

13° CONGRESSO NAZIONALE AIOM GIOVANI

2019 NEWS IN ONCOLOGY



Carcinoma della
prostata
resistente alla
castrazione:
dall'M0 allo stadio
avanzato.

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AGENDA

- **M0 CRPC**
- **mCRPC**
- **Genomic aberrations and clinical implications for mCRPC**
 - DDR and PARP inhibitors
 - PTEN loss and AKT inhibitors
 - MMR, CDK 12 and immunotherapy
- **Radiopharmaceuticals**

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Who are nmCRPC patients?

Biochemical
progression
while on ADT

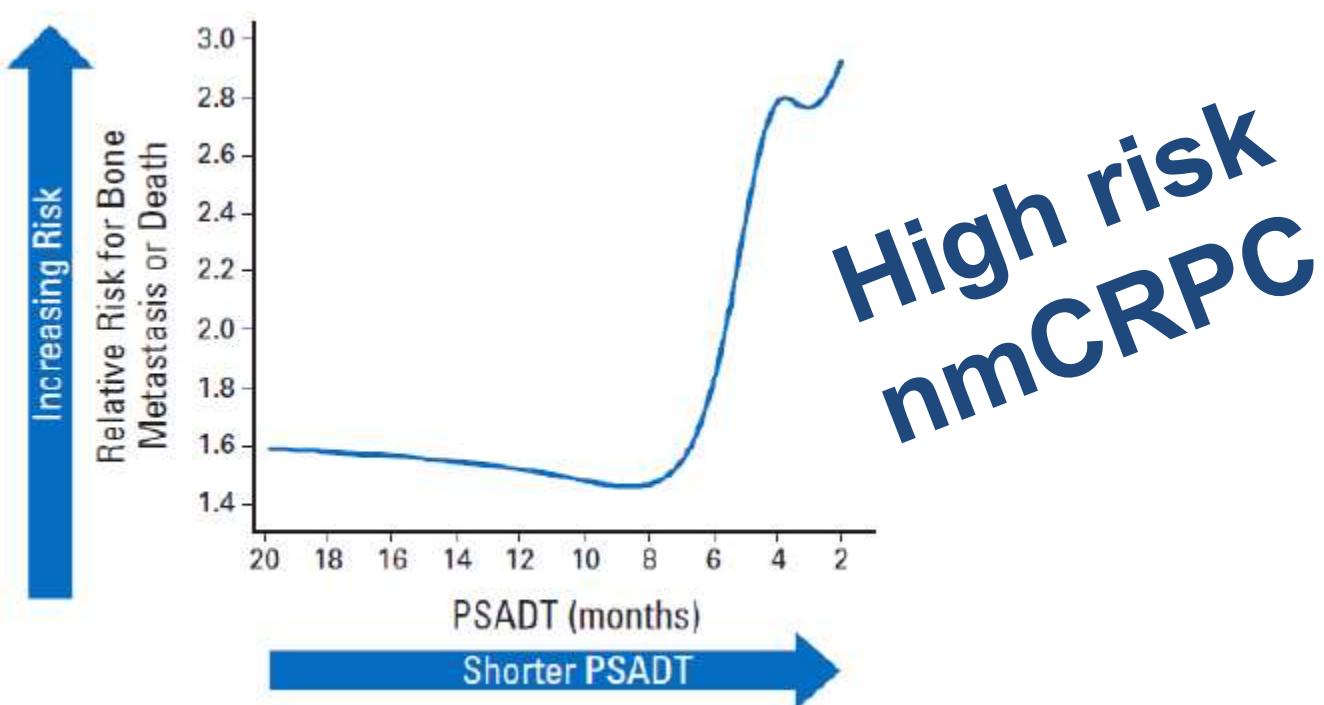


Serum testosterone
levels below 50
ng/dL



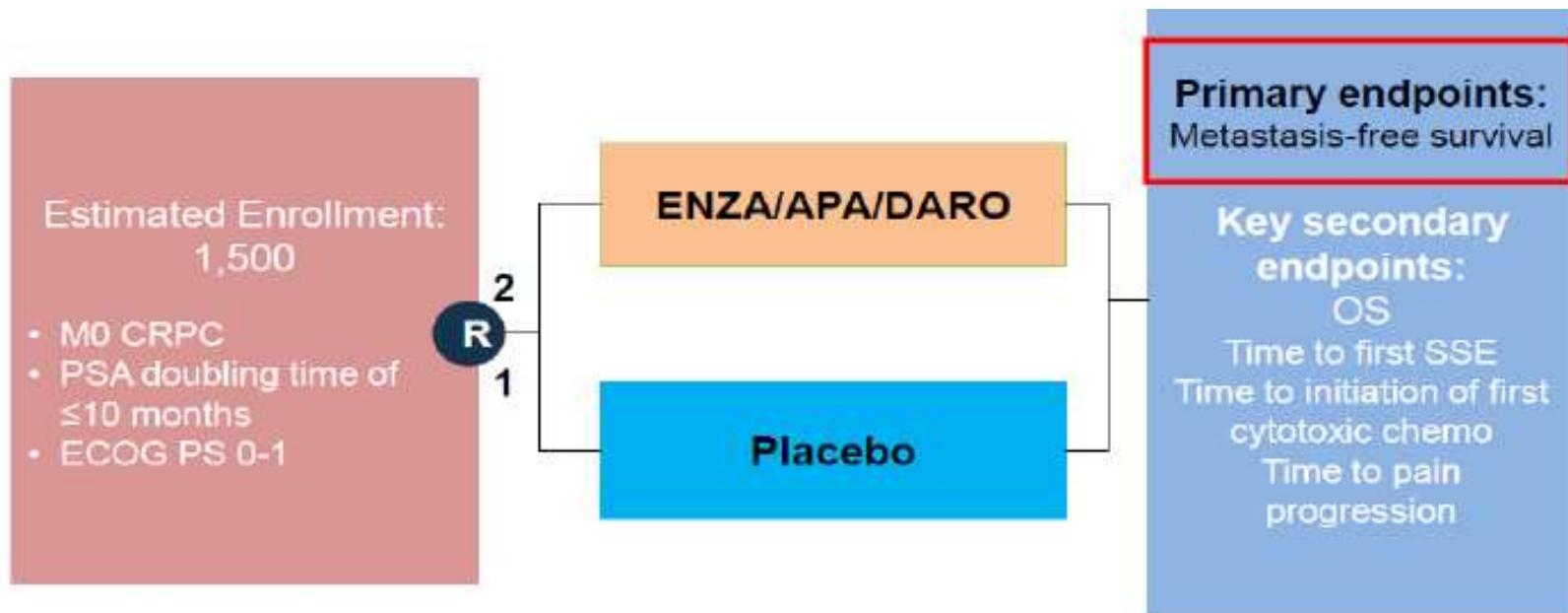
No
evidence of
metastasis

PSA Doubling time predicts outcomes in nmCRPC



1. Paller CJ et al. *Clin Adv Hematol Oncol*. 2013;11(1):14-23;
2. Arlen PM, et al. *J Urol*. 2008 Jun;179(6):2181-5;
3. Smith MR, et al. *J Clin Oncol*. 2013 Oct 20;31(30):3800-6;
4. Freedland SJ, et al. *J Clin Oncol*. 2007 May 1;25(13):1765-71;
5. Howard LE et al. *BJU Int*. 2017 Nov;120(5B):E80-E86.

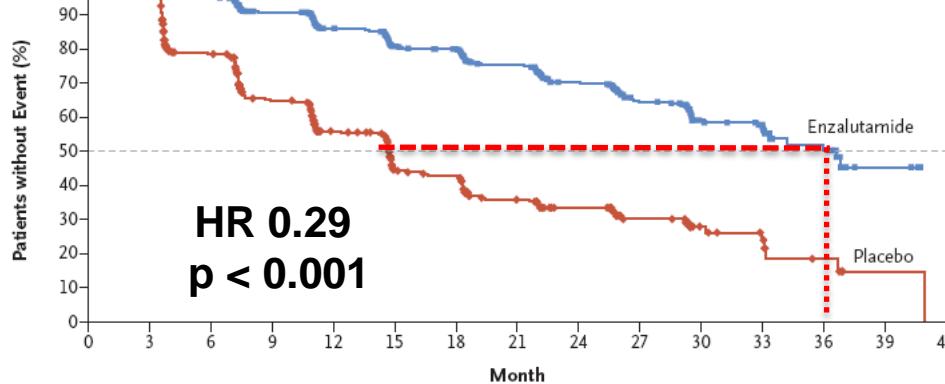
Phase III randomized trials in High-Risk nmCRPC



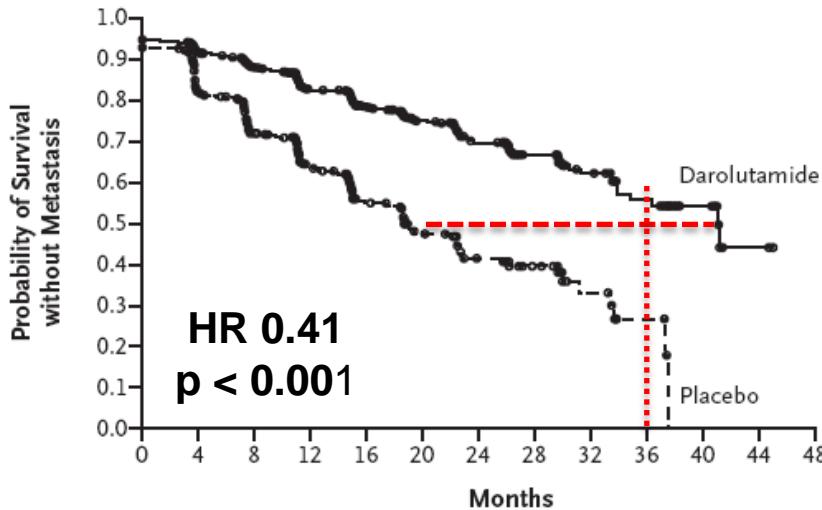
Similar trials with Enzalutamide (PROSPER)¹, Apalutamide (SPARTAN)², Darolutamide (ARAMIS)³

¹Hussain, NEJM 2018; ²Matthew, NJM 2018; ³Fizazi, NEJM 2019

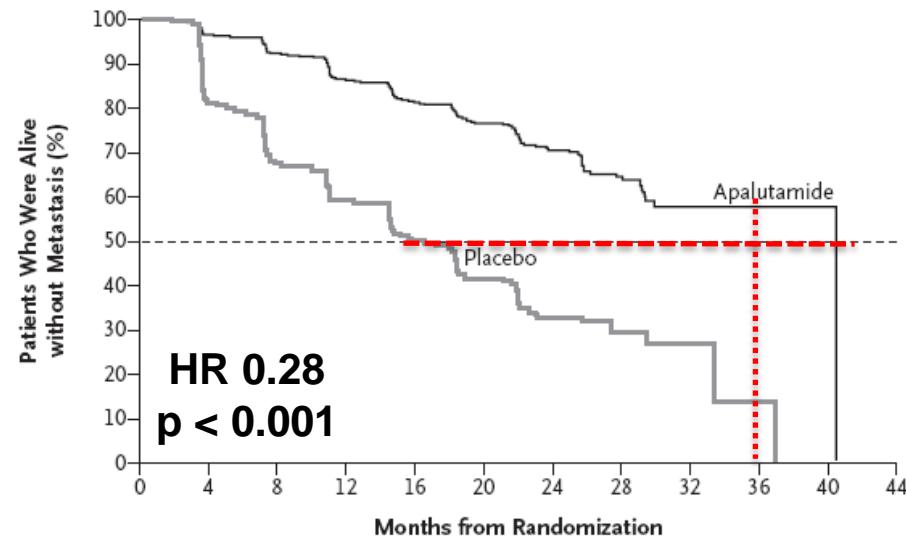
Metastasis-Free survival



Apalutamide



Enzalutamide



Darolutamide

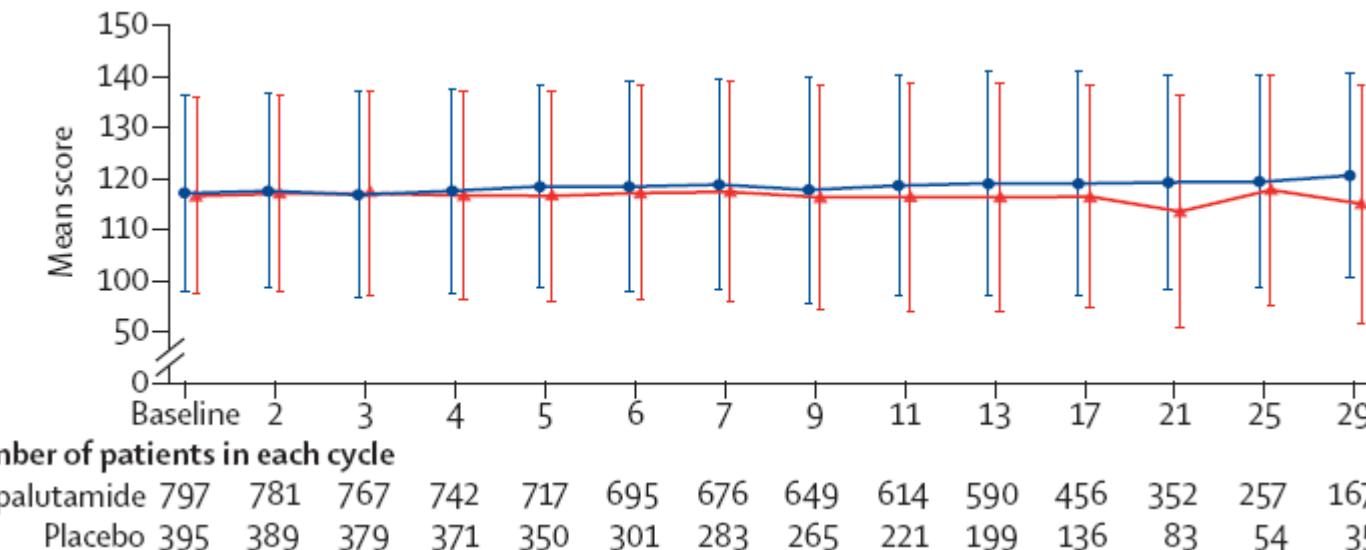
Secondary end points

	Apalutamide SPARTAN	Enzalutamide PROSPER	Darolutamide ARAMIS
Efficacy	TTPP NR vs. 3.7 mo HR 0.06 (95% CI 0.05 – 0.08)	37.2 mo vs. 3.9 mo HR 0.07 (95% CI 0.05 – 0.08)	33.2 mo vs. 7.3 mo HR 0.13 (95% CI 0.11–0.16)
	PFS 40.5 vs. 14.7 mo HR 0.29 (95% CI 0.24 – 0.36)	Not reported	36.8 vs. 14.8 mo HR 0.38 (0.32–0.45)
	Time to symptom. progression NR fav. apalutamide HR 0.45 (0.32–0.63)	Not reported	40.3 vs. 25.4 mo HR 0.65 (0.53-0.79)
	Time to subseq. therapy NR fav. apalutamide HR 0.44 (0.29–0.66)	39.6 vs. 17.7 mo HR 0.21 (0.17–0.26)	NR vs. 38.2 mo HR 0.43 (0.31–0.60)
	OS (Interim analysis) NR vs. 39 mo HR 0.70 , p = 0.07	NR fav. enza HR 0.80 p = 0.15	NR fav. Darolut HR 0.71 , p = 0.045

Secondary end points

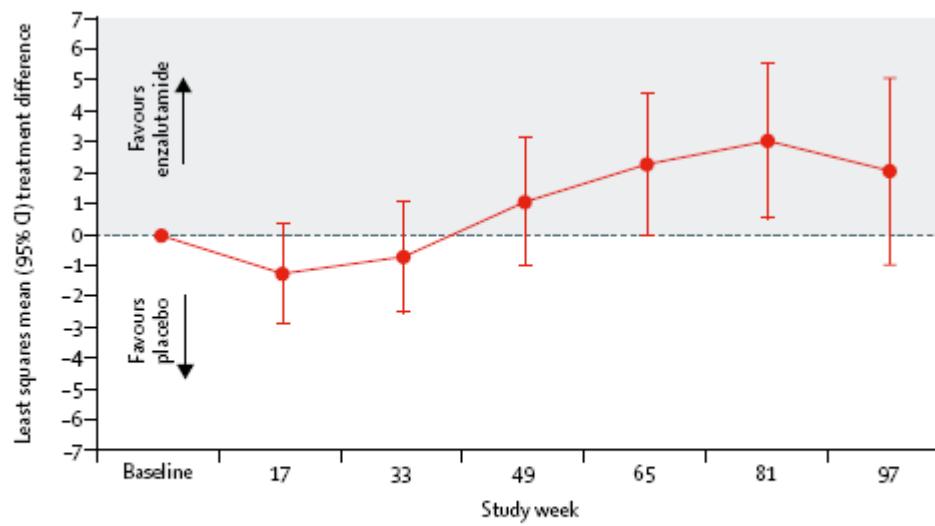
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	OS (Interim analysis) NR vs. 39 mo HR 0.70 , p = 0.07	NR fav. enza HR 0.80 p = 0.15	NR fav. Darolut HR 0.71 , p = 0.045
Safety	AEs profile SAEs: 24.8% vs. 23.1% Discont. 10.6% vs. 7%	SAEs: 24% vs. 18% Discont. 9% vs. 6%;	SAEs: 24.8% vs. 20% Discont. 8.9% vs. 8.7%
	Most frequent ≥3 AEs Hypert. 14.3% vs. 11.8% Rash: 5.2% vs. 0.3% Fracture: 2.7% vs. 0.8% Falls: 1.7% vs. 0.8%	Hypert. 5% vs. 2% Card. Ev. 4% vs. 2% Fatigue: 3% vs. 1%	Hypert. 3.1% vs. 2.2% Coronary-disorders: 1.7% vs. 0.4%

Impact on Health-related QoL FACT-P Score



Apalutamide

Saad , Lancet Oncol 2018



Enzalutamide

	..	815	718	621	522	427	354
Enzalutamide	..	815	718	621	522	427	354
Placebo	..	403	329	239	183	139	90

Tombal , Lancet Oncol 2019

comments and controversies

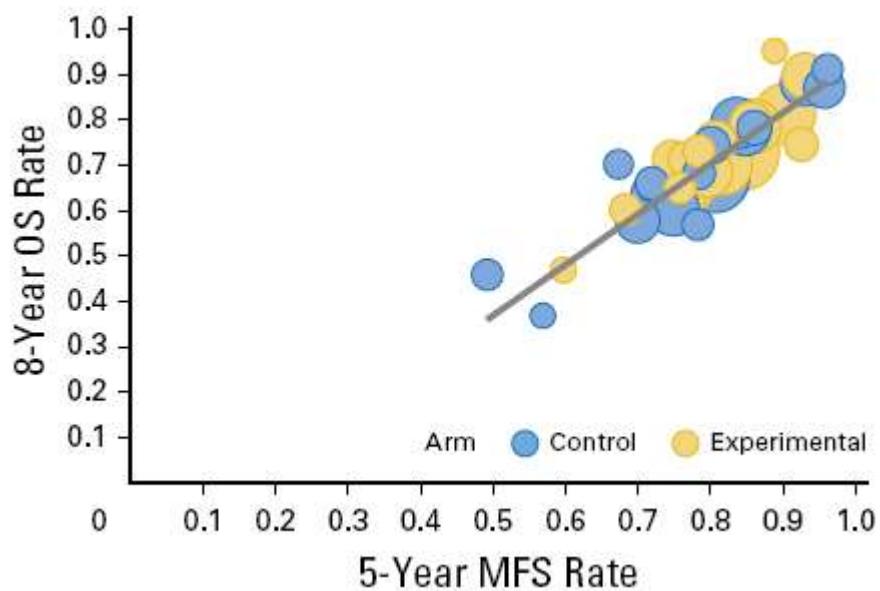
Metastasis-Free Survival in Prostate Cancer: Faster Drug Approvals, Better Drugs?

Potential limitations:

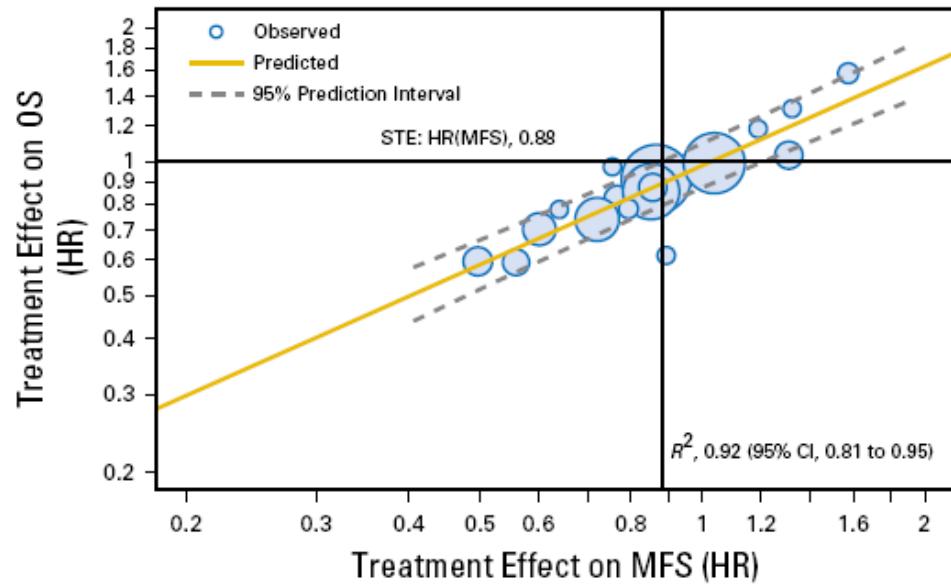
- local recurrence not excluded from MFS definition
- missing effect of site of metastases (visceral vs bone or lymph-nodes) and symptoms (symptomatic vs asymptomatic)
- influenced from frequency or modality of evaluation (CT vs PET vs MRI)

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

OS rate at 8-years vs MFS rate at 5-years

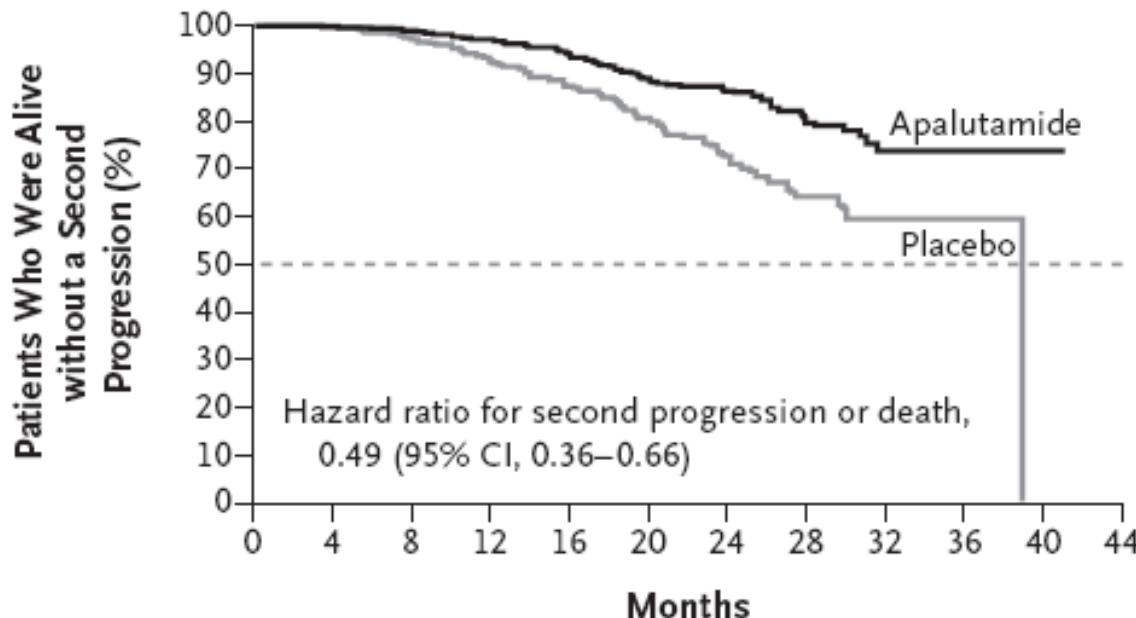


Treatment effects (HR) on OS vs Treatment effects on MFS (HR)



Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Secondary Progression-Free Survival



No. at Risk

Apalutamide	806	778	746	619	492	346	237	129	46	19	4	0
Placebo	401	386	357	279	206	150	87	39	14	2	0	0

Final remarks: nmCRPC

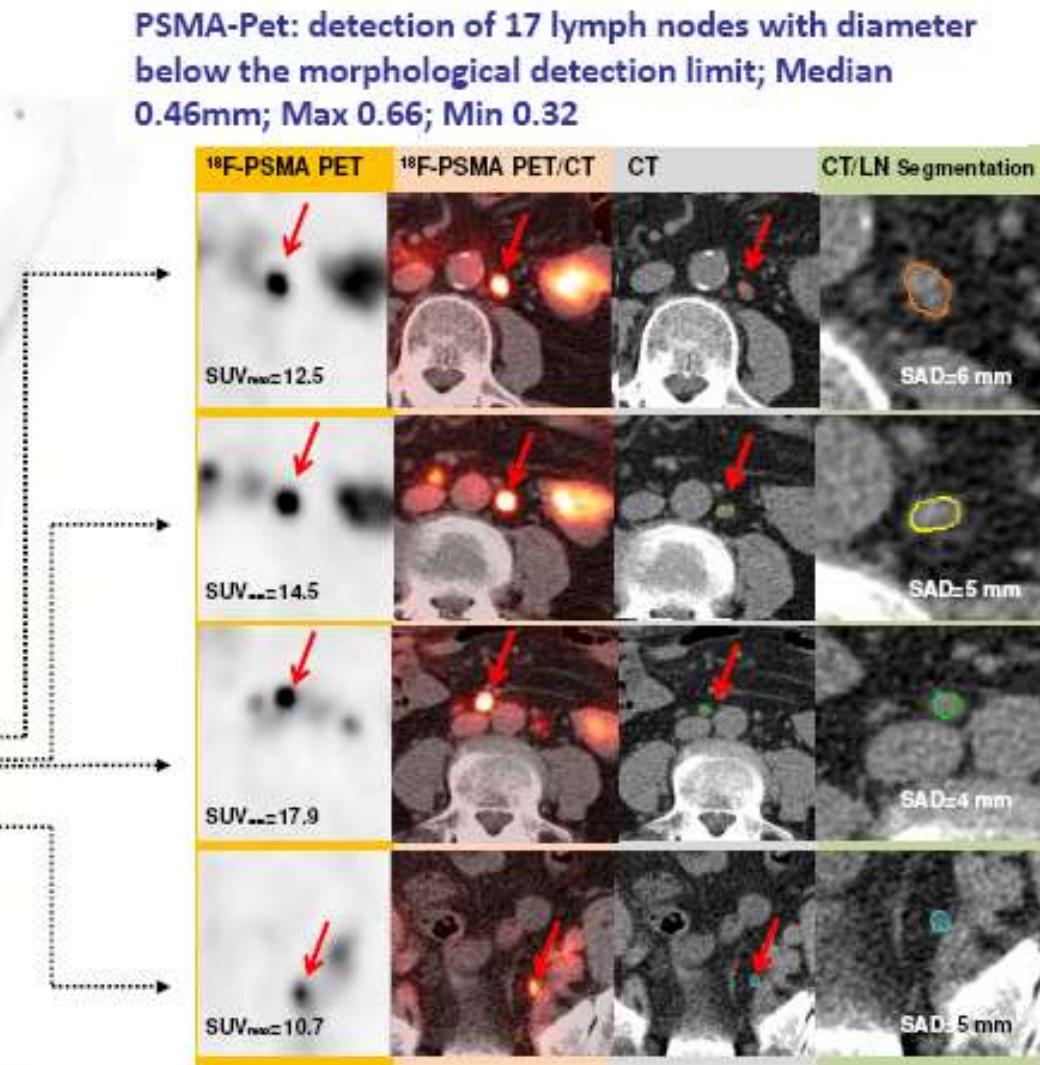
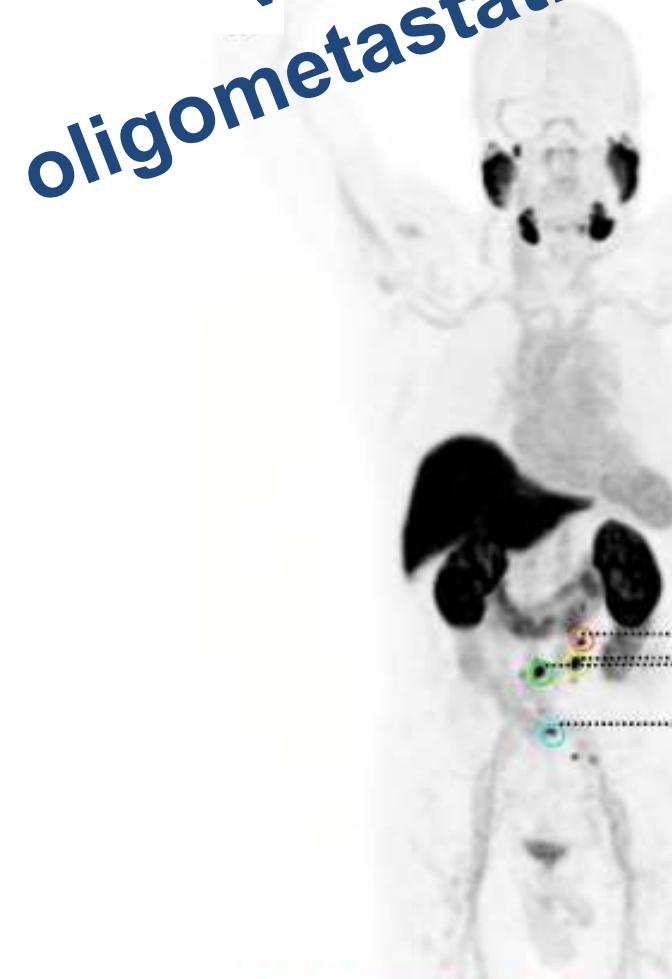
Enzalutamide, Apalutamide, Darolutamide

- Large benefit in MFS consistent in three randomized phase III trials
- Acceptable toxicity not effecting QoL
- Longer follow-up needed to assess OS benefit (likely)

Relevant considerations:

- Rare situation: nmCRPC High-risk (*PSA doubling time <10 mo*)
- Role of new generation imaging is an issue

nmCRPC vs oligometastatic



Little radioactivity in the bladder
Cleavage of the tracer in the kidneys
Renal storage of the chelator

Giesel et al., Clinical Genitourinary Cancer 2017

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Drugs approved for mCRPC

PRE-DOCE

Drug	control	OS Δ	HR	p
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
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

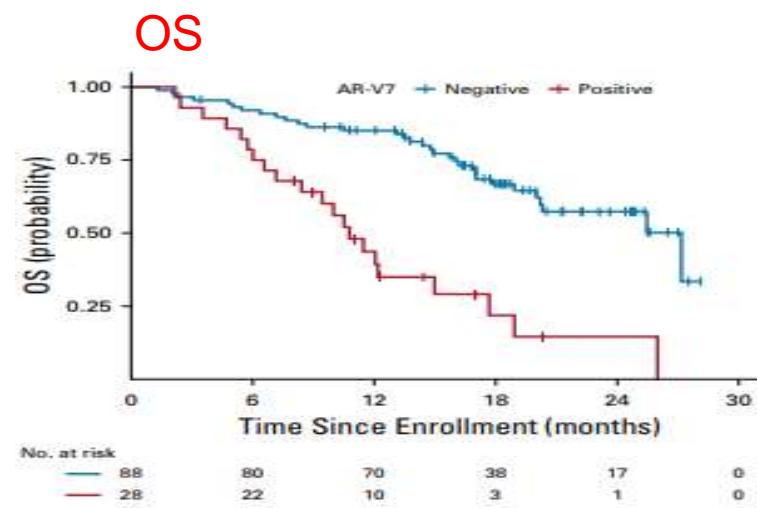
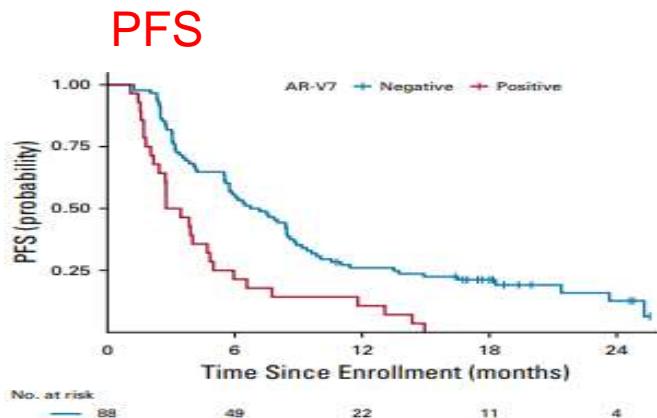
¹ Lancet 2013; ² NEJM 2014; ⁴ NEJM 2004; ⁵ Lancet 2010; ⁶ NEJM 2011; ⁷ NEJM 2012; ^{3,8} Lancet 2014

Cross resistance between Abiraterone and Enzalutamide

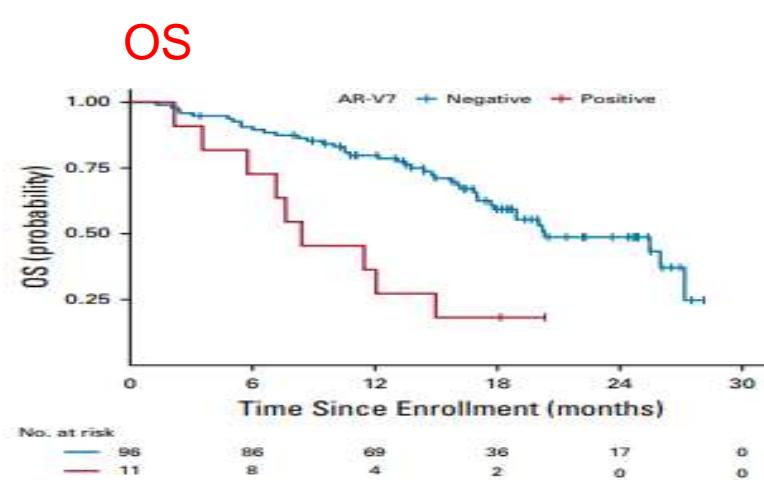
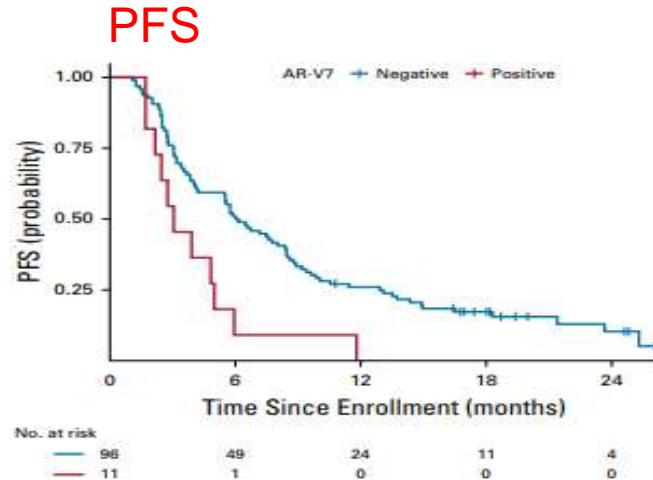
Author	Year published	N pts	Duration of 2 nd treatment	↓ PSA ≥ 50%	Median PFS
ENZ → ABI					
Loriot et al.	2013	38	3 mo	8%	2.7 mo
Noonan et al.	2013	30	13 wks	3%	3.6 mo
ABI → ENZ					
Schrader et al.	2013	35	4.9 mo	29%	-
Badrising et al.	2014	61	3 mo	21%	-
Bianchini et al.	2014	39	2.9 mo	23%	-
Schmid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

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



Epic- test



PSA decline

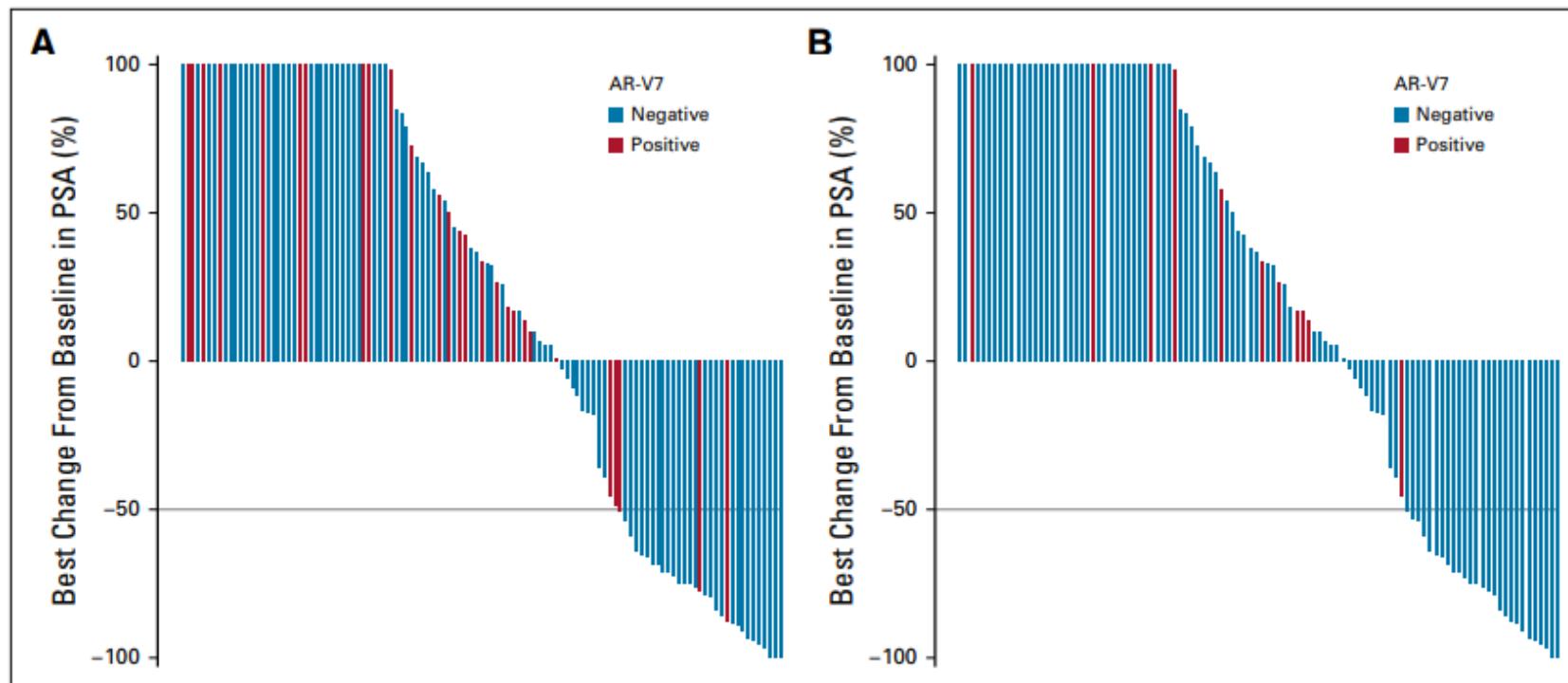
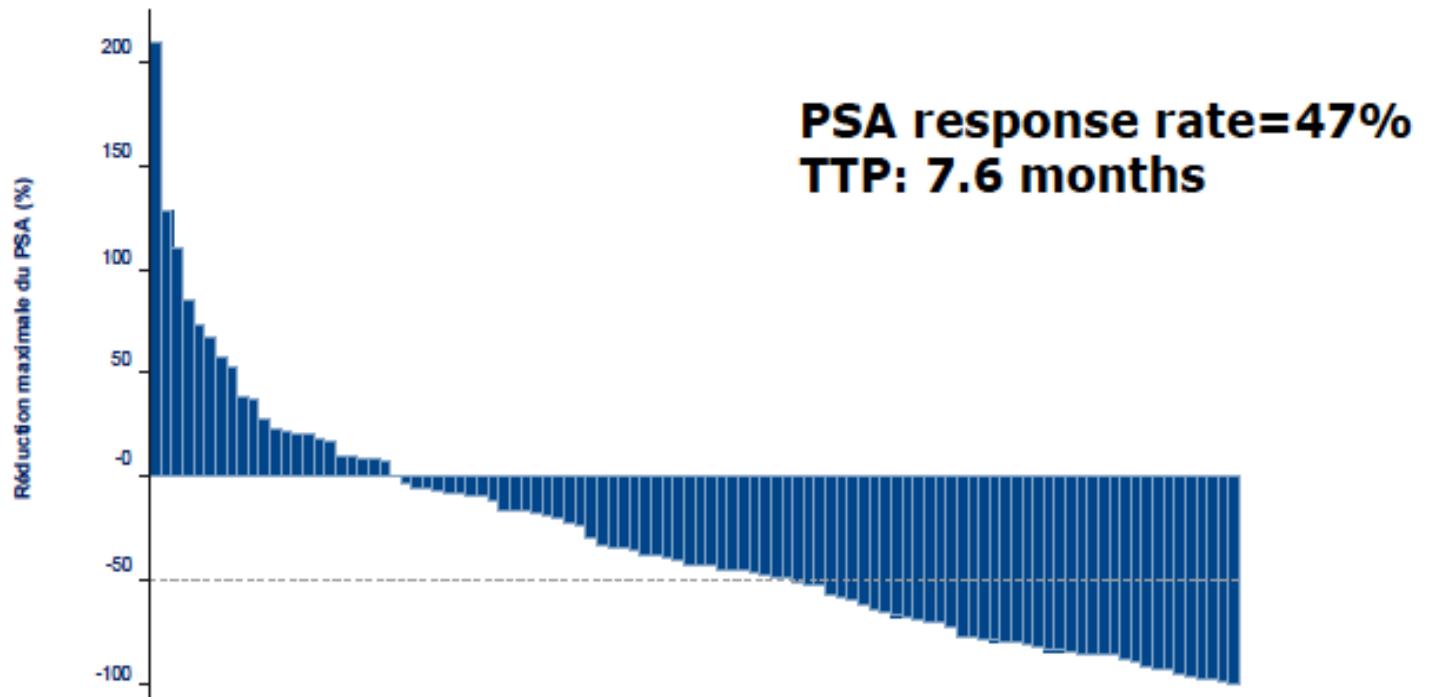


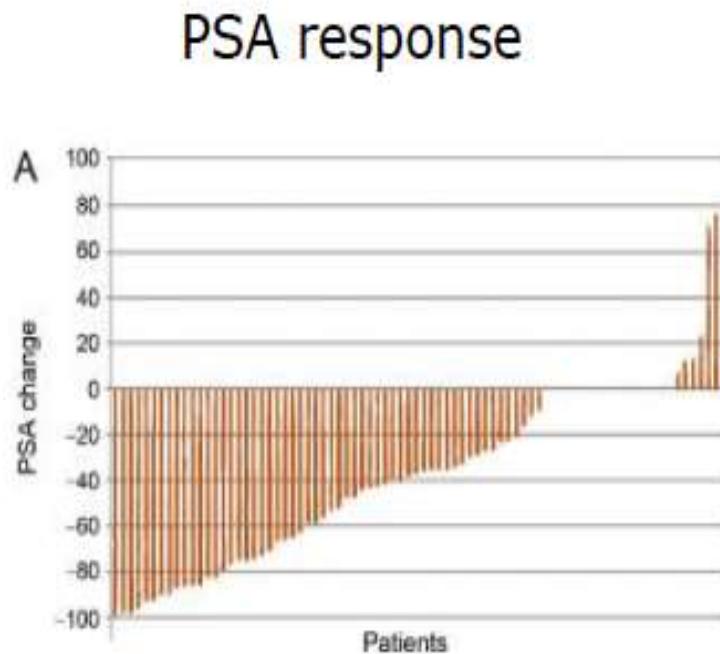
FIG 3. Prostate-specific antigen (PSA) waterfall plots of the best overall confirmed PSA decline from baseline with abiraterone or enzalutamide according to (A) Johns Hopkins University circulating tumor cell androgen receptor splice variant 7 (AR-V7) status and (B) Epic Sciences circulating tumor cell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

Docetaxel post abiraterone (COU-302)

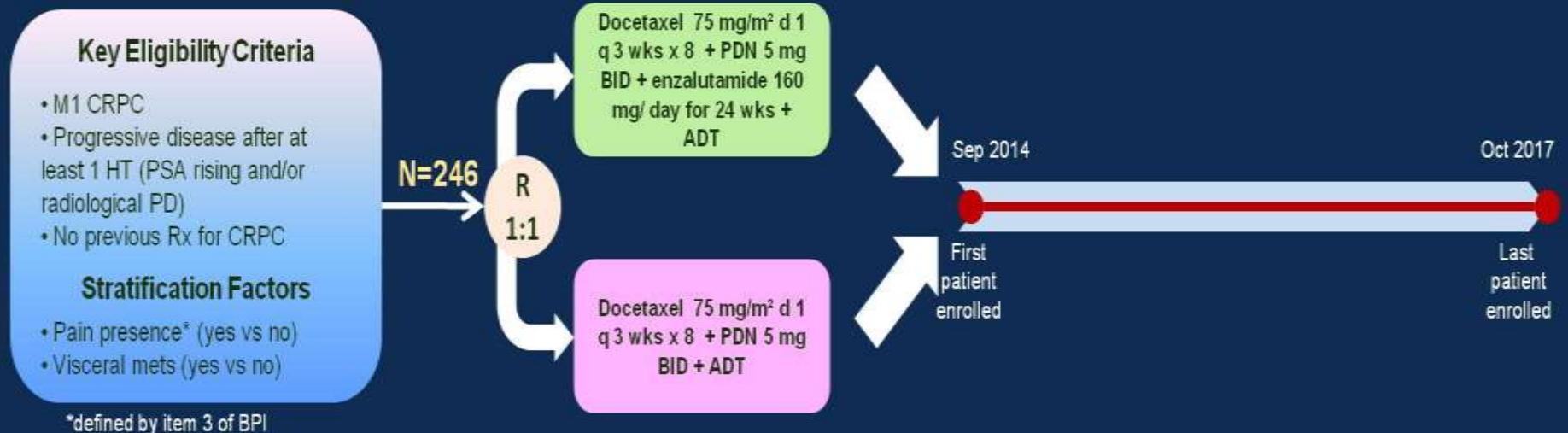


Cabazitaxel post-abiraterone and docetaxel

- 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



CHEIRON Study Design



Primary endpoint

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

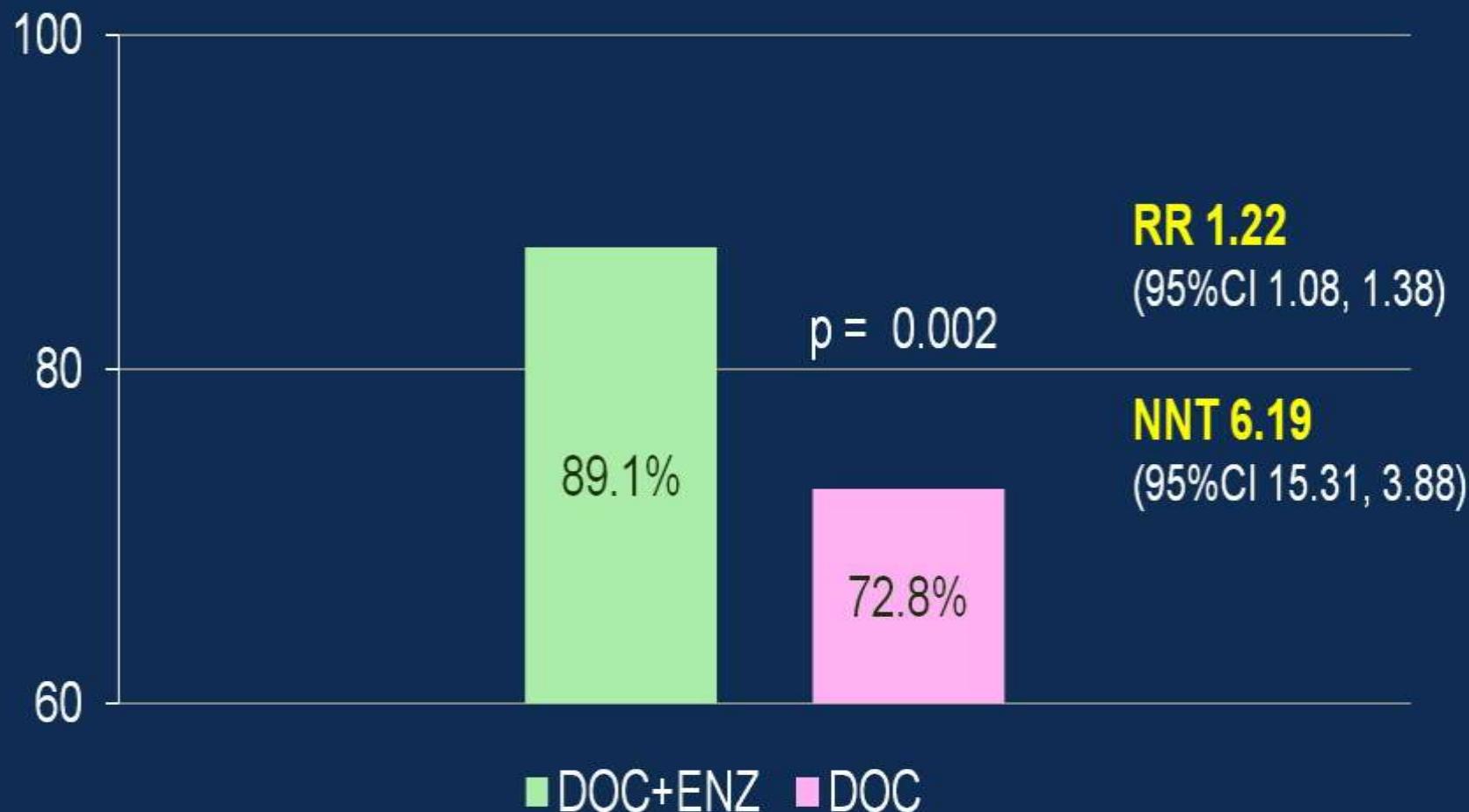
Statistical Design

- 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

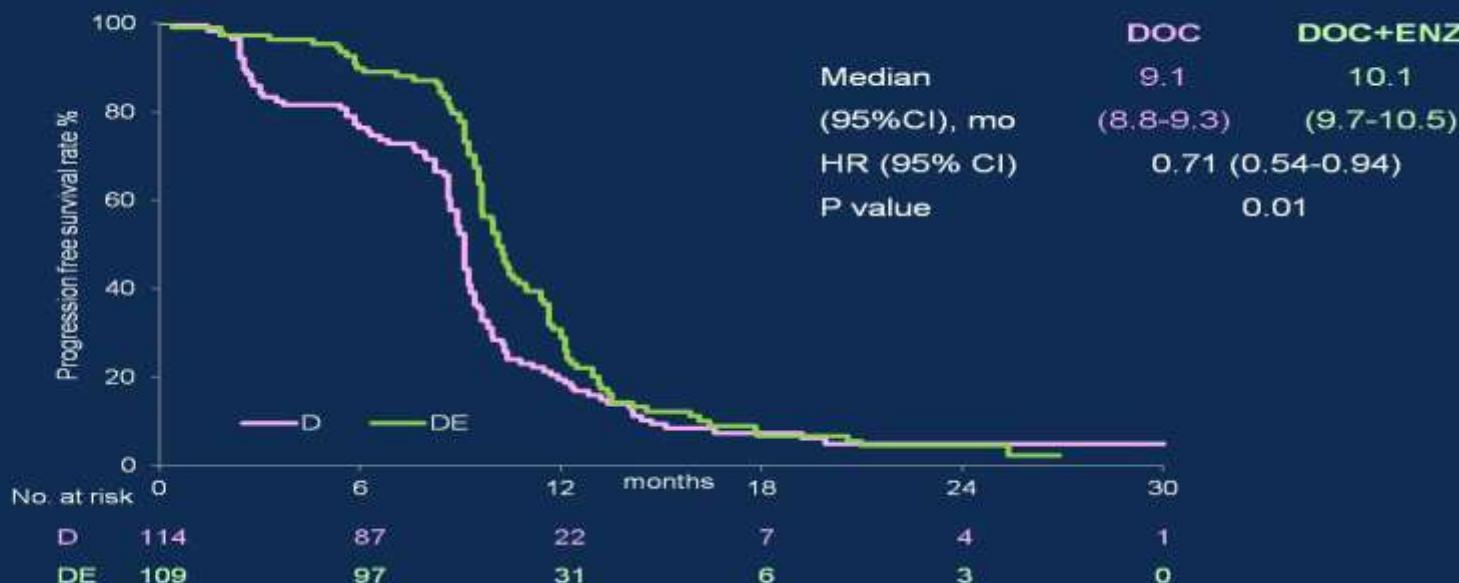
Secondary endpoints

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

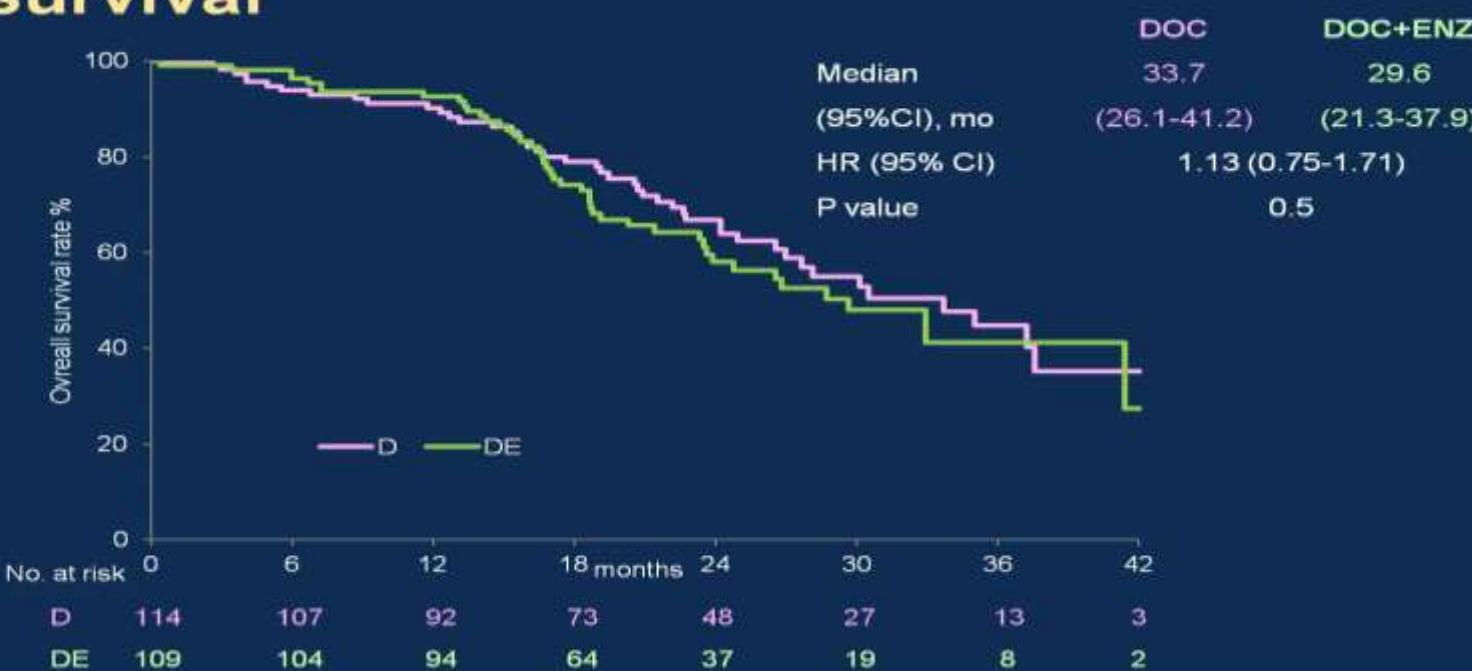
Rate of progression disease free patients at 6 mos after docetaxel start (primary endpoint)



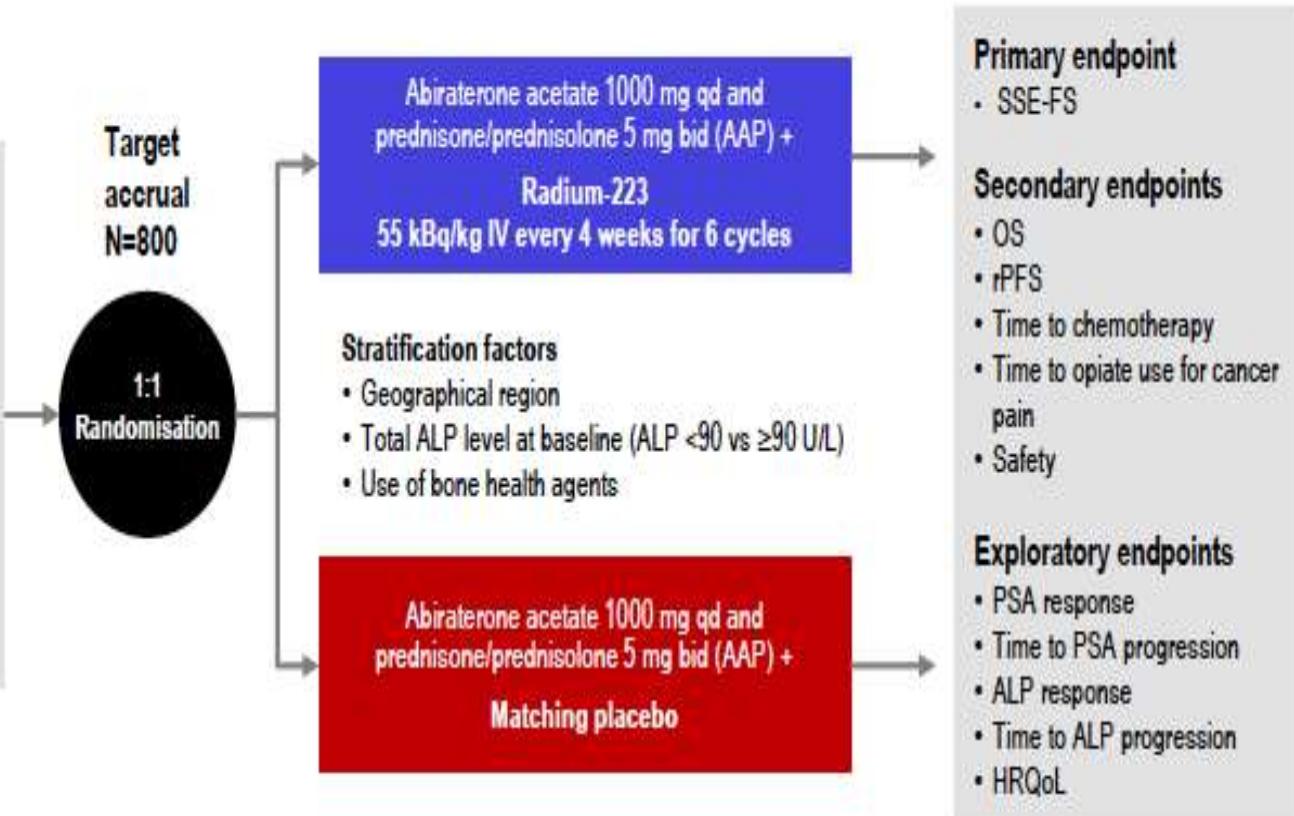
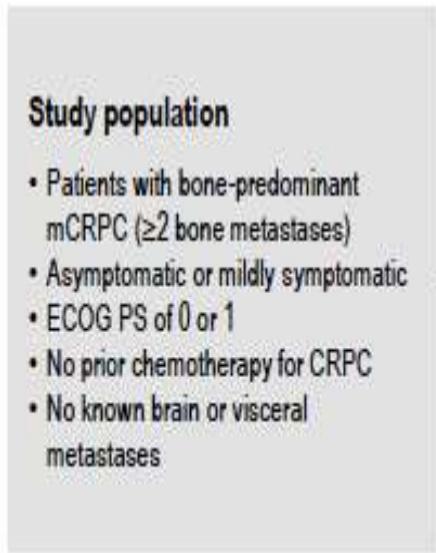
Progression free survival



Overall survival



ERA 223 (NCT02043678)

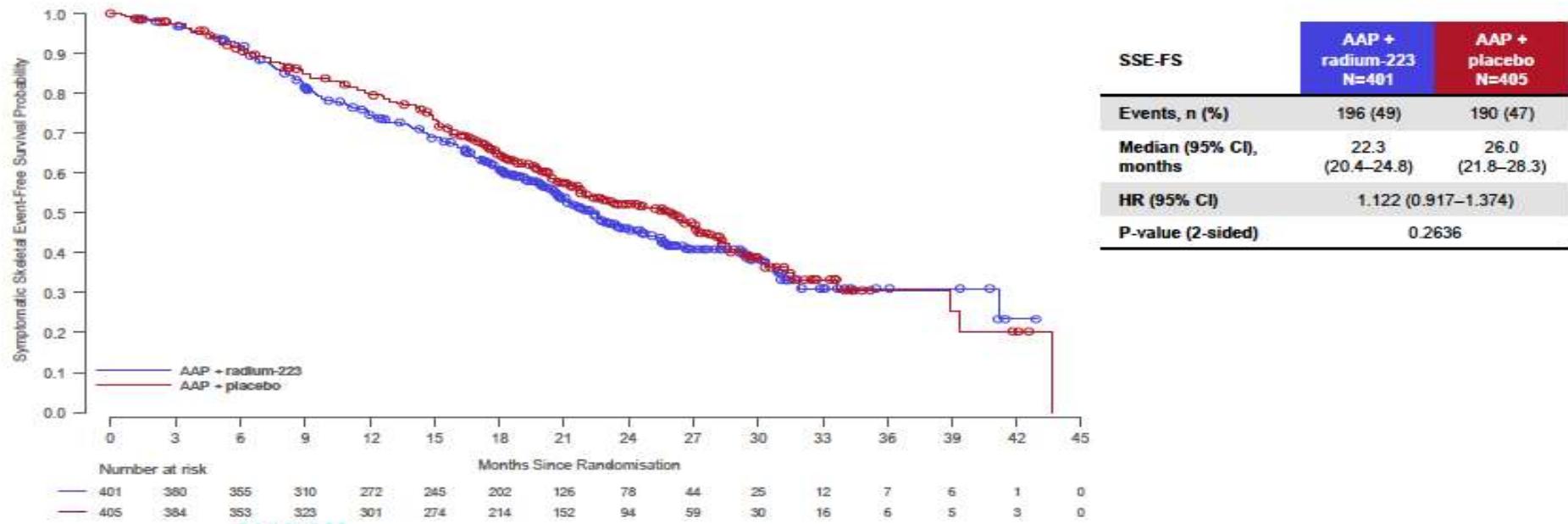


389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

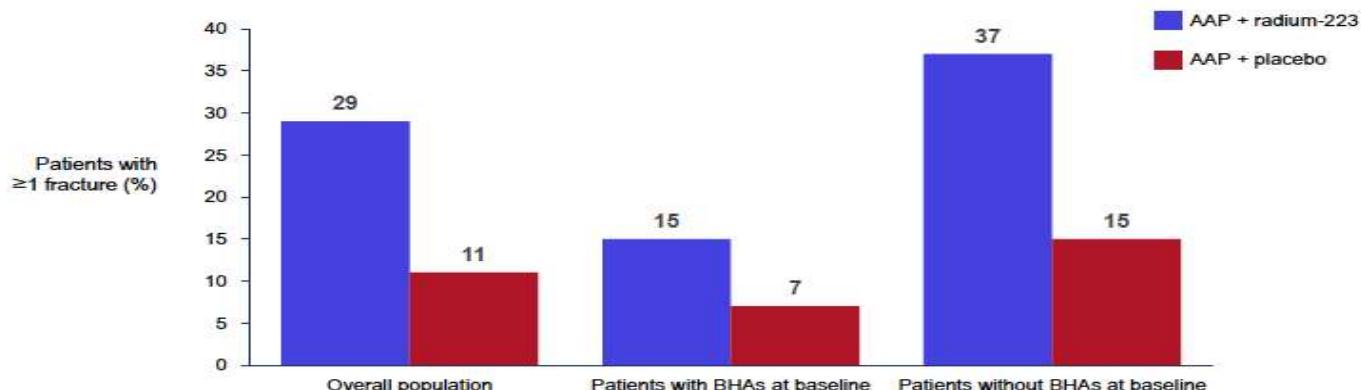
Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; initiation during the study prohibited to prevent confounding effects.

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)



Post-Hoc Subgroup Analysis of Fractures by Baseline BHA Use





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.

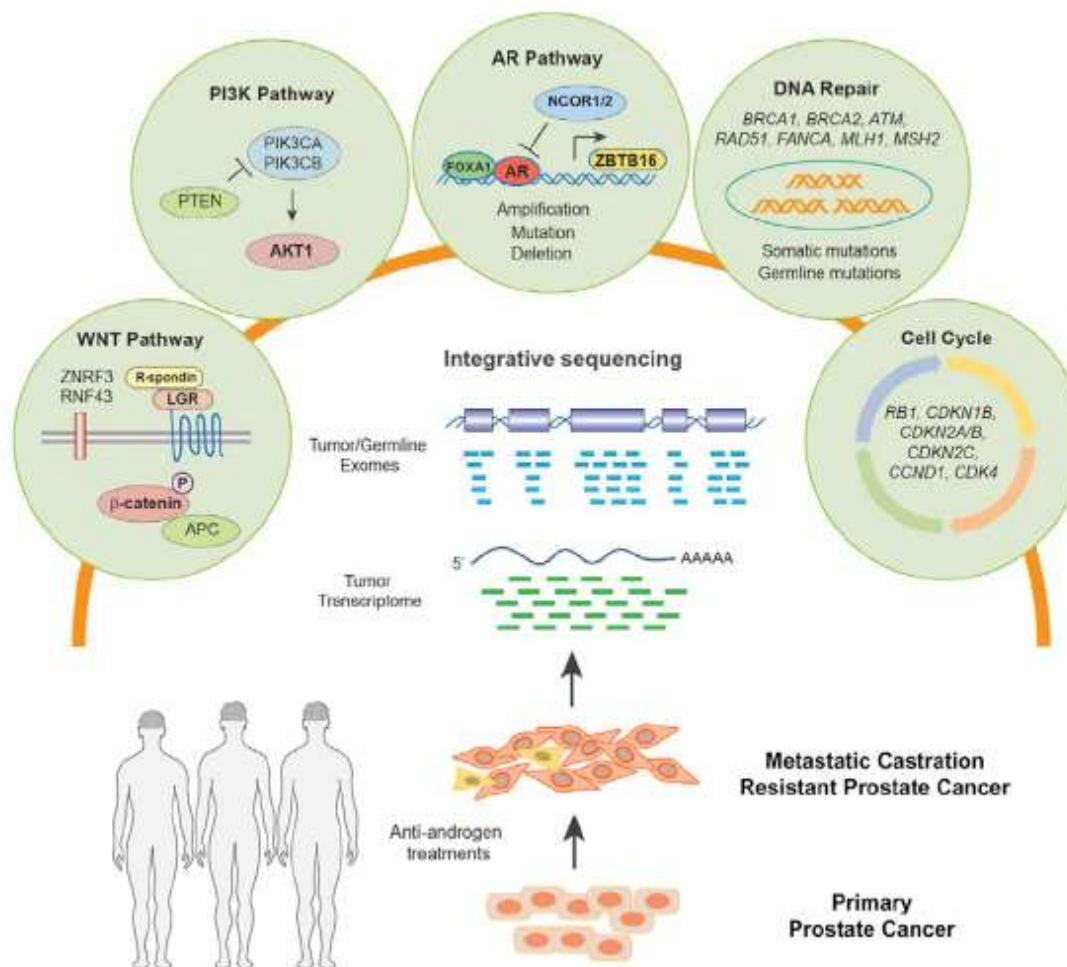


Xofigo in monoterapia o in associazione con un analogo dell'ormone di rilascio dell'ormone luteinizzante (*Luteinising Hormone-Releasing Hormone, LHRH*) è indicato per il trattamento di pazienti adulti affetti da carcinoma prostatico metastatico resistente alla castrazione (*metastatic Castration-Resistant 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 sistematici disponibili per il mCRPC.

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Integrative Clinical Genomics of Advanced Prostate Cancer

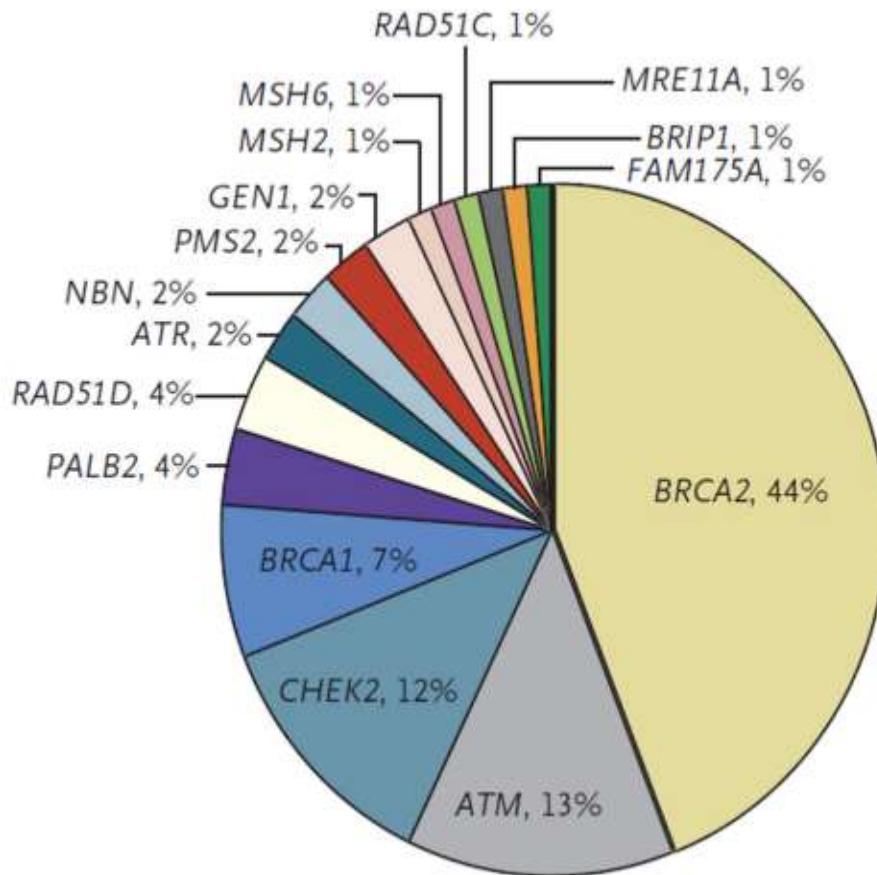


Highlights

- A multi-institutional integrative clinical sequencing of mCRPC
- Approximately 90% of mCRPC harbor clinically actionable molecular alterations
- mCRPC harbors genomic alterations in *PIK3CA/B*, *RSPO*, *RAF*, *APC*, β -catenin, and *ZBTB16*
- 23% of mCRPC harbor DNA repair pathway aberrations, and 8% harbor germline findings

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer



- 1/7 men with mPCa have inheritable genomic deleterious alteration.
- Among 700 mCRPC patients sequenced. 11.8% harboured germline mutations in DNA-repair genes.
- BRCA 1/2 and ATM are the commonest mutations.



- Treatment according to physician's choice.

- *Follow-up established by protocol: 3-4 weekly PSA, 12-16 weeks imaging re-evaluation

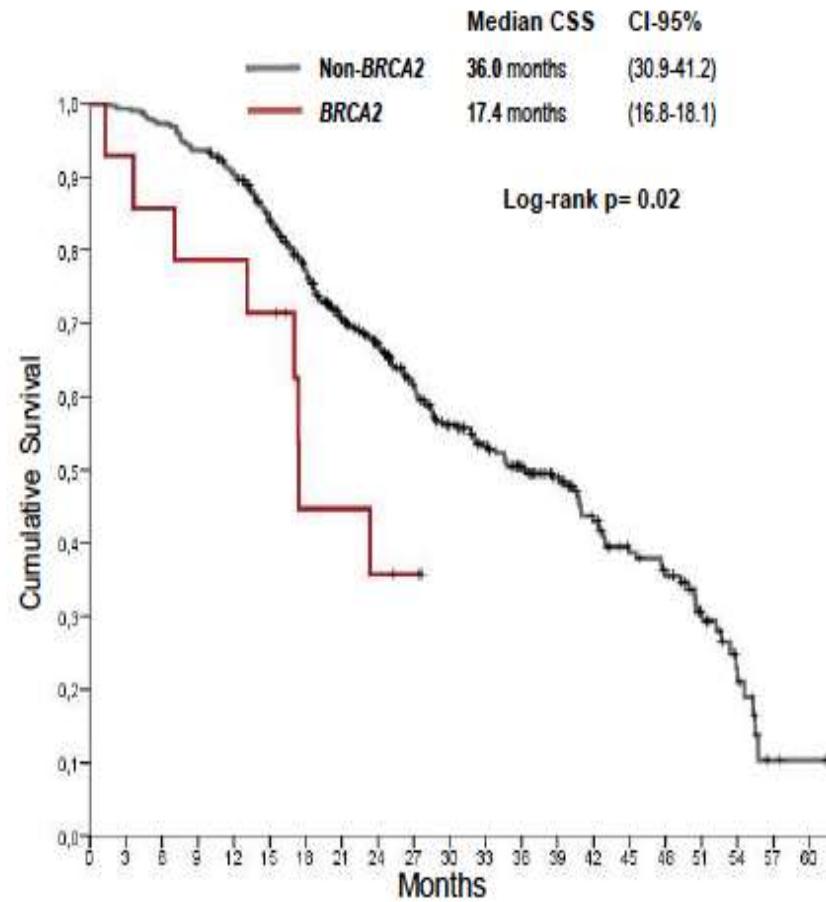
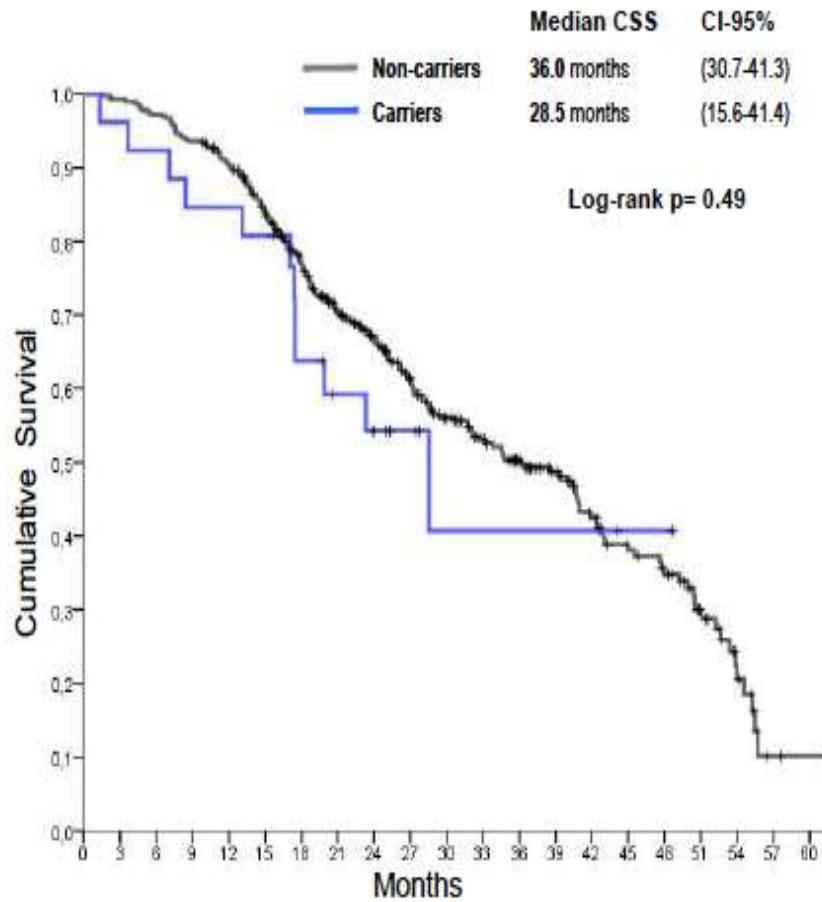
Sample size¹

Primary endpoint: CSS of *ATM*, *BRCA1*, *BRCA2*, *PALB2* germline mutation carriers vs non-carriers

CSS control arm	% Risk Group (<i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i>)	HR	Enrolment	Follow up	α	β	Total size	Events
30 months (m)	5%	3.0	30 m	8 m	0.05	0.20	408 pts	171

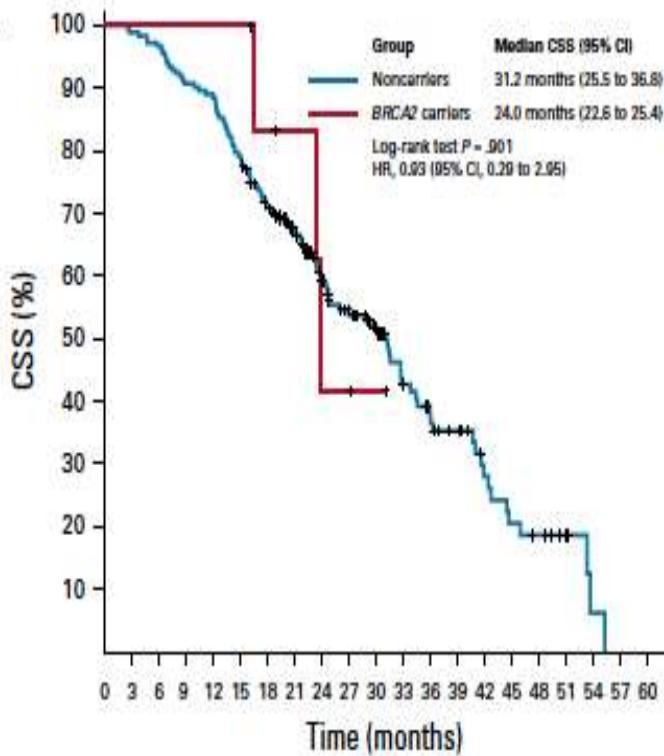
- Pre-planned statistical plan included the analyses by treatment and specific gene subgroups (*BRCA2* vs Non-*BRCA2* mutation carriers)

Cause Specific Survival from mCRPC

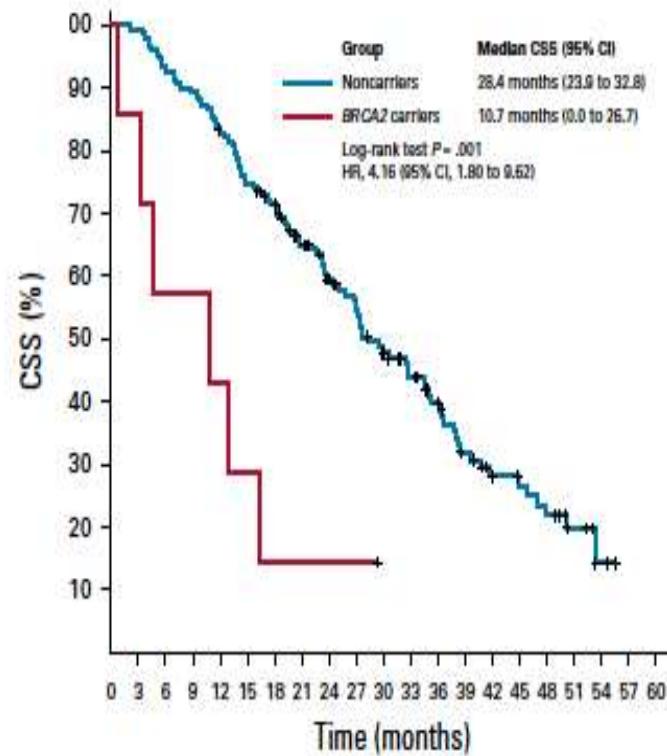


Impact of treatment sequencing in BRCA2 carriers

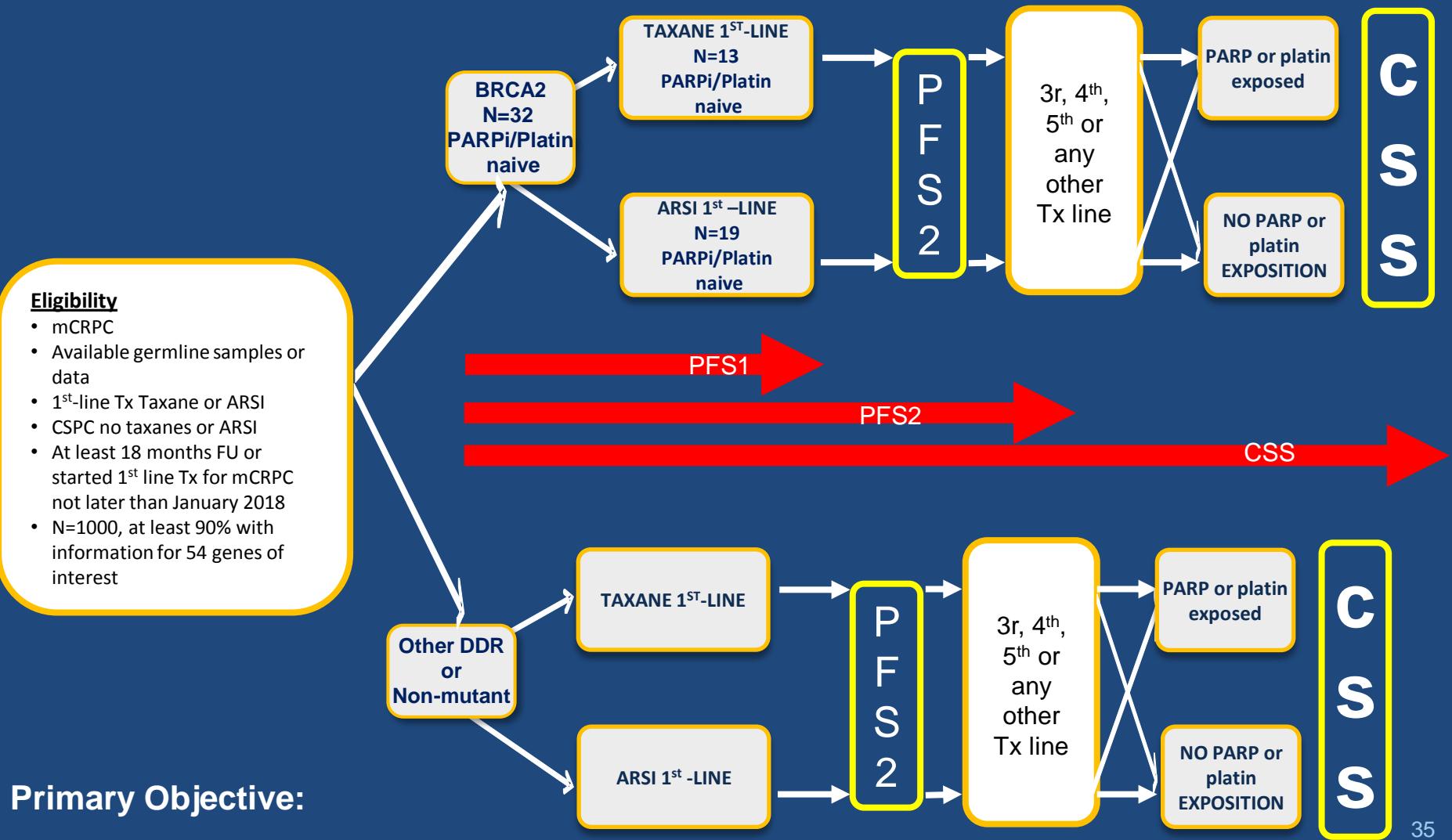
ASI-Tax



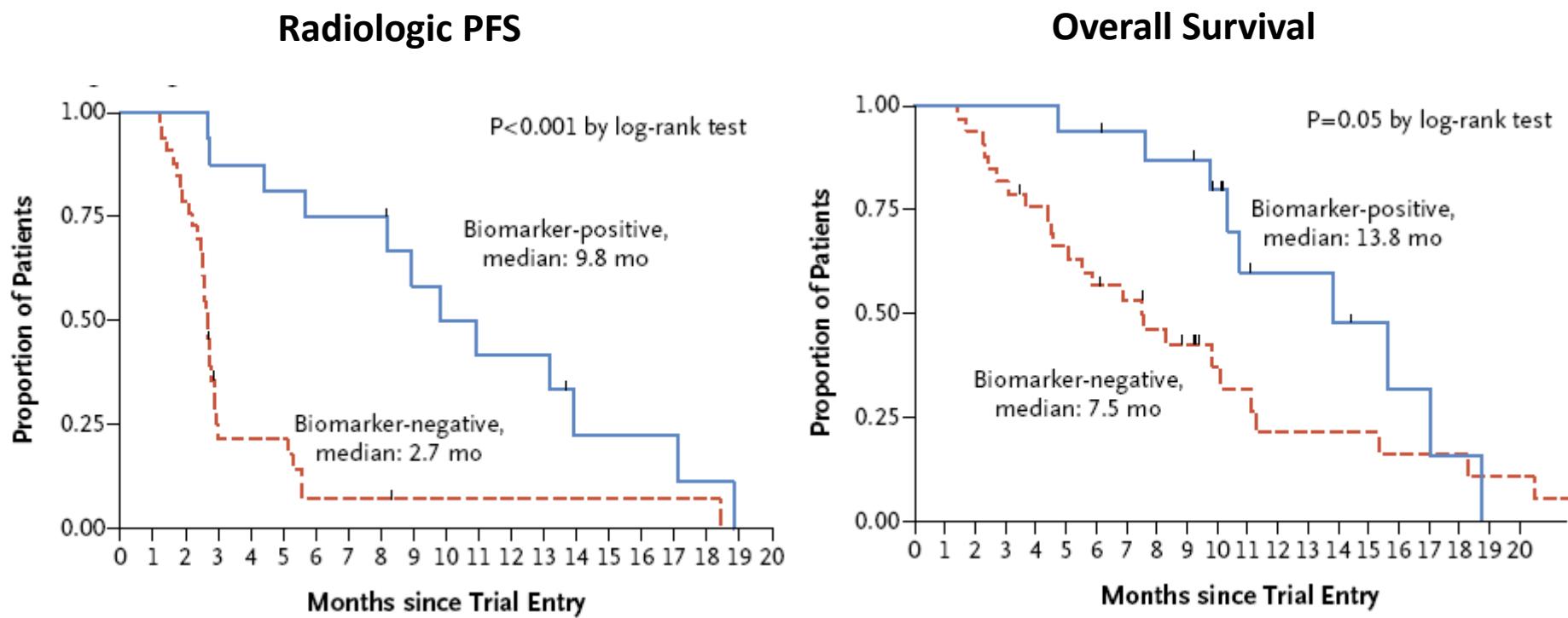
Tax-ASI



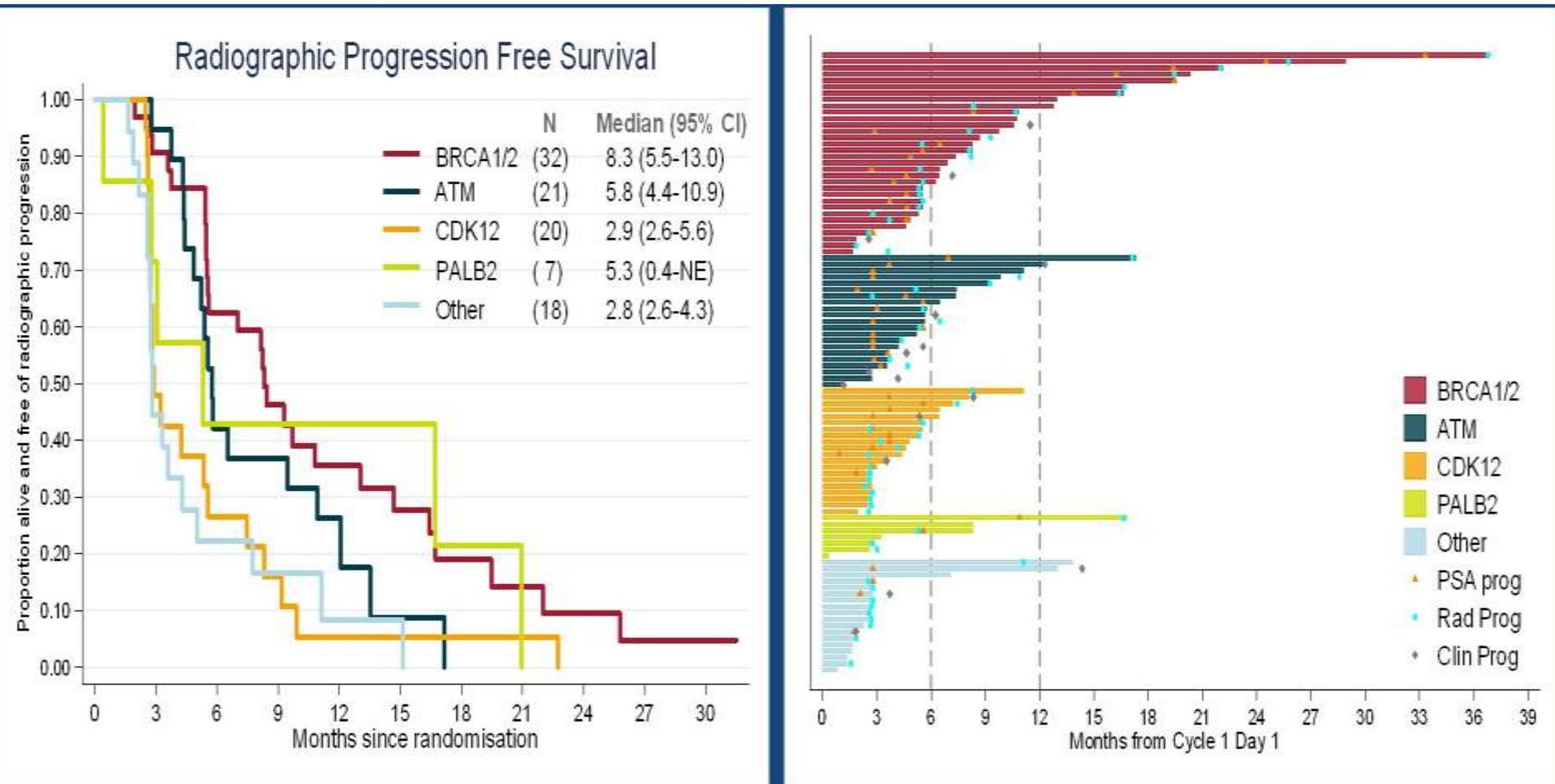
BRCA2MEN – Design



DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

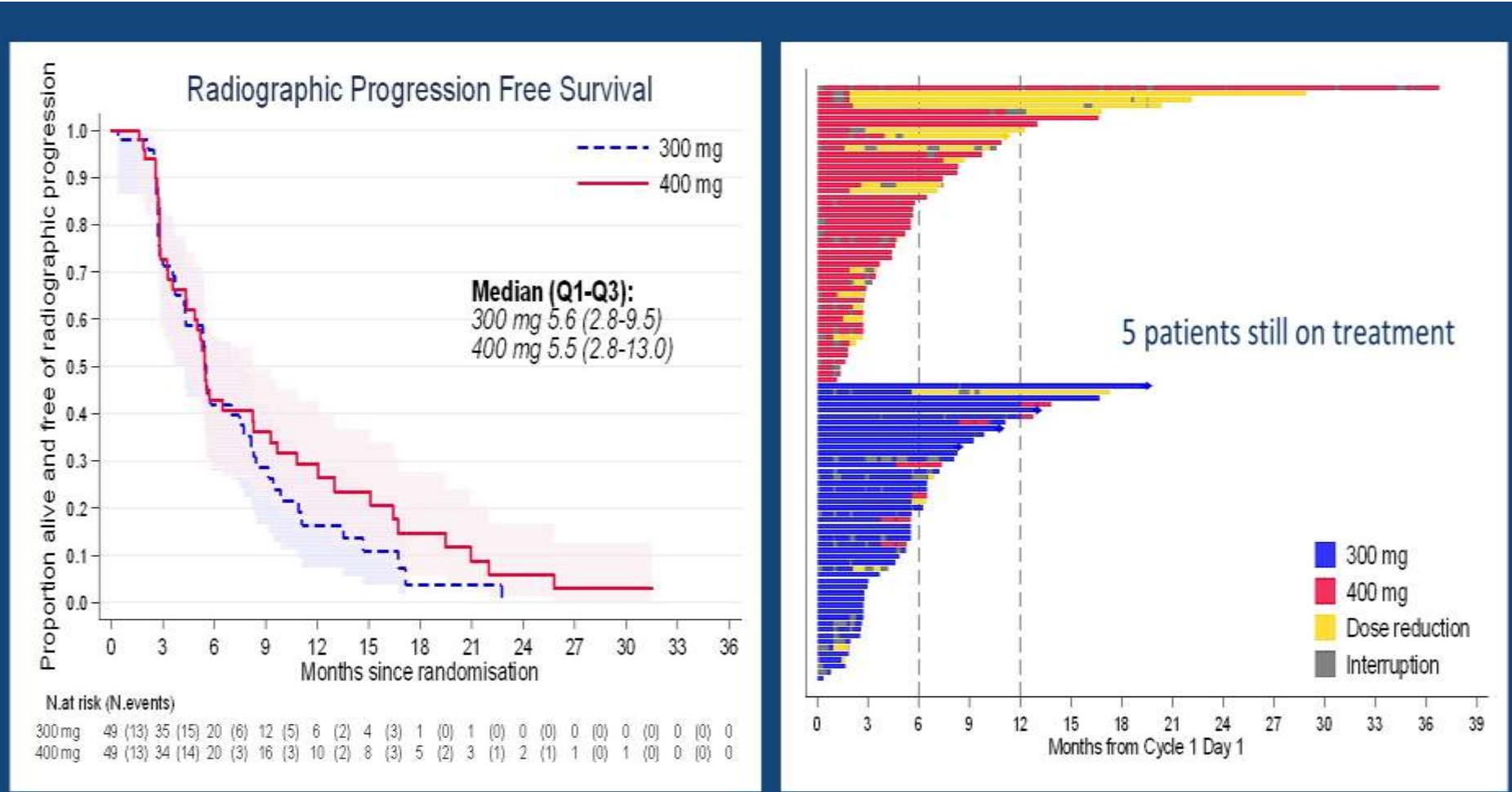


Gene subgroup may matter for olaparib sensitivity



*One patient with BRCA1/2+CDK12+Other mutations and two patients with PALB2+Other mutations were analysed in the BRCA1/2 and PALB2, respectively.

TOPARP B: OLAPARIB DOSE MAY MATTER



Analyses performed on ITT population (all 98 patients)

NCCN guidelines and a consensus conference support germline testing for gDDR defects

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

Veda N. Giri, Karen E. Keadle, William K. Kelly, Warren Abida, Gerald L. Andriole, Chris H. Bergman, Justin E. Belchman, Mitchell C. Besser, Amrit Blanca, Arthur Barnett, William J. Catalona, Kathleen A. Cooney, Matthew Cooperberg, David E. Crawford, Robert B. Den, Adam P. Dicker, Scott Eggenstein, Neil Fleshner, Matthew L. Fronstin, Franklin C. Hany, John Hoffman-Crosier, Mark D. Harwez, Colene Hjeltnes, William S. Isaacs, Christopher J. Kane, Philip Kantoff, R. Jeffrey Karnes, Lawrence J. Kornblith, Eric A. Klein, Daniel W. Lin, Kevin R. Leighlin, Grace Lin-Hiau S. Bruce Mallinowicz, Mark J. Massie, James R. Marks, Peter A. McCue, Martin M. Minas, Todd Morgan, Judi M. Meul, Ronald E. Myers, Sarah M. Nelson, Elias Obeid, Christian P. Parkwick, Stephen C. Phillips, David F. Penson, Daniel Pinsky, Curtis A. Pittman, Robert Plaskett, Peter A. Pinto, Wendy Pogue, Ganesh V. Raj, Timothy R. Rebbeck, Mark E. Rhodes, Matt T. Rosenberg, Howard Sandler, Oliver Sartor, Edward Schaeffer, Gordon F. Schwartz, Mark S. Shukin, Neal D. Shore, Brian Staskin, Howard R. Soule, Scott A. Timmins, Edward J. Trabishki, Robert Uzzo, Donald J. Vassal, Grenda, Patrick C. Walsh, Carl J. Weis, Richard Wender, and Leonard G. Gammie

Author affiliations and support information, if applicable appear at the end of this article.

Published in *JCO* on December 13, 2017.

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ABSTRACT

Purpose

Guidelines are limited for genetic testing for prostate cancer (PCA). The goal of this conference was to develop an expert consensus-driven working framework for comprehensive genetic evaluation of inherited PCA in the multigene testing era addressing genetic counseling, testing, and genetically informed management.

Methods

An expert consensus conference was convened including key stakeholders to address genetic counseling and testing, PCA screening, and management informed by evidence review.

Results

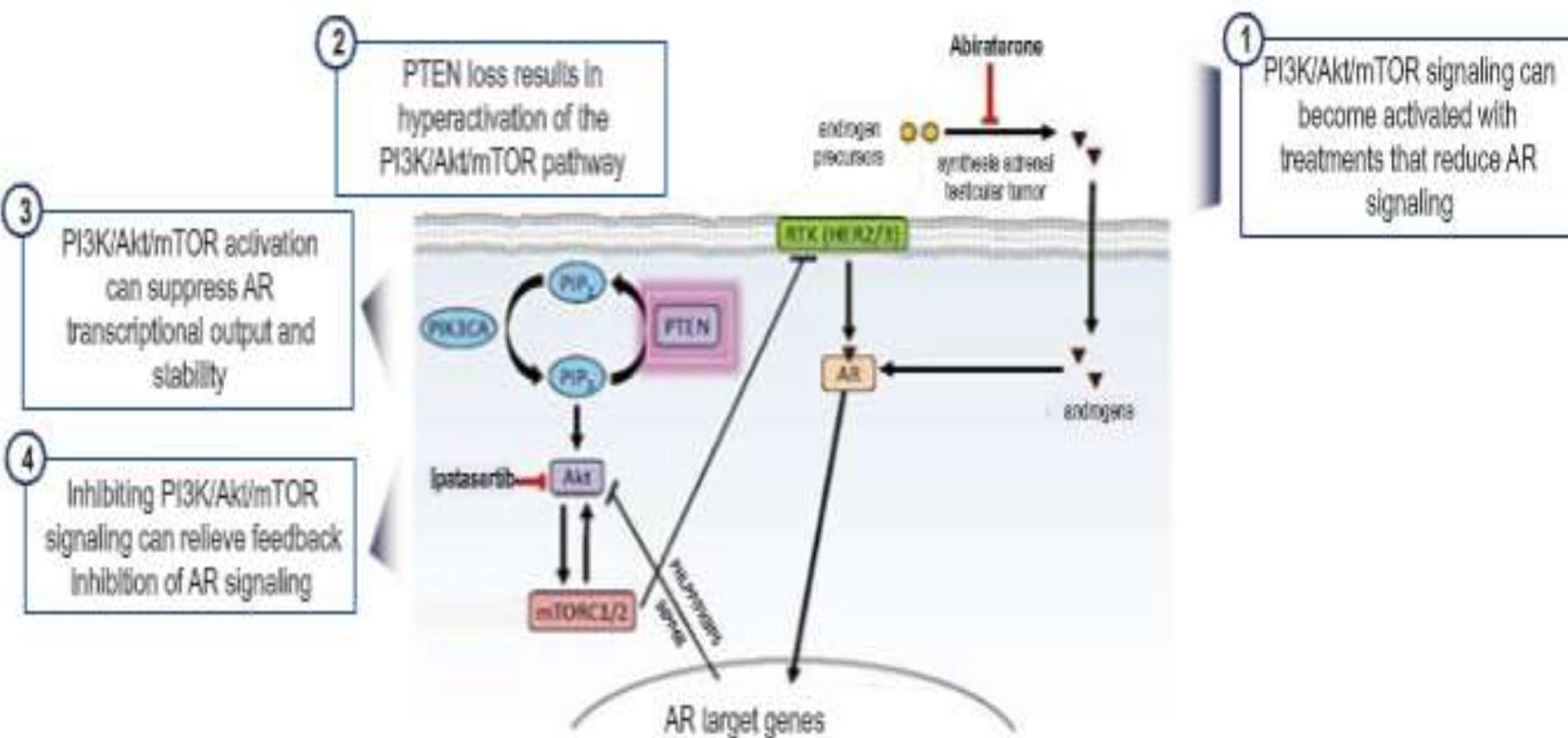
Consensus was strong that patients should engage in shared decision making for genetic testing. There was strong consensus to test *HDXB13* for suspected hereditary PCA, *BRCA1/2* for suspected hereditary breast and ovarian cancer, and DNA mismatch repair genes for suspected Lynch syndrome. There was strong consensus to factor *BRCA2* mutations into PCA screening discussions. *BRCA2* achieved moderate consensus for factoring into early-stage management discussion, with stronger consensus in high-risk/advanced and metastatic setting. Agreement was moderate to test all men with metastatic castration-resistant PCA, regardless of family history, with stronger agreement to test *BRCA1/2* and moderate agreement to test ATM to inform prognosis and targeted therapy.

Conclusion

To our knowledge, this is the first comprehensive, multidisciplinary consensus statement to address a genetic evaluation framework for inherited PCA in the multigene testing era. Future research should focus on developing a working definition of familial PCA for clinical genetic testing, expanding understanding of genetic contribution to aggressive PCA, exploring clinical use of genetic testing for PCA management, genetic testing of African American males, and addressing the value framework of genetic evaluation and testing men at risk for PCA—a clinically heterogeneous disease.

- All patients with metastatic prostate cancer should get germline testing
- BRCA2 mutation testing recommended; relative risks of prostate cancer in these carriers
- But we need more data on how the other aberrations impact familial risk and what other factors increase that risk
- Nevertheless, because we have accumulating evidence that these aberrations have functional consequences, sensitizing to PARP inhibitors or platinum, we already have some evidence that they are significant

INTERACTION BETWEEN ANDROGEN RECEPTOR AND PI3K/AKT PATHWAYS

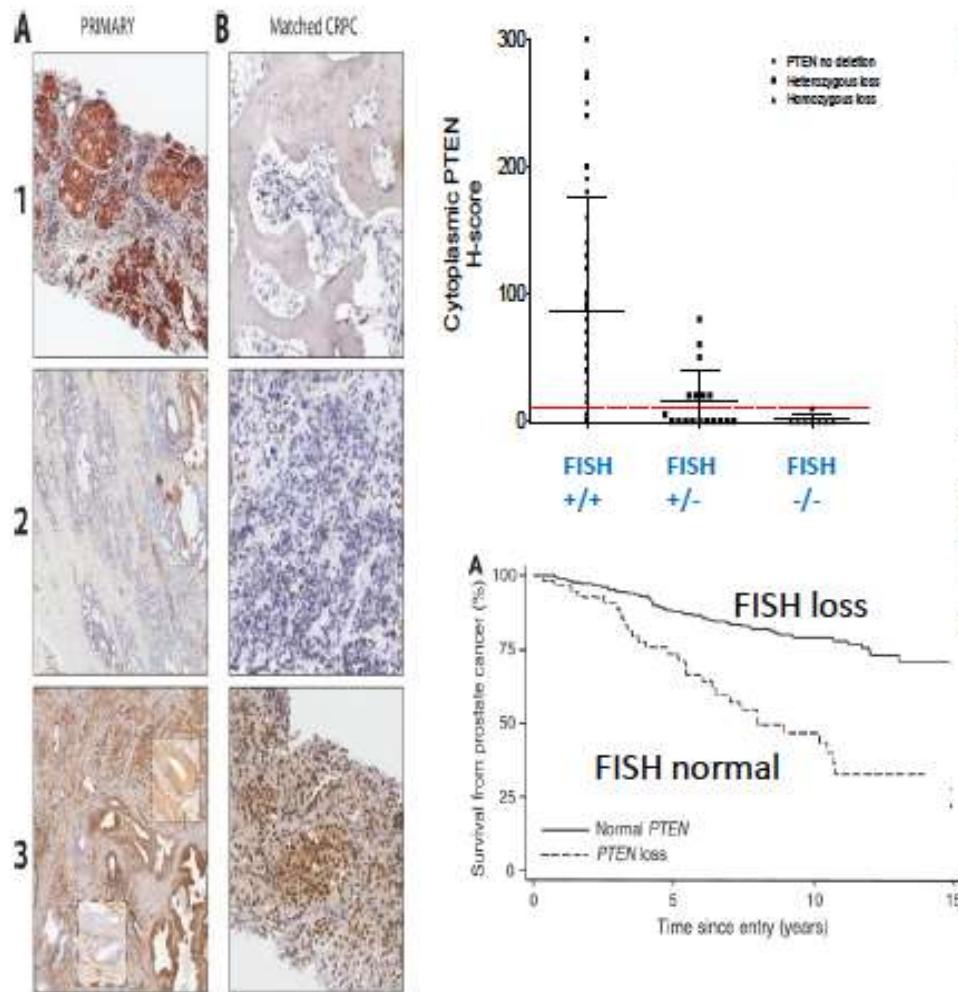


AKT, protein kinase B; AR, androgen receptor; mTOR, mammalian target of rapamycin; PIP₃, phosphatidylinositol-3-kinase; PIP₂, phosphatidylinositol-4,5-bisphosphate; PP2, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homology; RTK, receptor tyrosine kinase.

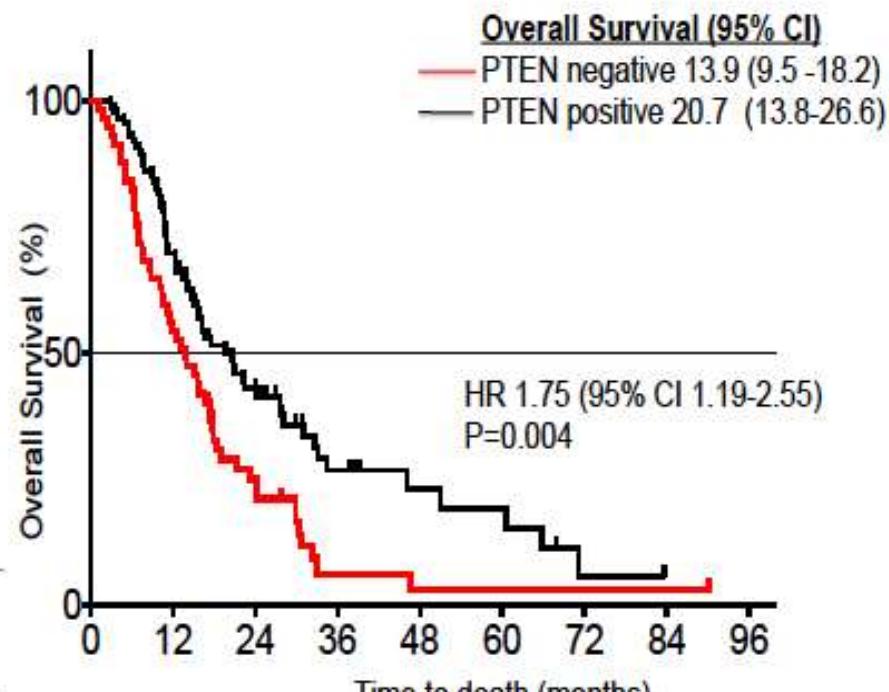
1. Carver et al. *Cancer Cell*. 2011. 2. Hodges et al. *Cancer Res*. 2011. 3. Muftah et al. *Cancer Cell*. 2011.

de Bono et al., Ipatasertib, ESMO 2016

PTEN is lost in 40-50% of mCRPC patients

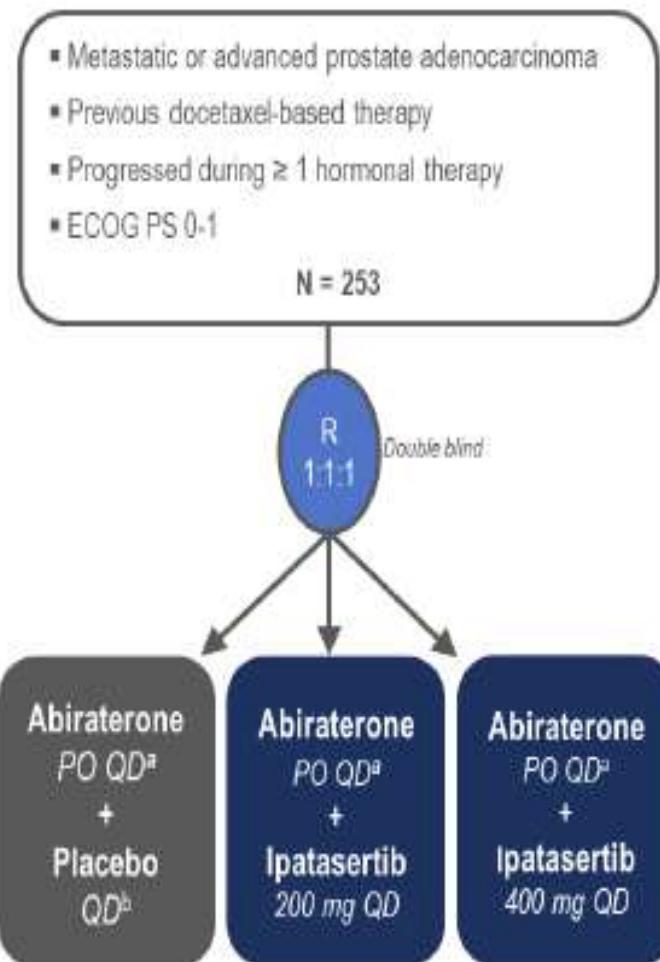


Metastatic Castration-Resistant Prostate Cancer



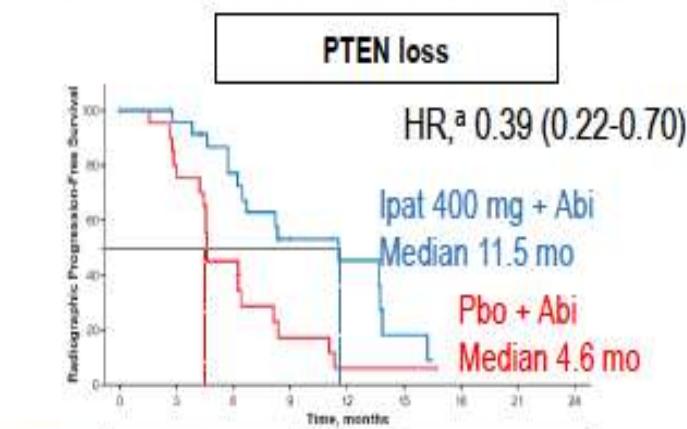
A.MARTIN: PHASE II TRIAL OF IPATASERTIB + ABIRATERONE IN PATIENTS WITH MCRPC

- 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

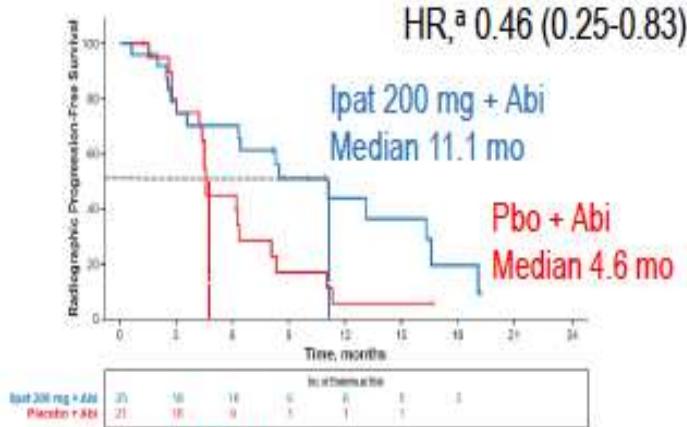


COPRIMARY ENDPOINT: RPFS WITH IPATASERTIB OR PLACEBO + ABIRATERONE BY ICR IHC

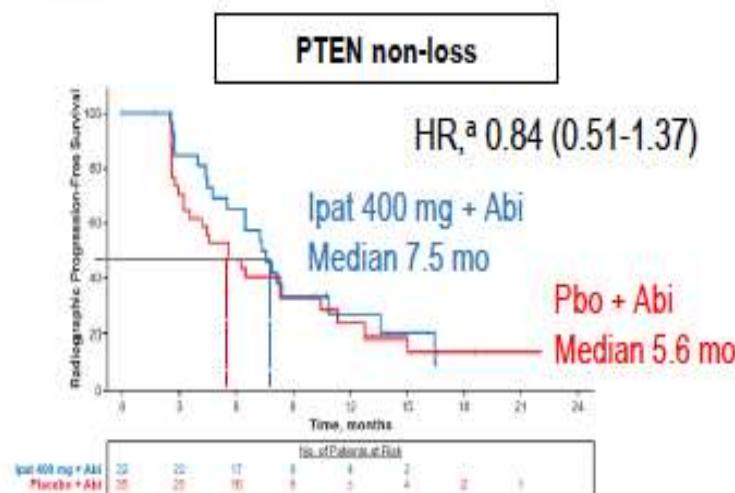
Ipatasertib 400 mg



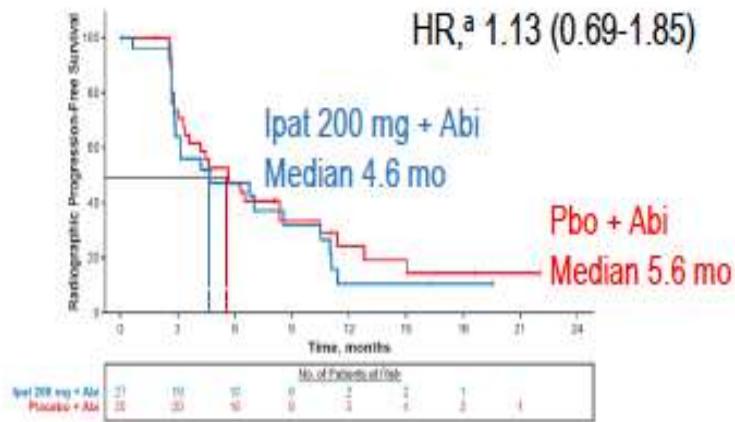
Ipatasertib 200 mg



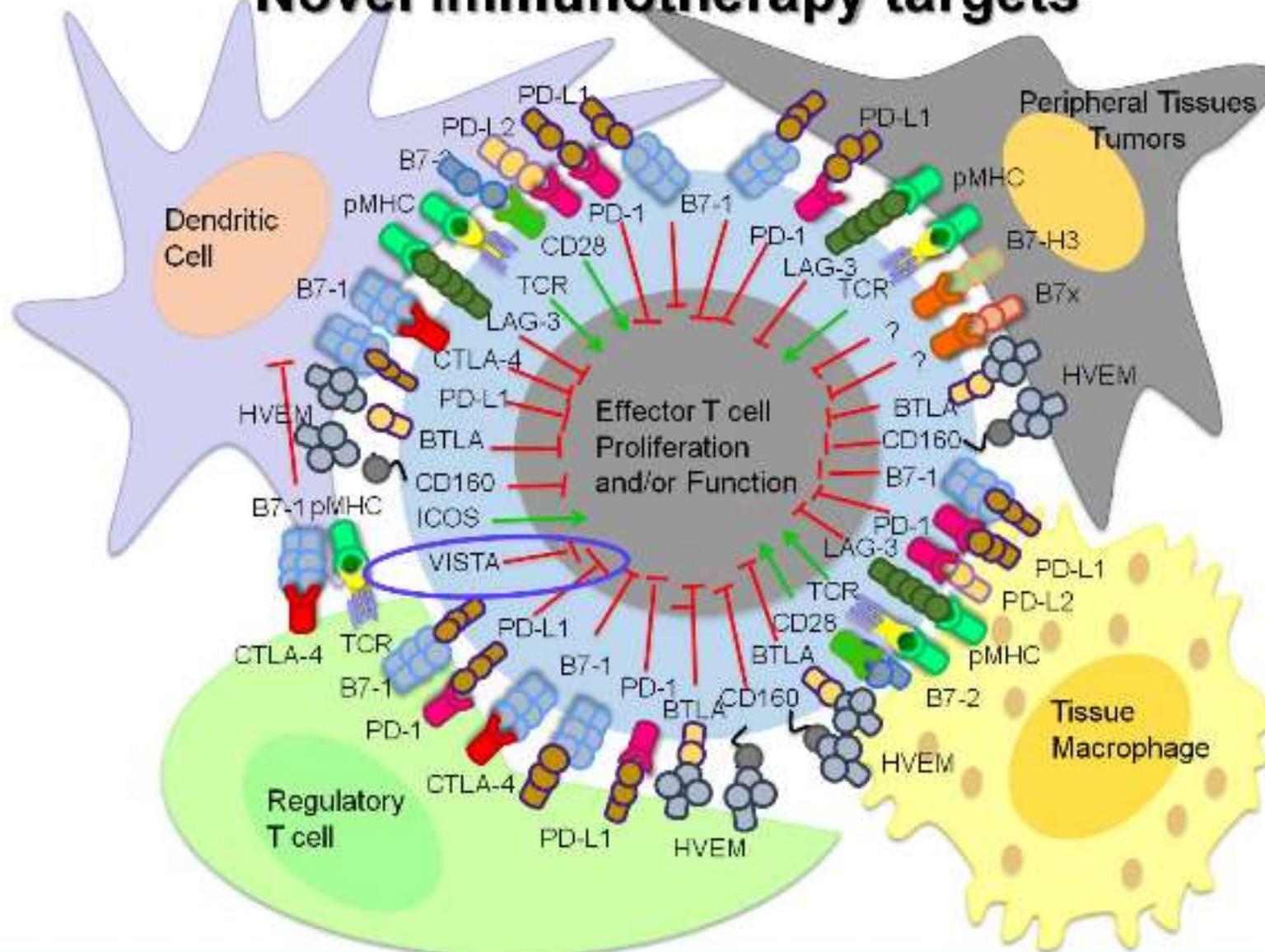
PTEN non-loss



HR,^a 1.13 (0.69-1.85)



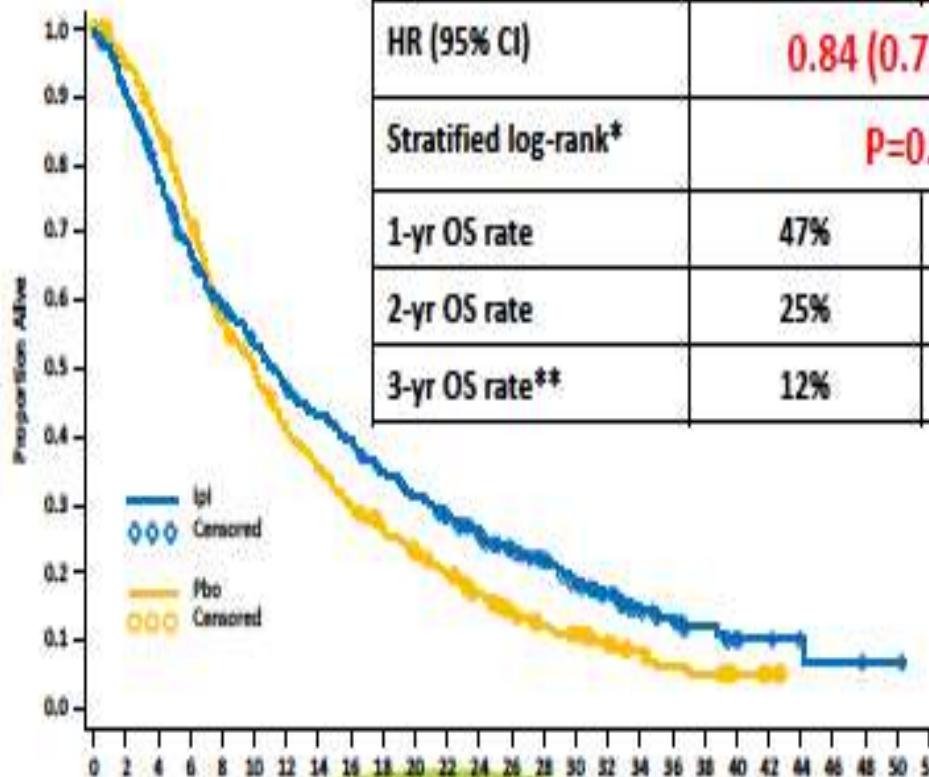
Novel immunotherapy targets



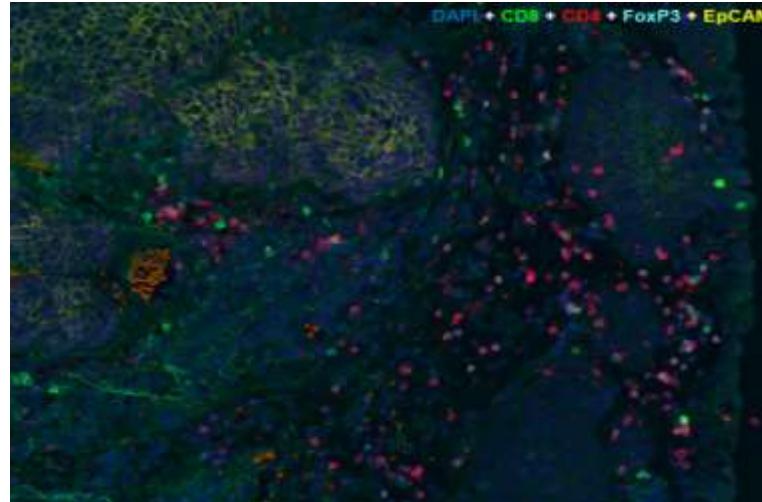
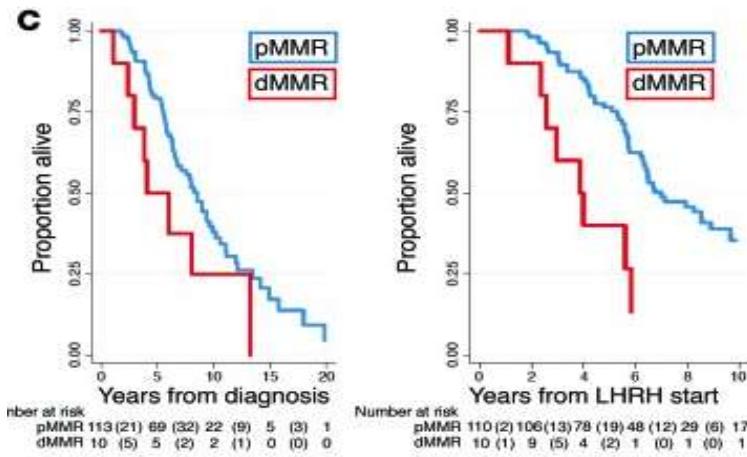
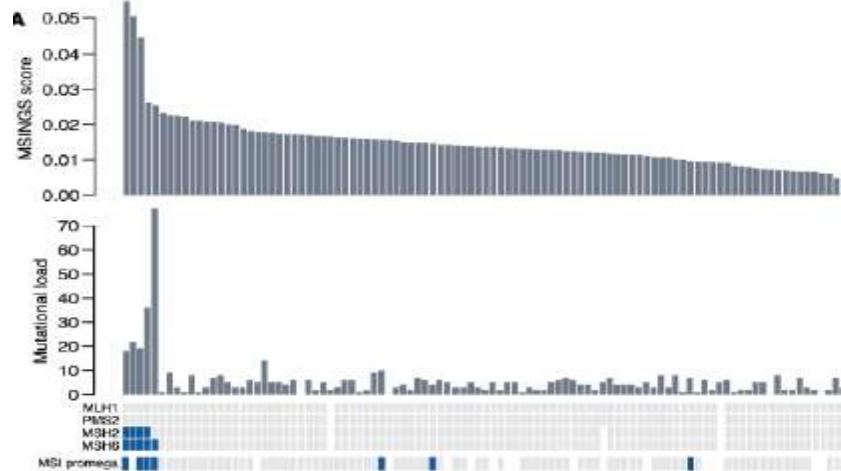
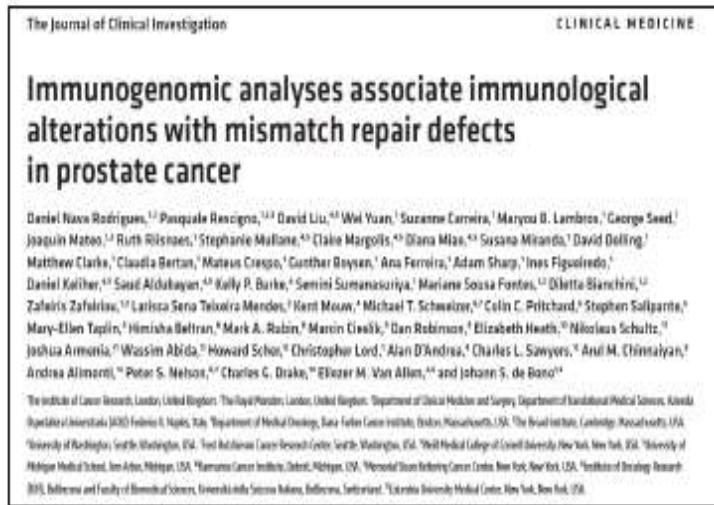
CTLA-4 targeting: Ipilimumab post-docetaxel phase III trial

Results: Updated OS

- n=799
- Primary endpoint= OS

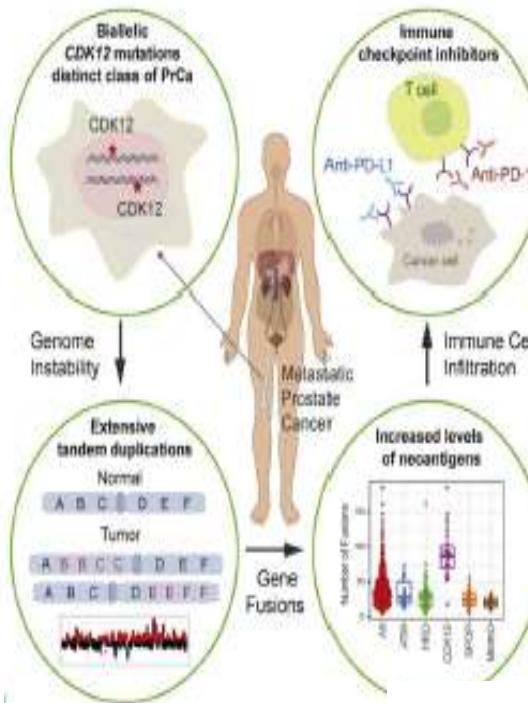


Mismatch DNA repair defects in lethal prostate cancer



Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer

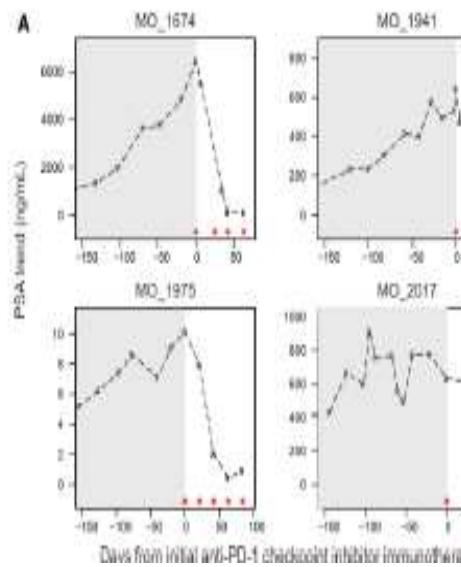
Yi-Mi Wu,^{1,2,20} Marcin Cieslik,^{1,2,20} Robert J. Lonigro,¹ Pankaj Vats,¹ Melissa A. Reimers,³ Xuhong Cao,¹ Yu Ning,¹ Lisha Wang,¹ Lakshmi P. Kunju,^{1,2,4} Navonil de Sarkar,⁵ Elisabeth I. Heath,^{6,7} Jonathan Chou,⁸ Felix Y. Feng,^{5,6,10,11} Peter S. Nelson,^{5,12,13} Johann S. de Bono,^{14,15} Weiping Zou,^{1,2,16} Bruce Montgomery,^{12,17} Ajai Alva,^{1,3} PCF/SU2C International Prostate Cancer Dream Team, Dan R. Robinson,^{1,2,*} and Arul M. Chinnaiyan^{1,2,4,18,19,21,*}



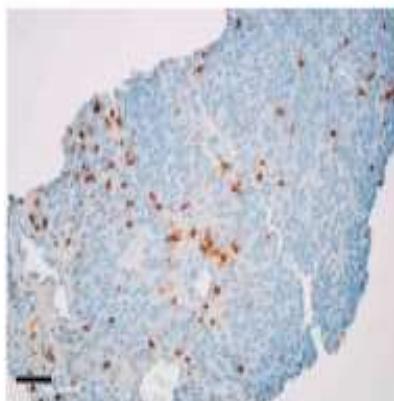
Pilot Clinical Study to Determine CDK12 Mutant Prostate Cancer Response to Checkpoint Inhibitor Immunotherapy

11 pts -5 tt anti PD1

- 1 pt excluded
- 2 pts +++PSA decline



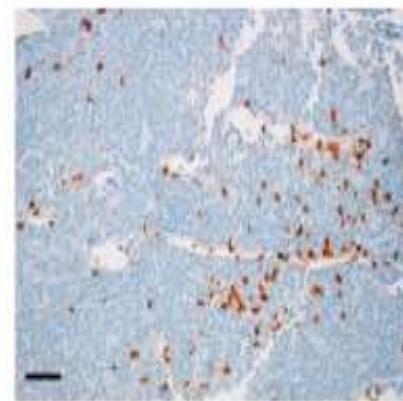
B



C

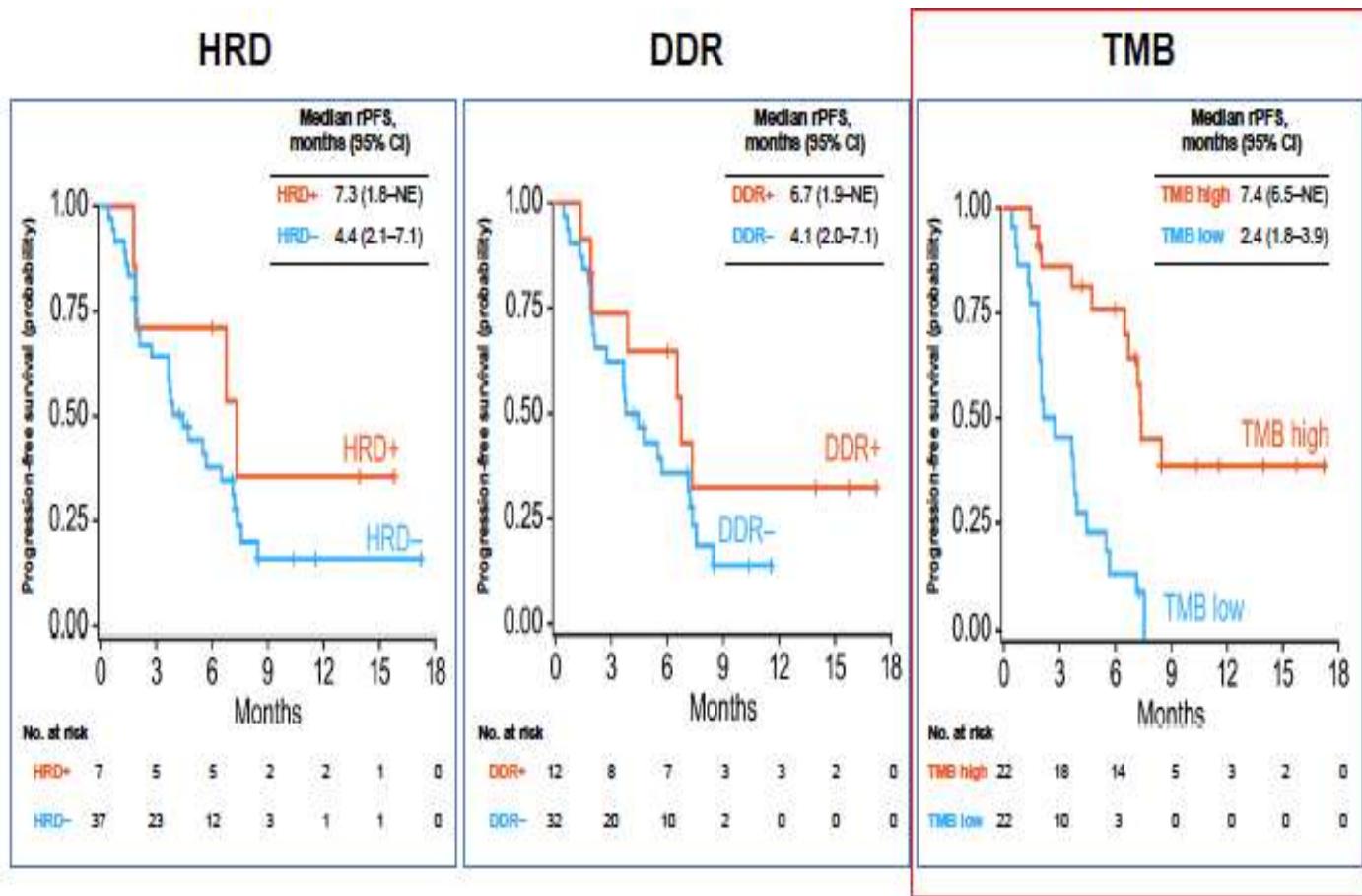


Prior to anti-PD-1 immunotherapy
Right external iliac LN. 2.4 cm. PSA 8.9 ng/mL



After 4 doses of anti-PD-1 immunotherapy
Right external iliac LN. 1.1 cm. PSA 0.9 ng/mL

Ipilimumab + Nivolumab: 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 ($P<0.001$)

NCT	Trial phase	Therapy	Primary endpoint
NCT01804465	II	ipilimumab + sipuleucel-T	impact of timing of ipilimumab (Immediate vs delayed) on the induction of Ig responses
NCT03040791 (ImmunoProst)	II	nivolumab	PSA response rate
NCT03061539	II	nivolumab + ipilimumab	composite response rate
NCT02601014 (STARVE-PC)	II	nivolumab + ipilimumab	change in PSA response
NCT03570619 (IMPACT)	II	nivolumab + ipilimumab	proportion of patients with CDK12 loss of function that respond to treatment
NCT03333616	II	nivolumab + ipilimumab	ORR
NCT03572478	I/II	nivolumab + rucaparib	DLT rate
NCT03338790	II	nivolumab + rucaparib/docetaxel/enzalutamide	ORR e RR-PSA
NCT02703623	II	abiraterone + apalutamide + ipilimumab/cabazitaxel+CBDCA	OS
NCT02861573 (KEYNOTE -365)	I	pembrolizumab + olaparib/docetaxel/enzalutamide/ abiraterone	% of pts with a decrease ≥50% in PSA
NCT03093428	II	pembrolizumab + Radium-223	extent of Immune Cell Infiltration
NCT03810105	II	durvalumab + olaparib	number of participants with an undetectable PSA
NCT03204812	II	durvalumab + tremilimumab	safety and tolerability
NCT02788773	II	durvalumab +/- tremelimumab	ORR
NCT03821246	II	atezolizumab +/- enzalutamide	changes in tumor-infiltrating effector CD3+ T cells

Final remarks: mCRPC

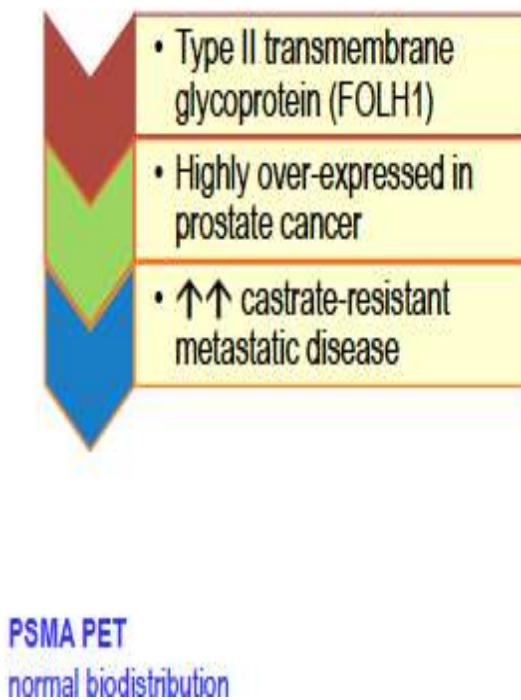
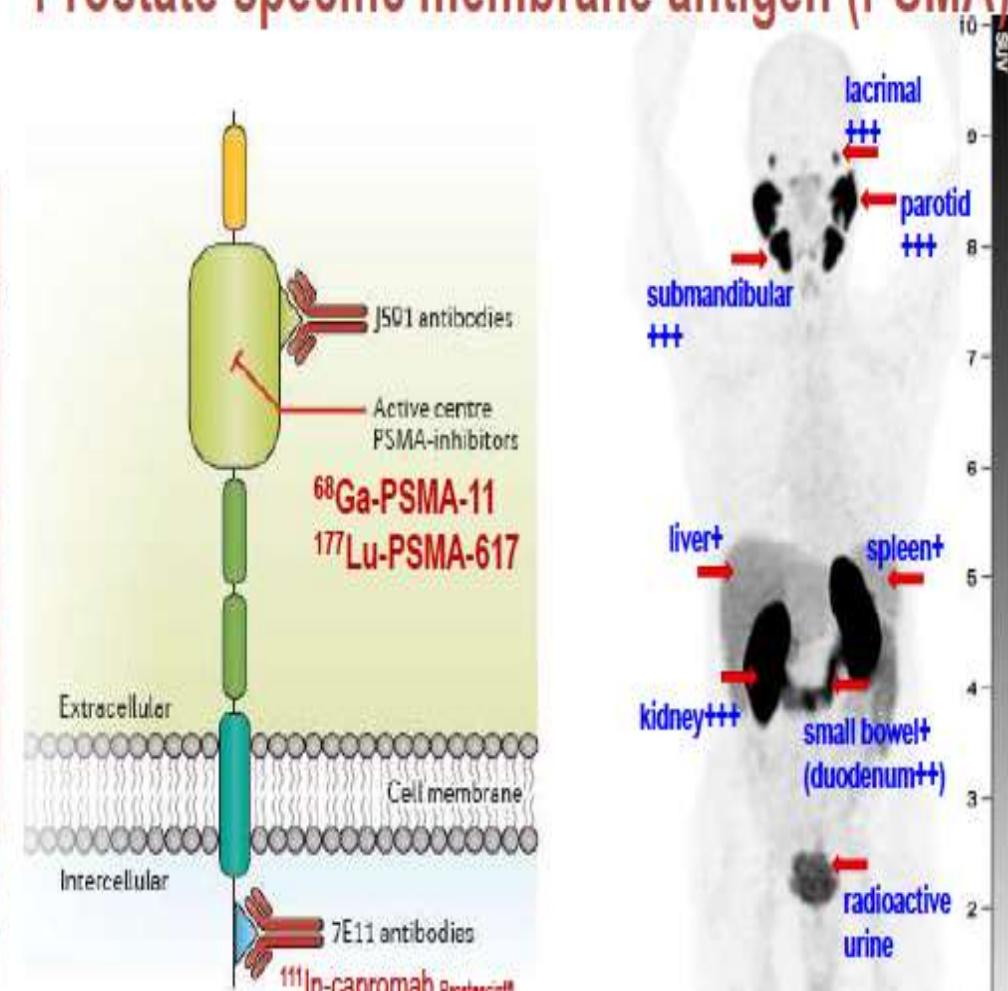
- mCRPC is a highly heterogenous disease. Molecular characterization may matter to distinguish lethal prostate cancer vs indolent disease
- gBRCA2 is an independent prognostic factor of CSS.
- Olaparib is active in gDDR+ mCRPC. However dose and gene subgroup may matter in olaparib sensitivity.
- PTEN loss is a predictive factor of response to AKT-inhibitor plus abiraterone. Phase III trial is ongoing.
- There is a strong rationale to select patient population for gDDR, MMR, biallelic CDK12 mutation for future immunotherapy trials

AGENDA

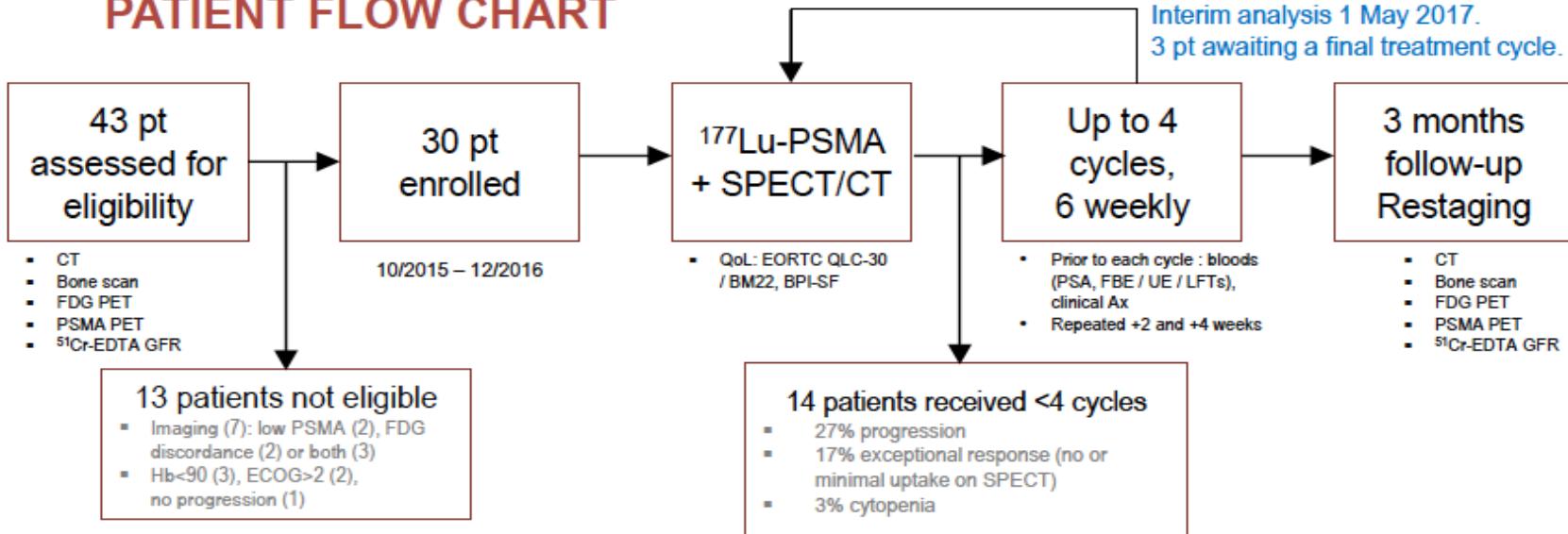
- M0 CRPC
- mCRPC
- Genomic aberrations and treatment implications of mCRPC
 - DDR and PARP inhibitors
 - PTEN loss and AKT inhibitors
 - MMR, CDK 12 and immunotherapy
- Radiopharmaceuticals

Prostate specific membrane antigen (PSMA)

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



PATIENT FLOW CHART



PATIENT ELIGIBILITY

Inclusion

- Castration-resistant
- Documented progression after
 - Docetaxel
 - Enzalutamide or abiraterone
- ECOG ≤2
- High uptake on PSMA PET

unless contraindicated or patient refused

Exclusion

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

ENDPOINTS

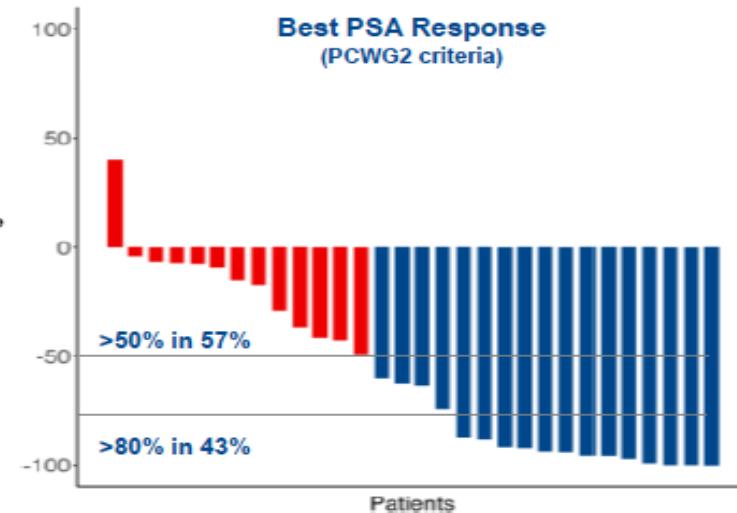
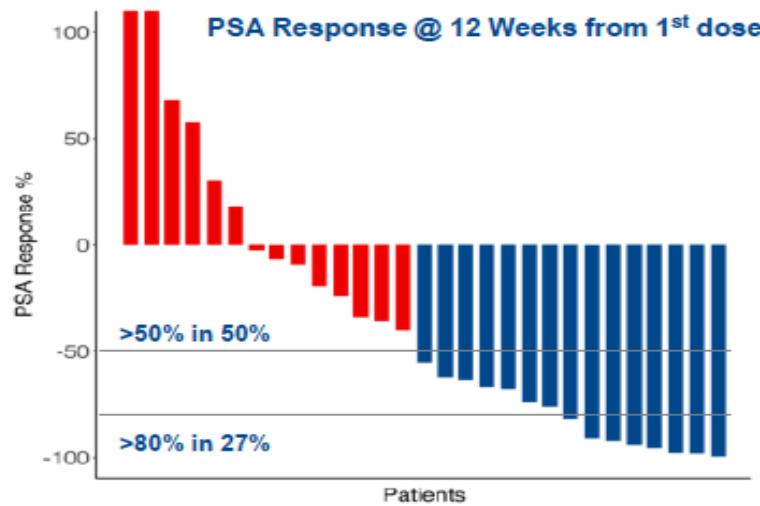
Primary

- Toxicity (CTCAE4)
- Activity
- PSA response (PCWG2)
- Quality of life (EORTC QLQ-C30, BPI-SF)
- Imaging response (RECIST, bone scan, PSMA/FDG PET)

Secondary

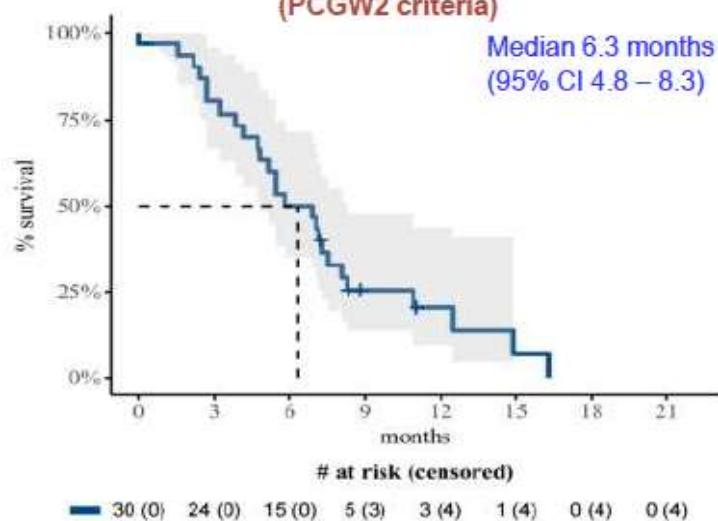
- Dosimetry to tumors and normal tissue
- Progression free and overall survival

1° ENDPOINT: PSA RESPONSE



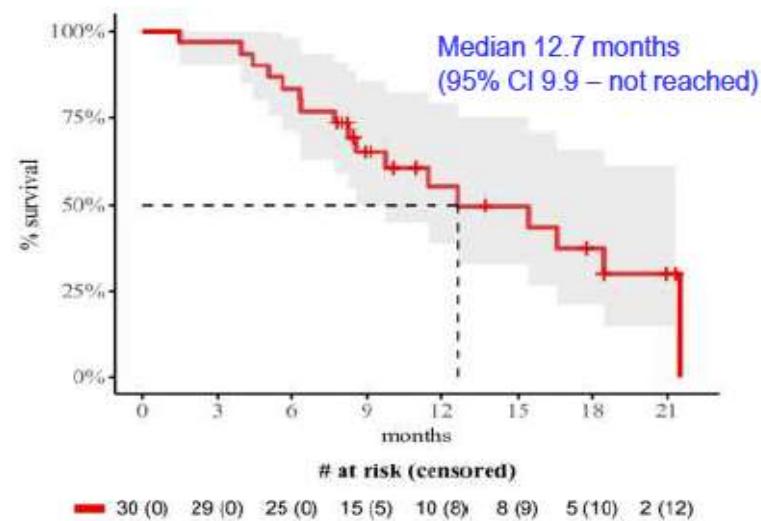
PSA PROGRESSION FREE SURVIVAL

(PCWG2 criteria)



OVERALL SURVIVAL

Median 12.7 months
(95% CI 9.9 – not reached)



CONCLUSIONS

In men with mCRPC who have progressed after standard therapies with PSMA-avid disease, LuPSMA has high response rates, limited toxicity with improvements in pain and well-being.

Warrants further evaluation:

- “TheraP Trial”: 200 pt multi-centre phase II RCT vs cabazitaxel (ANZUP / PCFA / ABX / ANSTO)
- LuPSMA + anti-PD1 Ab pilot study (Victorian Cancer Agency)
- LuPSMA + PARPi phase I study (PCF Challenge Award)



ABX *advanced biochemical compounds*

Conclusions

- mCRPC is a heterogenous disease and there is clear evidence of the continuous AR signal axis involvement
- Several agents have proven efficacy in both nmCRPC and mCRPC
- Best sequence is undefined for the lack of randomized trials
- Clinical factors still remain the main tools for decision making
- Molecular classification will guide future treatments (ARV-7, HRD deficiency and PTEN Loss potential predictive biomarkers)

