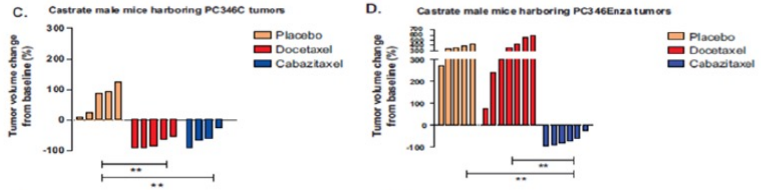
Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators



	Mitoxantrone	CBZP
Survie (mois)	12.7	15.1
Hazard ratio	0.70	
P value	<0.0001	



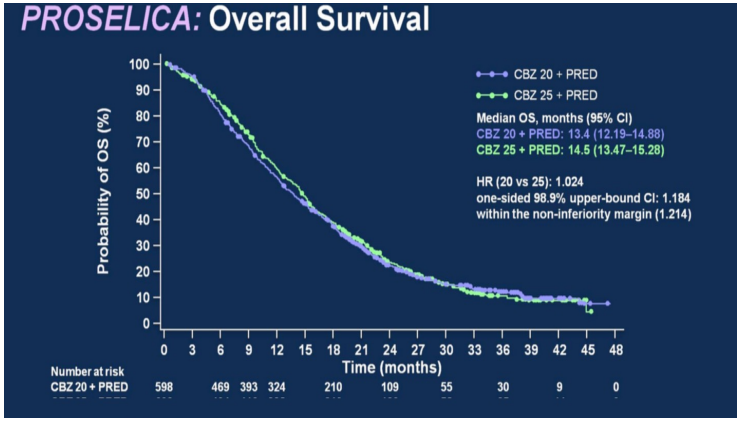
Xenograft model of CRPC with acquired resistance to enzalutamide



Intra-tumoral concentration Twice higher !!!

1) 20mg/m2 is as efficient as 25mg/m2 in overall survival !

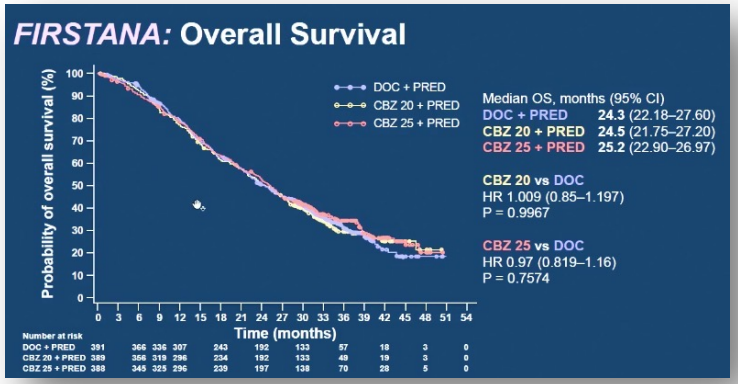
➔ But Less toxicity



2) Sometimes useful to use 25mg/m2 (if you want gretaer response)

	CBZ 20	CBZ 25
PSAresponse(%)	29.5	42.9
Tumor Response(%)	18.5	23.4
Grade 3-4 TEAE(%)	39.7	43.2
Serious TEAE (%)	30.5	43.2

3) No benefit for cabazitaxel in 1st line metatsatic CRPC setting compared to Docetaxel



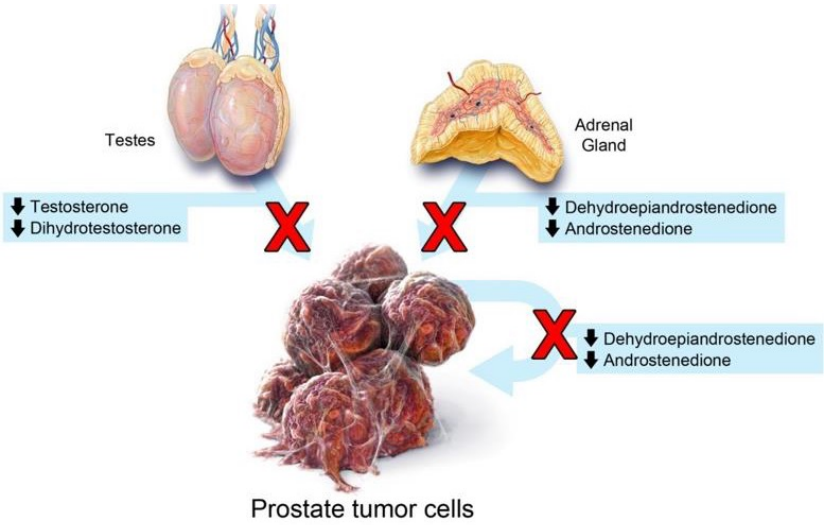
4) ALWAYS use GM-CSF !!!

New Hormonal Agents

Abiraterone

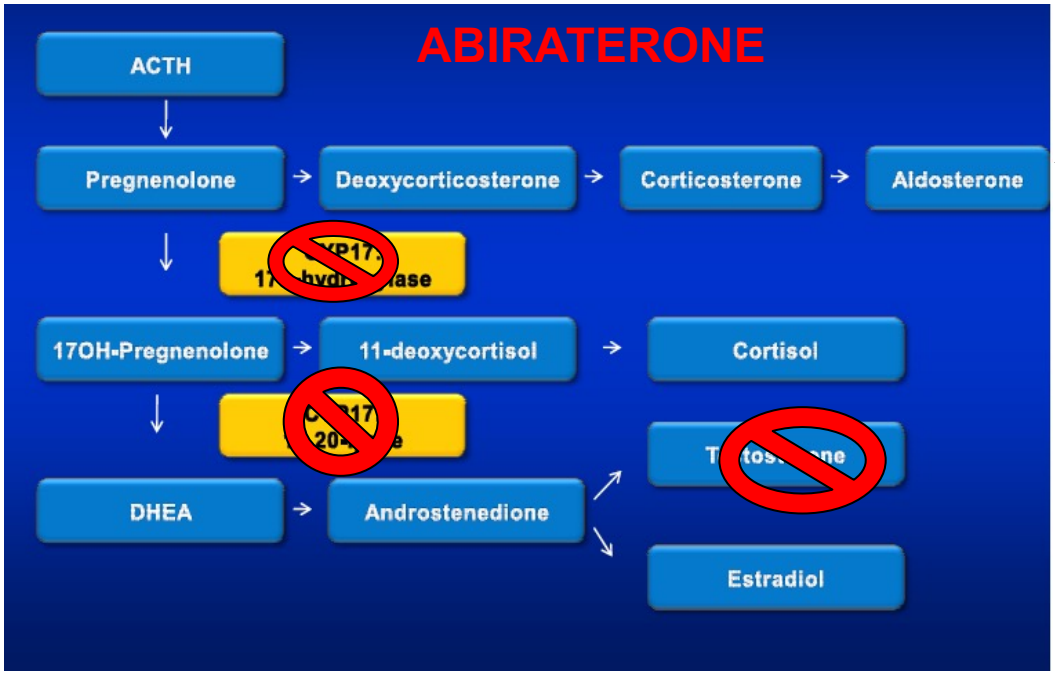
Enzalutamide

Abiraterone Acetate 1000mg/day



Prednisone is Mandatory

5 mg or 10mg a day with close follow-up !!!



Prednisone 10mg 1x/jour

Prednisone 5mg 1x/jour

Table 3. Adverse Events of Special Interest.*

Adverse Event	Abiraterone–Prednisone (N=542)	
	Grade 1–4	Grade 3 or 4
Fluid retention or edema	150 (28)	4 (<1)
Hypokalemia	91 (17)	13 (2)
Hypertension	118 (22)	21 (4)
Cardiac disorder†	102 (19)	31 (6)
Atrial fibrillation	22 (4)	7 (1)
ALT increased	63 (12)	29 (5)
AST increased	58 (11)	16 (3)

COU-AA-302 trial

	All Grades	Grade 3	Grade 4
Graded adverse events†			
Hypertension	219 (37)	121 (20)	0
Hypokalemia	122 (20)	57 (10)	5 (1)
ALT increased	98 (16)	31 (5)	2 (<1)
Hyperglycemia	75 (13)	26 (4)	1 (<1)
AST increased	87 (15)	25 (4)	1 (<1)
Bone pain	74 (12)	20 (3)	0
Cardiac disorder			
Any	74 (12)	15 (3)	5 (1)
Atrial fibrillation	8 (1)	2 (<1)	0

LATITUDE trial

CAUTION

Maybe try with 5mg but
INCREASE in case of symptoms !!!

➔ Blood pressure every week

➔Lab control every 2 weeks initially (K+, glycemia and liver)

➔ If HTA grade 3

NO SPIRONOLACTONE (>< abiraterone action) !!!
➔ EPLERENONE 25mg 1x/day

➔ LONG TERM adverse events related to castration, HTA and prednisone
(prevention osteopenia, hygienodietetic, sport)

SWITCH to Dexamethasone (0.5mg daily) in case of progression on AA-P

Fig. 2 Possible study consort diagram. *Including patients without any radiological or clinical progression; patients with no high grade adverse events related to CYP-17 inhibition. *AA* Abiraterone acetate, *P* prednisone, *D* dexamethasone

Table 2 Efficacy of steroid switch

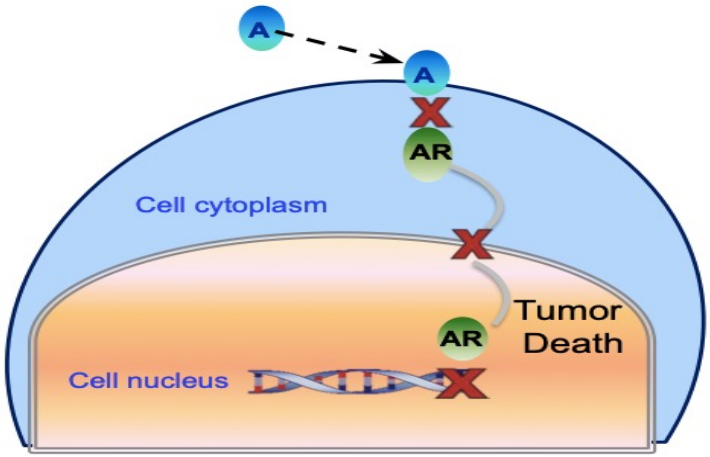
Study author	Median duration of previous AA + P	Time to PSA progression median	PFS median	OS median	Best PSA response (%)
Lorente et al. (2014)	6.3 months	11.7 weeks	NR	NR	≥50% (20)
Fenioux et al. (2018)	8.9 months	10.35 months	NR	NR	≥50% (48)
Romero-Laorden et al. (2018)	5.8 months	NR	11.8 months	20.9 months	≥50% (35)
Roviello et al. (2018)	2.4 months*	NR	10.8 Weeks	17.6 Weeks	≥50% (11)

NR not reported

*Reported as 9.9 weeks

Roviello, G, Sobhani, N, Corona, SP & D'Angelo, A 2020, 'Corticosteroid switch after progression on abiraterone acetate plus prednisone', *International Journal of Clinical Oncology*, vol. 25, pp. 240-246. https://doi.org/10.1007/s10147-019-01577-w

Enzalutamide super AR



Enzalutamide and apalutamide are AR signalling inhibitors: target multiple steps in the (AR) signalling pathway

Oral medication

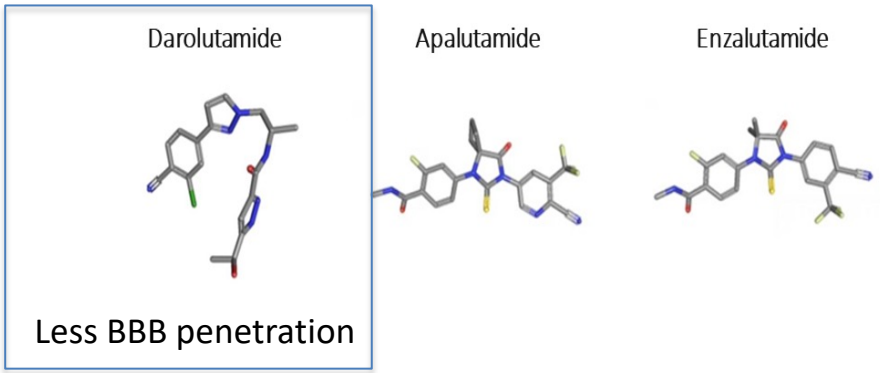
4 pills daily (1 uptake)

With or without food !

No need to add prednisone
Well tolerated
No need to closely monitor
!! Risk of Seizure

Table 3. Adverse Events, According to Grade.

Adverse Event	Enzalutamide (N=800)		Placebo (N=399)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
≥1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Frequent adverse events more common with enzalutamide*				
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6 (<1)	22 (6)	0
Clinically significant adverse events				
Cardiac disorder				
Any	49 (6)	7 (1)	30 (8)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing†	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

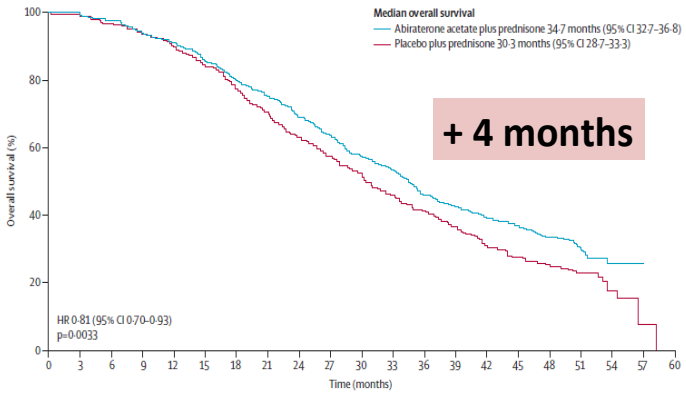


Drug	Substrate	Inhibits	Induces	Common DDIs
Abiraterone Acetate[a,b]	CYP3A4 (minor) SULT2A21 (major)	CYP2D6 (strong) CYP2C8 (moderate) CYP1A2 (weak)	–	Beta-blockers
Enzalutamide[c]	CYP2C8 CYP3A4/5	CYP2C8 (weak) P-gp	CYP3A4 (strong) CYP2C9, CYP2C19, CYP2D6 (moderate) CYP1A2 (weak)	Statins, DOACs, calcium channel blockers, opioids, PPIs, Iosartan
Apalutamide[d]	CYP2C8 CYP3A4	CYP2B6, CYP2C8 (moderate) CYP2C9, CYP2C19 CYP3A4 (weak)	CYP3A4, CYP2C19 (strong) CYP2C9 (weak) UGT, P-gp, BCRP, OATP1B1	Statins, DOACs, calcium channel blockers, opioids, PPIs, warfarin, clopidogrel, citalopram
Darolutamide[e]	CYP3A4, P-gp	BCRP	–	Rosuvastatin

NOAC

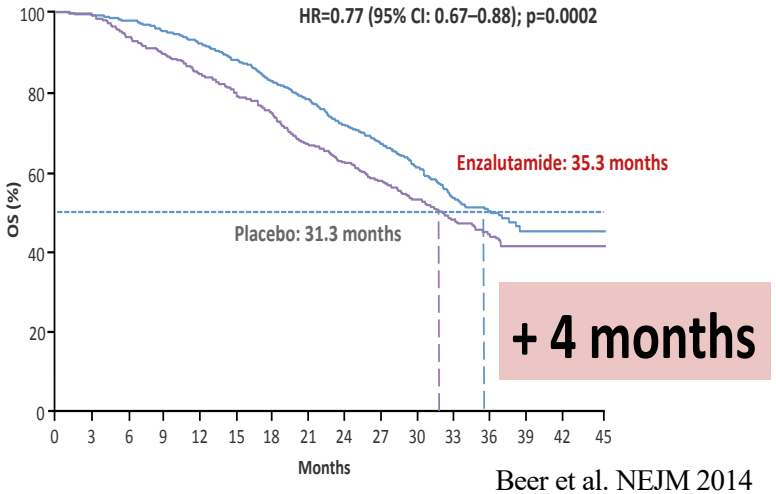
OVERALL SURVIVAL

COU-AA-302: Abiraterone
PRE Docetaxel



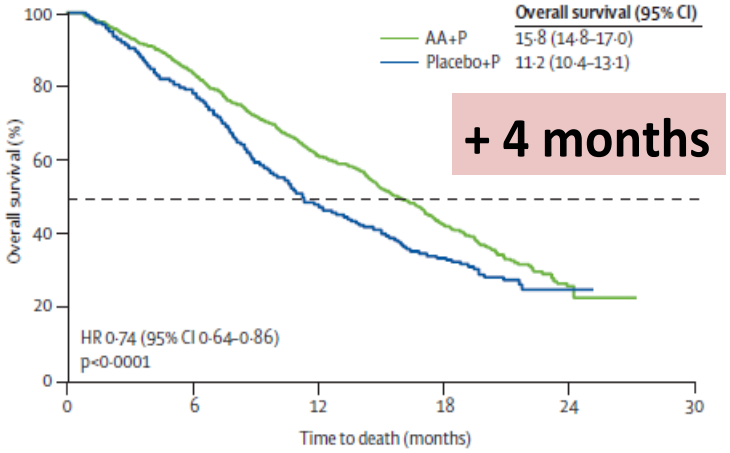
Ryan et al. Lancet Oncology 2015

PREVAIL: Enzalutamide
PRE Docetaxel



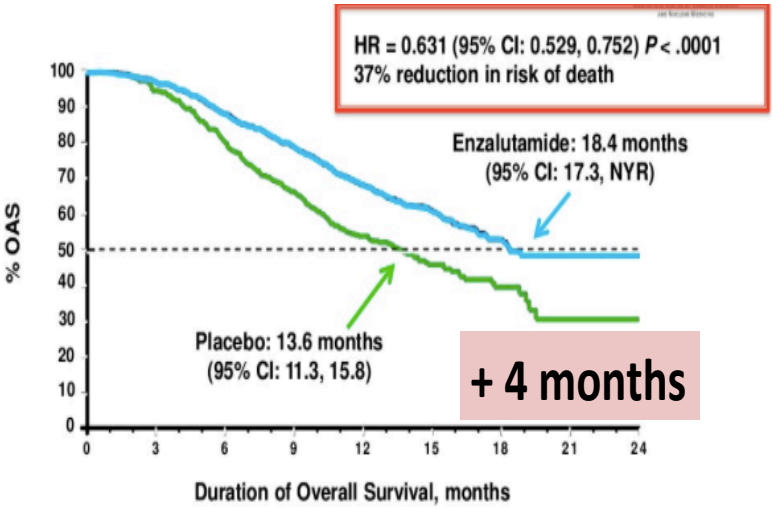
Beer et al. NEJM 2014

COU-AA-301: Abiraterone
POST Docetaxel



Fizazi et al. Lancet Oncology 2015

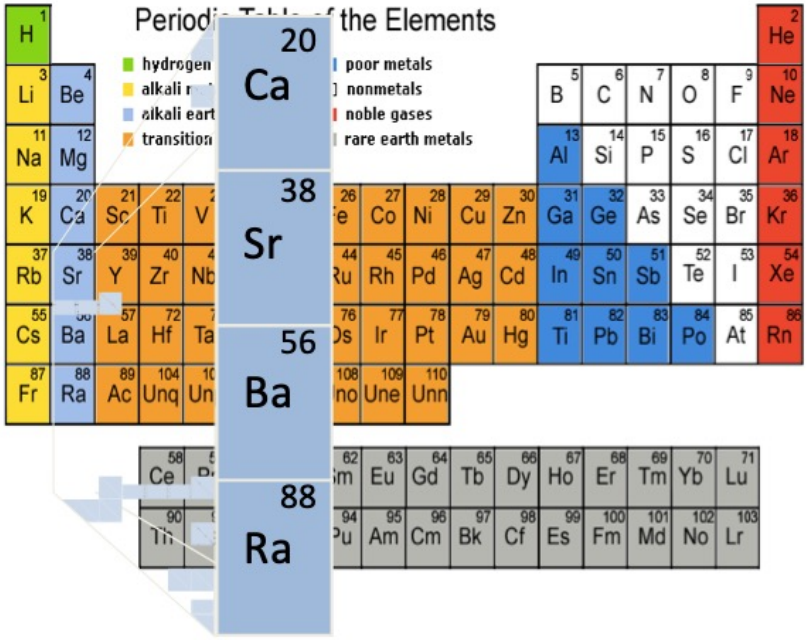
AFFIRM: Enzalutamide
POST Docetaxel

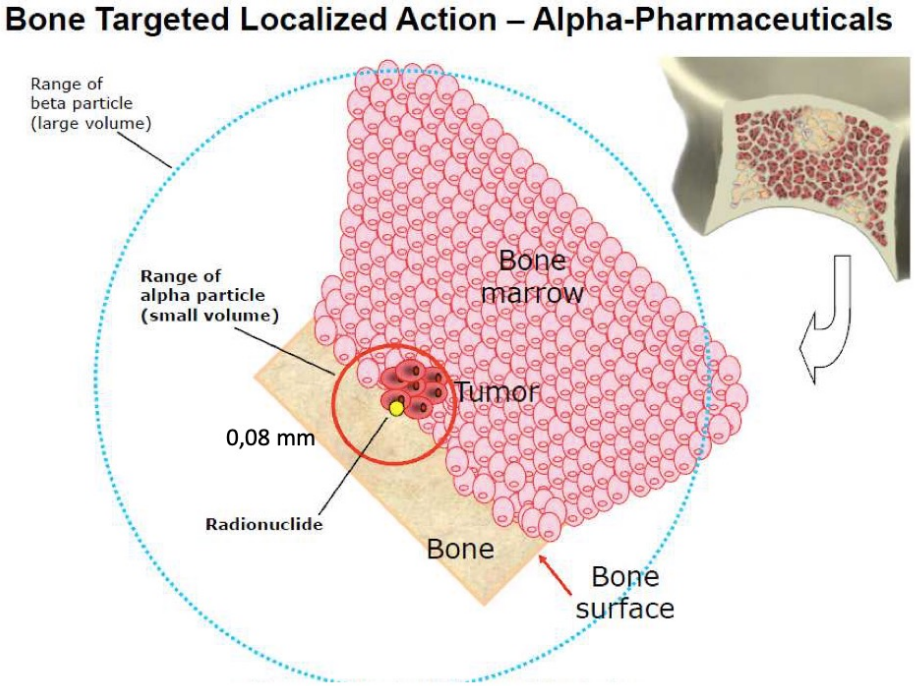


Scher et al. NEJM 2012

Bone targeted agent

Radium-223





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

Patients[1,2]

N=921
- CRPC with ≥2 symptomatic bone metastases
- No known visceral metastases
- Lymphadenopathy ≤3 cm only

Stratification[2]
- Prior docetaxel: Yes vs no
- Current bisphosphonate use: Yes vs no
- Total ALP: <220 U/L vs ≥220 U/L

Treatment[1,2]

2:1

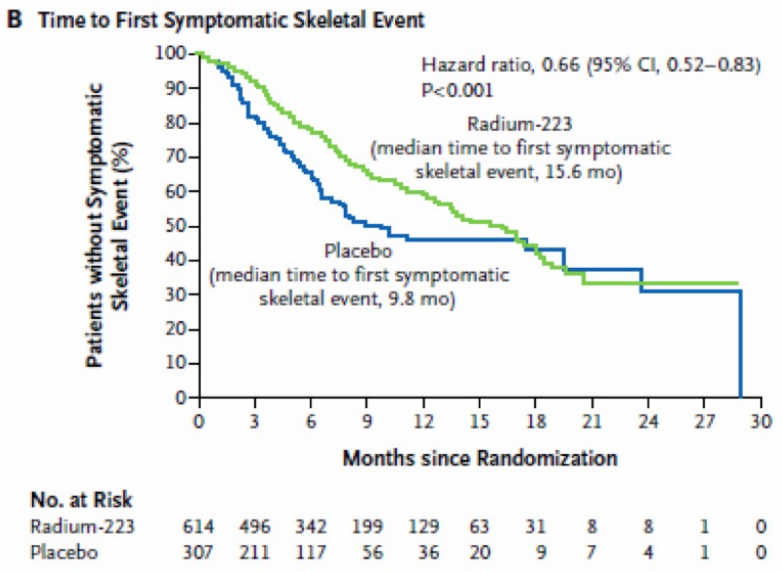
Xofigo® (radium Ra 223 dichloride) (50 kBq/kg) + Best standard of care (BSoC) (n=614)

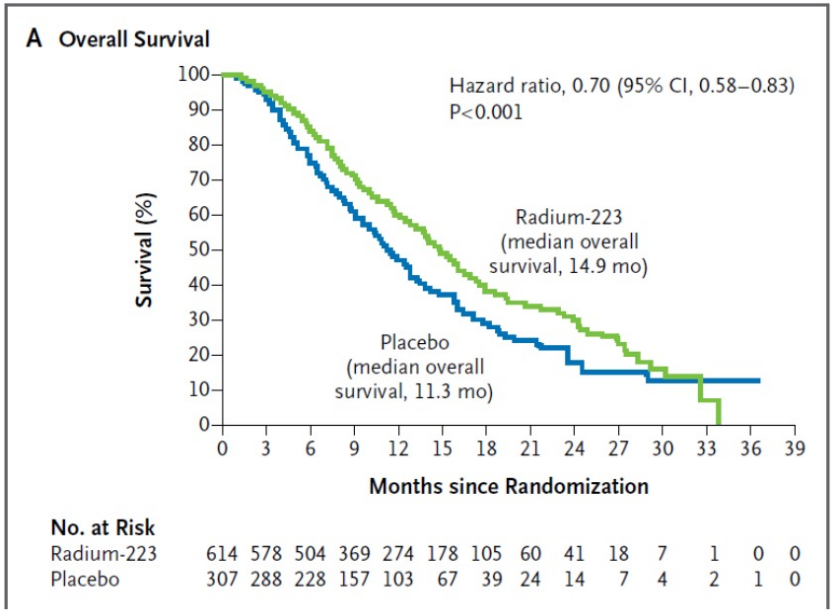
6 injections at 4-week intervals

Placebo (saline) + BSoC (n=307)

136 centers in 19 countries

Primary Endpoint[2]
Overall survival





Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)

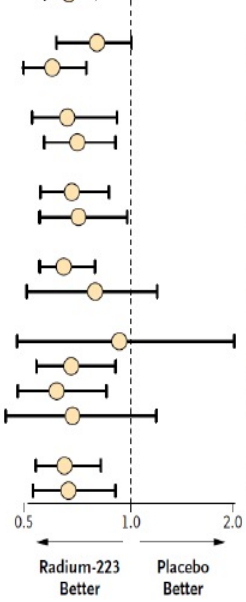


Figure 2. Subgroup Analysis of Hazard Ratios for Death in the Two Study Groups.

OPEN

Clinical aspects of mCRPC management in patients treated with radium-223

Elisa Lodi Rizzini[1,2*], Valeria Dionisi[2,3], Pietro Ghedini[1,2], Alessio Giuseppe Morganti[2,3],

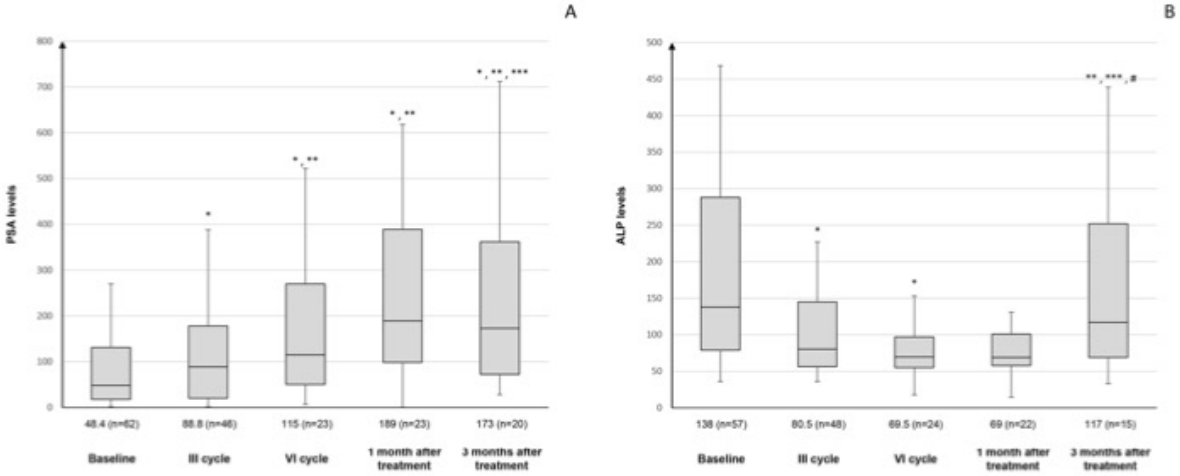


Figure 1. Levels of PSA (**A**) and ALP (**B**) at baseline, after the third and 6 cycles of radium-223, and at one and 3 months after treatment. Data are reported as median values and interquartile range. *$p < 0.05$ vs. baseline; **$p < 0.05$ vs after the 3rd cycle; ***$p < 0.05$ vs after the 6th cycle; $^{\#}p < 0.05$ vs. one month.

A portfolio of drugs in mCRPC

	N patients	Relative reduction in risk of death, %	HR (95% CI; P-value)
Abiraterone/P vs placebo/P (post-Docetaxel)[1]	1088	26	0.74 (0.64–0.86; P < 0.001)
Abiraterone/P vs placebo/P (pre-Docetaxel)[2]	1195	21	0.79 (0.66-0.95; P = 0.0035)
Enzalutamide vs placebo (post-Docetaxel)[3]	1199	37	0.63 (0.53–0.75; P < 0.0001)
Enzalutamide vs placebo (pre-Docetaxel)[4]	1717	29	0.71 (0.60–0.84; P <0.0001)
Docetaxel(q3w)/P vs mitoxantrone/P[5]	1006	24	0.76 (0.62–0.94; P = 0.009)
Cabazitaxel/P vs mitoxantrone/P (post-Docetaxel)[6]	755	30	0.70 (0.59–0.83; P < 0.0001)
Radium-223 vs. placebo (post-Docetaxel)[8]	921	31	0.70 (0.58–0.83; P < 0.001)

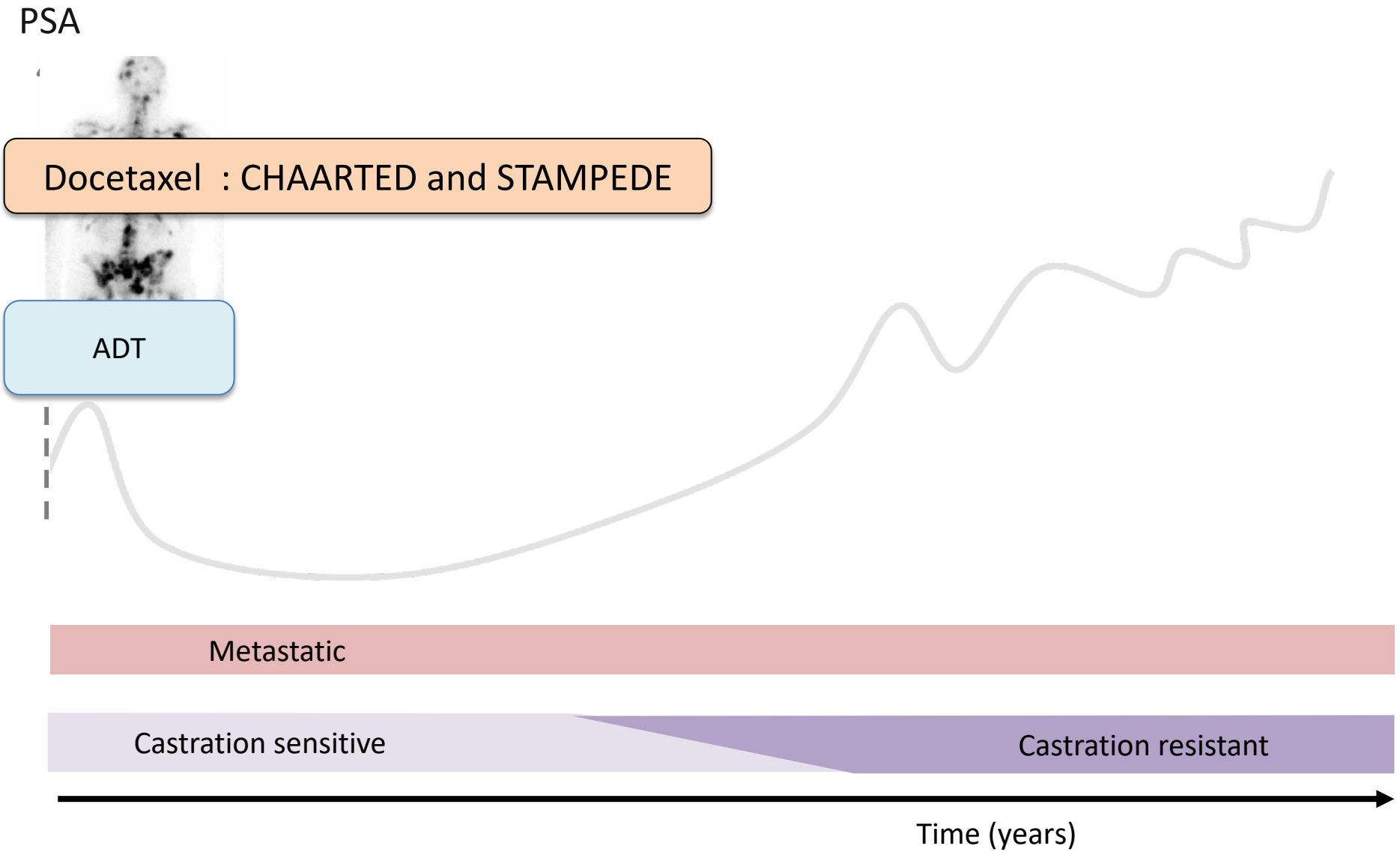
1. Fizazi K et al. Lancet Oncol 2012;13:983–92; 2. Rathkopf DE et al. Eur Urol 2014 (epub ahead of print); 3. Scher HI et al. NEJM 2012; 367: 1187-97; 4. Beer TM et al. NEJM 2014; 371:424-33; 5. Tannock IF et al. NEJM 2004;2351:1502–12; 6. de Bono JS et al. Lancet 2010; 76: 1147–54; 7. Kantoff PW et al. NEJM 2010;363: 411–22; 8. Parker C et al. NEJM 2013;369: 213-23

Strategies in metastatic Hormonosensitive Prostate Cancer

mHSPC

Improve the first-line setting in mHSPC (since 2015)

➔ INCREASE THE castration sensitive time duration !!!

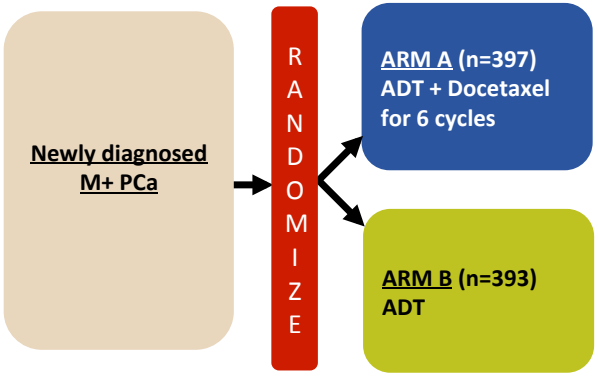


ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H.,

CHAARTED trial



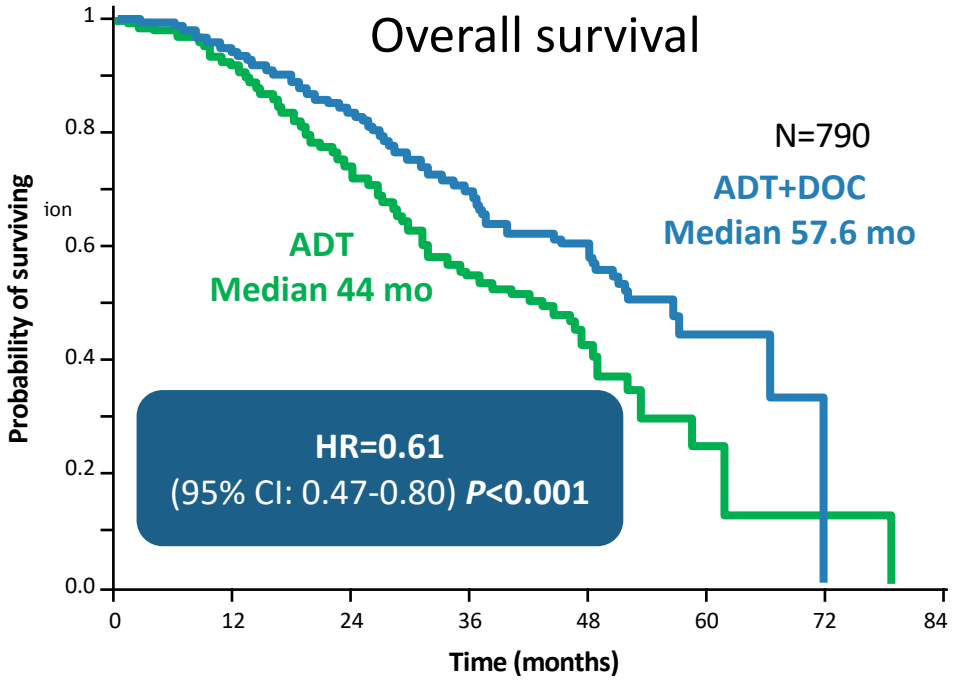
Primary endpoint:
Overall survival

Stratification
- Extent of mets : high vs low
- Age: >70 vs < 70
- ECOG 0-1 vs 2

ADT allowed up to 120 days prior to rand ion
Intermittent ADT not allowed

Docetaxel 75mg/m2 **6 cycles**

80% of ADT patients received at PD docetaxel !



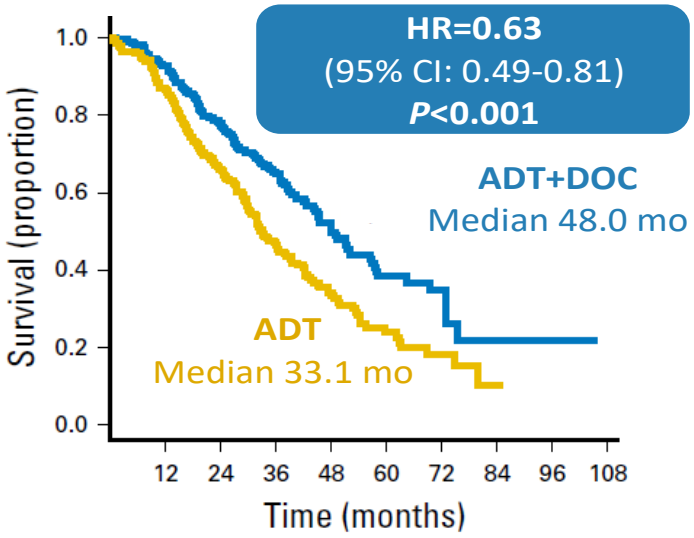
1. Sweeney C, et al. N Engl J Med. 2015;373:737-46

High volume metastatic disease

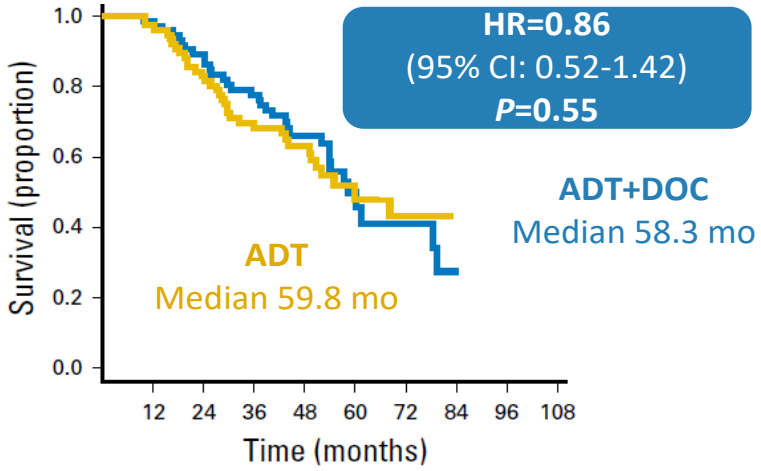
- visceral metastases and/or
- 4 or more bone metastases

(with at least 1 beyond pelvis and vertebral column)

High-volume* (N=421)



Low-volume (N=154)

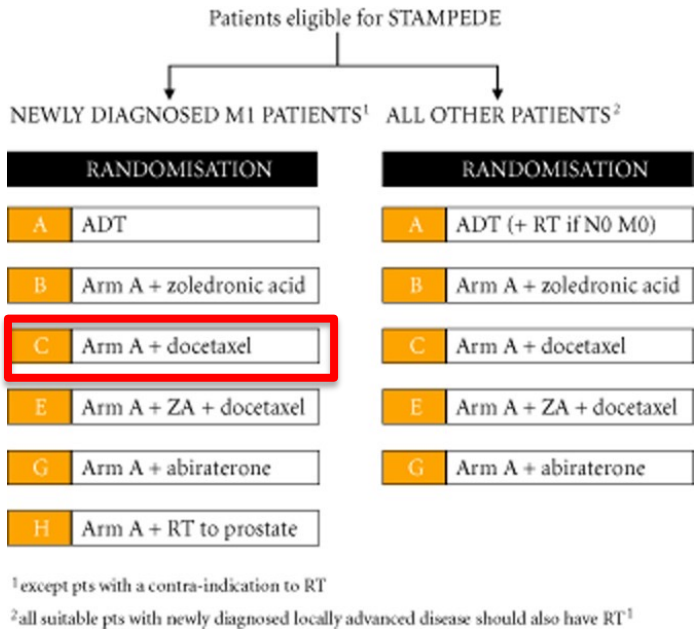


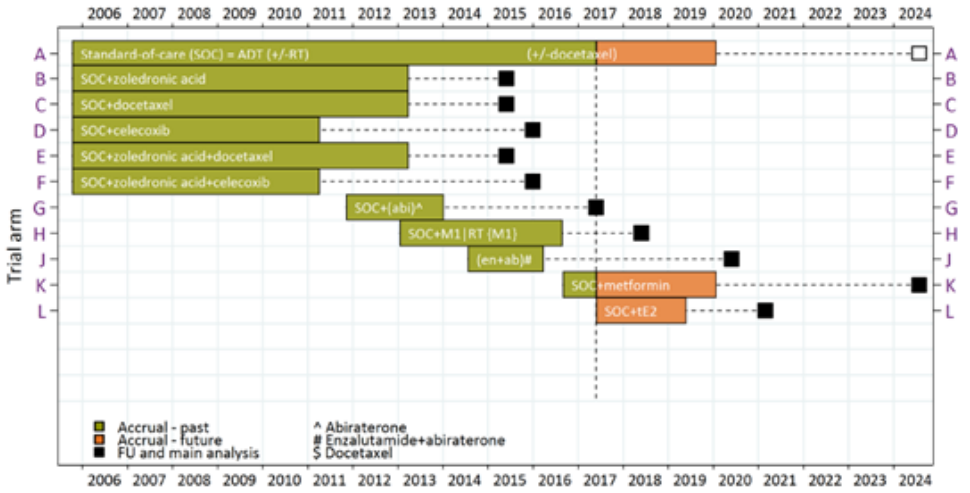
Strong rational for using chemo in HIGH VOLUME

On BONE SCAN and Thoraco-Abdo CT

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE) survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie,

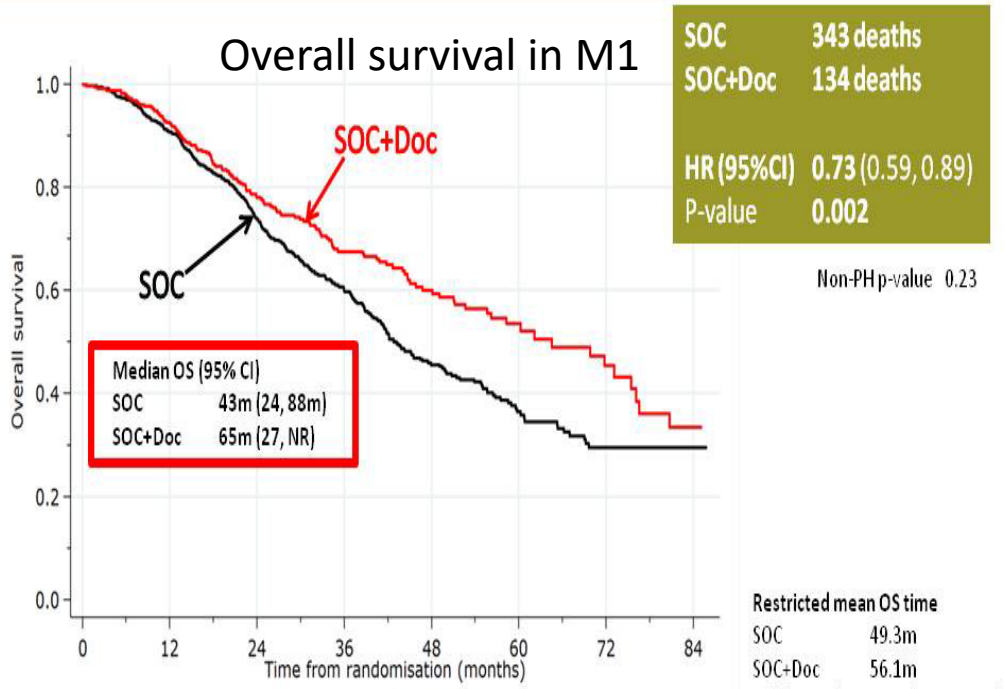




Note: dotted line represents activation of this protocol version

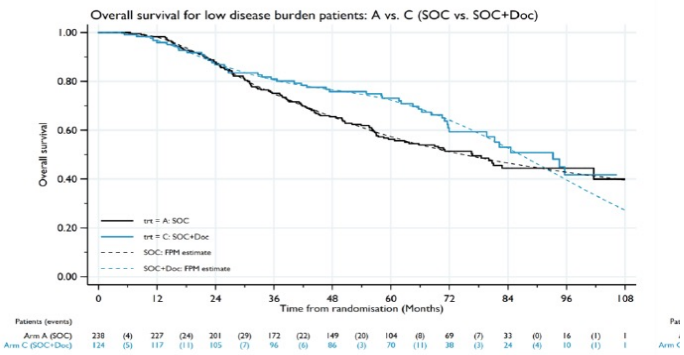
Docetaxel 75mg/m2 **6 cycles**

80% of ADT patients received at PD docetaxel !



Retrospective analyse
based on CHAARTED criteria

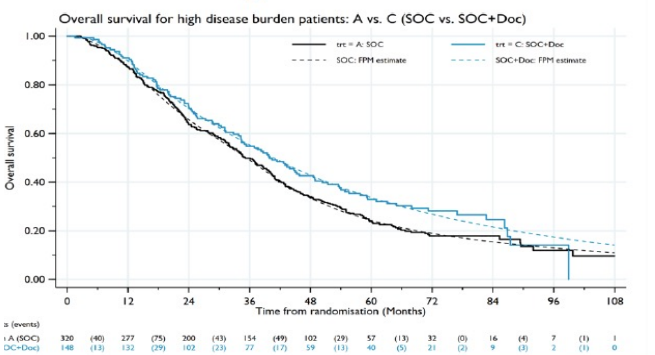
Low Burden



HR 0.76
95% CI 0.54 – 1.07
P = 0.107
Non-PH 0.809

5-yr survival:
A 57%
C 72%

High Burden



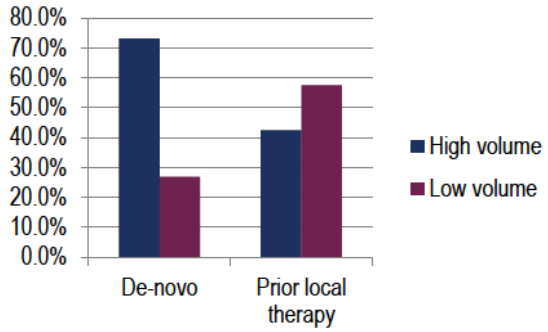
HR 0.81
95% CI 0.64 – 1.02
P = 0.064
Non-PH 0.251

5-yr survival:
A 24%
C 34%

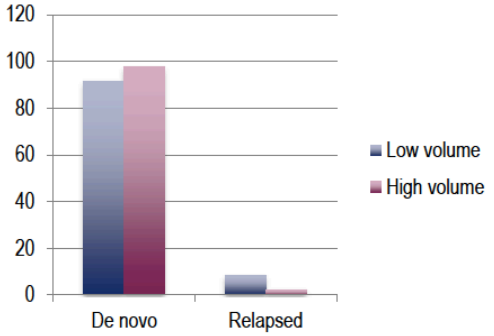
N. James, ESMO 2019

No difference based on disease burden

CHAARTED



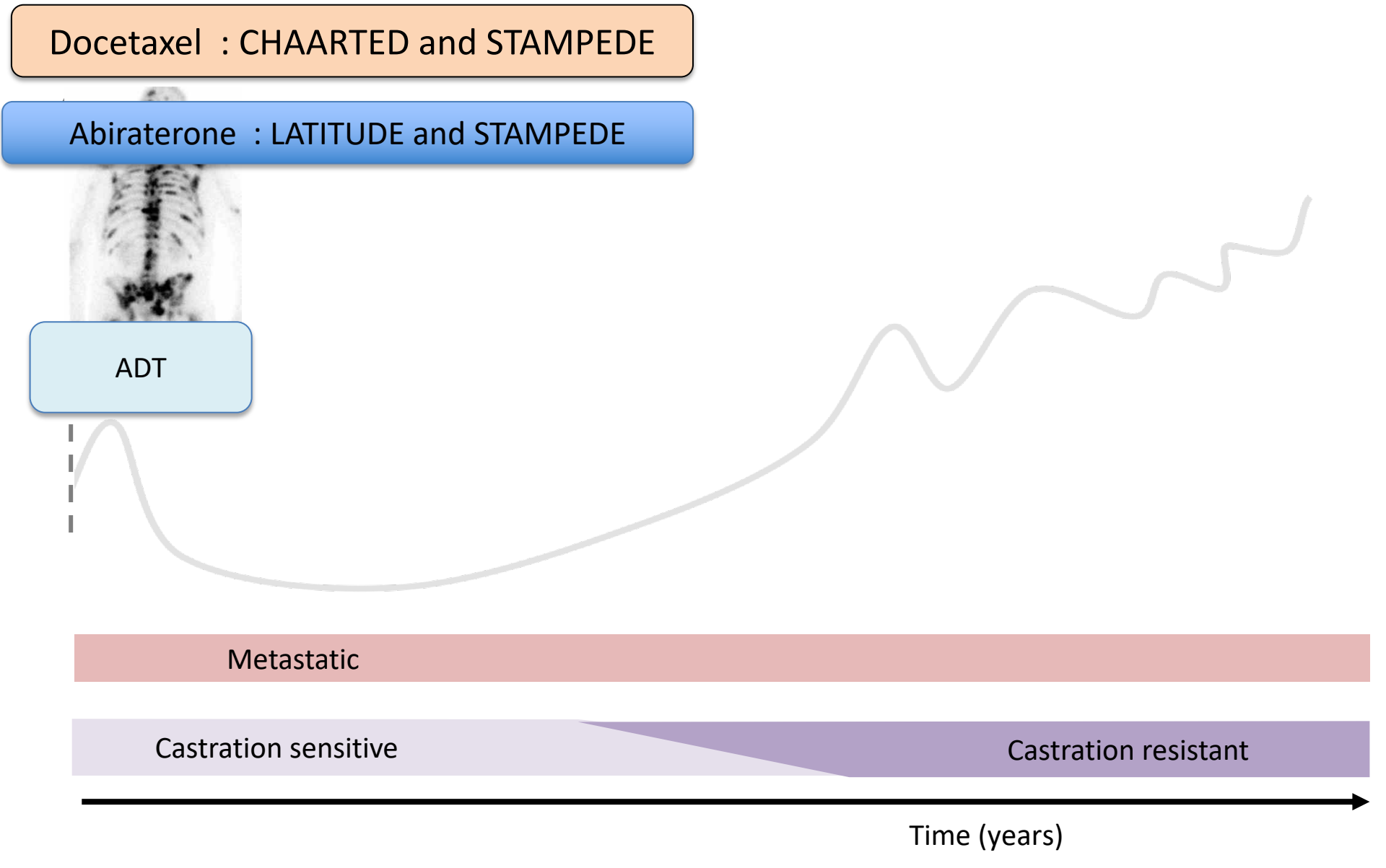
STAMPEDE



High volume in de novo metastatic patients!
Low volume in relapsed disease patients !

Mostly patients with de novo M1

Improve the first-line setting in mHSPC (since 2015)

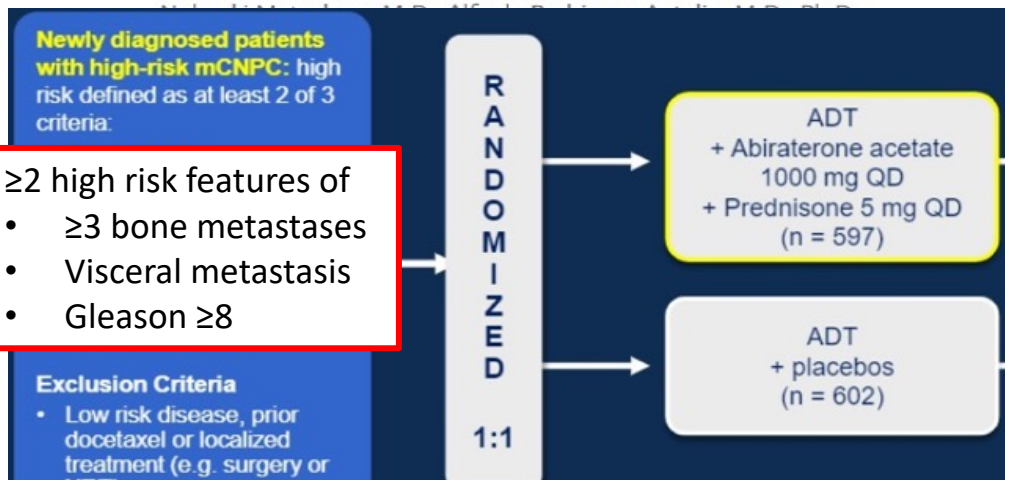


ORIGINAL ARTICLE

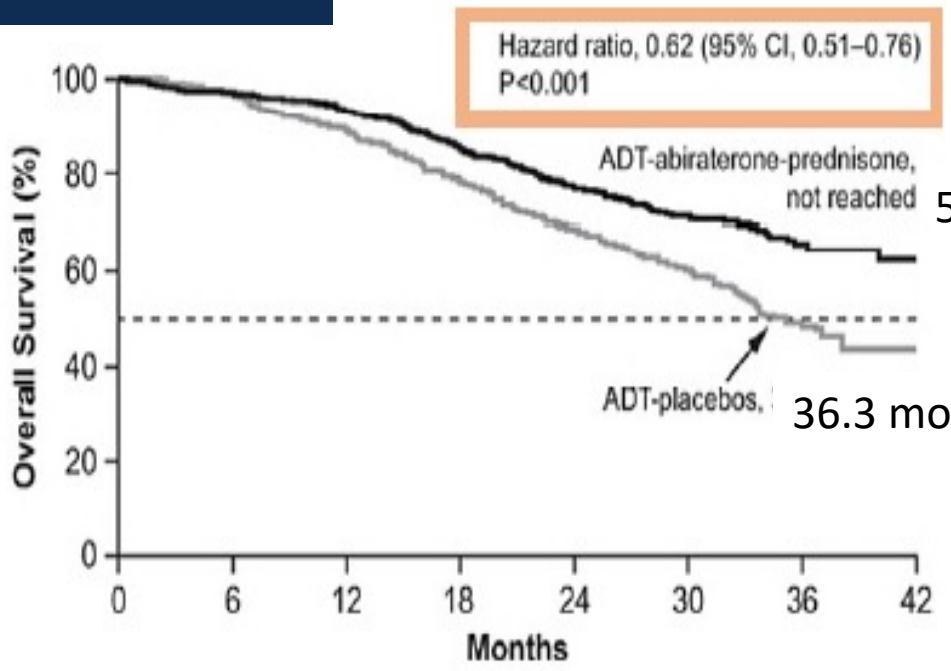
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D.,

LATITUDE Trial



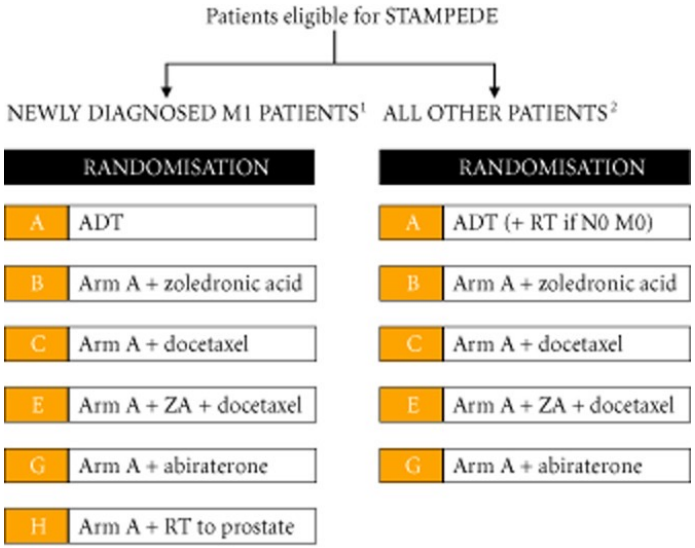
New SoC in mHSPC High Risk



ORIGINAL ARTICLE

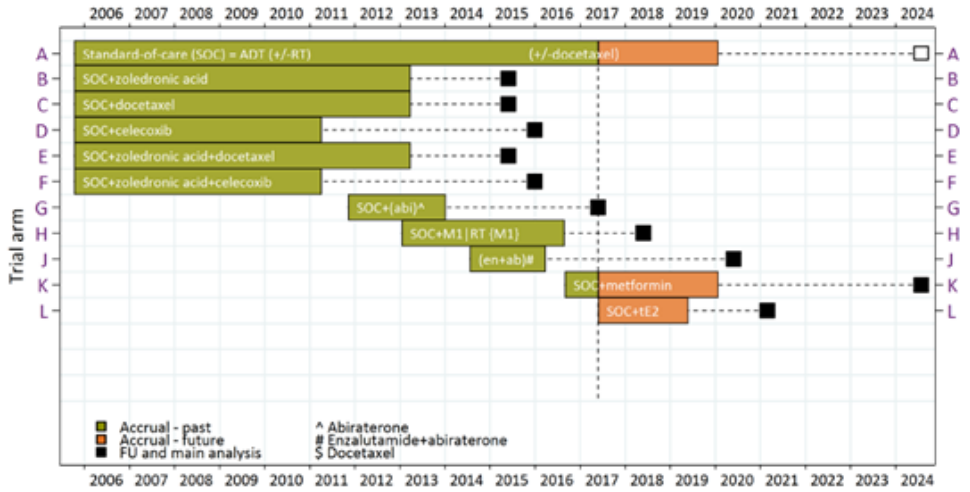
Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason,



[1] except pts with a contra-indication to RT

[2] all suitable pts with newly diagnosed locally advanced disease should also have RT[1]



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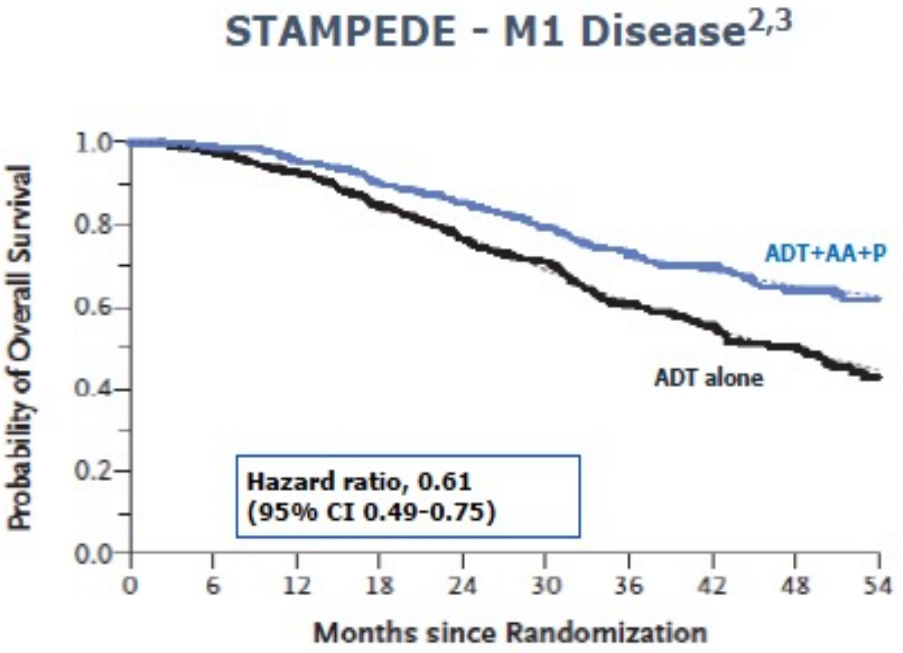
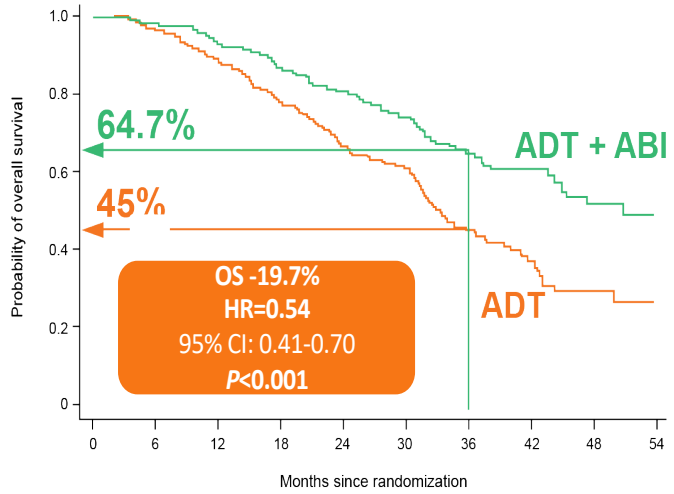
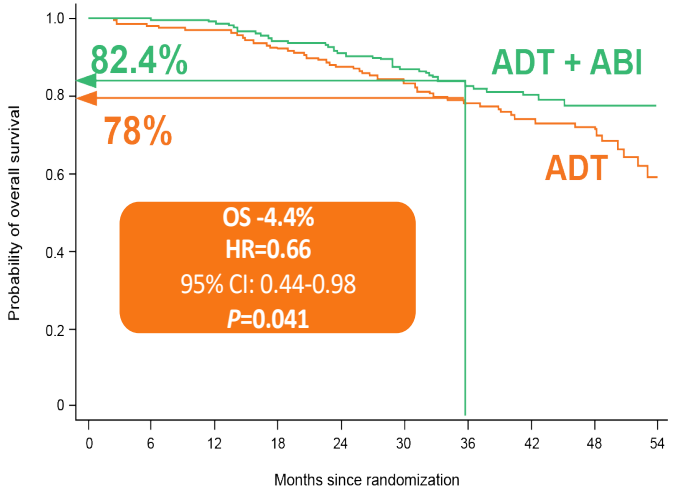


Retrospective analyse based on LATITUDE Risk

STAMPEDE
High-risk
(N=428)
Median FU:
41.5 mths



STAMPEDE
Low-risk
(N=473)
Median FU:
41.5 mths

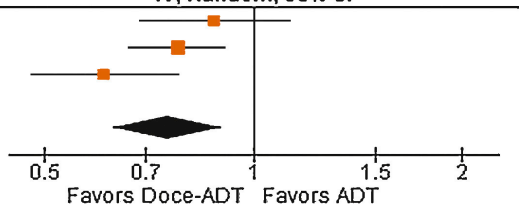


Hoyle A et al. Ann Oncol 2018;29(suppl 8):LBA4

A

Study or subgroup	log[Hazard ratio]	SE	Doce-ADT Total	ADT Total	Weight	Hazard ratio IV, Random, 95% CI
Gravis 2016	−0.1278	0.1315	192	193	28.9%	0.88 [0.68, 1.14]
James 2016	−0.2485	0.0852	592	1184	42.7%	0.78 [0.66, 0.92]
Sweeney 2015	−0.4943	0.133	397	393	28.5%	0.61 [0.47, 0.79]
Total (95% CI)			**1181**	**1770**	**100.0%**	**0.75 [0.63, 0.91]**

Heterogeneity: Tau² = 0.01; χ^2 = 4.07, df = 2 (p = 0.13); I^2 = 51%
Test for overall effect: Z = 3.00 (p = 0.003)



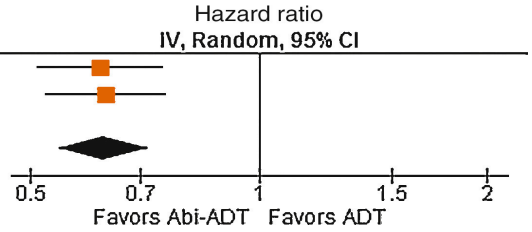
ADT + Docetaxel in mHSPC superior to ADT alone

- In High volume disease on bone scan and CT scan
- In *de novo* (low and high)

B

Study or subgroup	log[Hazard ratio]	SE	Abi-ADT Total	ADT Total	Weight	Hazard ratio IV, Random, 95% CI
Fizazi 2017	−0.478	0.0996	597	602	49.1%	0.62 [0.51, 0.75]
James 2017	−0.462	0.0979	960	957	50.9%	0.63 [0.52, 0.76]
Total (95% CI)			**1557**	**1559**	**100.0%**	**0.63 [0.55, 0.72]**

Heterogeneity: Tau² = 0.00; χ^2 = 0.01, df = 1 (p = 0.91); I^2 = 0%
Test for overall effect: Z = 6.73 (p < 0.00001)

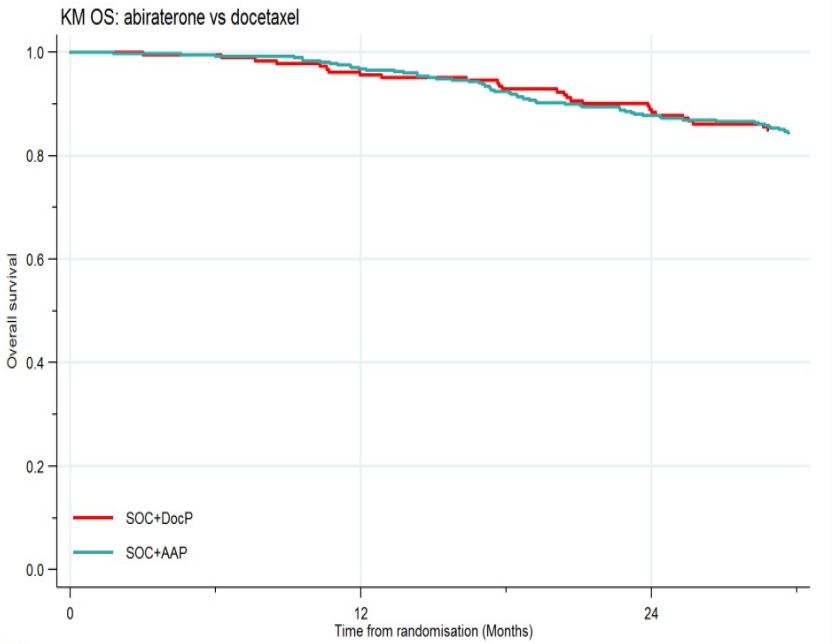


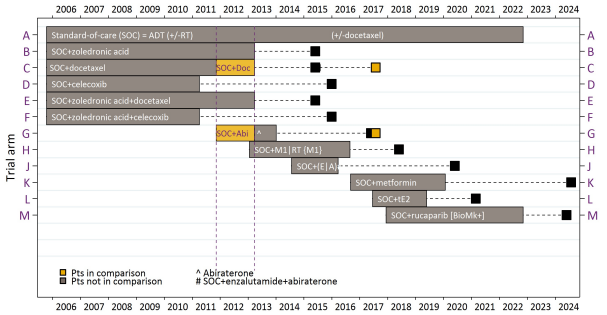
ADT + AA-P in mHSPC superior to ADT alone

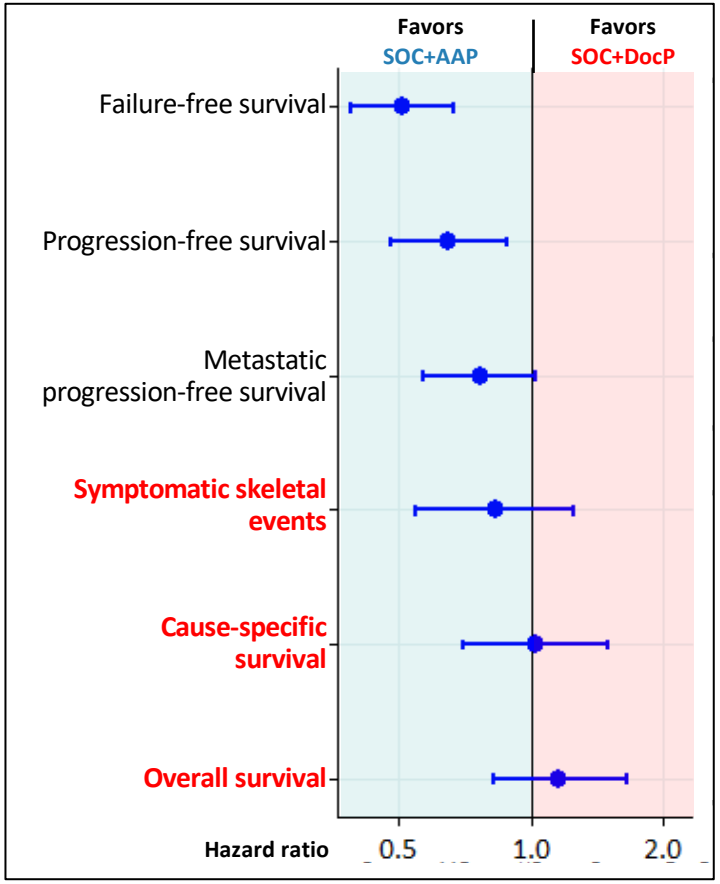
- In High risk disease (low or high volume)

STAMPEDE: ADT+ABI/P vs ADT+Doc/P

OS (primary end-point)



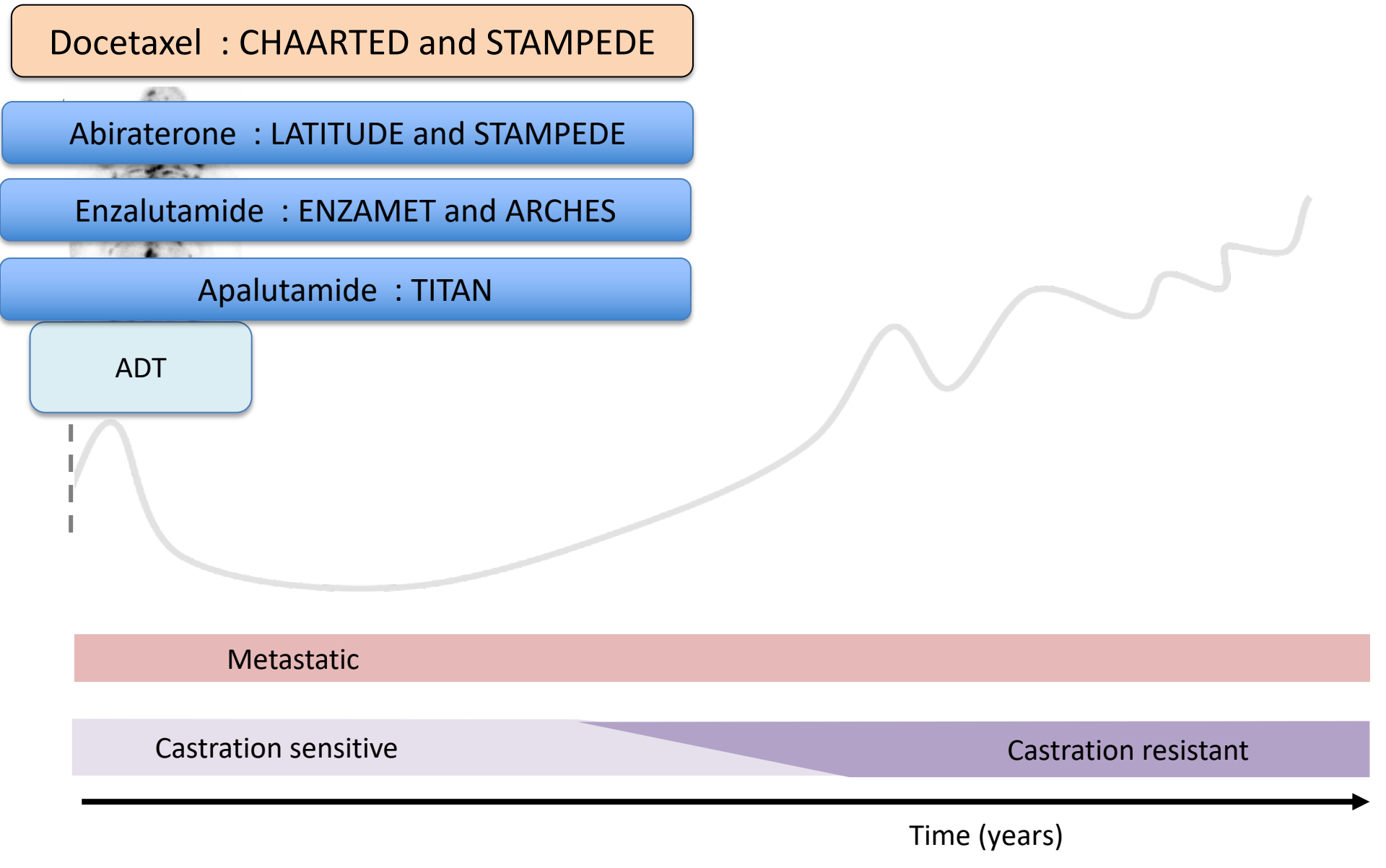




Well balanced population !
De novo vs relapsing
High vs low risk, volume

Sydes MR, et al. ESMO 2017 (podium presentation); Sydes MR, et al. Ann Oncol. 2018;doi:10.1093/annonc/mdy072.

Improve the first-line setting in mHSPC (since 2015)



In Metastatic Hormono-Naive Prostate Cancer

Trial	HR for OS	LP treatment	Follow-up (mo)
GETUG-15	0.88 (0.68-1.14)	127/193 (66%)	84
CHAARTED	0.72 (0.59-0.89)	187/393 (48%)	54
STAMPEDE Doc	0.81 (0.69-0.95)	372/1184 (31%)	78
STAMPEDE Doc+ZA	0.79 (0.66-0.96)	372/1184 (31%)	43
LATITUDE	0.66 (0.56-0.78)	345/602 (57%)	52
STAMPEDE Abi	0.61 (0.49-0.75)	310/957 (32%)	40
ARCHES	0.81 (0.53-1.25)	<133/576 (<23%)	14
TITAN	0.67 (0.51-0.89)	165/527 (31%)	23
ENZAMET	0.67 (0.52-0.86)	271/562 (48%)	34

Kyriakopoulos CE, J Clin Oncol 2018; Gravis G, Eur Urol 2015; Clarke N/James N, ESMO 2019, James N, Lancet 2016, Fizazi K, Lancet Oncol 2019, James N, NEJM 2019
Armstrong AJ, J Clin Oncol 2019, Chi K, NEJM 2019, Davis I, NEJM 2019

➔ **Need for a better selection of patients for chemotherapy or AR-targeted agents**

➔ **Need to demystify chemotherapy**

LP life prolonging therapies

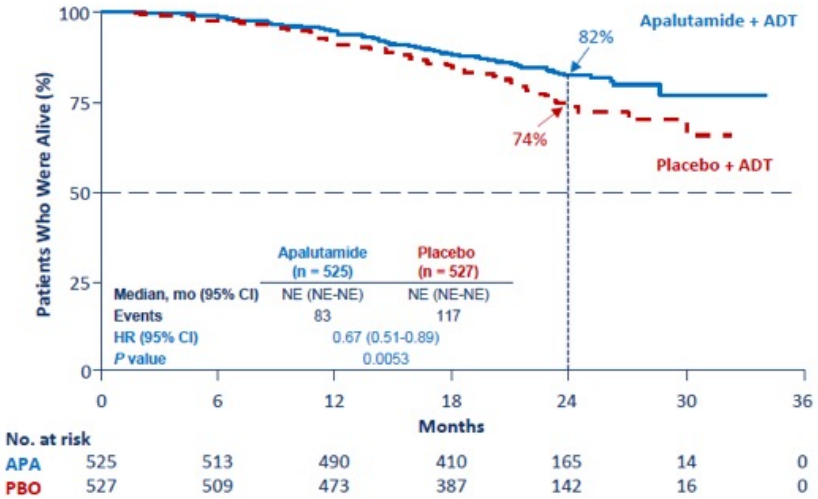
K. Fizazi presentation at ESMO 2019

ORIGINAL ARTICLE

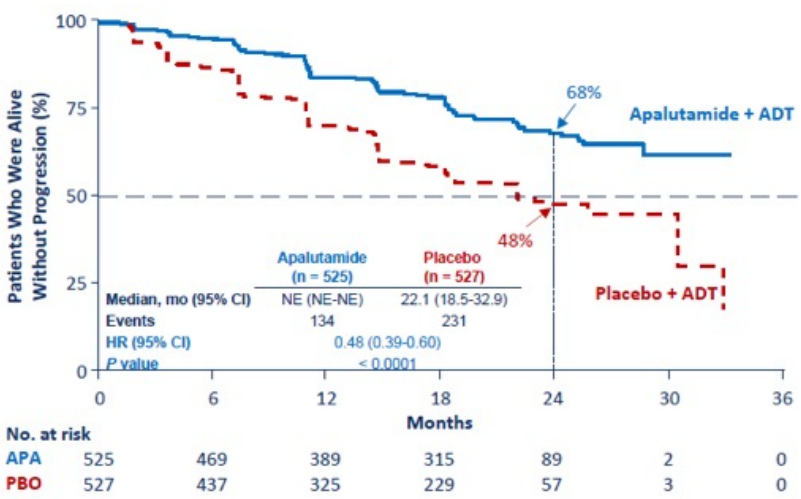
Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert

Apalutamide Significantly Reduced the Risk of Death by 33%



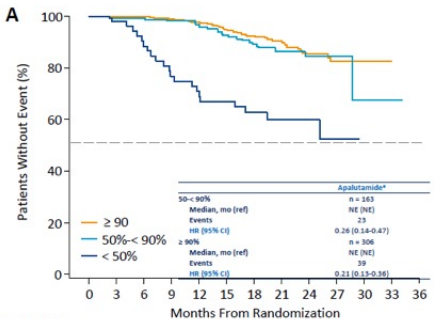
Apalutamide Significantly Reduced the Risk of Radiographic Progression or Death by 52%



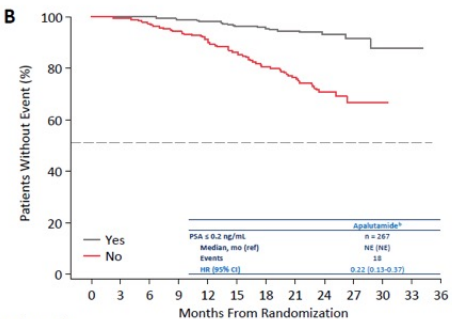
APA, apalutamide; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBO, placebo.

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

Patients who achieved reduction of PSA ≥ 90%, PSA 50%-< 90%, and PSA < 50% by 3 months



Patients who achieved PSA ≤ 0.2 ng/mL and those who did not by 3 months



Primary and HRQoL endpoints

Product	Docetaxel			ABIRATERONE+ADT		ENZALUTAMIDE+ADT		APALUTAMIDE
Study	GETUG-15[1,2]	CHAARTED[3]	STAMPEDE (Arm C) M1 pts[4]	LATITUDE[5,6]	STAMPEDE (arm G) M1 pts[7,12]	ARCHES[8]	ENZAMET[9]	TITAN[10]
Median follow-up	83.9 months	53.7 months	43 months	51.8 months	40 months	14.4 months	34 months	22.7 months
OS: - HR - (95% CI) - P-value - Benefit , mo - Active arm vs control arm, mo	**0.88** (0.68-1.1) 0.3 13.5 (62.1 vs 48.6)	**0.72** (0.59–0.89) 0.0017 10.4 (57.6 vs 47.2)	**0.76** (0.62-0.92) 0.005 15 (60 vs 45)	**0.66** (0.56-0.78) <0.0001 16.8 (53.3 vs 36.5)	**0.61** (0.49-0.75) NA NA NA	-	**0.67** (0.52-0.86) 0.002 ? (NR vs NR)	**0.67** (0.51-0.89) p=0.0053 ? (NR vs NR)
rPFS: - HR - (95% CI) - P-value - Benefit , mo - Active arm vs control arm, mo	-	-	-	**0.47** (0.39-0.55) < 0.001 18.2 (33.0 vs 14.8)	-	**0.39** (0.30, 0.50) <0.0001 ? (NR vs 19.4)	-	**0.48** (0.39-0.60) <0.0001 ? (NR vs 22.1)
HRQoL: EuroQol (EQ-5D) (Docetaxel and Abiraterone) HRQoL: FACT-P score change from baseline (Enzalutamide and Apalutamide)	-	-	Improved	Suggested Improvement	-	Not significant	-	Not significant

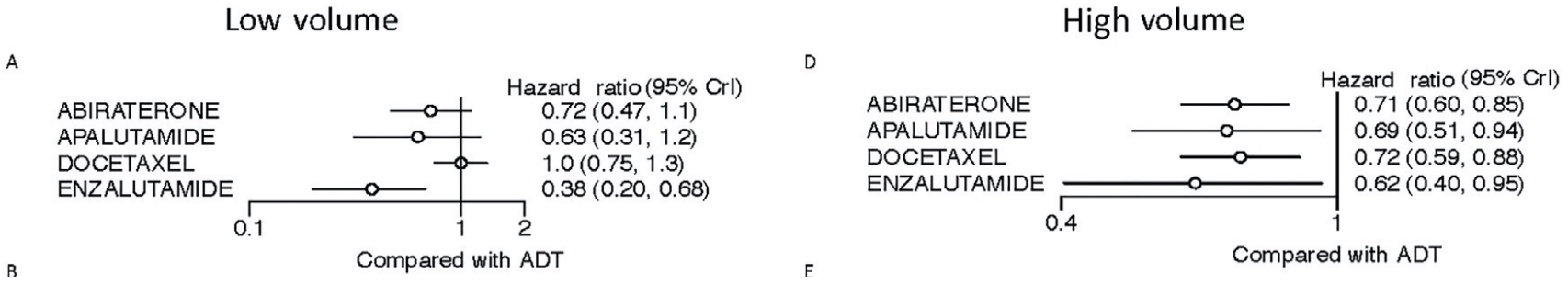
1. Gravis G, et al. Lancet Oncol 2013; 14(2): 149–158; 2. Gravis G, et al. Eur Urol. 2016 Aug;70(2):256-62; 3. Kyriakopoulos CE, et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087; 4. James ND et al. The Lancet 2016 387, 1163-1177; 5. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360; 6. Fizazi K, et al. ASCO-GU 2019. Poster and oral presentation (Abstract 141); 7. James N, et al N Engl J Med. 2017 Jul 27;377(4):338-351; 8. Armstrong AJ, et al. ASCO-GU 2019. Poster and oral presentation (Abstract 687); 9. Davis, ID. N Engl J Med. 2019 Jun 2. [Epub ahead of print]; 12. Hoyle AP, et al. Ann Oncol 2018;29(Suppl 8):LBA4 10. NCT02489318

European Association of Urology

Review – Prostate Cancer

Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cance A Systematic Review and Network Meta-analysis

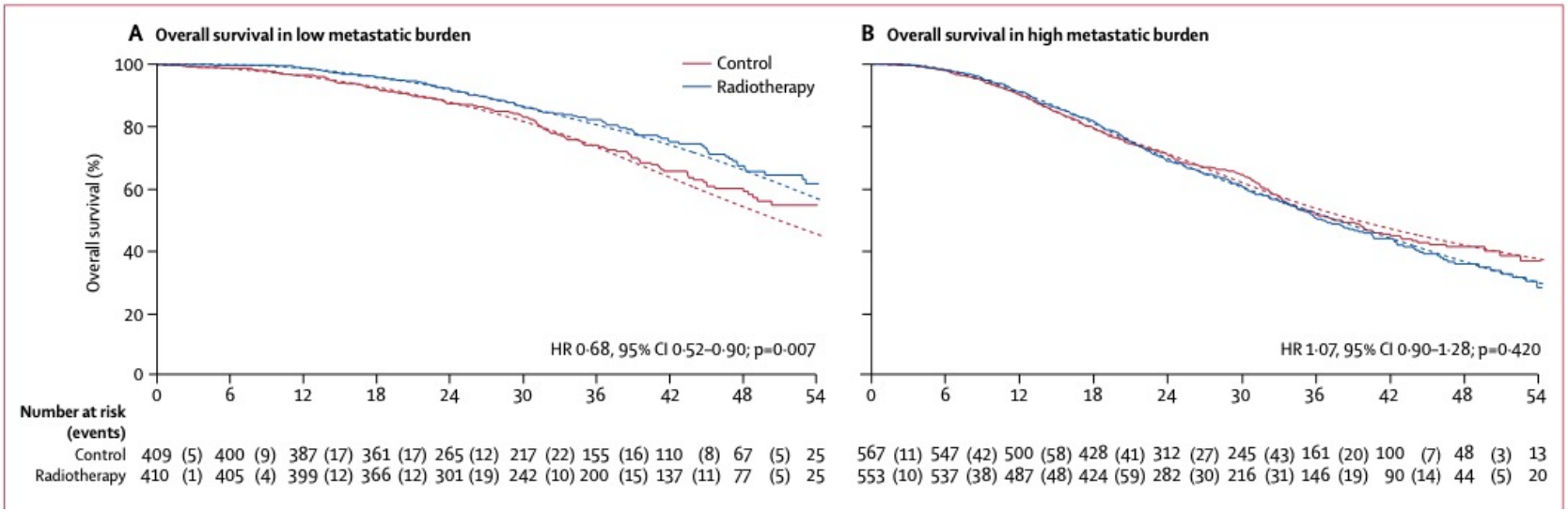
Niranjan J. Sathianathen [a,b], Samantha Koschel [a], Isaac A. Thangasamy [a], Jiasian Teh [a],



Enza, Apa and Abi are efficient in LOW and HIGH volume

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard,



In low volume, Radiotherapy on prostate bed + ADT is an option !
BUT no head to head comparison with other option !!!

EAU guidelines 2021

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 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. **HIGH VOLUME +++ (or de novo AND low volume)**	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. **High or low volume !**	Strong
Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong

Enza Not reimbursed
Apa in MNP

In Metastatic Hormono-naive Prostate Cancer

DOCETAXEL + ADT

AR TARGETED Agents + ADT

Improve significantly survival

Docetaxel
6 cycles

AR-targeted agents
AA-P
Apalutamide
Enzalutamide

2 excellent regimens and new standard of care

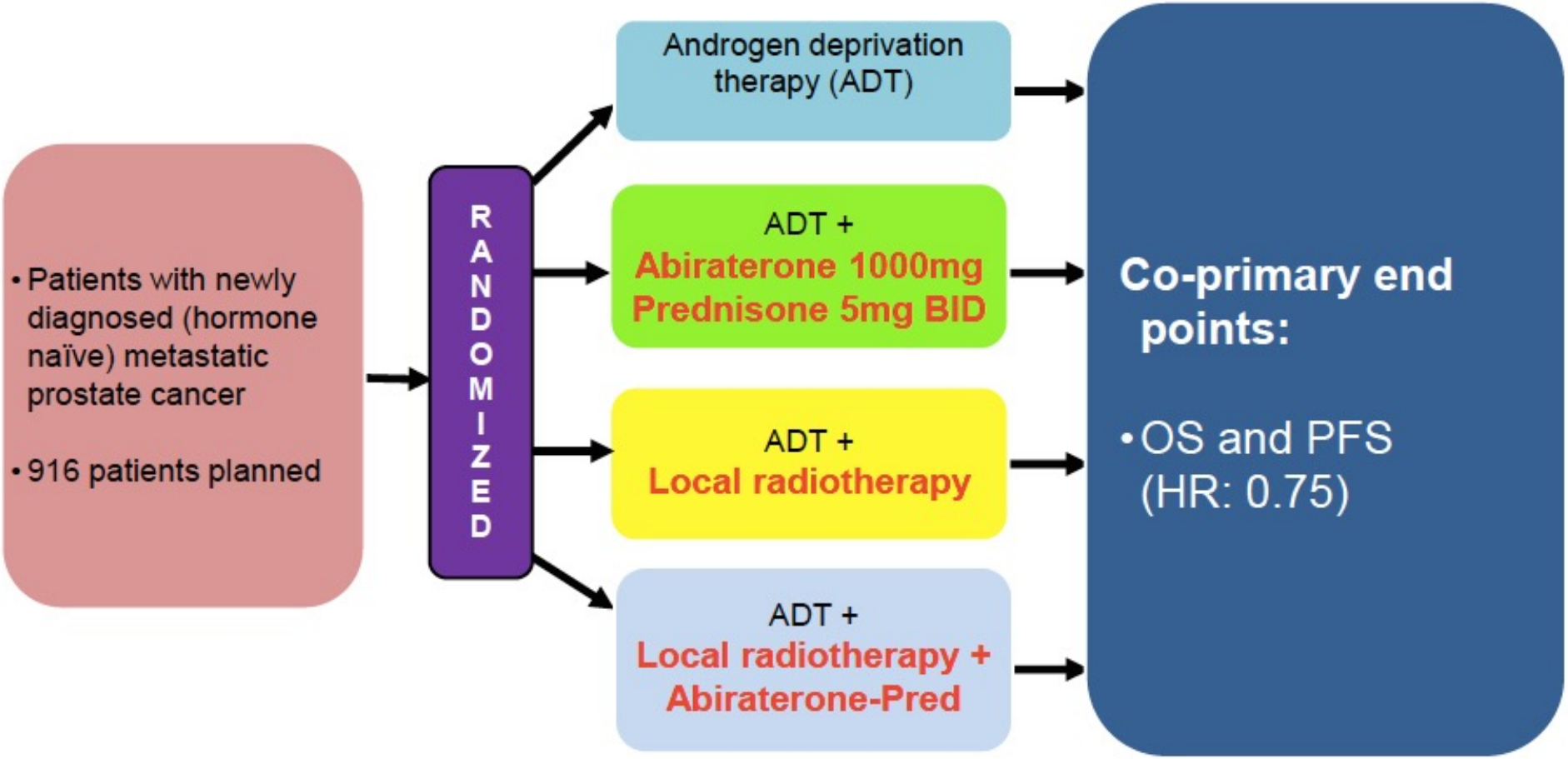
One of these 2 agent has to be proposed in mHSPC

All patients with mPC should receive Chemo and hormonal agent in the disease course

Criteria to consider for choosing 1-st line setting in mHSPC

	Pros	Cons
Docetaxel	- Only 6 cycles (4 months) - GM-CSF - Lower cost (34.000$)	- Transient Medrol shots - Initial and transient decrease QoL
AA-P	- Oral medication - No decrease of QoL	- Indefinite duration - Food-based restriction - More frequent control initially - Caution in • HTA, cardiac disease • Poorly controlled diabete • Gastric ulcers • osteoporosis - Higher cost (300.000$)
Apalutamide	Fewer visits Oral medication No food restriction No decrease of QoL	- Indefinite duration - Higher Cost (300.000$)

PEACE-1: European Phase III Trial of Abiraterone in patients with newly diagnosed metastatic prostate cancer



Study sponsor: Unicancer

Courtesy of K Fizazi

The Best Sequence

All patients with mPC should receive chemo and hormonal agent in the disease course

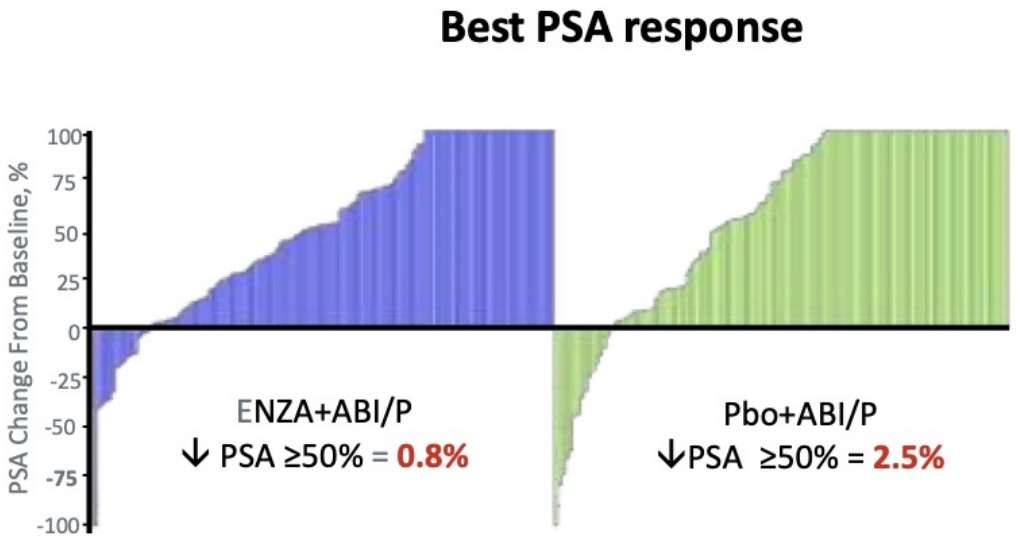
- If PD on docetaxel ➔ hormonal agent

- If PD on Hormonal agent ➔ Docetaxel

If treated with ADT + AR-targeted agent UPFRONT

➔ You loose time to use another hormonal agent

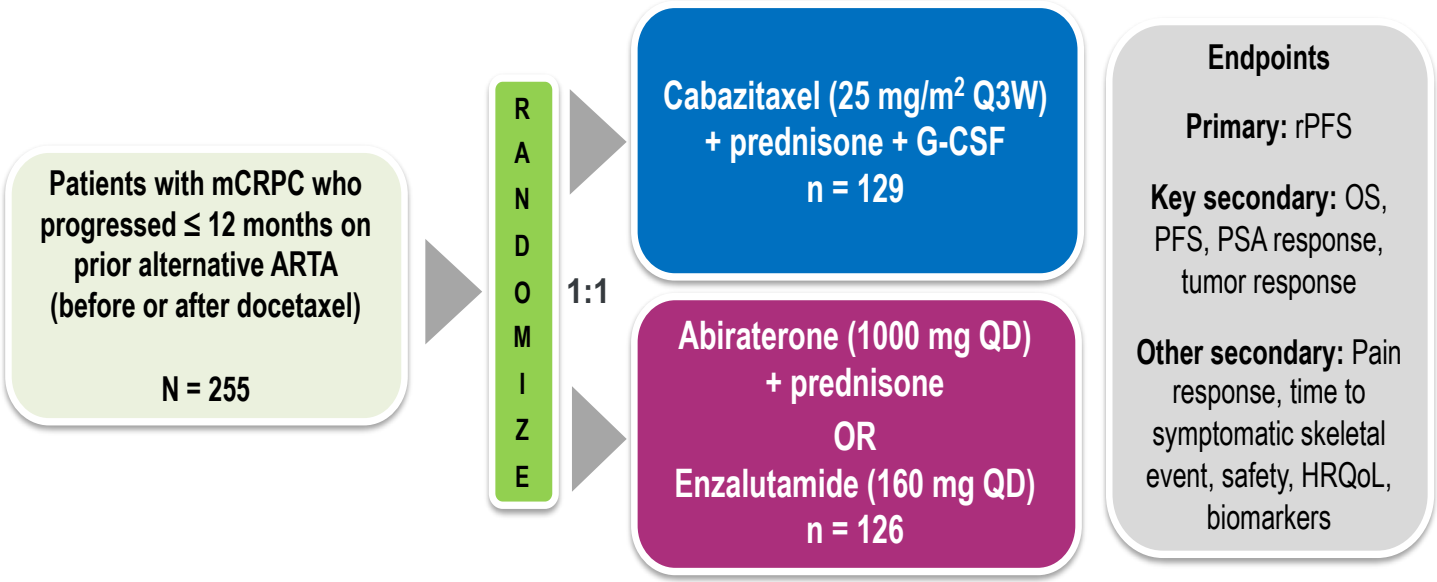
- PLATO - Prospective, phase IV, double-blind, Pbo-controlled trial in 251 chemo-naïve mCRPC with PSA response to ENZA >3 months
- Randomized at PSA progression to ENZA+ABI/P vs Pbo+ABI/P
- PFS* (primary endpoint): 5.7 vs 5.6 months, *P*=0.22



PFS: progression free survival (radiological progression or unequivocal clinical progression)

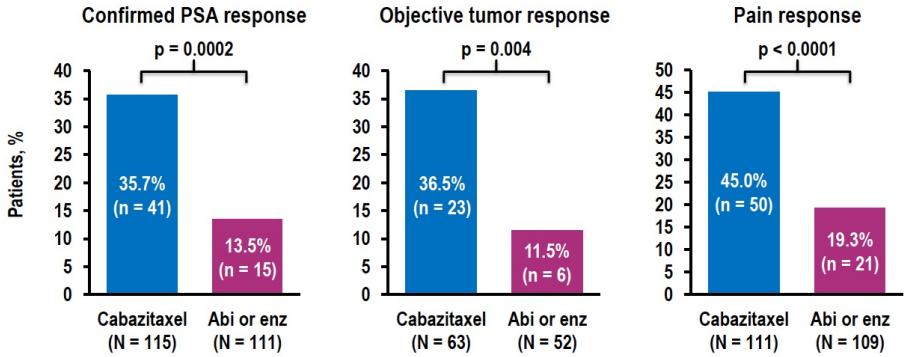
Attard G et al. J Clin Oncol 2018 ; 36: 2639-46

The CARD trial



De Wit et al. NEJM 2019 (epub ahead of print)

PSA, TUMOR AND PAIN RESPONSES



Response definitions
PSA: PSA reduction ≥ 50% from baseline, confirmed by a second value at least 3 weeks later. Tumor: complete or partial responses according to RECIST 1.1 criteria.
Pain: decrease ≥ 30% from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations ≥ 3 weeks apart without increase in analgesic usage score.

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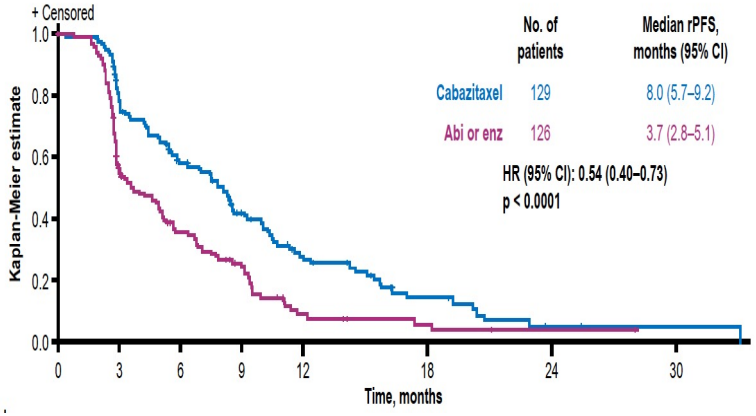
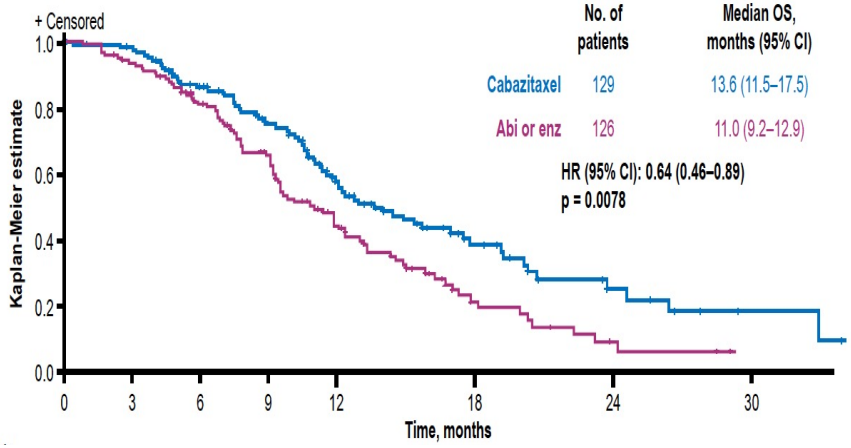
N, patients evaluable for PSA, tumor or pain response.
BPI-SF, Brief Pain Inventory - Short Form.

RADIOGRAPHIC PFS (PRIMARY ENDPOINT)



OVERALL SURVIVAL (KEY SECONDARY ENDPOINT)



➔ Use Cabazitaxel after docetaxel **AND** hormonal agent failure

GENETIC and Prostate cancer

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

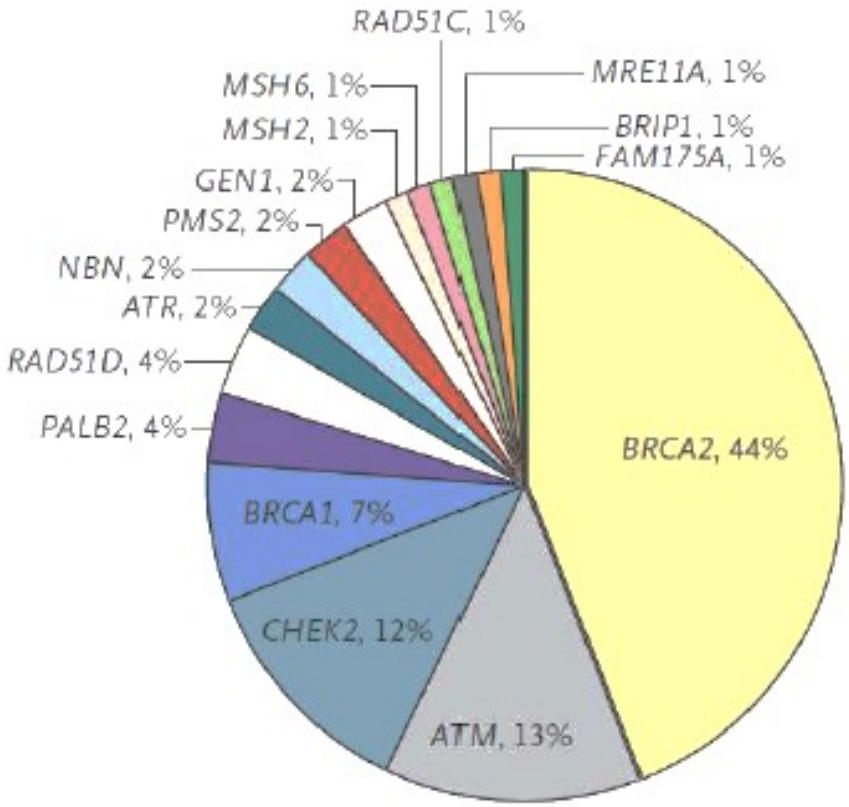
DNA Repair in Prostate Cancer: Biology and Clinical Implications

Joaquin Mateo [a,b], Gunther Boysen [a], Christopher E. Barbieri [c,d,e], Helen E. Bryant [f], Elena Castro [g], Pete S. Nelson [h,i], David Olmos [g,j], Colin C. Pritchard [h], Mark A. Rubin [d,]

BRCA2 mutation

12% in men with M1 PC
5% in men with localized PC
3% in general population

- ➔ 5-7 times higher risk of Pca
- ➔ higher Gleason Score and worse prognosis
- ➔ earlier age at death and shorter survival time



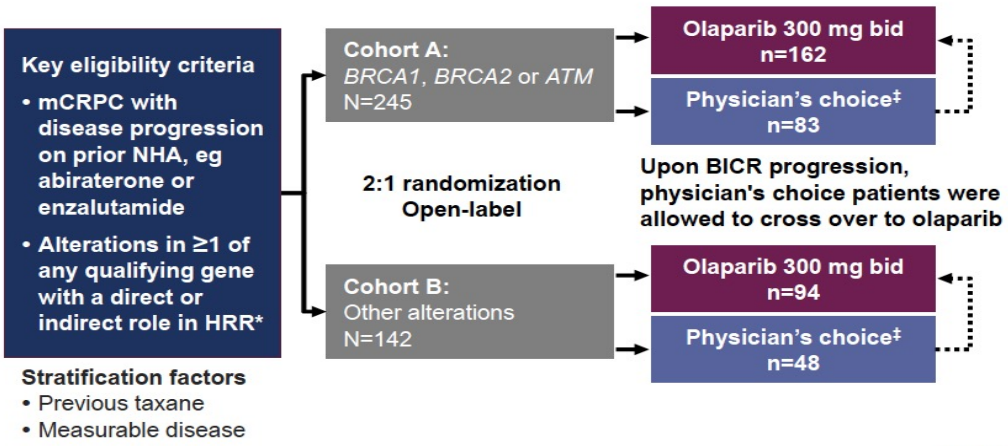
- ➔ Access to specific trial (PARPi; platinum)
- ➔ Probably better outcome with different treatment
- ➔ Depistage for family (onset at 40 y)

Robinson et al; Cell 2015

Final overall survival analysis of PROfound:

Olaparib vs physician's choice of enzalutamide or abiraterone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations

Johann de Bono,[1] Joaquin Mateo,[2] Karim Fizazi,[3] Fred Saad,[4] Neal Shore,[5]



Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

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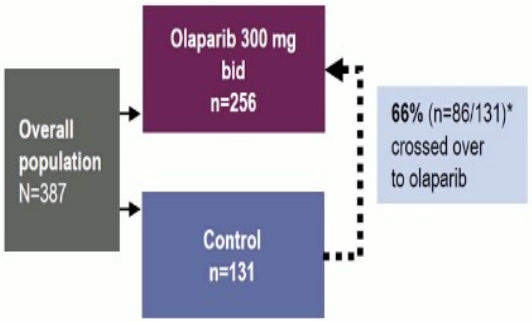
BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L

On biopsy !



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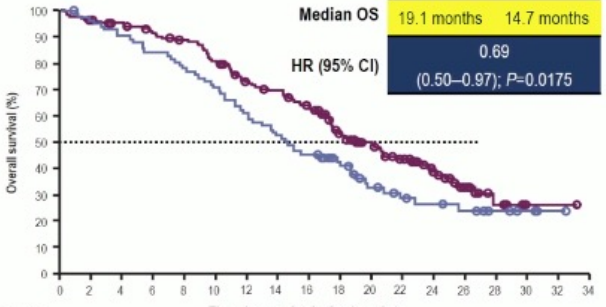
Olaparib improved OS in Cohort A (*BRCA1*, *BRCA2* or *ATM*)

Prespecified adjustment for crossover (final prespecified analysis)

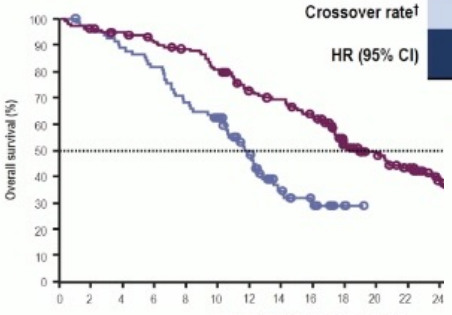
Cohort A

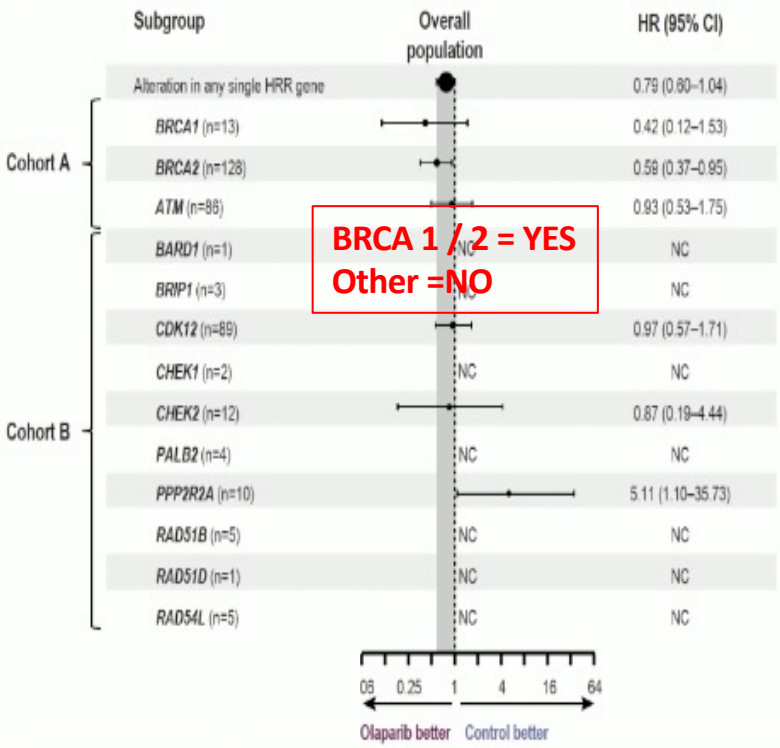
	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50–0.97); *P*=0.0175	



Cohort A with adjustment for crossover*

Crossover rate†	67% (56/83)
HR (95% CI)	0.42 (0.19–0.91)





BRCA 1 / 2 = YES
Other =NO

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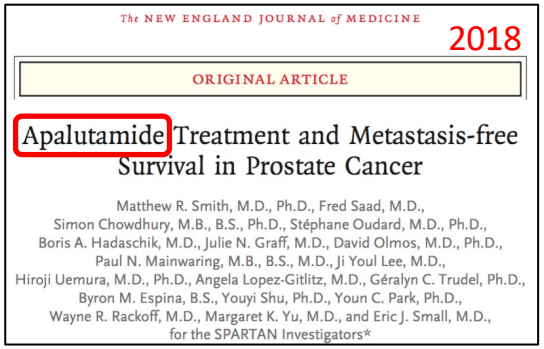
Conclusions

- In men with mCRPC pretreated with a prior NHA, there was **significantly improved OS with olaparib** vs enzalutamide/abiraterone in Cohort A **(*BRCA1*, *BRCA2*, and/or *ATM* altered mCRPC; 19.1 months vs 14.7 months; HR 0.69; *P*=0.0175)** despite crossover (n=56, 67%) from the control arm to olaparib

M0 CRPC

SPARTAN



The NEW ENGLAND JOURNAL of MEDICINE

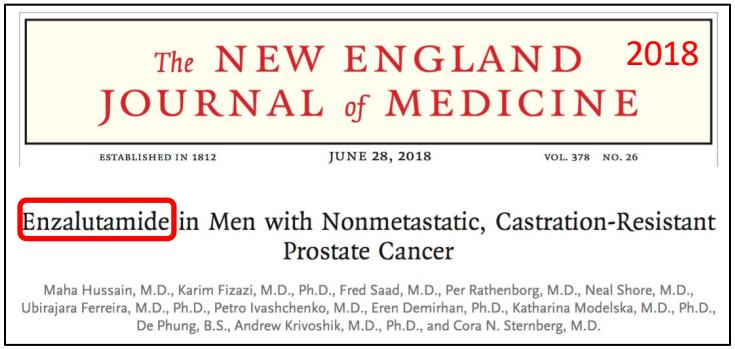
2018

ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

PROSPER



The NEW ENGLAND JOURNAL of MEDICINE

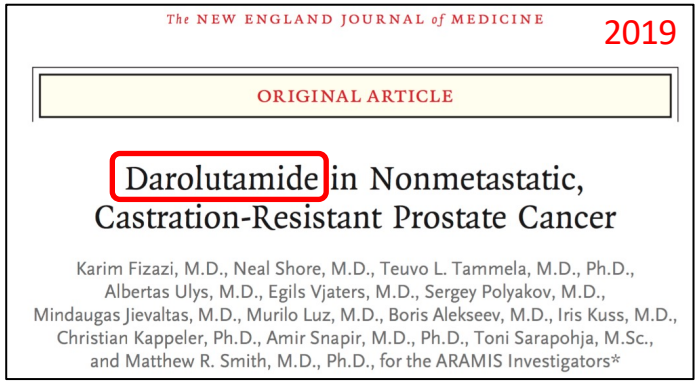
2018

ESTABLISHED IN 1812 JUNE 28, 2018 VOL. 378 NO. 26

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

ARAMIS



The NEW ENGLAND JOURNAL of MEDICINE

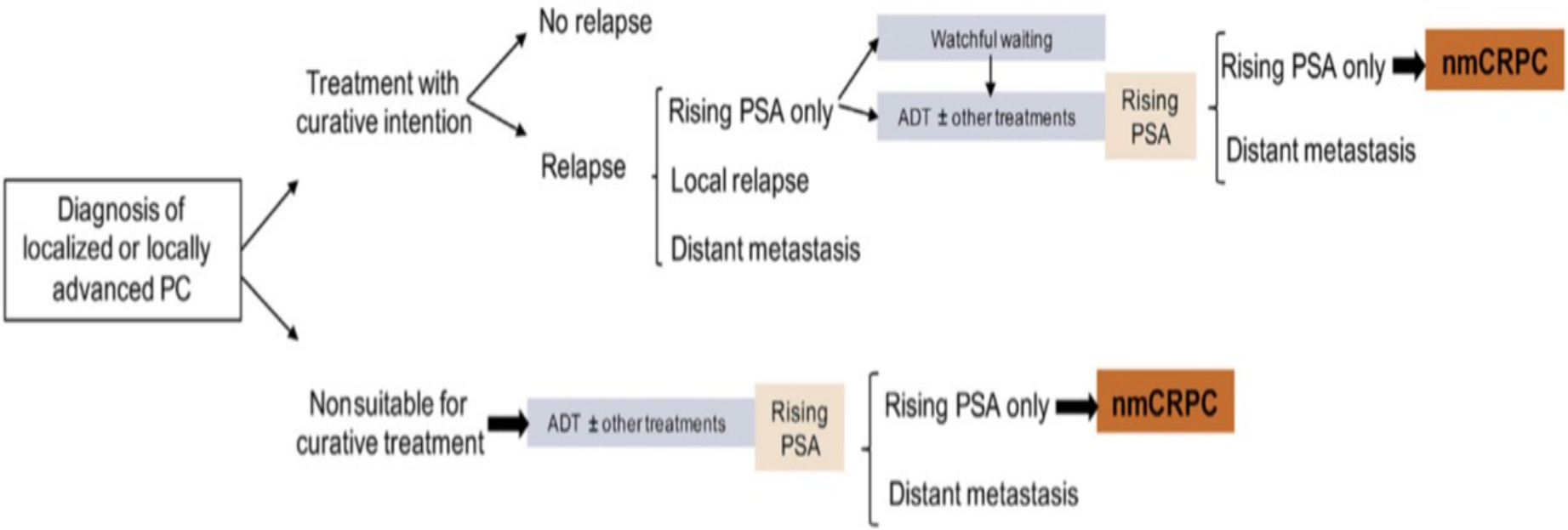
2019

ORIGINAL ARTICLE

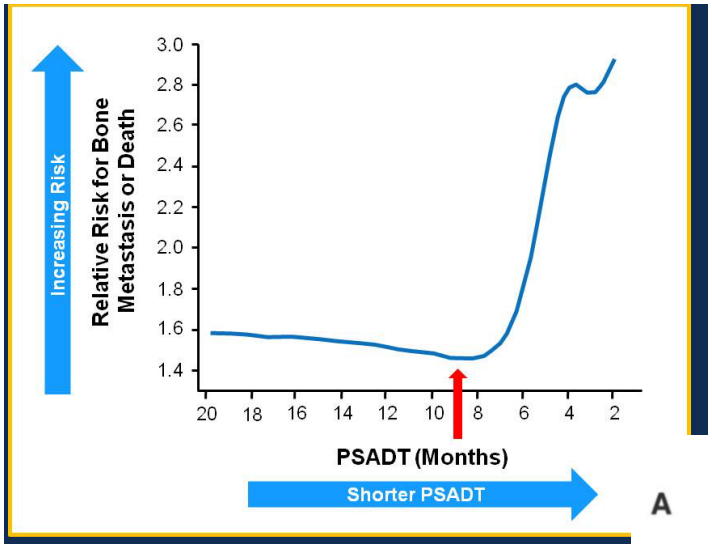
Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Karim Fizazi, M.D., Neal Shore, M.D., Teuvo L. Tammela, M.D., Ph.D., Albertas Ulys, M.D., Egils Vjaters, M.D., Sergey Polyakov, M.D., Mindaugas Jievaltas, M.D., Murilo Luz, M.D., Boris Alekseev, M.D., Iris Kuss, M.D., Christian Kappeler, Ph.D., Amir Snapir, M.D., Ph.D., Toni Sarapohja, M.Sc., and Matthew R. Smith, M.D., Ph.D., for the ARAMIS Investigators*

	No ADT	*Progressed on ADT*
No distant metastasis CT/BS	Localized or locally advanced PC	**nmCRPC**
Distant metastasis	mHNPC	mCRPC



PSA doubling time = best predictor of outcome

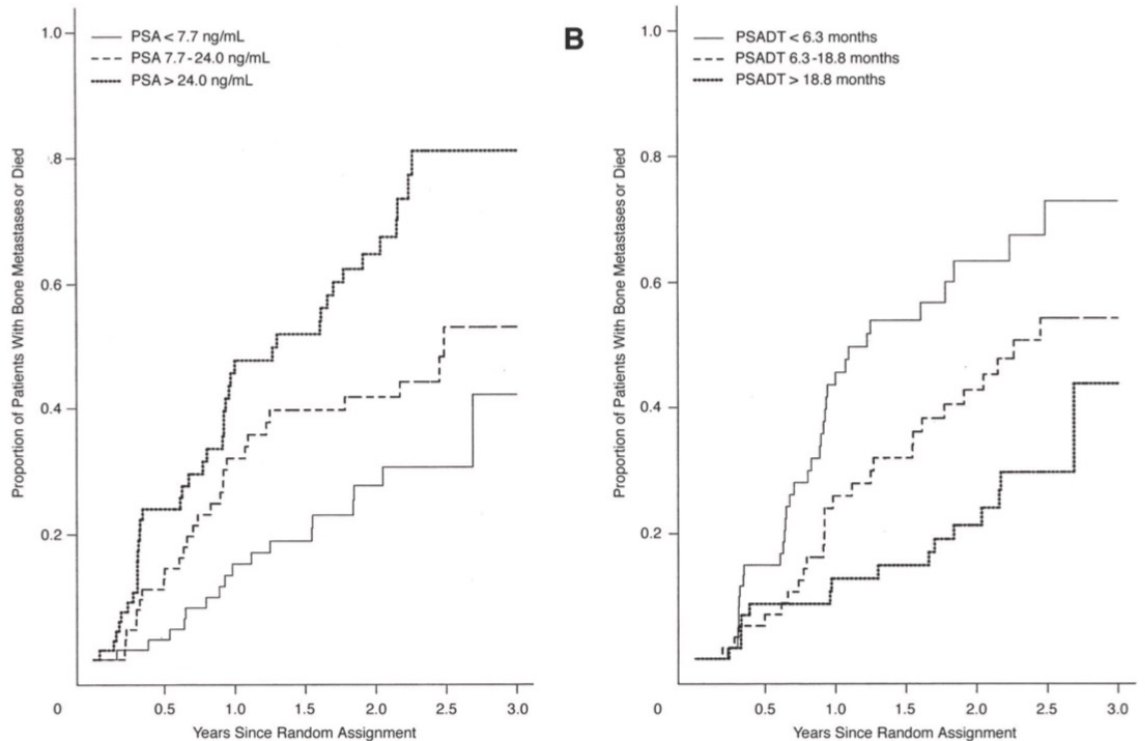


PSA-DT associated with

- time to bone metastases
- metastase free survival
- overall survival

Natural History of Rising Serum Prostate-Spe Antigen in Men With Castrate Nonmetastatic Prostate Cancer

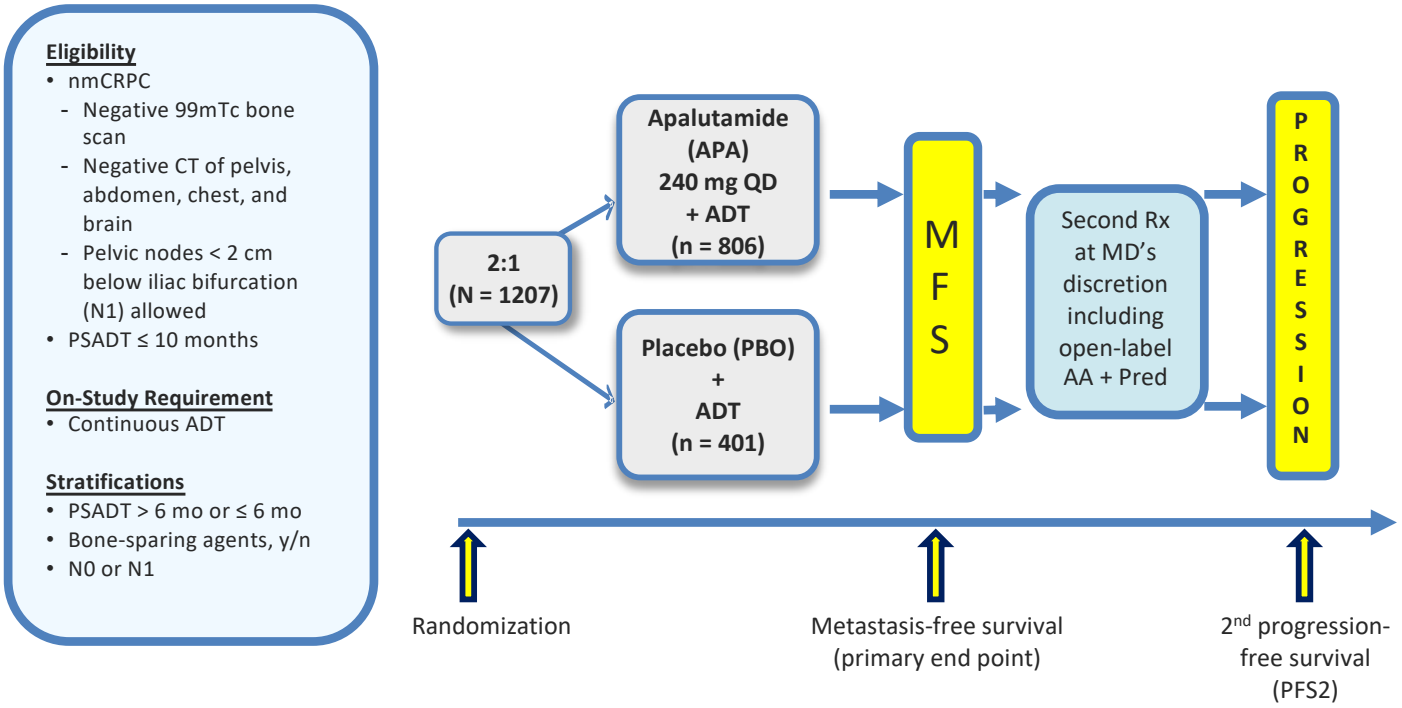
Matthew R. Smith, Fairooz Kabbinavar, Fred Saad, Arif Hussain, Marc C. Gittelma



3 randomised controlled phase III trials
MFS as the primary end-point
in patients with non-metastatic CRPC (M0 CRPC)

Apalutamide (**SPARTAN**) vs. Placebo
Enzalutamide (**PROSPER**) vs. placebo
or Darolutamide vs. placebo (**ARAMIS**), respectively.

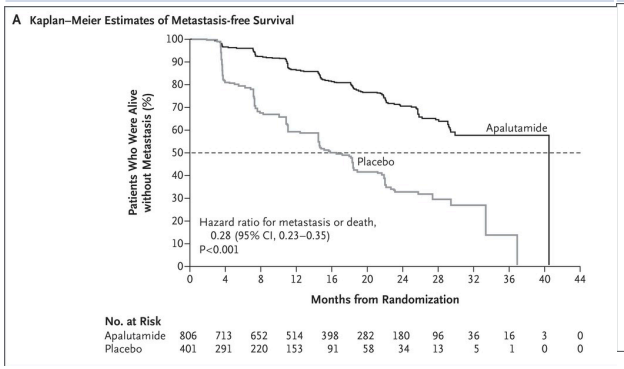
Same design

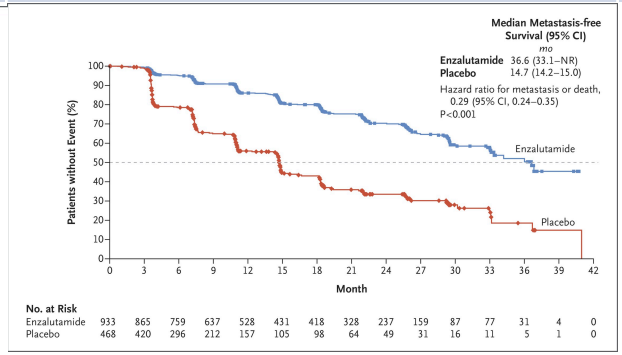


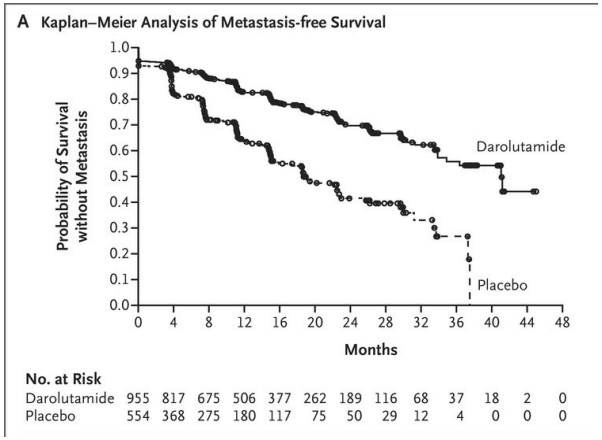
Smith et al. NEJM 2018: Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Metastasis Free Survival (primary endpoint)

SPARTAN (apalutamide)	PROSPER (enzalutamide)	ARAMIS (darolutamide)
Metastasis-free survival 40 vs 16 months HR 0.28, p<0,001	Metastasis-free survival 37 vs 15 months HR 0.29, p<0,001	Metastasis-free survival 40 vs 18 months HR 0.41, p<0,001







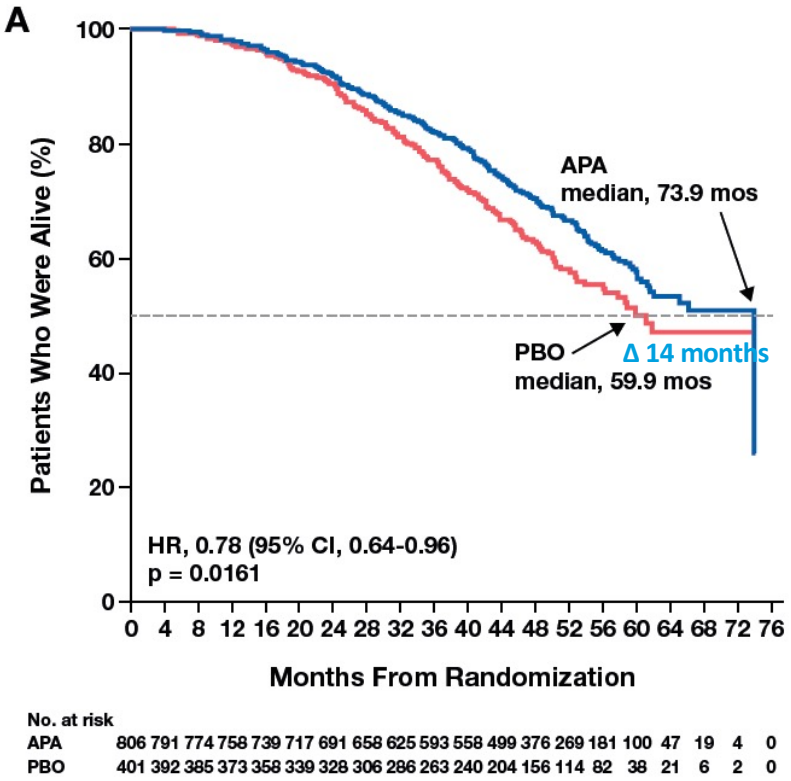
Smith et al. NEJM, 2018

Hussain et al. NEJM, 2018.

Fizazi et al.NEJM, 2019

No head to head product comparisons, so no conclusions can be made

Survival benefit



Median follow-up = 52 months

Overall Survival gain = 14 months

70 % of patients who received placebo received subsequent life-prolonging therapy

19% of patients who received placebo crossed over to receive open-label apalutamide at unblinding

Small et al. Poster presented at ASCO20 Virtual Scientific Program, May 29-31, 2020: Final Survival Results From SPARTAN, a Phase 3 Study of Apalutamide Versus Placebo in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

6.5.17 ***Guideline for non-metastatic castrate-resistant disease***

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

Emmanuel.seront@uclouvain.be