

PARP Inhibition

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7 August 2019 07:00 BST

AstraZeneca and MSD's Lynparza met the primary endpoint of significantly increasing the time patients selected for BRCA1/2 or ATM mutations live without radiographic disease progression vs. standard of care treatment

Only PARP inhibitor with positive Phase III results in four different cancer types (ovarian, breast, pancreatic and prostate)

AstraZeneca and MSD Inc., Kenilworth, N.J., US (MSD: known as Merck & Co., Inc. inside the US and Canada) today announced positive results from the Phase III PROfound trial of *Lynparza* (olaparib) in men with metastatic castration-resistant prostate cancer (mCRPC) who have a *homologous recombination repair gene mutation (HRRm) and have progressed on prior treatment with new hormonal anticancer treatments (e.g. enzalutamide and abiraterone).

Results from the trial showed a statistically-significant and clinically-meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) with *Lynparza* vs. enzalutamide or abiraterone in men with mCRPC selected for BRCA1/2 or ATM gene mutations, a subpopulation of HRR gene mutations. The safety and tolerability profile of *Lynparza* was generally consistent with previous trials.

Disclosures

- Grant support, consulting fees, and/or lecture fees from AstraZeneca, Astellas, Bayer, Essa Janssen, Pfizer, Roche and Sanofi

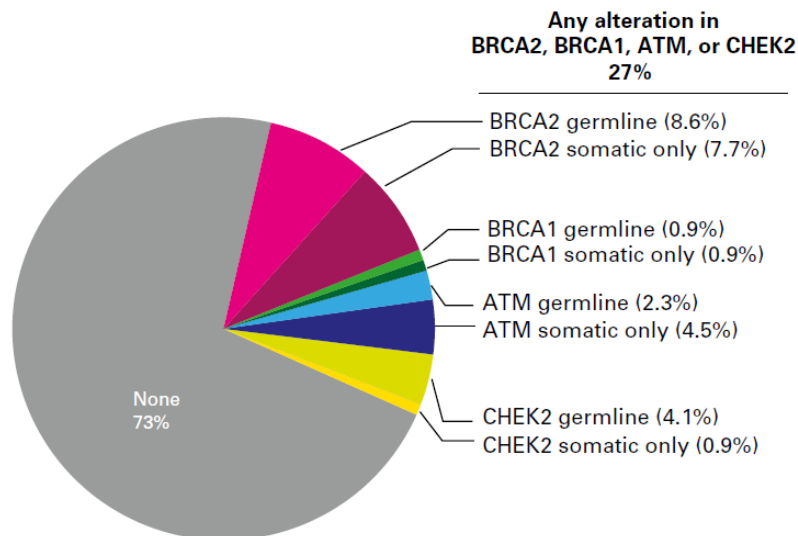
Outline

- Rationale and MOA for PARP inhibition in prostate cancer
- Monotherapy studies
- Combination studies

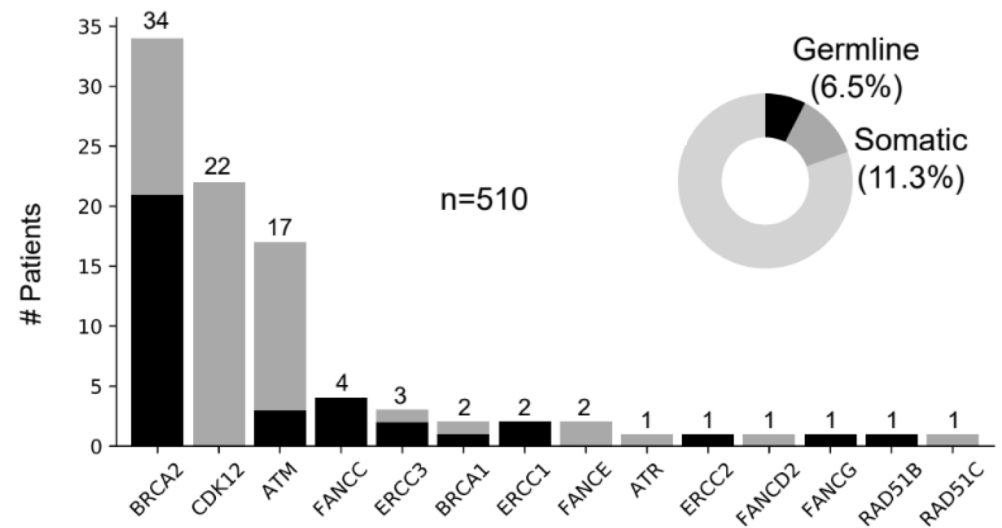
Metastatic Prostate Cancer Frequently Harbours Alterations in DNA Damage Repair Pathway Genes

MSKCC Population

Germline + Somatic Alteration Frequencies



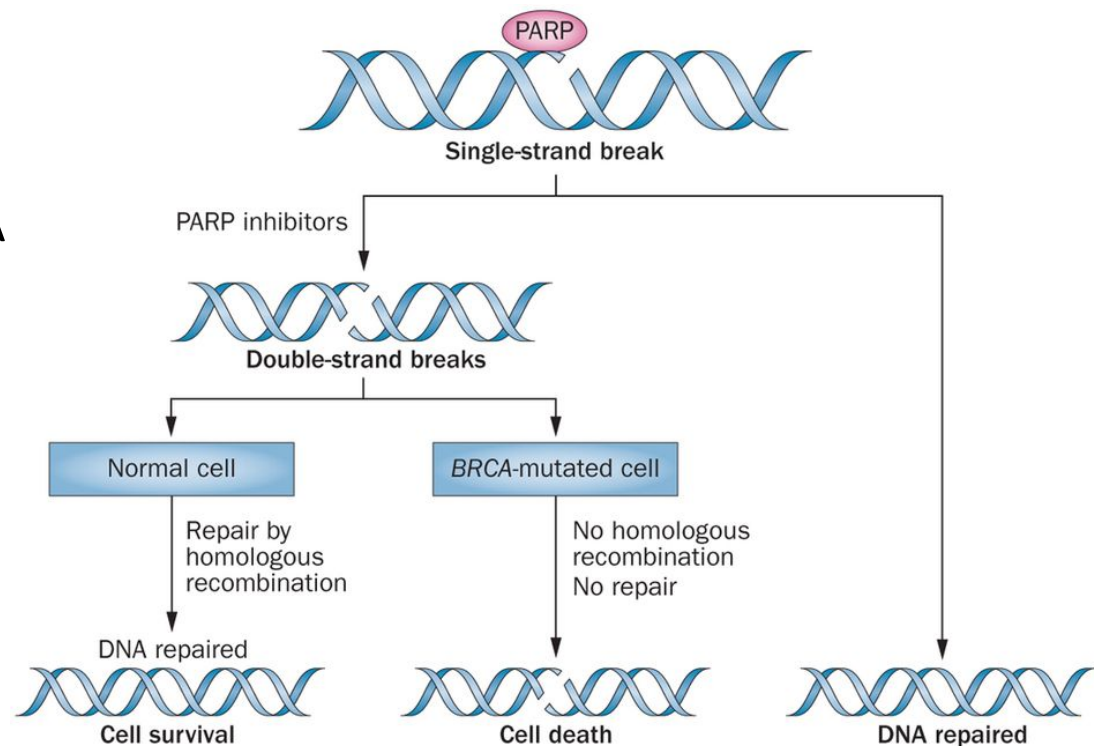
British Columbia Population



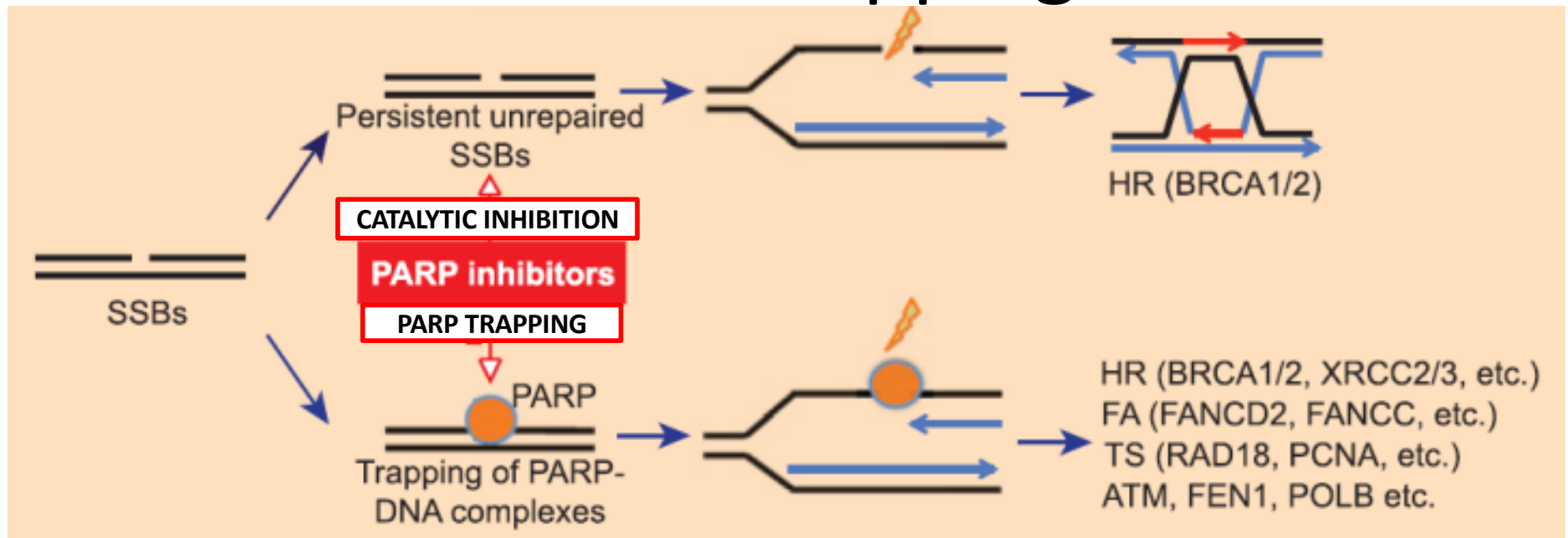
Unpublished

Poly (ADP-ribose) Polymerase Inhibition and Synthetic Lethality in Homologous Recombination Repair Deficient Cells

- PARP1 plays a key role in ssDNA repair via BER
 - Binds to sites of DNA damage and serves as a platform to recruit DNA repair proteins
 - Adds poly (ADP-ribose) units to target proteins (PARylation)
- Inhibition of PARP1 catalytic activity prevents PARylation leading to replication fork collapse and dsDNA breaks which would normally be repaired by HR



PARP Trapping

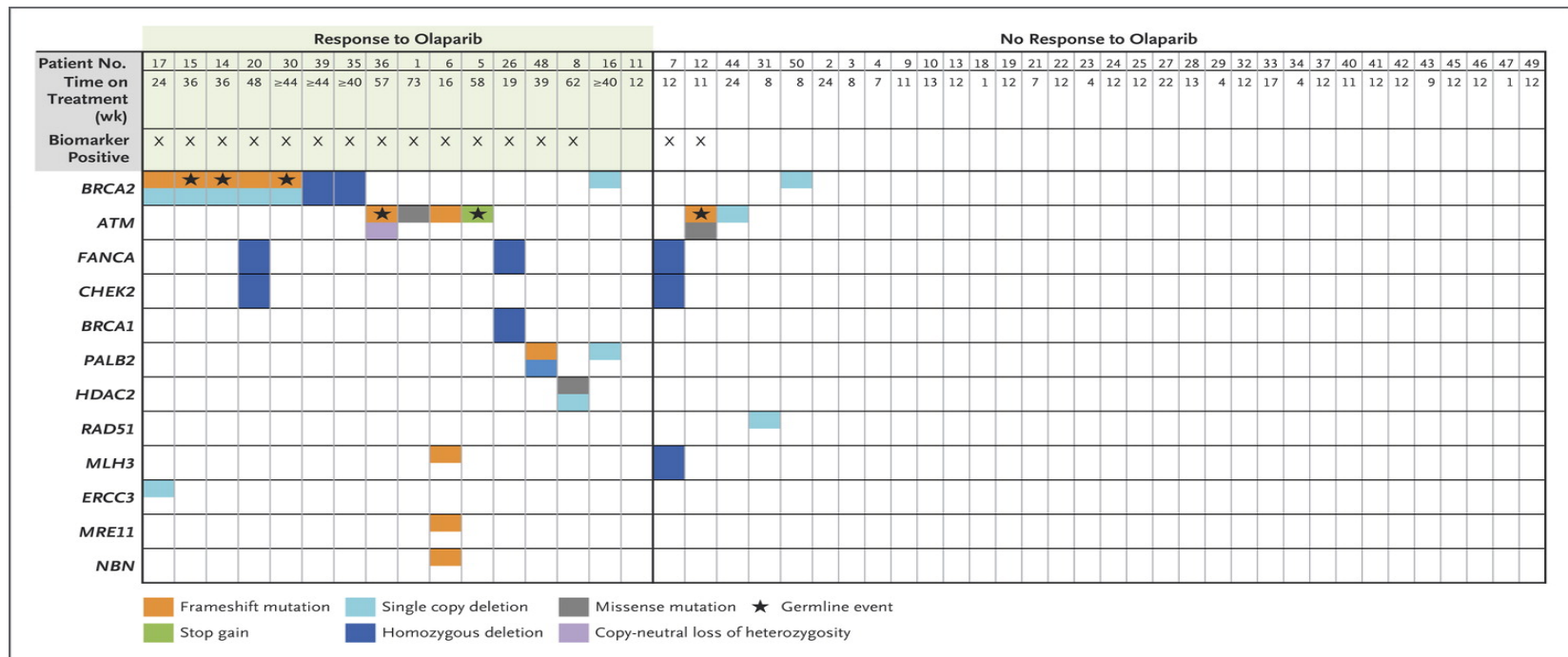


Properties of PARP inhibitors

	Olaparib	Veliparib	Talazoparib	Niraparib	Rucaparib
MW	434.5	244.3	380.8	320.4	323.4
PARP1 IC ₅₀	5 nM ^b	1.2 nM ^a	0.56 nM ^a	3.8 nM ^b	0.65 nM ^a
PARP2 IC ₅₀	1 nM ^b	0.41 nM ^a	0.15 nM ^a	2.1 nM ^b	0.08 nM ^a
Trapping ^b	++	+	++++	+++	++

J Murai, et al. Cancer Res 72:5588-5599, 2012; B Carney, et al. Nat Comm, 9:176, 2018

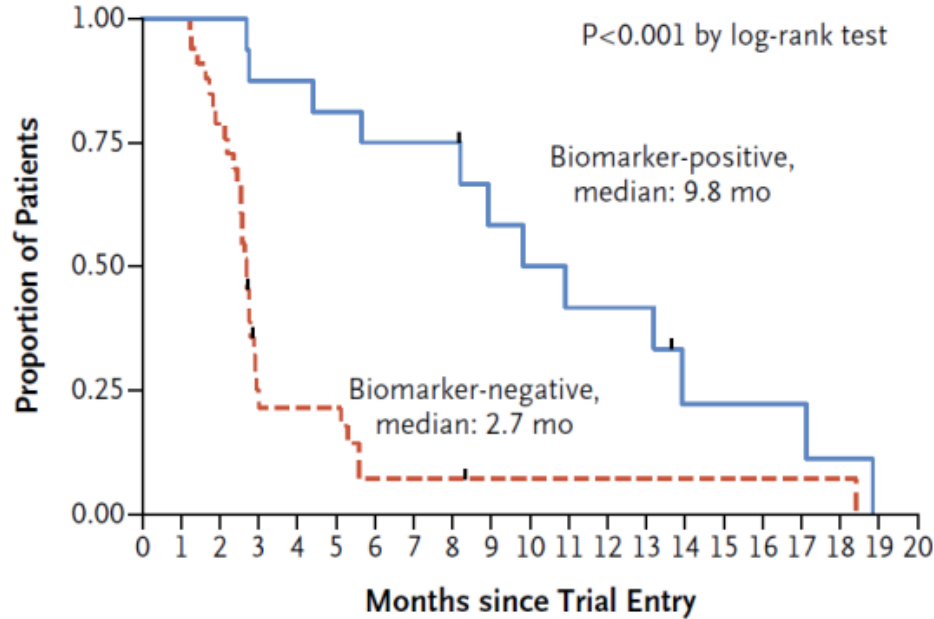
Olaparib: TOPARP A



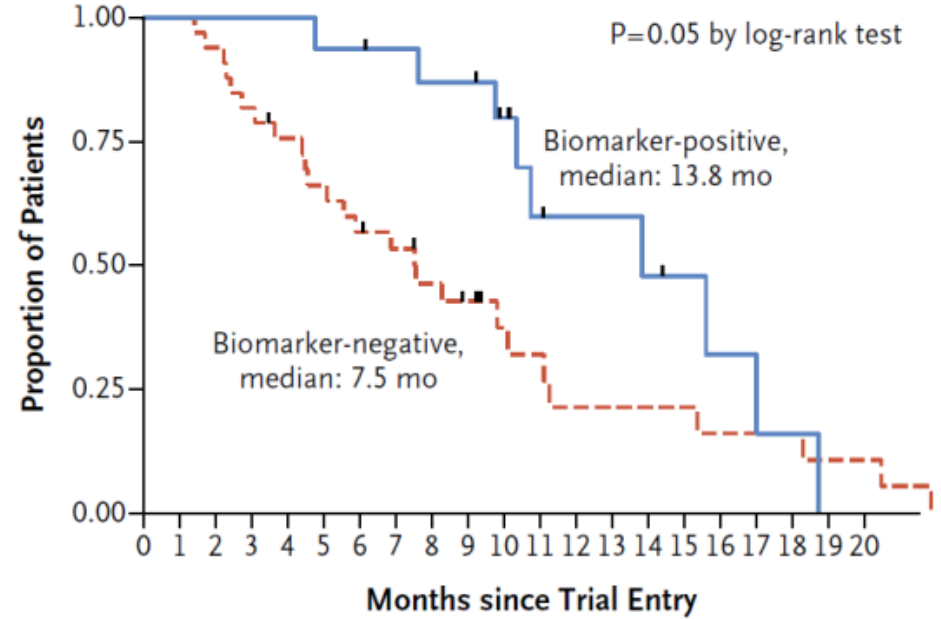
14/16 biomarker-positive patients (88%) had a response to olaparib
 2/33 biomarker-negative patients (6%) were classified as having a response

Olaparib: TOPARP A

A Radiologic Progression-free Survival



B Overall Survival



Olaparib: TOPARP B

- 711 screened → 161 with DDRm (23%) → 98 enrolled (14%) → 92 evaluable
- Biallelic events not required: BRCA2: 32.7%, ATM: 21.4%, CDK12: 21.4%, PALB2: 7.1%, Other: 21.4%

	Total (n=92)			Dose group					
				300mg (n=46)			400mg (n=46)		
	resp/n	%	95% CI	resp/n	%	95% CI	resp/n	%	95% CI
Composite Response (confirmed)	43/92	46.7%	36.3-57.4	18/46	39.1%	25.1-54.6	25/46	54.3%	39.0-69.1
RECIST Response	14/70	20.0%	11.4-31.3	6/37	16.2%	6.2-32.0	8/33	24.2%	11.1-42.3
PSA Response ≥50%	30/89	33.7%	24.0-44.5	13/43	30.2%	17.2-46.1	17/46	37.0%	23.2-52.5
CTC conversion	28/55	50.9%	37.1-64.6	13/27	48.1%	28.7-68.1	15/28	53.6%	33.9-72.5
RECIST / PSA response	32/92	34.8%	25.1-45.4	13/46	28.3%	16.0-43.5	19/46	41.3%	27.0-56.8

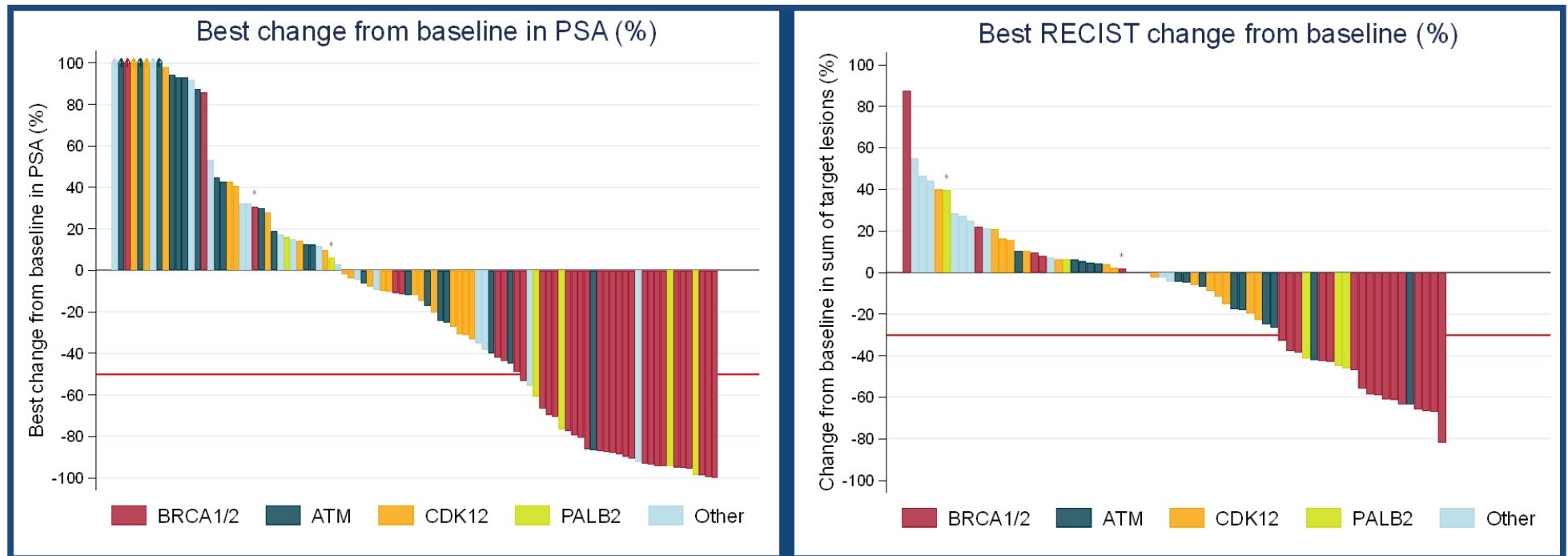
- Median rPFS 5.6 months (300 mg) and 5.5 months (400 mg)

Olaparib: TOPARP B

	Group 1: BRCA1/2 (n=30)		Group 2: ATM (n=19)		Group 3: CDK12 (n=20)		Group 4: PALB2 (n=7)		Group 5: Other (n=20)	
	resp/n	%	resp/n	%	resp/n	%	resp/n	%	resp/n	%
Composite Response (confirmed)	25/30	83.3%	7/19	36.8%	5/20	25.0%	4/7	57.1%	4/20	20.0%
RECIST Objective Response	11/21	52.4%	1/12	8.3%	0/18	0.0%	2/6	33.3%	0/17	0.0%
PSA response $\geq 50\%$	23/30	76.7%	1/19	5.3%	0/20	0.0%	4/6	66.7%	2/17	11.8%
CTC conversion	17/22	77.3%	5/10	50.0%	5/12	41.7%	0/2	0.0%	3/11	27.3%
RECIST / PSA response	24/30	80.0%	2/19	10.5%	0/20	0.0%	4/7	57.1%	2/20	10.0%

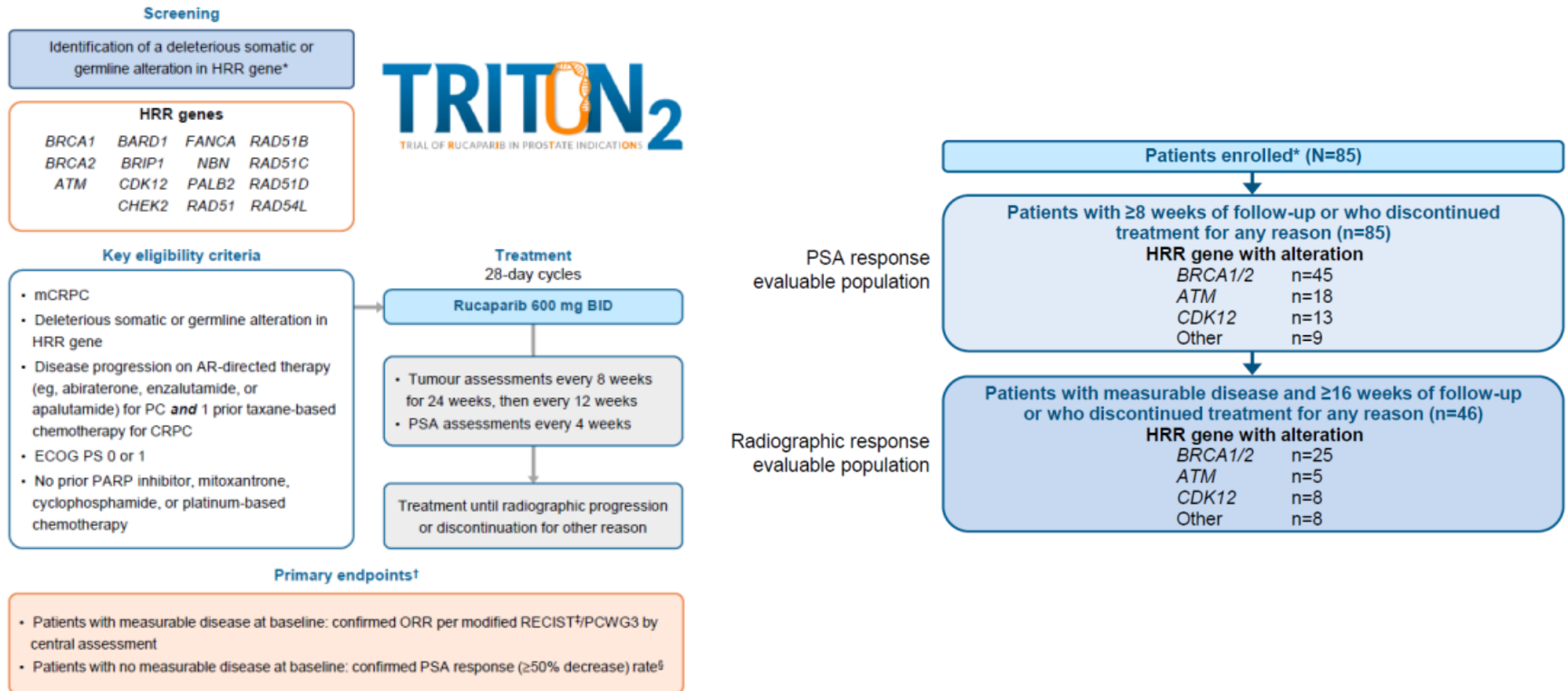
J Mateo, et al. J Clin Oncol 37, 2019 (suppl; abstr 5005)

Olaparib: TOPARP B

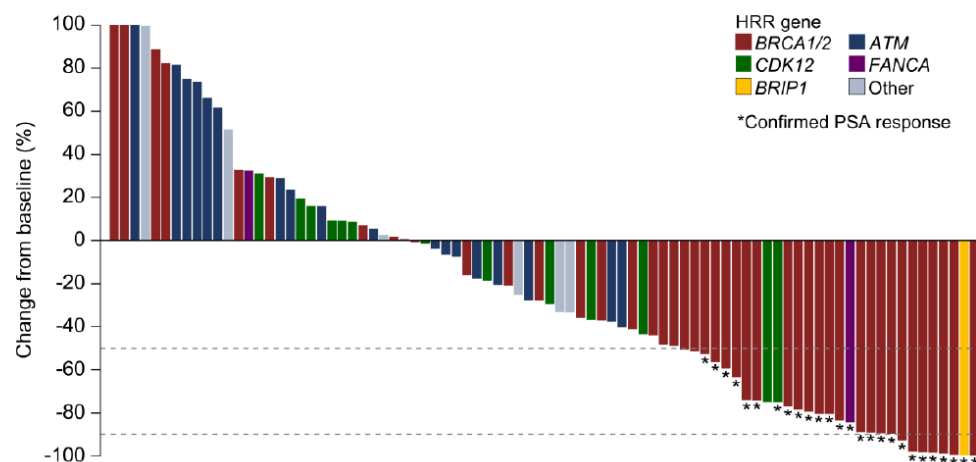


J Mateo, et al. J Clin Oncol 37, 2019 (suppl; abstr 5005)

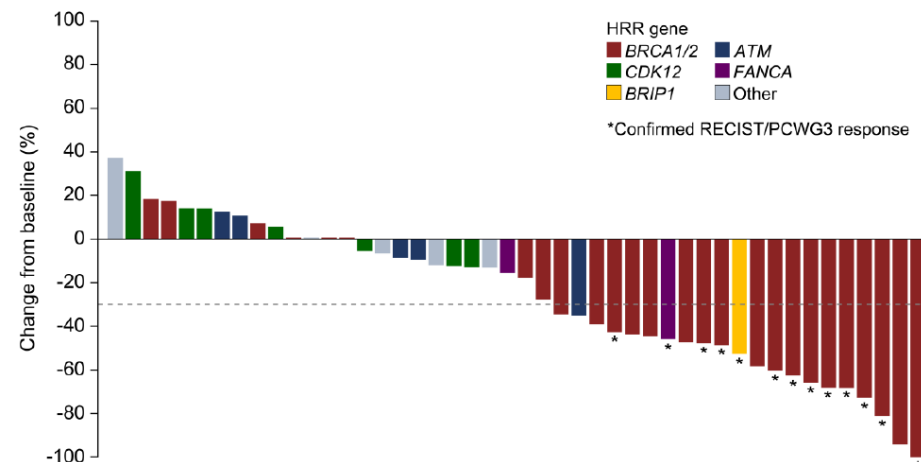
Rucaparib: TRITON2



Rucaparib: TRITON2



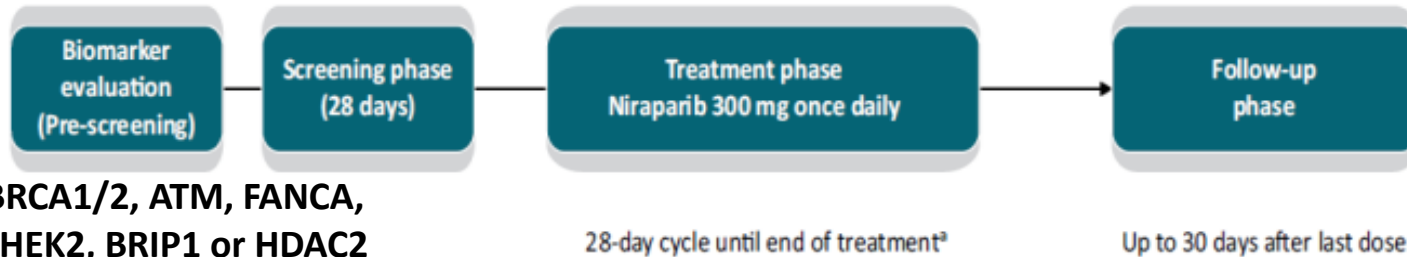
PSA response rate	By HRR gene with alteration, n/N (%) [95% CI]			
	BRCA1/2	ATM	CDK12	Other
All evaluable patients	23/45 (51.1%) [35.8–66.3]	0/18 (0%) [0.0–18.5]	1/13 (7.7%) ^a [0.2–36.0]	2/9 (22.2%) ^b [2.8–60.0]



Characteristic	By HRR gene with alteration			
	BRCA1/2 (n=25)	ATM (n=5)	CDK12 (n=8)	Other (n=8)
ORR, n (%) [95% CI] ^a	11 (44.0%) [24.4–65.1]	0 [0.0–52.2]	0 [0.0–36.9]	2 (25.0%) [3.2–65.1]
Complete response, n (%)	0	0	0	0
Partial response, n (%)	11 (44.0%)	0	0	2 (25.0%) ^b
Stable disease, n (%)	9 (36.0%)	4 (80.0%)	5 (62.5%)	5 (62.5%)
Progressive disease, n (%)	4 (16.0%)	1 (20.0%)	2 (25.0%)	1 (12.5%)
Not evaluable, n (%)	1 (4.0%)	0	1 (12.5%)	0

W Abida, ESMO Congress 2018; ClinicalTrials.gov: NCT02952534

Niraparib: GALAHAD



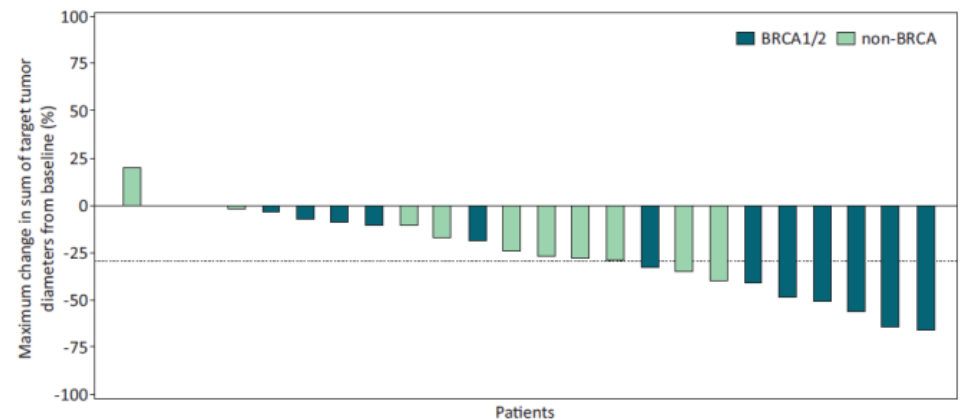
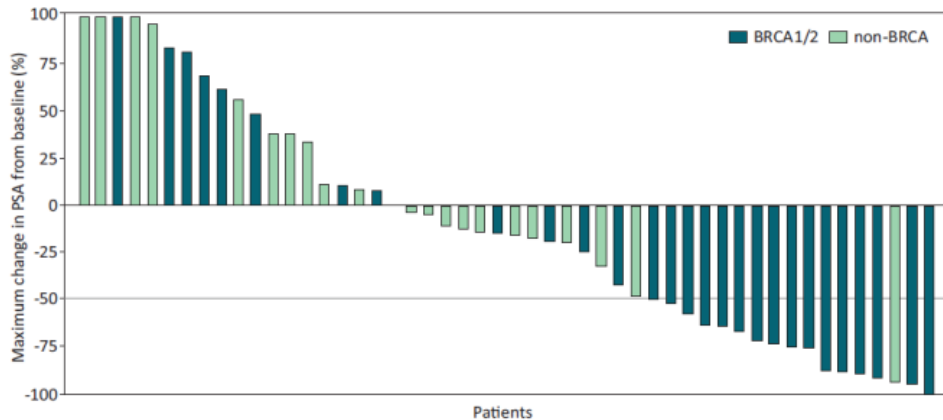
Eligibility

- Men with histologically or cytologically confirmed mCRPC
- Biomarker positive for DRD
- Progressed on / after
 - ≥1 line of taxane-based CTx and
 - ≥1 line of ARSI therapy
- No prior treatment with a PARP inhibitor or platinum-based CTx

- **Primary endpoint:** objective response rate (ORR) of soft tissue (visceral or nodal disease) as defined by RECIST 1.1^b
- **Key secondary endpoint:** composite response rate (RR), defined as ORR according to RECIST 1.1 criteria, or conversion of circulating tumor cell (CTC) to <5/7.5 mL blood, or ≥50% decline in prostate specific antigen (PSA50)
- **Other secondary endpoints:** duration of objective response, defined as time from complete response (CR) or partial response (PR) to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurs first
- **Safety:** adverse events, vital signs, laboratory tests, physical examinations, etc.

Niraparib: GALAHAD

	All Biallelic DRD (N = 50)	
	BRCA1/2 (N=29)	Non-BRCA (N=21)*
	n/N % (95% CI)	n/N % (95% CI)
Composite RR	18/29 62.1 (42.3, 79.3)	5/21 23.8 (8.2, 47.2)
Objective RR ^b	6/16 37.5 (15.2, 64.6)	2/15 13.3 (1.7, 40.5)
PSA50	15/29 51.7 (32.5, 70.6)	1/21 4.8 (0.1, 23.8)
CTC Conversion (<5/7.5 mL blood)	12/29 41.4 (23.5, 61.1)	4/21 19.0 (5.5, 41.9)
CTC Response	6/29 20.7 (8, 39.7)	2/21 9.5 (1.2, 30.4)



MR Smith, et al. J Clin Oncol 37(7_suppl) (March 1 2019) 202-202; ClinicalTrials.gov: NCT02854436

Summary: PARP Inhibitor Monotherapy Trials in mCRPC Patients Post-ARPI and Post-Taxane

	Olaparib TOPARP-B				Rucaparib TRITON2				Niraparib GALAHAD	
	BRCA	ATM	CDK12	Other	BRCA	ATM	CDK12	Other	BRCA	Other
PSA50	77% (23/30)	5% (1/19)	0 (0/20)	26% (6/23)	51% (23/45)	0 (0/18)	8% (1/13)	22% (2/9)	52% (15/29)	5% (1/21)
ORR	52% (11/21)	8% (1/21)	0 (2/18)	9% (2/23)	44% (11/25)	0 (0/5)	0 (0/8)	25% 2/8	38% (6/16)	13% (2/15)

Selected Adverse Events	Olaparib TOPARP-B		Rucaparib TRITON2		Niraparib GALAHAD	
<i>Grade</i>	<i>All</i>	<i>3-4</i>	<i>All</i>	<i>3-4</i>	<i>All</i>	<i>3-4</i>
Anemia	69%	34%	28%	15%	NR	26%
Thrombocytopenia	27%	6%	NR	NR	NR	15%
Neutropenia	18%	5%	NR	NR	NR	8%
Fatigue	54%	7%	45%	5%	NR	NR
Nausea	31%	1%	42%	4%	NR	NR
Vomiting	26%	0	20%	0	NR	NR

NR = Not Reported

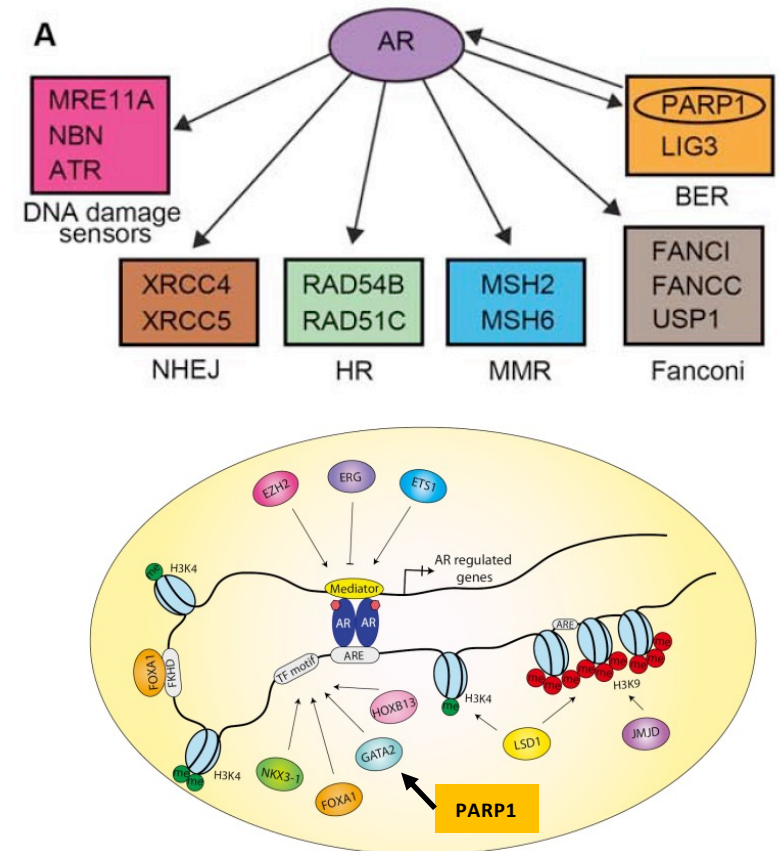
Other Ongoing PARP Inhibitor Monotherapy mCRPC Trials

Trial	Phase	N	Setting	Experimental Arm	Control Arm	Biomarker Selection	Primary Outcome
TALAPRO1 NCT03148795	II	100	Post-ARPI Post-Taxane	Talazoparib	N/A	DDR likely to sensitize to PARP inhibition	ORR
TRITON3 NCT02975934	III	400	Post-ARPI	Rucaparib	Abiraterone or enzalutamide or docetaxel	BRCA1, BRCA2, ATM	rPFS
PROfound NCT02987543	III	340	Post-ARPI	Olaparib	Abiraterone or enzalutamide	Cohort A: BRCA1, BRCA2, ATM Cohort B: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L	rPFS

ARPI = Androgen Receptor Pathway Inhibitor

Combination PARP + AR Pathway Inhibition

- AR promotes DNA damage repair
- ADT upregulates PARP-mediated repair pathways with synthetic lethality between ADT and PARP inhibition
- PARP1 regulates AR-mediated transcriptional activation

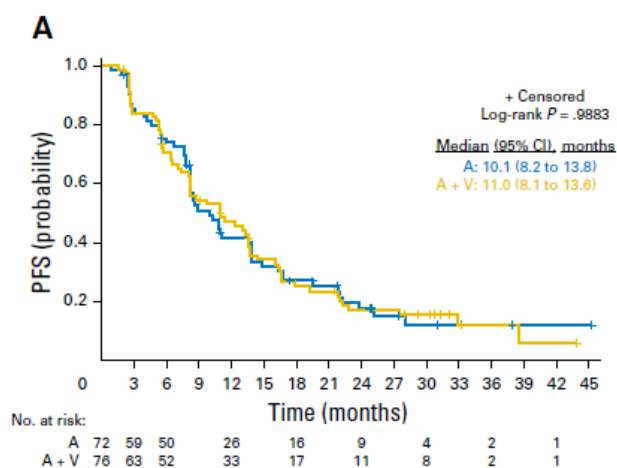


JF Goodwin, et al. Cancer Discov 3:1254, 2013; WR Polkinghorn, et al. Cancer Discov 3:1245, 2013; M Asim, et al. Nat Commun 8: 374, 2017; MJ Schiewer, et al. Cancer Discov 2:1134, 2012

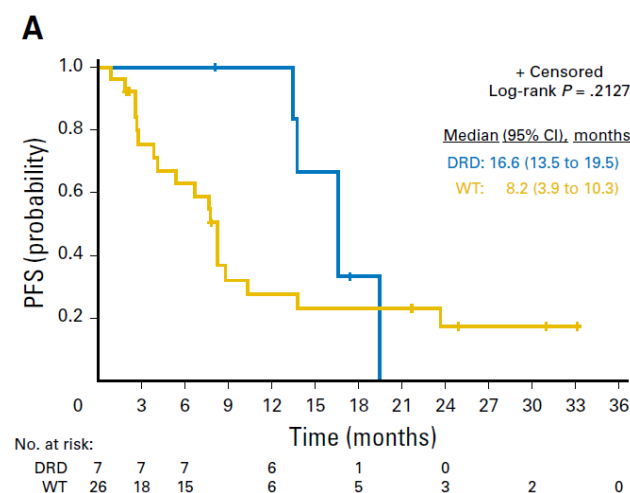
Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012

Maha Hussain, Stephanie Daignault-Newton, Przemyslaw W. Twardowski, Costantine Albany, Mark N. Stein, Lakshmi P. Kunju, Javed Siddiqui, Yi-Mi Wu, Dan Robinson, Robert J. Lonigro, Xuhong Cao, Scott A. Tomlins, Rohit Mehra, Kathleen A. Cooney, Bruce Montgomery, Emmanuel S. Antonarakis, Daniel H. Shevrin, Paul G. Corn, Young E. Whang, David C. Smith, Megan V. Caram, Karen E. Knudsen, Walter M. Stadler, Felix Y. Feng, and Arul M. Chinnaiyan

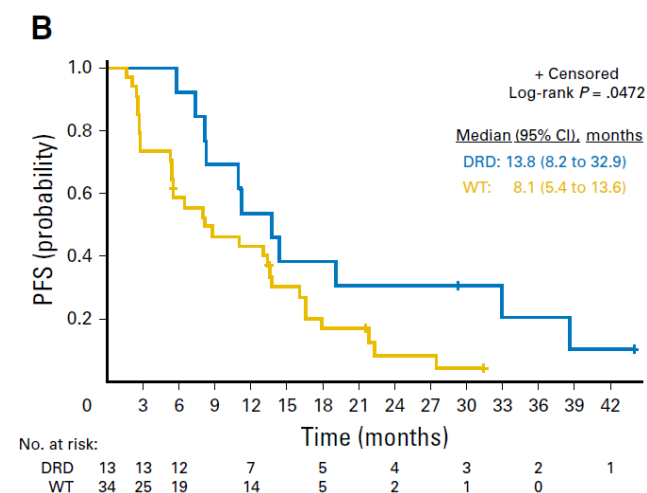
All Patients



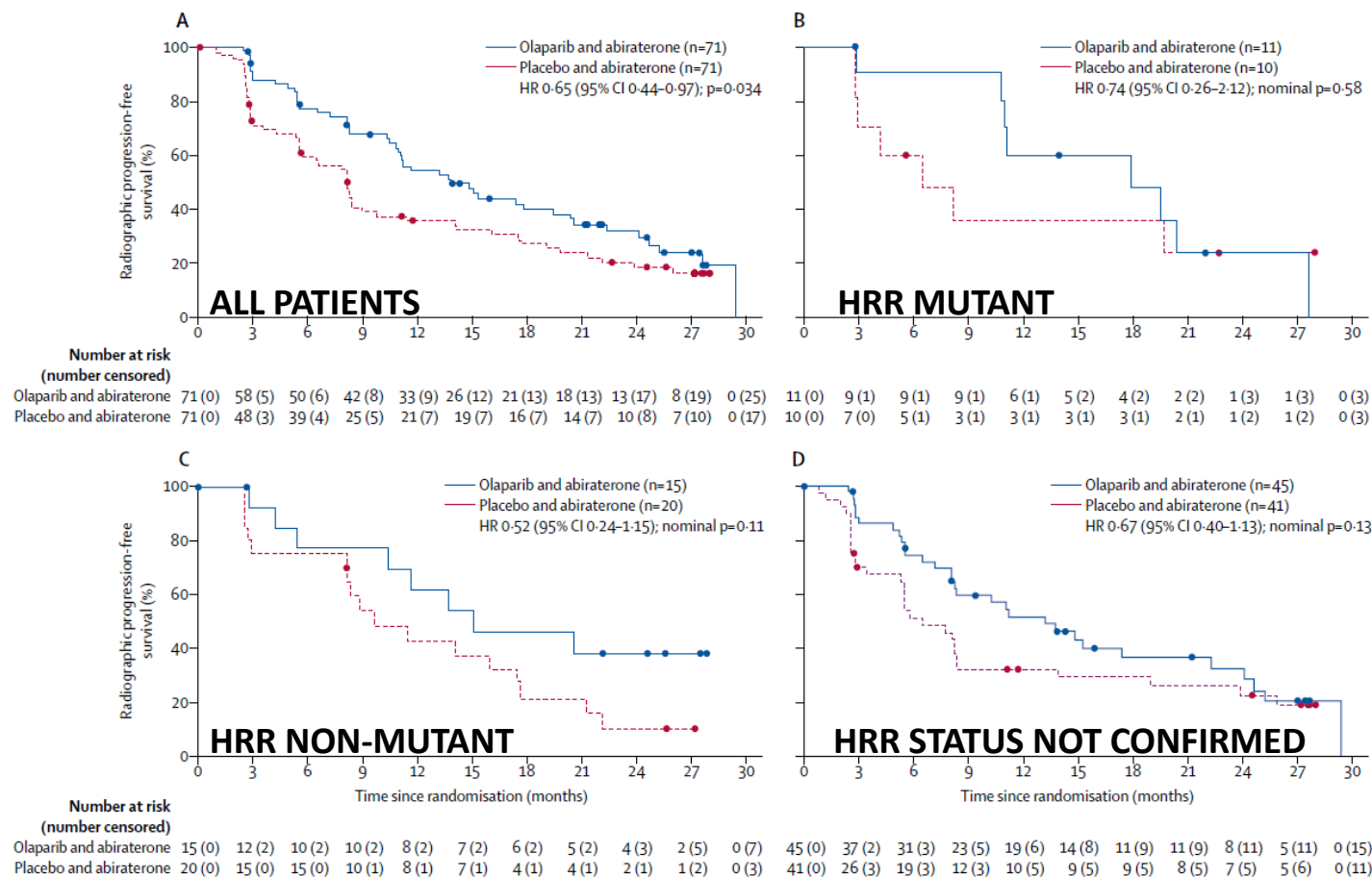
Abiraterone



Abiraterone + Veliparib



Olaparib + Abiraterone in HRR Mutation Positive and Negative Patients



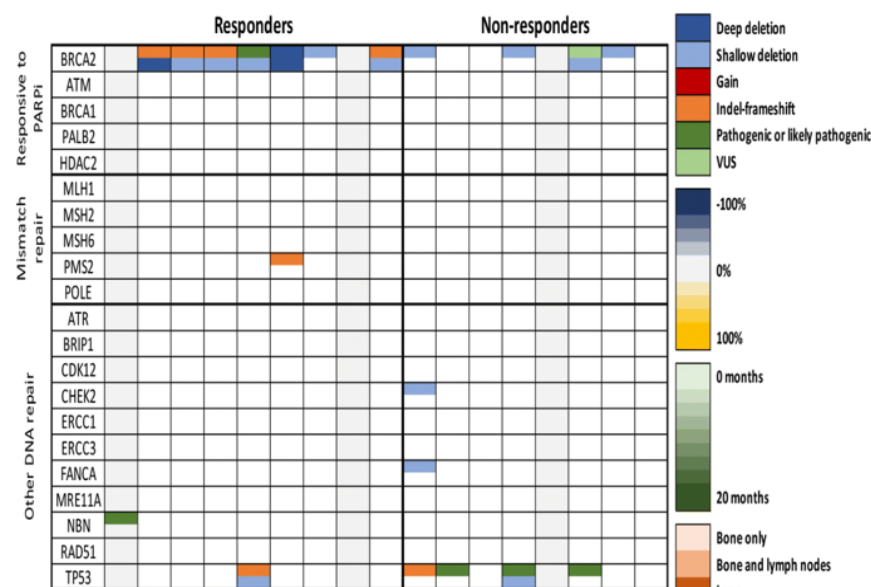
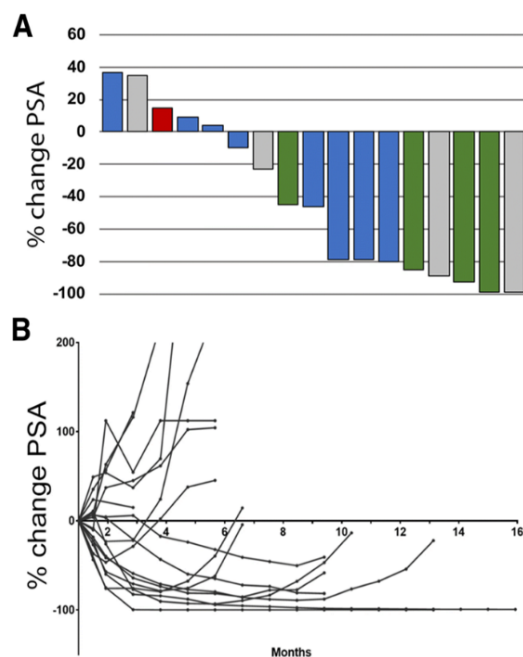
N Clarke, et al. Lancet Oncol 9: 975–86, 2018

Ongoing Phase III Combination PARP + AR Pathway Inhibition Trials

Trial	N	Setting	Experimental Arm	Control Arm	Biomarker Selection	Primary Outcome
PROpel NCT03732820	720	mCRPC 1 st line	Olaparib + abiraterone	Placebo + abiraterone	All comers	rPFS
MAGNITUDE NCT03748641	1000	mCRPC 1 st line	Niraparib + abiraterone	Placebo + abiraterone	Cohort 1 (N = 400): BRCA1, BRCA2, FANCA, PALB2, CHEK2, BRIP1, HDAC2, ATM Cohort 2 (N = 600): no DRD	rPFS
TALAPRO2 NCT03395197	872	mCRPC 1 st line	Talazoparib + enzalutamide	Placebo + enzalutamide	All comers	rPFS

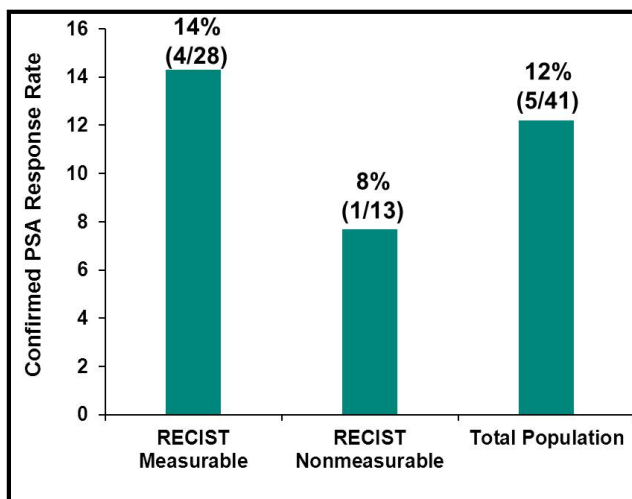
Combination PARP inhibition + Immunotherapy

Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations



Combination PARP inhibition + Immunotherapy

KEYNOTE-365 Cohort A: Pembrolizumab + Olaparib



Confirmed Response	RECIST-Measurable Disease n = 28
ORR, % (95% CI)	7 (1-23)
DCR ≥6 mo, % (95% CI)	32 (16-52)
Best response, n (%)	
CR	0
PR	2 (7)
SD of any duration	13 (46)
PD	9 (32)
Not evaluable ^c	0
No assessment ^d	4 (14)

Exploratory HRD Analysis

- Conducted for baseline samples of all patients, using Guardant360 ctDNA panel
 - Includes *BRCA1/2* and partial *ATM* genes
- Formalin-fixed, paraffin-embedded tissue was analyzed with WES^a
 - Genes evaluated: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*

	Pembrolizumab + Olaparib N = 41
Guardant360 ctDNA panel, n	
Patients with detectable ctDNA	37
HRP	36
<i>ATM</i> R3008H mutation ^b	1
WES analysis, n	
Soft tissue available for analysis	17
Qualified WES results	12
HRP	11
<i>BRIP1</i> frameshift mutation ^c	1

KEYLYNK-010 underway: Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in mCRPC (NCT03834519)

- 780 Patients, Primary endpoint OS

Summary

- Somatic and germline DNA damage repair gene defects are common in metastatic prostate cancer - we need to identify these patients
- PARP inhibitors as monotherapy have high levels of anti-tumour activity in mCRPC patients with identified alterations in DNA repair genes, especially BRCA2
 - Clear that defective HRR is required, what this will translate into for specific predictive biomarkers remains to be refined
 - Tissue, assays, genes, mono- vs bi-allelic, mutational signatures, etc.
- Phase 3 trials of combinations of PARP inhibitors with AR pathway inhibitors and immune check-point inhibitors are underway in selected and unselected patients