10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

PARP inhibitors: Single agents and combinations

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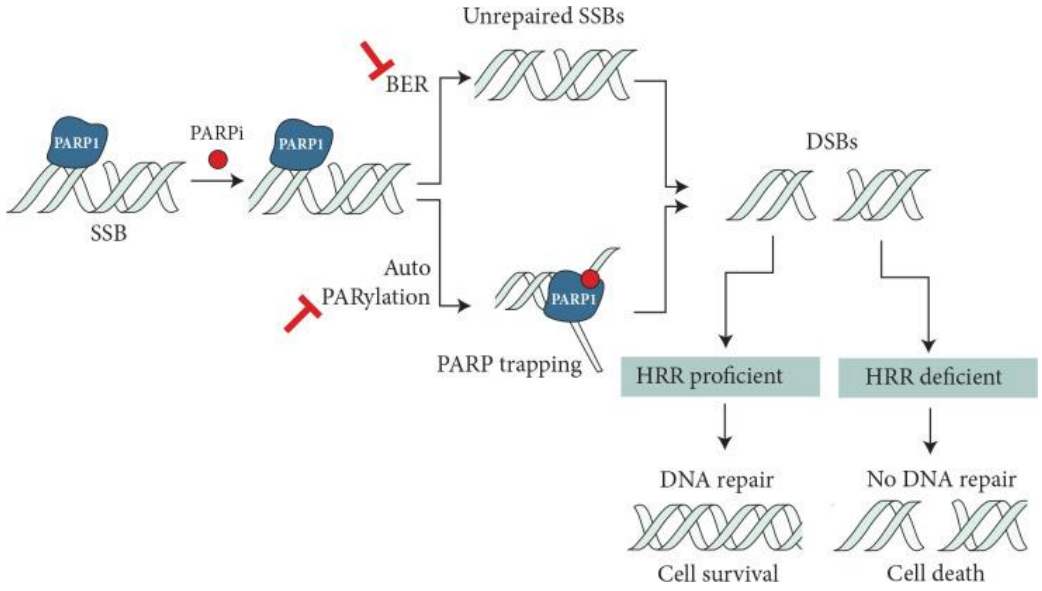
Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Astra Zeneca, Bayer, Janssen, Synlab
Receipt of honoraria or consultation fees	Astra Zeneca, Astellas, Bayer, Clovis, Janssen, MSD, Novartis, Pfizer,Telix
Stock shareholder	None
Travel, accomodation, expenses:	Astra Zeneca, Astellas, Bayer, Janssen

Mechanisms of PARP inhibitors activity in HRR-deficient cells



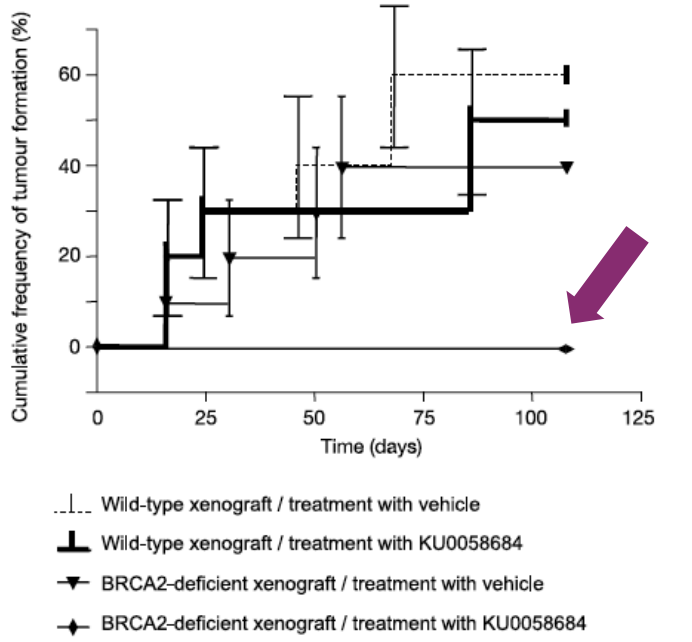
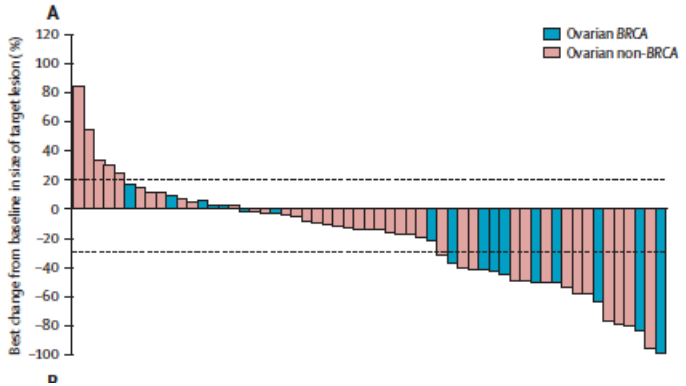
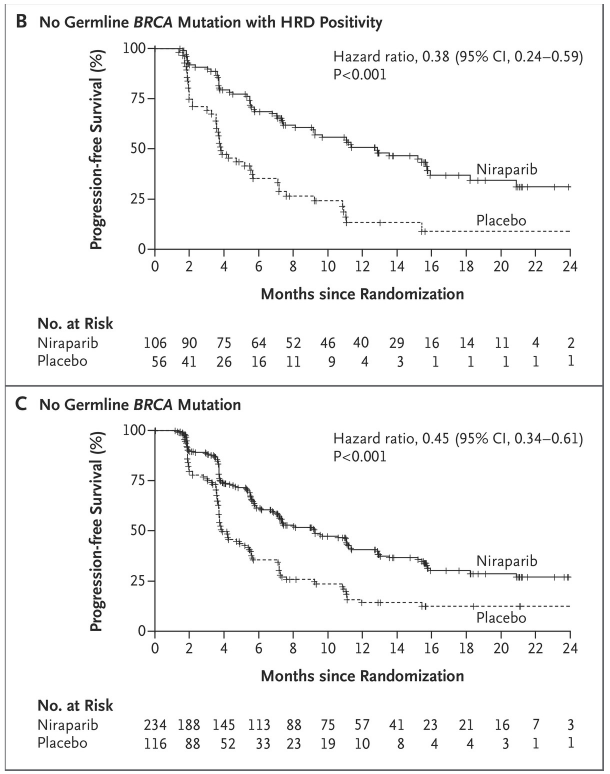


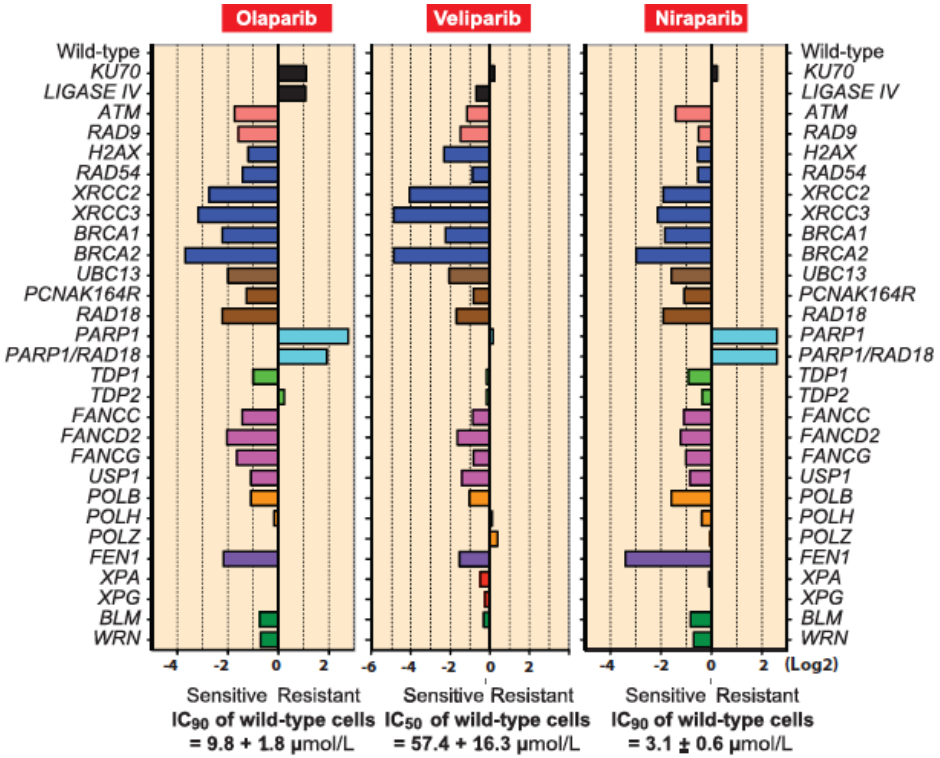
Figure 3 PARP inhibition selectively blocks the growth of BRCA2-deficient tumours *in vivo*. BRCA2-deficient ES cells or wild-type cells were injected into nude mice. Animals were then treated with either KU0058684 or vehicle. Significant differences in tumour formation were seen between the BRCA2-deficient xenograft/KU0058684 treatment cohort and the BRCA2-deficient xenograft/vehicle treatment cohort ($P = 0.03$) and also between the BRCA2-deficient xenograft/KU0058684 treatment cohort and the wild-type xenograft/KU0058684 treatment cohort ($P = 0.01$). Similar data were obtained in an independent experiment. Error bars represent one standard deviation around the mean.

Mateo et al, Ann Oncol, 2019; Farmer et al Nature 2005

Activity of PARPi beyond *BRCA* mutations

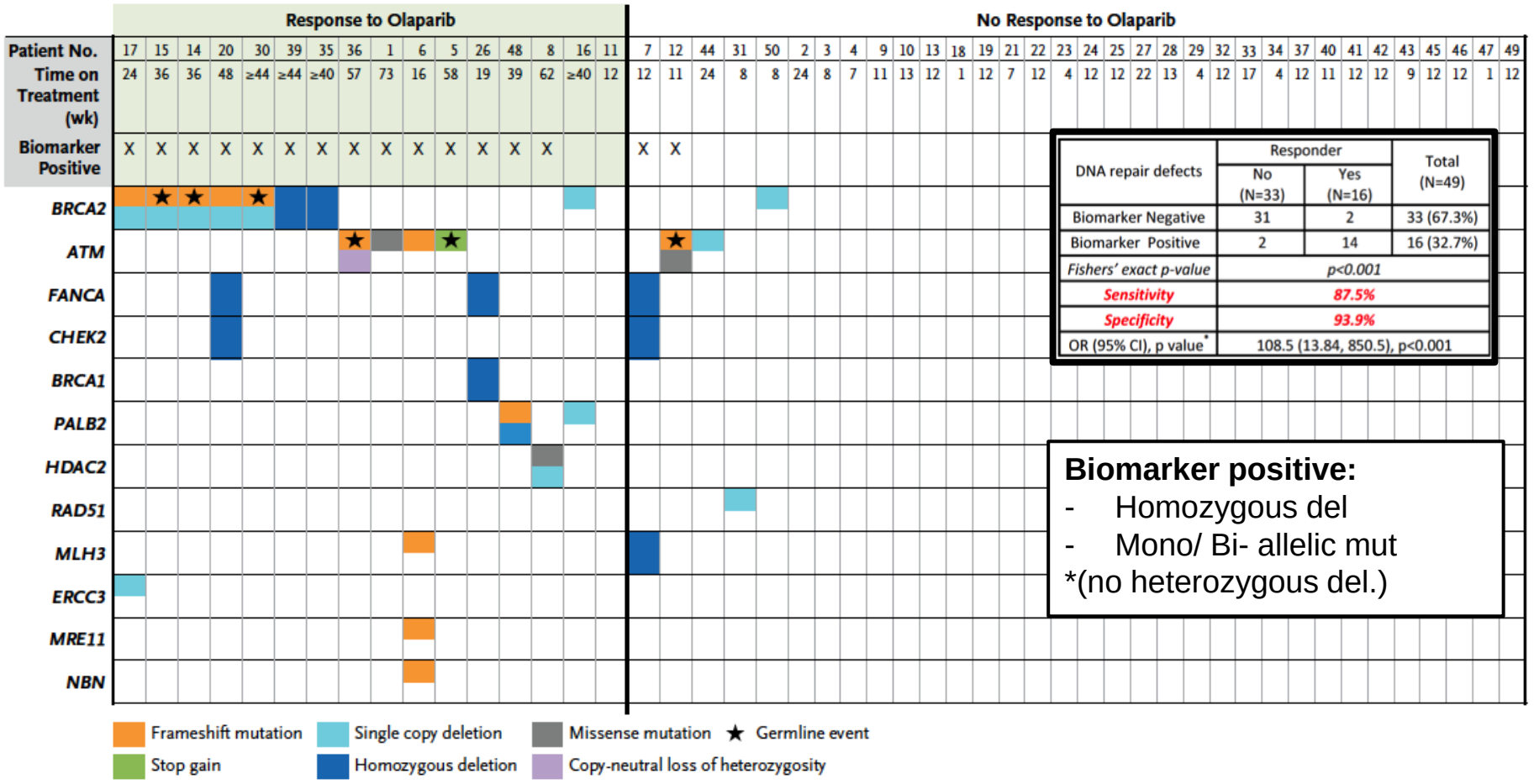






Gelmon, Lancet Onco, 2011; Mirza et al, NEJM, 2016; Murai et al, Cancer Res, 2012

TOPARP-A : Olaparib monotherapy for mCRPC



DNA repair defects	Responder		Total (N=49)
	No (N=33)	Yes (N=16)	
Biomarker Negative	31	2	33 (67.3%)
Biomarker Positive	2	14	16 (32.7%)
Fishers' exact p-value	*p<0.001*		
Sensitivity	***87.5%***		
Specificity	***93.9%***		
OR (95% CI), p value*	108.5 (13.84, 850.5), p<0.001		

Biomarker positive:
- Homozygous del
- Mono/ Bi- allelic mut

*(no heterozygous del.)

Mateo et al, NEJM, 2015

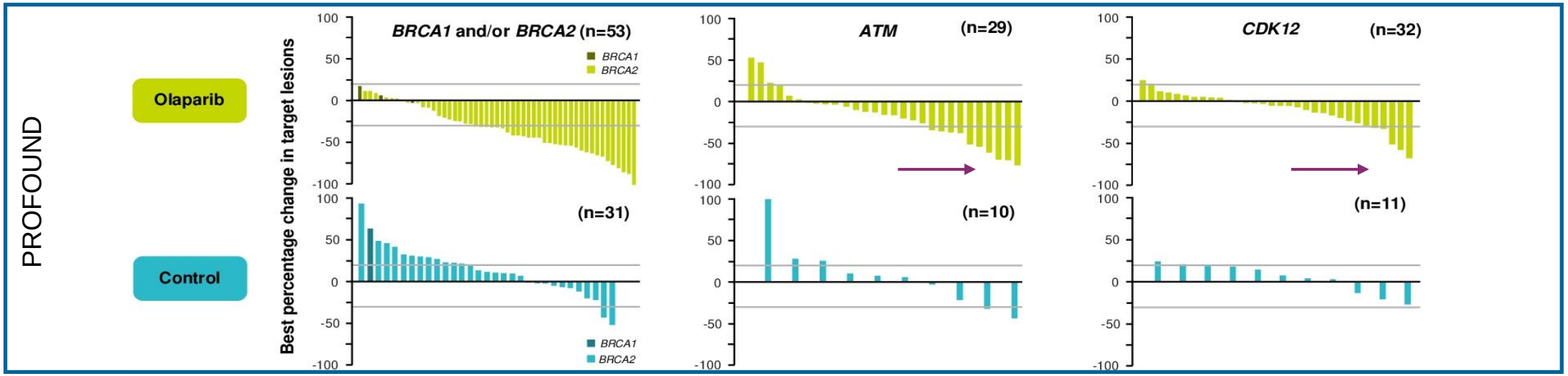
Trials of PARP inhibitor monotherapy in mCRPC

	TOPARP-A	TOPARP-B	PROfound	TRITON2	TALAPRO-1	GALAHAD
Drug	Olaparib			Rucaparib	Talazoparib	Niraparib
Study design and population	Phase 2, single arm. Unselected for DDR alterations mCRPC after progression to taxane *N* = 50	Phase 2, single arm mCRPC after taxanes *N* = 98	Phase 3 (Cohort A: *ATM, BRCA1, BRCA2* alterations; Cohort B: any of 12 other DDR prespecified genes) mCRPC after progression to ARSi *N* = 387	Phase 2, single arm mCRPC after progression to ARSi and taxane *N* = 193	Phase 2, single arm mCRPC after progression to ARSi and taxane *N* = 127	Phase 2, single arm mCRPC after progression to ARSi and taxane *N* = 223
Primary objective	Composite endpoint [ORR (RECIST), PSA decline ≥50%, CTC response]	Composite endpoint [ORR (RECIST), PSA decline ≥50%, CTC response]	rPFS in pts with alterations in ATM, BRCA1, BRCA2 (Cohort A)	ORR (RECIST/PCWG3) in pts with DDR alterations	ORR (RECIST) in pts with DDR alterations	ORR (RECIST) in pts with biallelic *BRCA1/2* alterations
Results	Composite endpoint: 33% in all pts 88% in pts with DDR alterations 6% in pts with no DDR alterations	Composite endpoint: 54% with 400 mg b.i.d. 39% wth 300 mg b.i.d.	rPFS 7.4 vs. 3.6 m (Cohort A vs. control) rPFS 5.8 vs. 3.5 m (Cohort A+B vs. control) OS 19.1 vs. 14.7 m (Cohort A vs. control) OS 14.1 vs. 11.5 m (Cohort B vs. control)	ORR 43.5% in BRCA1/2 pts PSA ≥50% decline: 66% in BRCA1/2 pts ORR 10.5% in ATM pts ORR 11.1% in CHEK2 ORR 0% in CDK12 pts ORR 28.6% in other DDR altered pts	ORR 30% in all pts in the study ORR 46% in BRCA1/2 altered pts ORR 25% in PALB2; ORR 12% in ATM pts PSA ≥50% decline: 46% in all pts PSA ≥50% decline: 66% in BRCA1/2 pts	ORR 41% in BRCA1/2 altered pts ORR 9% in non-BRCA1/2 DDR altered pts Composite RR in BRCA1/2 63% Composite RR in non-BRCA1/2 DDR: 17%
Specimen tested	Tumor tissue Central/local	Tumor tissue Central/local	Tumor tissue Central analysis	Plasma or tumour tissue Central/local	Tumour tissue Central/local	Plasma or tumor tissue Central analysis
Test used	Targeted customized NGS panel	Targeted customized NGS panel	FoundationOne	FoundationOne	FoundationOne	Resolution-HRD; FoundationOne
Genes screened	113 genes[a]	113 genes[a]	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51C, RAD51D, RAD54L*	*ATM,BRAD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51C, RAD51D, RAD54L*	*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*	*ATM, BRCA1,BRCA2, BRIP1, CHEK2, FANCA, HDAC2, PALB2*
Genomic alteration required	Mono- and biallelic DDR alterations	Mono- and biallelic DDR alterations	Mono- and biallelic DDR alterations	Mono- and biallelic DDR alterations	Mono- and biallelic DDR alterations	Biallelic or germline DDR alterations

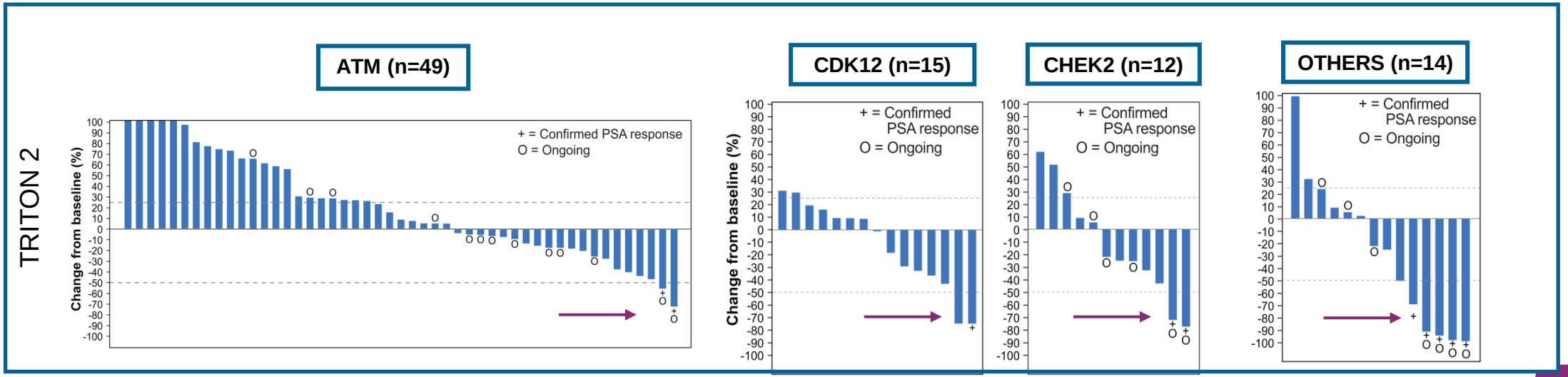
Lozano et al, Curr Opin Urol, 2022

Sensitivity to PARP inhibitors depends on the gene altered

PROFOUND



TRITON 2



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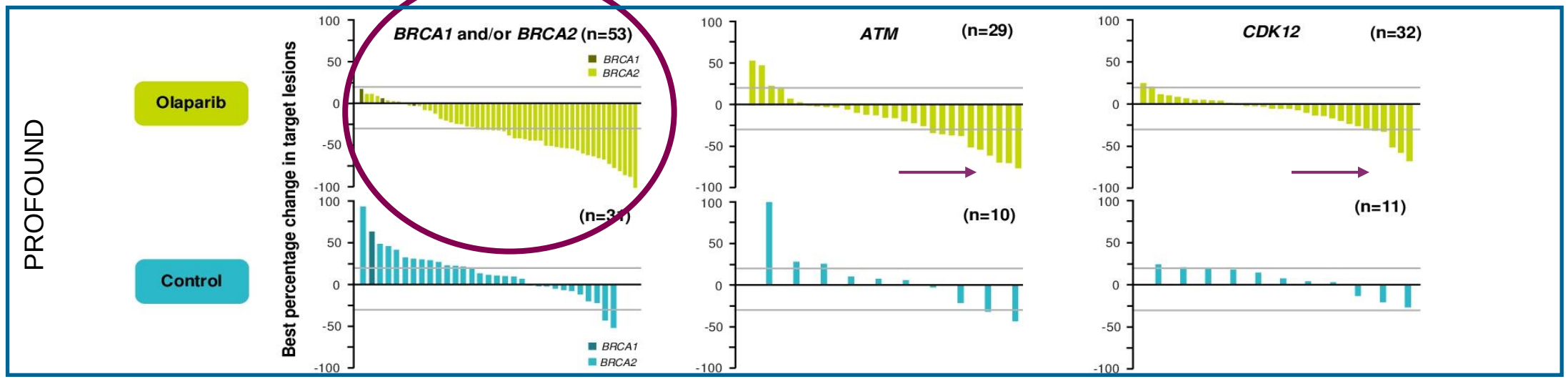
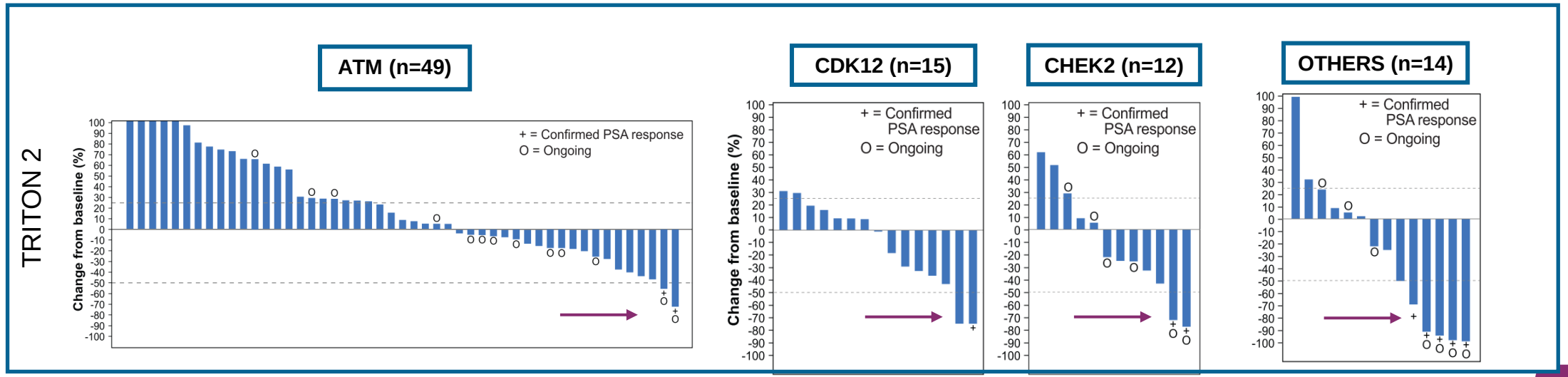
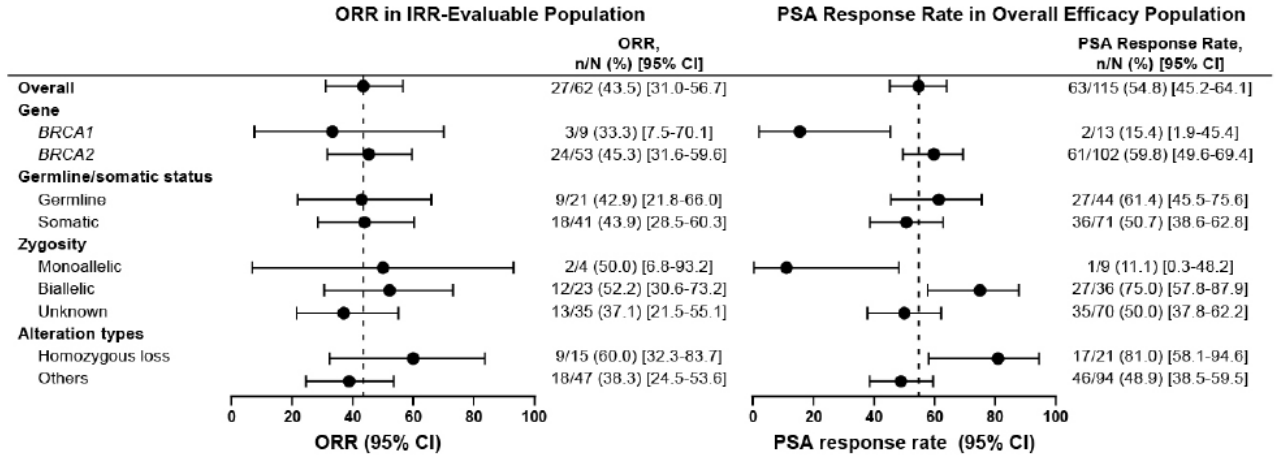


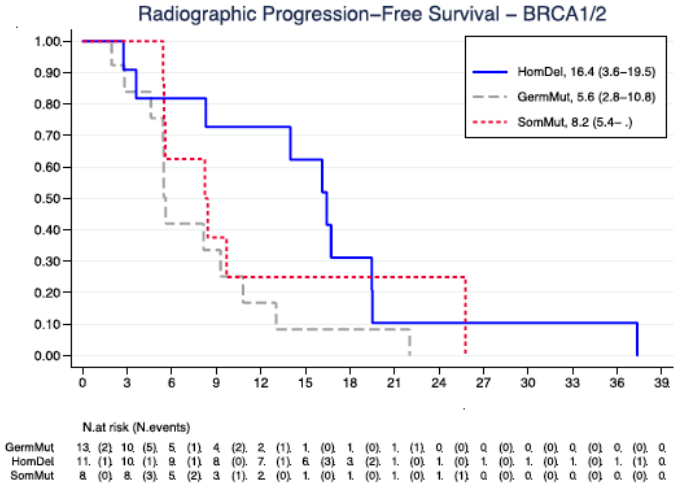


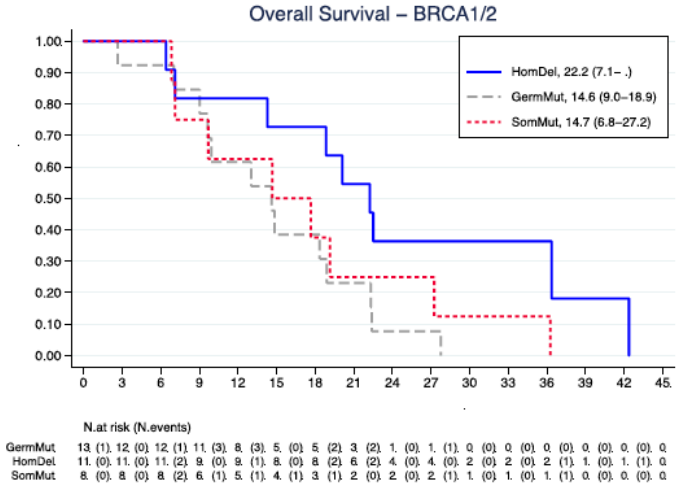
Response to PARP inhibitors in *BRCA1/2* patients may depend on the type of alteration

TRITON 2
(Rucaparib)



TOPARP-B
(Olaparib)





Abida et al, JCO, 2020; Carreira et al, Cancer Discov, 2021

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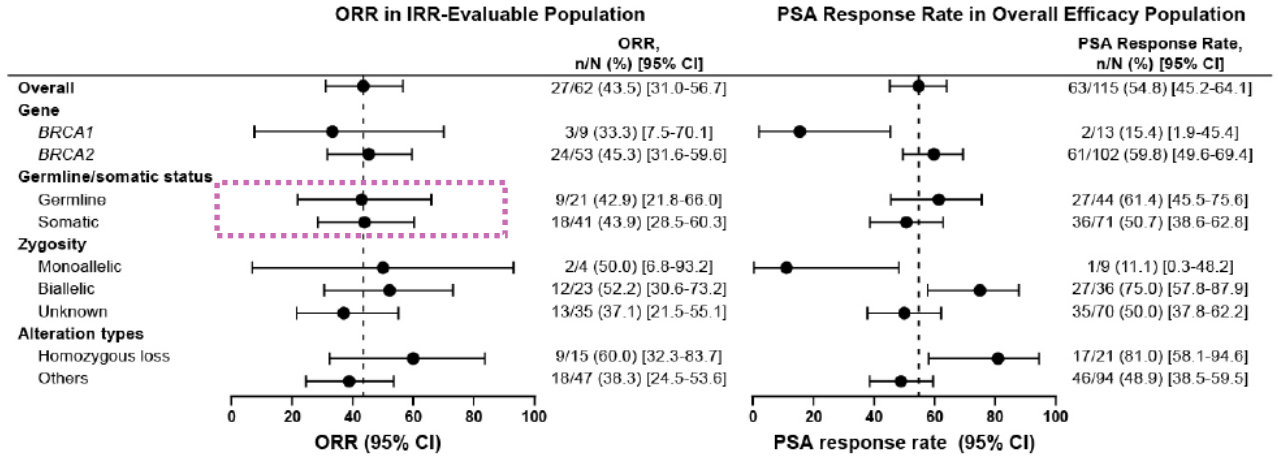

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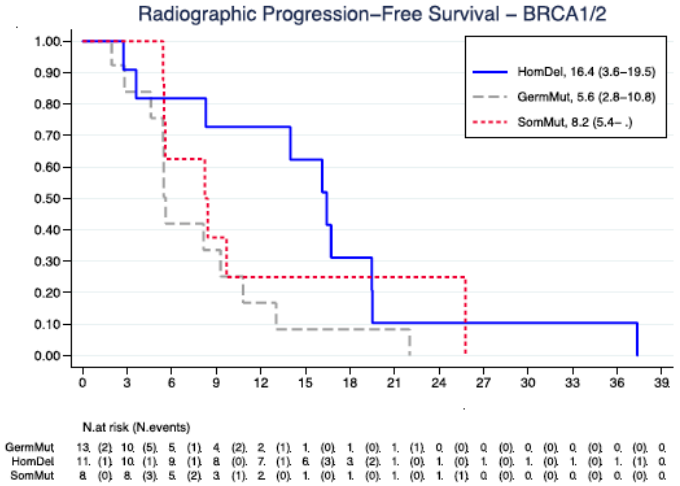

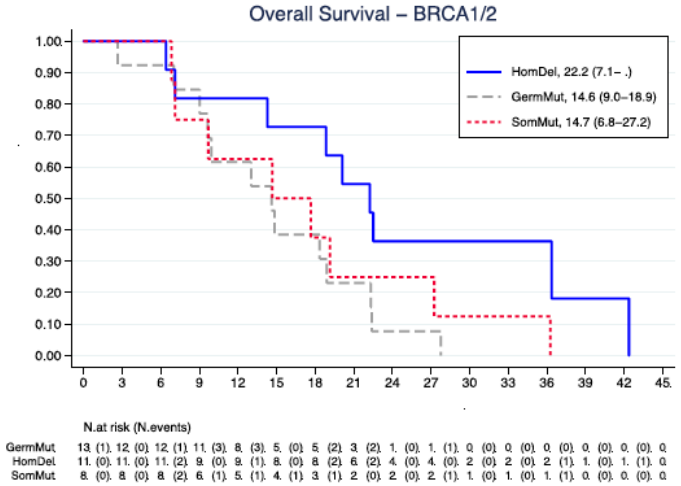

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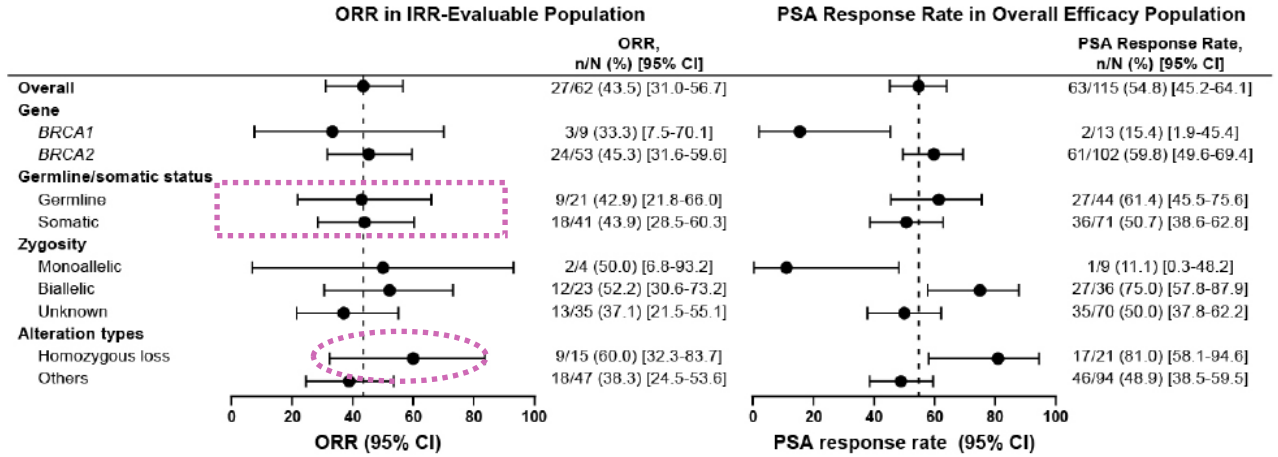
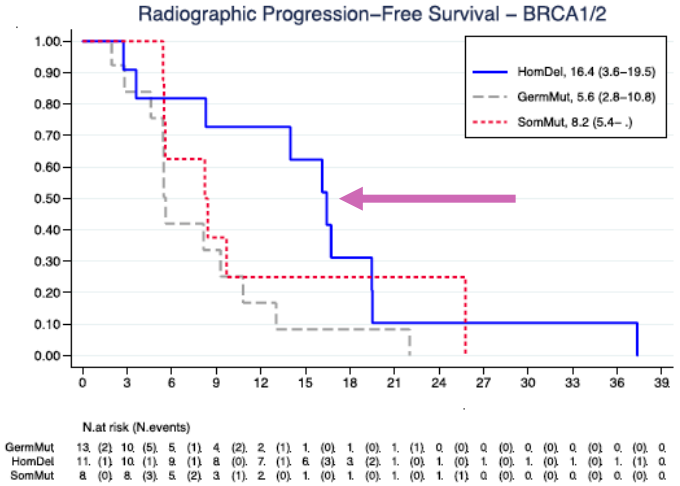
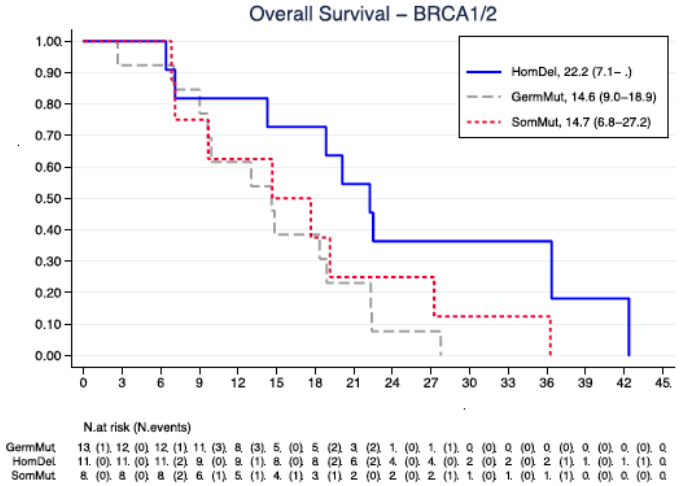


TOPARP-B
(Olaparib)

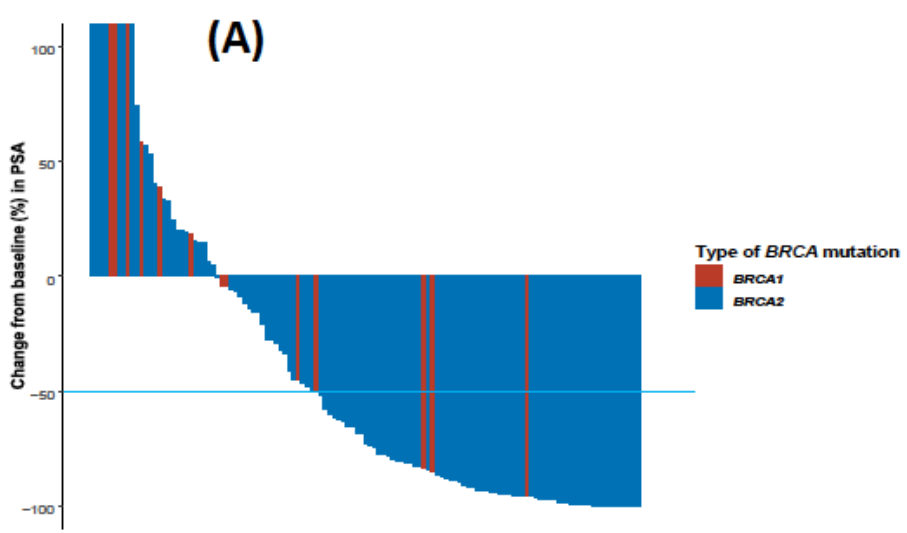


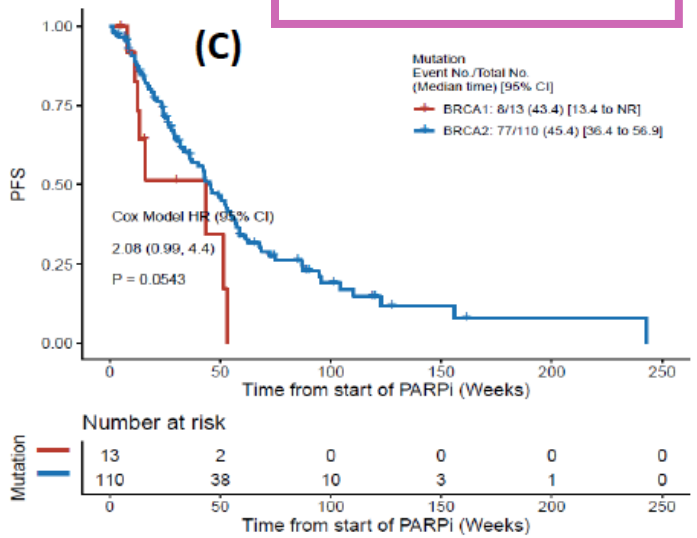


Abida et al, JCO, 2020; Carreira et al, Cancer Discov, 2021

Differential activity of PARPi in *BRCA1* and *BRCA2* altered tumors

	TOPARP-A[14]		TOPARP-B[15]		PROfound[1]		TRITON2[2]		TALAPRO-1[16]		Pooled Data	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*
Outcome	n/N	n/N	n/N	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N (95% CI)	n/N	n/N (95% CI)	n/N (%) (95% CI)	n/N (%) (95% CI)
PSA_{50}	0/1	7/7	1/2	22/28	NR	NR	2/13	61/102	2/5	26/41	5/21 (23.8) (4.4 to 43.2)	116/178 (65.2) (58.2 to 72.2)
ORR	NE	5/5	0/1	11/20	0/5	24/43	3/9	24/53	2/4	15/37	5/19 (26.3) (5.1 to 47.5)	79/158 (50.0) (42.2 to 57.8)
rPFS, months	NE	NR	NE	8.2 (5.5 to 13.0)	2.1 (1.4 to 5.5)	10.8 (9.2 to 13.1)	8.7 (1.8 to 10.7)	9.7 (8.3 to 14.0)	NR	8.8 (5.6 to 19.2)	4.1 (1.0 to 16.8)	10.1 (8.9 to 11.6)
No. of patients evaluable for rPFS				30	8	81	13	102		41	21	254





Markowski &Antonarakis, JCO, 2020; ; Taza et al JCO Precis Oncol 2021

PROfound study design

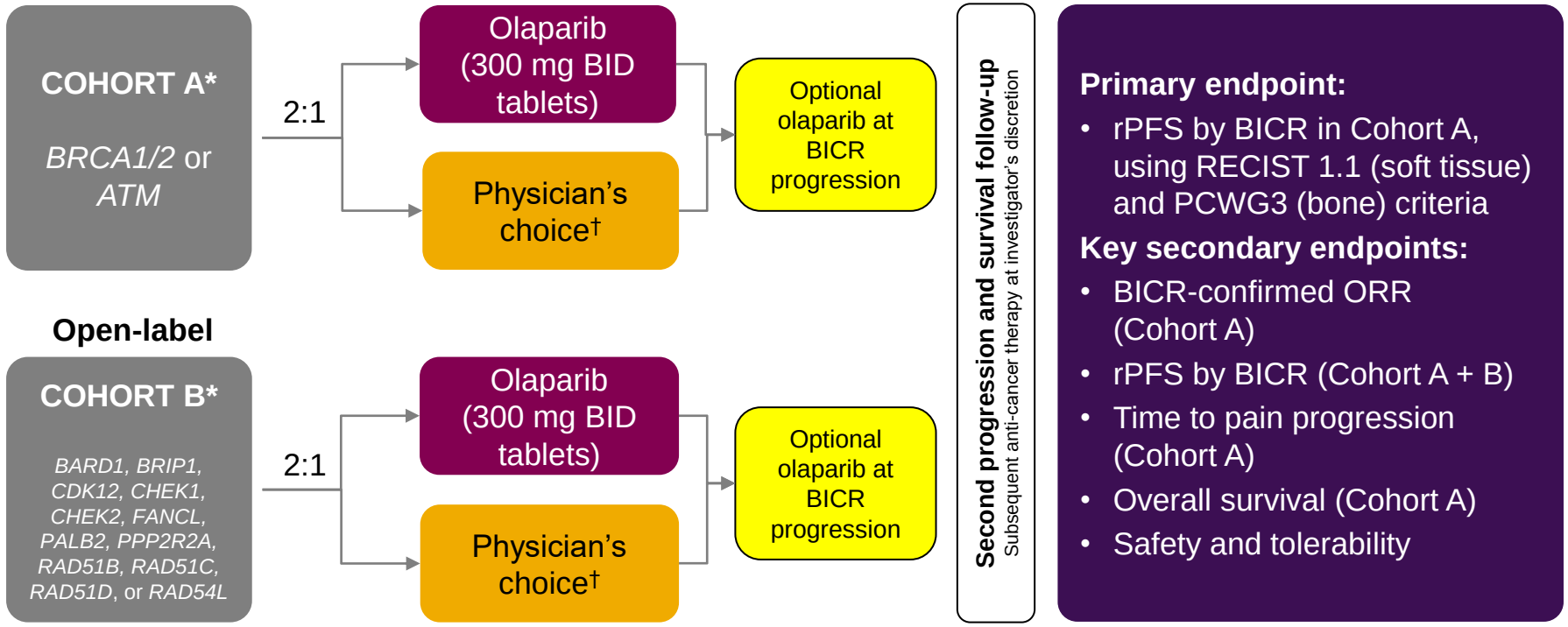
Documented evidence of mCRPC

Qualifying HRR mutation in tumour tissue (central review)

Investigator-assessed **radiographic progression on prior NHA** (e.g. abiraterone acetate and/or enzalutamide) **for mPC and/or CRPC**

ECOG PS 0–2

No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer



Primary endpoint:

- rPFS by BICR in Cohort A, using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria

Key secondary endpoints:

- BICR-confirmed ORR (Cohort A)
- rPFS by BICR (Cohort A + B)
- Time to pain progression (Cohort A)
- Overall survival (Cohort A)
- Safety and tolerability

Patient randomisation will be stratified by:

- Prior taxane therapy (yes/no)
- Measurable disease at baseline (yes/no)

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

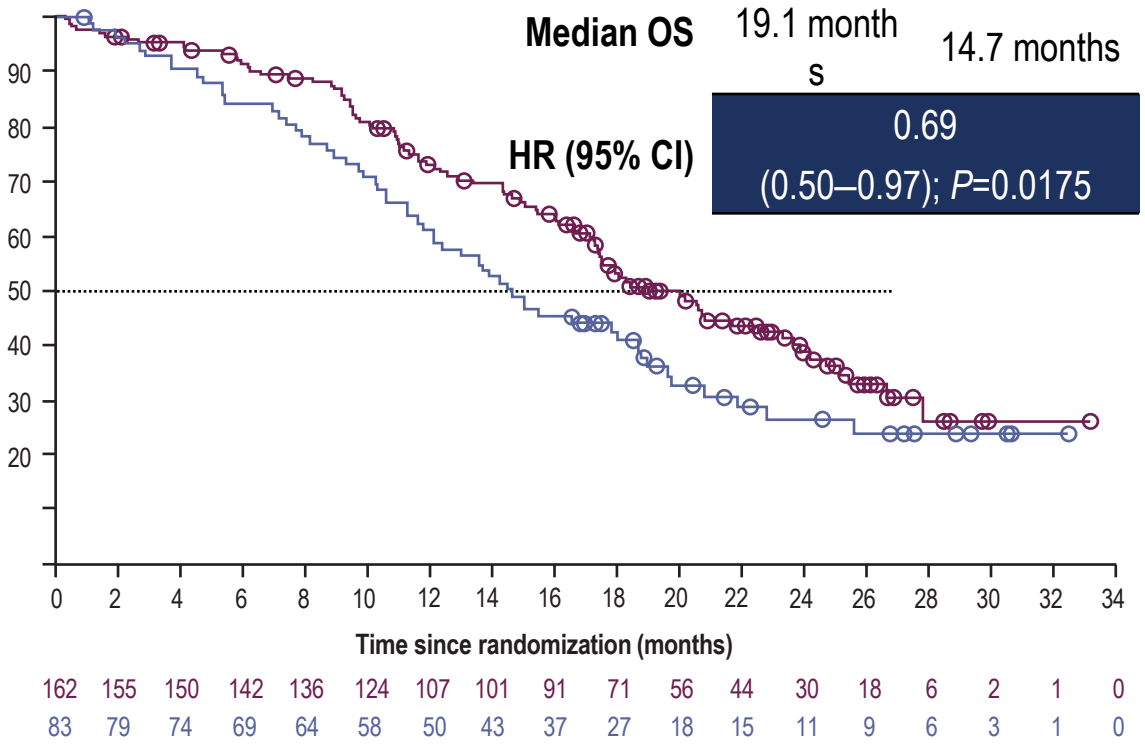
BICR=blinded independent central review; BID=twice daily; CRPC=castration-resistant prostate cancer; EGOC PS=Eastern Cooperative Oncology Group Performance Score; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; mPC=metastatic prostate cancer; NHA=new hormonal agent; nmCCRPC=non-metastatic castration-resistant prostate cancer; ORR=objective response rate; PARP=poly(ADP-ribose) polymerase; PARPi=poly(ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumours; rPFS=radiographic progression-free survival

1. de Bono J, et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona. Abstract 847PD; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02987543 (last accessed April 2020); 3. de Bono JS et al. Poster presented at: ASCO Annual Congress; June 2–6, 2017; Chicago, IL. Abstract TPS5091

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

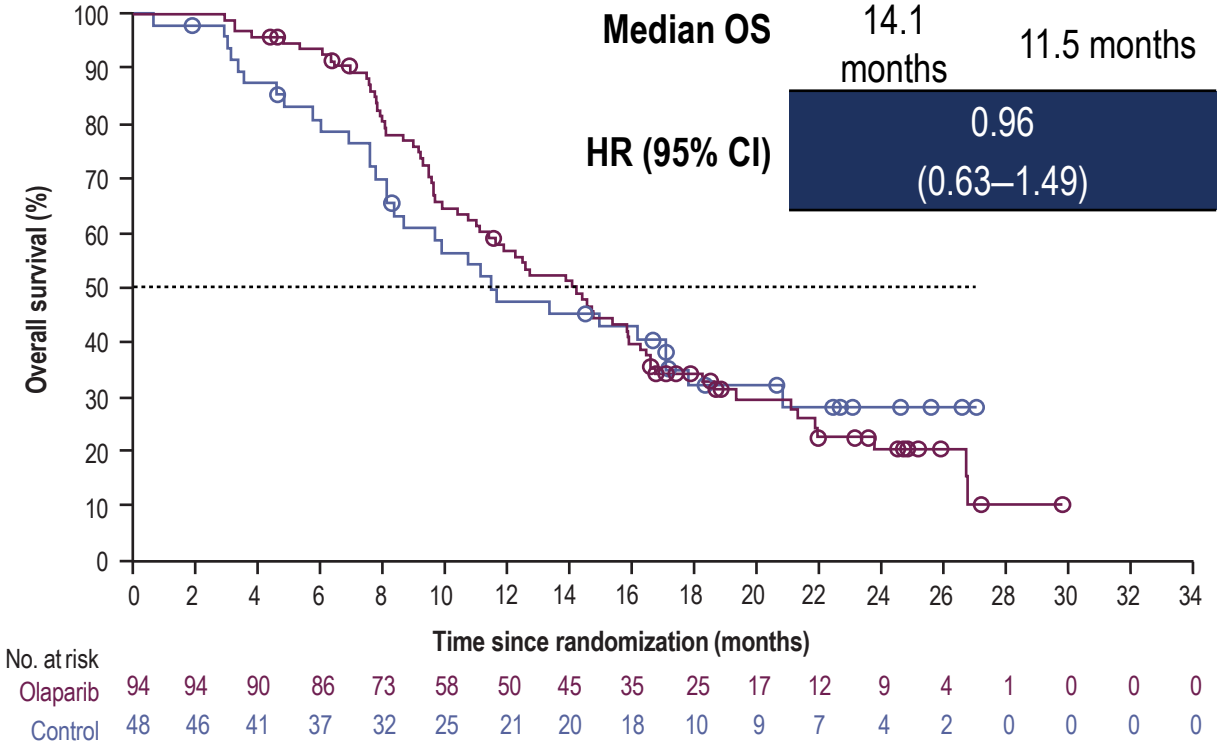
Cohort A

	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50–0.97); *P*=0.0175	



Cohort B

	Olaparib (N=94)	Control (N=48)
Events, n (%)	69 (73)	31 (65)
Median OS	14.1 months	11.5 months
HR (95% CI)	0.96 (0.63–1.49)	



Hussain et al, NEJM, 2020

PROfound study design

65% had previously received taxanes

Documented evidence of mCR

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Investigator-assessed **radiographic progression on prior NHA** (e.g. abiraterone acetate and/or enzalutamide) **for mPC and/or CRPC**

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No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer

RT A*

BRCA1/2 or *ATM*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

→ Optional olaparib at BICR progression

Open-label

COHORT B*

BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or *RAD54L*

2:1

- Olaparib (300 mg BID tablets)
- Physician's choice†

→ Optional olaparib at BICR progression

Second progression and survival follow-up
Subsequent anti-cancer therapy at investigator's discretion

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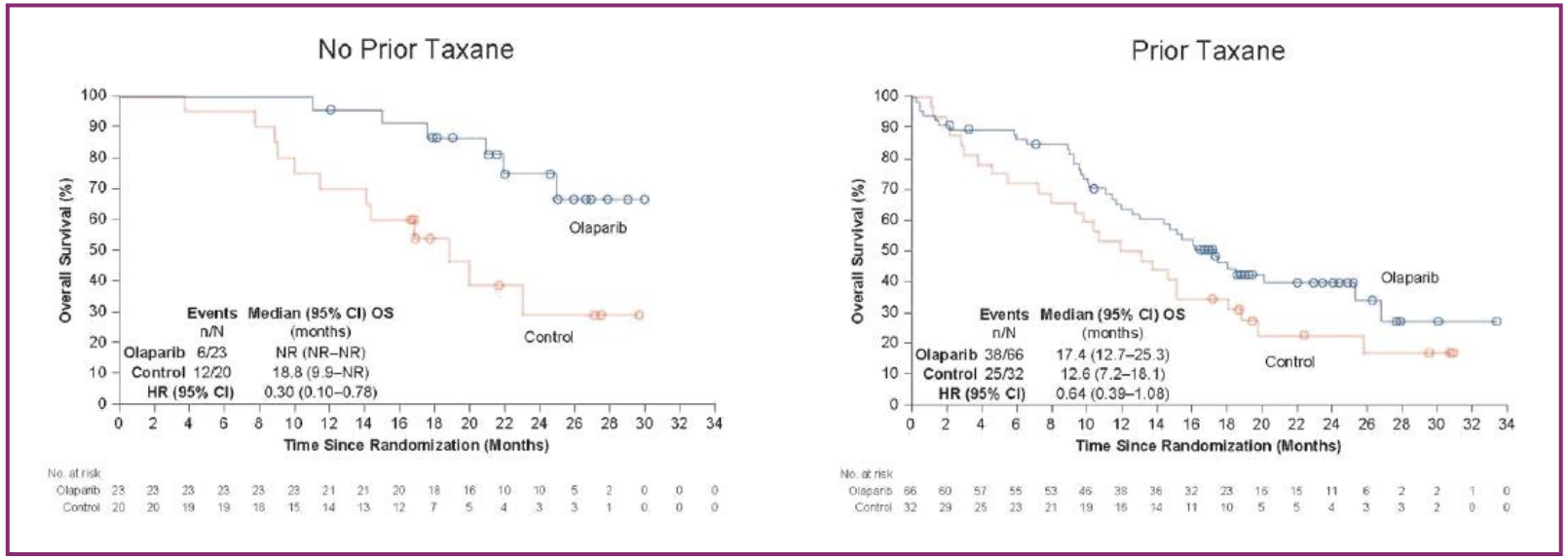
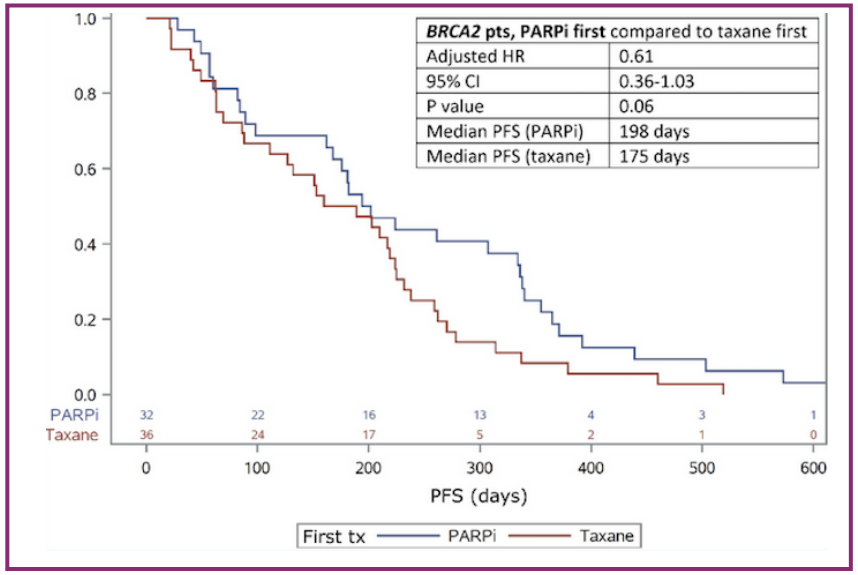
BRCA1/2: Improved outcomes with PARPi before taxanes





Hussain et al, NEJM, 2020; Presented by Dr Su at ASCO 2021

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No prior treatment with a PARPi or any DNA-damaging cytotoxic chemotherapy for prostate cancer

65% had previously received taxanes

ORT A*

BRCA1/2 or *ATM*

2:1

Olaparib (300 mg BID tablets)

Physician's choice†

Optional olaparib at BICR progression

Control: 2L NHT

Open-label

COHORT B*

BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or *RAD54L*

2:1

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Physician's choice†

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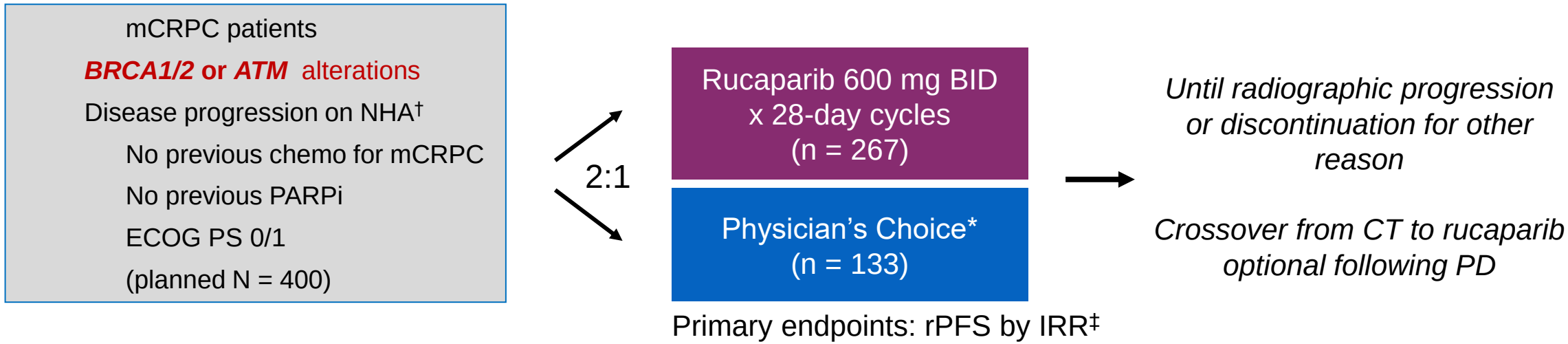
†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

BICR=blinded independent central review; BID=twice daily; CRPC=castration-resistant prostate cancer; EGOC PS=Eastern Cooperative Oncology Group Performance Score; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; mPC=metastatic prostate cancer; NHA=new hormonal agent; nmCCRPC=non-metastatic castration-resistant prostate cancer; ORR=objective response rate; PARP=poly(ADP-ribose) polymerase; PARPi=poly(ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumours; rPFS=radiographic progression-free survival

1. de Bono J, et al. Presented at ESMO 2019, 27th September – 1st October, Barcelona. Abstract 847PD; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02987543 (last accessed April 2020); 3. de Bono JS et al. Poster presented at: ASCO Annual Congress; June 2–6, 2017; Chicago, IL. Abstract TPS5091

TRITON3: Rucaparib vs physician's choice therapy in mCRPC with HRR gene alterations

- Randomized, multicenter, open-label phase III study

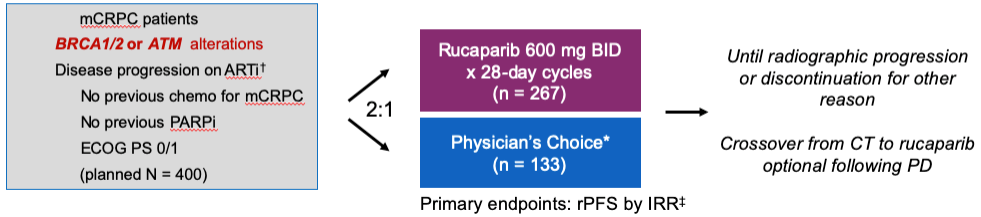


***Docetaxel + prednisone 75 mg/m² in 21-day cycles (max 10 cycles) or abiraterone + prednisone 1000 mg QD or enzalutamide 160 mg QD.**
†Abiraterone, enzalutamide, or investigational agent.
‡Modified RECIST to document soft tissue disease and PCCTWG v.3 criteria to document radiographic progression of bone lesions.

Ryan et al. ASCO GU 2018. Abstr TPS389. NCT02975934.

TRITON3 Phase 3 Trial of Rubraca® (rucaparib) Achieves Primary Endpoint in Men with Metastatic Castration-Resistant Prostate Cancer with BRCA or ATM Mutations

- Randomized, multicenter, open-label phase III study



Primary endpoints: rPFS by IRR‡

- *TRITON3 study evaluating Rubraca monotherapy versus chemotherapy or second-line androgen deprivation therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) with mutations in BRCA or ATM achieved the primary endpoint of improved radiographic progression-free survival (rPFS) by independent radiology review (IRR)*

  – Median rPFS of 11.2 months for Rubraca vs 6.4 months for control group in the BRCA subgroup
  – Median rPFS of 10.2 months for Rubraca vs 6.4 months for control group in the ITT population (inclusive of all patients with a BRCA or ATM mutation enrolled in TRITON3)

Significant Improvement in rPFS in the BRCA Patient Population

The Rubraca arm (n=201) achieved statistical significance over the control arm (n=101) for the primary endpoint of rPFS with a hazard ratio of 0.50 (95% CI: 0.36-0.69). The median PFS for the population of patients with BRCA mutations treated with Rubraca was 11.2 months vs 6.4 months among those who received physician's choice (p<0.0001).

rPFS in Exploratory ATM Mutation Subgroup

In the exploratory subgroup of men with tumor ATM mutations (n=103), the hazard ratio for rPFS was 0.97 (95% CI: 0.59-1.52). Median rPFS in the Rubraca arm (n=69) was 8.1 months vs 6.8 months in the control arm (n=34) with a nominal p-value (p=0.8421).

Secondary Endpoint of Overall Survival Summary

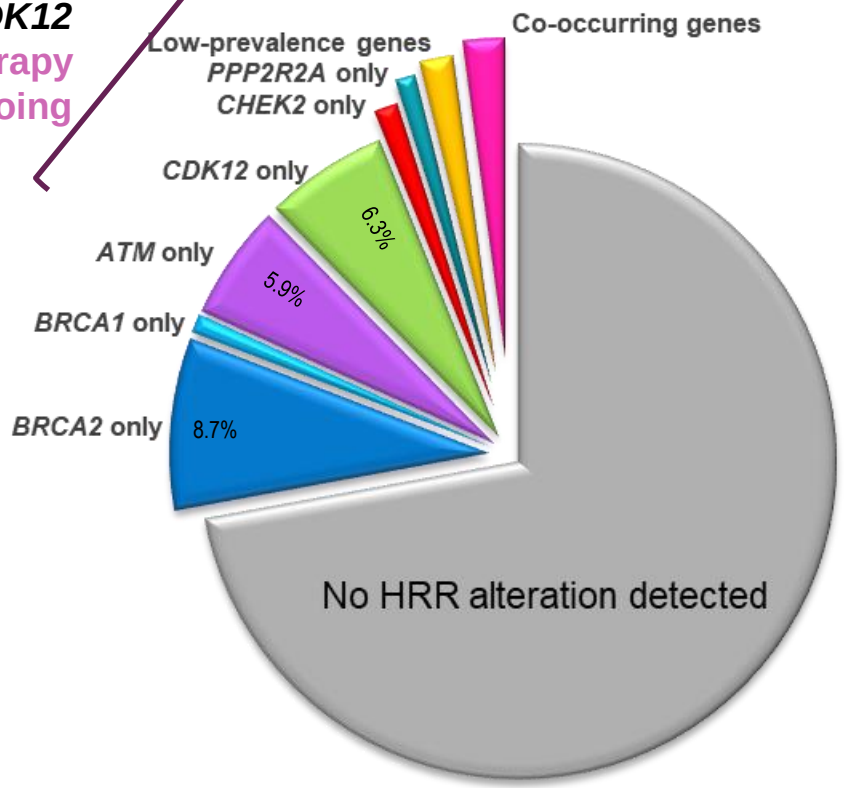
The hazard ratio for the interim analysis of the secondary endpoint of overall survival (OS) in the BRCA subgroup and ITT population, which are not yet mature, favored Rubraca. The hazard ratio for OS in the exploratory subgroup of ATM, which is mature, favored the control arm. The 95% confidence intervals for these OS analyses included less than one for the exploratory endpoint ATM, signifying no statistical difference in outcomes between Rubraca and control.

Clovis Oncology. Press release on 3rd Oct 2022

Current scenario of iPARP by HR alterations in mCRPC

≈ 5% Unfrequent HRR alterations
Further evidence needed

≈ 12% *ATM, CDK12*
No PARPi in monotherapy
Several Combination studies ongoing



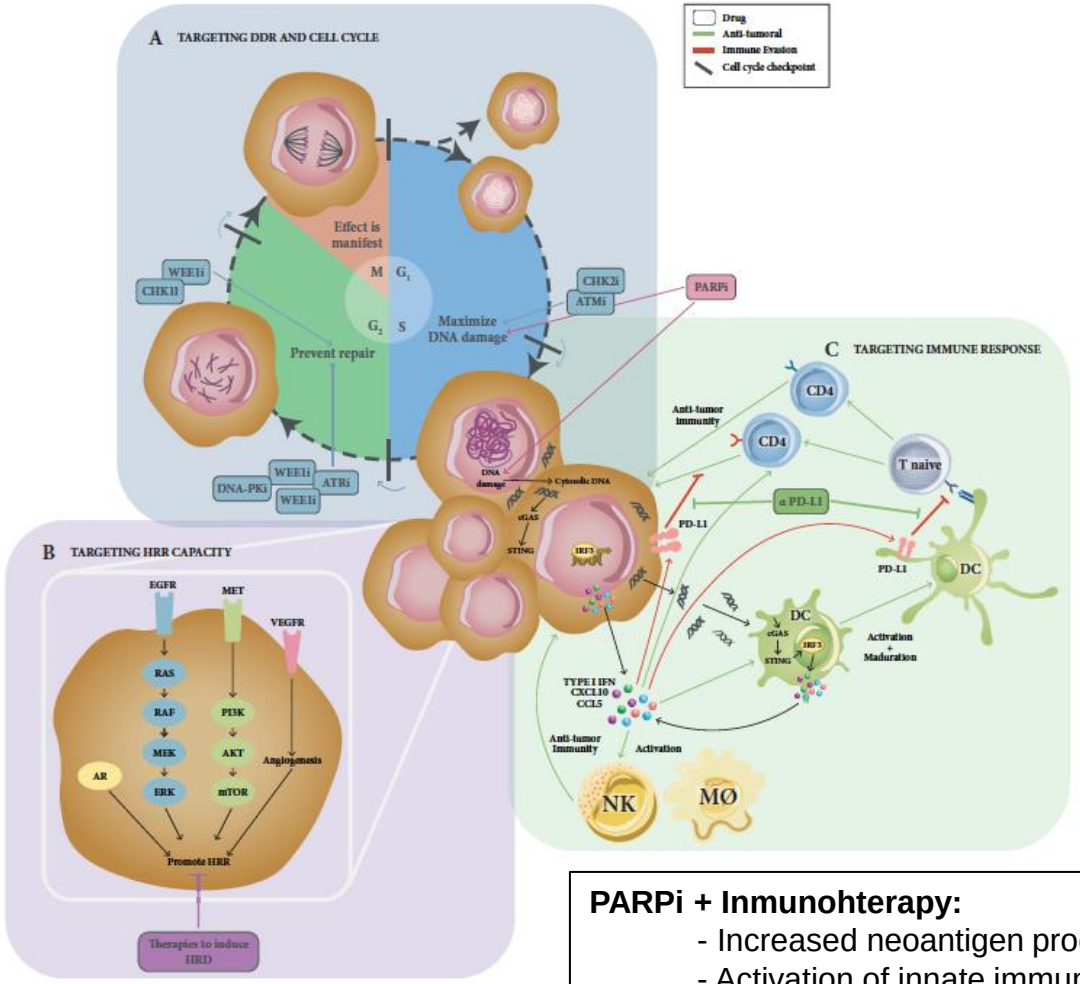
≈ 9% *BRCA1/2*
PARPi

≈ 70% No HRR detected
NO PARPi in monotherapy
Several combination studies

Rational combinations of PARPi with other agents

PARPi + compounds targeting alternative DDR nodes
- Accumulation of DNA damage
- Prevention of DNA repair

PARPi + compounds that target pathways that modulate HR function:
- AR pathway
- VEGFR pathway
- PI3K/AKT pathway



PARPi + Inmunohterapy:
- Increased neoantigen production and T-cell activation
- Activation of innate immune system

Mateo et al, Ann Oncol, 2019

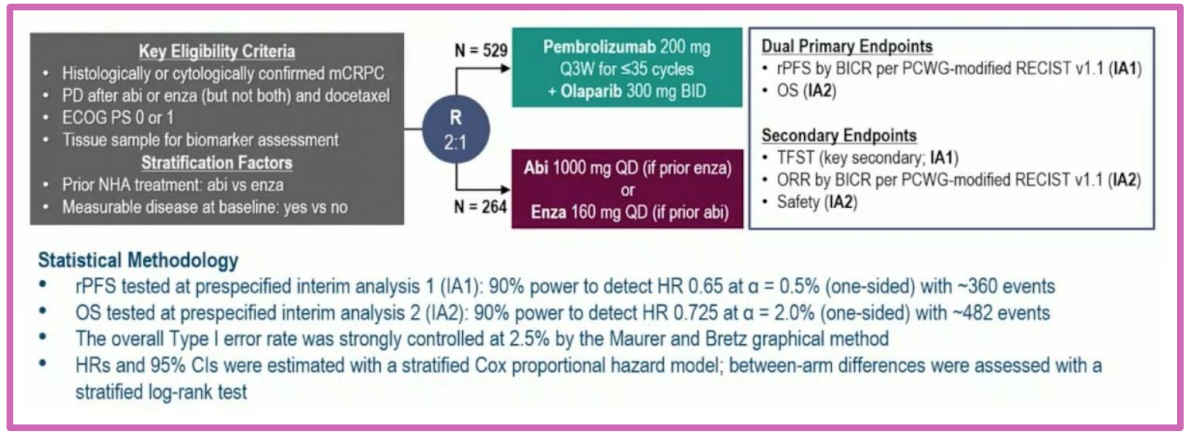
Multiple combination trials with PARPi in mCRPC

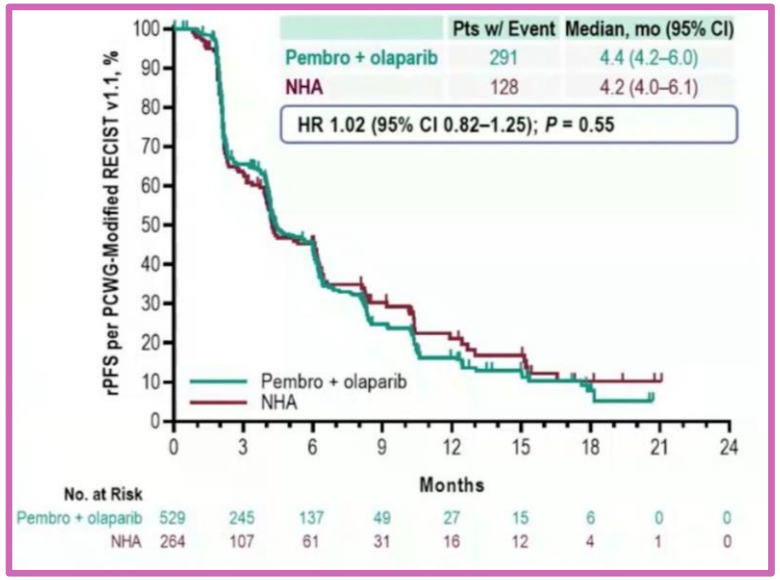
Agent	Olaparib	Niraparib	Rucaparib	Talazoparib
AR therapy				
▪ Abiraterone	**PROpel**	**MAGNITUDE**		
▪ Enzalutamide			**CASPAR**	**TALAPRO-2/-3**
Immunotherapy				
▪ Avelumab				**Javelin PARP Medley**
▪ Cetrelimab		**QUEST**		
▪ Durvalumab	**NCT03810105**			
▪ Pembrolizumab	**KEYLYNK-010**			
▪ Nivolumab			**CheckMate 9KD**	
Other agents				
▪ Radium-223	**NCT03317392**	**NCT03076203**		
▪ Chemotherapy			**PLATI-PARP**	
▪ ^{177}Lu PSMA	**NCT03874884**			
▪ Cediranib	**NCT02893917**			

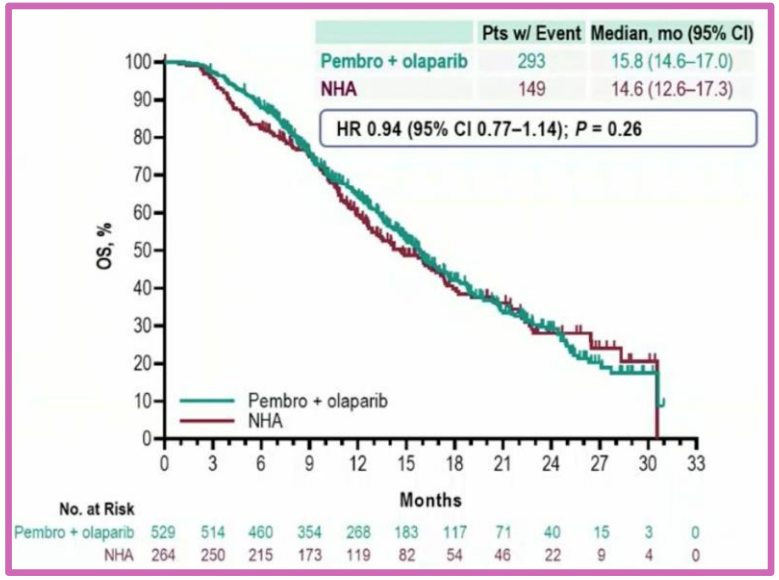
Phase III

Earlier phase

KEYLINK- 010



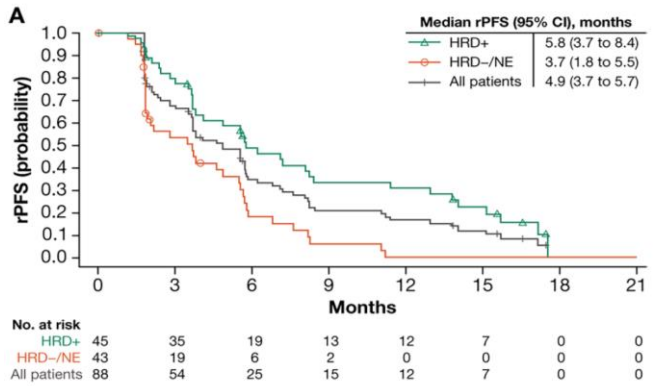


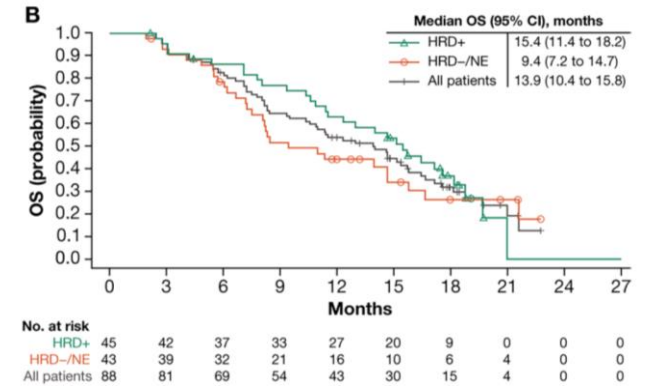


Presented by Dr Yu at ESMO 2022

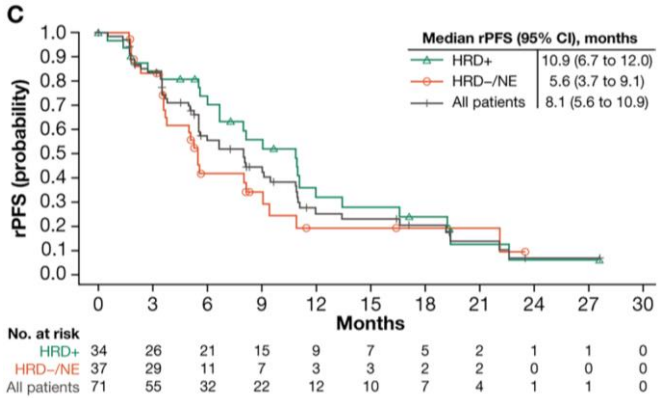
CheckMate 9KD: Nivolumab + Rucaparib

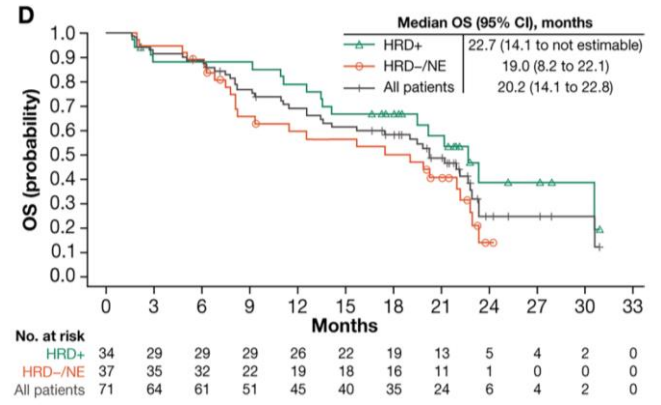
Cohort A1: post-chemo

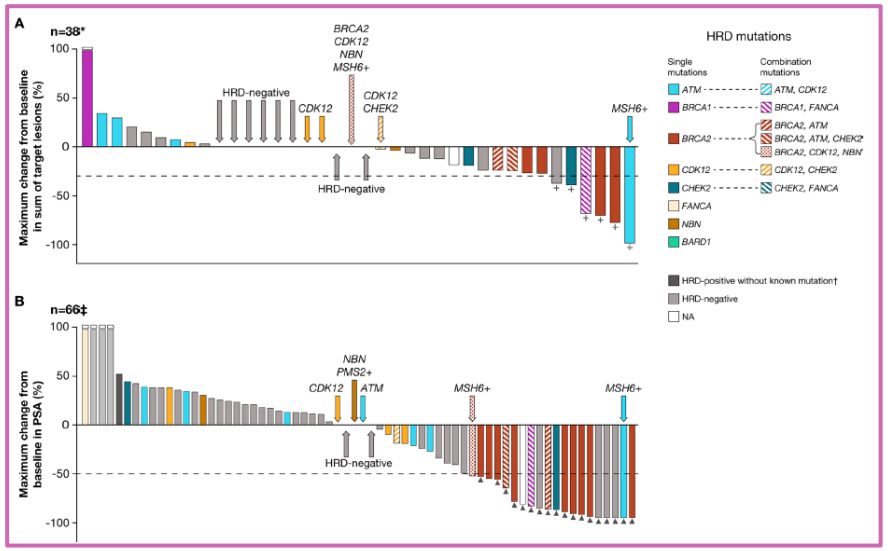




Cohort A2: chemo-naïve





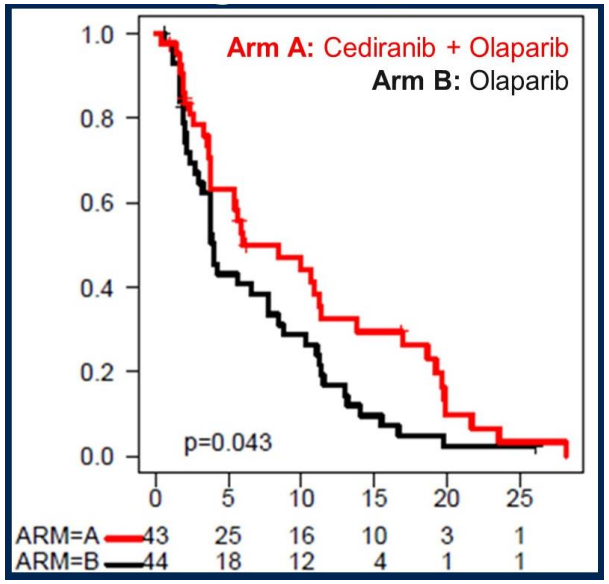


	Cohort A1 (postchemotherapy) (N=88)			Cohort A2 (chemotherapy-naïve) (N=71)		
	Overall	HRD-positive	HRD-negative/not evaluable	Overall	HRD-positive	HRD-negative/not evaluable
Objective response*						
Evaluable patients, n†	58	29	29	39	20	19
Confirmed ORR (95% CI), %	10.3 (3.9 to 21.2)	17.2 (5.8 to 35.8)	3.4 (0.1 to 17.8)	15.4 (5.9 to 30.5)	25.0 (8.7 to 49.1)	5.3 (0.1 to 26.0)
BOR, n (%)						
Complete response	0	0	0	0	0	0
Partial response	6 (10.3)	5 (17.2)	1 (3.4)	6 (15.4)	5 (25.0)	1 (5.3)
Stable disease	31 (53.4)	16 (55.2)	15 (51.7)	26 (66.7)	11 (55.0)	15 (78.9)
Progressive disease	18 (31.0)	5 (17.2)	13 (44.8)	5 (12.8)	3 (15.0)	2 (10.5)
Unable to determine	3 (5.2)	3 (10.3)	0	2 (5.1)	1 (5.0)	1 (5.3)
PSA response‡						
Evaluable patients, n§	84	44	40	66	31	35
Confirmed PSA_{50}-RR (95% CI), %	11.9 (5.9 to 20.8)	18.2 (8.2 to 32.7)	5.0 (0.6 to 16.9)	27.3 (17.0 to 39.6)	41.9 (24.5 to 60.9)	14.3 (4.8 to 30.3)
Confirmed or unconfirmed PSA_{50}-RR (95% CI), %	19.0 (11.3 to 29.1)	29.5 (16.8 to 45.2)	7.5 (1.6 to 20.4)	31.8 (20.9 to 44.4)	48.4 (30.2 to 66.9)	17.1 (6.6 to 33.6)

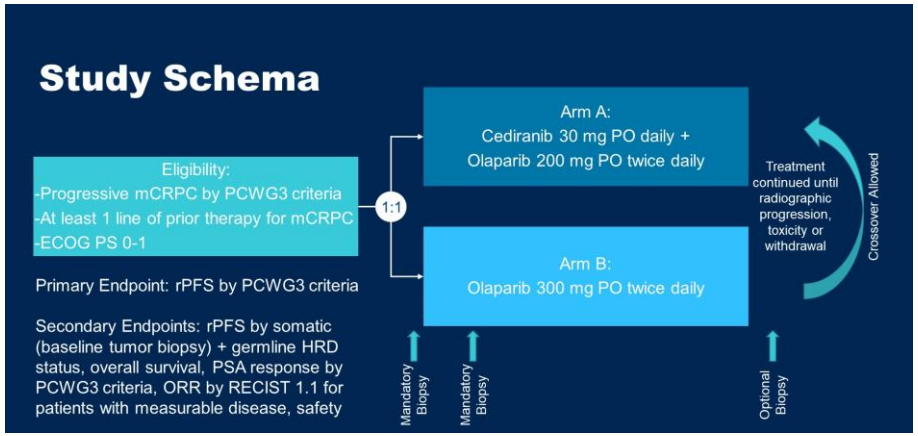
*Confirmed complete or partial response per PCWG3.
†Patients with measurable disease at baseline.
‡A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50%; a second consecutive value obtained at least 3 weeks later was required for confirmation of PSA responses.
§Patients with a baseline and at least one postbaseline PSA assessment.
BOR, best overall response; HRD, homologous recombination deficiency; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{50}-RR, PSA response rate.

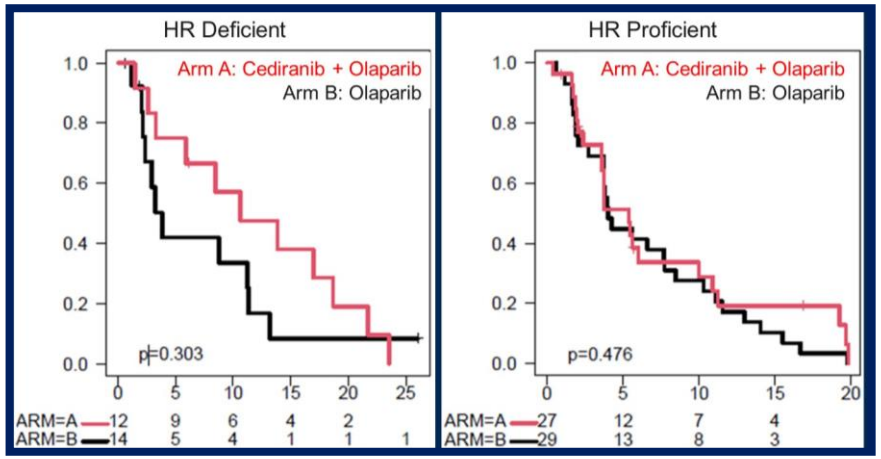
Fizazi et al, J Immunother Cancer, 2022

Phase II trial of olaparib +/- cediranib in mCRPC patients



	Arm A: Cediranib + Olaparib (N=44)	Arm B: Olaparib (N=43)
Events, N	36	41
Median, mo	8.47	3.97
HR, 95% CI	0.625, 0.395-0.990	
P-value	0.0453	





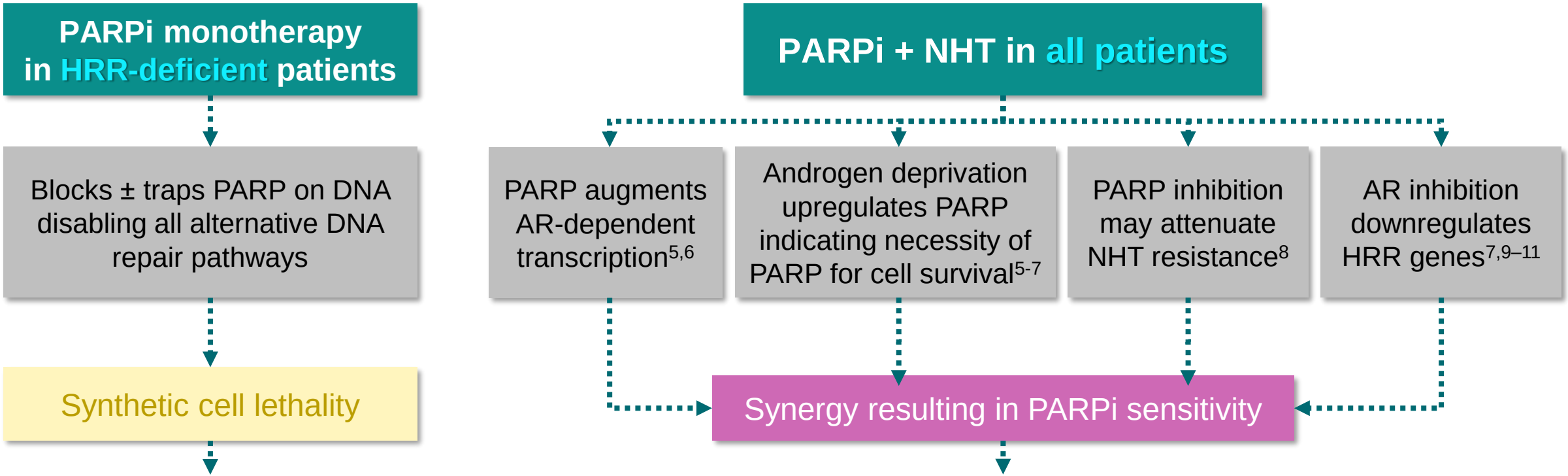
HR Deficient		
	Arm A: C+O	Arm B: O
Events, N	11	11
Median, mo	10.63	3.83
HR, 95% CI	0.640, 0.272-1.504	
P-value	0.3063	

HR Proficient		
	Arm A: C+O	Arm B: O
Events, N	22	29
Median, mo	5.37	4.03
HR, 95% CI	0.814, 0.462-1.436	
P-value	0.4781	

Rationale for Inducing Sensitivity to PARP Inhibition in All-comers

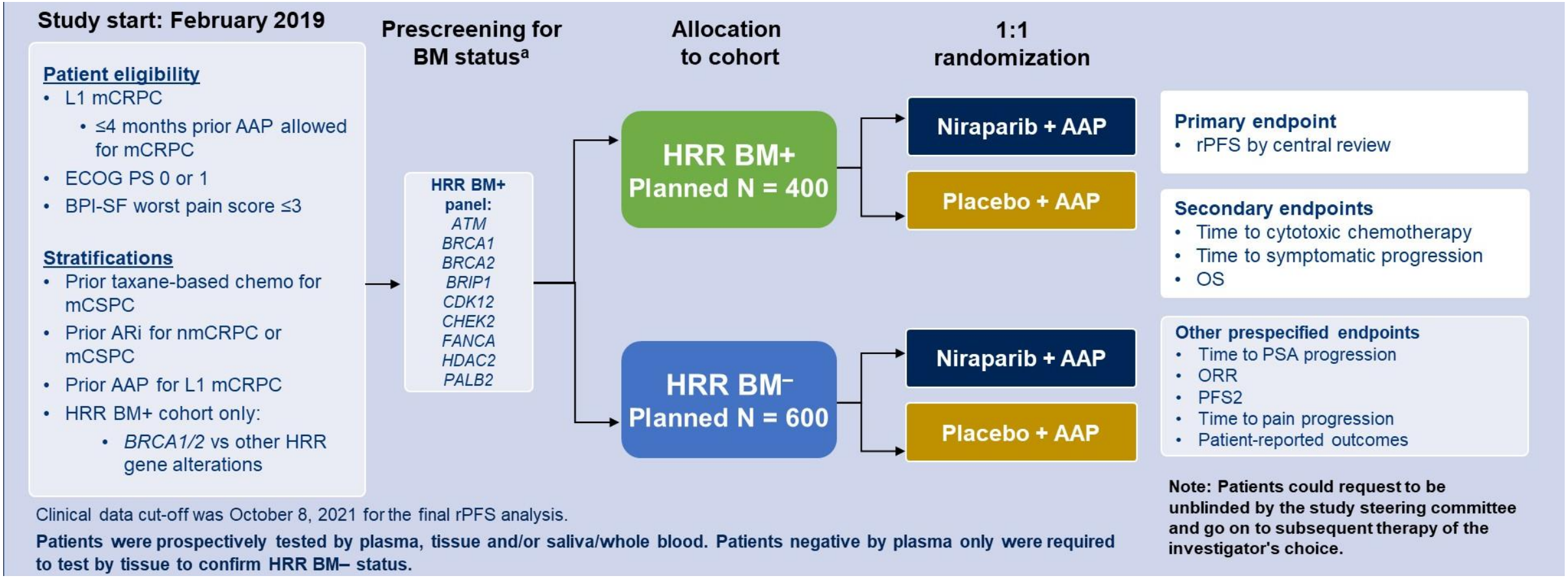
Synergy Between NHT and PARPi

PARP is involved in AR-dependent transcription and is upregulated by androgen deprivation. NHTs induce HRR-deficiency-like phenotype in cells *without* a-priori HRR- (e.g., BRCA) mutations, providing a **rationale for combining PARPi with NHT** to explore their synergistic anti-tumour activity in **HRR-unselected** patient population



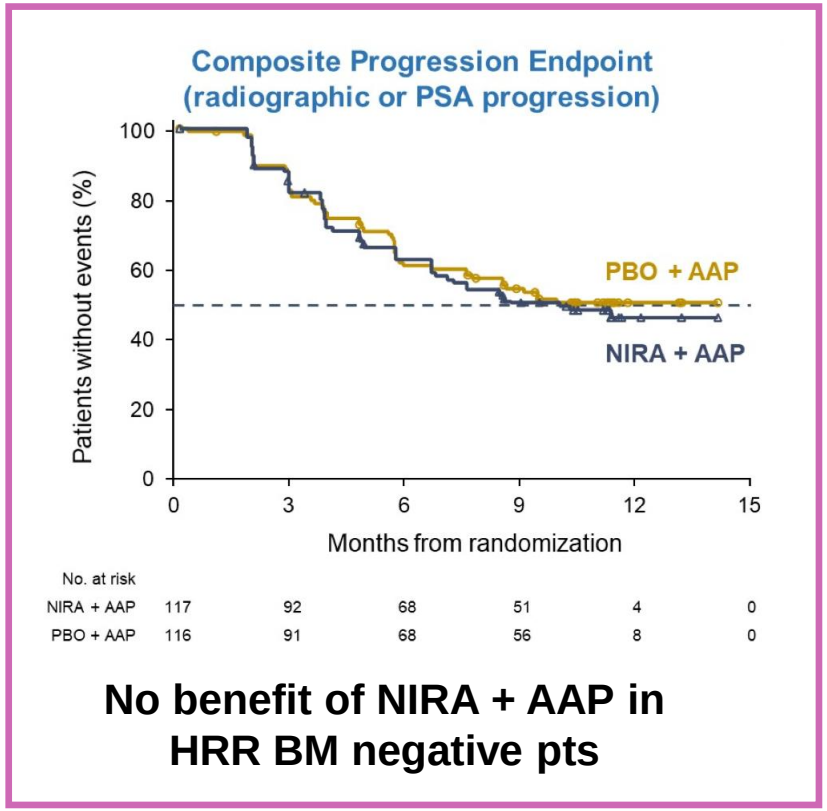
__1__. Schiewer MJ, et al. Cancer Discov. 2012. __2.__ Polkinghorn WR, et al. Cancer Discov. 2013. __3.__ Asim M, et al. Nat Commun. 2017. __4.__ Mateo J, et al. N Engl J Med. 2015. __5__. Schiewer MJ, et al. Cancer Discovery. 2012. __6__. Gui B, et al. PNAS. 2019. __7__. Asim M, et al. Nat Commun. 2017. __8__. Chakraborty G, et al. Clin Cancer Res. 2020. __9__. Cerrato A, et al. J Exp Clin Cancer Res. 2016. __10__. Javle M, et al. Ther Adv Med Oncol. 2011. __11__. Polkinghorn WR, et al. Cancer Discov. 2013.

MAGNITUD: AAP +/- Niraparib as 1L treatment for mCRPC

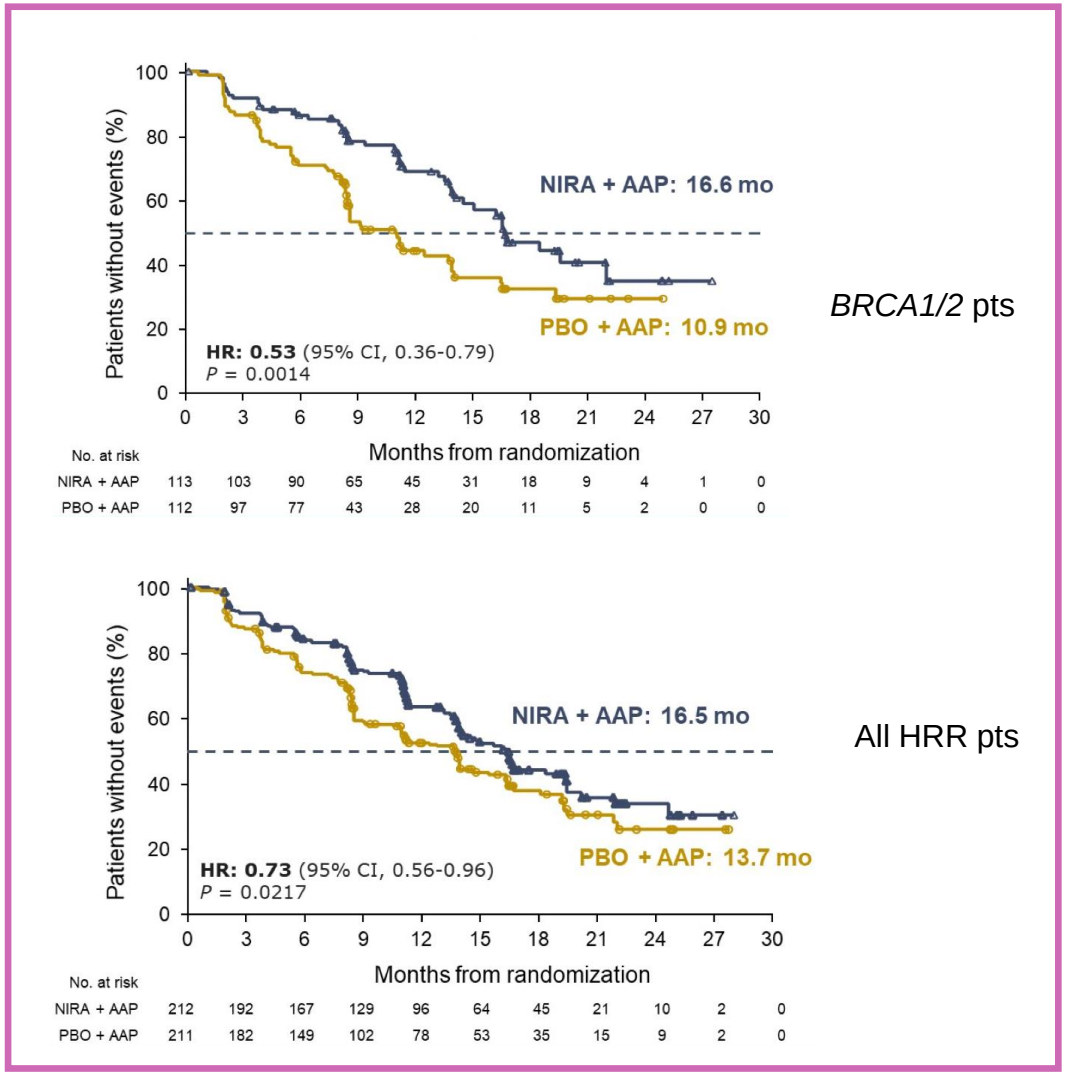


Presented by Dr Chi at ASCO GU 2021

MAGNITUD: AAP +/- Niraparib as 1L treatment for mCRPC

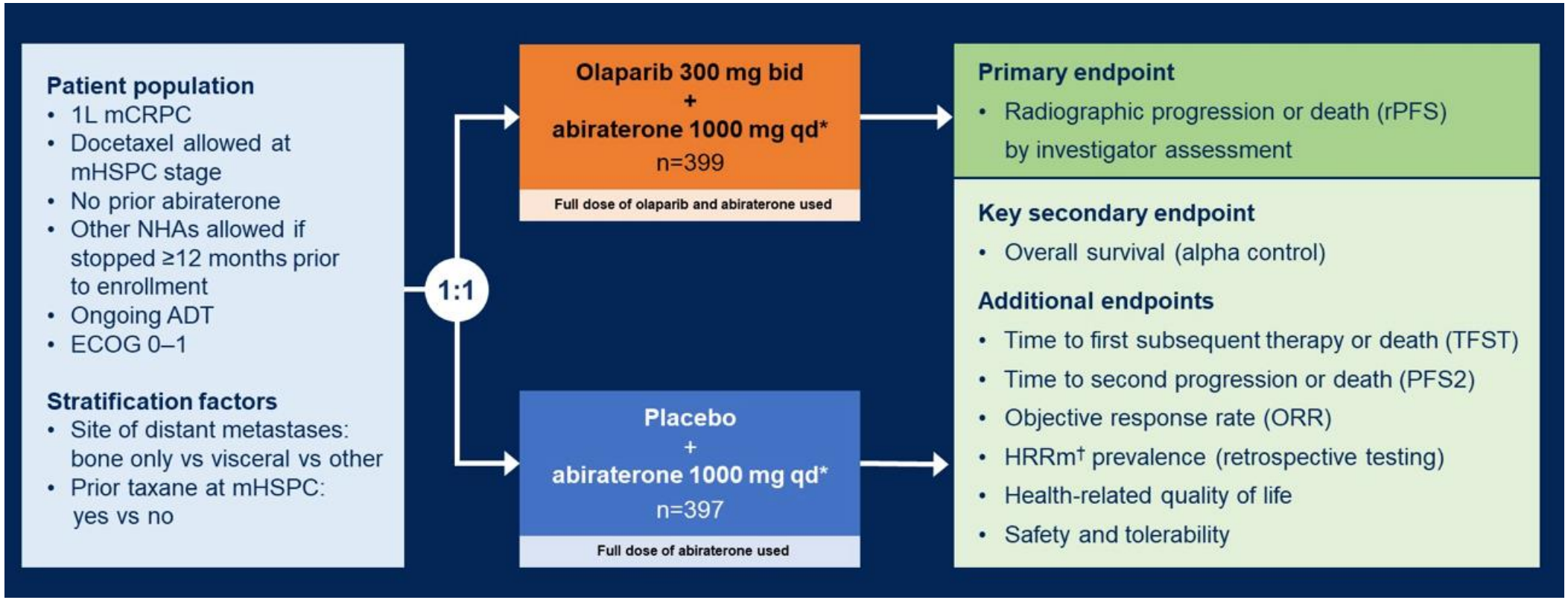


No benefit of NIRA + AAP in HRR BM negative pts



Presented by Dr Chi at ASCO GU 2021

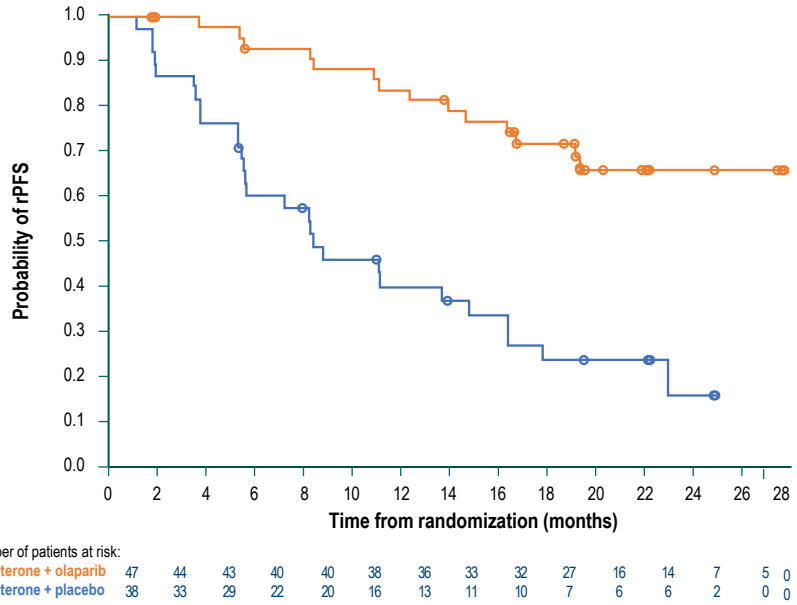
PROPEL: AAP +/- Olaparib as 1L treatment for mCRPC



Presented by Dr Saad at ASCO GU 2021

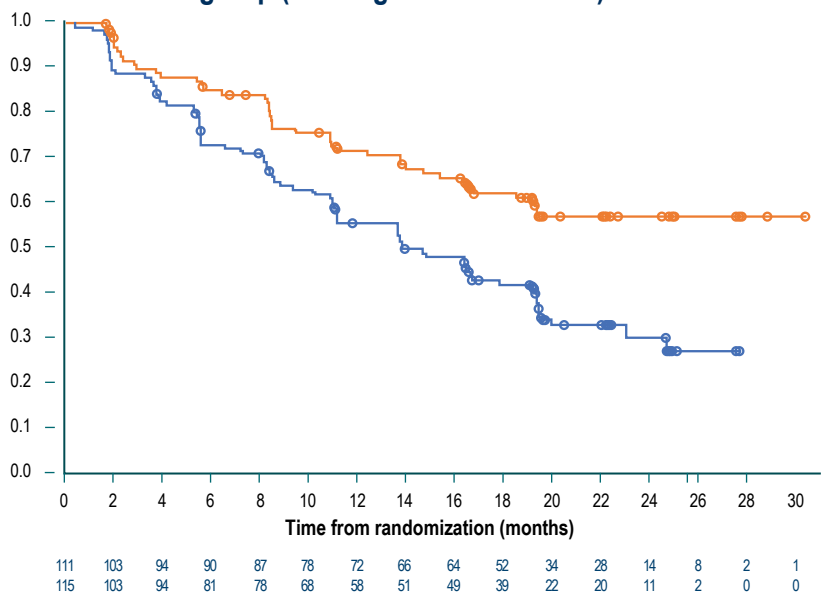
PROPEL: AAP +/- Olaparib as 1L treatment for mCRPC

BRCAm subgroup (investigator assessment)



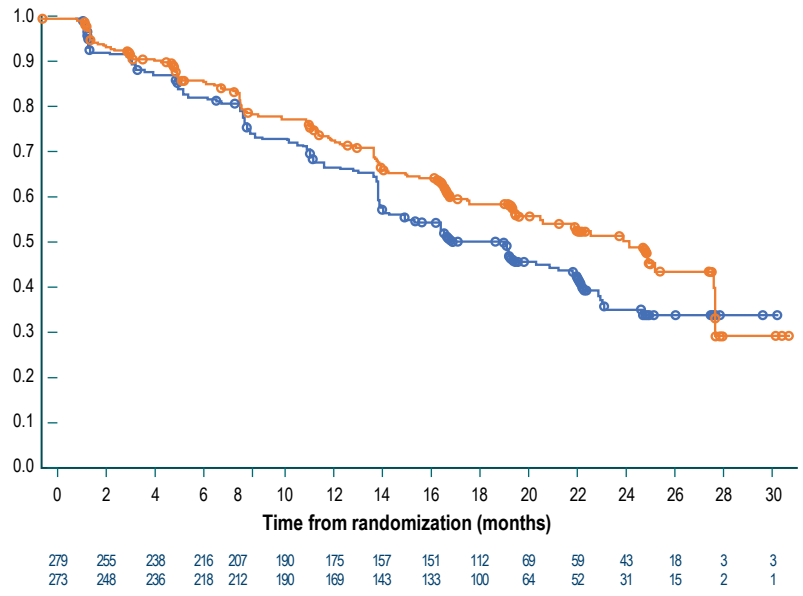
	Abiraterone + olaparib (n=47)	Abiraterone + placebo (n=38)
Events, n (%)	14 (29.8)	28 (73.7)
Median rPFS (months)	NR	8.4
HR (95% CI)	0.23 (0.12–0.43)	

HRRm subgroup (investigator assessment)



	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=115)
Events, n (%)	43 (38.7)	73 (63.5)
Median rPFS (months)	NR	13.9
HR (95% CI)	0.50 (0.34–0.73)	

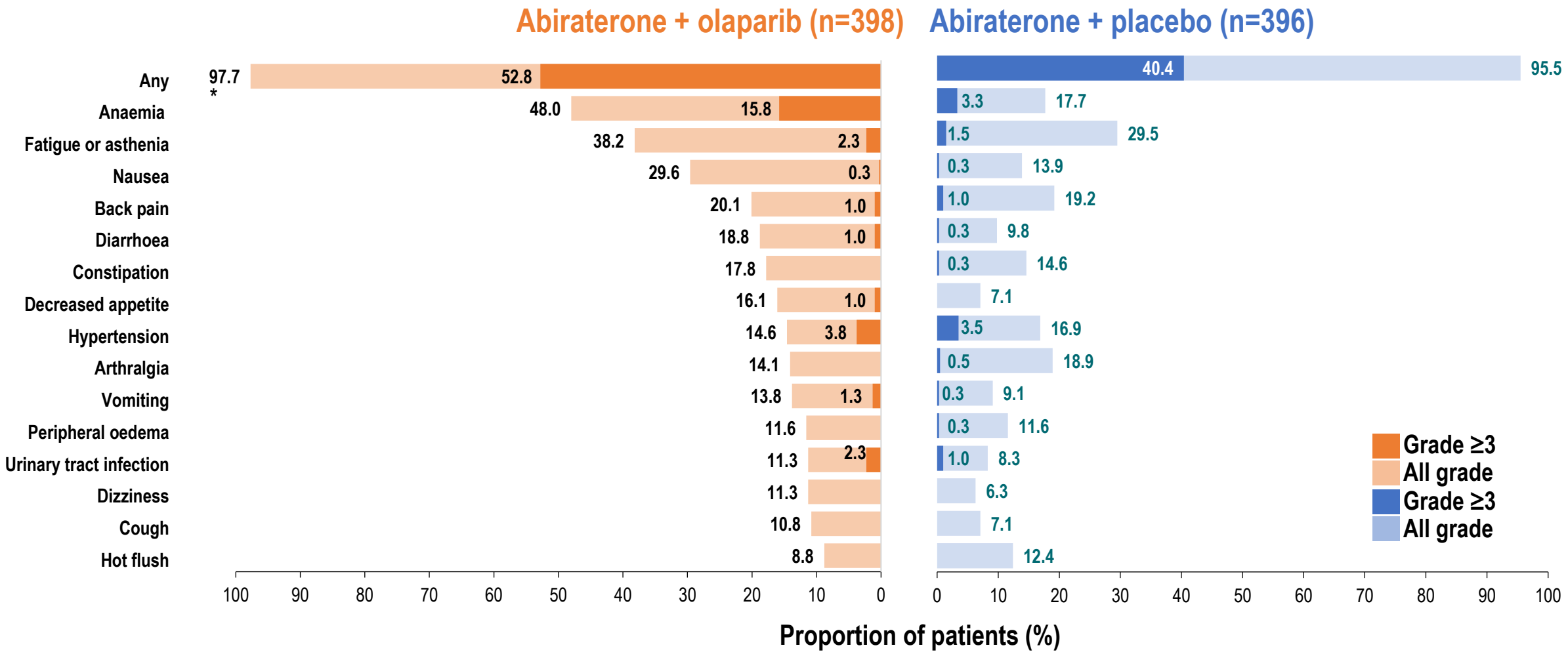
Non-HRRm subgroup (investigator assessment)



	Abiraterone + olaparib (n=279)	Abiraterone + placebo (n=273)
Events, n (%)	119 (42.7)	149 (54.6)
Median rPFS (months)	24.1	19.0
HR (95% CI)	0.76 (0.60–0.97)	

Presented by Dr Saad at ESMO 2022

PROpel: most common AEs (in ≥10% patients)



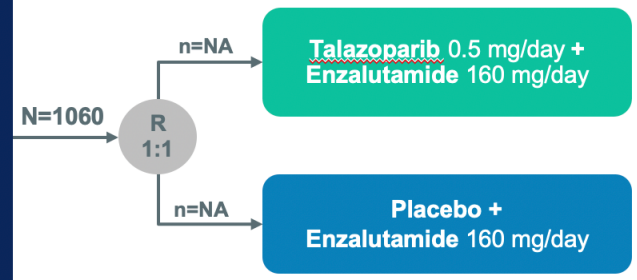
Presented by Dr Saad at ESMO 2022

TALAPRO-2: Enzalutamide +/- Talazoparib as 1L treatment for mCRPC

Key eligibility criteria
- 1L mCRPC

Stratification
- Previous NHT or taxane-based chemotherapy for CSPC
- HRR alteration status

Two patient populations for final analyses:
- All comers (HRR agnostic)
- HRR deficient only



Primary Endpoint
- rPFS in DDR unselected and DDRm

Key Secondary Endpoints
- OS
- ORR
- PSA response
- Time to PSA progression
- Time to chemotherapy

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced positive topline results from the Phase 3 TALAPRO-2 study of TALZENNA® (talazoparib), an oral poly ADP-ribose polymerase (PARP) inhibitor, in combination with XTANDI® (enzalutamide) compared to placebo plus XTANDI in men with metastatic castration-resistant prostate cancer (mCRPC), with or without homologous recombination repair (HRR) gene mutations. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) compared with placebo plus XTANDI. The results of the primary endpoint exceeded the pre-specified hazard ratio of 0.696.

Results showed a trend toward improved overall survival, a key secondary endpoint, at the time of the analysis, but these data are not yet mature. Benefits were also observed in other secondary endpoints, including investigator assessed rPFS, prostate specific antigen (PSA) response, time to PSA progression, and overall response rate. Other secondary endpoints are being analyzed. At the time of topline analysis, the safety of TALZENNA plus XTANDI were generally consistent with the known safety profile of each medicine.

Pfizr Inc. Press release on 4th Oct 2022

TAKE HOME MESSAGE

PARPi in monotherapy:

- Clear benefit for BRCA2 and BRCA1 pts
- Limited efficacy for ATM, CDK12 or in unselected patients
- Further data needed for rare alterations, i.e. PALB2

PARPi in combination:

- Most trials still ongoing
- with Immunotherapy:
    - limited efficacy in unselected patients
    - no data on the benefit of adding it to PARPi in HRD
- with NHT:
    - improved rPFS : BRCA1/2 > non-BRCA HRR > unselected pts