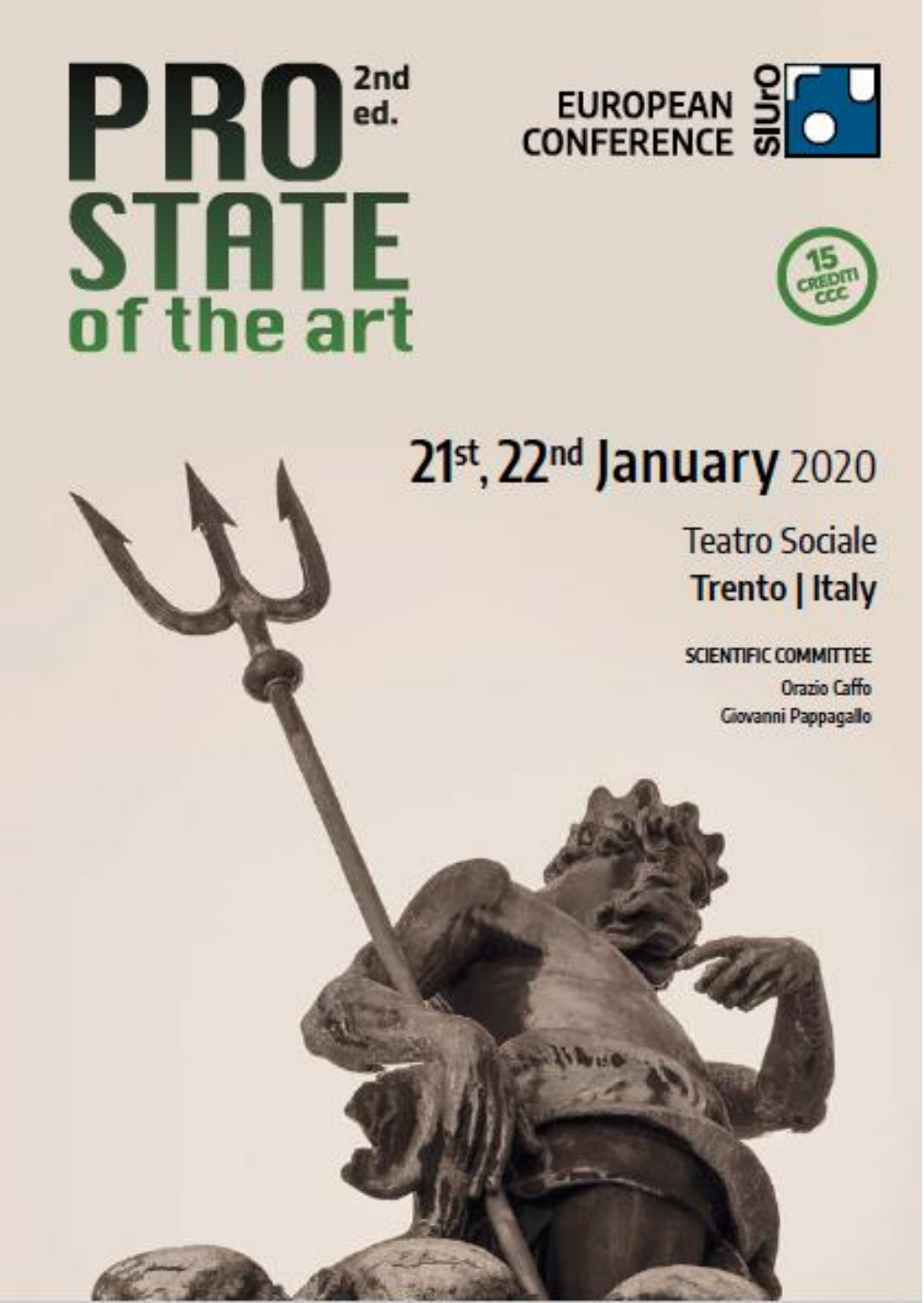

Management of mCRPC: State of the art

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Disclosure

No conflict of interest related to the following presentation

AGENDA

- **mCRPC**
  -sequencing strategies
  -combinations

- **Radiopharmaceuticals**

- **Genomic aberrations and clinical implications for mCRPC**

- DDR and PARP inhibitors

- PTEN loss and AKT inhibitors

- MMR, CDK 12 and immunotherapy

AGENDA

- **mCRPC**
  -sequencing strategies
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- **Genomic aberrations and clinical implications for mCRPC**

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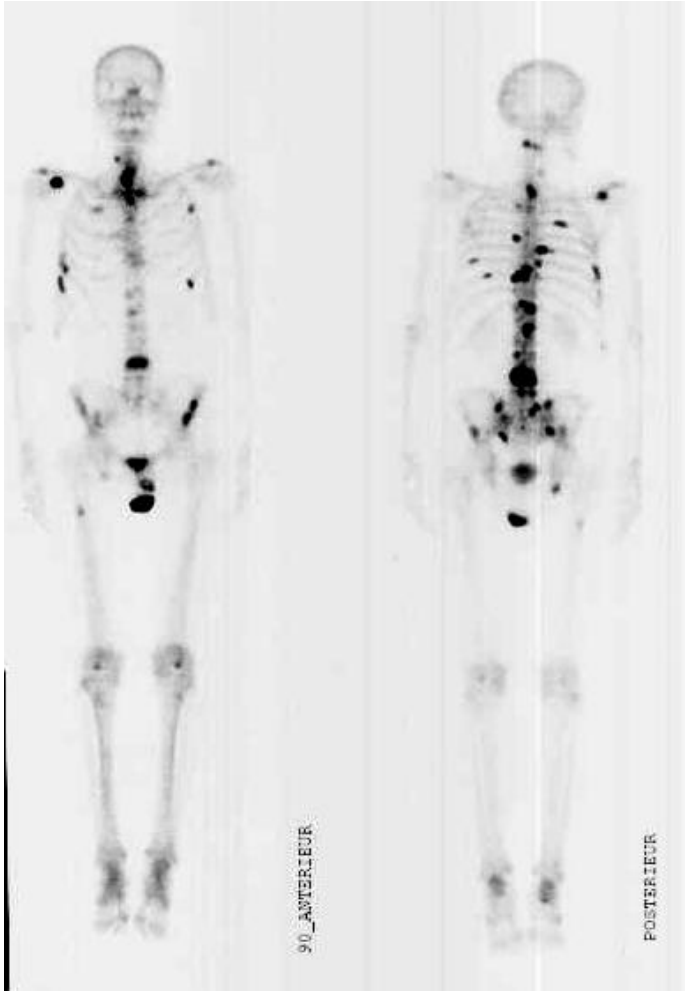
- MMR, CDK 12 and immunotherapy

Prostate Cancer is Hormone-Dependent

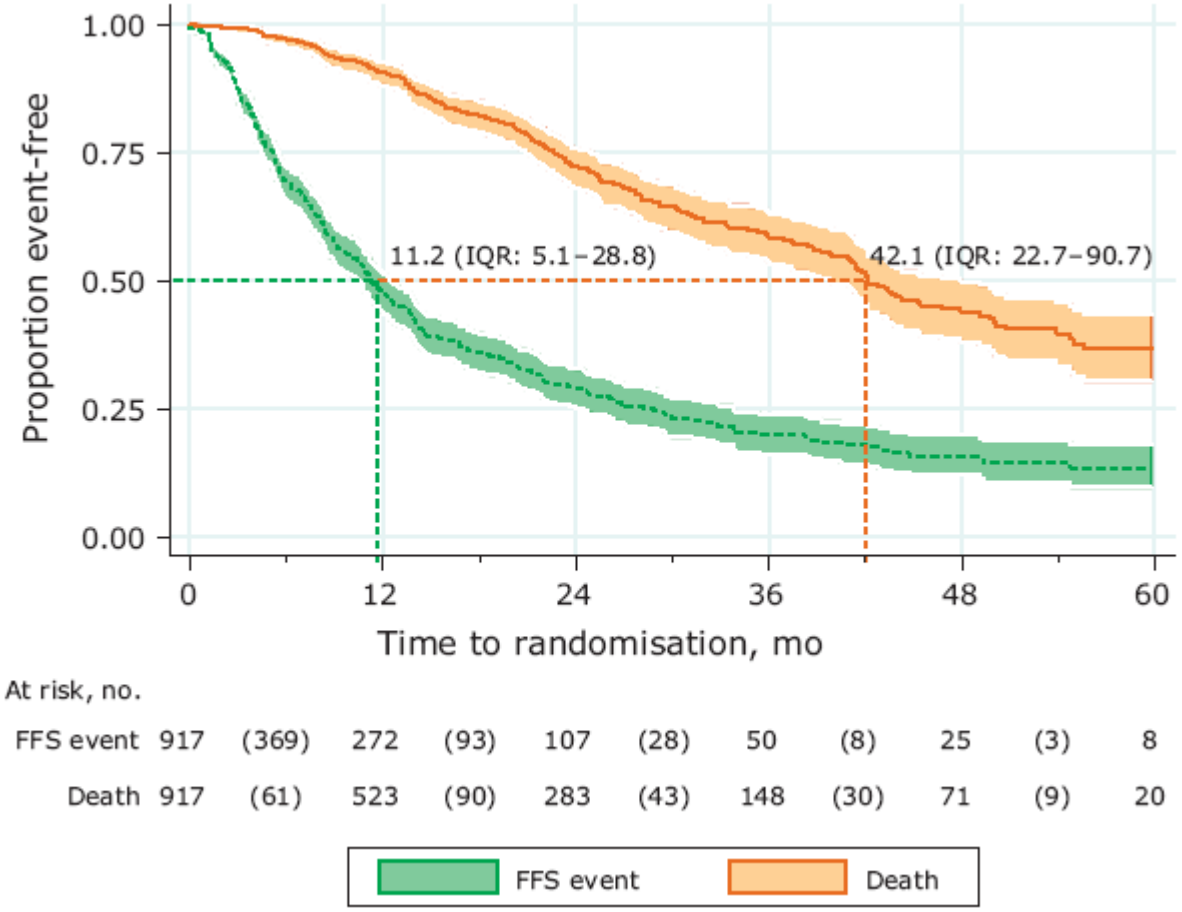


“Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease”

Charles B. Huggins
Nobel Lecture
December 13, 1966

http://nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-lecture.html (access March 2016)

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)



James, Eur Urol 2014

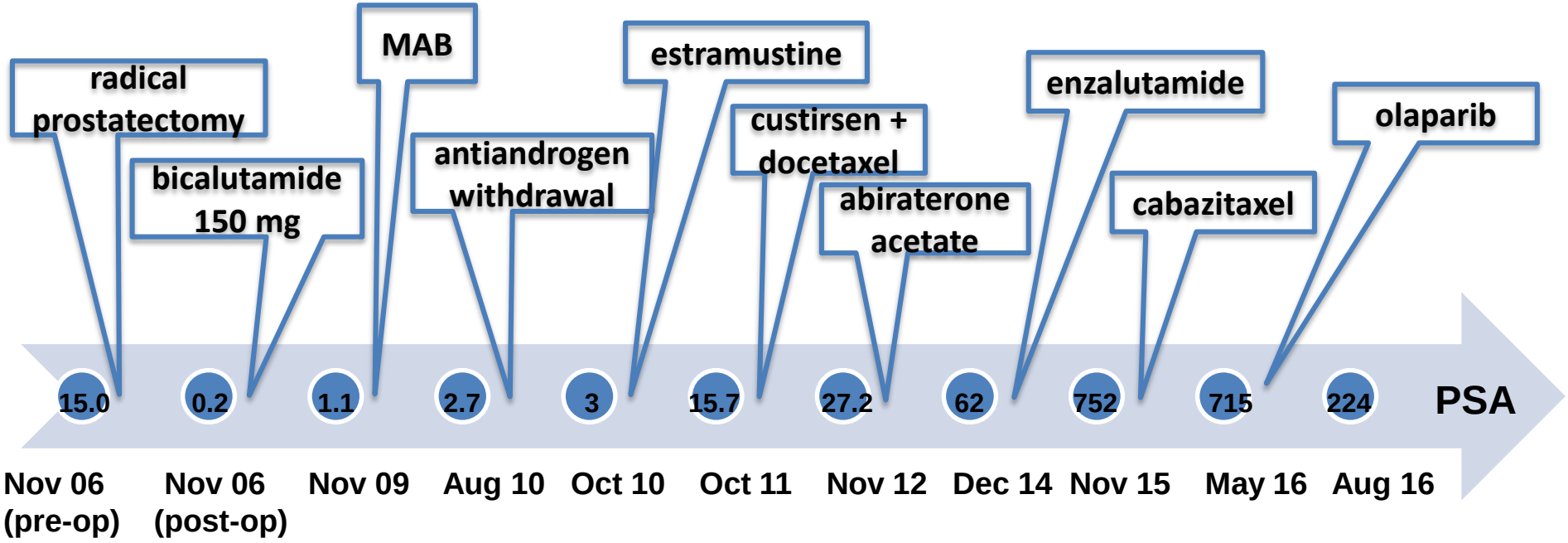
First line treatment for mCRPC

	Drug	control	OS Δ	HR	p
PRE-DOCE	abiraterone[1]	PLACEBO+PDN	4.4 mo	0.81	0.003
	enzalutamide[2]	PLACEBO	2.2 mo	0.71	<0.001
	radium-223[3]	PLACEBO	4.6 mo	0.74	0.03
	docetaxel[4]	MITOX	2.5 mo	0.76	<0.001
POST-DOCE	cabazitaxel[5]	MITOX	2.4 mo	0.70	<0.001
	abiraterone[6]	PLACEBO+PDN	3.9 mo	0.65	<0.001
	enzalutamide[7]	PLACEBO	4.8 mo	0.63	<0.001
	radium-223[8]	PLACEBO	3.1 mo	0.71	0.003

[1] Lancet 2013; [2] NEJM 2014; [4] NEJM 2004; [5] Lancet 2010; [6] NEJM 2011; [7] NEJM 2012; [3,8] Lancet 2014

Case report

- ✓ 56 year old BRCA 2 patient
- ✓ No remarkable past medical history
- ✓ November 2006: radical prostatectomy, pT3a N0 M0 G 8=4+4
  PSA pre-op 15
- ✓ Received 8 different agents for the development of mCRPCA
  (bone and nodal mets)

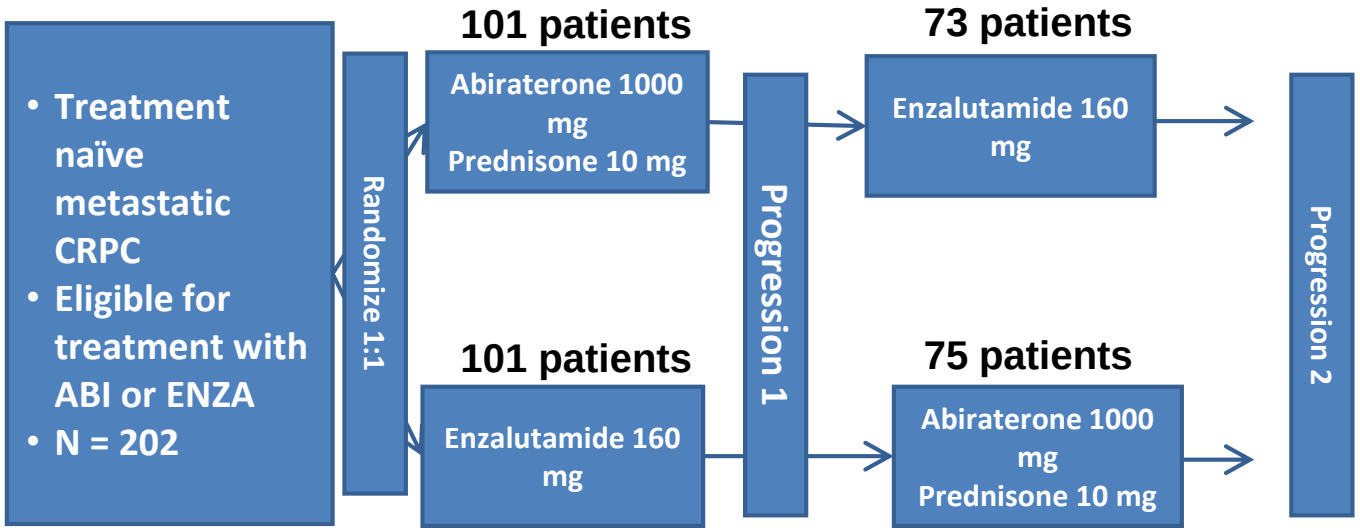


Cross resistance between Abiraterone and Enzalutamide

Author	Year published	N pts	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
ENZ → ABI					
Loriot et al.	2013	38	3 mo	8%	2.7 mo
Noonan et al.	2013	30	13 wks	3%	3.6 mo
ABI → ENZ					
Schrader et al.	2013	35	4.9 mo	29%	-
Badrising et al.	2014	61	3 mo	21%	-
Bianchini et al.	2014	39	2.9 mo	23%	-
Schmid et al.	2014	35	2.8 mo	10%	-
Brasso et al.	2014	137	3.2 mo	18%	-

Zhang T. et al Expert opinion Pharmacology 2014;16:1-9

Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial



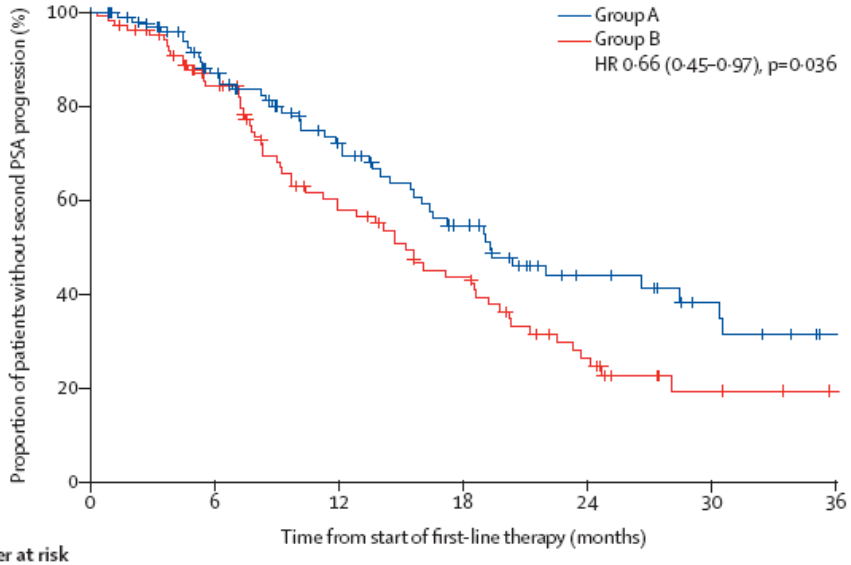
Primary end point:

- **Time to second PSA progression**
- **PSA response (>30%)**

Khalaf, Lancet Oncol 2019

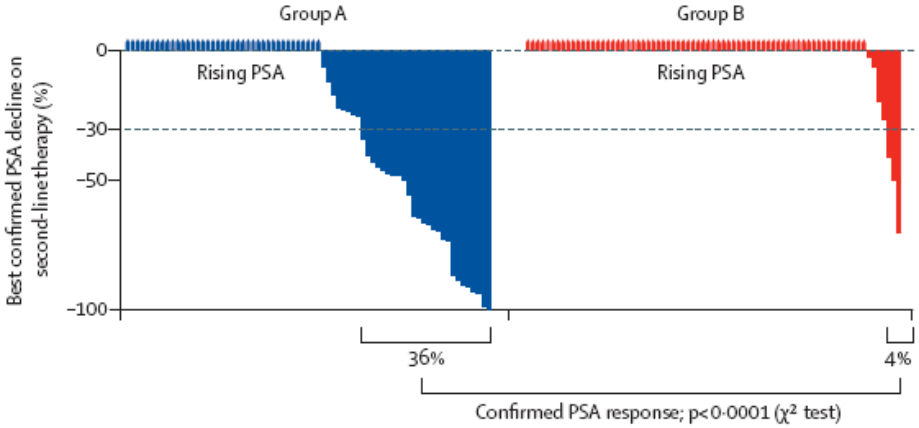
Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial

Time to second PSA Progression



Number at risk (number censored)						
Group A	76 (13)	53 (24)	34 (31)	18 (41)	11 (46)	5 (50)
Group B	75 (11)	43 (22)	30 (25)	15 (29)	6 (35)	3 (38)

Best PSA decline (≥30%) during second line treatment

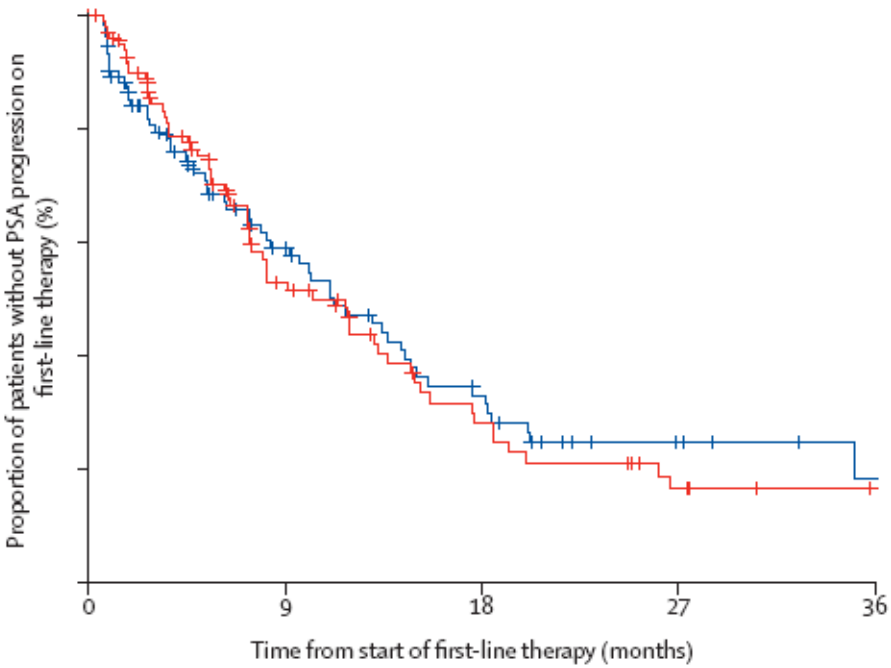


Group A: Abi-Enza
Group B: Enza-Abi

Khalaf, Lancet Oncol 2019

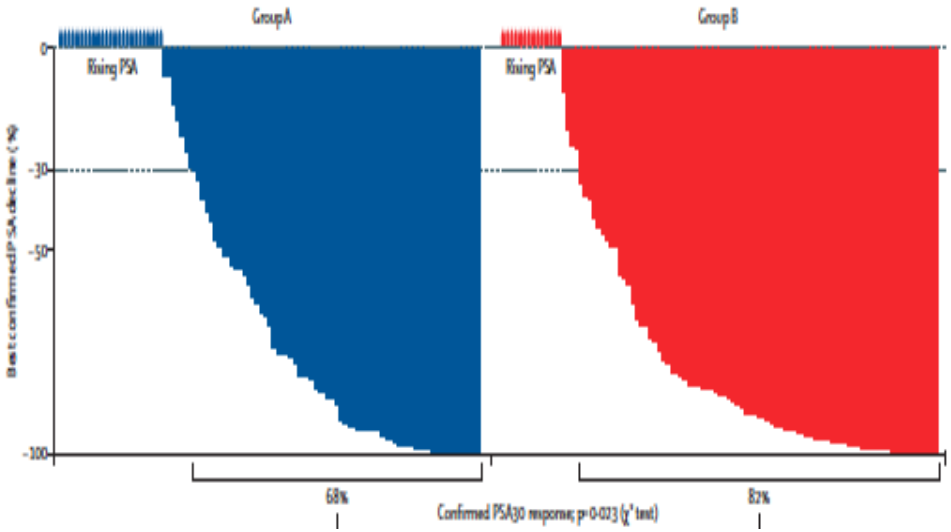
Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial

Time to PSA Progression
First line



101 (0)	42 (23)	20 (28)	7 (36)	3 (39)
101 (0)	37 (24)	16 (30)	7 (33)	3 (37)

Best PSA decline (≥30%)
during first line treatment

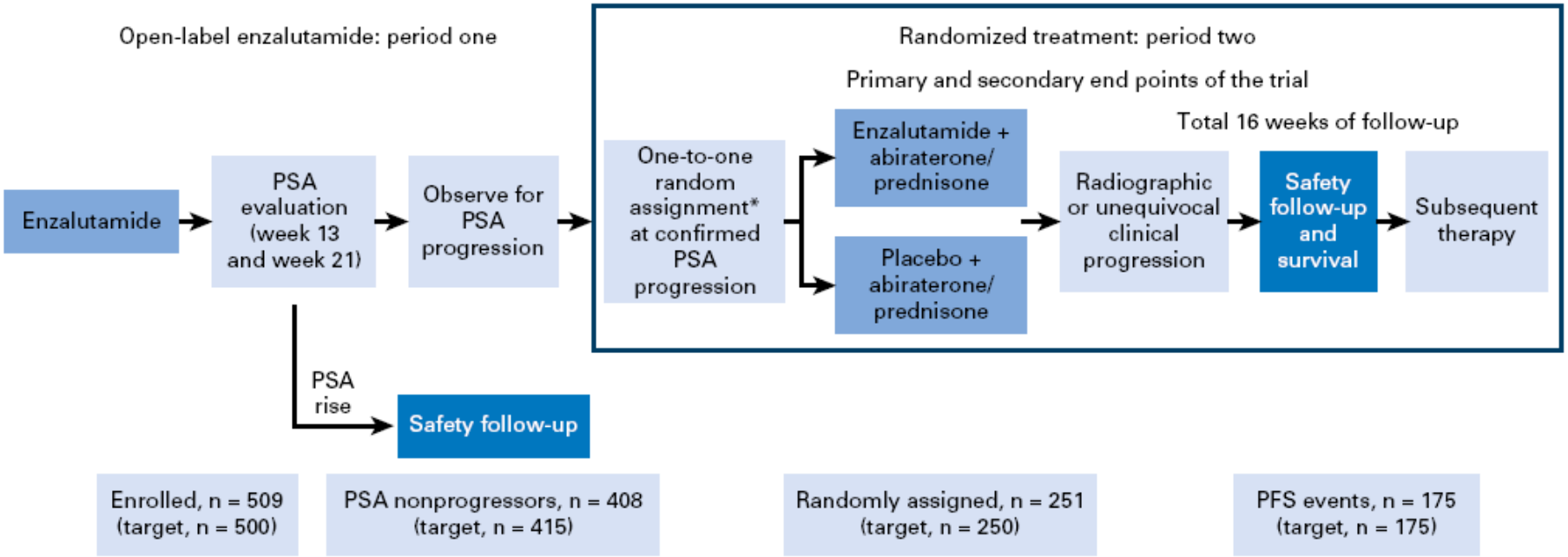


Group A: Abi-Enza
Group B: Enza-Abi

Khalaf, Lancet Oncol 2019

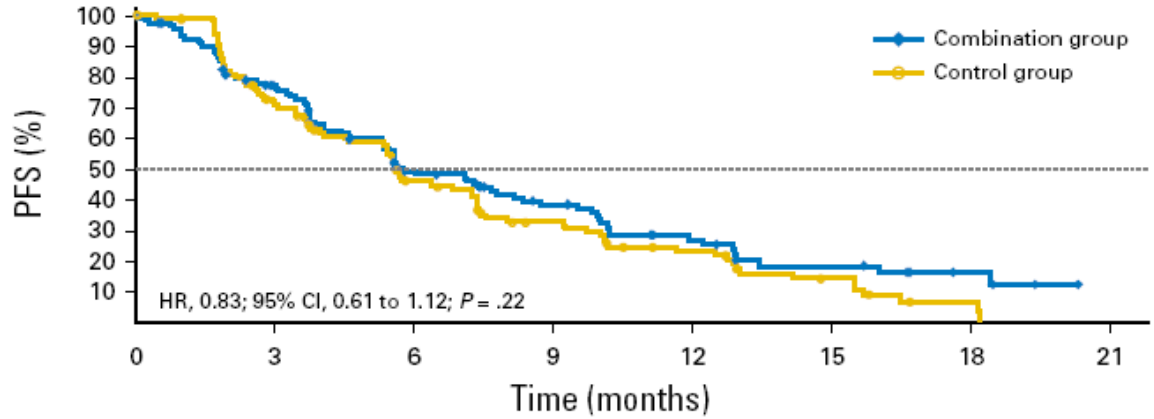
Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment

PLATO study Design



Attard, J Clin Onc 2018

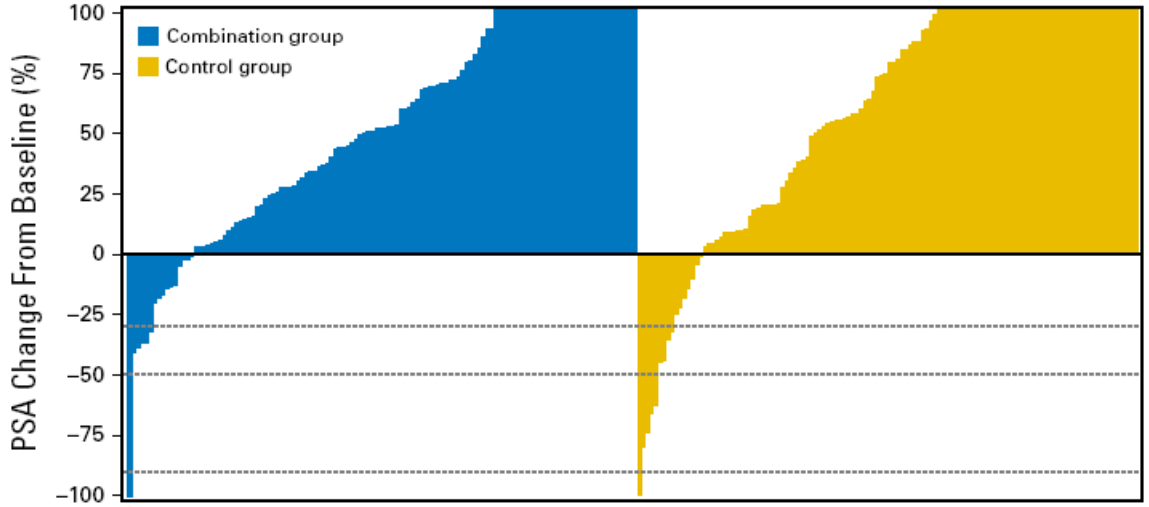
Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment



Progression-free Survival

No. at risk:								
Combination group	126	85	49	32	17	10	4	0
Control group	125	78	46	28	17	8	2	0

PSA Change from Baseline

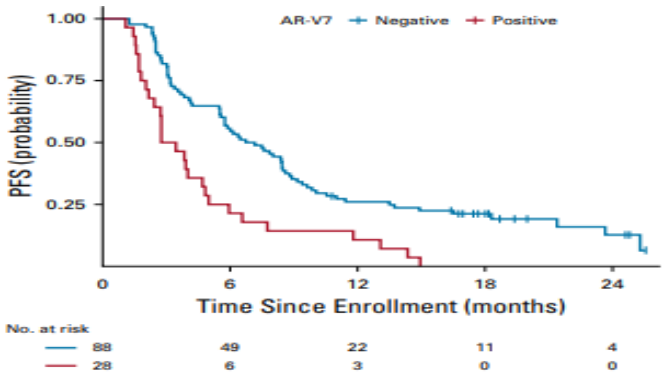


Attard, J Clin Onc 2018

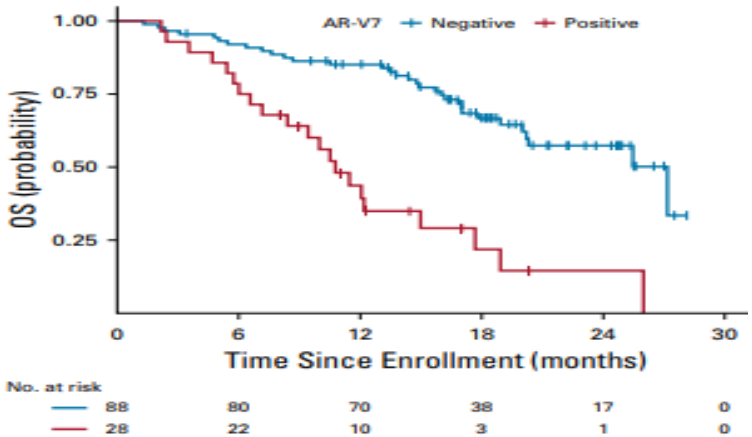
Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study

Adna- test

PFS

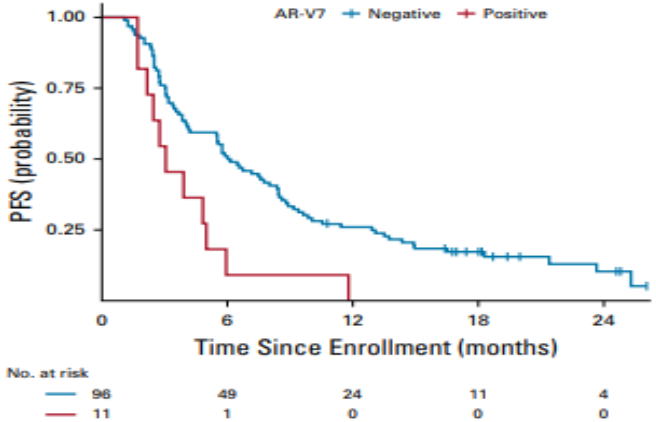


OS



Epic- test

PFS



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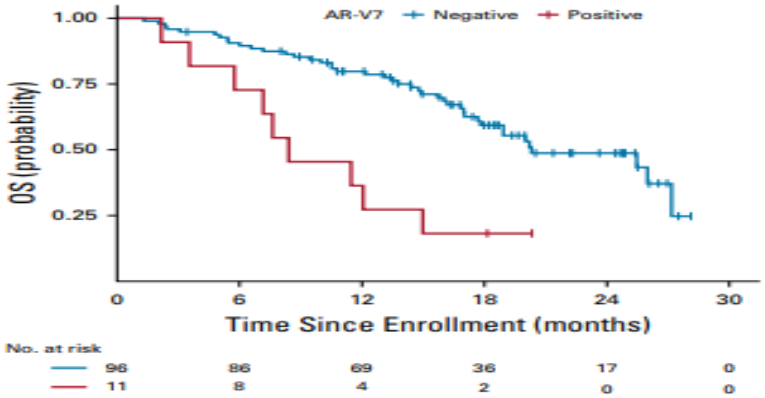


Armstrong A. JCO 2019 May 1;37(13):1120-1129.

PSA decline

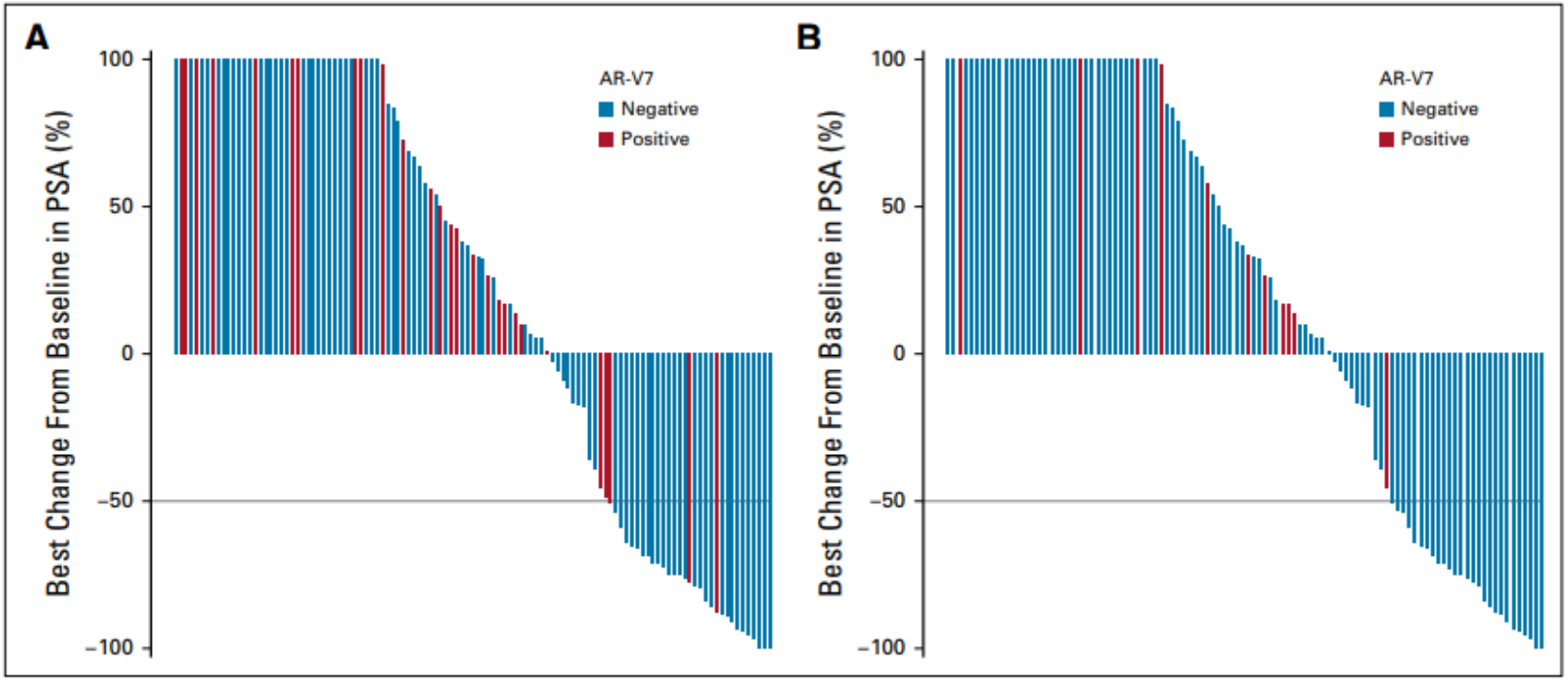
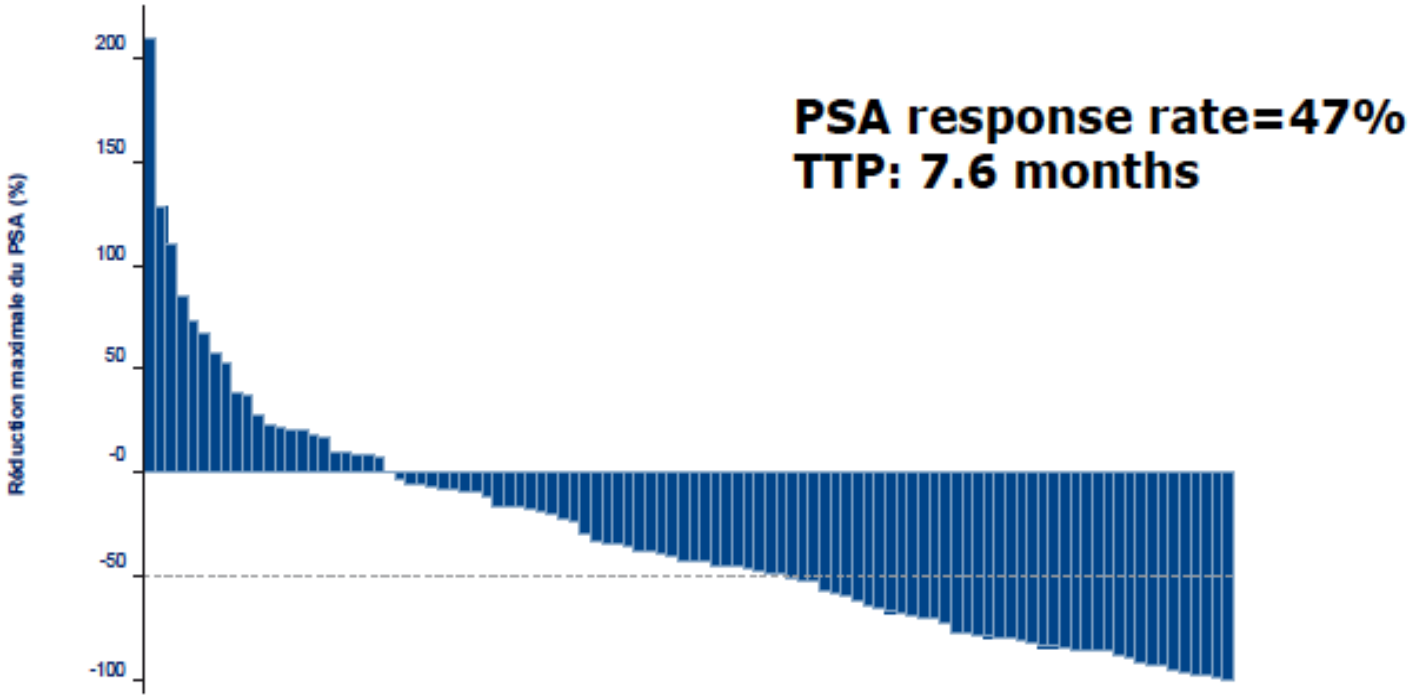


FIG 3. Prostate-specific antigen (PSA) waterfall plots of the best overall confirmed PSA decline from baseline with abiraterone or enzalutamide according to (A) Johns Hopkins University circulating tumor cell androgen receptor splice variant 7 (AR-V7) status and (B) Epic Sciences circulating tumor cell AR-V7 status.

Armstrong A. JCO 2019 May 1;37(13):1120-1129.

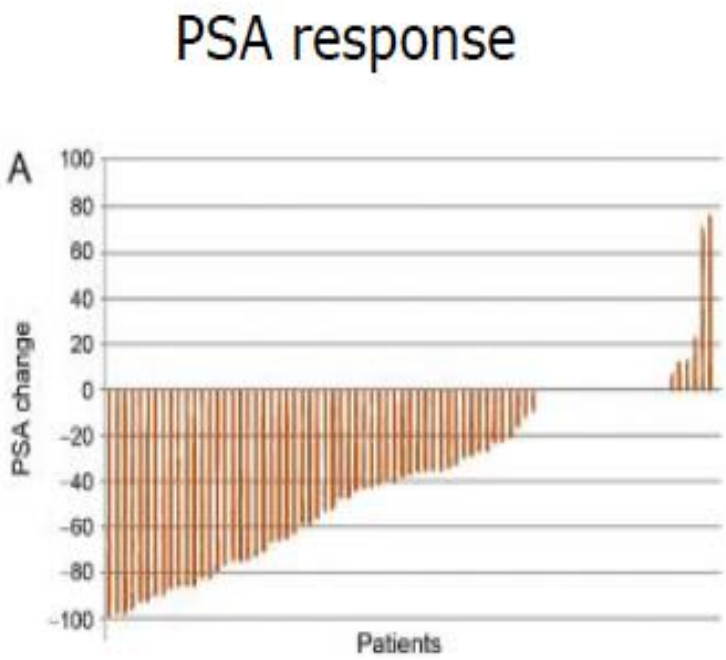
Docetaxel post abiraterone (COU-302)



De Bono J EU Urol 2016

Cabazitaxel post-abiraterone and docetaxel

- n=79 pts
- PSA response>30%: **62%**
- PSA response>50%: **35%**
- PFS: 4.4 mo
- OS: 11 mo
- *In vitro*: Caba active against both enza-S and enza-R cells



Al Nakouzi N, Eur Urol 2015

CARD: STUDY DESIGN

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTA (before or after docetaxel)

N = 255

RANDOMIZE **1:1**

Cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF
n = 129

Abiraterone (1000 mg QD) + prednisone
OR
Enzalutamide (160 mg QD)
n = 126

Endpoints

Primary: rPFS

Key secondary: OS, PFS, PSA response, tumor response

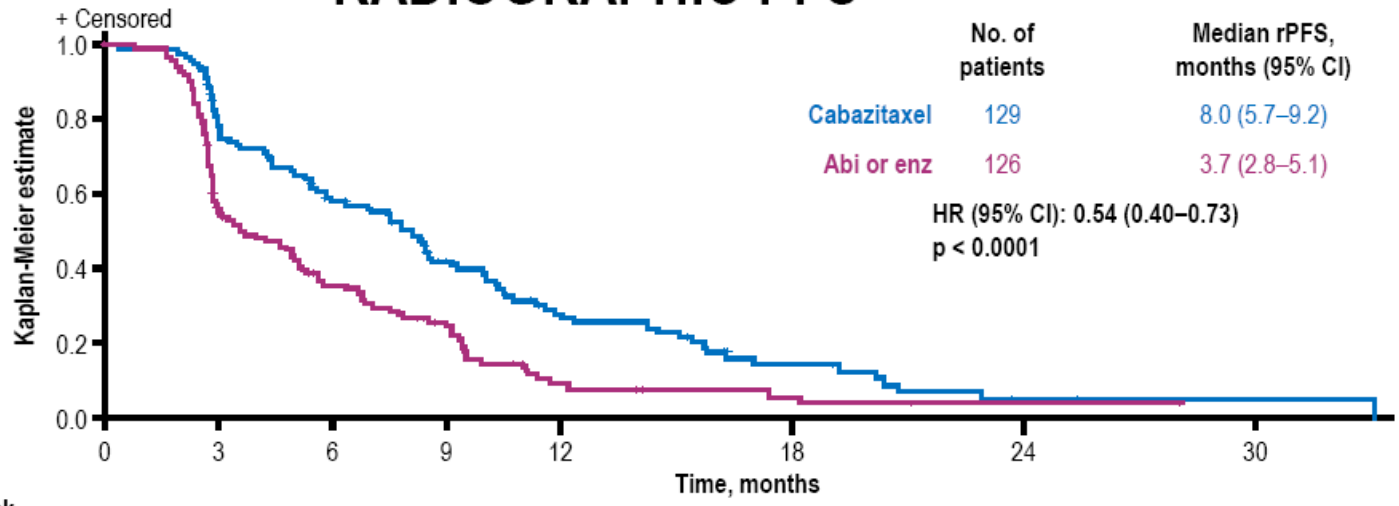
Other secondary: Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

Stratification factors:

- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs > 6–12 months)
- Timing of ARTA (before vs after docetaxel)

ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QD, once daily; Q3W, every 3 weeks; rPFS, radiographic progression-free survival.

RADIOGRAPHIC PFS

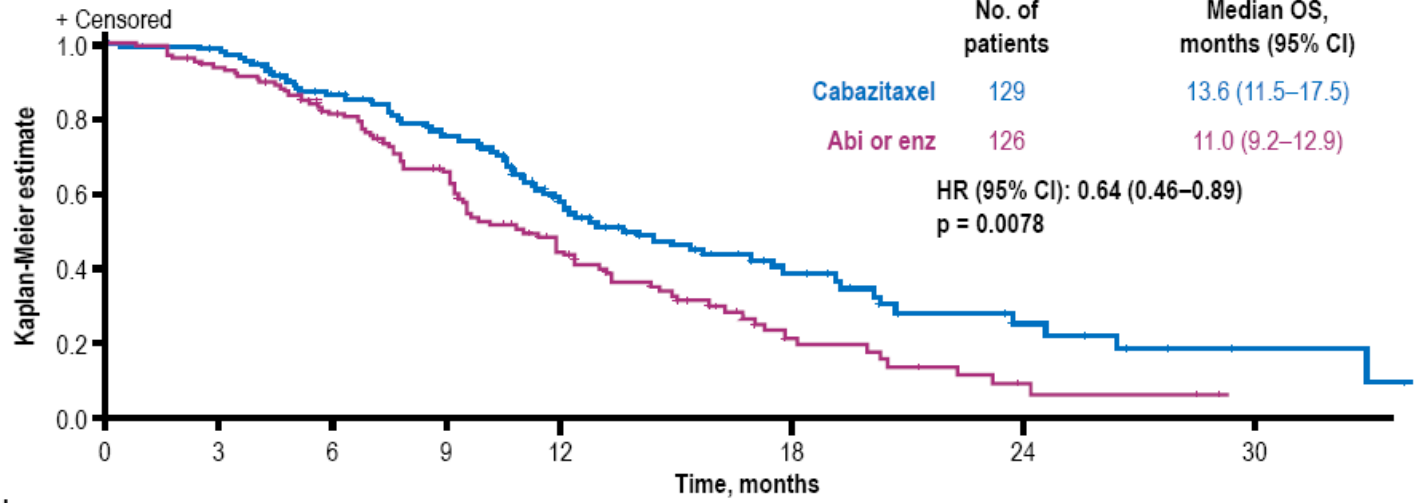


	No. of patients	Median rPFS, months (95% CI)
Cabazitaxel	129	8.0 (5.7–9.2)
Abi or enz	126	3.7 (2.8–5.1)

HR (95% CI): 0.54 (0.40–0.73)
p < 0.0001

No. at risk								
Cabazitaxel	129	91	64	41	23	9	2	1
Abi or enz	126	61	36	22	7	3	1	0

OVERALL SURVIVAL



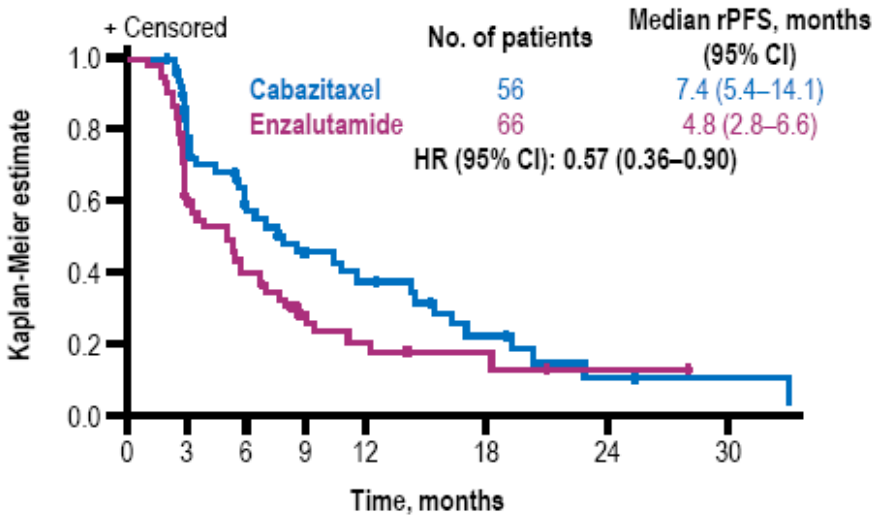
	No. of patients	Median OS, months (95% CI)
Cabazitaxel	129	13.6 (11.5–17.5)
Abi or enz	126	11.0 (9.2–12.9)

HR (95% CI): 0.64 (0.46–0.89)
p = 0.0078

No. at risk								
Cabazitaxel	129	122	96	77	51	21	8	2
Abi or enz	126	116	88	64	39	11	3	0

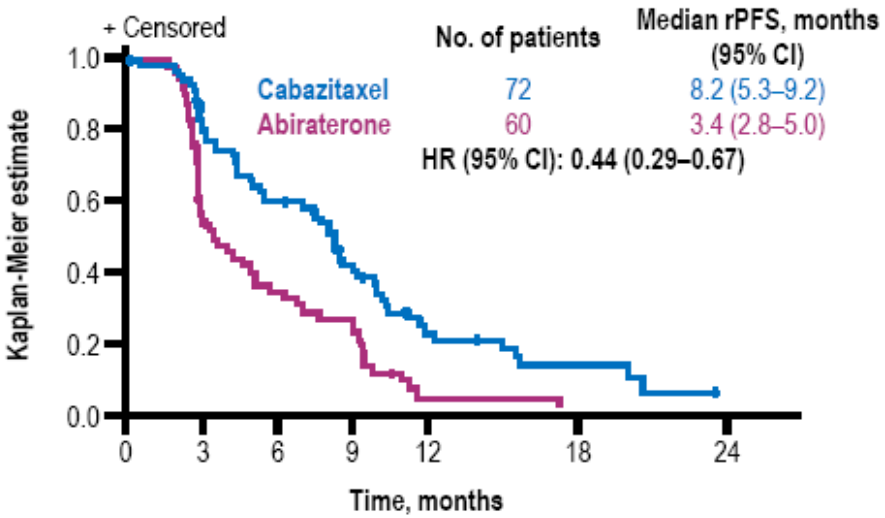
RADIOGRAPHIC PFS: IMPACT OF SEQUENCE*

Enzalutamide after docetaxel and abiraterone



No. at risk								
Cabazitaxel	56	36	24	16	13	6	2	1
Enzalutamide	66	32	19	9	6	3	1	0

Abiraterone after docetaxel and enzalutamide



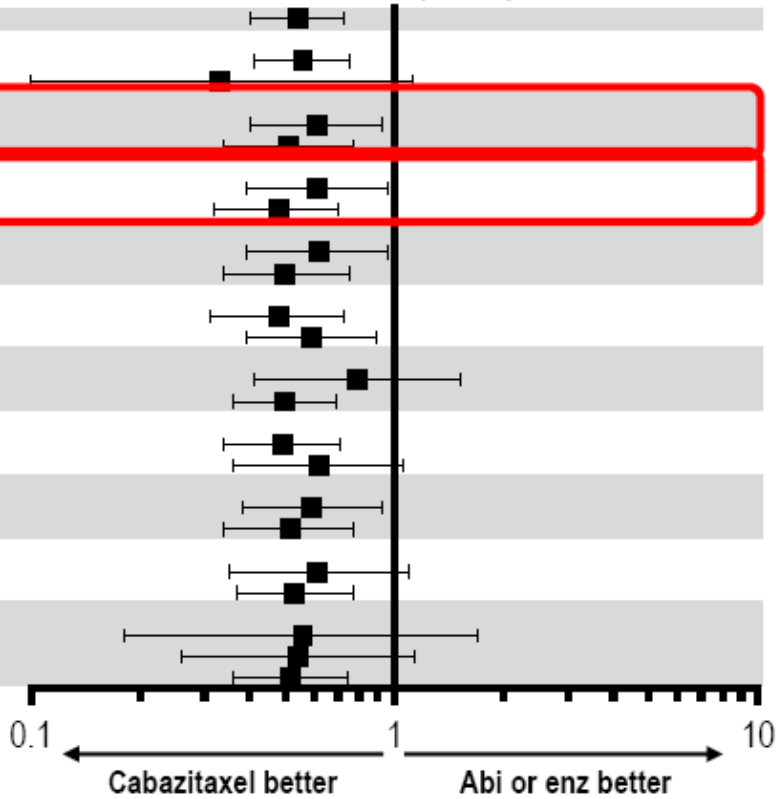
No. at risk							
Cabazitaxel	72	54	40	25	10	3	0
Abiraterone	60	29	17	13	1	0	0

BARCELONA 2019 ESMO congress

*Post-hoc analysis.

RADIOGRAPHIC PFS: PREPLANNED SUBGROUPS

Subgroup	No. of patients	HR for rPFS (95% CI)
All patients	255	0.54 (0.40–0.73)
ECOG PS		
0–1	242	0.56 (0.41–0.75)
2	13	0.33 (0.10–1.13)
Time from prior alternative ARTA initiation to progression		
≤ 6 months	127	0.61 (0.40–0.92)
> 6–12 months	128	0.51 (0.34–0.77)
Timing of prior alternative ARTA		
Before docetaxel	99	0.61 (0.39–0.96)
After docetaxel	156	0.48 (0.32–0.70)
Duration of first androgen deprivation therapy		
< 12 months	113	0.62 (0.39–0.96)
≥ 12 months	140	0.50 (0.34–0.75)
Age		
< 70 years	120	0.48 (0.31–0.73)
≥ 70 years	135	0.59 (0.39–0.89)
Visceral metastases		
Yes	46	0.79 (0.41–1.52)
No	209	0.50 (0.36–0.69)
Gleason 8–10 at diagnosis		
Yes	154	0.49 (0.34–0.71)
No	88	0.62 (0.36–1.05)
M1 disease at diagnosis		
Yes	109	0.59 (0.38–0.92)
No	142	0.52 (0.34–0.77)
Prior therapy with curative intent for localized disease		
Yes	68	0.61 (0.35–1.09)
No	168	0.53 (0.37–0.77)
Type of progression		
PSA only	21	0.56 (0.18–1.70)
Radiologic, no pain	39	0.54 (0.26–1.13)
Pain	176	0.52 (0.36–0.74)



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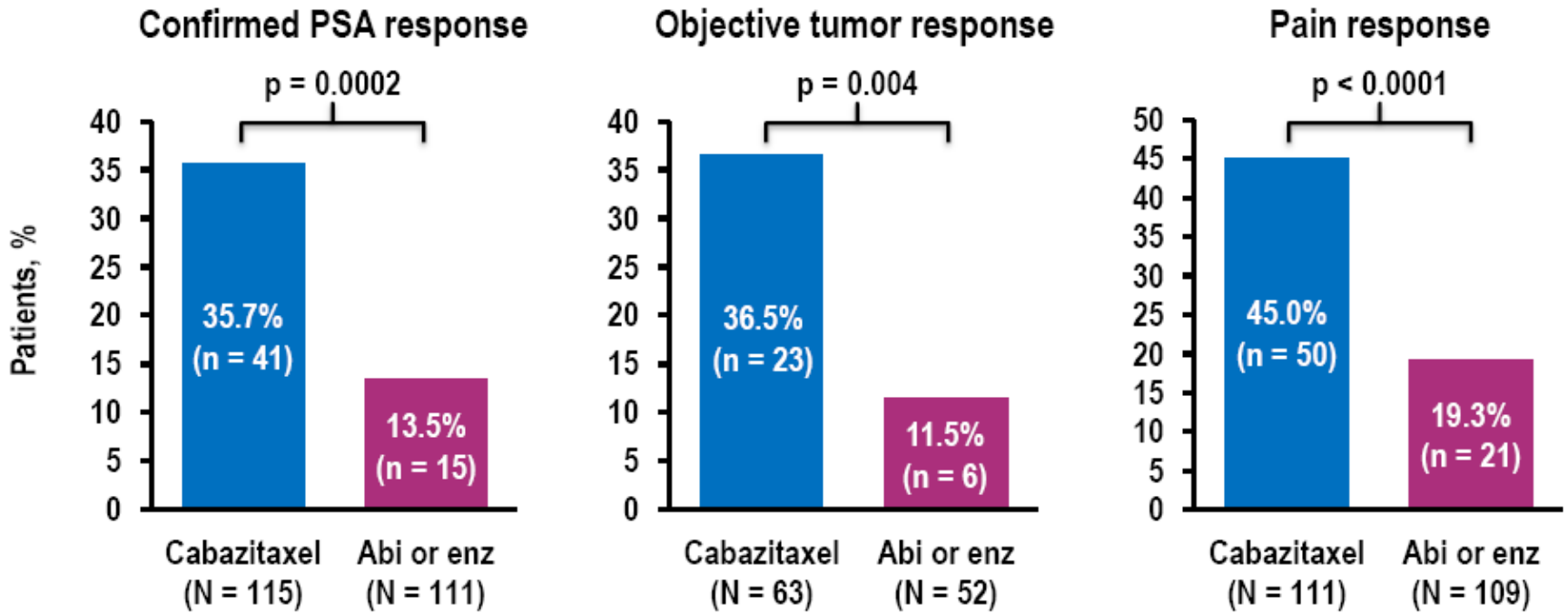
PSA, TUMOR AND PAIN RESPONSES



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.

N, patients evaluable for PSA, tumor or pain response.

BPI-SF, Brief Pain Inventory - Short Form.

AGENDA

- **mCRPC**
  -sequencing strategies
  -combinations

- **Radiopharmaceuticals**

- **Genomic aberrations and clinical implications for mCRPC**

- DDR and PARP inhibitors

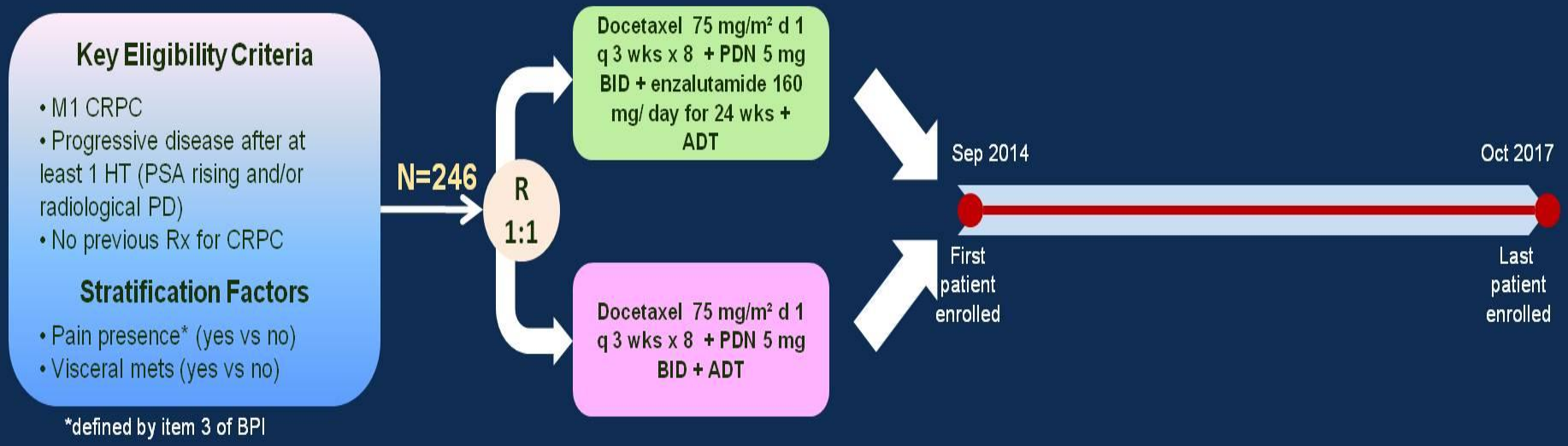
- PTEN loss and AKT inhibitors

- MMR, CDK 12 and immunotherapy

Combining drug X to docetaxel: a failing strategy so far…

- Doc + Oblimersen
- Doc + DN-101
- Doc + Bevacizumab
- Doc + VEGF-Trap
- Doc + Lenalidomide
- Doc + Atrasentan
- Doc + Zibotentan
- Doc + GVAX
- Doc + Dasatinib
- Doc + Custirsen

CHEIRON Study Design



Primary endpoint

- Rate of pts w/out progression (according to PCWG2) at 6 mos after docetaxel first administration (end of treatment)

Statistical Design

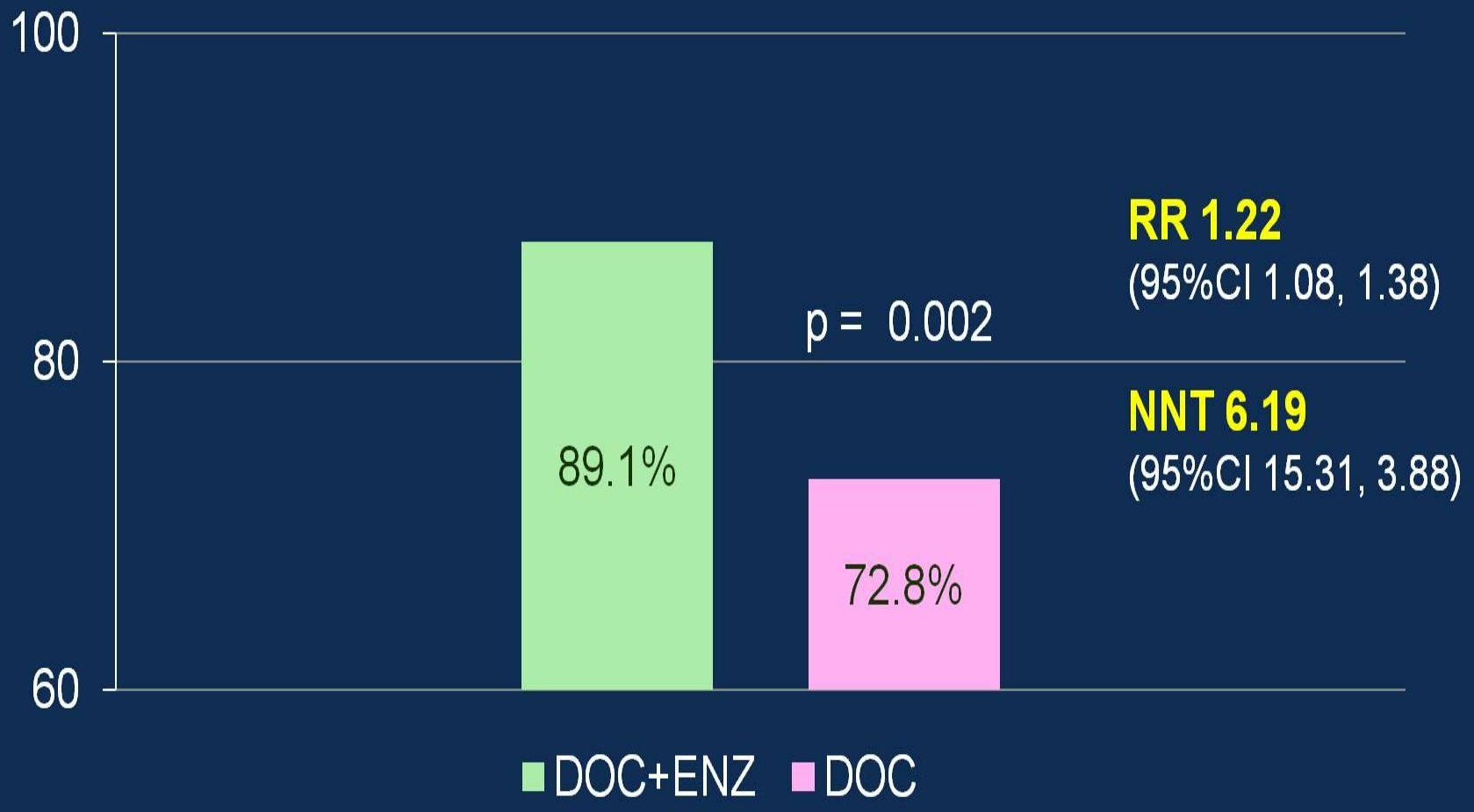
- Target of 232 pts provides 80% power to detect a target difference in PD-free rate of 15% (50% vs 65%) with an α-error of 0.10

Secondary endpoints

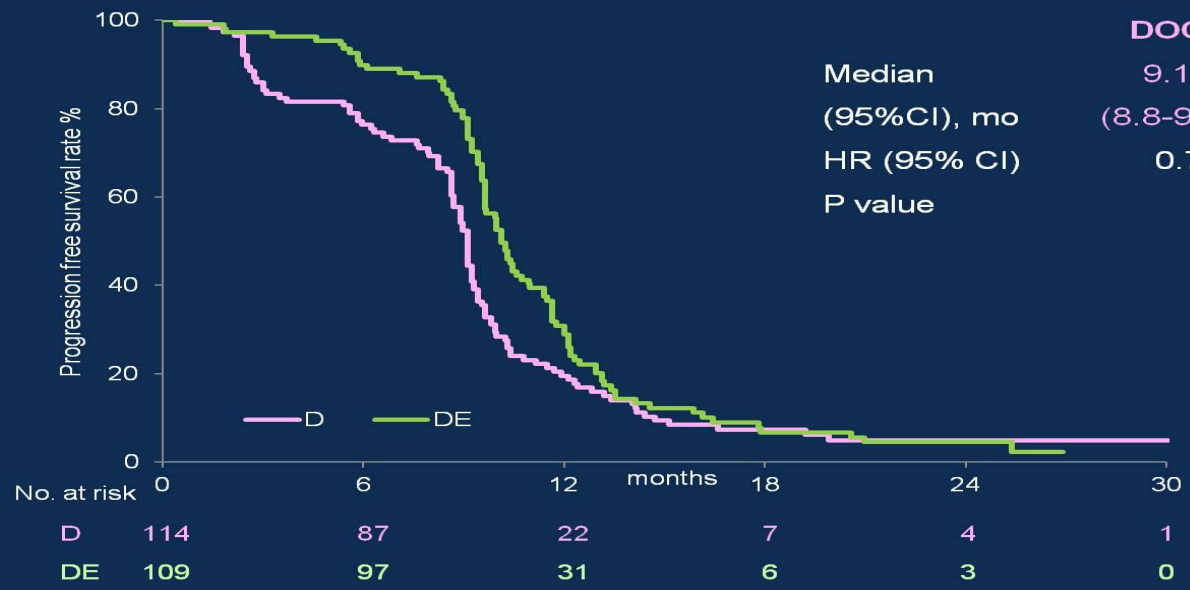
- ORR
- bRR
- PFS
- rPFS
- OS
- Safety
- Pain (BPI)
- QoL (FACT-P)

Presented by: Orazio Caffo

Rate of progression disease free patients at 6 mos after docetaxel start (primary endpoint)



Progression free survival



	DOC	DOC+ENZ
Median	9.1	10.1
(95%CI), mo	(8.8-9.3)	(9.7-10.5)
HR (95% CI)	0.71 (0.54-0.94)	
P value	0.01	

Overall survival

	DOC	DOC+ENZ
Median	33.7	29.6
(95%CI), mo	(26.1-41.2)	(21.3-37.9)
HR (95% CI)	1.13 (0.75-1.71)	
P value	0.5	

Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial

mCRPC
n.743

- ECOG 0-2
- Adequate organ function
- previous ARTA

R

1 → **Carboplatin AUC 4 + Cabazitaxel 25 mg/mq + 10 mg of prednisone**

1 → **Cabazitaxel 25 mg/mq + 10 mg of prednisone plus placebo**

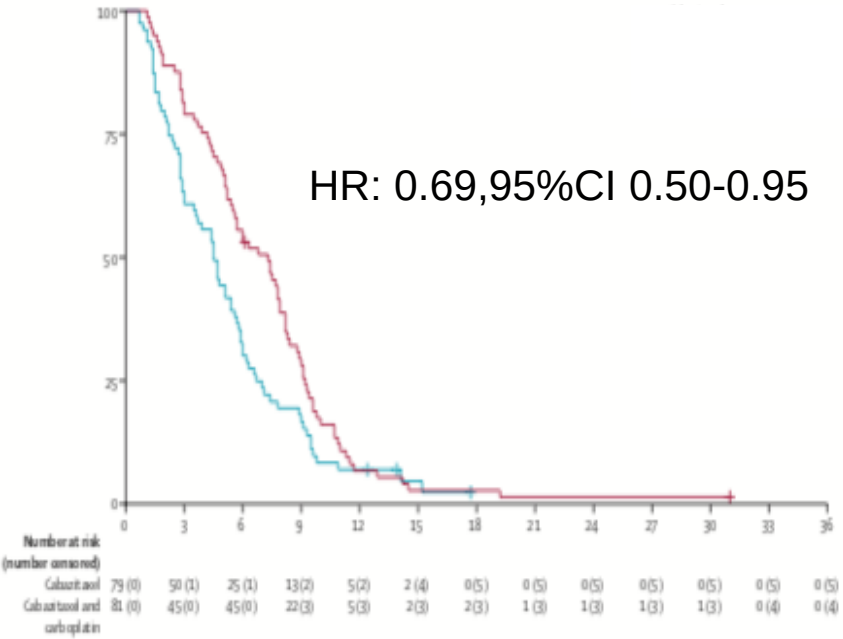
Primary end point: PFS

Secondary end point:
- PSA response
- **overall survival (OS)**
- **Safety and toxicity**
- **Effect of aggressive variant of PCA on response**

Com P. et al. Lancet Oncol 2019

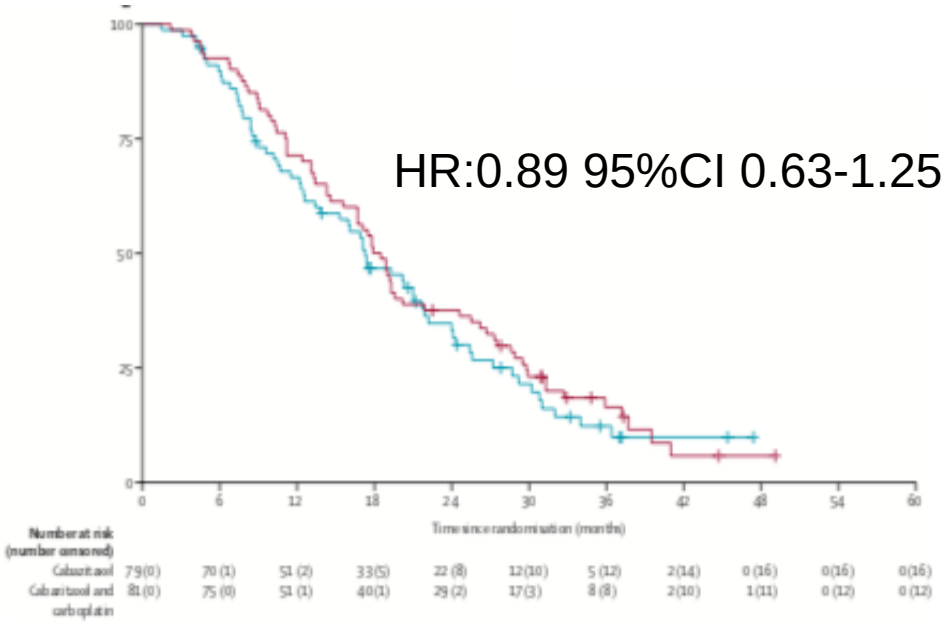
Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial

PFS



HR: 0.69,95%CI 0.50-0.95

OS



HR:0.89 95%CI 0.63-1.25

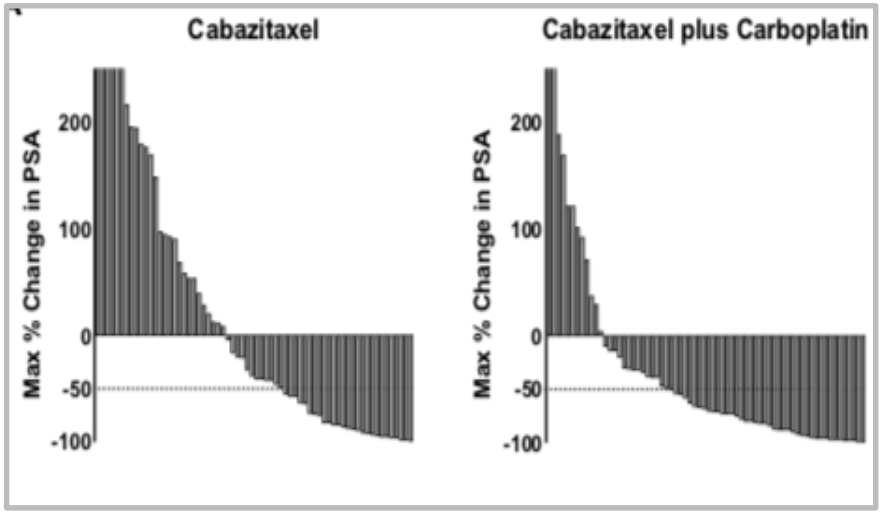
Com P. et al. Lancet Oncol 2019

Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial

	Cabazitaxel group (n=79)				Cabazitaxel and carboplatin group (n=81)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Fatigue	49 (62%)	7 (9%)	0	0	51 (63%)	16 (20%)	0	0
Nausea	25 (32%)	1 (1%)	0	0	49 (60%)	5 (6%)	0	0
Diarrhoea	38 (48%)	2 (3%)	0	0	48 (59%)	4 (5%)	0	0
Constipation	12 (15%)	0	0	0	30 (37%)	2 (2%)	0	0
Dyspnea	14 (18%)	3 (4%)	0	0	27 (33%)	7 (9%)	0	0
Vomiting	14 (18%)	0	0	0	27 (33%)	1 (1%)	0	0
Alopecia	14 (18%)	0	0	0	24 (30%)	0	0	0
Paresthesia	7 (9%)	0	0	0	15 (19%)	0	0	0
Dysgeusia	8 (10%)	0	0	0	14 (17%)	0	0	0
Neuropathy	3 (4%)	1 (1%)	0	0	13 (16%)	0	0	0
Pain	6 (8%)	5 (6%)	0	0	8 (10%)	1 (1%)	0	0
Dizziness	6 (8%)	0	0	0	13 (16%)	1 (1%)	0	0
Anorexia	5 (6%)	1 (1%)	0	0	12 (15%)	2 (2%)	0	0
Weight loss	3 (4%)	0	0	0	9 (11%)	0	0	0
Oedema	11 (14%)	0	0	0	10 (12%)	0	0	0
Fever	3 (4%)	0	0	0	8 (10%)	1 (1%)	0	0
Haematuria	3 (4%)	0	0	0	6 (7%)	4 (5%)	0	0
Hypotension	1 (1%)	1 (1%)	0	0	4 (5%)	3 (4%)	0	0
Abdominal pain	2 (3%)	2 (3%)	0	0	4 (5%)	3 (4%)	0	0
Dehydration	1 (1%)	3 (4%)	0	0	3 (4%)	7 (9%)	0	0
Pneumonia	0	4 (5%)	0	0	0	3 (4%)	0	0
Thromboembolic event	0	0	0	1 (1%)	0	2 (2%)	1 (1%)	0
Febrile neutropenia	0	1 (1%)	0	0	0	3 (4%)	1 (1%)	0
Urinary tract infection	1 (1%)	1 (1%)	0	0	0	2 (2%)	2 (2%)	0
Fracture	0	0	0	0	0	2 (2%)	0	0
Hypomagnesaemia	6 (8%)	0	0	0	33 (41%)	1 (1%)	0	0
Anaemia	16 (20%)	3 (4%)	0	0	23 (28%)	18 (22%)	1 (1%)	0
Thrombocytopenia	4 (5%)	0	1 (1%)	0	18 (22%)	8 (10%)	3 (4%)	0
Hyperglycaemia	12 (15%)	2 (3%)	0	0	15 (19%)	1 (1%)	0	0
Neutropenia	3 (4%)	3 (4%)	0	0	2 (2%)	6 (7%)	7 (9%)	0
Lymphopenia	8 (10%)	1 (1%)	0	0	3 (4%)	4 (5%)	1 (1%)	0
Hypokalaemia	7 (9%)	0	0	0	10 (12%)	2 (2%)	1 (1%)	0
Elevated aspartate aminotransferase	5 (6%)	0	0	0	10 (12%)	0	0	0
Hypocalcaemia	5 (6%)	0	0	0	9 (11%)	0	0	0
Elevated creatinine	7 (9%)	1 (1%)	0	0	8 (10%)	0	0	0

Values are n (%). Grade 1–2 adverse events that occurred in 10% or more of patients in either group and grade 3–5 events that occurred in 2% or more patients in either group are shown.

Table 2: Adverse events in the phase 2 part of the study



Com P. et al. Lancet Oncol 2019

ERA 223 (NCT02043678)

Study population

- Patients with bone-predominant mCRPC (≥2 bone metastases)
- Asymptomatic or mildly symptomatic
- ECOG PS of 0 or 1
- No prior chemotherapy for CRPC
- No known brain or visceral metastases

Accrual dates 3/2014 – 8/2016

Target accrual N=800

1:1 Randomisation

Abiraterone acetate 1000 mg qd and prednisone/prednisolone 5 mg bid (AAP) + Radium-223 55 kBq/kg IV every 4 weeks for 6 cycles

Abiraterone acetate 1000 mg qd and prednisone/prednisolone 5 mg bid (AAP) + Matching placebo

Stratification factors

- Geographical region
- Total ALP level at baseline (ALP <90 vs ≥90 U/L)
- Use of bone health agents

Primary endpoint

- SSE-FS

Secondary endpoints

- OS
- rPFS
- Time to chemotherapy
- Time to opiate use for cancer pain
- Safety

Exploratory endpoints

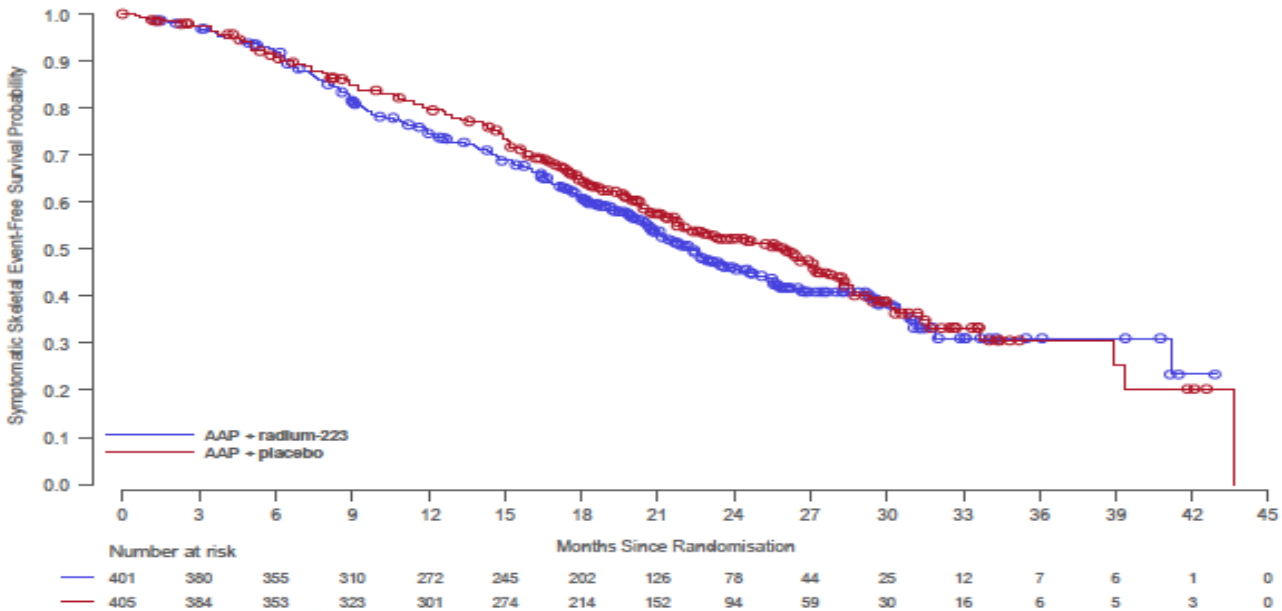
- PSA response
- Time to PSA progression
- ALP response
- Time to ALP progression
- HRQoL

389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; initiation during the study prohibited to prevent confounding effects.

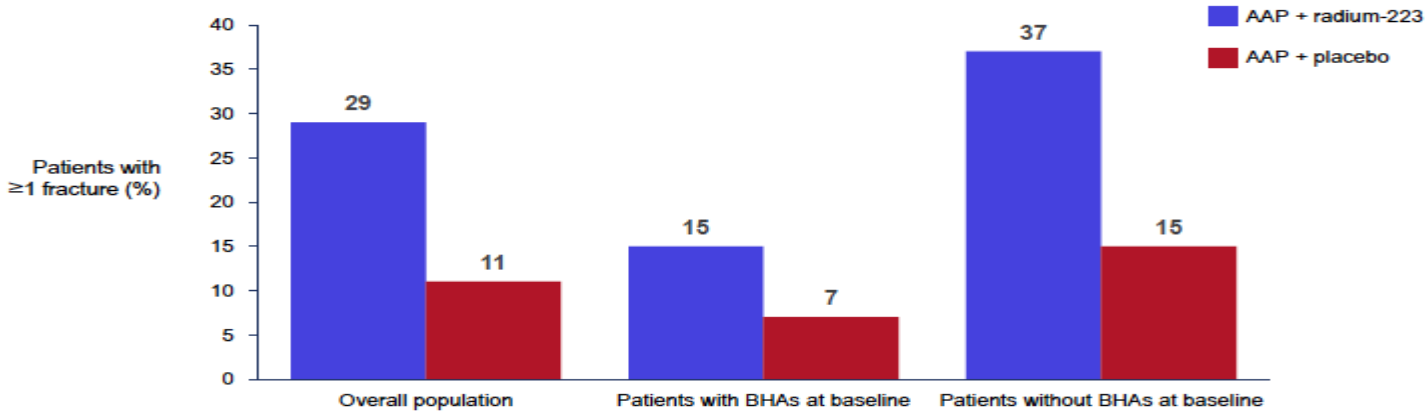
ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival; SSE-FS, symptomatic skeletal event-free survival.

Symptomatic Skeletal Event-Free Survival (ITT)



SSE-FS	AAP + radium-223 N=401	AAP + placebo N=405
Events, n (%)	196 (49)	190 (47)
Median (95% CI), months	22.3 (20.4–24.8)	26.0 (21.8–28.3)
HR (95% CI)	1.122 (0.917–1.374)	
P-value (2-sided)	0.2636	

Post-Hoc Subgroup Analysis of Fractures by Baseline BHA Use



MUNICH 2018 ESMO congress

AAP, abiraterone acetate and prednisone/prednisolone; BHA, bone health agent; NE, not estimable.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 9-12 July 2018

Share

News 13/07/2018

PRAC recommends restricting use of prostate cancer medicine Xofigo

Following a review of data showing a possible risk of earlier death and an increase in fractures with Xofigo (radium-223 dichloride), the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended restricting the use of this cancer medicine to patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments.

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

More information is provided below.

AIFA
Agenzia Italiana del Farmaco

Xofigo in monoterapia o in associazione con un analogo dell'ormone di rilascio dell'ormone luteinizzante (*Luteinising Hormone-Releasing Hormone*, LHRH) è indicato per il trattamento di pazienti adulti affetti da carcinoma prostatico metastatico resistente alla castrazione (*metastatic Castration-Resistant Prostate Cancer,* mCRPC), con metastasi ossee sintomatiche e senza metastasi viscerali note, in progressione dopo almeno due precedenti linee di terapia sistemica per il mCRPC (diverse dagli analoghi del LHRH) o non eleggibili ai trattamenti sistemici disponibili per il mCRPC.

AGENDA

- **mCRPC**
  -sequencing strategies
  -combinations

- **Radiopharmaceuticals**

- **Genomic aberrations and clinical implications for mCRPC**

- DDR and PARP inhibitors

- PTEN loss and AKT inhibitors

- MMR, CDK 12 and immunotherapy

Prostate specific membrane antigen (PSMA)

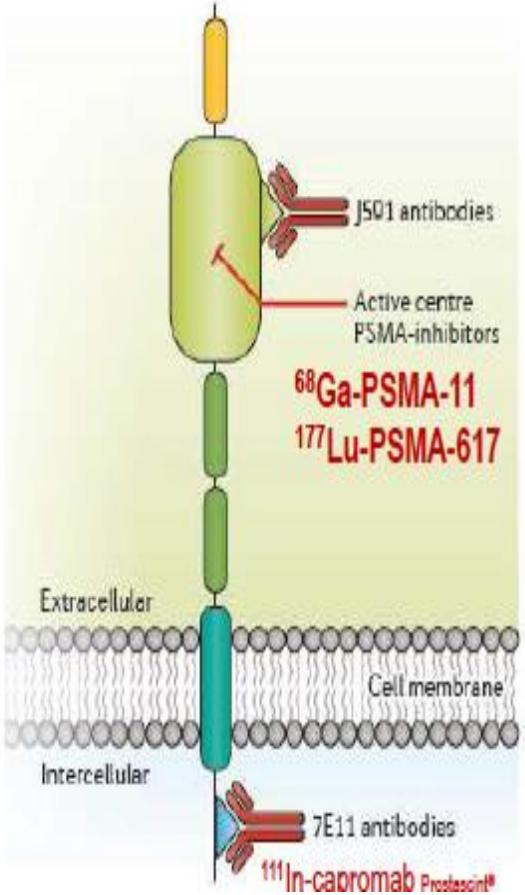
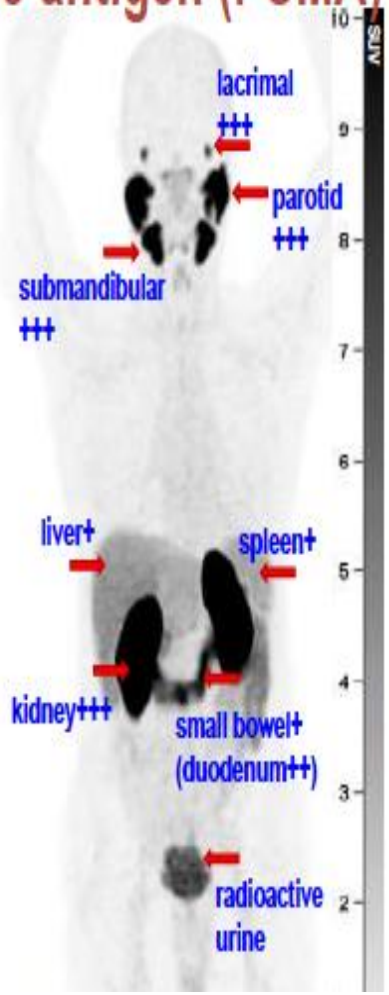


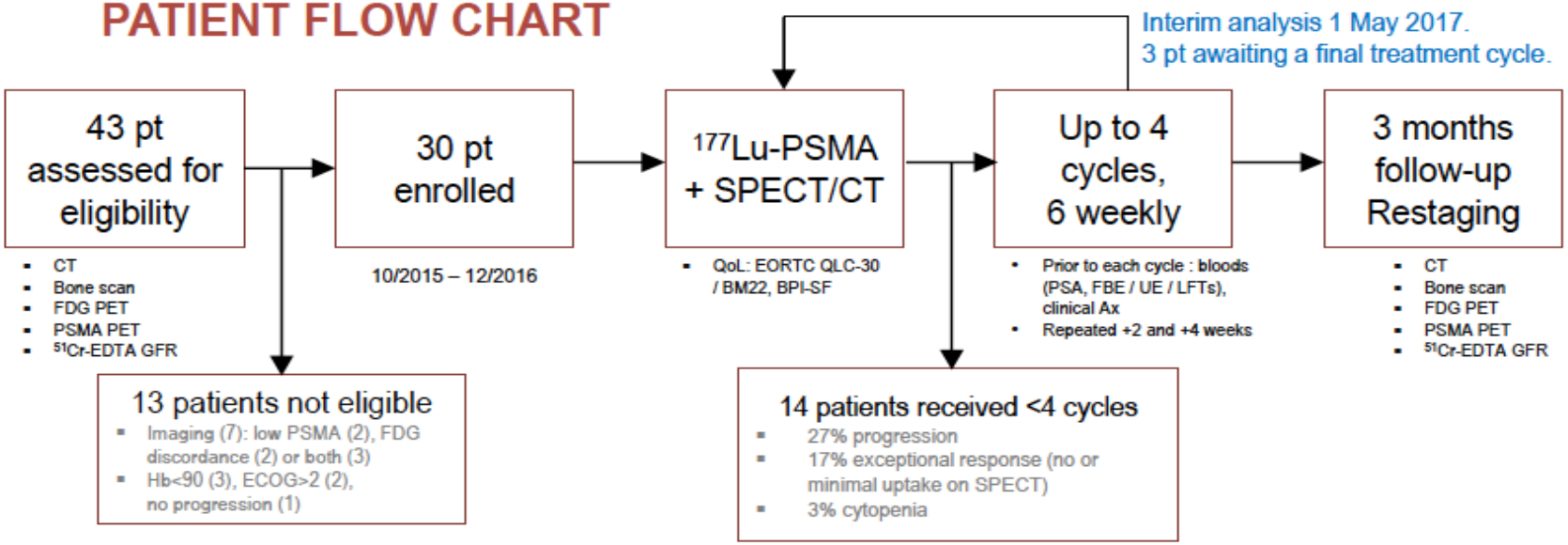
Image from Maurer T et al. Nat Rev Urol. 2016 Apr;13(4):226-35



- Type II transmembrane glycoprotein (FOLH1)
- Highly over-expressed in prostate cancer
- ↑↑ castrate-resistant metastatic disease

PSMA PET
normal biodistribution

PATIENT FLOW CHART



PATIENT ELIGIBILITY

Inclusion

- Castration-resistant
- Documented progression after (unless contraindicated or patient refused)
  - Docetaxel
  - Enzalutamide or abiraterone
- ECOG ≤ 2
- High uptake on PSMA PET

Exclusion

- GFR < 40 ml/min
- Platelet < 75,000
- Neutrophil < 1.5
- Hb < 9.0
- Albumin < 25
- FDG PET/CT demonstrating discordant disease

ENDPOINTS

Primary

- Toxicity (CTCAE 4)
- Activity
  - PSA response (PCWG2)
  - Quality of life (EORTC QLQ-C30, BPI-SF)
  - Imaging response (RECIST, bone scan, PSMA/FDG PET)

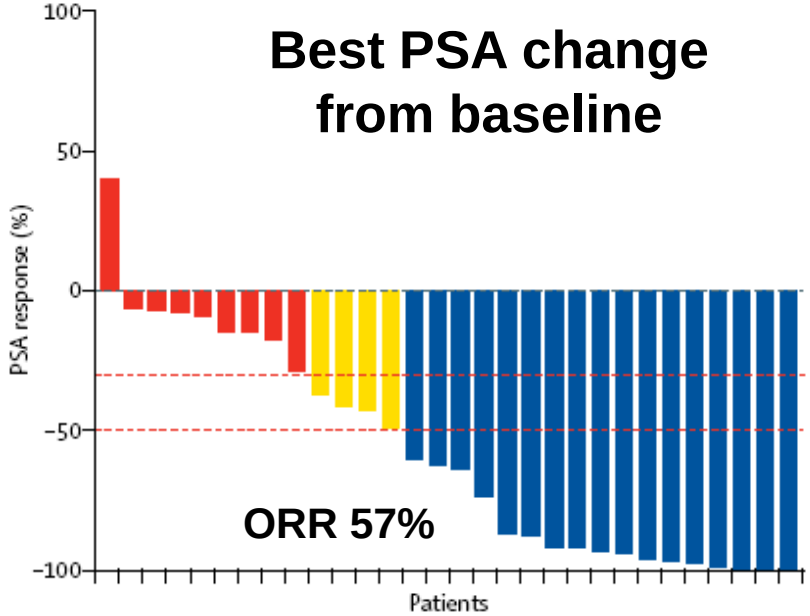
Secondary

- Dosimetry to tumors and normal tissue
- Progression free and overall survival

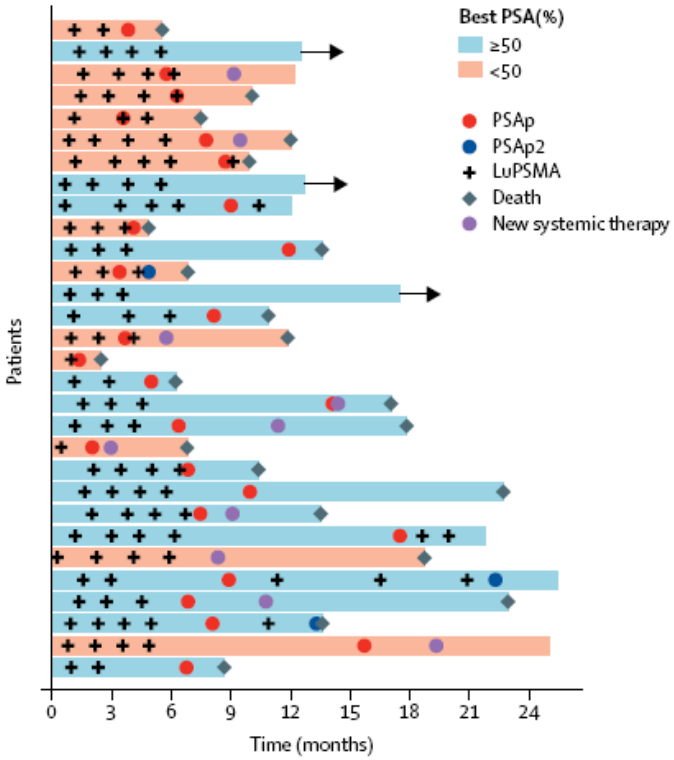
Hofman, Lancet Oncol 2018

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Best PSA change from baseline



Time to PSA progression



Imaging Response

	Bone scintigraphy	Soft-tissue lesions (nodal and visceral;* n=17)
Complete response	n/a	5 (29%)
Partial response	n/a	9 (53%)
Stable disease	11 (37%)†	0
Progressive disease	9 (30%)	2 (12%)
Not performed (clinical progression or death)	9 (30%)	0
Not performed (death from other cause)	1 (3%)	1 (6%)

Hofman, Lancet Oncol 2018

AGENDA

- **M0 CRPC**

- **mCRPC**
  -new prognostic markers
  -combinations

- **Radiopharmaceuticals**

- **Genomic aberrations and clinical implications for mCRPC**

- DDR and PARP inhibitors

- PTEN loss and AKT inhibitors

- MMR, CDK 12 and immunotherapy

PROfound STUDY DESIGN

Key eligibility criteria

- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Cohort A: *BRCA1, BRCA2* or *ATM* N=245

- Olaparib 300 mg bid n=162
- Physician's choice‡ n=83

2:1 randomization
Open-label

Upon BICR progression, physician's choice patients were allowed to cross over to olaparib

Cohort B: Other alterations N=142

- Olaparib 300 mg bid n=94
- Physician's choice‡ n=48

Stratification factors

- Previous taxane
- Measurable disease

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

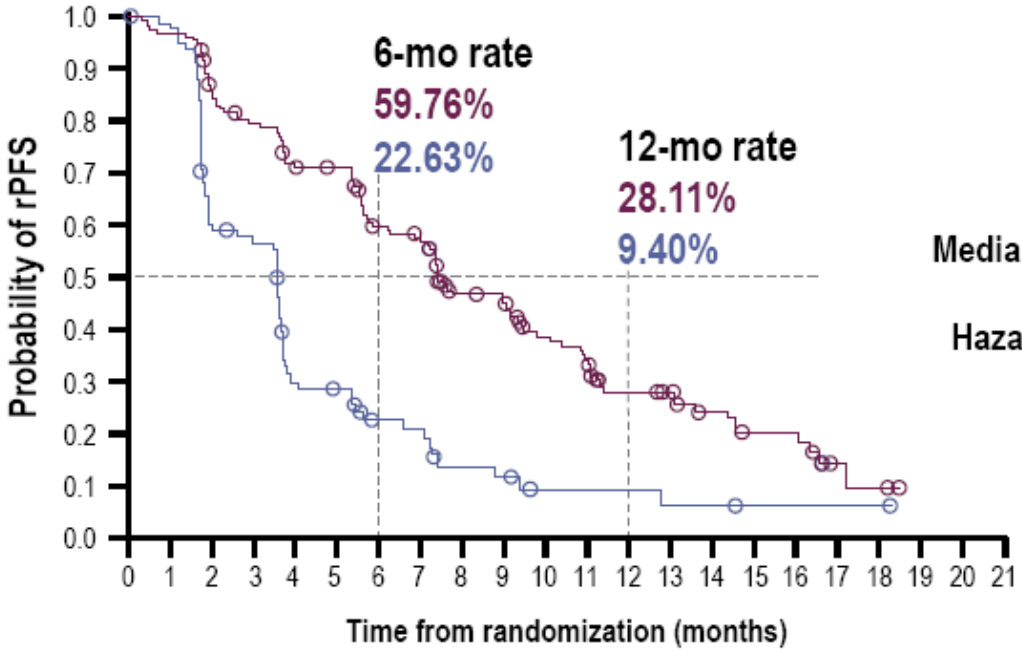
***An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test**

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

No. at risk																						
Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

EFFICACY SUMMARY BY COHORT

	Cohort A	Cohort B	Cohorts A+B
N (Olaparib/ Physician's choice)	162/ 83	94/ 48	256/ 131
rPFS (BICR)			
Hazard ratio (95% CI)	**0.34 (0.25, 0.47) P<0.0001**	0.88 (0.58, 1.36)	**0.49 (0.38, 0.63) P<0.0001**
rPFS (investigator-assessed)*			
Hazard ratio (95% CI)	0.24 (0.17, 0.34)	0.60 (0.39, 0.93)	0.36 (0.27, 0.47)
ORR (BICR)			
%, Olaparib vs Physician's Choice Odds ratio (95% CI)	**33.3 vs 2.3% 20.86 (4.18, 379.18) P<0.0001**	3.7 vs 8.3% Not calculated†	21.7 vs 4.5% 5.93 (2.01, 25.40)
OS (interim)			
Hazard ratio (95% CI)	**0.64 (0.43, 0.97) P=0.0173**	0.73 (0.45, 1.23)	0.67 (0.49, 0.93)

Denotes multiplicity-controlled endpoint

Crossover >80%

BARCELONA 2019 ESMO congress

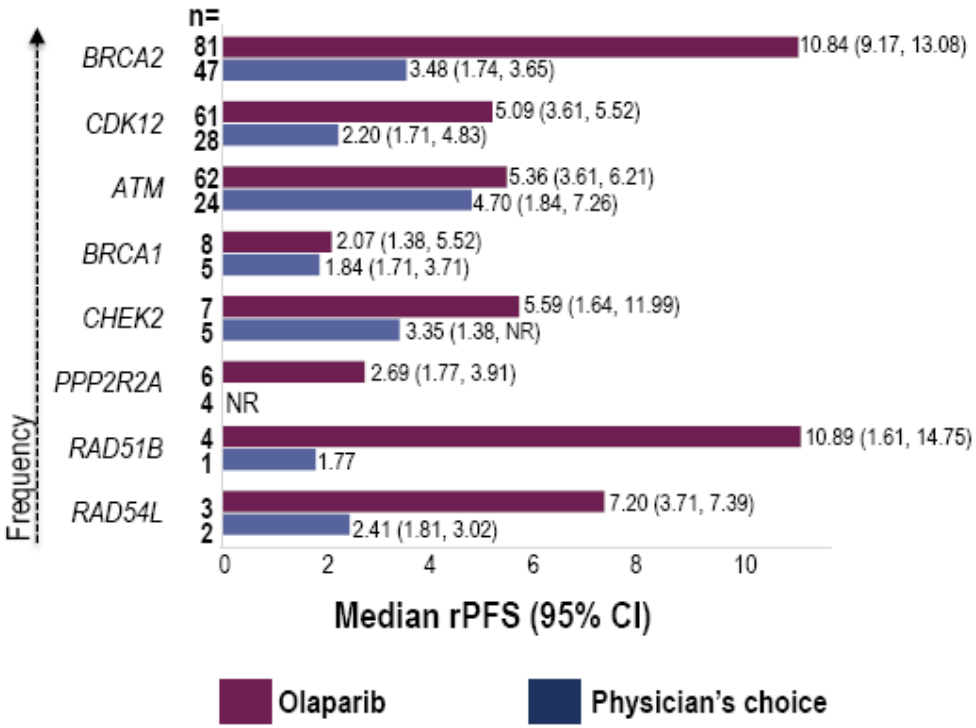
* Pre-specified sensitivity analysis

†N=2 responders each for olaparib vs ph

Exploratory analysis

GENE-BY-GENE rPFS

- 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)
- 97% of patients were randomized based on alterations in 8/15 single genes
- There is evidence of clinical activity of olaparib in patients with alterations in genes other than *BRCA1* or *BRCA2*
- Gene-level analysis is complex and exploratory, and comparisons may be confounded by multiple factors



NR, not reached

Prostate Cancer Phase II experience: BRCA2 response concordance

	Reported Phase 1/2 trials with PARPi in pretreated mCRPC		
Study Drugs	**Study**	**Primary Endpoint**	**Efficacy Data**
Olaparib	TOPARP-A	RR	16/49 patients had a response (33%; 95% CI, 20 - 48)- (retrospective status assessment
	TOPARP-B	ORR	BRCA2 ~80%
Rucaparib	TRITON 2-ongoing	ORR	BRCA1/2 44.0%; **(preliminary)**
Niraparib	GALAHAD-ongoing	Composite response rate	biallelic BRCA1/2 65 % **(preliminary)**

Mateo et al ASCO 2019
Abida ESMO 2019
Smith et al ESMO 2019

(radiological response and/or PSA50% fall and/or CTC count conversion)

Ongoing Phase III studies in Prostate Cancer

	Ongoing Trials with PARPi in Prostate Cancer			
Study Drugs	**Study Name (NCT #)**	**Phase**	**Patient Population**	**Primary Endpoint**
Enzalutamide + Talazoparib vs Enzalutamide + Placebo	TALAPRO-2 (NCT03395197)	3	L1 mCRPC,	PFS
Rucaparib vs Abiraterone, Enzalutamide, or Docetaxel	**TRITON 3 (NCT02975934)**	**3**	**germline or somatic BRCA1, BRCA2, or ATM mutations and mCRPC who previously progressed on an androgen-receptor signaling inhibitor and who have not received chemotherapy**	**PFS**
Niraparib + Abiraterone vs Placebo + Abiraterone	MAGNITUDE (NCT03748641)	3	L1 tmCRPC (DDRm cohort / no DDR cohort)	PFS
Abiraterone +/- Olaparib	PROpel (NCT03732820)	3	L1 mCRPC	PFS
Pembrolizumab + Olaparib vs Enzalutamide or Abiraterone	KEYLINK-010 (NCT03834519)	3	mCRPC progressed on Abiraterone or Enzalutamide	PFS, OS

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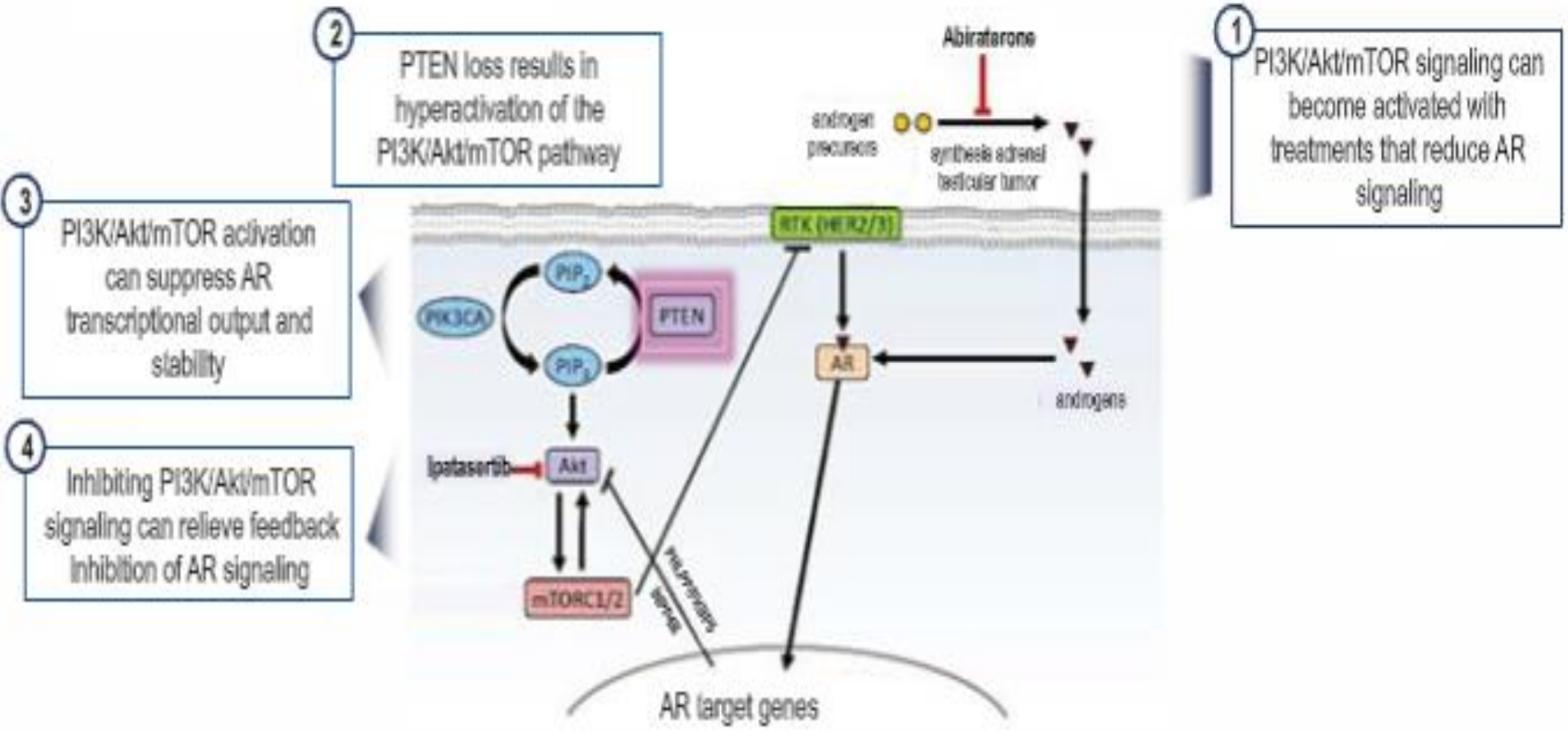
INTERACTION BETWEEN ANDROGEN RECEPTOR AND PI3K/AKT PATHWAYS



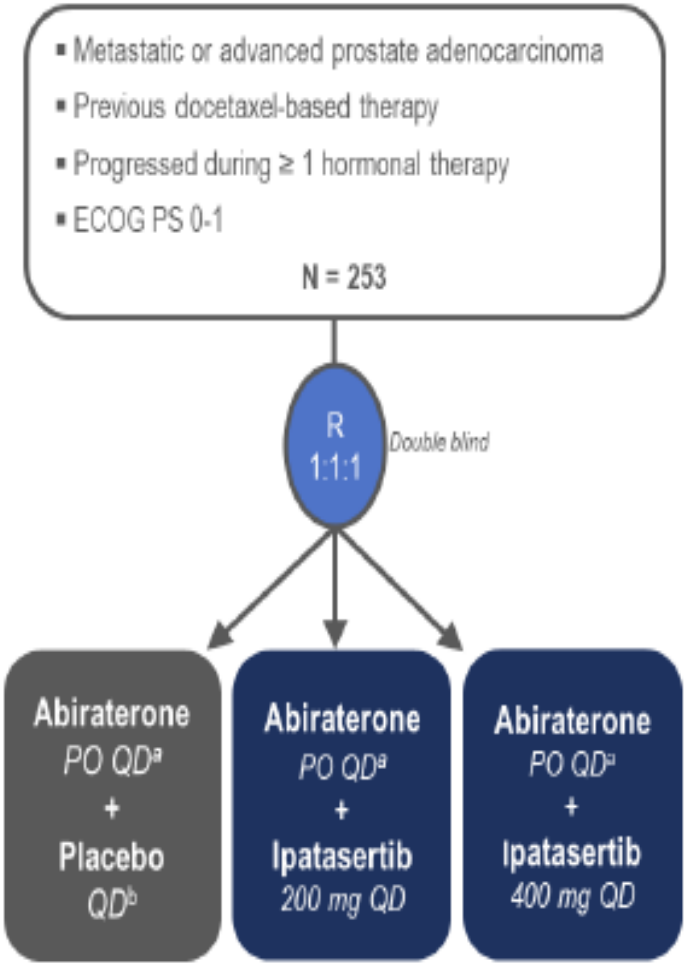
Akt, protein kinase B; AR, androgen receptor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; PIP2, phosphatidylinositol-4-5-bisphosphate; PIP3, phosphatidylinositol-3,4-5-trisphosphate; PTEN, phosphatase and tensin homology; RTK, receptor tyrosine kinases.

1. Carver et al. Cancer Cell. 2011. 2. Hodgson et al. Cancer Res. 2011. 3. Mulholland et al. Cancer Cell. 2011.

de Bono et al, Ipatasertib, ESMO 2016

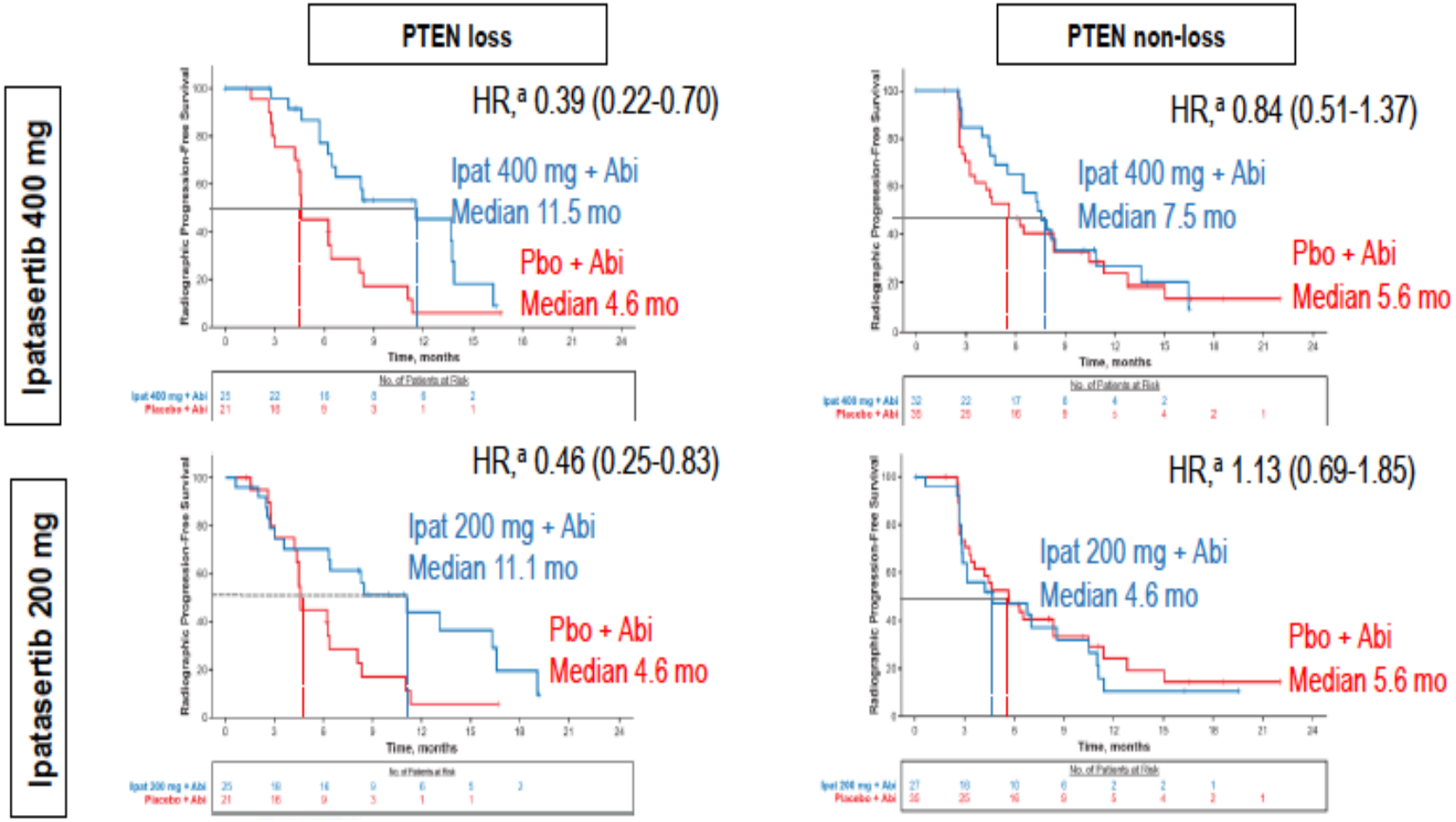
A.MARTIN: PHASE II TRIAL OF IPATASERTIB + ABIRATERONE IN PATIENTS WITH MCRPC

- Patients were stratified by:
  - Enzalutamide (yes or no)
  - Number of chemotherapy regimens (1 vs > 1)
  - Type of progression (PSA only vs other)
- Coprimary efficacy endpoints were rPFS in the ITT population and in patients whose tumors had PTEN loss **via ICR IHC**
- These biomarker analyses are for hypothesis generation and do not have adequate power to detect meaningful differences between the treatment arms



De Bono et al, ESMO 2018

COPRIMARY ENDPOINT: RPFS WITH IPATASERTIB OR PLACEBO + ABIRATERONE BY ICR IHC



De Bono et al. ESMO 2018

AGENDA

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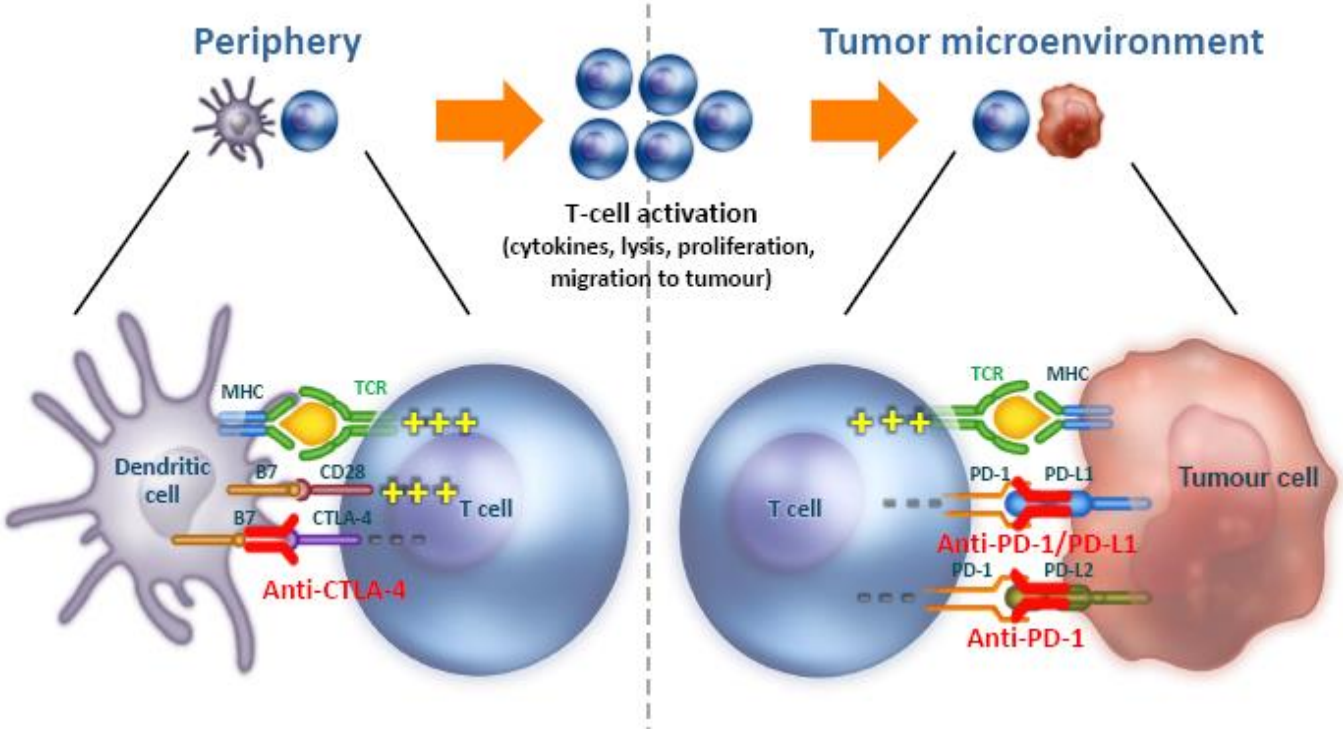
Targeting different immune checkpoints

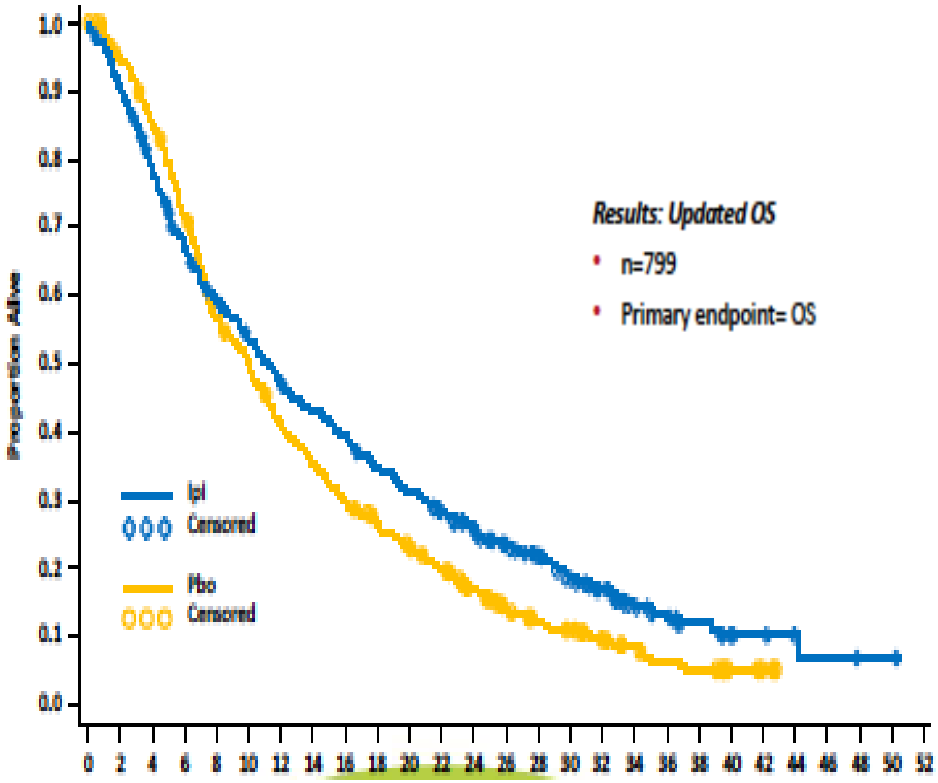


CTLA-4 pathway blockade

PD-1 and PD-L1 pathway blockade

CTLA-4 targeting: Ipilimumab post-docetaxel phase III trial

Overall Survival

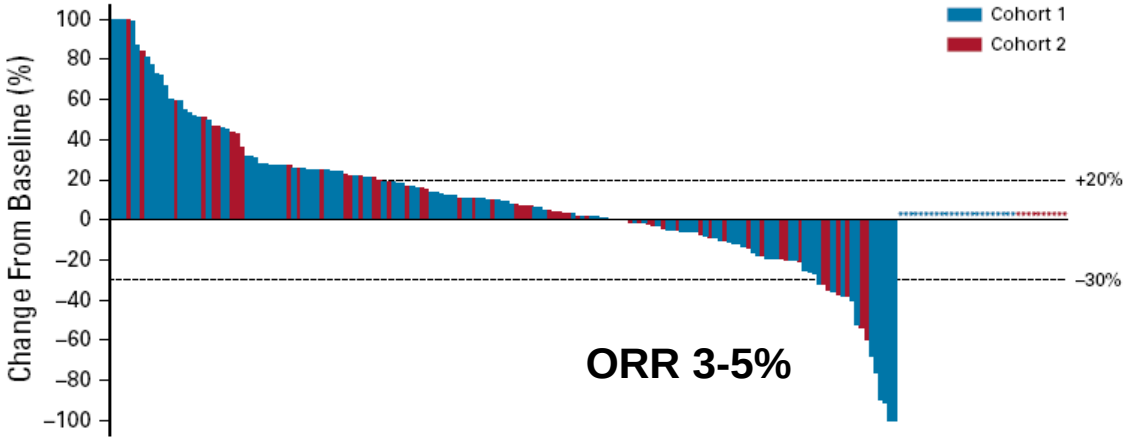


	Ipi (n=399)	Pbo (n=400)
Median OS, mo (95% CI)	11.2 (9.6–12.6)	10.0 (8.4–11.2)
HR (95% CI)	0.84 (0.72–0.98)	
Stratified log-rank*	P=0.03	
1-yr OS rate	47%	41%
2-yr OS rate	25%	17%
3-yr OS rate**	12%	6%

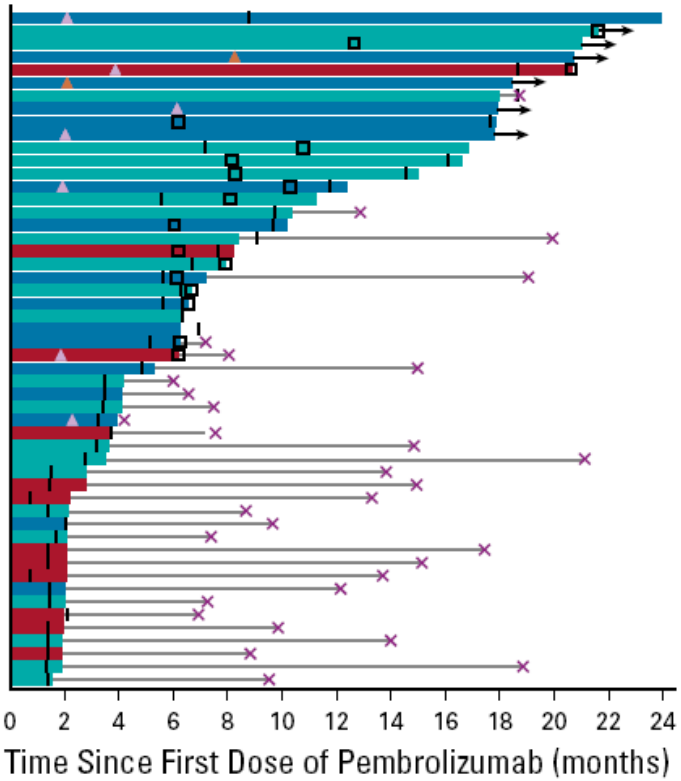
Fizazi K, ESMO 2018

Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study

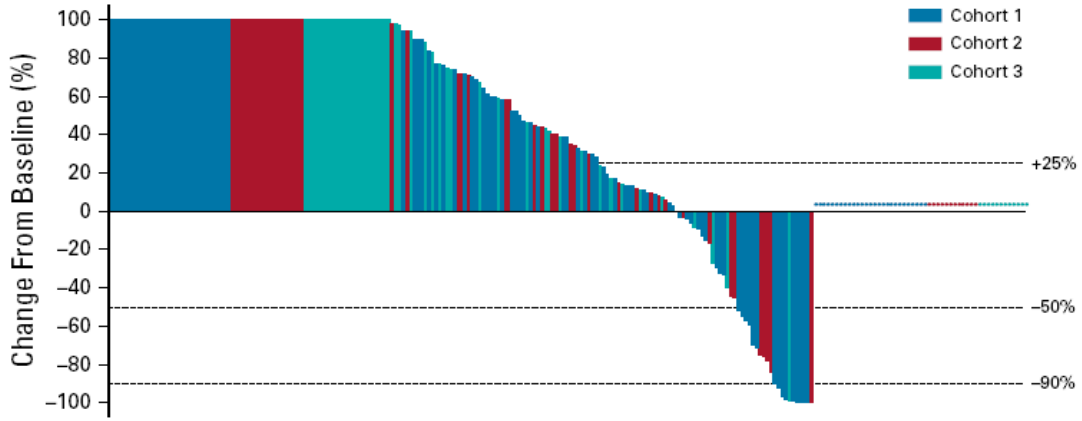
Tumor size change from baseline



Response over time



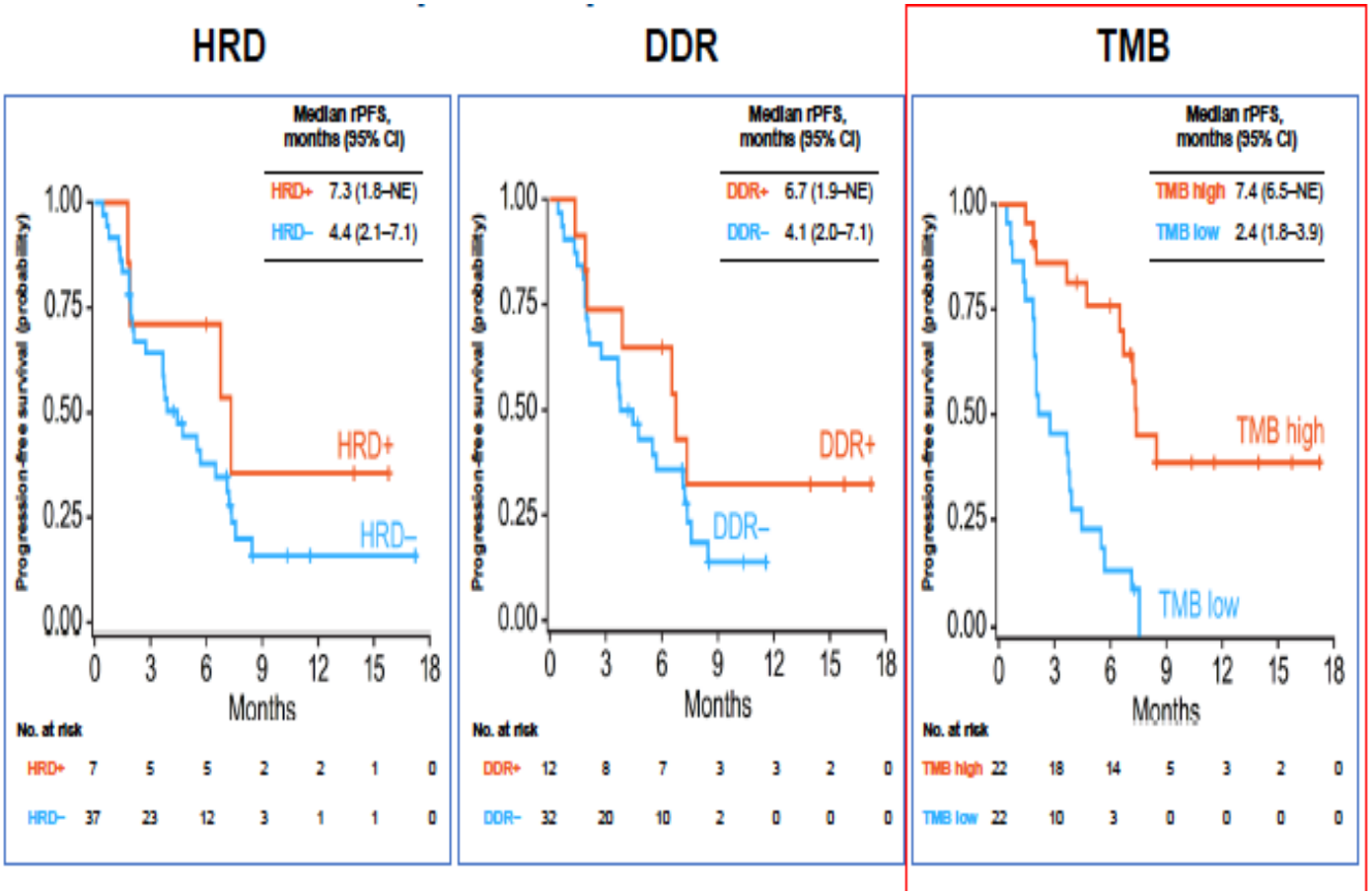
PSA change from baseline



Antonarakis, J Clin Onc 2019

Ipilimumab + Nivolumab in mCRPC Checkmate-050

Association of HRD, DDR, TMB with rPFS



- Enhanced rPFS benefit was observed in patients with HRD+ OR DDR+ tumours
- High TMB was associated with rPFS vs low TMB (P<0.001)

Chekmate 050, ASCO GU2019

Conclusions

- There are several treatment options for mCRP
- There is clear evidence that sequencing two ARTA should not be routinely recommended in clinical practice
- mCRPC is a highly heterogenous disease but molecular classification is leading the Target Therapy Era
- gBRCA2 is an independent prognostic factor of CSS.
- Olaparib is active in gDDR+ mCRPC. However dose and gene subgroup may matter in olaparib sensitivity.
- PTEN loss in a predictive factor of response to AKT-inhibitor plus abiraterone. Phase III trial is ongoing.
- Immunotherapy has a potential role in mCRPC, predictive biomarkers are needed in order to optimize patients selection