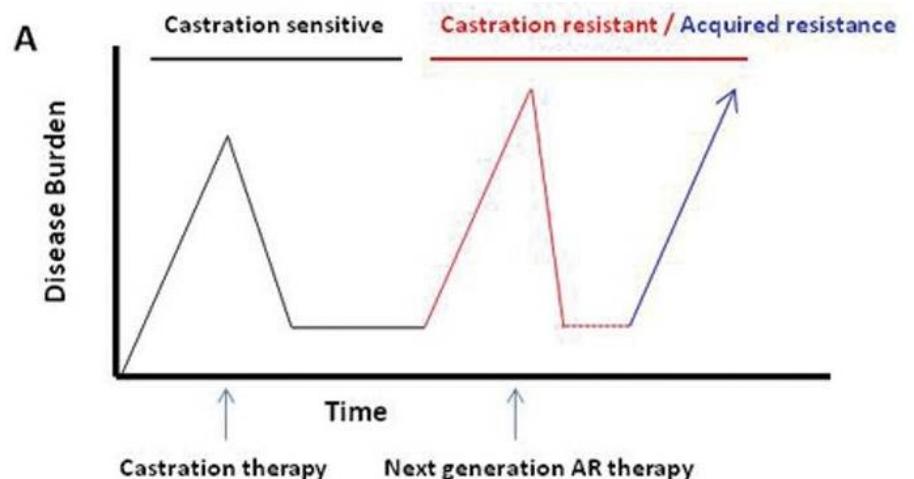

Futuro del cáncer de próstata avanzado: papel de los biomarcadores y el diagnóstico molecular

Dr Pablo Maroto
Hospital de Sant Pau. Barcelona

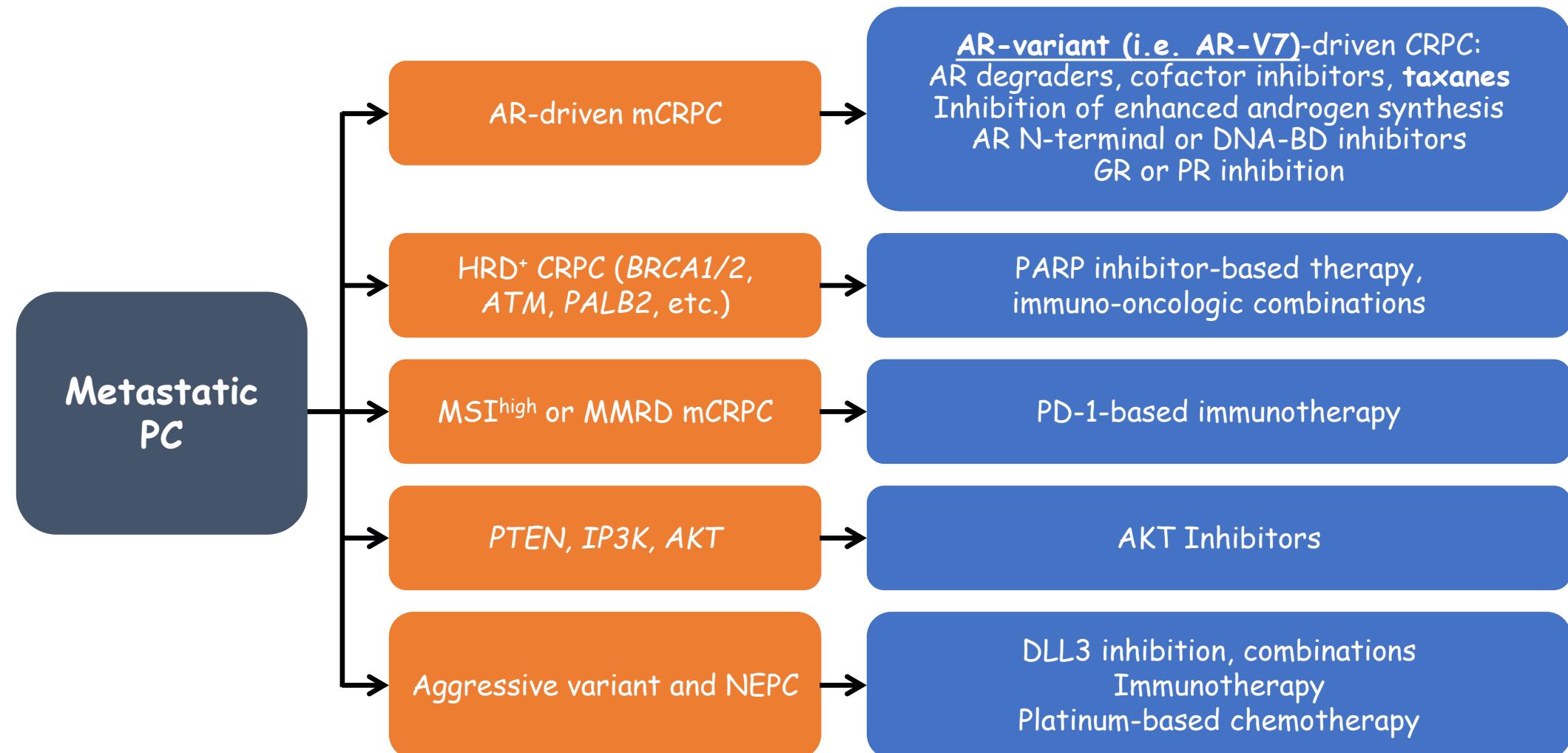




B

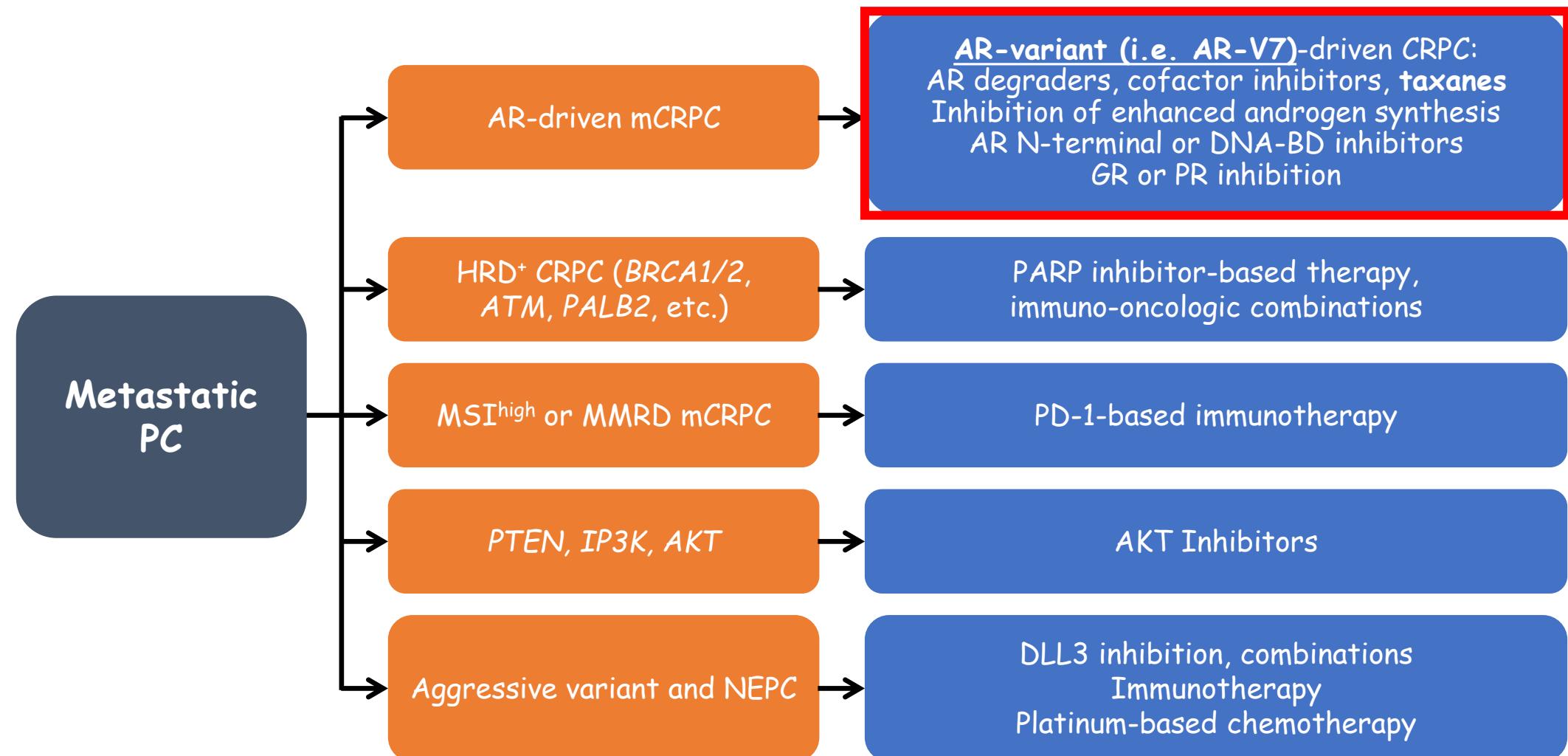
	<u>RESTORED AR SIGNALING</u>	<u>AR BYPASS SIGNALING</u>	<u>COMPLETE AR INDEPENDENCE</u>
Clinical Relapse Profile	AR ⁺ , Rising PSA	AR ⁺ , Rising PSA	AR ^{low/neg} , low PSA
Histological Features	Adenocarcinoma	Adenocarcinoma	SCC/NEPC, novel subtypes?
Molecular Features	<ul style="list-style-type: none"> • AR activating mutations • AR active splice variants • Intratumoral DHT synthesis from adrenal precursors 	<ul style="list-style-type: none"> • GR upregulation 	<ul style="list-style-type: none"> • RB deletion • TP53 deletion/mutation • MYCN gain • AURKA gain

Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas

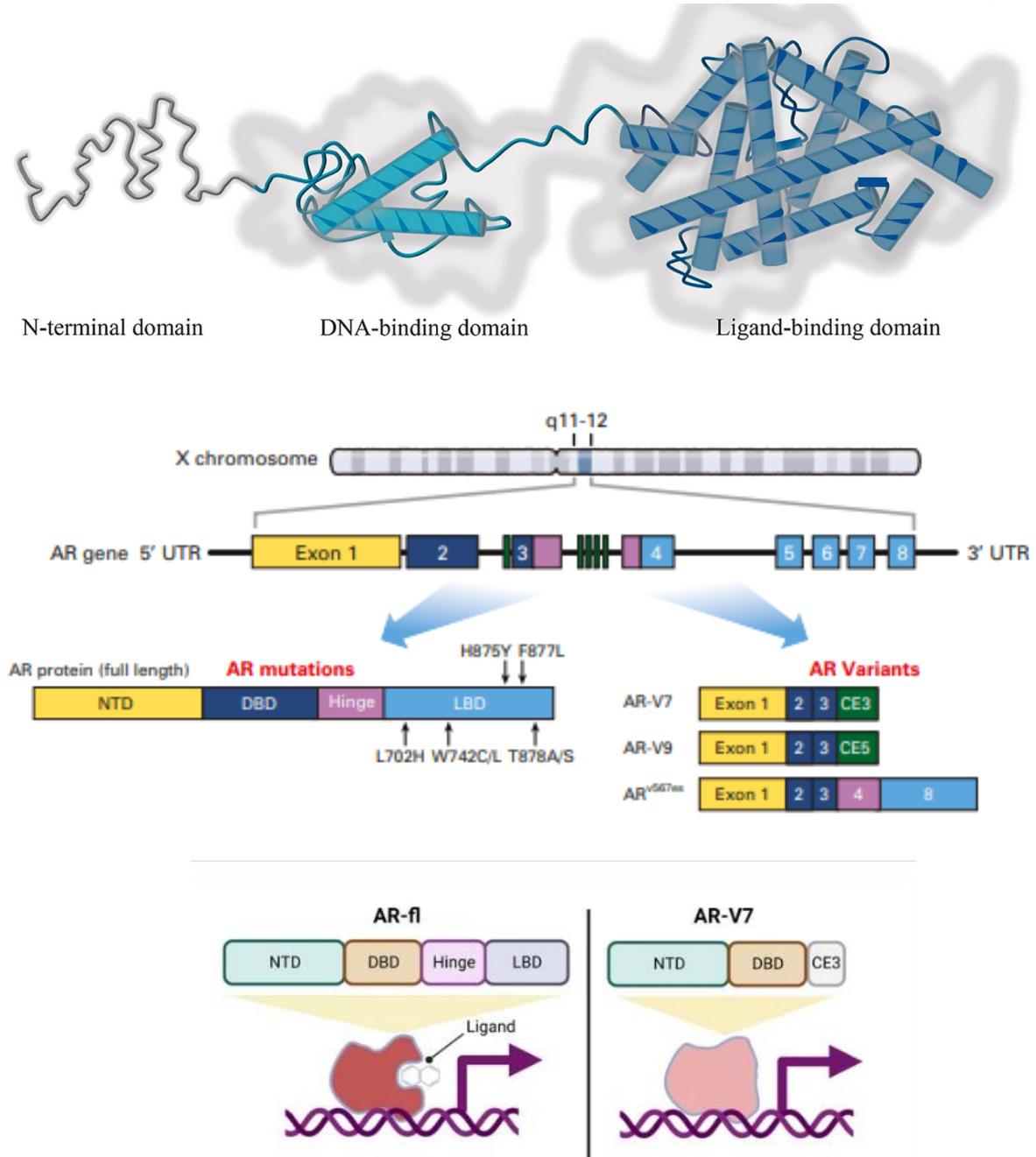
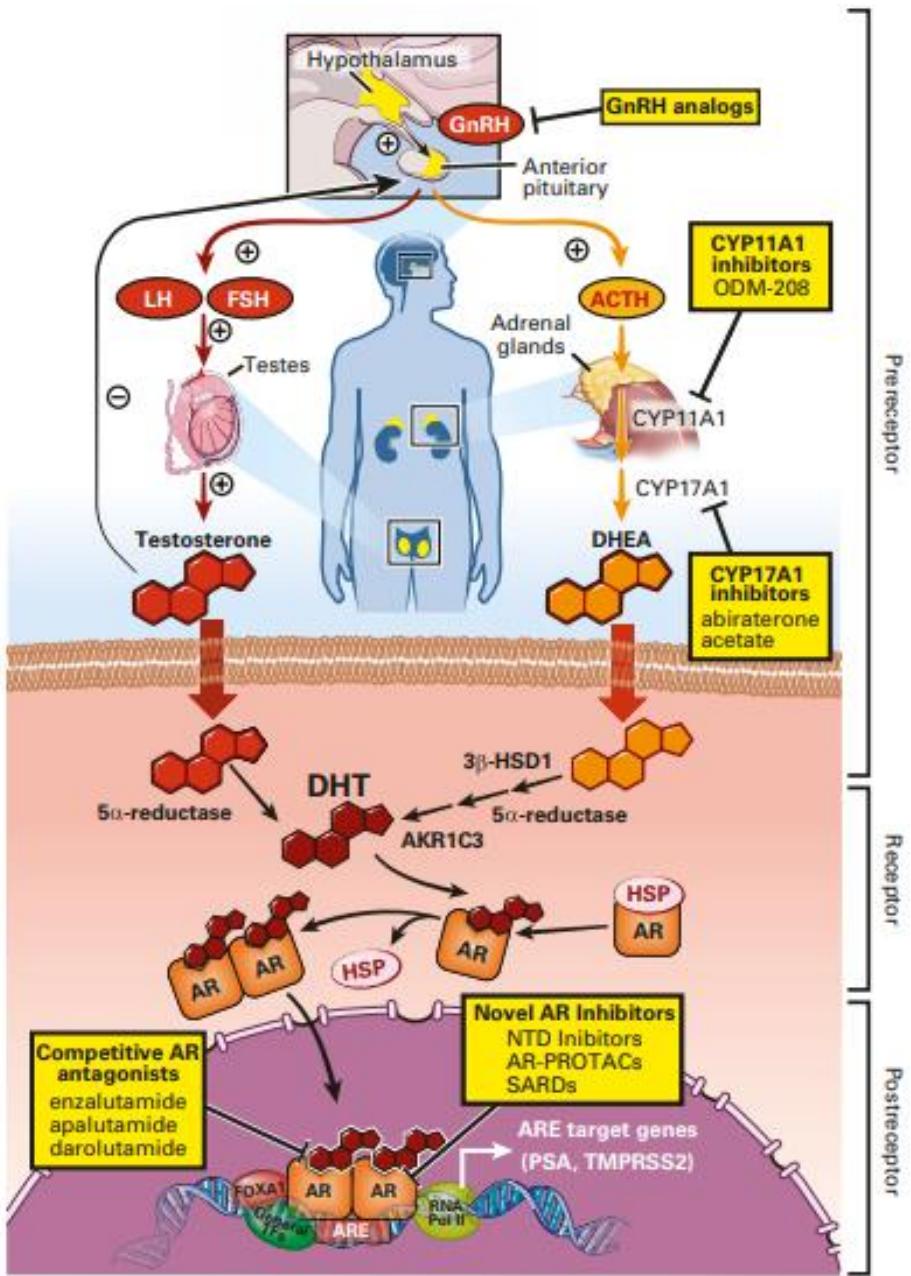


AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor

Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas

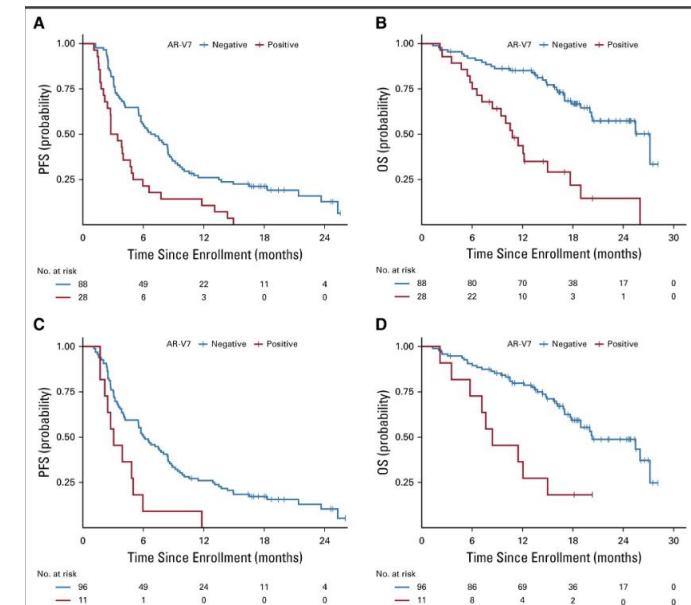


AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor

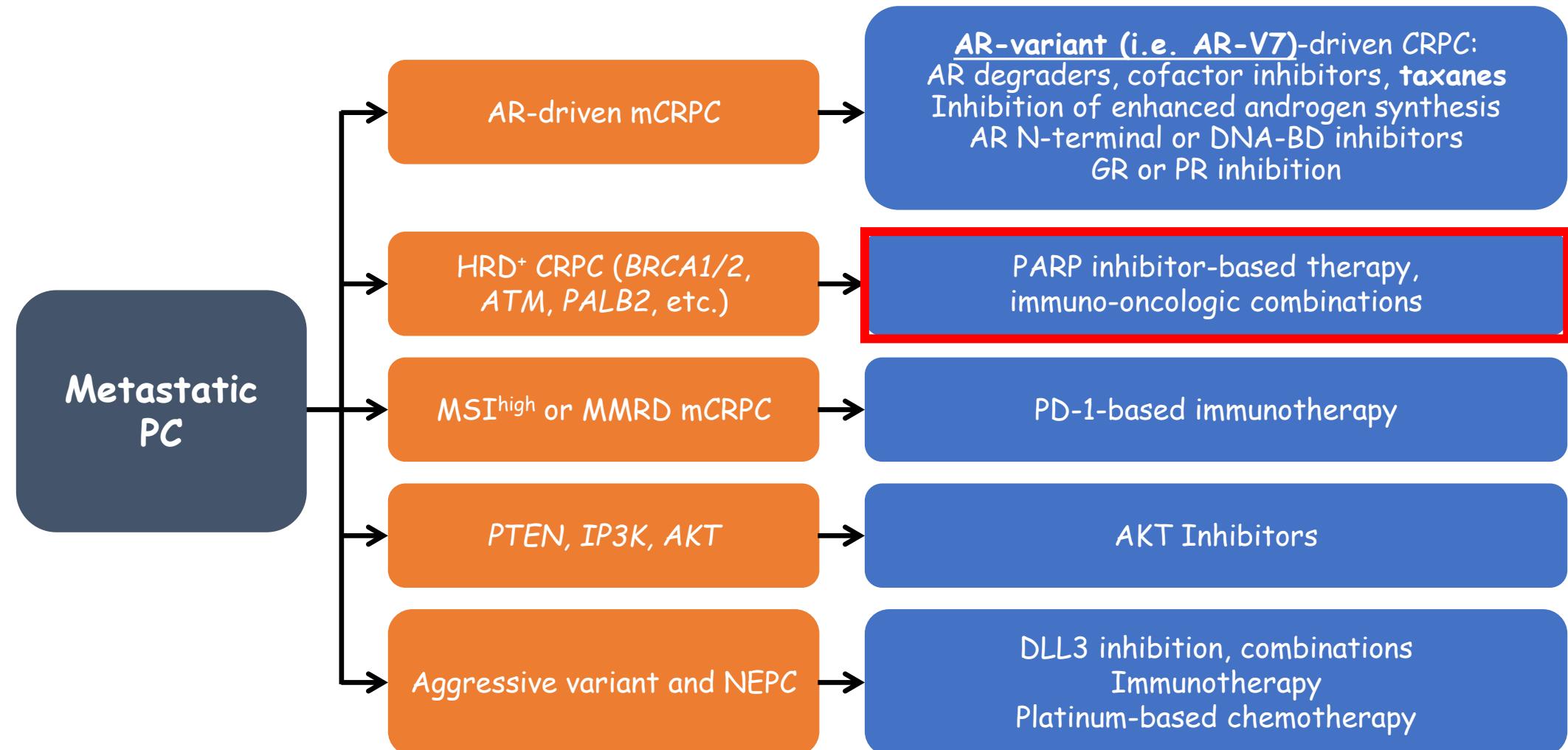


Implicaciones terapéuticas

- Valor pronóstico de alguna de las variantes
(*Prophecy Study. Armstrong AJ, et al. J Clin Oncol 2018*)
- ¿Selección de la terapia dirigida al RA de primera línea?
 - **F877L mutation:** Potencial Resistencia a tratamientos dirigidos al AR, específicamente Apa/Enza, pero no Darolutamida
 - Selección de pacientes para Qt (*Scher et al. JAMA Oncol 4:1179-1186, 2018*)
- Desarrollo de fármacos cuya diana sea el fragmento N-terminal

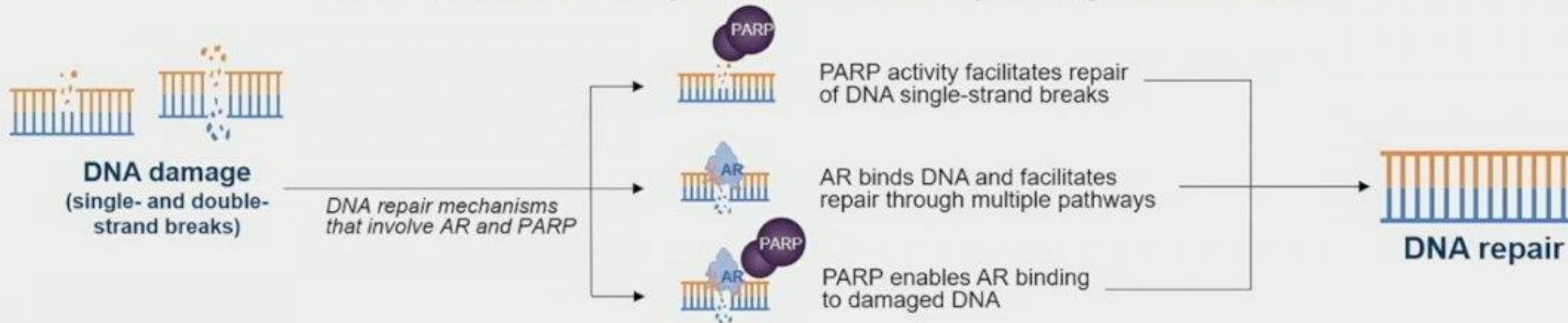


Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas

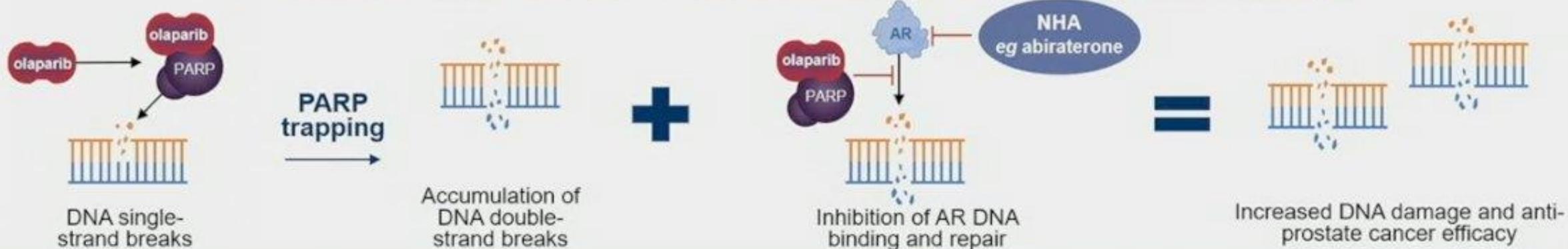


AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor

PARP and AR are important for DNA repair in prostate cancer

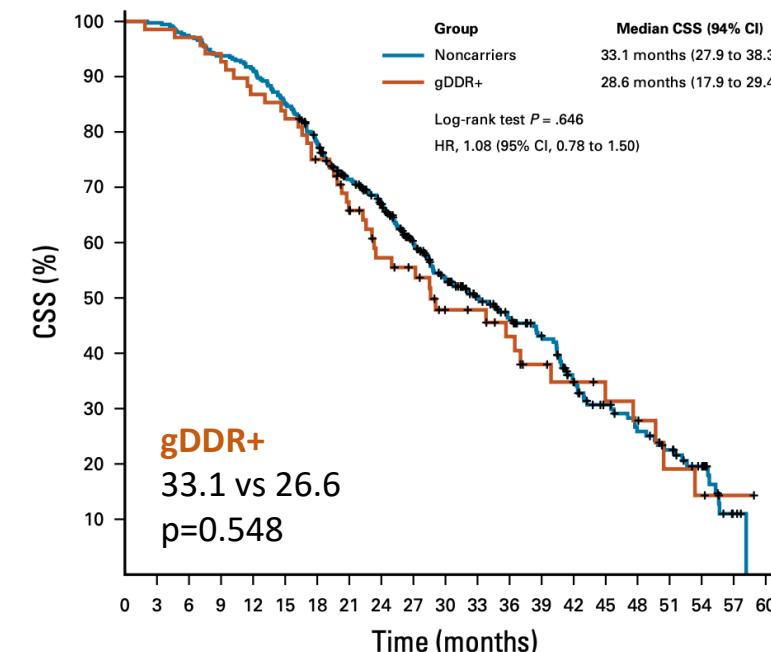
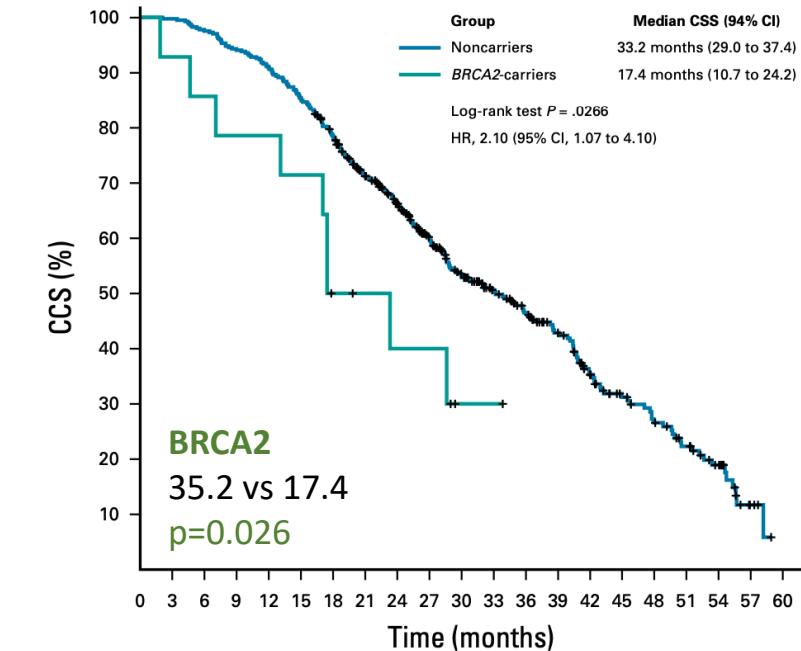
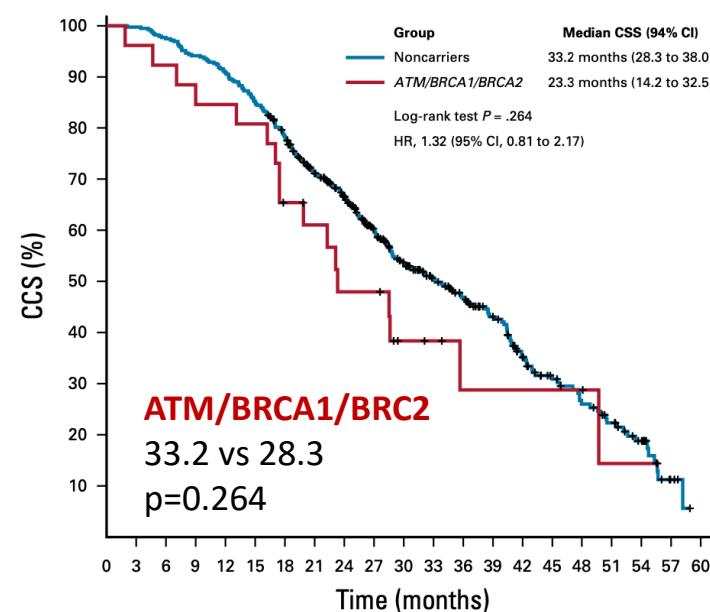


Inhibition of PARP and AR in combination results in more DNA damage



PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer

Gene/Group	PROREP AIR-B, % (n = 419)
ATM	1.91
BRCA1	0.95
BRCA2	3.34
PALB2	0
Primary aim genes	6.21
107 genes study panel	16.23
DDR genes in BROCA panel*	7.40



PARPi and prostate cancer

PARPi MONOTHERAPY

- ✓ **Olaparib (PROFOUND)** → BRCA1/BRCA2/ATM: m-rPFS HR 0.34 (7 vs 4 m); mOS HR 0.69 (19 vs 15m); ORR: 33%vs 2%
HRR+: m rPFS HR 0.49.
- ✓ **Rucaparib (TRITON 2)** → BRCA1/2: ORR: 44% (CR: 11%); DOR \geq 6m: 54%; m-rPFS 9 m; 12m-OS: 73%
- ✓ **Niraparib (GALAHAD)** → BRCA1/2: ORR: 34.2% (CR: 3%); m-rPFS 8 m; mOS: 13m
- ✓ **Talazoparib** → HRR+: ORR : 33%
BRCA2: ORR: 46% (post-hoc)

PARPi COMBINATIONS

- **Abiraterona + Olaparib (PROPEL)**
- **Abiraterona + Niraparib (MAGNITUDE)**
- **Enzalutamida + Talazoparib (TALAPRO-2)**

MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-

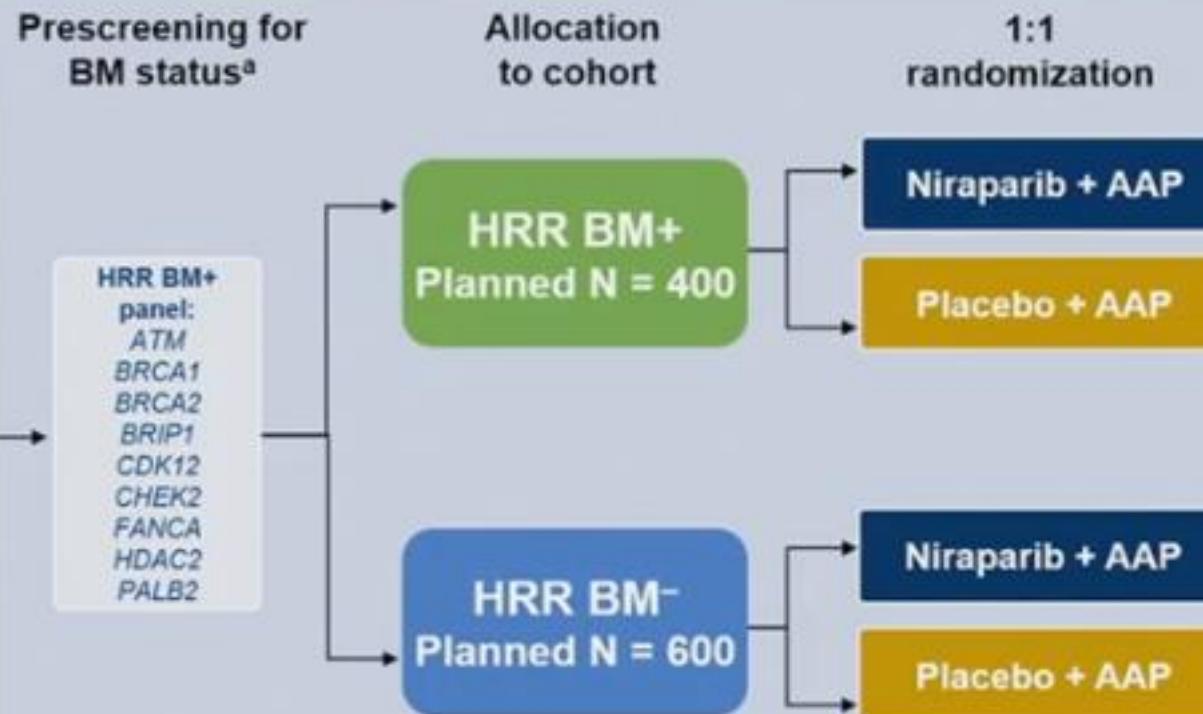
Study start: February 2019

Patient eligibility

- L1 mCRPC
 - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications

- Prior taxane-based chemo for mCSPC
- Prior ARI for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
 - BRCA1/2 vs other HRR gene alterations



Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM- status.

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARI, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory-Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

*Tissue and Plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (ctDNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel.

Primary endpoint

- rPFS by central review

Secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints

- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

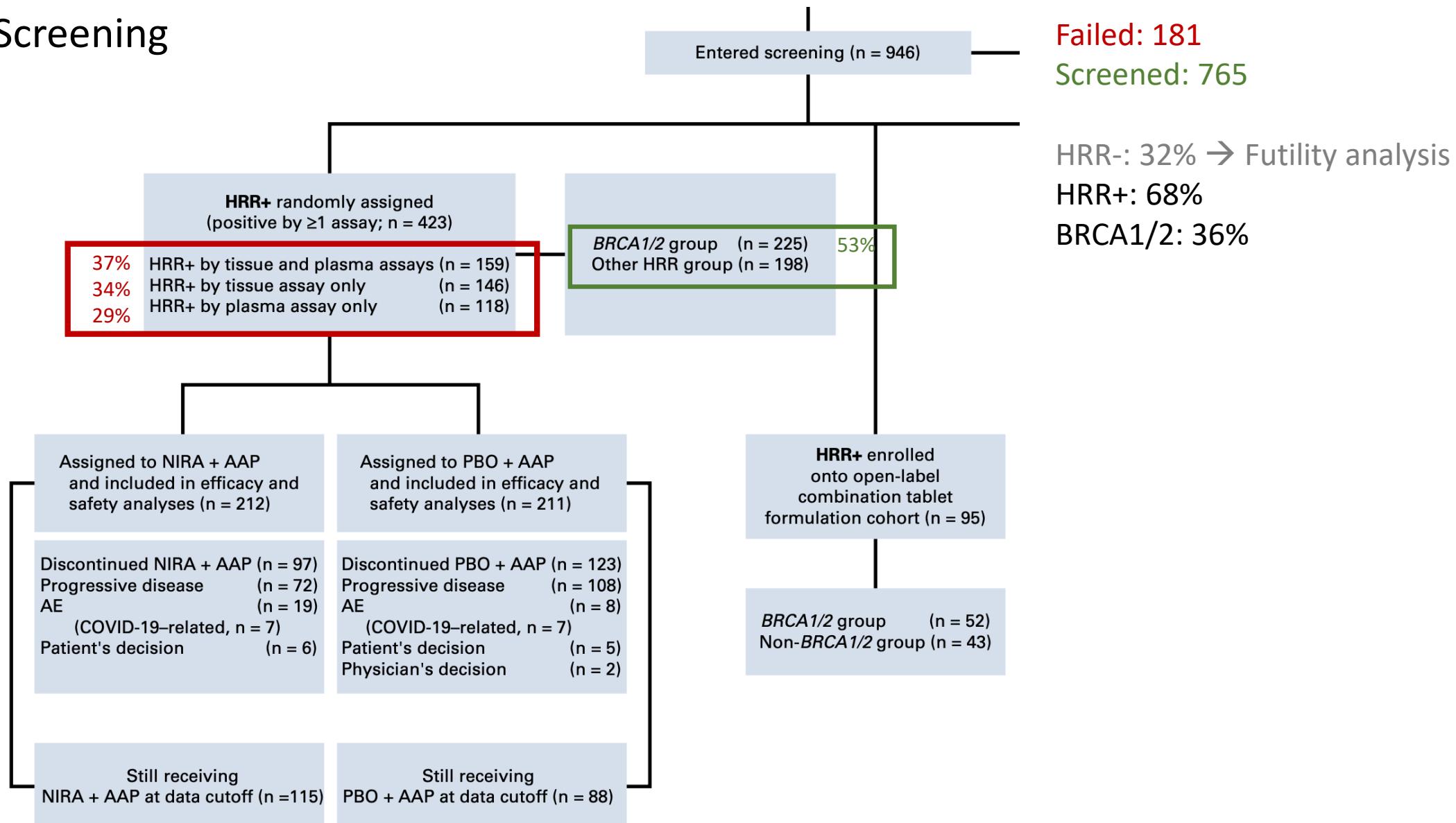
Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.



MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-

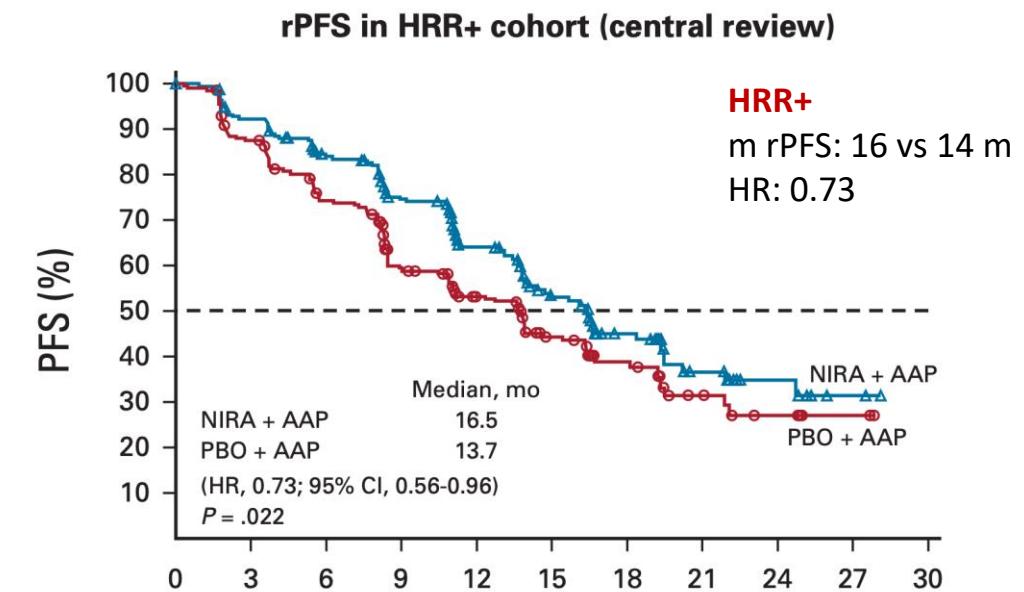
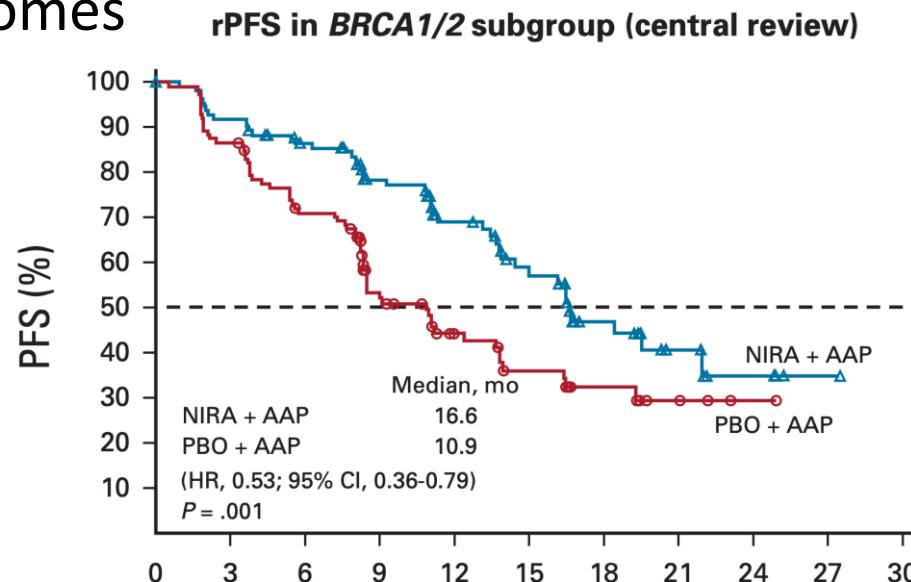
Screening



MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-

Outcomes



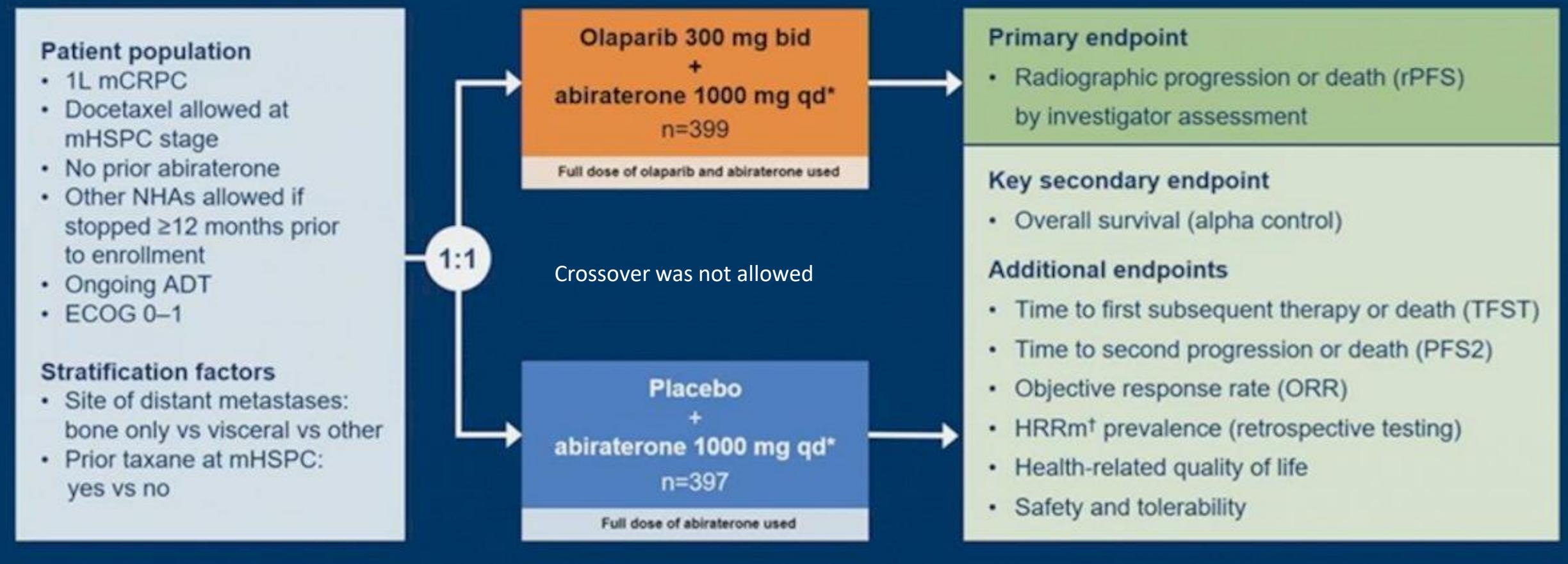
BRCA1/2 arm subgroup:

- ORR: 52% (CR: 18%) vs 31% (CR: 14%)
- TSP: HR 0.85 (NR vs 24 m)
- TCC: HR 0.56 (NR vs 27 m)
- OS: HR 0.88 (95% 0.55-1.34)

HRR+ subgroup:

- ORR: 62% (CR: 22%) vs 28% (CR: 11%)
- TCC and TSP analysis were not significant.

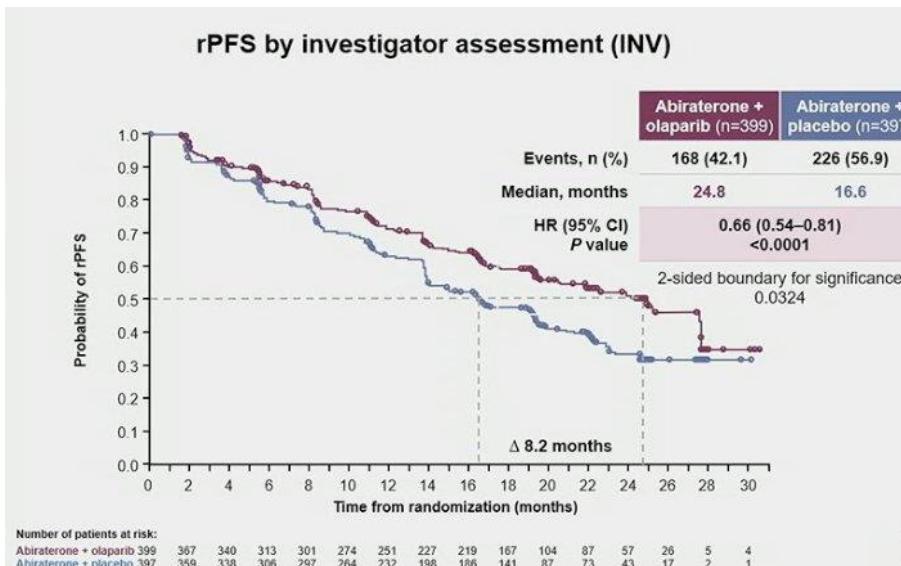
PROpel: a global randomized double-blind phase III trial



- Enrollment was not based on HRR status.
- Both tumour tissue (archival) and blood sample were collected **retrospectively** in 98%.
- Genes assessed (14): ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L
- Three groups: **HRRm**, **non-HRRm**, and **HRR unknown**.

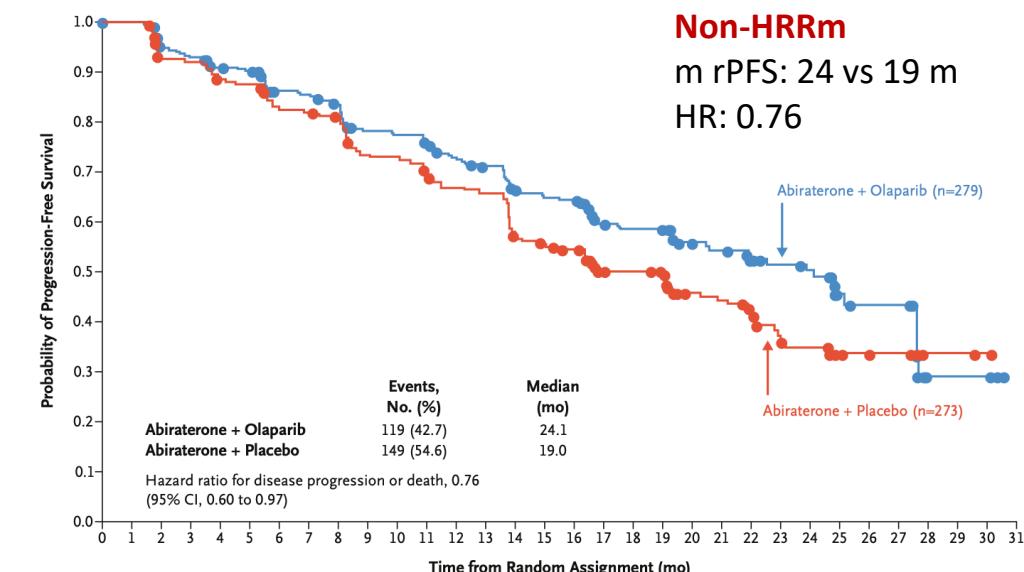
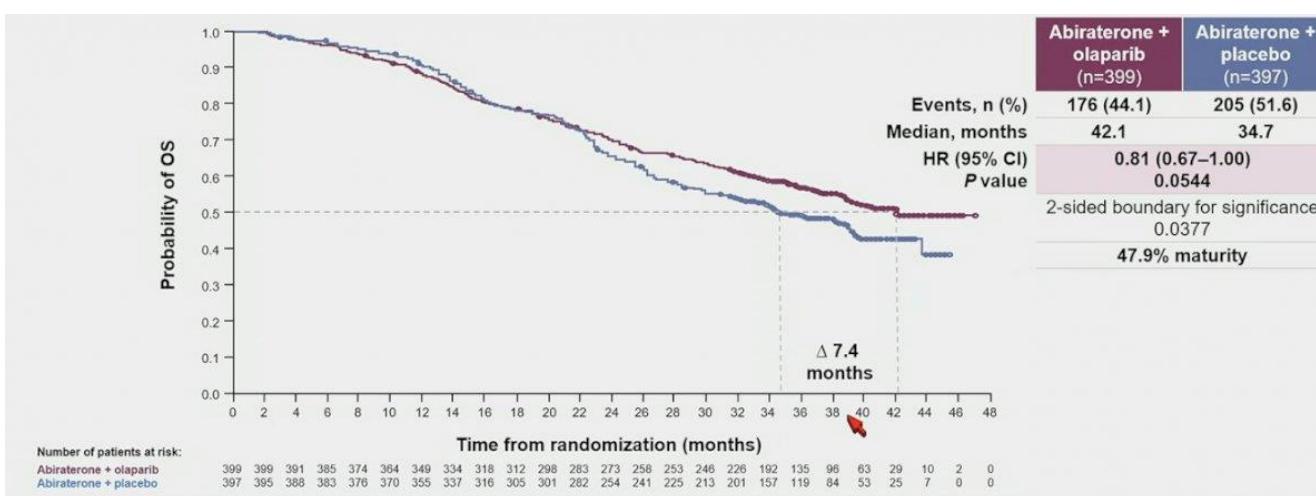
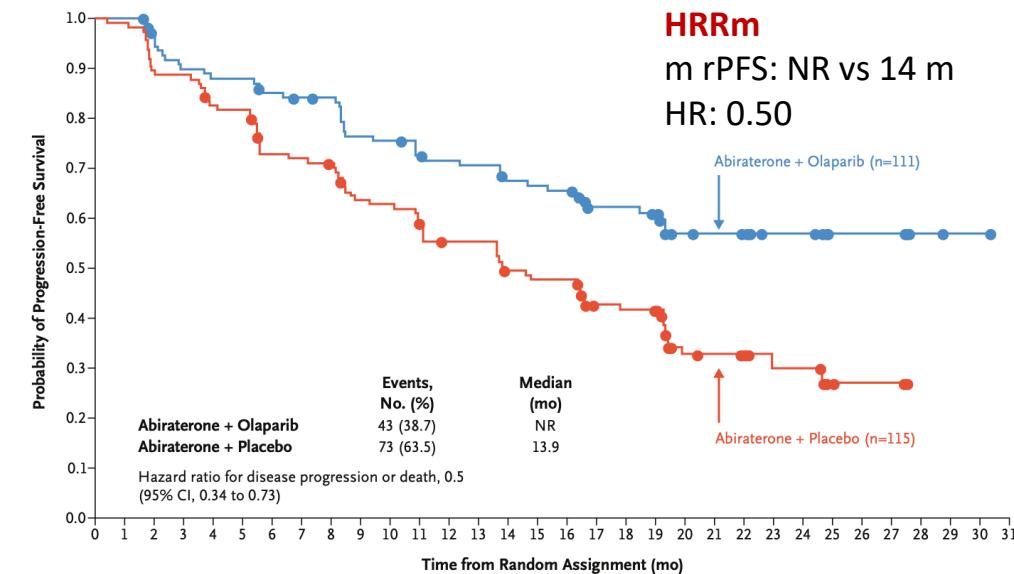
PROpel: a global randomized double-blind phase III trial

Outcomes



All comers

m rPFS: 25 vs 17 m
 HR: 0.66



OLAPARIB (Lynparza) – AstraZeneca

Oncologic Drugs Advisory Committee Meeting - April 28, 2023

Table 1: PROpel: rPFS and OS by BRCA Mutation Status*

	ITT (N=796, 100%)		BRCAm ¹ (N=85, 11%)		Undetermined BRCA status ² (N=284, 35%)		non-BRCAm ³ (N=427, 54%)	
	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P	Olaparib + AA/P	Placebo + AA/P
rPFS (INV)								
Median in months (range)	25 (20, 28)	17 (14, 19)	NR (19, NR)	8 (6, 15)	NR (10, NR)	19 (14, 22)	22 (17, 25)	17 (14, 19)
HR ⁴ (95%CI)	0.66 (0.54, 0.81)		0.24 (0.12, 0.46)		0.66 (0.46, 0.94)		0.85 (0.66, 1.11)	
rPFS (BICR)								
Median in months (range)	28 (20, NR)	16 (14, 19)	NR (NR, NR)	8 (4, 16)	NR (19, NR)	19 (14, 22)	20 (17, 28)	17 (14, 19)
HR ⁴ (95%CI)	0.61 (0.49, 0.74)		0.19 (0.1, 0.37)		0.59 (0.41, 0.85)		0.82 (0.62, 1.08)	
OS								
Median in months (range)	42 (38, NC)	35 (31, 39)	NR (NR, NR)	23 (18, 34)	NR (40, NR)	38 (28, 39)	37 (33, NR)	38 (31, NR)
HR ⁴ (95%CI)	0.81 (0.67, 1.00)		0.3 (0.15, 0.6)		0.73 (0.52, 1.03)		1.06 (0.81, 1.39)	

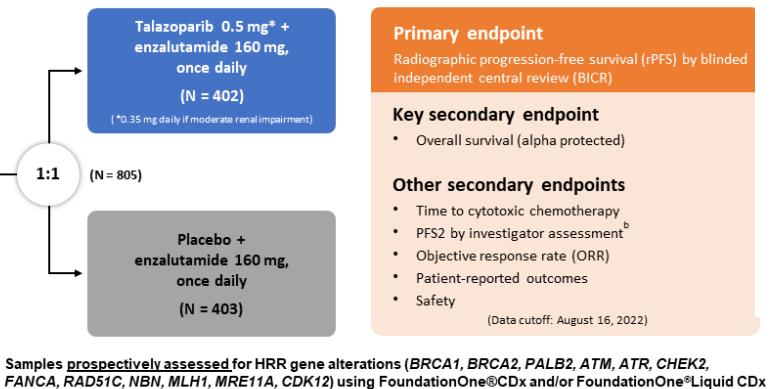
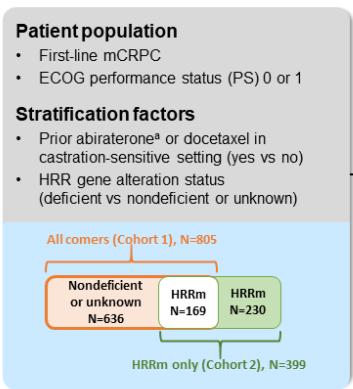
*rPFS results were based on data from the pre-specified interim analysis of rPFS with 84% information fraction and OS results were based on pre-specified final OS analysis.

FDA analyzed PROpel data for subgroups based on likelihood of BRCA mutation.

- **BRCAm**: positive by either tumor tissue or ctDNA tests.
- **Non-BRCAm**: negative positive by either tumor tissue or ctDNA tests.
- **Undetermined BRCA**: negative results by only one test or unknown results for both tests

TALAPRO-2 Primary Endpoint: rPFS by BICR

TALAPRO-2

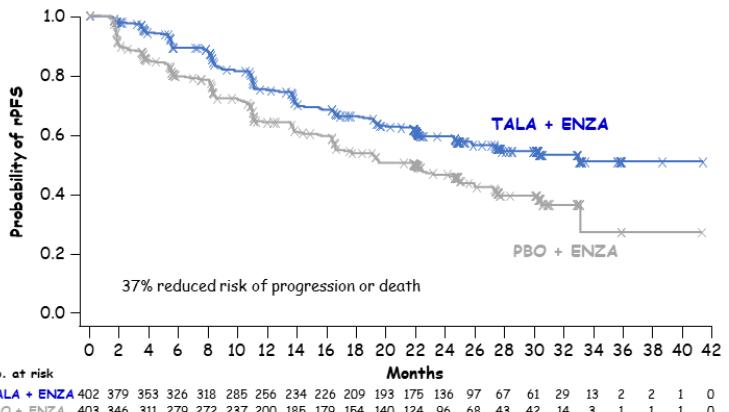


To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in a hierarchical stepwise procedure to preserve the overall type I error.

TALAPRO-2 (Part 1) Data Available in Appendix

We report results only from the all-comers cohort 1 of men unselected for HRR gene alterations

^aTwo patients in each treatment arm received prior orteronel. ^bTime from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first. ECOG-Eastern Cooperative Oncology Group; HRR=homologous recombination repair; HRRm=HRR mutation; mCRPC=metastatic, castration-resistant prostate cancer. Agarwal N, et al. LBA 17. ASCO GU 2023.



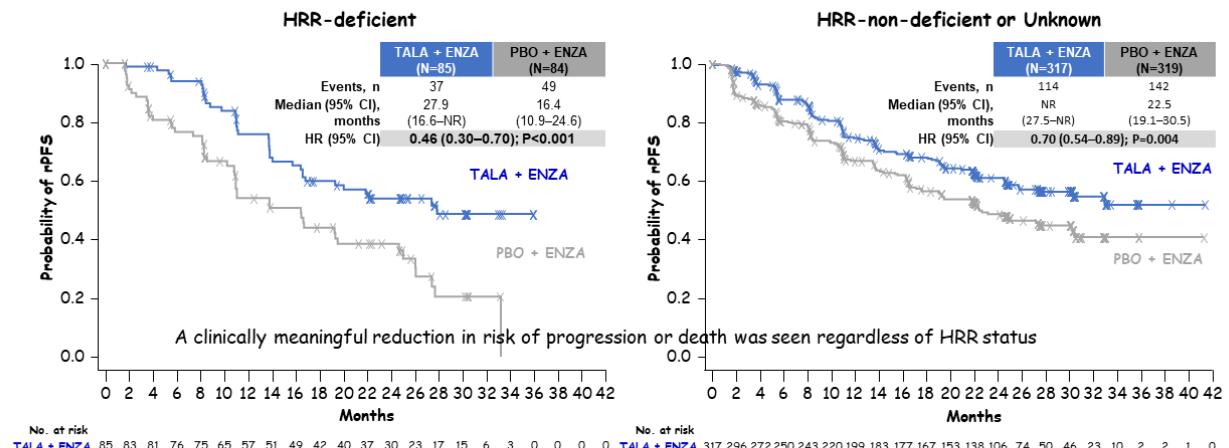
	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	NR (27.5-NR)	21.9 (16.6-25.1)
HR (95% CI)	0.63 (0.51-0.78); P<0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI 0.50-0.81); P<0.001

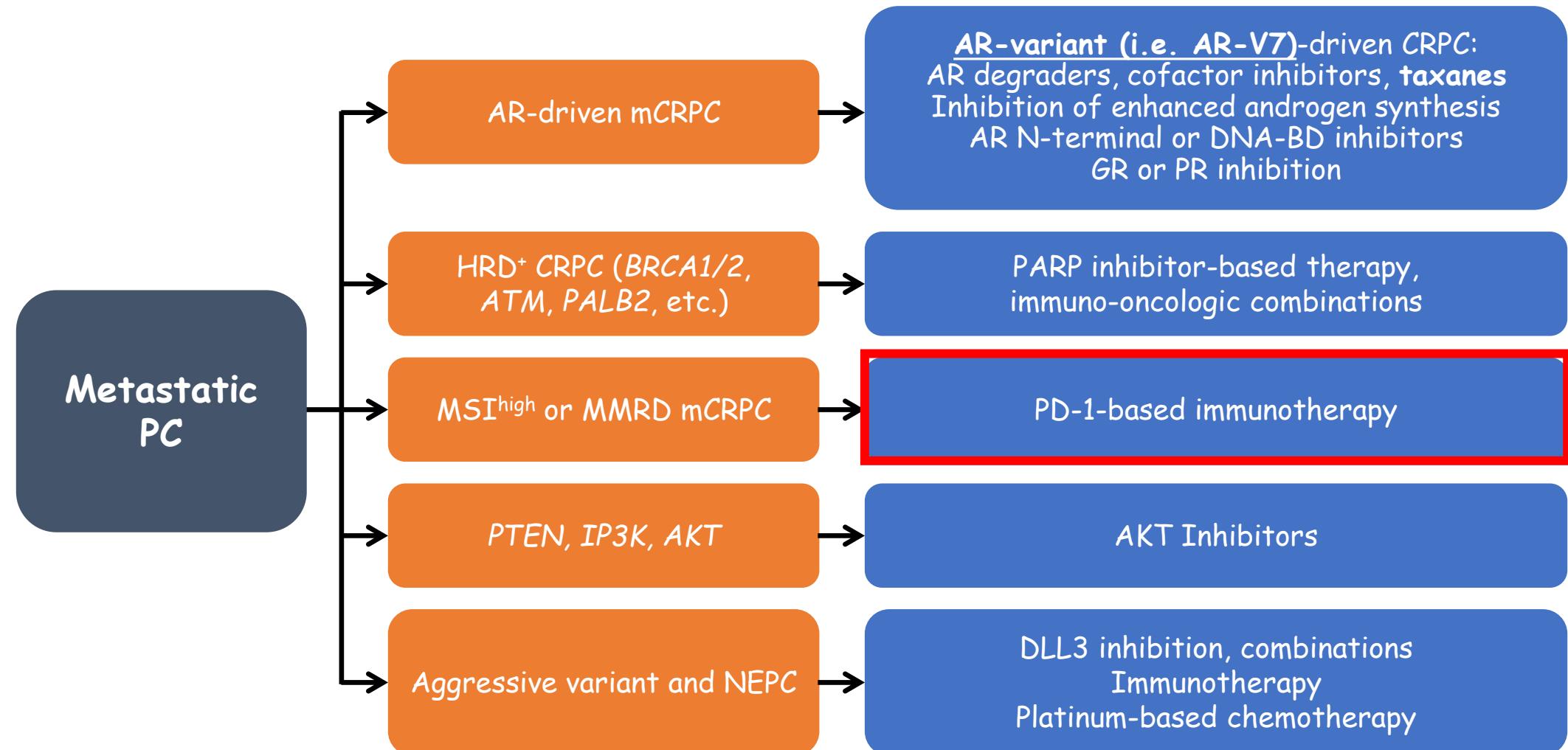
^aStratified HRs and two-sided P values are reported throughout this presentation unless otherwise stated. BICR=blinded independent central review; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; NR=not reached; PBO=placebo; rPFS=radiographic progression-free survival; TALA=talazoparib. Agarwal N, et al. LBA 17. ASCO GU 2023.

TALAPRO-2: rPFS by BICR by HRR Gene Status



HRR=homologous recombination repair; BICR=blinded independent central review; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; NR=not reached; PBO=placebo; rPFS=radiographic progression-free survival; TALA=talazoparib. Agarwal N, et al. LBA 17. ASCO GU 2023.

Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas



AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor



PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

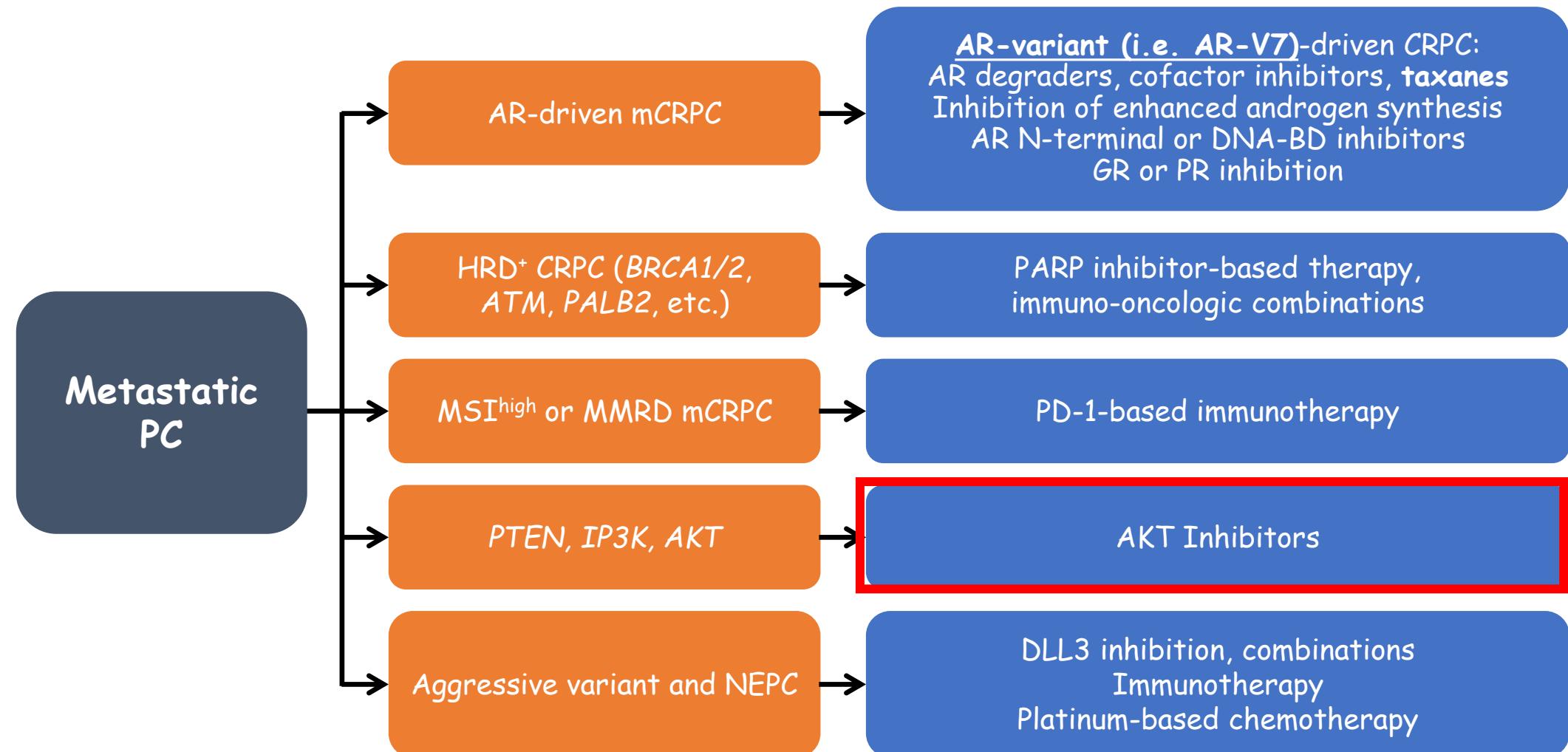
Dung T. Le, M.D., Jennifer N. Uram, Ph.D., Hao Wang, Ph.D., Bjaame R. Bartlett, B.S., Holly Kemberling, R.N., Aleksandra D. Eyring, M.Pharm., Andrew D. Skora, Ph.D., Brandon S. Luber, Sc.M., Nilofer S. Azad, M.D., Dan Laheru, M.D., Barbara Biedrzycki, Ph.D., C.N.R.P., Ross C. Donehower, M.D., Atif Zaheer, M.D., George A. Fisher, M.D., Ph.D., Todd S. Crocenzi, M.D., James J. Lee, M.D., Ph.D., Steven M. Duffy, M.D., Richard M. Goldberg, M.D., Albert de la Chapelle, M.D., Ph.D., Minoru Koshiji, M.D., Ph.D., Feriyi Bhajjee, M.D., Thomas Huebner, M.D., Ralph H. Hruban, M.D., Laura D. Wood, M.D., Ph.D., Nathan Cuka, M.D., Drew M. Pardoll, M.D., Ph.D., Nickolas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Shabin Zhou, M.D., Ph.D., Toby C. Cornish, M.D., Ph.D., Janis M. Taube, M.D., Robert A. Anders, M.D., Ph.D., James R. Eshleman, M.D., Ph.D., Bert Vogelstein, M.D., and Luis A. Diaz, Jr., M.D.

May 30, 2015 | DOI: 10.1056/NEJMoa1500596

	N	Objective response rate		DOR range (months)
		n (%)	95% CI	
Non-CRC (continued)	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

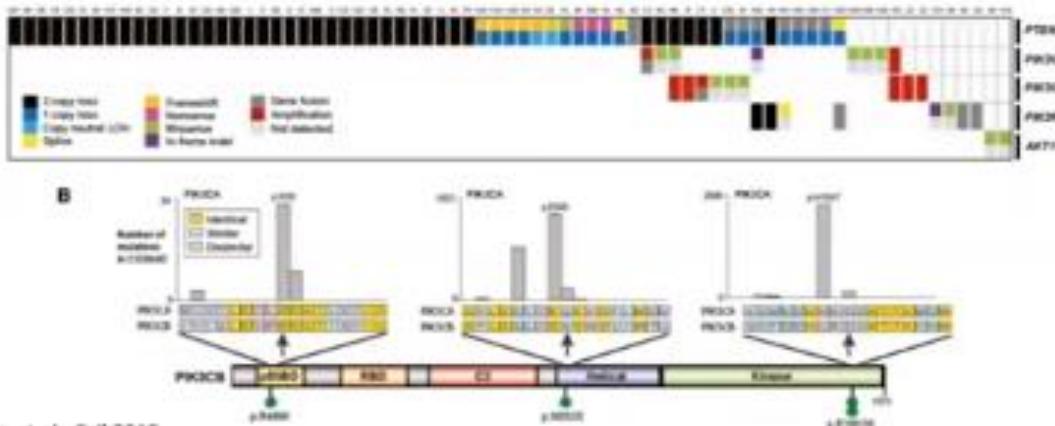
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas

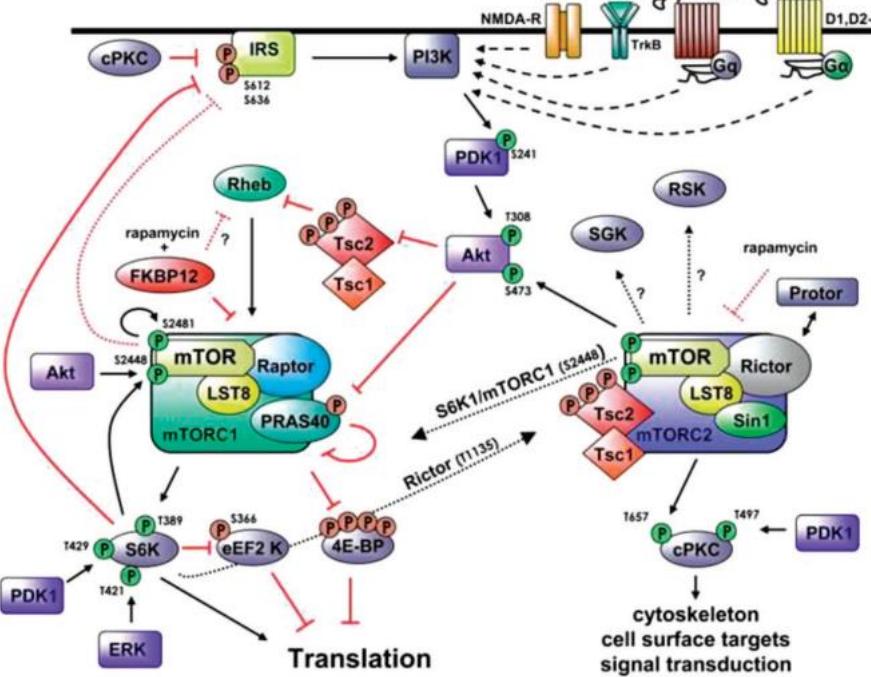


AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor

- In prostate cancer:**
- ~40% PTEN loss most deep homozygous deletion
- usually early (truncal) events
- activating hotspot mutations in *AKT1* and *PIK3CA* less common



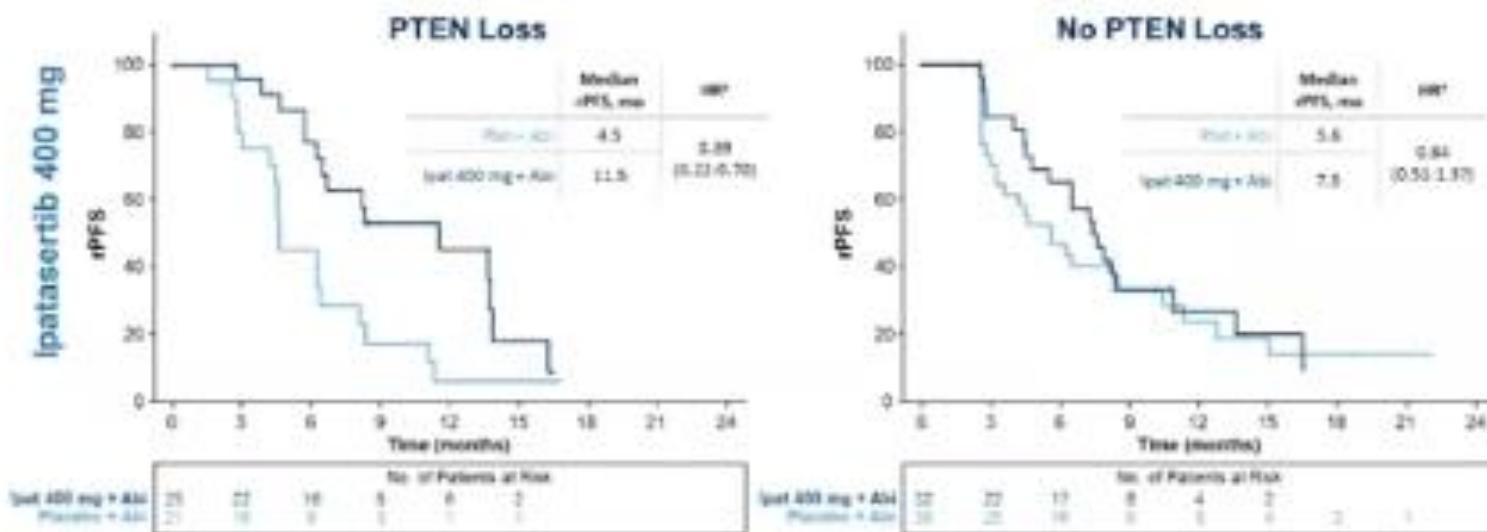
- PTEN loss leads to greater PI3K activity in castrate conditions, thereby supporting resistance to AR inhibition
- Single agent targeting of the PI3K pathway in non-biomarker selected breast or CRPC has minimal activity in phase II trials
 - DLTs
 - functional redundancy, complex compensatory mechanisms
 - challenges with biomarker selection



AKT Inhibition by Ipatasertib in mCRPC: The A.MARTIN Randomized Phase II Trial

A randomized Phase II study of AKT blockade with ipatasertib and abiraterone, vs abiraterone alone, in 253 patients with mCRPC after docetaxel chemotherapy

Combined Ipatasertib and Abiraterone Improved rPFS in Patients With mCRPC With PTEN Loss



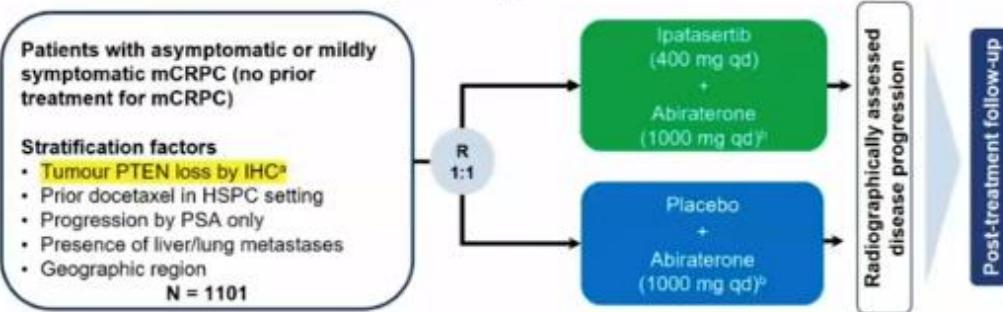
Abi, abiraterone; ipat, ipatasertib; PFS, placebo; mCRPC, metastatic castration-resistant prostate cancer; PTEN, phosphatase and tensin homolog; rPFS, radiological progression-free survival.

*Unstratified HR (95% CI).

© 2019 ASH. Clin Cancer Res. 2019;25(3):926-934.

PTEN null mCRPC defined by Cell Signaling antibody IHC

IPATential150 study design



- Co-primary endpoints: investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- Secondary endpoints included: OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

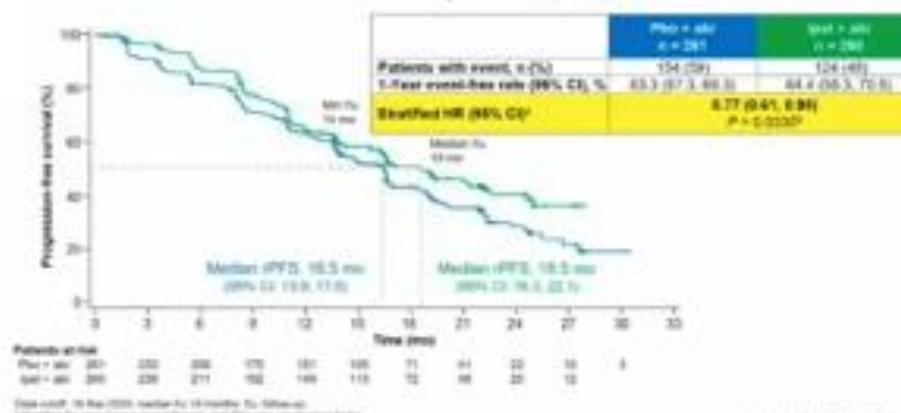
HSPC, hormone-sensitive prostate cancer; NGS, next-generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomized.

*PTEN loss was defined as a minimum of 50% of the specimen's tumour area with no detectable PTEN staining (by Ventana IHC assay using SP215 antibody).

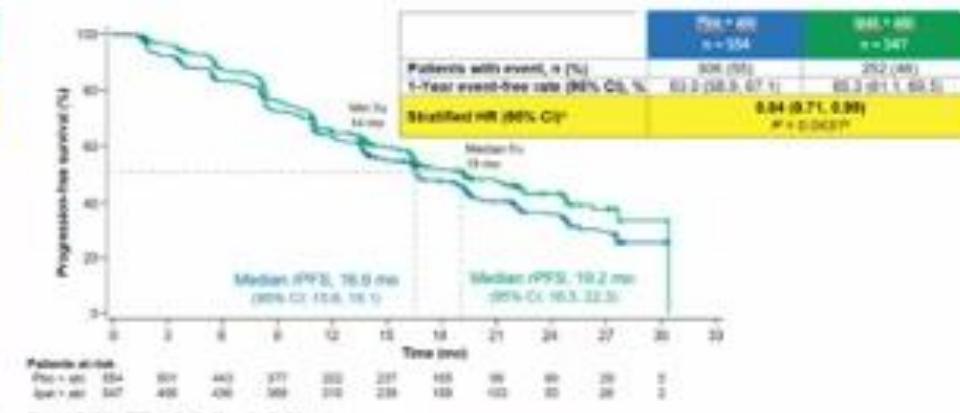
†Abiraterone (1000 mg qd) plus prednisone/prednolone (5 mg bid).

de Bono J. (IPATential150). ESMO 2020. <https://bit.ly/31s8ge>

rPFS in the PTEN-loss by IHC population



rPFS in the ITT population

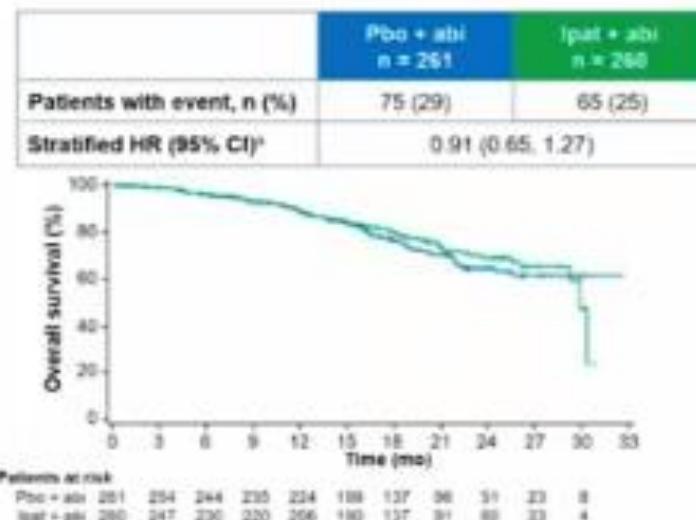


- Primary endpoint was met with prolonged rPFS by PTEN-loss IHC but not in ITT group
- Similar benefits in overall and duration of objective response in PTEN loss group (but not with PSA response or TTP)

IPATential150

Overall survival

PTEN loss by IHC



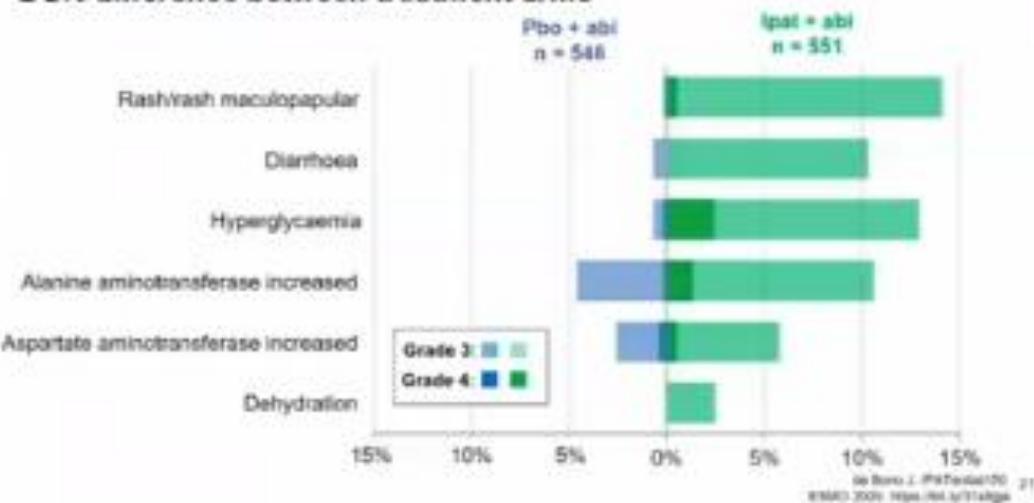
Data cutoff, 16 Mar 2020; median follow-up, 19 months.

^aStratified for prior taxane-based therapy and PSA-only progression factor.

^bStratified for prior taxane-based therapy, PSA-only progression factor and tumour PTEN loss status by IHC.

Grade 3 and 4 AEs

≥ 2% difference between treatment arms

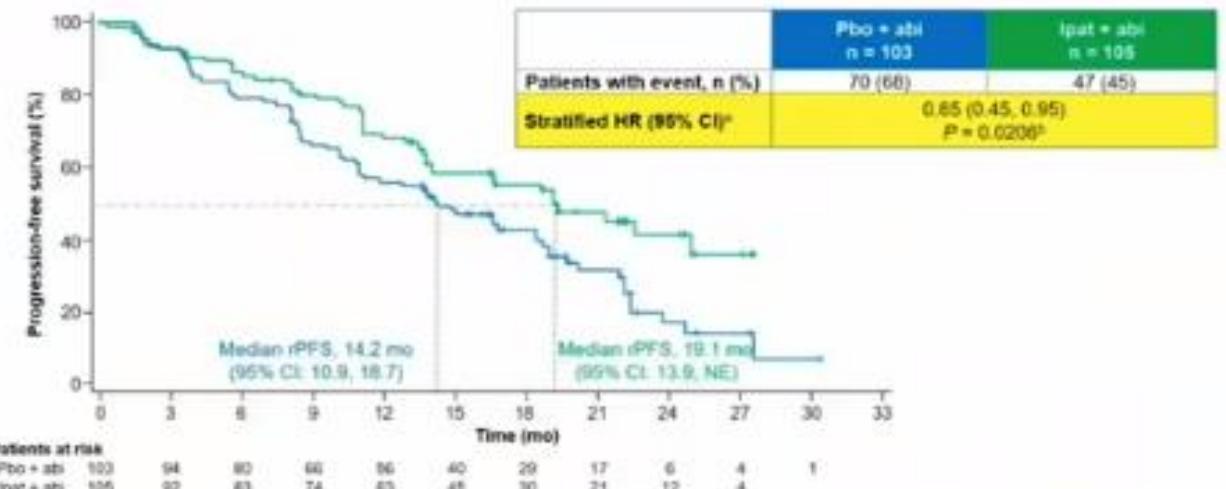


- 39% vs 70% grade 3-4
- 5% vs 21% discontinuation, 6% vs 39% dose reduction

Activation of the AKT pathway and outcomes in patients treated with or without ipatasertib in metastatic castration-resistant prostate cancer (mCRPC): next-generation sequencing data from the Phase III IPATential150 trial

Abstract 5056

rPFS in the NGS-defined PTEN-loss population



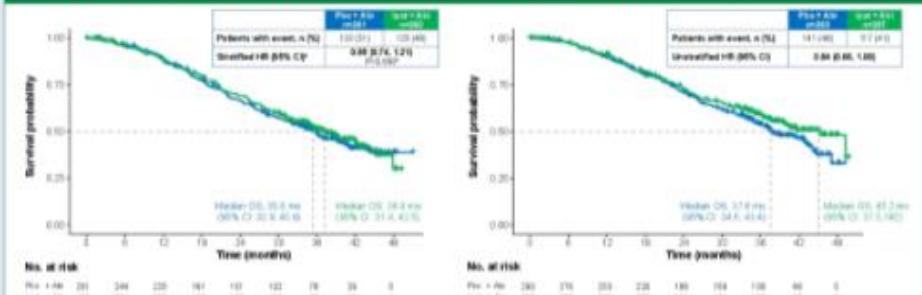
Date last eff., 16 Mar 2020; median follow-up, 18 months.

^aStratified for prior taxane-based therapy and PSA-only progression factor. ^bDescriptive.

de Bono J. IPATential150. 18 ESMO 2020. <https://bit.ly/31vAqge>

~20% of the ITT population – not able to obtain tissue; insufficient tissues; low tumor content

Figure 2. OS in patients with PTEN loss tumors by IHC (A) and with PTEN-intact tumors by IHC (B)

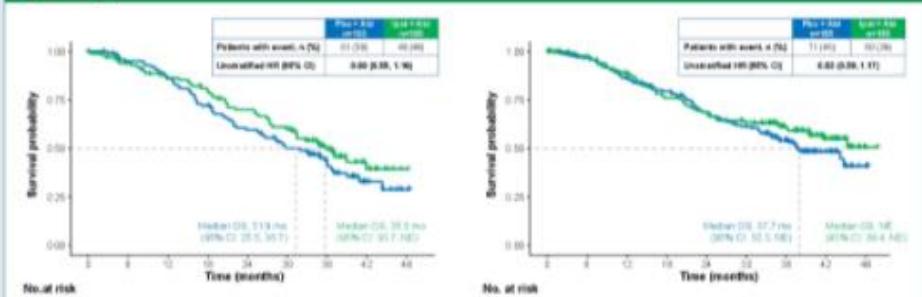


Abi, abiraterone; Ipat, ipatasertib; NE, not evaluable; Pbo, placebo.

^a Stratified for prior taxane-based therapy and PSA-only progression factor.

^b Not statistically significant at $\alpha = 0.0172$ level.

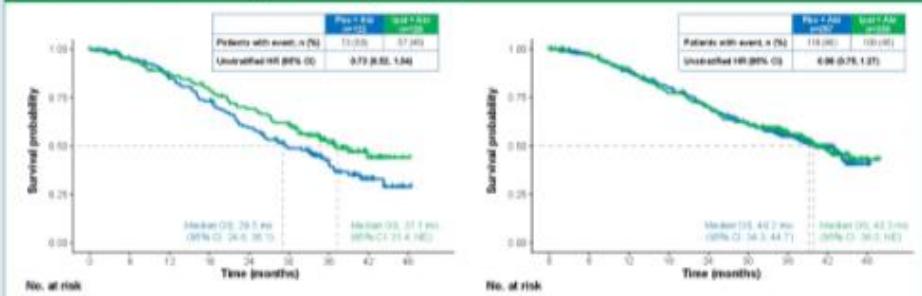
Figure 3. OS in patients with PTEN loss tumors by NGS^{a,b} (A) and with PTEN wild-type tumors by NGS^{a,b} (B)



^a PTEN-inactivating alterations were from homozygous deletion, heterozygous deletion, dominant negative mutations or bi-allelic inactivation (1 protein-truncating mutation, splice-site mutation or confirmed somatic missense or non-frame-shift mutation in PTEN that is under loss of heterozygosity).

^b Patients with PTEN status unknown by NGS were excluded.

Figure 4. OS in patients with PIK3CA/AKT1/PTEN-altered^a tumors by NGS (A) and in patients with PIK3CA/AKT1/PTEN wild-type tumors by NGS (B)



^a AKT1 alteration by NGS included mutations that result in an amino acid substitution at the E17, L52 or Q79 residues (n=9); PIK3CA alteration by NGS included mutations that result in an amino acid substitution at the R85, G108, K111, G118, N348, C420, E463, E542, E546, Q548, M1943, H1947 or G1048-residues (n=48).

Abstract 108: Updated overall survival (OS) analysis for ProCAID: a randomised, double blind, placebo-controlled phase II trial of capivasertib with docetaxel versus docetaxel alone in metastatic castration resistant prostate cancer (mCRPC)

Simon J Crabb¹, Gareth Griffiths¹, Denise Dunkley¹, Nichola Downs¹, Mary Ellis¹, Mike Radford¹, Michelle Light¹, Josh Northey¹, Amy Whitehead¹, Sam Wilding¹, Claire Rooney², Carol Salinas de Souza², Alison J Birtle³, Vincent Khoo⁴, Robert J Jones⁵

¹Southampton Clinical Trials Unit, University of Southampton, Southampton, UK; ²Translational Medicine, Oncology R&D, AstraZeneca, Cambridge, UK; ³Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK; ⁴The Royal Marsden NHS Foundation Trust, London, UK; ⁵University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK

Biomarker-positive if PTEN deficient by IHC and/or alteration in PIK3CA, PTEN, or AKT1 by NGS (tumor tissue or ctDNA)

Table 2. Survival outcomes

	24-month OS (probability; 95% CI)		36-month OS (probability; 95% CI)		Median OS (months; 95% CI)			
	Docetaxel + capivasertib	Docetaxel + placebo	Docetaxel + capivasertib	Docetaxel + placebo	Docetaxel + capivasertib	Docetaxel + placebo	Hazard ratio (95% CI)	p value
ITT population (N=150)	0.54 (0.41–0.65)	0.40 (0.28–0.51)	0.26 (0.14–0.39)	0.22 (0.11–0.35)	25.3 (20.1–31.2)	20.3 (17.5–24.2)	0.70 (0.47–1.05)	0.09
Prior ARTA therapy (n=101)	0.51 (0.35–0.64)	0.27 (0.15–0.41)	0.18 (0.07–0.32)	0.07 (0.01–0.23)	25.0 (17.7–31.1)	17.6 (14.4–20.3)	0.57 (0.36–0.91)	
No prior ARTA therapy (n=49)	0.61 (0.38–0.77)	0.65 (0.42–0.81)	0.46 (0.23–0.67)	0.52 (0.28–0.72)	31.1 (20.1–41.1)	NR (22.7-NR)	1.43 (0.63–3.23)	

Figure 1. Overall survival, with respect to treatment arm allocation, within the intent to treat population

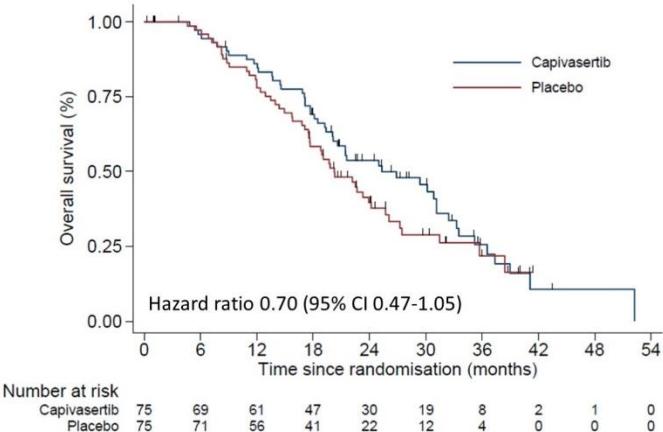
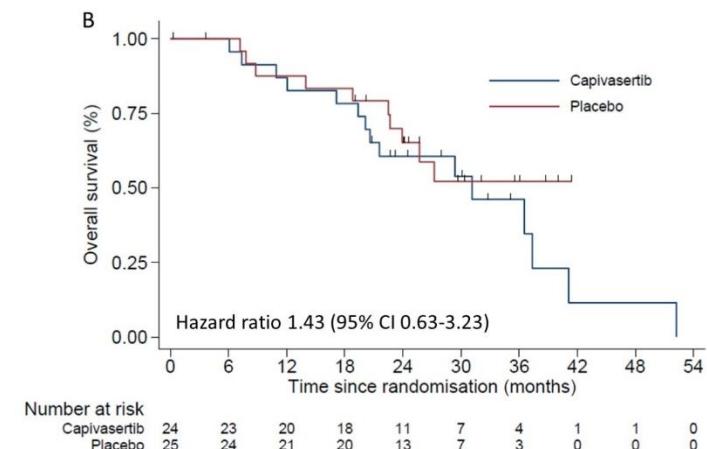
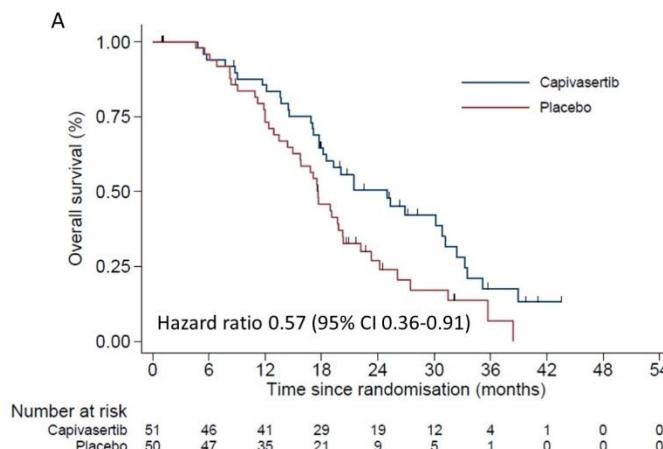


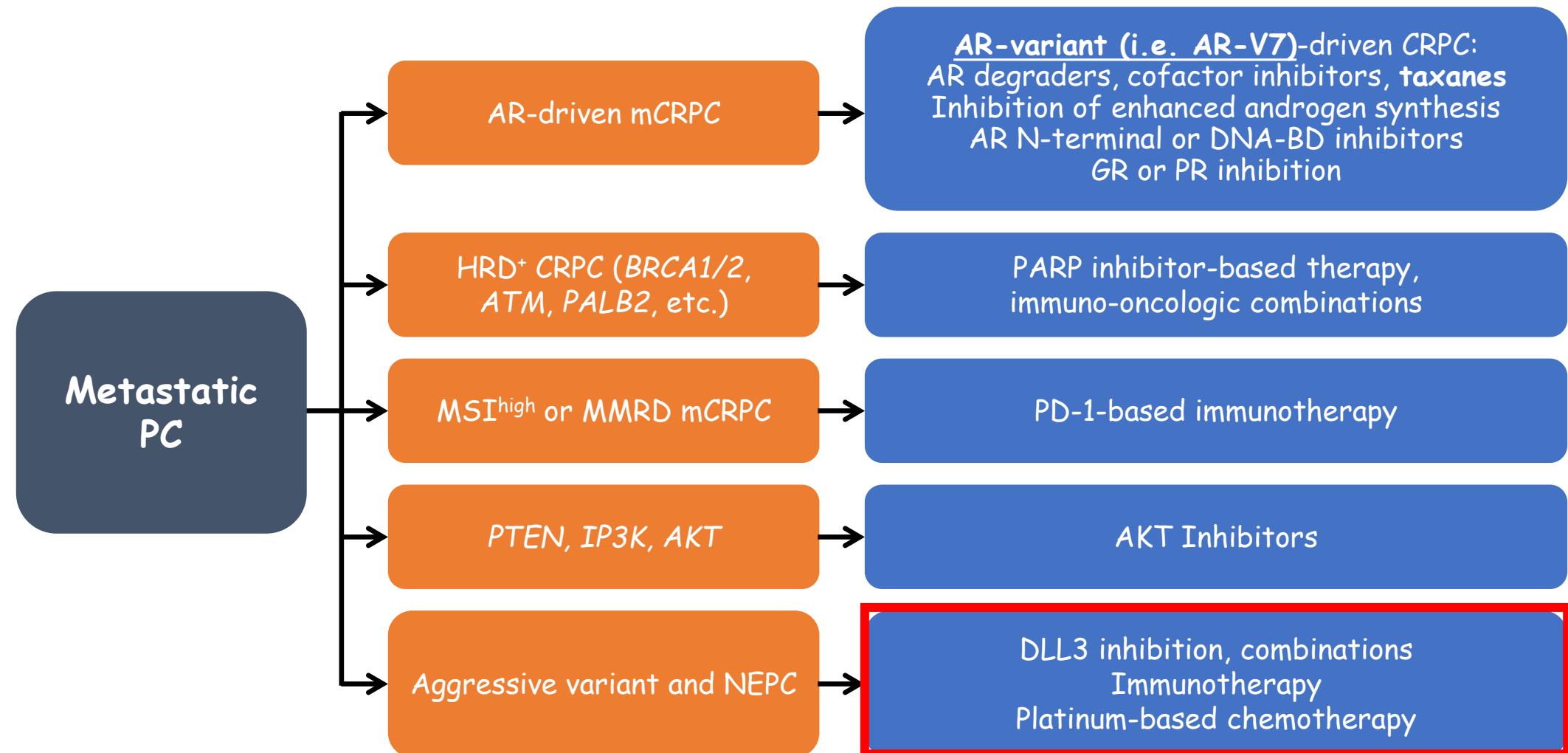
Figure 2. Overall survival, with respect to treatment arm allocation, within (A) the subgroup that received prior androgen receptor-targeted agent (ARTA) therapy prior to entering ProCAID, (B) the subgroup that had not received prior ARTA therapy



Awaiting results from ongoing trials:

- CCTG Umbrella Trial. NCT03385655
- RE-AKT Ph II: ENZA +/- Capivasertib in mCRPC. NCT02525068
- CAPItello-281: ABI +/- Capivasertib in mCSPC. NCT04493853
- CAPItello-280: Docetaxel +/- Capivasertib in mCRPC

Potencial Clasificación Molecular del Cáncer de Próstata e implicaciones terapéuticas



AR, androgen receptor; (m)CRPC, (metastatic) castration-resistant prostate cancer; DLL3, delta-like ligand 3; DNA-BD, DNA binding domain; GR, glucocorticoid receptor; HRD, homologous recombination deficiency; MMRD, mismatch repair deficient; MSI, microsatellite instability; NEPC, neuroendocrine prostate cancer; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PR, progesterone receptor

#5055: Biallelic loss of *TP53*, *PTEN*, and *RB1* associates with aggressive clinical features and poor outcomes in metastatic castration resistant prostate cancer (mCRPC)

Authors: ¹Corinne Maurice-Dror, ²Nicolette M. Fonseca, ²Cameron Herberst, ²Edmond M. Kwan, ¹Catarina Kollmannsberger, ²Wilson Tu, ¹Daniel J. Khalaf, ³Matti Annala, ^{1,2}Elena Schönlau, ²Cecily Q. Bernales, ²Gráinne Donnellan, ¹Joanna Vergidis, ¹Krista Noonan,

¹Daygen L. Finch, ¹Muhammad Zulfiqar, ¹Stacy Miller, ²Alexander W. Wyatt, ^{1,2}Kim N. Chi

¹BC Cancer, British Columbia, Canada, ²Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, British Columbia, Canada, ³ Faculty of Medicine and Life Sciences and Biomeditech Institute, University of Tampere, Tampere, Finland

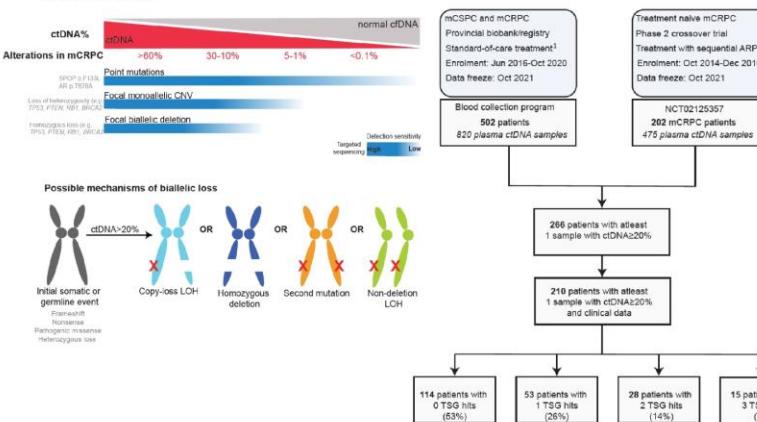
BACKGROUND

- Deleterious alterations in *PTEN*, *TP53* and *RB1* tumor suppressor genes (TSGs) are potential markers of AR pathway inhibitor resistance and poor outcomes in patients with metastatic prostate cancer, and are frequently lost with neuroendocrine/small cell differentiation.
- Loss of *PTEN* and *TP53* are truncal events and occur in 30-40% of mCRPC.
- RB1* loss is seen in ~12% of cases and is acquired later in the disease course.
- Genomic profiling of plasma derived circulating tumor DNA (ctDNA) is a minimally invasive approach of detecting tumor suppressor gene loss.

Objective: To examine the outcomes and clinical features of mCRPC patients harboring biallelic loss in 0, 1, 2 or all 3 aforementioned TSGs.

METHODS

- 210 metastatic prostate cancer patients with at least one sample containing ctDNA% ≥20% at any time throughout their treatment course were identified.
- ctDNA ≥20% was utilized to reduce false negatives when evaluating copy number loss of *PTEN*, *TP53* or *RB1*.
- Targeted sequencing of plasma cell-free DNA sample was performed with a custom 72-gene prostate cancer panel.
- PSA progression free survival (PSA PFS), overall survival (OS) and PSA declines ≥50% from baseline (PSA50 response rate (RR)) were retrospectively determined.



References: ¹Warner E, Herberst C et al, BRCA2, ATM and CDK12 defects differentially shape prostate tumor driver genomics and clinical aggression. Clin Cancer Res. 2021; 27 (6): 1650-1662. ²Annala M et al, Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Dis. 2018; 8 (4):444-57. ³Aparicio AM et al, Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer. Clin Cancer Res. 2013; 19 (13):3621-30.

- Aggressive disease features, such as liver metastases, are enriched in patients with biallelic loss of TSGs
- Combined TSG loss is associated with poor clinical outcomes on standard of care first-line mCRPC therapies

Correspondence to Dr. Kim N Chi (kchi@bccancer.bc.ca)

Acknowledgements: The investigators would like to thank the patients, their families and caregivers

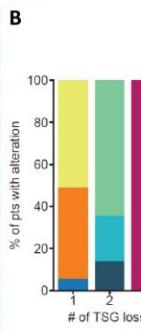


RESULTS

Patient characteristics and proportion with combined TSG loss

Baseline Characteristics*		Patients (n=210)
Median age, years (range)		69 (48-98)
De-Novo metastatic disease, % (n)		61 (124)
≤12 mo. from androgen deprivation therapy to 1st line CRPC treatment, % (n)		40 (83)
Treatment intensification for mCSPC % (n)		22 (46)
ECOG 0-1 % (n)		51 (91)
Alk Phos > ULN % (n)		39 (76)
LDH > ULN % (n)		38 (63)
Visceral metastases % (n)		23 (40)
ctDNA% (range)		42.2 (20.6-99.7)
First Line Treatment % (n)		
ARPI		91 (187)
Taxane Chemotherapy		4 (9)
Median Follow-up, months (range)		16.26 (0.37-110.7)

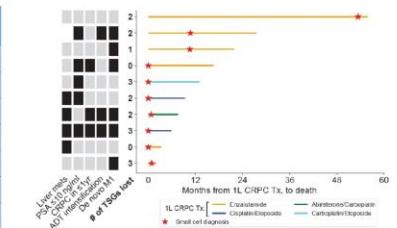
*of patients with available data



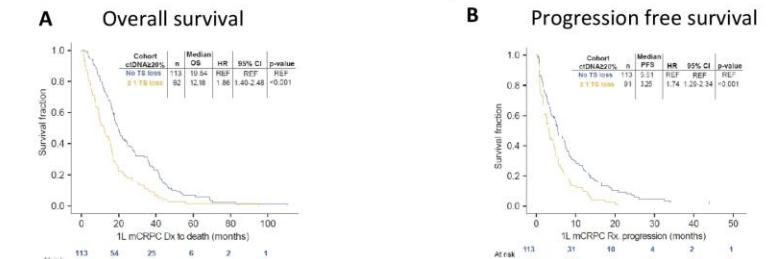
Few tumors with 3 TSG loss meet classic aggressive variant criteria

AVPC criteria ^a evaluated for 3TSG loss patients (n=15) n/n with available data (%)	Initial Diagnosis	mCRPC
Small cell histology	0/14 (0)	3/6 (50)
Exclusive visceral mets	0/15 (0)	0/15 (0)
Predominant lytic bone lesions	0/14 (0)	0/13 (0)
Bulky pelvic LNs or Tumor mass (>5cm)	2/14 (14)	N/A
Low PSA (>10) plus high-volume (>20) bone mets	1/15 (7)	1/12 (8)
Neuroendocrine features (tumor / blood)	0/0 (0)	2/2 (100)
ADT to mCRPC ≤6 months	2/15 (13)	N/A

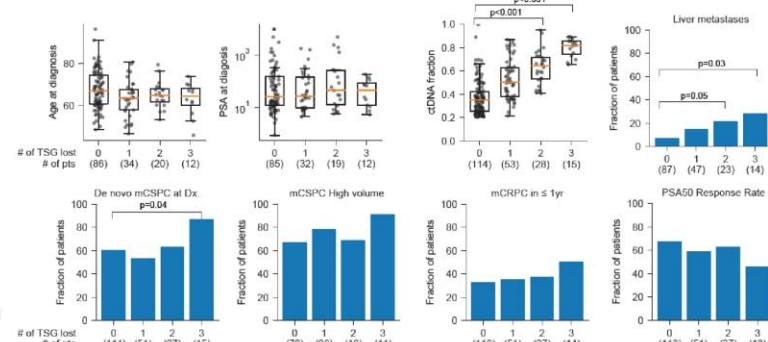
Most small cell prostate cancer have biallelic loss of ≥2 TSGs



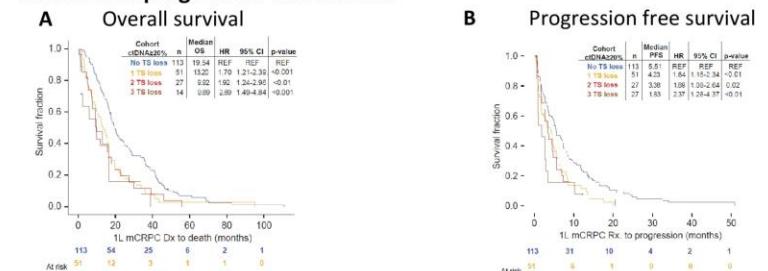
Biallelic loss of ≥1 TSGs is associated with poor outcomes



Increasing biallelic TSG loss is associated with high risk features



Cumulative biallelic TSGs loss is associated with incremental reduction in overall and progression free survival



#5055: Biallelic loss of *TP53*, *PTEN*, and *RB1* associates with aggressive clinical features and poor outcomes in metastatic castration resistant prostate cancer (mCRPC)

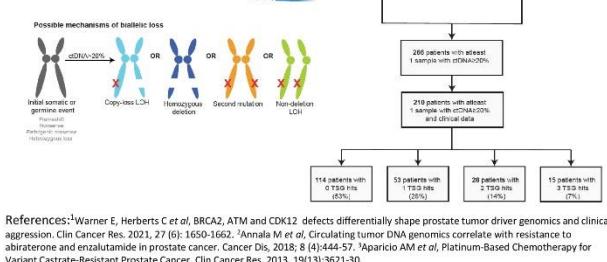
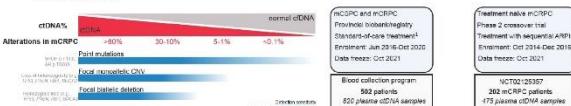
Authors: ¹Corinne Maurice-Dror, ²Nicolette M. Fonseca, ²Cameron Herberts, ²Edmond M. Kwan, ¹Catarina Kollmannsberger, ²Wilson Tu, ¹Daniel J. Khalaf, ³Matti Annala, ^{1,2}Elena Schönlau, ²Cecily Q. Bernales, ²Gráinne Donnellan, ¹Joanna Vergidis, ¹Krista Noonan, ¹David L. Finch, ³Mohammed Zulfikar, ¹Stacy Miller, ²Alexander W. Wyatt, ^{1,2}Kim N. Chi

¹Faculty of Medicine and Life Sciences and Biomeditech Institute, University of Tampere, Tampere, Finland

Few tumors with 3 TSG loss meet classic aggressive variant criteria

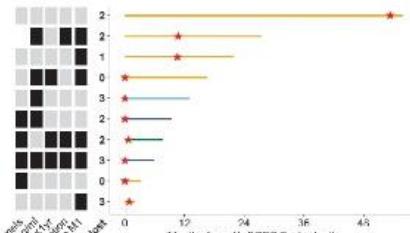
AVPC criteria ^a evaluated for 3TSG loss patients (n=15) n/n with available data (%)	Initial Diagnosis	mCRPC
Small cell histology	0/14 (0)	3/6 (50)
Exclusive visceral mets	0/15 (0)	0/15 (0)
Predominant lytic bone lesions	0/14 (0)	0/13 (0)
Bulky pelvic LNs or Tumor mass (>5cm)	2/14 (14)	N/A
Low PSA (<=10) plus high-volume (>20) bone mets	1/15 (7)	1/12 (8)
Neuroendocrine features (tumor/ blood)	0/0 (0)	2/2 (100)
ADT to mCRPC ≤6 months	2/15 (13)	N/A

- ctDNA% ≥20% at any time throughout their treatment course were identified.
- ctDNA ≥20% was utilized to reduce false negatives when evaluating copy number loss of *PTEN*, *TP53* or *RB1*.
- Targeted sequencing of plasma cell-free DNA sample was performed with a custom 72-gene prostate cancer panel.
- PSA progression free survival (PSA PFS), overall survival (OS) and PSA declines ≥50% from baseline (PSA50 response rate (RR)) were retrospectively determined.



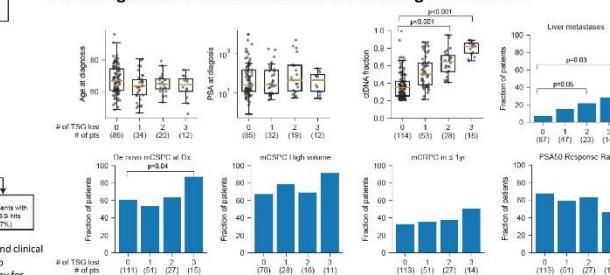
References:^a Warner E, Herberts C et al, BRCA2, ATM and CDK12 defects differentially shape prostate tumor driver genomics and clinical aggression. Clin Cancer Res. 2021; 27 (6): 1650-1662. Annala M et al, Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Dis. 2018; 8 (4):444-57. Aparicio AM et al, Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer. Clin Cancer Res. 2013; 19(13):3621-30.

Most small cell prostate cancer have biallelic loss of ≥2 TSGs



AVPC criteria ^a evaluated for 3TSG loss patients (n=15) n/n with available data (%)	Initial Diagnosis	mCRPC
Small cell histology	0/14 (0)	3/6 (50)
Exclusive visceral mets	0/15 (0)	0/15 (0)
Predominant lytic bone lesions	0/14 (0)	0/13 (0)
Bulky pelvic LNs or Tumor mass (>5cm)	2/14 (14)	N/A
Low PSA (<=10) plus high-volume (>20) bone mets	1/15 (7)	1/12 (8)
Neuroendocrine features (tumor/ blood)	0/0 (0)	2/2 (100)
ADT to mCRPC ≤6 months	2/15 (13)	N/A

Increasing biallelic TSG loss is associated with high risk features

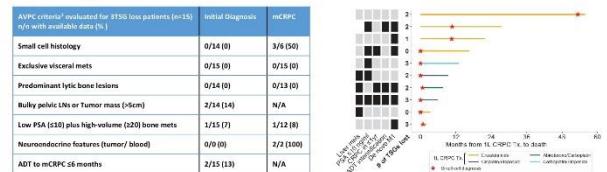


Patients with metastases, are enriched in patients with biallelic loss of TSGs Poor clinical outcomes on standard of care first-line mCRPC therapies

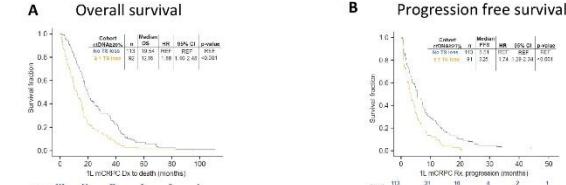


RESULTS

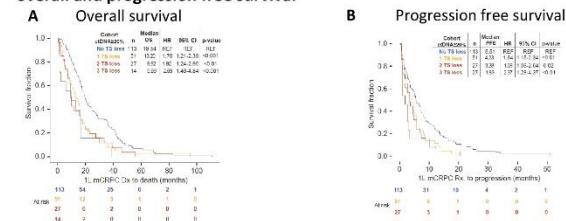
Few tumors with 3 TSG loss meet classic aggressive variant criteria



Biallelic loss of ≥1 TSGs is associated with poor outcomes



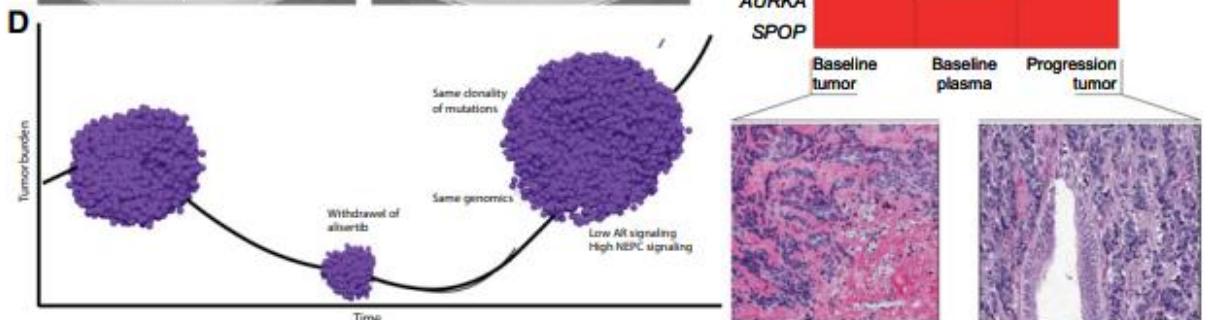
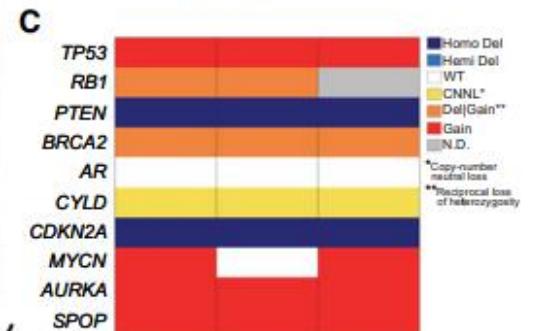
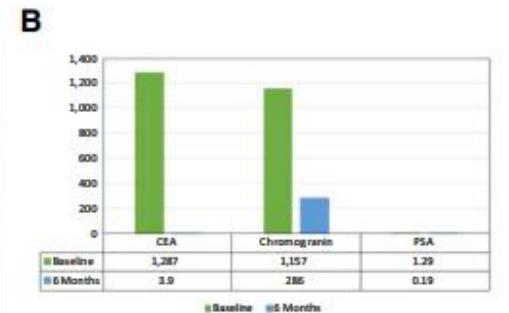
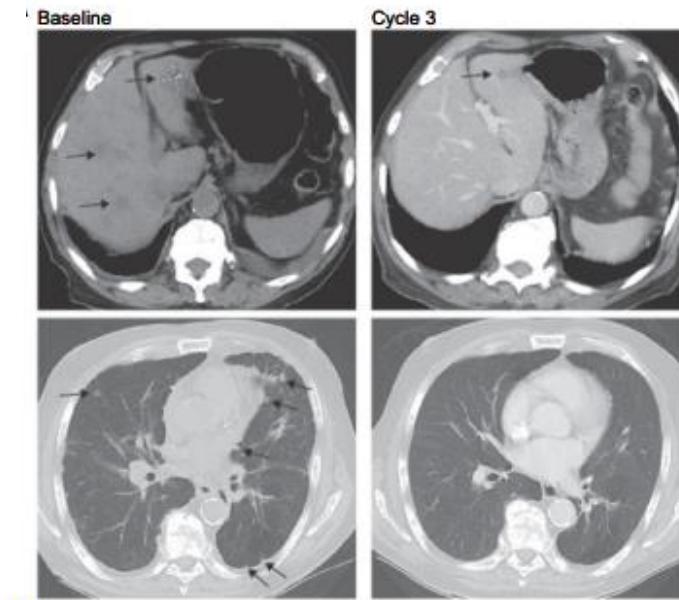
Cumulative biallelic TSGs loss is associated with incremental reduction in overall and progression free survival

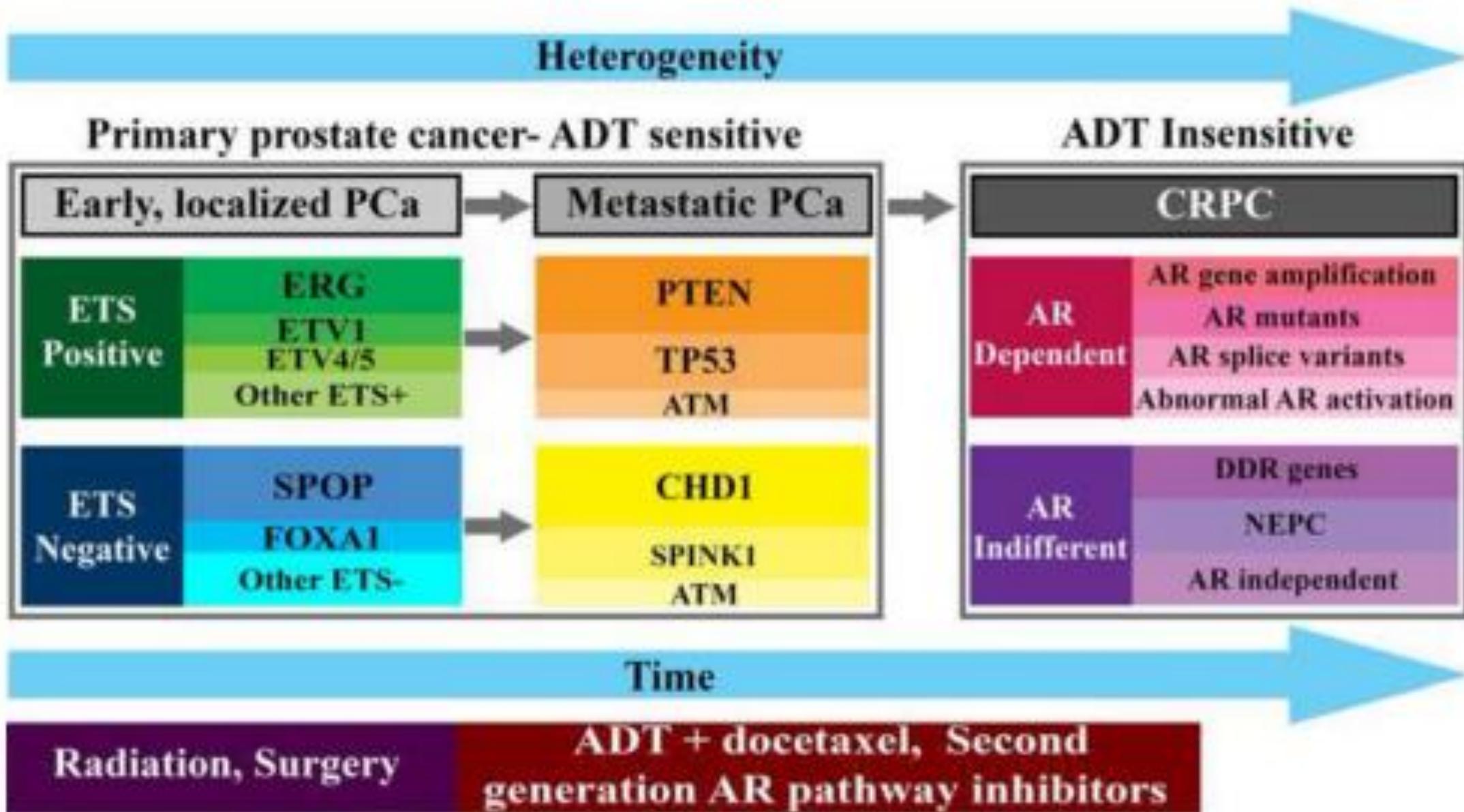




A Phase II Trial of the Aurora Kinase A Inhibitor Alisertib for Patients with Castration-resistant and Neuroendocrine Prostate Cancer: Efficacy and Biomarkers

Criterio Inclusión
 AP compatible
 Expresión de marcadores
 Progresión en el contexto de no elevación de PSA





A black and white photograph of a dense urban skyline, likely Barcelona, featuring a variety of architectural styles. In the foreground, there are several buildings with traditional tiled roofs and ornate facades. A prominent feature is a tall, detailed Gothic-style tower on the right side, which appears to be the Sagrada Família. The sky is filled with large, billowing clouds, creating a dramatic and somewhat somber atmosphere.

Gracias