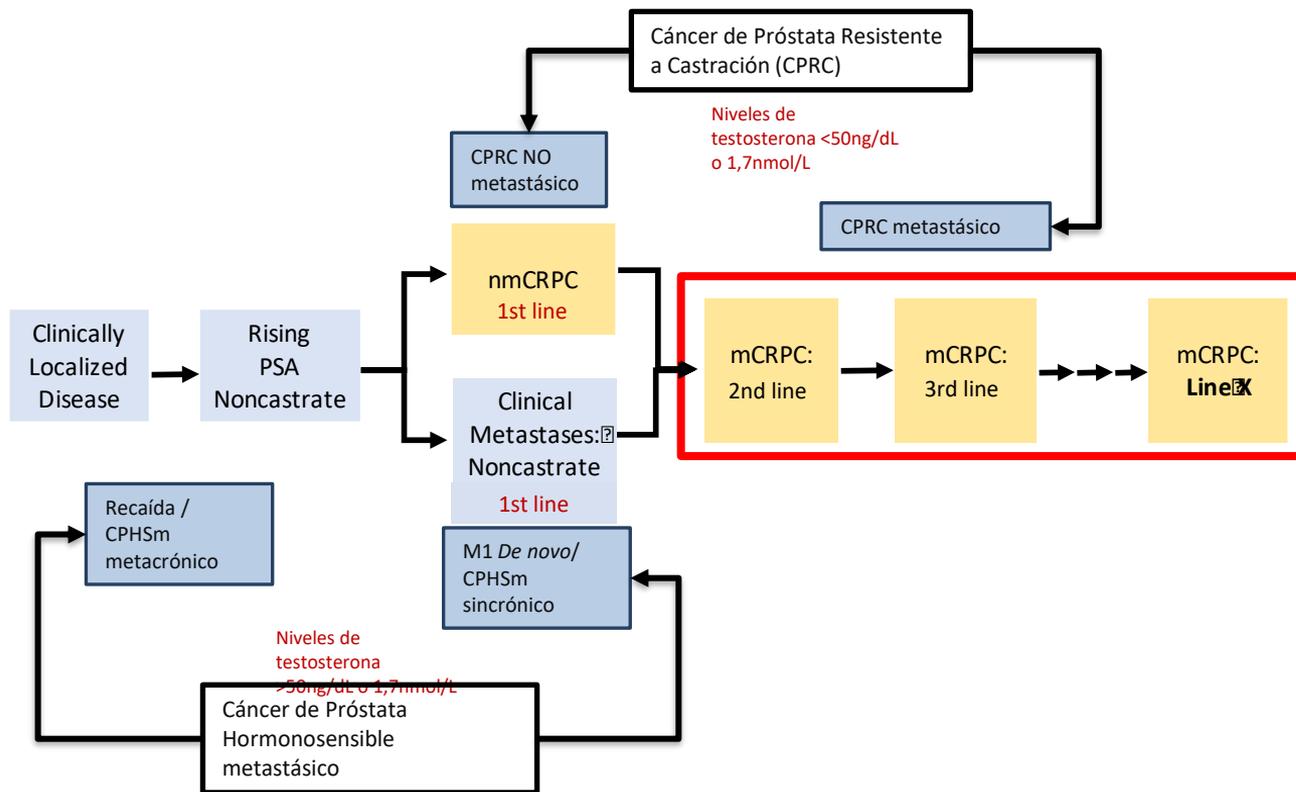
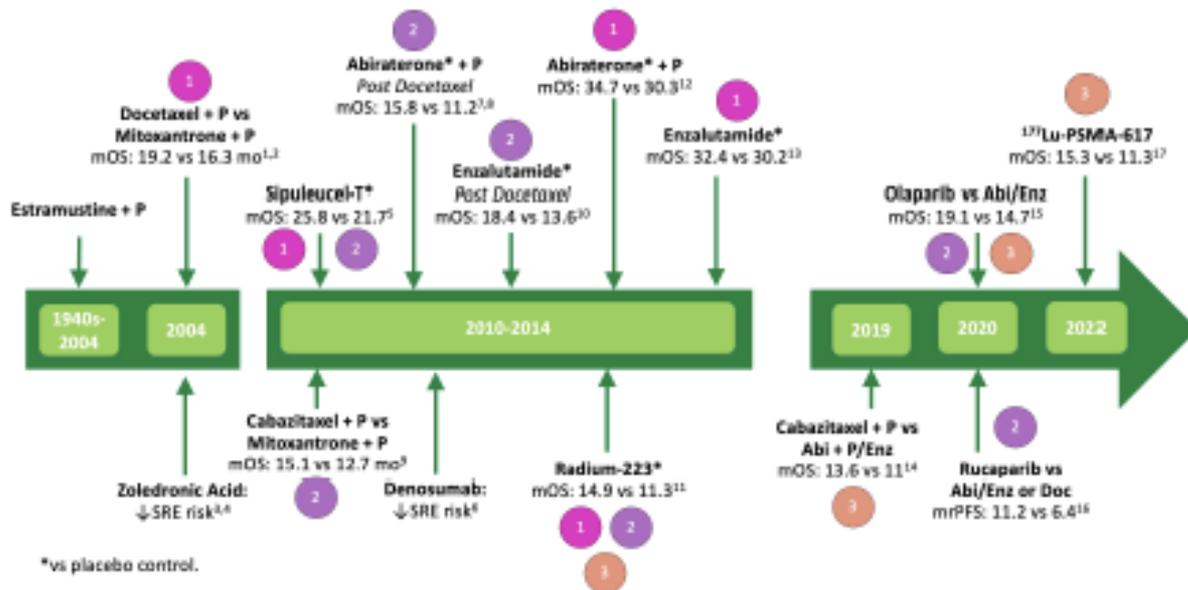




iPARP en cáncer de próstata. Estado del arte y alternativas futuras

Escenarios clínicos en cáncer de próstata

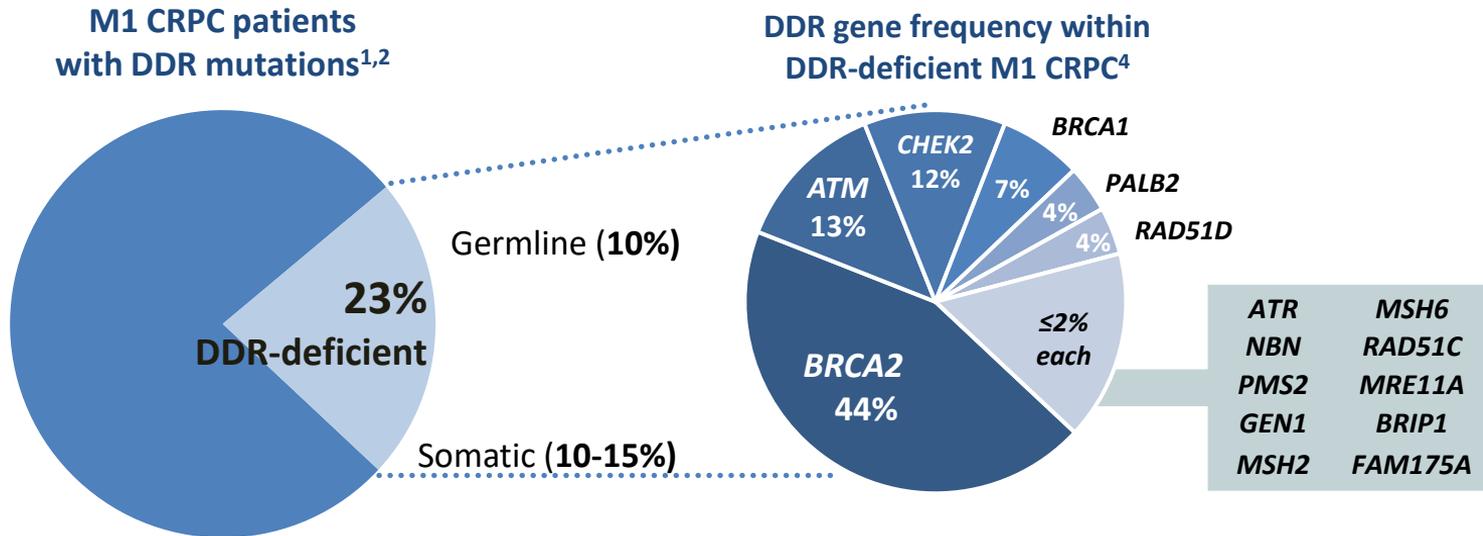




1. Terriak. NEJM. 2004;351:1202. 2. Berchuck. JCO. 2008;26:242. 3. Saad. J Nat Cancer Inst. 2002;94:1456. 4. Saad. J Nat Cancer Inst. 2004;96:876. 5. Scaife. NEJM. 2012;366:411. 6. de Boro. Lancet. 2012;379:1147. 7. de Boro. NEJM. 2012;366:1995. 8. Fizal. Lancet Oncol. 2012;13:885. 9. Fizal. Lancet. 2011;377:823. 10. Scher. NEJM. 2012;367:1147. 11. Parker. NEJM. 2013;369:215. 12. Rea. NEJM. 2014;371:424. 13. de Wit. et al. NEJM. 2018;379:2408. 14. Hussain. NEJM. 2012;366:1026. 15. Fizal. NEJM. 2012;366:1026. 16. Fizal. NEJM. 2012;366:1026.

DDR Frequency in Prostate Cancer

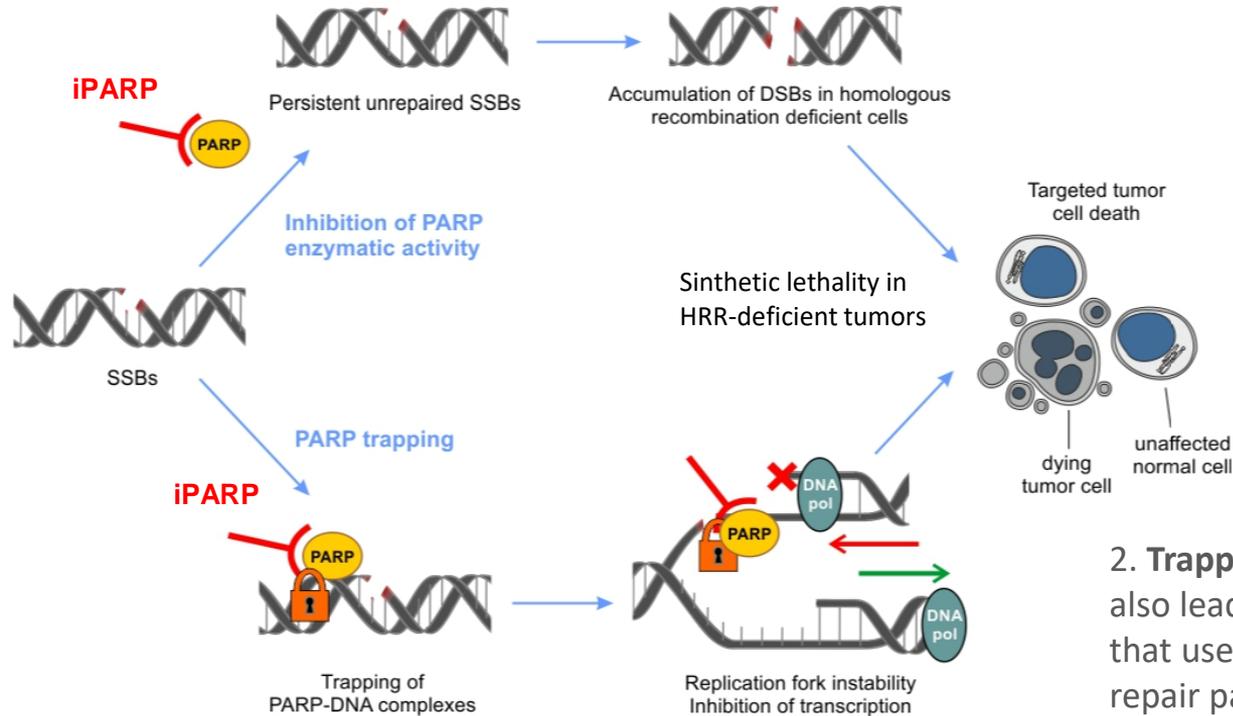
- A large proportion of prostate cancers (23%, metastatic CRPC) are characterized by the presence of DNA repair gene defects, primarily in HRR genes^{1,2}
- *gBRCA2 mutations*, in prostate cancer in particular, are associated with poorer outcome³



CRPC=castration-resistant prostate cancer; DDR=DNA damage repair; HRR=homologous recombination repair.

1. Lang SH, et al. *Int J Onc.* 2019;55:597-616. 2. Robinson D, et al. *Cell.* 2015;161:1215-1228. 3. Oh M, et al. *Prostate.* 2019;79:880-895. 4. Pritchard CC, et al. *N Engl J Med.* 2016;375:443-453

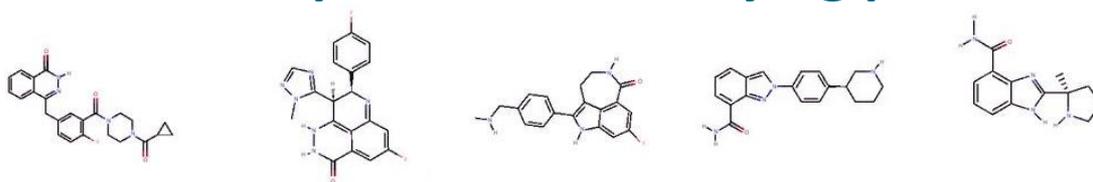
Dual cytotoxic mechanism of PARP inhibitors



1. **Catalytic inhibition** interferes with the repair of SSBs, leading to replication fork damage that requires homologous recombination repair (HRR).

2. **Trapping of PARP–DNA complexes** also leads to replication fork damage that uses HR repair and additional repair pathways including Fanconi pathway (FA), template switching (TS), ATM, FEN1 (replicative flap endonuclease), and polymerase β .

Several PARPis are in development, with varying preclinical potency



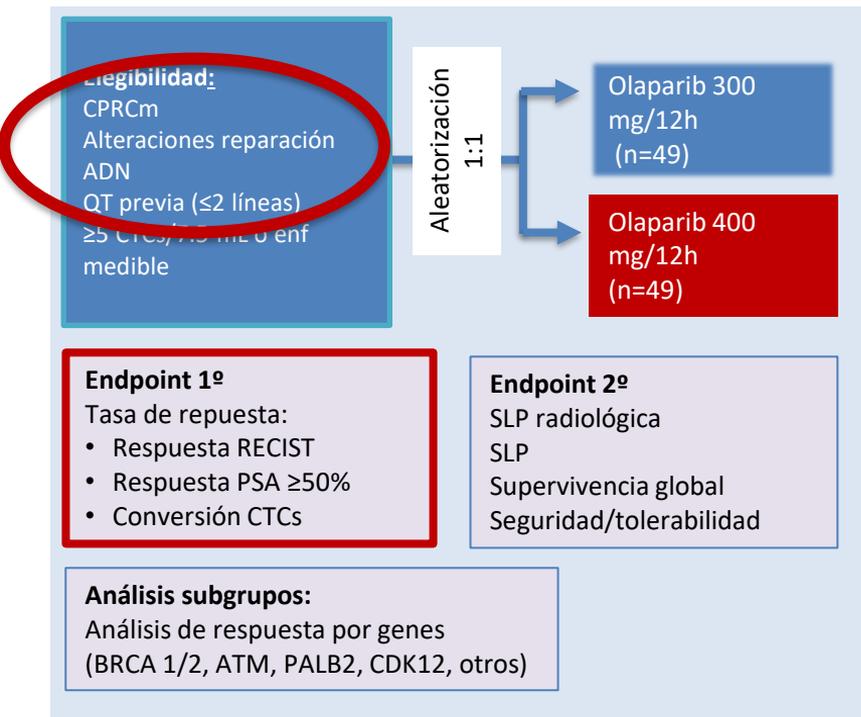
PARP Inhibitor	Olaparib	Talazoparib	Rucaparib	Niraparib	Veliparib
Dosis	300 mg BID	1 mg QD	600 mg BID	300 mg QD	400 mg BID
Actividad inhibidora catalítica de PARP <i>in vitro</i> *	++++	++++	+++	++	++
Actividad trapping de PARP <i>in vitro</i>	++	+++	++	++	-
Indicaciones aprobadas EMA	Ovario, mama, próstata, pancreas	Mama	Ovario	Ovario	-

*Concentration for 50% PARP=poly (ADP-ribos)
 1. Lord CJ, et al. *Scien*
 3. Murai J, et al. *Mol C*



iPARP en monoterapia. Evidencia

ENSAYO TOPARP-B



Población global (N=98)

	TOTAL	300 mg	400 mg
Respuesta compuesta	43/92 (46,7%)	18/46 (39,1%)	25/46 (54,3%)
RECIST	14/70 (20%)	6/37 (16,2%)	8/33 (24,2%)
PSA	30/89 (33,7%)	13/43 (30,2%)	17/46 (37%)
CTC	28/55 (50,9%)	13/27 (48,1%)	15/28 (53,6%)
RECIST o PSA	32/92 (34,8%)	13/46 (28,3%)	19/46 (41,3%)

Mayor beneficio en pacientes con mutación

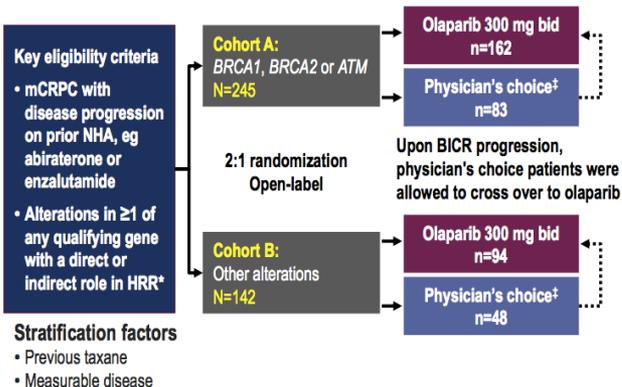
	BRCA 1/2	ATM	CDK12	PALB2	Otros
Respuesta compuesta	25/30 (83,3%)	7/19 (36,8%)	5/20 (25%)	4/7 (57,1%)	4/20 (20%)
RECIST	11/21 (52,4%)	1/12 (8,3%)	0/18 (0%)	2/6 (33%)	0/17 (0%)
PSA	23/30 (76,7%)	1/19 (5,3%)	0/20 (0%)	4/6 (66,7%)	2/17 (11,8%)
CTC	17/22 (77,3%)	5/10 (50%)	5/12 (41,7%)	0/2 (0%)	3/11 (27,3%)
RECIST/PSA	24/30 (80%)	2/19 (10,5%)	0/20 (0%)	4/7 (57,1%)	2/20 (10%)

TOPARP trials helped to

- Identify the **anti-tumor activity of olaparib** in mCRPC
- The **importance of DDR gene defects** for therapy
- The **differential response** per variable DDR gene defects
- The **importance of dose**



PROfound STUDY DESIGN



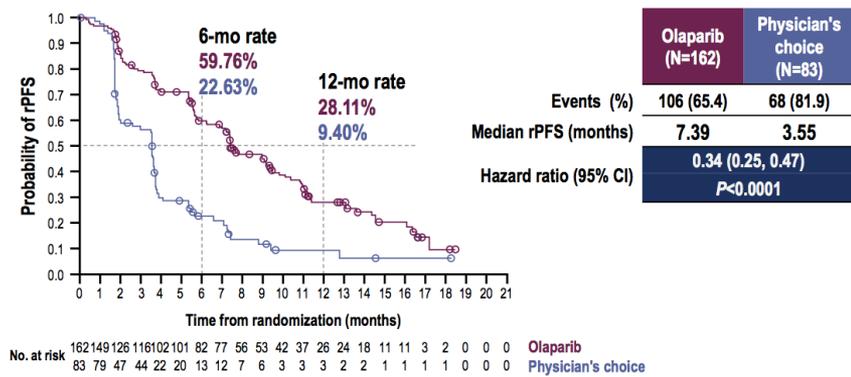
Primary Endpoint

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

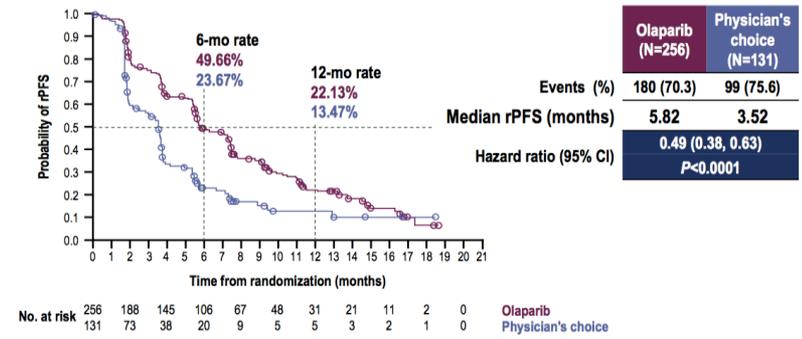
Key Secondary Endpoints

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

COHORT A (BRCA1, BRCA2, ATM)



COHORT B (Other alterations)

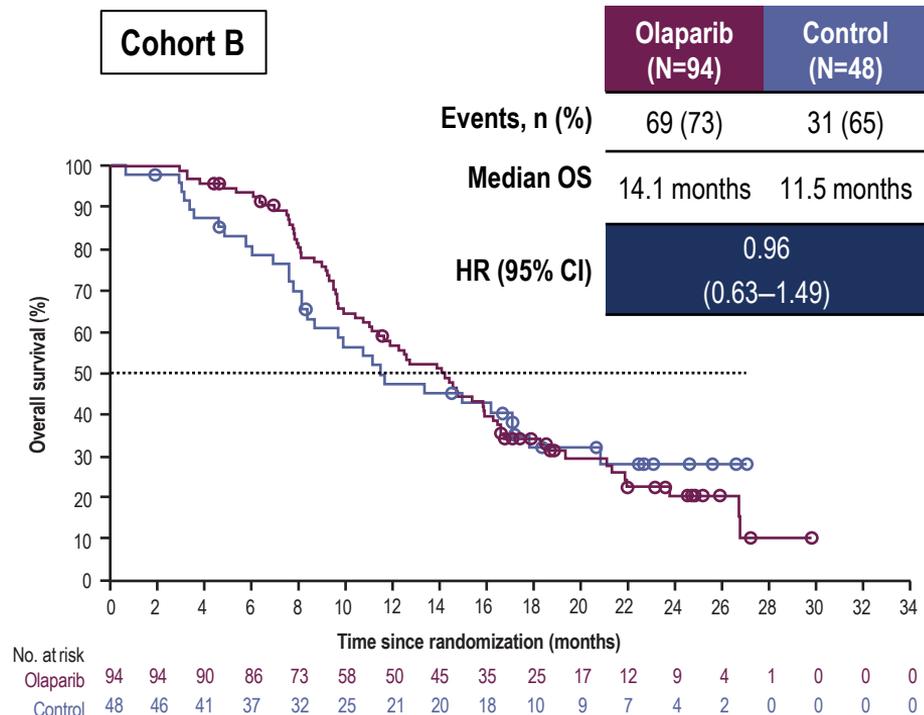
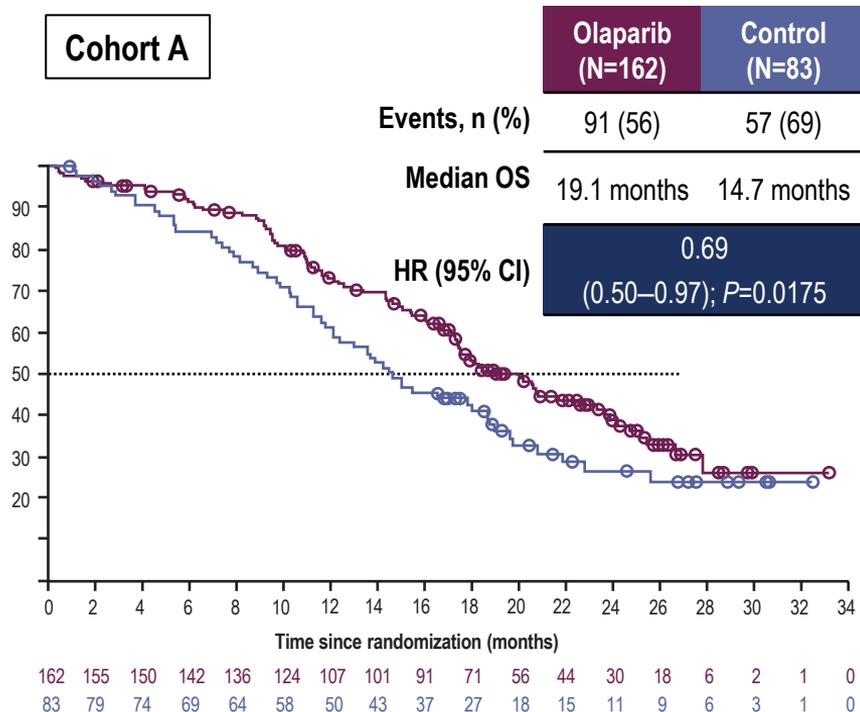


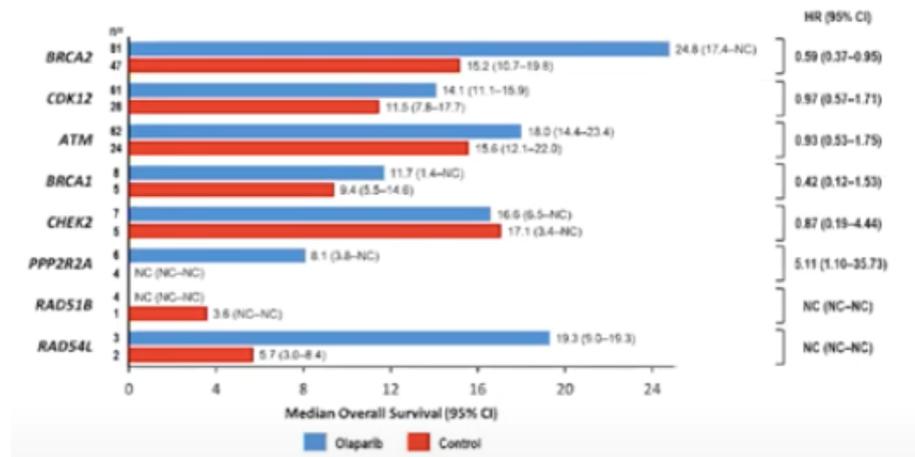
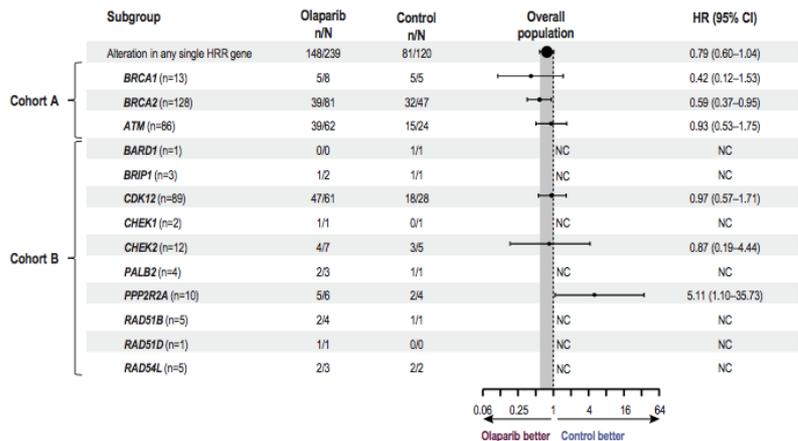
*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/ or RAD54L in their tumor tissue

DOCETAXEL → 60%



PROfound: improved OS in Cohort A (BRCA1/2, ATM)





Patients with tumours harbouring a **BRCA1** or **BRCA2** alteration appeared to derive the greatest OS benefit from olaparib

	BRCA1/2 (n)	Confirmed ORR	Confirmed PSA response rate
TOPARP (Olaparib)	n=32 Mono- and Bi-allelic	11/21 (52.4%) [29.8-74.3]	23/30 (76.7%) [57.5-90.1]
TRITON (Rucaparib)	n=115 Mono- and Bi-allelic	27/62 (43.5%) [31-56.7]	63/115 (54.8%) [45.2-64.1]
TALAPRO (Talazoparib)	n=46 Mono- and Bi-allelic	17/41 (41.5%) [N/A]	28/46 (60.9%) [N/A]
GALAHAD (Niraparib)	n=46 Bi-allelic only	12/29 (41%) [23.5-61.1]	23/46 (50%) [34.9-65.1]

Studies cannot be directly compared as the inclusion criteria, previous therapies, genomic aberrations for eligibility, etc, are different

Olaparib in *BRCA1/2* altered mCRPC: Before or after docetaxel

Table 2. Subgroup analyses of rPFS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median rPFS, months		HR (95% CI)
		Olaparib	pcNHA	Olaparib	pcNHA	
Cohort A	Yes	72 (67.9)	47 (90.4)	7.4	1.9	0.28 (0.19, 0.41)
	No	34 (60.7)	21 (67.7)	7.4	4.1	0.55 (0.32, 0.97)
Cohorts A+B	Yes	124 (72.9)	70 (83.3)	5.8	2.6	0.39 (0.29, 0.53)
	No	56 (65.1)	29 (61.7)	5.8	4.8	0.77 (0.50, 1.22)

Table 3. Subgroup analyses of OS by prior taxane status in patients

	Prior taxane	Number of events, n (%)		Median OS, months		HR (95% CI)
		Olaparib	pcNHA	Olaparib	pcNHA	
Cohort A	Yes	39 (36.8)	30 (57.7)	17.3	11.7	0.57 (0.36, 0.93)
	No	15 (26.8)	9 (29.0)	20.7	19.1	0.84 (0.38, 2.01)
Cohorts A+B	Yes	73 (42.9)	49 (58.3)	15.8	11.4	0.61 (0.43, 0.88)
	No	24 (27.9)	14 (29.8)	20.7	19.1	0.87 (0.45, 1.72)

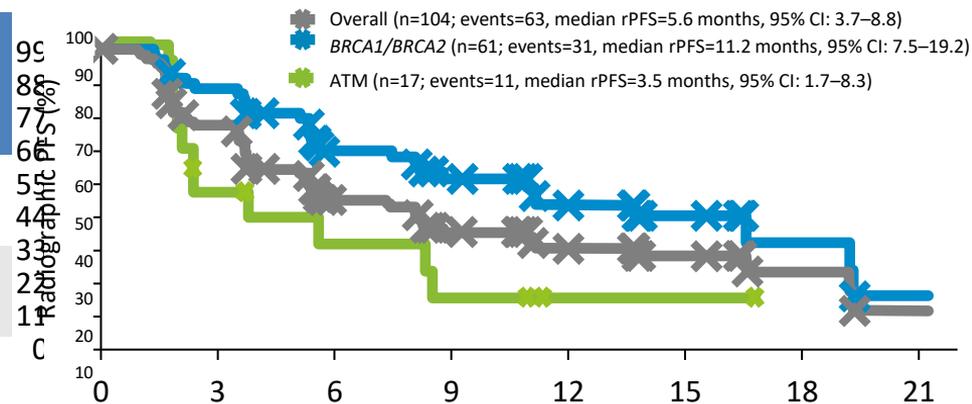
TALAPRO-1: Summary of Efficacy

Open-label phase 2 study (NCT03148795) evaluating talazoparib in men with mCRPC and DDR alterations

Response Rates

Response, %	By gene subgroup				Total (N=86)
	<i>BRCA1/2</i> (n=46)*	<i>PALB2</i> (n=4)	<i>ATM</i> (n=18)	Other (n=18) [†]	
Objective response [‡]	46	25	12	0	30
PSA decline $\geq 50\%$ from baseline [§]	66	75	7	6	46

rPFS (BICR; antitumor activity population)*



No. of patients at risk (no. censored)

	0	3	6	9	12	15	18	21
Overall:	104 (0)	72 (7)	38 (18)	26 (22)	16 (29)	10 (34)	4 (39)	1 (40)
<i>BRCA1/BRCA2</i> :	61 (0)	52 (1)	31 (10)	23 (14)	15 (19)	9 (24)	4 (28)	1 (29)
<i>ATM</i> :	17 (0)	8 (2)	5 (3)	3 (3)	1 (5)	1 (5)	0 (6)	0 (6)

Talazoparib is not approved by Regulatory Agencies for use in M1 CRPC.

*Includes 1 patient with both *BRCA2* and *PALB2* alterations and 2 patients with both *BRCA2* and *ATM* alterations.

[†]*ATR, CHEK2, FANCA, MLH1, MRE11A, NBN, RAD51C.*

[‡]Only patients with measurable disease per investigator.

[§]Number of patients reported for each gene subgroup refer to those evaluable for objective response only. A greater number of patients were evaluable for the PSA decline data reported in this table.

PFS=progression-free survival

1. de Bono JS, et al. *Lancet Oncology*. Published online August 10, 2021. doi:10.1016/S1470-2045(21)00376-4

Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

Matthew R Smith, Howard I Scher, Shahneen Sandhu, Eleni Efsthathiou, Primo N Lara Jr, Evan Y Yu, Daniel J George, Kim N Chi, Fred Saad, Olof Ståhl, David Olmos, Daniel C Danila, Gary E Mason, Byron M Espina, Xin Zhao, Karen A Urtishak, Peter Francis, Angela Lopez-Gitlitz, Karim Fizazi, on behalf of the GALAHAD investigators*

Ensayo GALAHAD

Ensayo fase II, brazo único

Elegibilidad:

CPRCm
ECOG PS 0-1
Prog tras QT previa
Prog tras abi/enza o ambos
Alt reparación ADN

N=127
Niraparib 300 mg c/24h

Endpoint 1º

Tasa de respuesta objetiva en pts BRCA+ con enf medible (inicialmente, respuesta compuesta)

Endpoint 2º

Respuesta en pacientes no-BRCA
Respuesta CTC0
Supervivencia global

Alteraciones reparación ADN: Resolution HRD

ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2, PALB2

DRD-positive: alteration with known pathogenic consequences including **homozygous deletions; rearrangements; and nonsense, missense, frame-shift, and splice-site mutations.**

Patients who had been enrolled with **monoallelic or non-pathogenic DRD were excluded** from the final analysis

	Measurable BRCA cohort* (n=76)	Measurable non-BRCA cohort† (n=47)
Objective response rate	26 (34.2%; 23.7–46.0)	5 (10.6%; 3.5–23.1)
Complete response	2 (3%)	0
Partial response	24 (32%)	5 (11%)

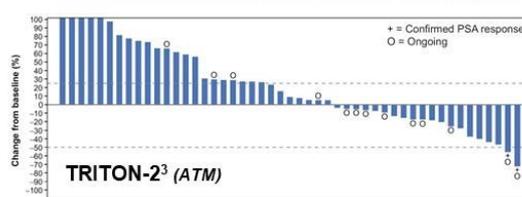
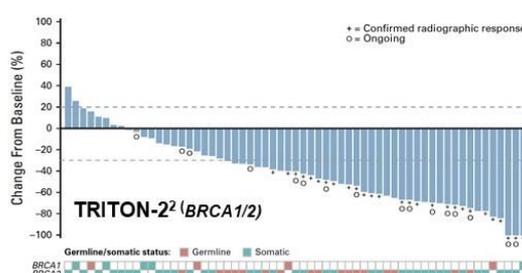
Data are n (%; 95% CI) or n (%). *Primary efficacy analysis cohort. †Objective response rate in measurable non-BRCA patients was a secondary efficacy endpoint.

Table 2: Objective response rates

	BRCA2	BRCA2 enf medible	No BRCA
Resp CTC	24%	25%	8%
SG	13m	10,9m	9,6m
SLPr	8,1m	5,8m	3,7m
TTPSAP	5,1m	5,6m	3,7m
TTSRE	13,8m	13,8m	10,8m

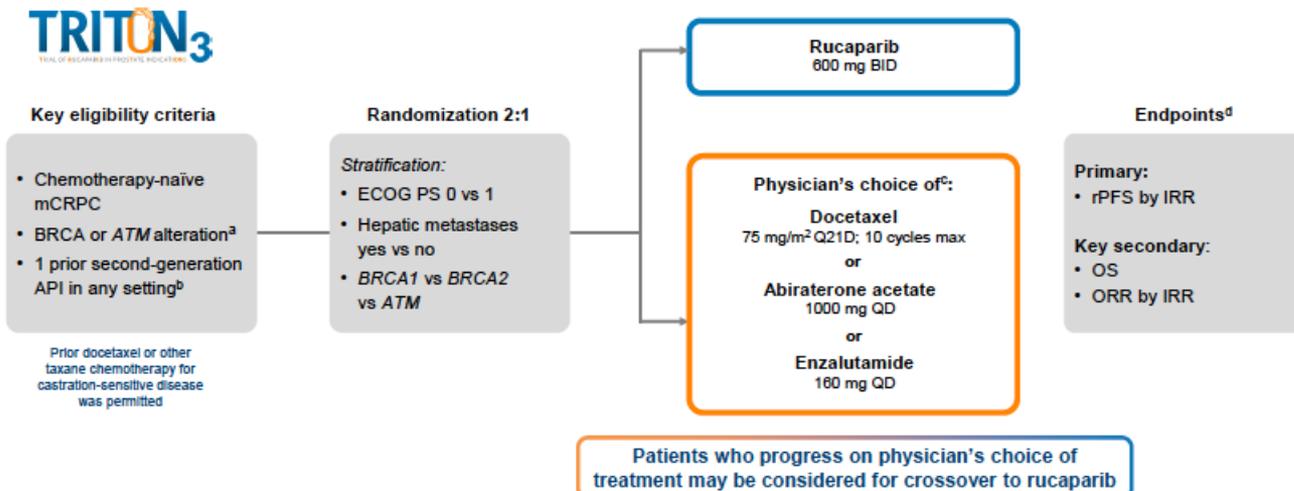


	TOPARP-B ¹	TRITON2 ^{2,3}	TALAPRO-1 ⁴	GALAHAD ⁵
Drug	Olaparib	Rucaparib	Talazoparib	Niraparib
Study design & population	Phase 2, single arm mCRPC after taxanes (ARSi allowed) N=98	Phase 2, single arm mCRPC after ARSi and taxane N= 193	Phase 2, single arm mCRPC ARSi and taxane N=127	Phase 2, single arm mCRPC ARSi and taxane N=223
Primary objective	Composite endpoint: ORR, PSA50, CTC conversion	ORR in pts with DDR alterations	ORR in pts with DDR alterations	ORR in biallelic BRCA1/2
Results	Composite response (1 st endpoint) -By gene: 85% BRCA1/2 37% ATM 25% CDK12 57% PALB2 20% other -By dose cohort: 54% with 400 mg bid 39% with 300 mg bid	ORR (1 st endpoint) 43.5% BRCA1/2 10.3% ATM	ORR (1 st endpoint) 46% BRCA 1/2 23% PALB2	ORR (1 st and 2 nd endpoint): 26% BRCA1/2 5% non-BRCA DDR PSA50 (exploratory endpoint) 43% BRCA1/2 5% non-BRCA DDR
Specimen tested	Tumor tissue Central			Plasma or tumor tissue Central analysis
Test used	Targeted customized NG:			Resolution-HRD [®] FoundationOne CDx [®]
Genes screened	113 DDR genes			A1, BRCA2, CHEK2, MRE11A, NBN, ...
Genomic alt. required				Biallelic or germline DDR alt.



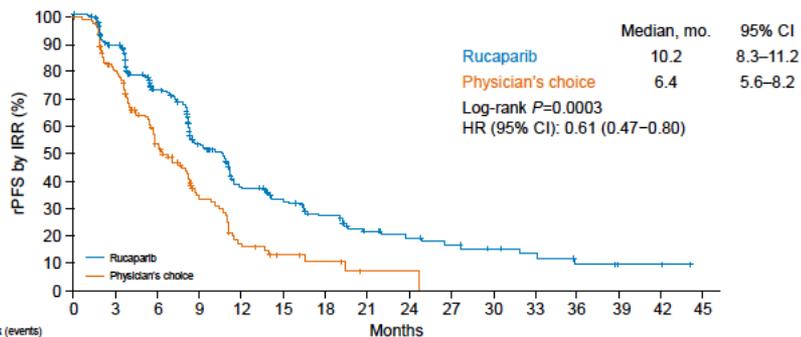


The largest number of BRCA2, BRCA1 and ATM mCRPC



Gene altered	Rucaparib (n=270)	Physician's choice		Total (n=405)
		Docetaxel (n= 75)	2 nd ARPI (n=60)	
BRCA1	29 (11%)	9 (12%)	6 (10%)	44 (11%)
BRCA2	172 (64%)	51 (68%)	35 (58%)	258 (64%)
ATM	69 (26%)	15 (20%)	19 (32%)	103 (25%)

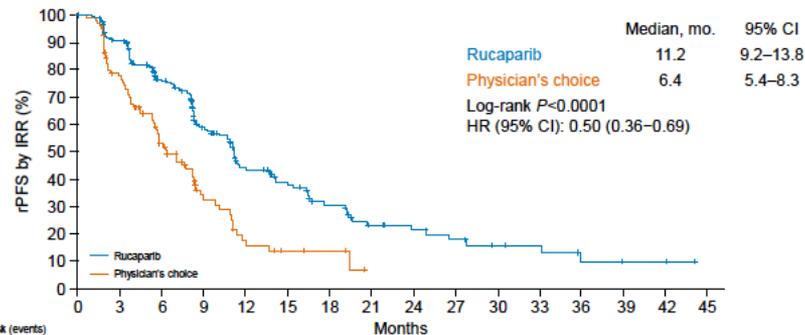
rPFS by IRR in the ITT Population



Patients at risk (events)

Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Rucaparib	270 (0)	220 (29)	155 (68)	99 (108)	61 (135)	46 (142)	31 (150)	19 (156)	15 (158)	12 (160)	9 (161)	7 (162)	4 (164)	2 (164)	2 (164)	0 (164)
Physician's choice	135 (0)	97 (25)	58 (56)	28 (74)	13 (88)	6 (91)	4 (92)	1 (93)	1 (93)	0 (94)						

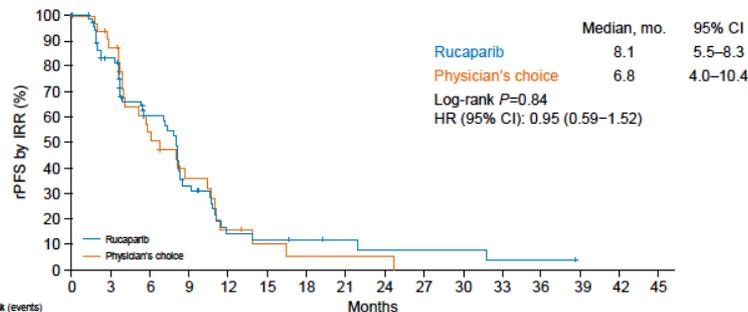
rPFS by IRR in the BRCA Subgroup



Patients at risk (events)

Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Physician's choice	101 (0)	69 (21)	42 (42)	19 (55)	9 (64)	4 (66)	3 (66)	0 (67)								

rPFS by IRR in the ATM Subgroup



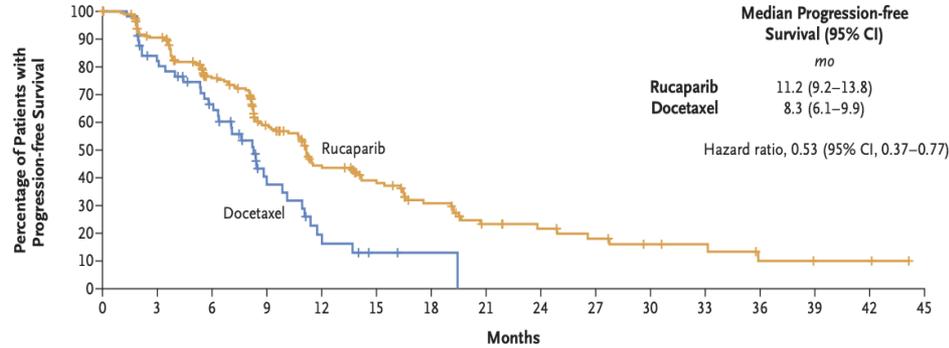
Patients at risk (events)

Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Rucaparib	69 (0)	51 (11)	31 (24)	16 (38)	6 (46)	5 (47)	4 (47)	3 (47)	2 (48)	2 (48)	1 (49)	1 (49)	0 (49)	
Physician's choice	34 (0)	28 (4)	16 (14)	9 (19)	4 (24)	2 (25)	1 (26)	1 (26)	1 (26)	0 (27)				

TRITON-3 trial BRCA-mut

Ruca vs Docetaxel

A Rucaparib vs. Docetaxel in the BRCA Subgroup

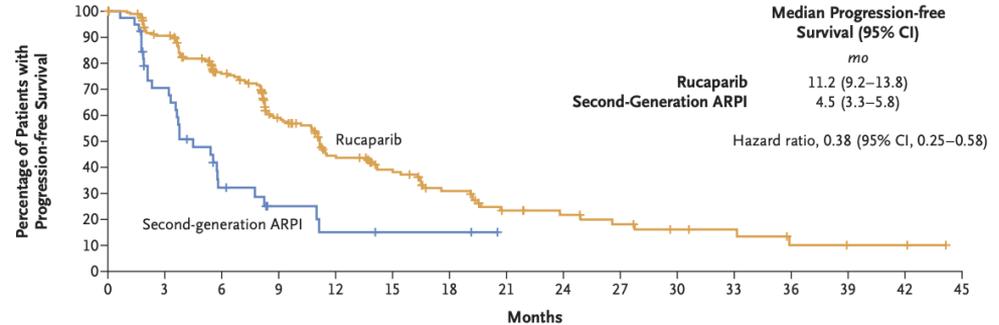


No. at Risk (no. of events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Docetaxel	60 (0)	44 (10)	32 (18)	14 (29)	6 (36)	2 (38)	1 (38)	0 (39)								

Ruca vs NAH

B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup



No. at Risk (no. of events)

Rucaparib	201 (0)	169 (18)	124 (44)	83 (70)	55 (89)	41 (95)	27 (103)	16 (109)	13 (110)	10 (112)	7 (113)	6 (113)	3 (115)	2 (115)	2 (115)	0 (115)
Second-generation ARPI	41 (0)	25 (11)	10 (24)	5 (26)	3 (28)	2 (28)	2 (28)	0 (28)								

Current approvals of PARPi for prostate cancer

EMA

- OLAPARIB is indicated as monotherapy for the treatment of adult patients with mCRPC and **BRCA1/BRCA2** mutations (**germline and/or somatic**) who have progressed following prior therapy that included **an androgen receptor-directed therapy**

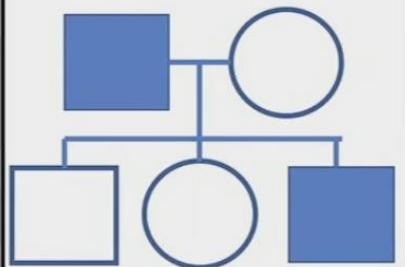
FDA

- OLAPARIB is a treatment option for patients with **mCRPC** and a pathogenic mutation (germline and/or somatic) in a HRR gene (**BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51C, RAD51D or RAD54L**) who have been treated previously with **androgen receptor-directed therapy**.
- RUCAPARIB is a treatment option of patients with mCRPC and a pathogenic **BRCA1/BRCA2** mutation (germline and/or somatic) who have been treated with **androgen receptor-directed therapy and a taxane based chemotherapy**. If the patients is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

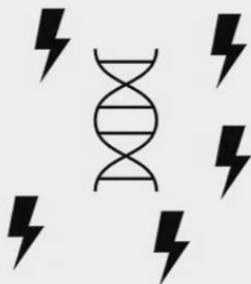


Homologous Recombination Deficiency

- Inherited



- Acquired



Can we do something to the patient or the tumor that makes HR become deficient?



Genetic testing is now standard of care in prostate cancer

Guidelines	Genomic testing recommendations	Germline testing for PC
NCCN Clinical Practice Guidelines in Oncology ¹	✓	✓
ESMO 2020 Guidelines ²	✓	✓
AUA/ASTRO/SUO 2022 Guidelines ³	✓	✓
EAU2022 Guidelines ³	✓	✓

ASTRO= American Society for Radiation Oncology; AUA=American Urological Association; EAU=European Association of Urology; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network; SUO=Society of Urologic Oncology

Different diagnostic strategies can be considered to assess for HR alterations

	Advantages	Disadvantages
Tumour tissue testing	<p>Gold standard (High clinical sensitivity)</p> <p>Fresh or archival tumour samples can be used (but older samples can have lower success rates)</p> <p>Can detect both germline and somatic mutations</p>	<p>High failure rate, especially for older samples</p> <p>Tissues for sampling may be in locations that are not safe or amenable to biopsy</p> <p>Single-site biopsies do not capture intra-individual heterogeneity (across metastases in an individual or changes over time or with disease progression)</p>
Plasma ctDNA testing	<p>Non-invasive, safer, serial analysis</p> <p>Can detect both germline and somatic mutations</p> <p>Useful where no tissue is available or when re-biopsy is undesirable</p> <p>Capture relative contribution of metastases in different anatomical sites</p>	<p>Low levels of tumour fraction can lead to false negative results CHIP may lead to false positives</p> <p>Blood collection must be timed in order to evaluate progressive disease</p> <p>Relative sensitivity at a prospective cohort level is unknown (clinical validation in PC still limited)</p>
Germline testing (Blood or saliva)	<p>Assess familial risk</p> <p>Easy to obtain samples from blood, saliva or buccal swabs</p>	<p>Misses alterations of somatic origin (\approx 50% of HR alterations)</p>

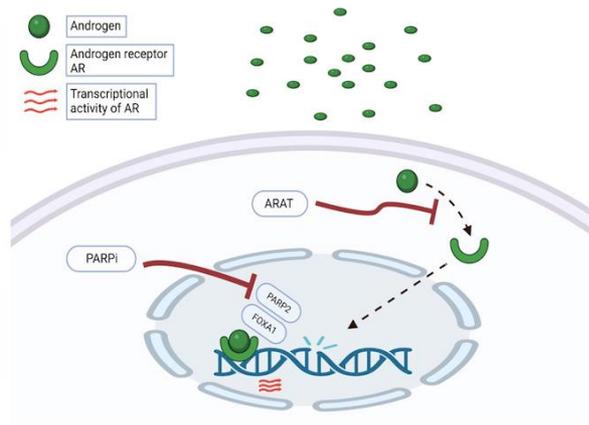
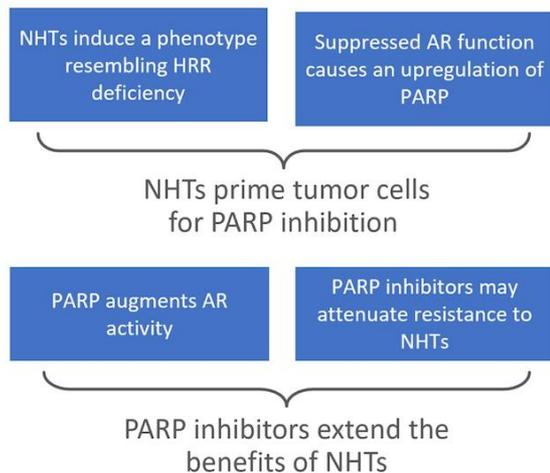


iPARP en combinación. Evidencia



Crosstalk between Androgen Receptor and DDR pathway

The rationale for combining PARPi with NHT



Adapted from Bin Gui et al., *PNAS* 2019 June, DOI <https://doi.org/10.1073/pnas.1908547116>

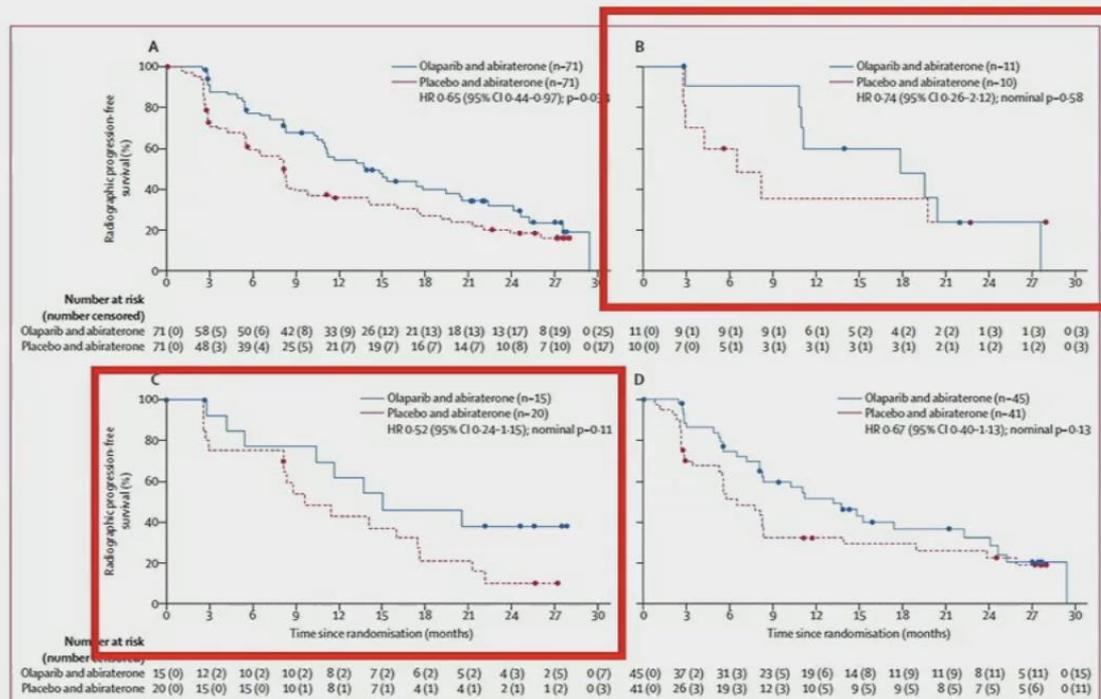


Pre-Clinical Observations- AR, PARP-1

- Androgen Deprivation Therapy (ADT) upregulates PARP activity
- PARP-1 is required for Androgen Receptor activity
- Androgen Receptor Signaling is Necessary for DNA repair



Phase 2: Abiraterone/Pred + Placebo vs. Abi/Pred + Olaparib



Lancet Oncol 2018; 19: 975-86

Figure 2: Radiographic progression-free survival in the (A) Intention-to-treat population, (B) HRR mutation-positive subgroup, (C) wild-type HRR subgroup, and (D) partially characterised HRR status subgroup
 HRR=homologous recombination repair. HR=hazard ratio.



Three Trials to Note- Combination ARi + PARPi

- MAGNITUDE: Abiraterone/Prednisone + Niraparib vs. Abi/Pred + Placebo
- PROPEL: Abiraterone/Prednisone + Olaparib vs. Abi/Pred + Placebo
- TALAPRO: Enzalutamide + Talazoparib vs. Enzalutamide +Placebo



MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study ³

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

Prescreening for BM status^a

HRR BM+ panel:
 ATM
 BRCA1
 BRCA2
 BRIP1
 CDK12
 CHEK2
 FANCA
 HDAC2
 PALB2

Allocation to cohort

HRR BM+
 Planned N = 400

HRR BM-
 Planned N = 600

1:1 randomization

Niraparib + AAP

Placebo + AAP

Niraparib + AAP

Placebo + AAP

Primary endpoint

- rPFS by central review

Secondary endpoints

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

Other prespecified endpoints

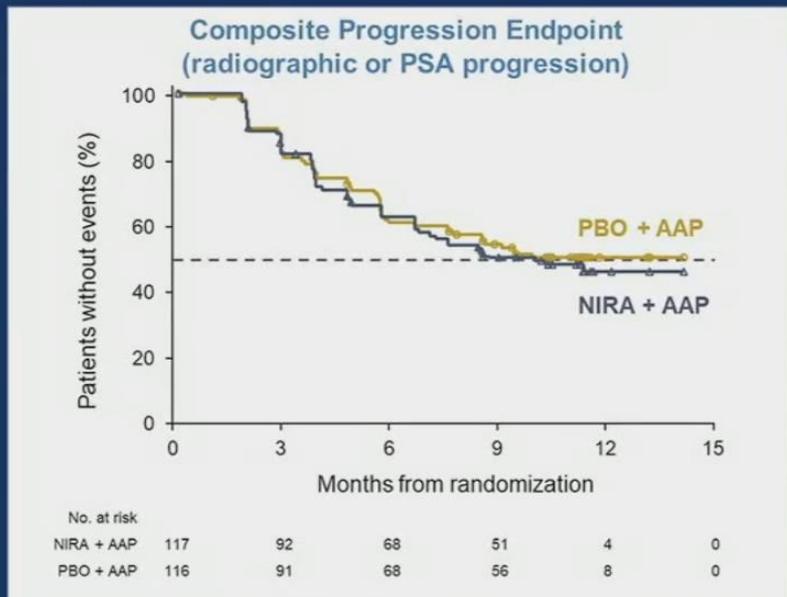
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

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

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.

MAGNITUDE **HRR BM⁻** : Prespecified Early Futility Analysis No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint^a (N = 233)
HR = 1.09^b (95% CI 0.75-1.59)
[futility was defined as ≥ 1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

^bBreakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

^arPFS or PSA progression, whichever occurred first

AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen; rPFS, radiographic progression free survival



ORIGINAL ARTICLE

Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial ☆

K. N. Chi^{1*}, S. Sandhu^{2,3}, M. R. Smith^{4,5}, G. Attard^{6,7}, M. Saad⁸, D. Olmos⁹, E. Castro¹⁰, G. Roubaud¹¹, A. J. Pereira de Santana Gomes¹², E. J. Small¹³, D. E. Rathkopf^{14,15}, H. Gurney¹⁶, W. Jung¹⁷, G. E. Mason¹⁸, S. Dibaj¹⁹, D. Wu²⁰, B. Diorio²¹, K. Urtishak¹⁸, A. del Corral²², P. Francis²³, W. Kim²⁰ & E.fstathiou²⁴

In conclusion, the MAGNITUDE IA2 results support the treatment regimen of niraparib plus AAP in patients with *BRCA1/2*-altered mCRPC, with demonstration of continued improvements in rPFS, time to symptomatic progression, and time to initiation of cytotoxic chemotherapy (Supplementary Figure S8, available at <https://doi.org/10.1016/j.annonc.2023.06.009>). Thus, these results reinforce the need for genomic testing for patients with mCRPC in the first-line setting to identify those patients who would potentially derive optimal benefit in response to treatment with PARP inhibitors, such as niraparib.

July 2023

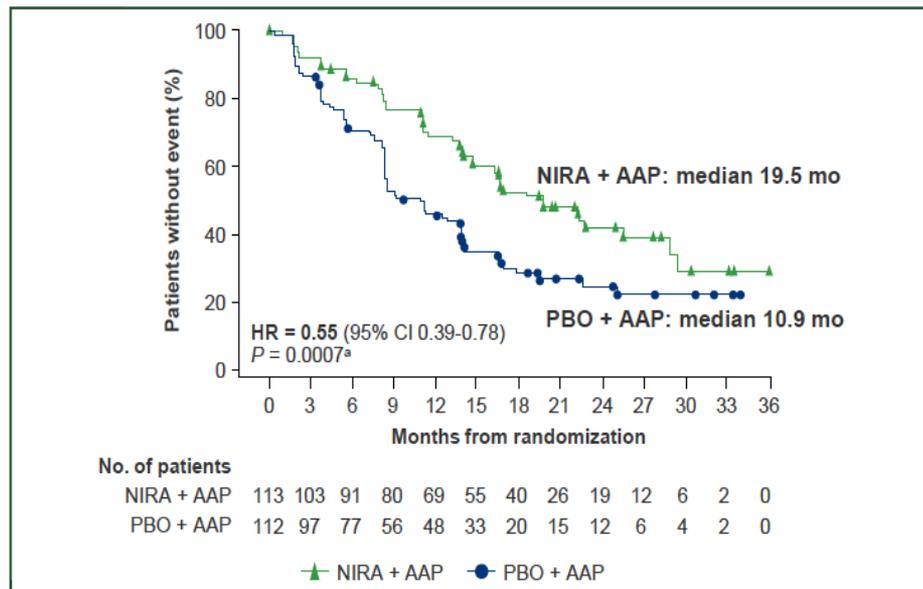


Figure 1. Radiographic progression-free survival at IA2 by blinded independent central review in the *BRCA1/2* subgroup.



PROpel: Phase III trial design

Patient population

- 1L mCRPC
- **Asymptomatic, mildly symptomatic, symptomatic**
- No prior abiraterone
- **Other NHAs allowed if stopped ≥ 12 months prior to enrollment**
- ECOG 0–1

Stratification factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

Abiraterone 1000 mg qd*
+
olaparib 300 mg bid
n=399

Full dose of abiraterone and olaparib

Abiraterone 1000 mg qd*
+
placebo
n=397

Full dose of abiraterone

Primary endpoint

- rPFS by investigator assessment (sensitivity analysis by blinded independent central review)

Key secondary endpoint

- OS

Additional preplanned analyses:

- TFST
- PFS2
- HRQoL
- HRRm status (by tissue and ctDNA after randomization and before primary analysis; see supplement)
- Safety and tolerability

DCO1: 30 July 2021
rPFS (primary)

DCO2: 14 March 2022
OS (interim)

DCO3: 12 October 2022
OS (final pre-specified)
current dataset

Analysis timeline:



*In combination with prednisone or prednisolone 5 mg bid.

bid, twice daily; ctDNA, circulating tumor DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair mutation; HRQoL, health-related quality of life; mHSPC, metastatic hormone-sensitive prostate cancer; PFS2, time to second progression or death; qd, once daily; TFST, time to first subsequent therapy or death.



PROpel: primary rPFS results (DCO1)¹

Abiraterone + olaparib significantly prolonged rPFS versus abiraterone + placebo in the ITT population

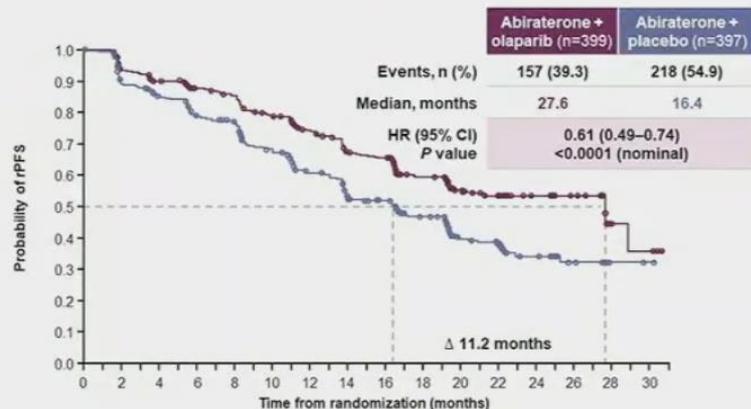
rPFS by investigator assessment (INV)



Number of patients at risk:

Abiraterone + olaparib 399	367	340	313	301	274	251	227	219	167	104	87	57	26	5	4
Abiraterone + placebo 397	359	338	306	297	254	232	198	186	141	87	73	43	17	2	1

rPFS by blinded independent central review (BICR)



Number of patients at risk:

Abiraterone + olaparib 399	353	332	314	303	275	249	221	215	161	86	80	53	28	5	4
Abiraterone + placebo 397	345	322	294	282	245	209	177	168	126	73	62	38	16	2	1

DCO1: 30 July 2021.

Median duration of follow-up for investigator-assessed rPFS for censored patients was 19.3 months in the abiraterone and olaparib arm, and 19.4 months in the abiraterone and placebo arm (19.3 and 19.2 months, respectively, for BICR).

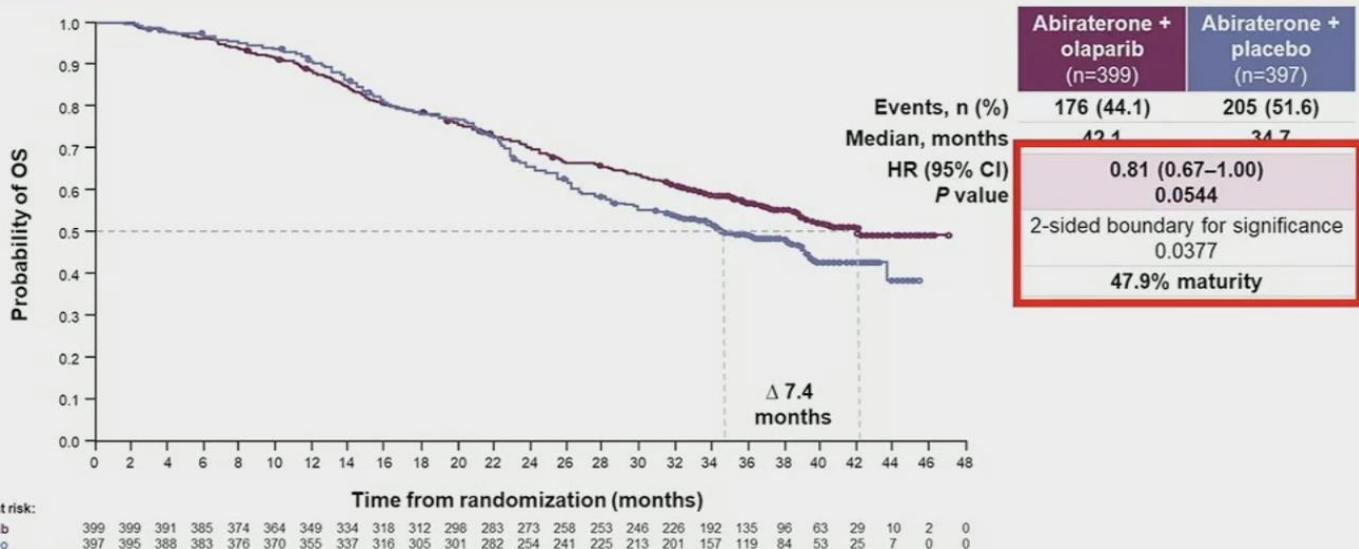
ITT, intention-to-treat.

1. Clarke N *et al.* *NEJM Evidence* 2022;1(9). Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical society.



PROpel: OS at final pre-specified analysis (DCO3)

In the ITT population, median OS was >7 months longer in the abiraterone + olaparib arm



DCO3: 12 October 2022.

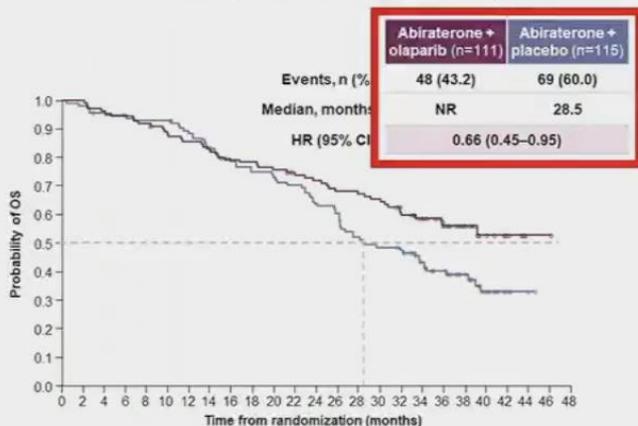
Median (range) duration of follow-up for censored patients at DCO3 was 36.6 months (8.3–47.0) in the abiraterone + olaparib arm and 36.5 months (2.9–45.3) in the abiraterone + placebo arm.



PROpel: OS in HRRm and non-HRRm subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

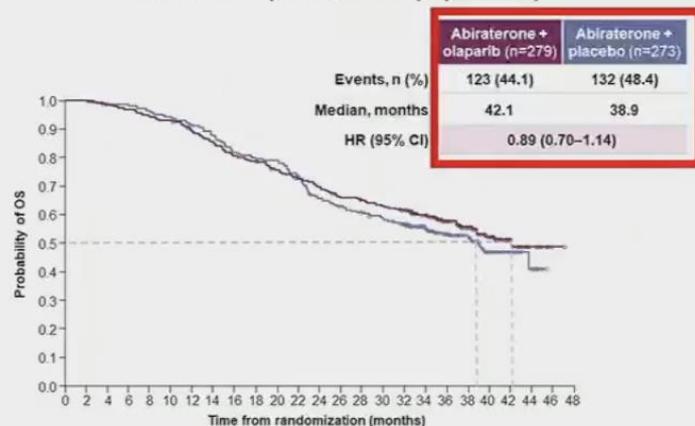
HRRm (28.4% of ITT population)



Number of patients at risk:

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Abiraterone + olaparib	111	111	107	105	102	95	94	90	87	85	83	79	77	73	72	70	62	56	42	22	14	7	1	1	0
Abiraterone + placebo	115	113	109	107	105	105	99	92	85	82	80	77	70	66	57	53	51	49	32	22	12	4	1	0	0

Non-HRRm (69.3% of ITT population)



Number of patients at risk:

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Abiraterone + olaparib	279	279	275	271	263	260	247	236	223	218	207	198	190	179	175	170	160	134	92	73	48	22	9	1	0
Abiraterone + placebo	273	273	270	267	262	256	247	237	222	216	214	198	177	168	162	155	145	114	84	59	39	21	6	0	0

DCO3: 12 October 2022.

The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.



PROpel: Subgroup Analysis by *BRCAM* Status



N = 796	<i>BRCAM</i> N= 85 (11%) 47 vs 38	Undetermined <i>BRCAM</i> status N= 284 (35%) 138 vs 146	Non-<i>BRCAM</i> N= 427 (54%) 214 vs 213
rPFS (Investigator assessment)			
Median (olaparib vs placebo)	NR ^b , 8	NR , 19	22, 17
HR (95% CI)	0.24 (0.12, 0.46)	0.66 (0.46, 0.94)	0.85 (0.66, 1.11)
OS			
Median (olaparib vs placebo)	NR , 23	NR , 38	37 , 38
HR (95% CI)	0.3 (0.15, 0.6)	0.73 (0.52, 1.03)	1.06 (0.81, 1.39)

Efficacy is largely attributed to the effects of *BRCAM*.

Source: FDA's analysis

a. rPFS by investigator assessment
b. NR= not reached

Approved PARP Inhibitors in Prostate Cancer

Drug	Timing	Targets
Olaparib	mCRPC, either before	(Cohort A) BRCA1, BRCA2, ATM, P1, CDK12, L, PALB2, AD51C, or
Rucaparib		BRCA1, BRCA2

May 31, 2023: FDA Approves
Abiraterone/Prednisone + Olaparib in mCRPC
Patients with BRCA1 BRCA2 mutations

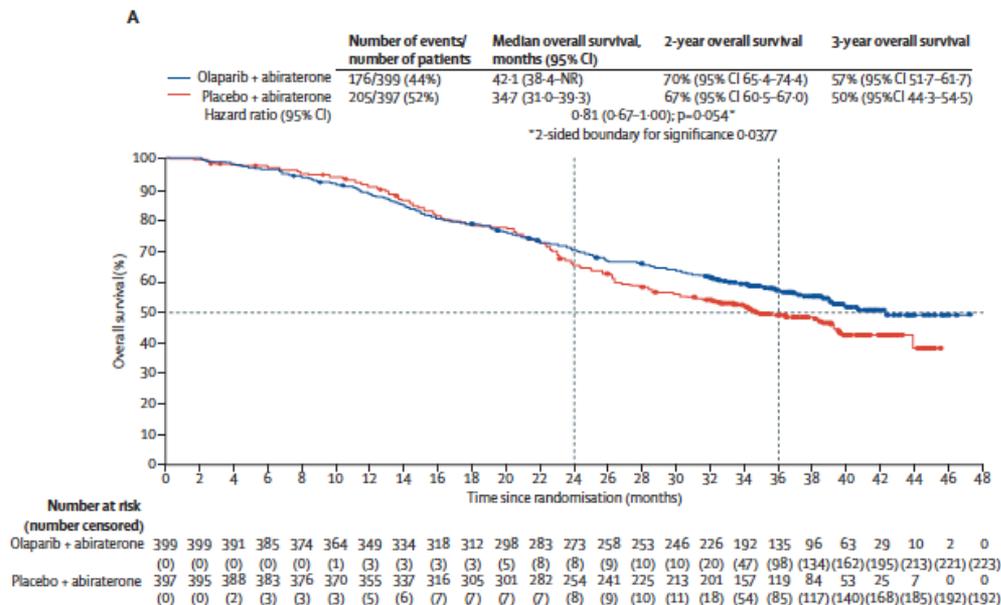
Unanswered Questions:

- Will PARPi work patients without Homologous Recombination Deficiency?
- Are there other stages of the disease for which PARPi should be used in those with Homologous Recombination Deficiency?

Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

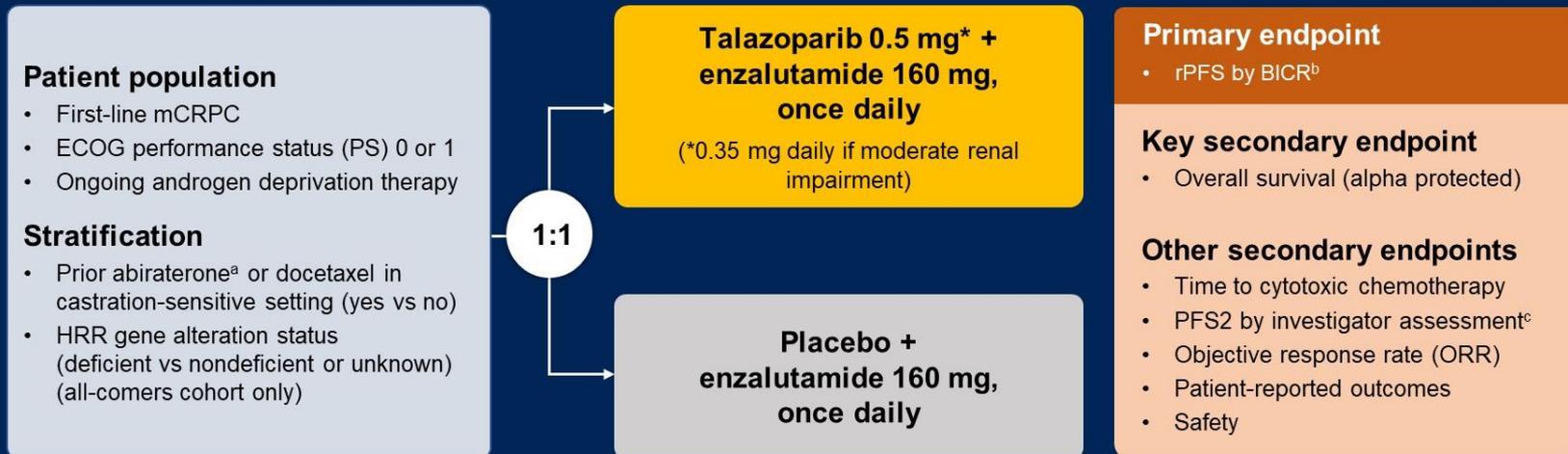


Fred Saad, Noel W Clarke, Mototsugu Oya, Neal Shore, Giuseppe Procopio, João Daniel Guedes, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlümann, Jae Young Joung, Mikio Sugimoto, Oliver Sartor, Yu-Zhen Liu, Christian Poehlein, Laura Barker, Paula Michelle del Rosario, Andrew J Armstrong



Lancet oncology sept 23

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study



Samples prospectively assessed for HRR gene alterations (*BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*) using FoundationOne[®]CDx and/or FoundationOne[®]Liquid CDx

BICR=blinded independent central review; rPFS=radiographic progression-free survival.

^aOne patient in each treatment arm received prior orteronel. ^bPer RECIST version 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). ^cTime from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

TALAPRO-2: Study Cohorts and Enrollment

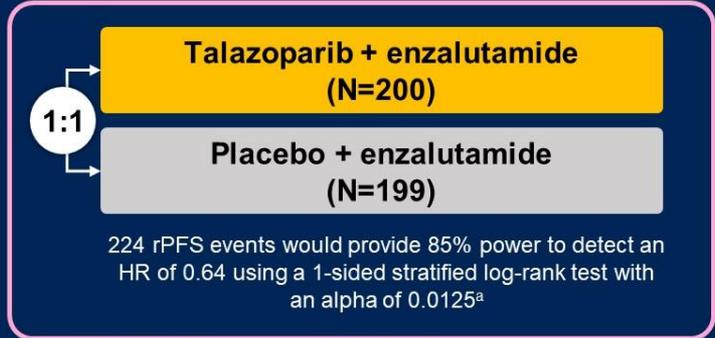
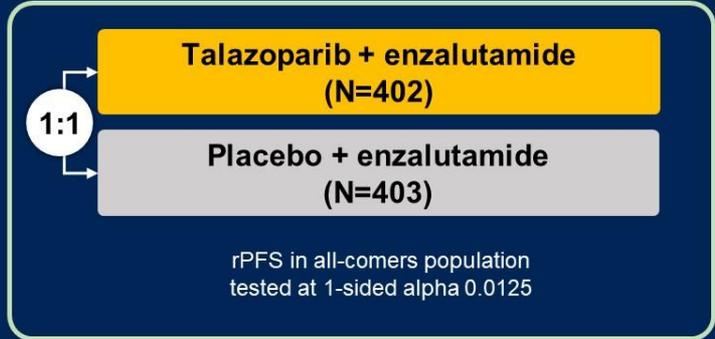
All-comers (Cohort 1), N=805

Recruited first, data cutoff: August 16, 2022



HRRm only (Cohort 2), N=399

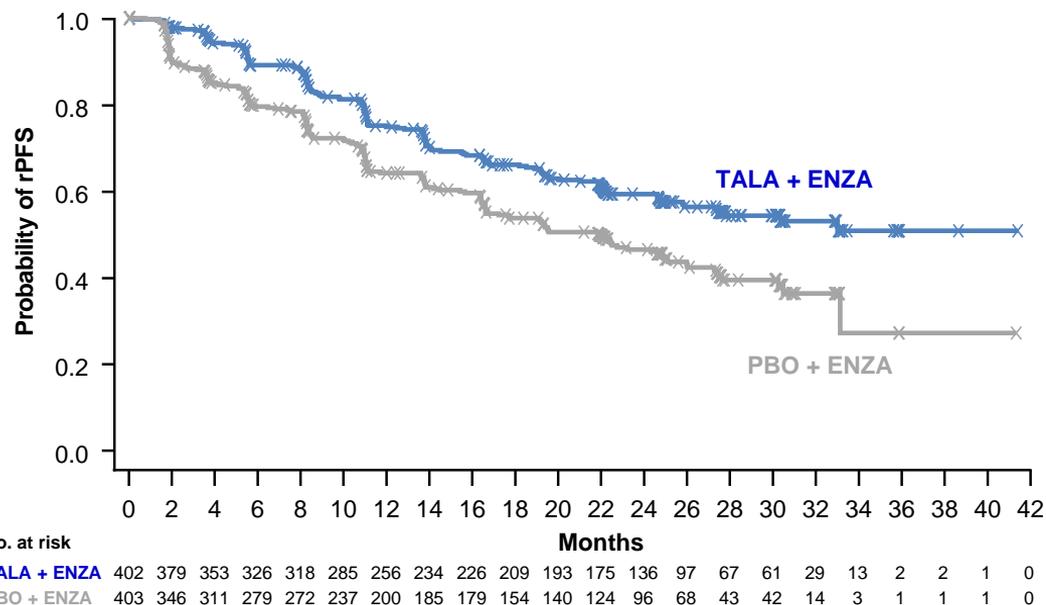
Recruitment continued after completion of enrollment in cohort 1, data cutoff: October 3, 2022



^aAn interim analysis (IA) was planned with ~70% of the total required events. The HRRm cohort would be stopped for efficacy if the pre-specified efficacy boundary was crossed ($P \leq 0.003$). As the efficacy boundary was crossed at the IA rPFS, this became the final analysis. Survival and safety follow-up is continuing. All other endpoints are final.

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	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	

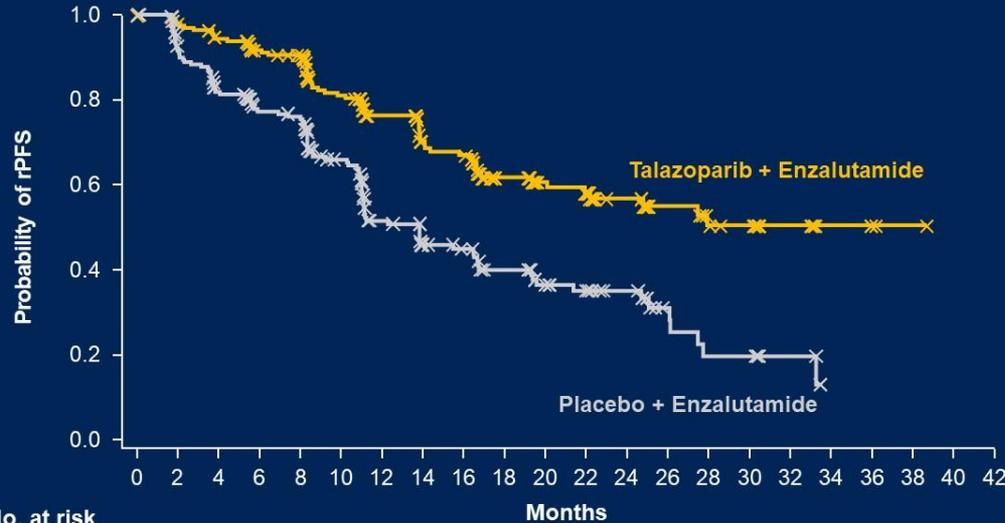
Median follow-up for rPFS was 24.9 and 24.6 months, respectively

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

⁵Stratified 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 HRR-Deficient Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 55% reduced risk of progression or death



No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
TALA + ENZA	200	191	180	168	163	131	107	86	82	60	49	45	34	26	21	19	9	4	2	1	0	0
PBO + ENZA	199	171	149	131	126	96	67	51	47	38	29	25	21	11	7	7	4	0	0	0	0	0

	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	0.45 (0.33–0.61); P < 0.0001	

Median follow-up for rPFS was 17.5 and 16.8 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); P < 0.0001

Stratified hazard ratios (HRs) and 2-sided P values are reported throughout this presentation unless otherwise stated.

- **BRCA1/2 are great predictive biomarkers for PARP inhibitors**
- **Efficacy of Enzalutamide + Talazoparib is as good as other ARi + PARPi combinations**

Trial	Therapies	rPFS HRRm (CI)	rPFS BRCA1/2 (CI)
TALAPRO-2 ¹	Enzalutamide + Talazoparib	0.45 (0.33-0.61)	0.20 (0.11-0.36)
PROpel ²	Abiraterone + Olaparib	0.50 (0.34-0.73)	0.23 (0.12-0.43)
MAGNITUDE ³	Abiraterone + Niraparib	0.73 (0.56-0.96)	0.53 (0.36-0.79)

¹Fizazi et al, ASCO GU, 2023

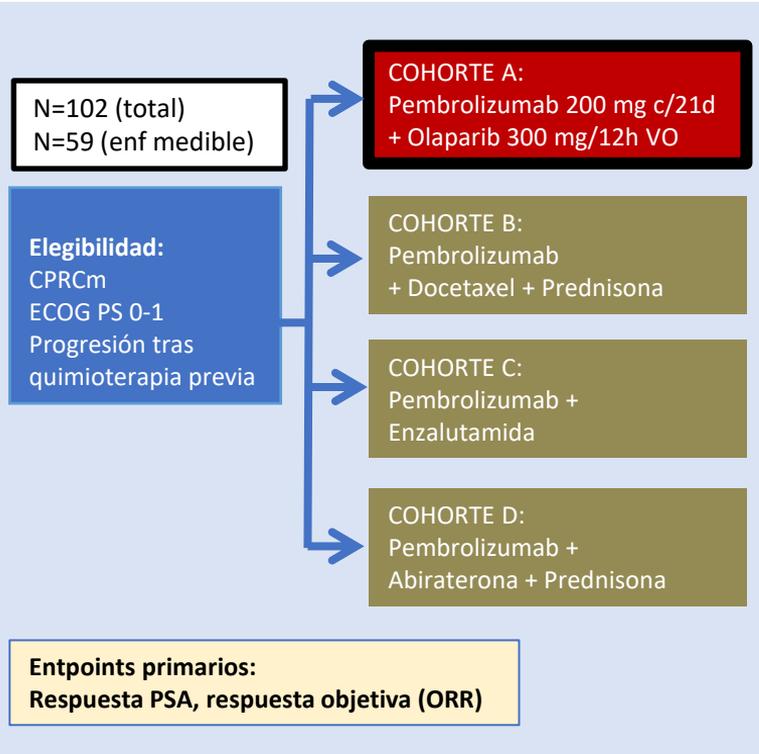
²Clarke et al, NEJM Evidence, 2022

³Chi et al, JCO, 2023

Pembrolizumab plus Olaparib in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort A Study

Ensayo KEYNOTE-365 – Cohorte A

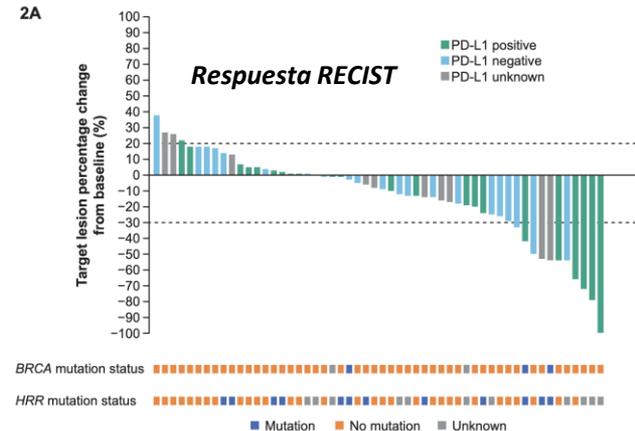
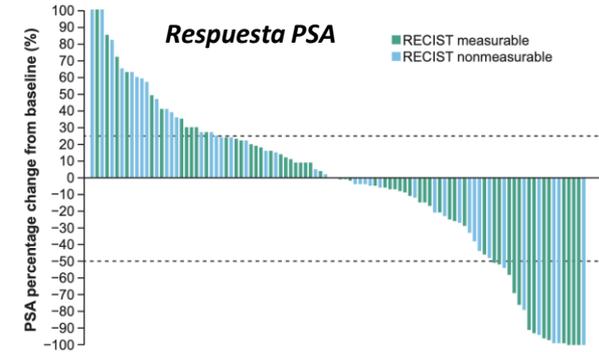
Ensayo fase Ib/II



>90% tratados con Abi/Enza previa
 40% cabazitaxel previo
 18% con mutación HRR
 4% con mutación BRCA2

20% eventos adversos inmunes grado 3-5

N=104 (N=59*)	
Resp PSA	15%
ORR*	8,5%
Mediana DOR	24 m
Mediana SLPr	4,5 m
Mediana SG	14 m



Ensayo KEYLINK-010

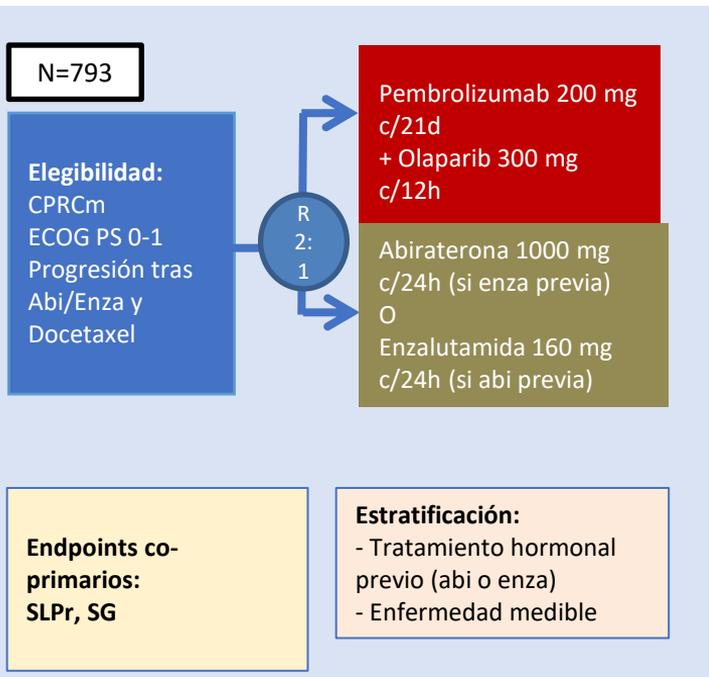
Ensayo fase III

Mutación HRR: 26,1%

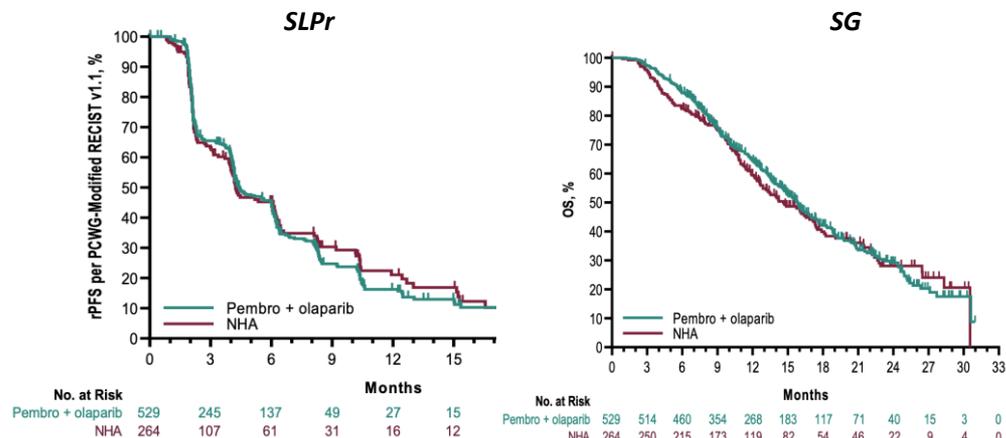
Mutación BRCA: 9,8%



Pembrolizumab Plus Olaparib vs Abiraterone or Enzalutamide for Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer: Randomized Open-Label Phase 3 KEYLYNK-010 Study

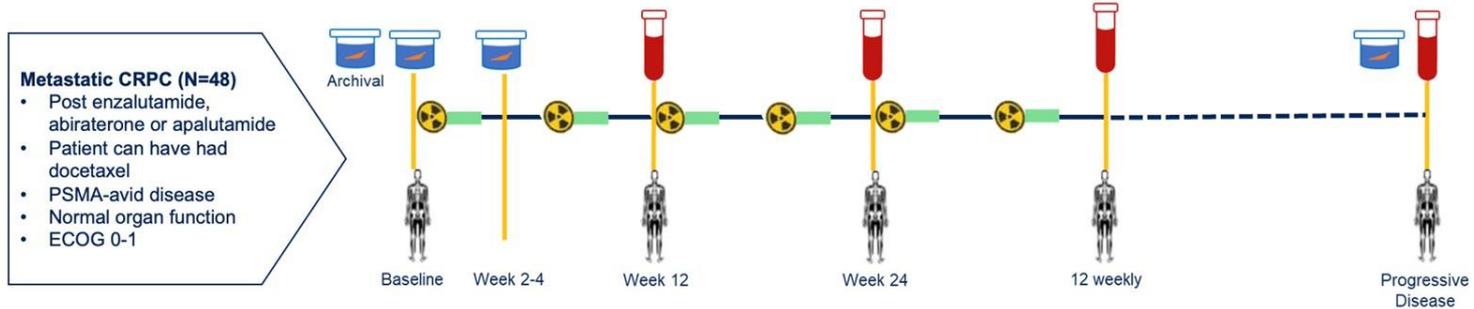


	Pembro + Ola	Abi/Enza	HR (95%CI); p-val
SG	15,8 m	14,6 m	HR 0,94 (0,77-1,14); p=0,26
SLPr	4.4 m	4.2 m	HR 1.02 (0.82-1,25); p=0,55
ORR	16,8%	5,9%	-



LuPARP

Lu-PSMA + 14-21 days olaparib starting around the time of Lu-PSMA infusion



Short-term Safety?

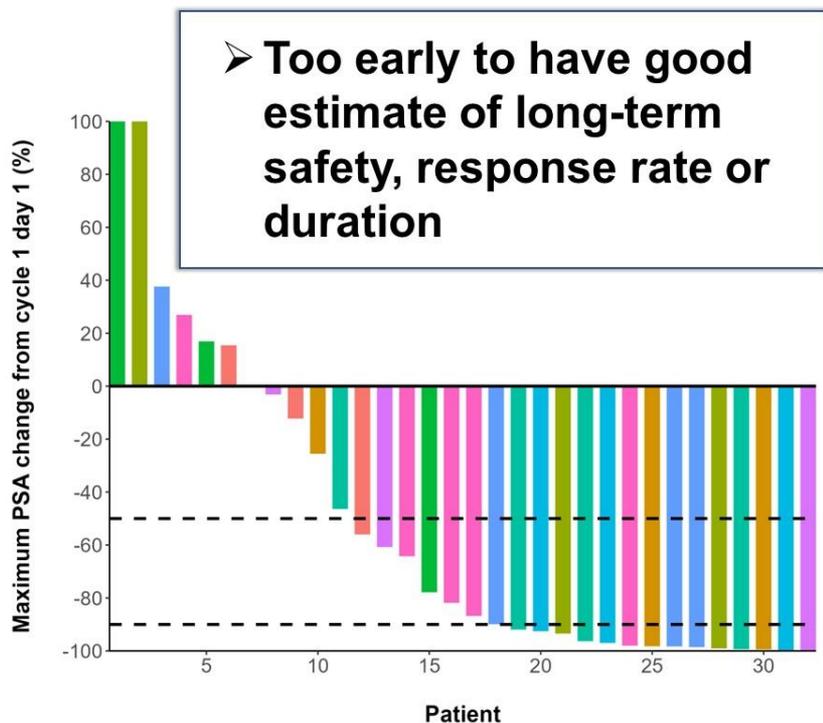
Long-term Safety?

Responses and Duration?

32 patients

- 0 DLTs
- 3 Treatment Delays
- 0 Treatment Discontinuation

So far, PSA responses are similar to LuPSMA alone



Study	Therapy	PSA 50	PSA 90 (80)
LuPARP	LuPSMA + olaparib	66%	44%
VISION ¹	LuPSMA	46%	(33%)
TheraP ²	LuPSMA	66%	38%

¹Sartor et al, NEJM, 2021

²Hofman et al, Lancet, 2021

PARPi + ARPI trials for earlier stage disease

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



Consideraciones finales

- Es imprescindible ofrecer TG a los pacientes con cáncer de próstata avanzado (somático y germinal)
- BRCA2 es un biomarcador de mal pronóstico en CaP y predictor de respuesta a iPARP
- En pacientes con CPRCm y deficiencia de la vía HRR, especialmente BRCA después del tratamiento con NAH debe ofrecerse el tratamiento con iPARP
- En pacientes con CPRCm y alteraciones en otros genes HRR habría que considerar iPARP a lo largo de la evolución

MUCHAS GRACIAS

