Taller Guard: Medicina de precisión en cáncer de próstata avanzado

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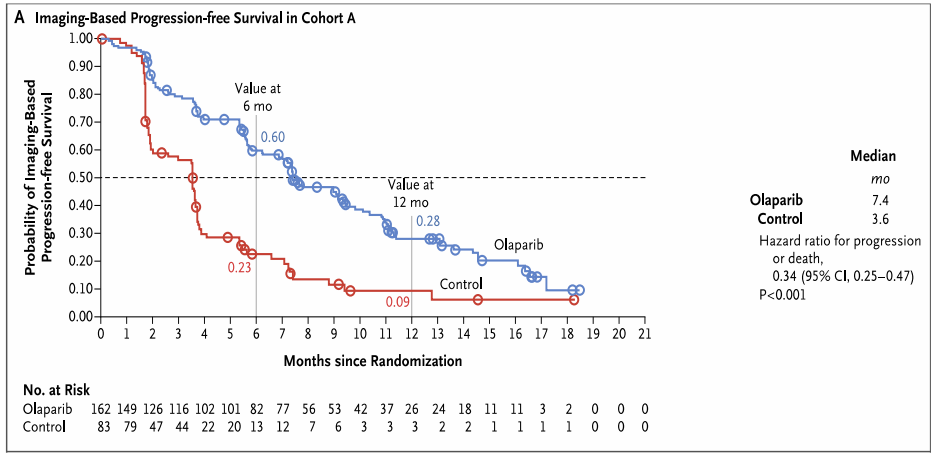
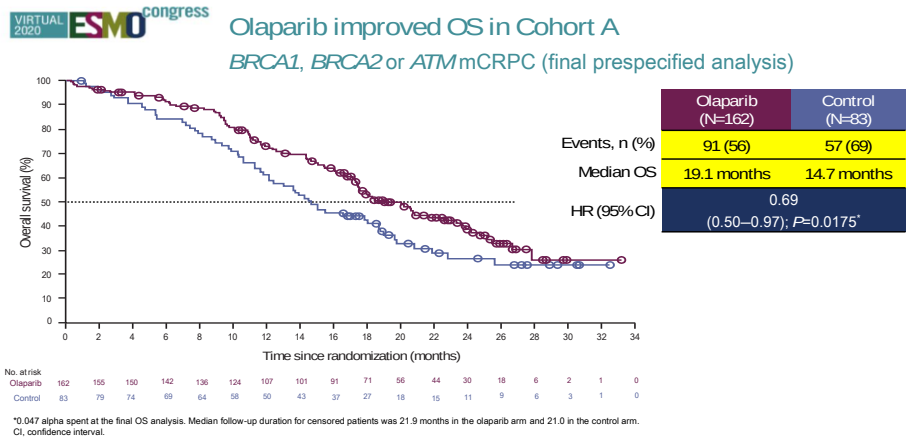
	Olaparib			Rucaparib		Niraparib	Talazoparib	
Trial	TOPARP-A	TOPARP-B	PROFOUND	TRITON2	TRITON 3	GALAHAD	TALAPRO	ZZ-First
Phase	Phse 2	Phase 2 adaptative	Phase 3	Phase 2 single arm	Phase 3 (2:1)	Phase 2, Single arm	Phase 2 single arm	F2 (2:1)
Treatment		Olaparib	Olaparib vs abi/enza	Rucaparib	Rucaparib vs Abi/eza/Doce	Niraparib	Talazoparib	Enza +- Talazoparib
Scenario	CPRCm pre-treated (Taxane & ARSI)	CPRCm pre-treated (Taxane)	CPRCm pre-treated (ARSI)	CPRCm pre-treated (Taxane + ARSI)	CPRCm pretreated (ADT + 1 ARSI)	CRPCm pre-treated (taxane ARSI)	CPRCm pre-treated taxane ARSI)	CPHSm naive
N	50	98	387	360	Aprox 400	291	89 (enf medible)	54
Endpoint 1º	ORR	CR	PFSr (BRCA/ATM)	ORR (BRCA)	PFSr	ORR (gBRCA / BRCA bialélico)	ORR	PCS-CR
HRR alterations	HRR (any)	HRR (any)	Cohort A: BRCA1, BRCA2, ATM Cohort B: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANC1, PALB2, PPPR2A, RAD51C, RAD51B, RAD51D, RAD54L	15 genes (germinal or somatic , mono- o bi-allelic): BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L)	BRCA1, BRCA2 or ATM mutant	8 genes (biallelic): BRCA1, BRCA2, ATM, FANCA, PALB2, CHEK2, BRUP1, HDAC2 o BRCA germinal)	11 genes (mono or biallelic): BRCA1, BRCA2, CHECK2, ATM, ATR, FANCA, MLH1, MREN1A, NBN, PALB2, RAD51C)	-
Molecular Testing	Academic Lab	Academic Lab	Central Lab (tissue)	Local/central (Blood /Tissue)	Local/Central (Tissue) and ctDNA	Local/Central (Tissue) and ctDNA	Central/local (Foundation Medicine)	Academic Lab

Profound

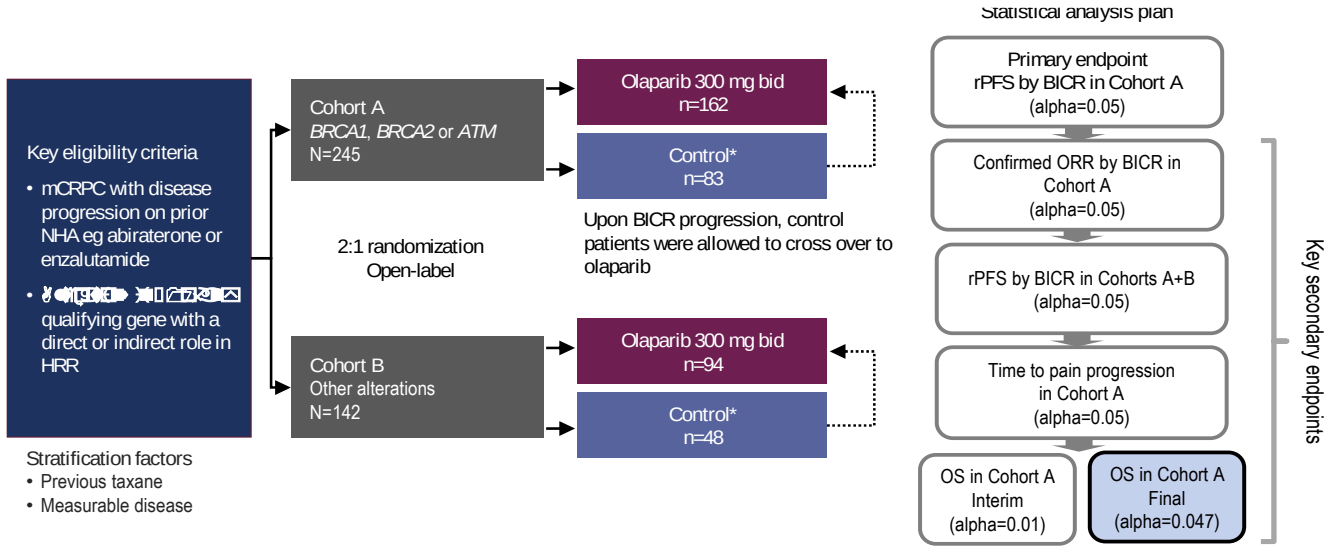
Olaparib for Metastatic Castration-Resistant Prostate Cancer

J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain

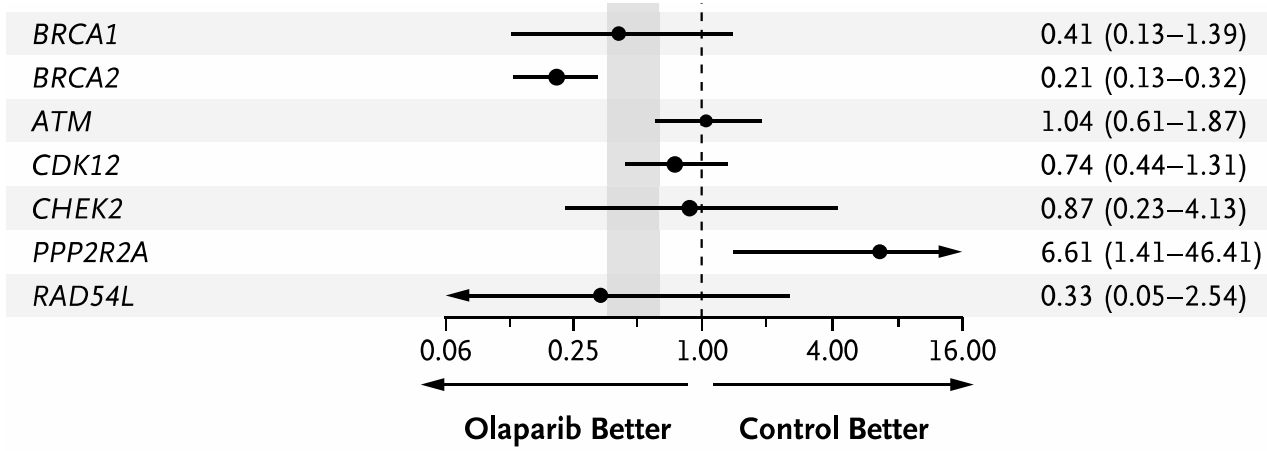




*0.047 alpha spent at the final OS analysis. Median follow-up duration for censored patients was 21.9 months in the olaparib arm and 21.0 in the control arm.
CI, confidence interval.



Patients randomized between April 2017 and November 2018; DCO for final OS: 20 March 2020



Combinación iPARP + ARPI

Trial	Therapies	rPFS HRRm (CI)	rPFS BRCA1/2 (CI)	Prior ARPI	Prior taxane
TALAPRO-2[1]	**Enzalutamide + Talazoparib**	**0.45 (0.33-0.61)**	**0.20 (0.11-0.36)**	**8%**	**29.4%**
PROpel[2]	Abiraterone + Olaparib	0.50 (0.34-0.73)	0.23 (0.12-0.43)	0.15%	24.5%
MAGNITUDE[3]	Abiraterone + Niraparib	0.73 (0.56-0.96)	0.53 (0.36-0.79)	3.1%	20.1%

[1]Fizazi et al, ASCO GU, 2023
[2]Clarke et al, NEJM Evidence, 2022
[3]Chi et al, JCO, 2023

Propel: abiraterona + olaparib

Patient population
- 1L treatment at mCRPC stage
- Docetaxel allowed in mHSPC stage*
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrolment
- Ongoing ADT
- ECOG performance status 0–1

R 1:1 N=796

Olaparib 300 mg PO BID + **abiraterone** 1000 mg QD†
n=399
Full dose of olaparib and abiraterone used

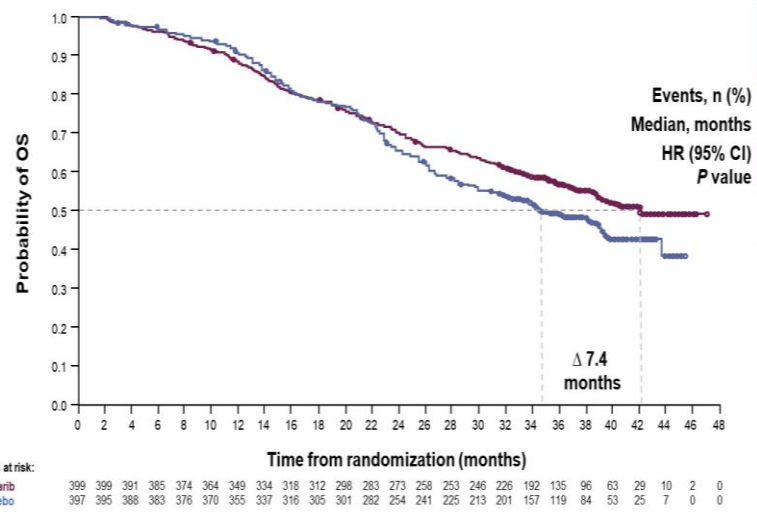
Placebo + **abiraterone** 1000 mg QD†
n=397
Full dose of abiraterone used

Primary endpoint
- Radiographic progression or death (rPFS) by investigator assessment

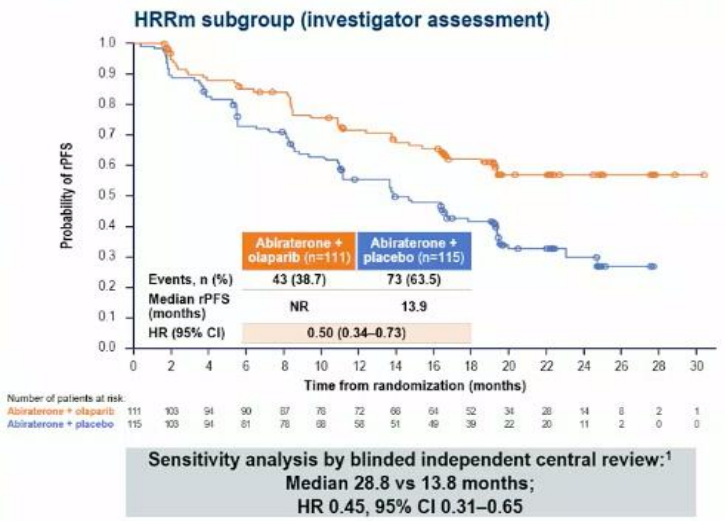
Key secondary endpoints:
- Overall survival (alpha control)

Additional endpoints:
- Time to first subsequent therapy or death
- Time to second progression or death
- Objective response rate
- HRRm prevalence (retrospective testing)‡
- Health-related quality of life
- Safety and tolerability

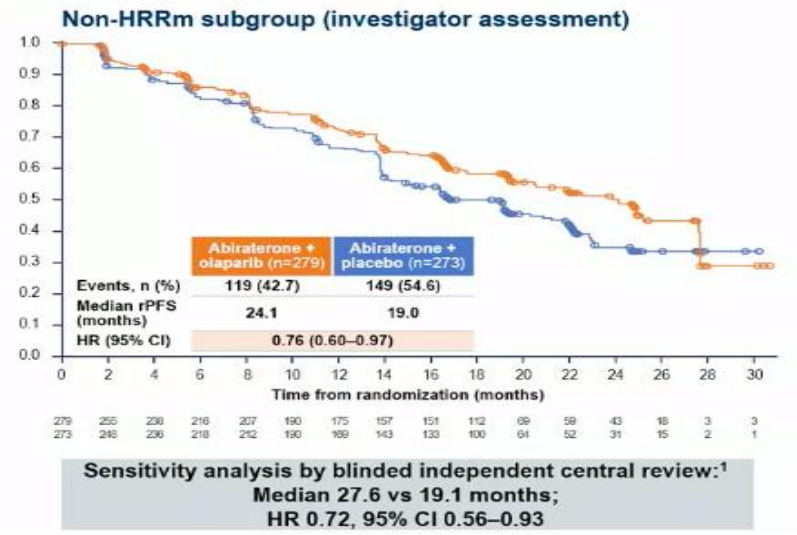
Stratification factors:
1. Site of distant metastases: bone only vs. visceral vs. other
2. Prior taxane at mHSPC: yes vs. no



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
	47.9% maturity	



Sensitivity analysis by blinded independent central review:[1]
Median 28.8 vs 13.8 months;
HR 0.45, 95% CI 0.31–0.65

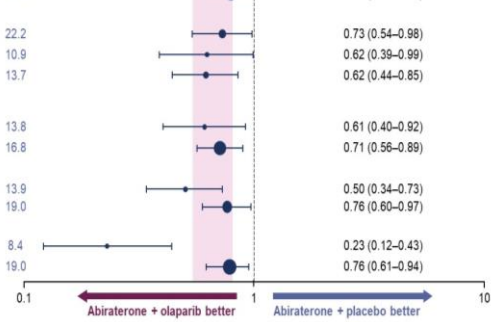


Sensitivity analysis by blinded independent central review:[1]
Median 27.6 vs 19.1 months;
HR 0.72, 95% CI 0.56–0.93

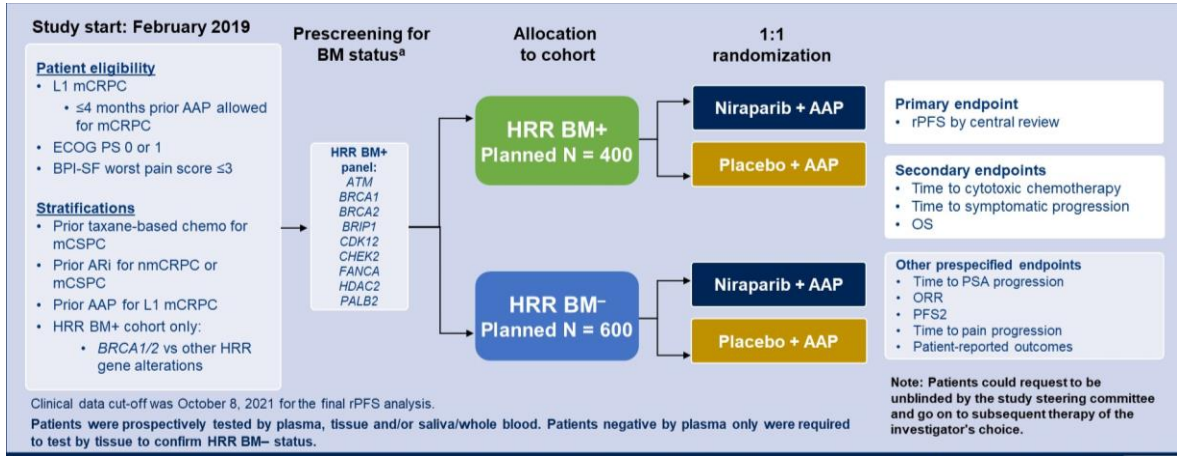
PROpel: rPFS in subgroups (DCO1)[1]

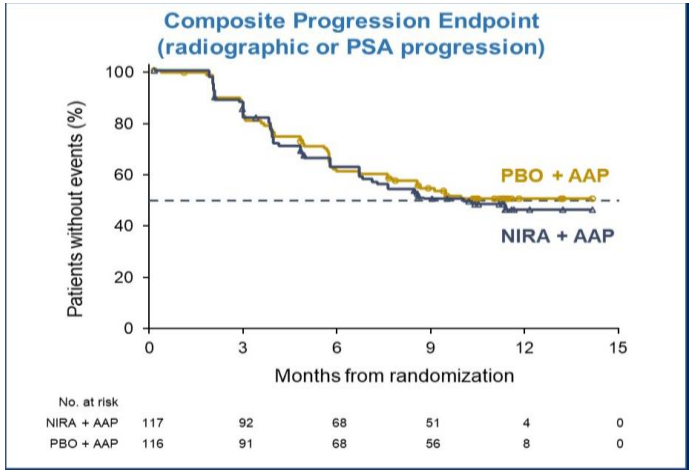
rPFS benefit observed across all subgroups

	Number of events/ patients	Median rPFS, months		HR (95% CI)
All patients	394/796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization, years				
<65	106/227	NR	16.4	0.51 (0.35–0.75)
≥65	288/569	22.0	16.7	0.78 (0.62–0.98)
Site of distant metastases				
Bone only	177/434	27.6	22.2	0.73 (0.54–0.98)
Visceral	71/105	13.7	10.9	0.62 (0.39–0.99)
Other	146/257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	95/189	27.6	13.8	0.61 (0.40–0.92)
No	299/607	24.8	16.8	0.71 (0.56–0.89)
HRRm status*				
HRRm	116/226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	268/552	24.1	19.0	0.76 (0.60–0.97)
BRCAm status*				
BRCAm	42/85	NR	8.4	0.23 (0.12–0.43)
Non-BRCAm	342/693	24.1	19.0	0.76 (0.61–0.94)

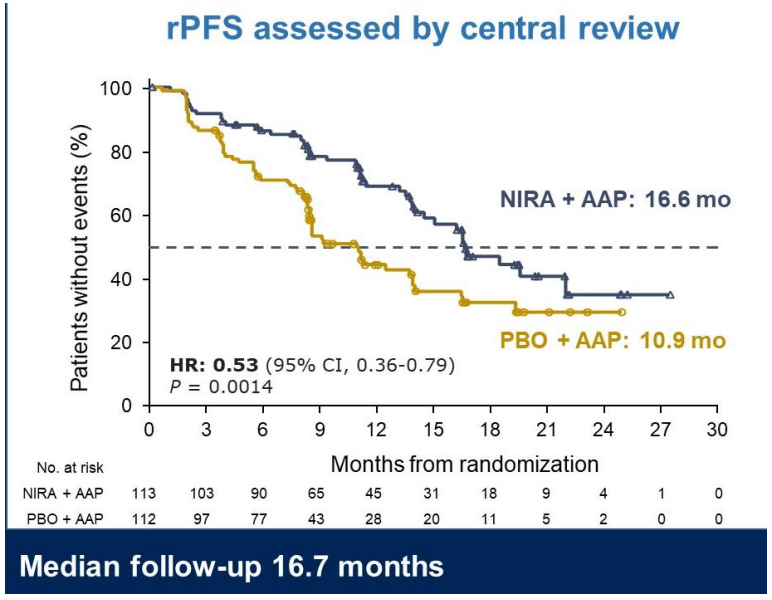


MAGNITUDE: Niraparib + Abiraterona

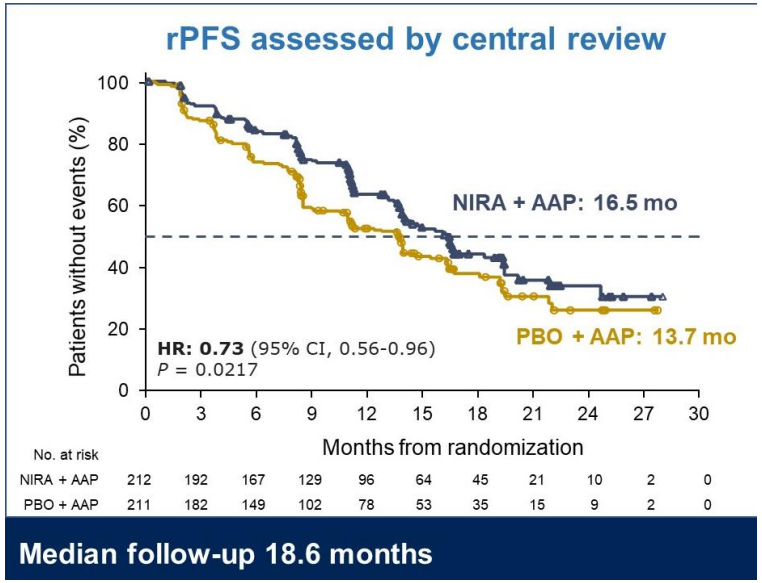


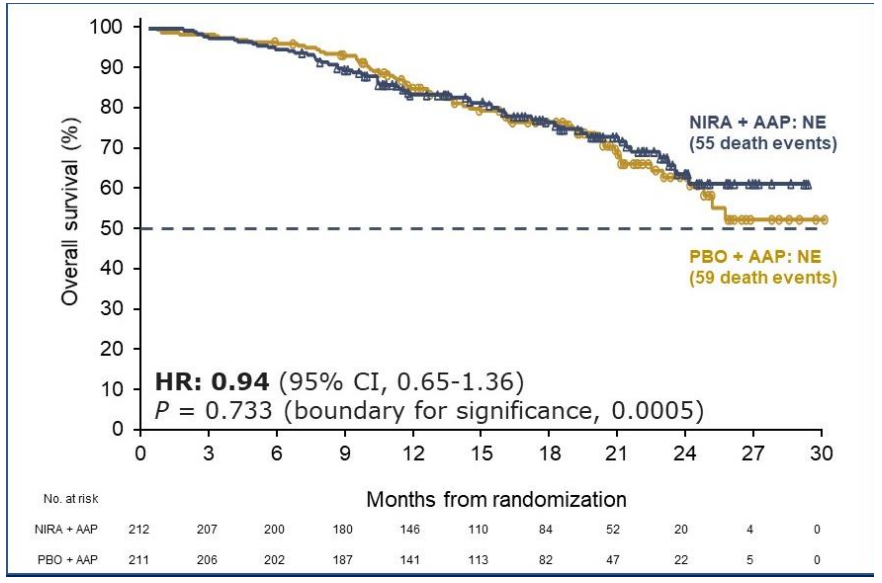


Población BRCA 1/2 mutada

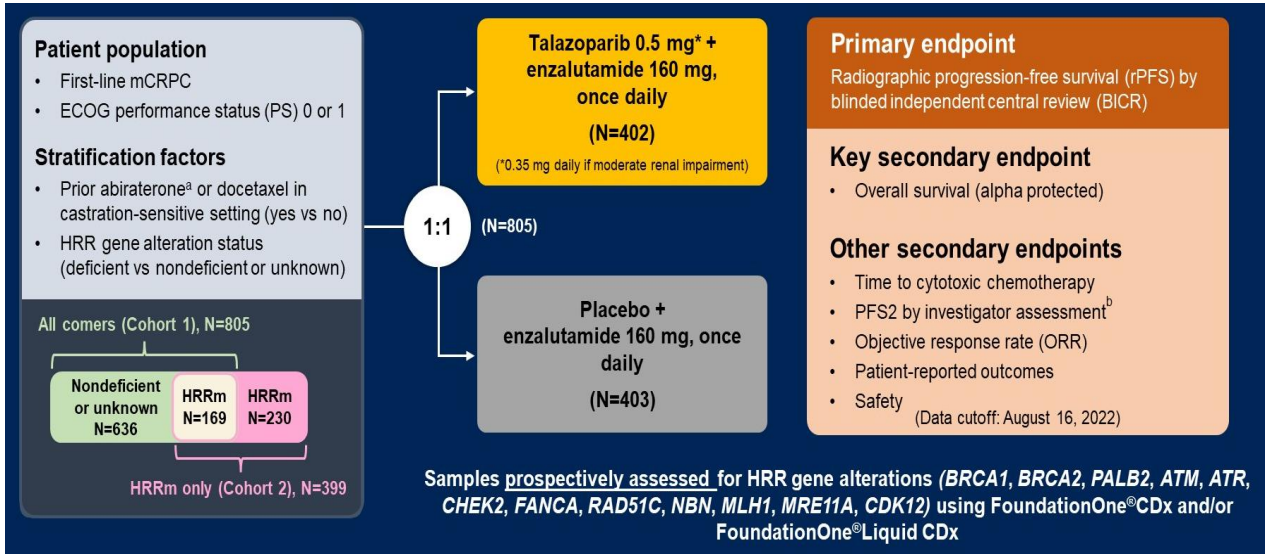


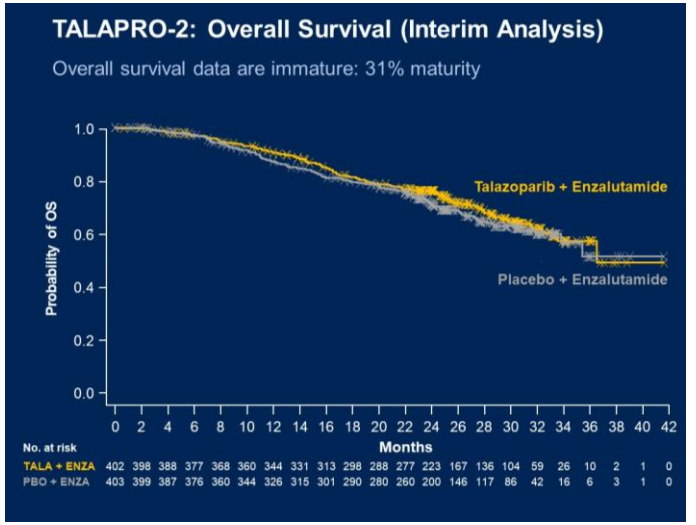
Población HRR mutados

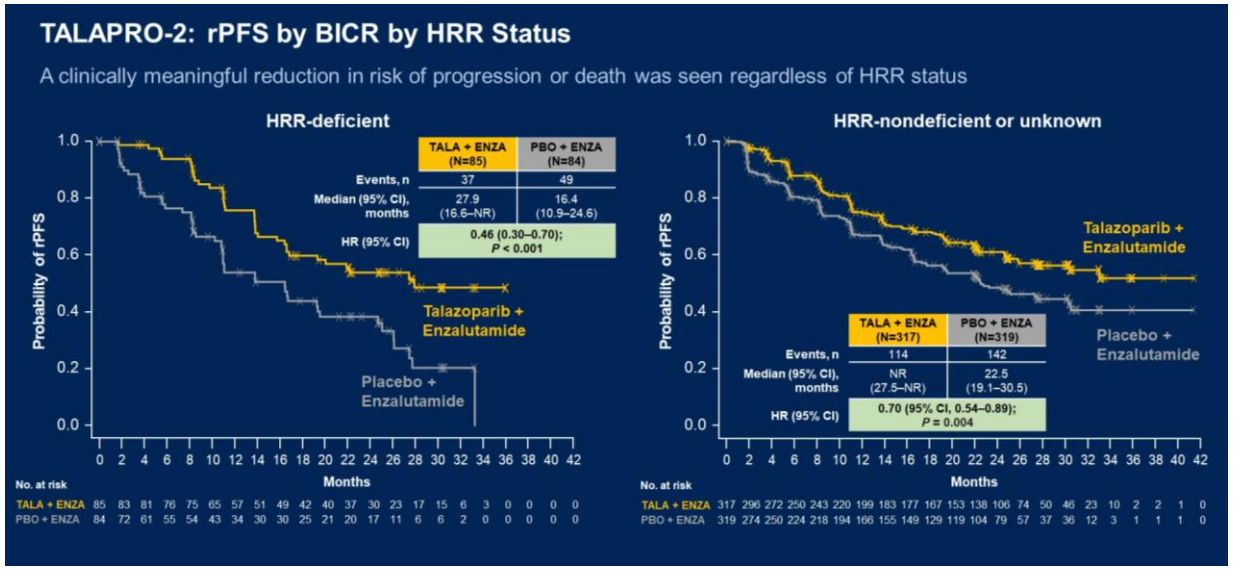


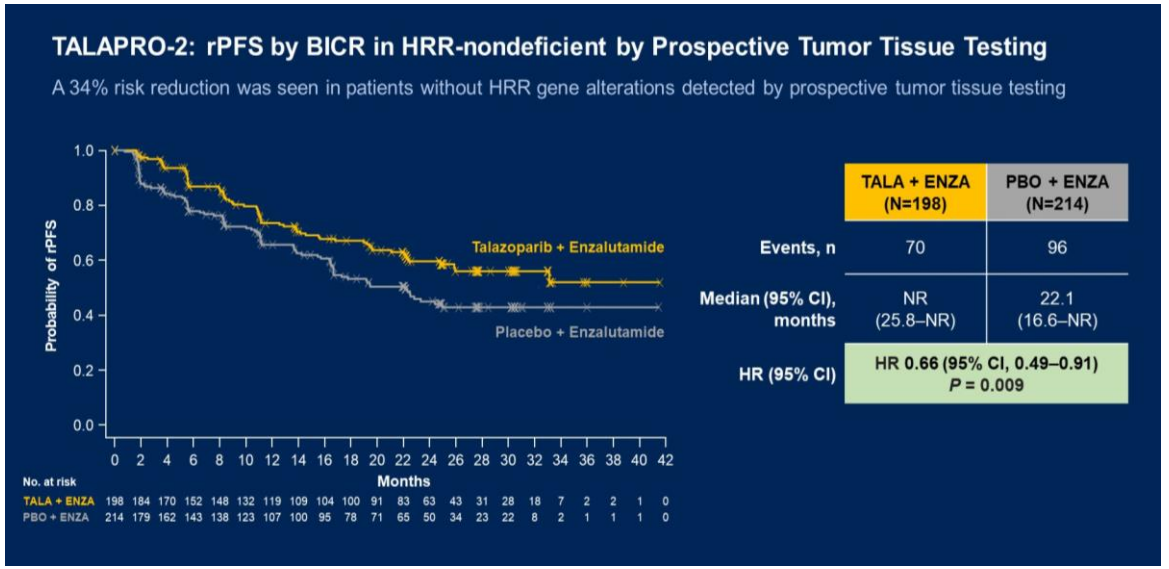


Talapro 2: enzalutamida + talazoparib









ARPi + PARPi phase 3 trials in mCRPC

		MAGNITUD[1]		PROPEL[2,3]		TALAPRO-2[4]	
	AR signaling inhibitor	Abiraterone (AA)		Abiraterone (AA)		Enzalutamide	
	PARP inhibitor	Niraparib		Olaparib		Talazoparib	
STUDY DESIGN	Inclusion criteria	1L mCRPC BPI-[illegible] [illegible] AA for mCRPC HRR alt only		1L mCRPC ECOG PFS 0-1 No prior AA in mCRPC ARSi allowed if stopped [illegible]12 m. prior All comers		1L mCRPC ECOG PFS 0-1 Docetaxel and AA for mHSCP allowed All comers	
STUDY DESIGN	Molecular testing	**Prospective** Plasma: Resolution Biosciences Tissue: FoundationOne®CDx		**Retrospective** Tissue: FoundationOne®CDx Plasma:FoundationOne®Liquid CDx		**Prospective** Tissue: FoundationOne®CDx Plasma: FoundationOne®Liquid CDx	
STUDY DESIGN	Genes analyzed	*ATM, BRCA1, BRCA2, BRP1, CDK12, CHEK2, FANCA, HDAC2, PALB2*		*ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*		*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	
STUDY DESIGN	Stratification factors	Prior docetaxel for mHSPC Prior ARSi for nmCRPC or mHSPC **Prior AA for 1L mCRPC** BRCA1/2 vs non-BRCA HRR		Site of metastases Prior taxane at mHSCP		**HRR status** Prior AA or docetaxel for mHSCP	
STUDY DESIGN	Primary endpoint	**rPFS by central review in HRRm**		**rPFS by investigator in all comers**		**rPFS by central reviewer in all comers**	
POPULATION		*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*	*Experimental arm*	*Control arm*
POPULATION	Patients	212	211	399	397	402	403
POPULATION	HRRm	**100%**	**100%**	**28%**	**29%**	**21%**	**21%**
POPULATION	Age, median (range), y	69 (45-199)	69 (43-88)	69 (43-91)	70 (46-88)	71 (41-90)	71 (36-91)
POPULATION	PSA at study entry (ng/mL)	21.4 (0-4826.5)	17.4 (0.1-4400)	17.9 (6.09-67)	16.81 (6.26-53.3)	18.2 (0.1-2796)	16.2 (0.1-2285)
POPULATION	ECOG 0 1	130 (61%) 82 (39%)	146 (69%) 65 (31%)	286 (72%) 112 (28%)	272 (68%) 124 (31%)	259 (64%) 143 (36%)	271 (67%) 132 (33%)
POPULATION	Site of metastases Bone Visceral	183 (86.3%) **51 (24.1%)**	170 (80.6%) 39 (18.5%)	349 (88%) 55 (14%)	339 (85%) 60 (15%)	349 (87%) 57 (14%)	342 (85%) 77 (19%)
POPULATION	Prior docetaxel mHSPC	41 (19.3%)	44 (20.9%)	90 (23%)	89 (22%)	86 (21%	93 (23%)
POPULATION	Prior ARPi for nmCRPC/mHSPC	8 (3.8%)	5 (2.4%)	1 (0.3%)	0	21 (5%)	25 (6%)
POPULATION	Prior ARPi for L1 mCRPC	**50 (23.6%)**	**48 (22.7%)**	0	0	0	0

ARPi + PARPi

rPFS benefit: BRCA > HRRm

		MAGNITUD[1]	PROPEL[2,3]	TALAPRO-2[4]
EFFICACY	rPFS all comers	_____	**24.8 vs 16.6 months** **HR 0.66** (95% CI 0.54-0.81) P<0.001	**NR vs 21.9 months** **HR 0.63** (95% CI 0.5-0.78) P<0.001
	rPFS *BRCA* subgroup	**16.6 vs 10.9 months** **HR 0.53** (95%CI 0.36-0.79) P=0.0014	**NR vs 8.4 months** **HR 0.23** (95% CI 0.12-0.43)	Not reported
	rPFS HRRm subgroup	**16.5 vs 13.7 months** **HR 0.73** (95%CI 0.56-0.96) P=0.0217	**NR vs 13.9 months** **HR 0.50** (95% CI 0.34-0.73)	**27.9 vs 16.4 months** **HR 0.46** (95% CI 0.3-0.7) P<0.001
	rPFS non-HRR/unknown	_____	**24.1 vs 19 months** **HR 0.76** (95%CI 0.60-0.97)	**NR vs 22.5 months** **HR 0.70** (95% CI 0.54-0.89) P<0.001
	Time to PSA progression	18.5 vs 9.3 months HR 0.57 (95% CI 0.43-0.76) P<0.001	NR vs 12 months HR 0.55 95% CI 0.45-0.68)	26.7 vs 17.5 months HR 0.72 (95% CI 0.58-0.89) P=0.002
	Objective Response Rate (ORR)	**60% vs 28%** P<0.001 CR: 22% vs 18%; PR 38% vs 34%	**58% vs 48%** P=0.041 CR: 4% vs 6%; PR 54% vs 42%	**62% vs 44%** P=0.005 CR: 38% vs 18%; PR 24% vs 26%

This is not a head-to-head comparison and the trials cannot be directly compared.

1. Presented at ASCO GU 2022 by Dr K Chi; 2. Clarke et al, NEJM Evid 2022; 3. Presented by Dr Saad at ESMO 2022; 4. Presented by Dr Agarwal at ASCO 2023

ARPi + PARPi

rPFS benefit: BRCA > HRRm > non-HRRm

		MAGNITUD[1]	PROPEL[2,3]	TALAPRO-2[4]
EFFICACY	rPFS all comers	———	**24.8 vs 16.6 months** **HR 0.66** (95% CI 0.54-0.81) P<0.001	**NR vs 21.9 months** **HR 0.63** (95% CI 0.5-0.78) P<0.001
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ARPi + PARPi

rPFS benefit: BRCA > HRRm > all comers > non-HRRm

		MAGNITUD[1]	PROPEL[2,3]	TALAPRO-2[4]
EFFICACY	rPFS all comers	———	**24.8 vs 16.6 months** **HR 0.66** (95% CI 0.54-0.81) P<0.001	**NR vs 21.9 months** **HR 0.63** (95% CI 0.5-0.78) P<0.001
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	rPFS non-HRR/unknown	———	**24.1 vs 19 months** **HR 0.76** (95%CI 0.60-0.97)	**NR vs 22.5 months** **HR 0.70** (95% CI 0.54-0.89) P<0.001
	Time to PSA progression	18.5 vs 9.3 months HR 0.57 (95% CI 0.43-0.76) P<0.001	NR vs 12 months HR 0.55 95% CI 0.45-0.68)	26.7 vs 17.5 months HR 0.72 (95% CI 0.58-0.89) P=0.002
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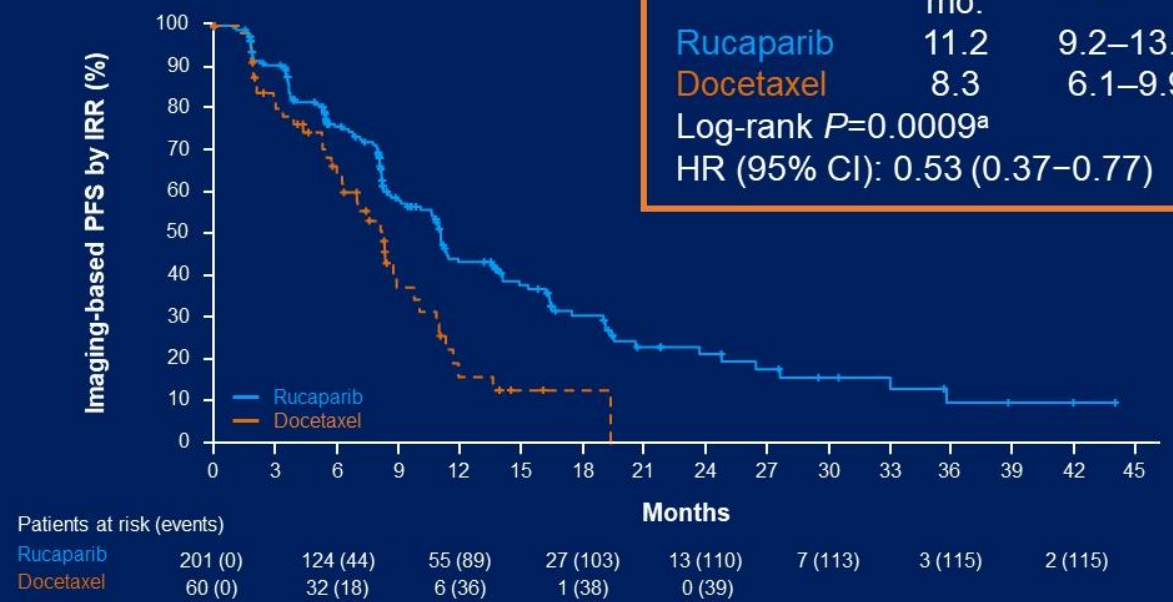
How do PARPi compare with taxanes?

Rucaparib vs Docetaxel



BRCA subgroup

	Median, mo.	95% CI
Rucaparib	11.2	9.2–13.8
Docetaxel	8.3	6.1–9.9

Log-rank *P*=0.0009[a]
HR (95% CI): 0.53 (0.37−0.77)

ITT population

	Median, mo.	95% CI
Rucaparib	10.2	8.3-11.2
Docetaxel	8.3	6.1–10.1

Log-rank *P*=0.0066
HR (95% CI): 0.64 (0.46-0.88)

ATM unlikely to benefit from Rucaparib vs taxanes

Combinación iPARP+ ARPI en CPHS

Trial Name	PARP inhibitor	AR pathway inhibitor	Radiotherapy	Biomarker Selected	Phase	Trial Number
AMPLITUDE	Niraparib	Abiraterone	No	Yes	III	NCT04497844
FAALCON	Olaparib	Abiraterone	Yes	No	II	NCT04748042
TALAPRO-3	Talazoparib	Enzalutamide	No	Yes	III	NCT04821622
ZZ-First	Talazoparib	Enzalutamide	No	No	II	NCT04332744
	Talazoparib	Abiraterone	No	No	II	NCT04734730
	Olaparib	Abiraterone	No	Yes	II	NCT05167175
ASCLEPluS	Niraparib	Abiraterone	Yes	No	I/II	NCT04194554
	Niraparib	Abiraterone	Yes	No	II	NCT04947254
GUNS	Niraparib	Abiraterone	No	Yes	II	NCT04812366

Situación actual de iparps en cancer de próstata

- En CPRC ya está todo dicho o debemos avanzar?
- Cuáles son la preguntas que quedan por responder?
- Cómo podemos plantearnos contestarlas?
- Propuestas

- Y en CPHS?

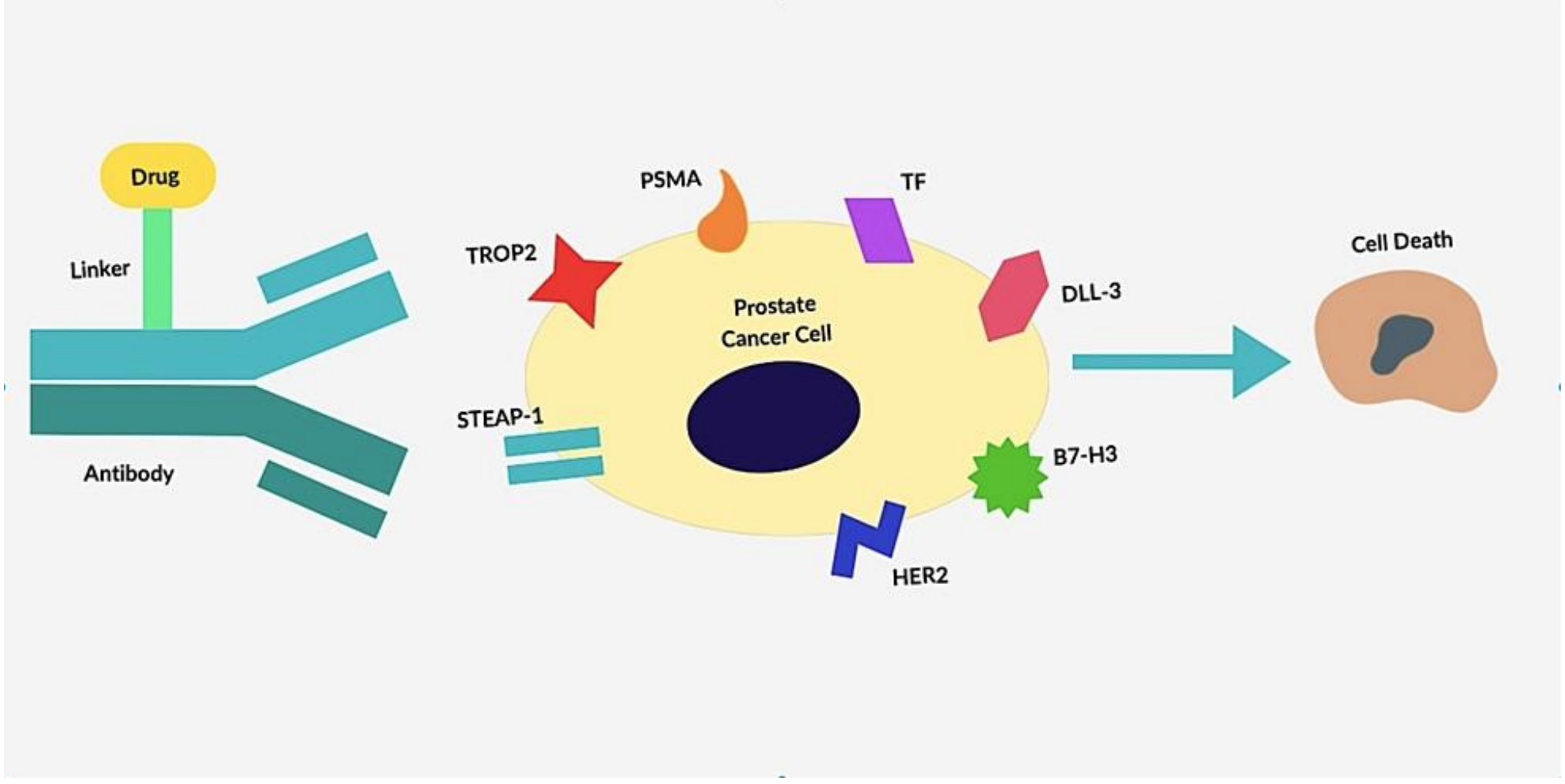
AVPC: aggressive variant prostate cáncer

- Patients must meet at least one of the following AVPC criteria:
  - 1.- Histologically proven small cell (neuroendocrine) prostate carcinoma
  - 2.- Exclusive visceral metastases.
  - 3.- Predominantly lytic bone metastases identified by plain x-ray or CT scan.
  - 4.- Bulky (>/= 5cm in longest dimension) lymphadenopathy or high-grade tumor mass in prostate/pelvis.
  - 5.- Low PSA (</= 10ng/mL) at initial presentation (prior to androgen ablation or at symptomatic progression in the castrate-setting) plus high volume (>/= 20) bone metastases.
  - 6.- Elevated serum lactate dehydrogenase (>/=2 x upper limit of normal) or elevated serum carcinoembryonic antigen (>/= 2 x upper limit of normal) in the absence of other etiologies.
  - 7.- Short interval (</= 180 days) to castrate-resistant progression following initiation of hormonal therapy.
  - 8.- Known loss or mutation (by CLIIA certified molecular testing, IHC and/or DNA sequencing) in at least 2 of the following: Tp53, RB1 and PTEN.

Propuestas para AVPC

- En el contexto de CPRC ?
- En el contexto de CPHS ?
- Profundización en estudios moleculares para caracterizar mejor esta población ?

Antibody drugs conjugates and targets in prostate cancer cells



Antibody drugs conjugates and targets in prostate cancer cells: trials results

Study/reference	Report date	Phase	Enrollment (n)	Antibody target	Intervention	Payload	Disease setting	Inclusion criteria	Histology	Primary endpoint	ORR (%)	Median OS

Antibody drugs conjugates and targets in prostate cancer cells: trials in progress

Study/reference	Launch date	Phase	Antibody target	Intervention	Payload	Disease setting	Histology	Primary endpoint	Activity
NCT04381832 [14]	2020	I/II	TROP-2	Sacituzumab-Govitecan + adenosine receptor antagonist combinations	SN-38	mCRPC after progression on abiraterone and < 2 prior lines of chemotherapy	Prostate carcinoma	ORR	Active, in recruitment
NCT03725761 [15]	2018	I/II	TROP-2	IMMU-132	SN-38	mCRPC > 1 prior line of enzalutamide or abiraterone	Prostate carcinoma	PSA response rate	Active, in recruitment
NCT05489211 [16]	2022	I/II	TROP-2	Dato-DXd monotherapy and in combination	DXd	Advanced or metastatic solid tumors	Multiple	ORR	Active, in recruitment
NCT04644068 [17]	2020	I/II	HER2/TROP-2	Trastuzumab-DXd + PARPi/Dato-DXd + PARPi	DXd	Advanced or metastatic solid tumors	Multiple	Safety	Active, in recruitment
NCT02465060 [18]	2015	II	HER2	Ado-trastuzumab emtansine	Maytansinoid-1	Advanced refractory solid tumors/lymphomas/multiple myeloma	Multiple	ORR	Active, in recruitment
NCT03602079 [19]	2018	II	HER2	A166	Duostatin-5	Refractory locally advanced/metastatic solid tumors with HER2 expression or amplification	Multiple	Safety	Active, not recruiting
NCT03729596 [20]	2018	II	B7-H3	MGC018	Duocarmycin	Advanced solid tumors	Multiple	Safety	Active, in recruitment

Nuevos antiandrógenos en CPRC

- TAS3681: AR antagosnist for full length and AR-splice variant — Phase I/II
- Cirtuvivint: pan CLK/DYRK inhibitor — Phase I/II
  - En combinación con ARSI
- EPI-7386: small molecule targetin AR-N terminal domain (NYH) — Phase I
- Bavdegalutamide (ARV-110): PROTAC protein degrader, targeting wild-type and mutant AR — Phase I/II
- ODM-208: non-steroidal CYP11A1 inhibitor: active in LBD mutation — Phase II