HRPC: How to Sequence Multiple Therapies

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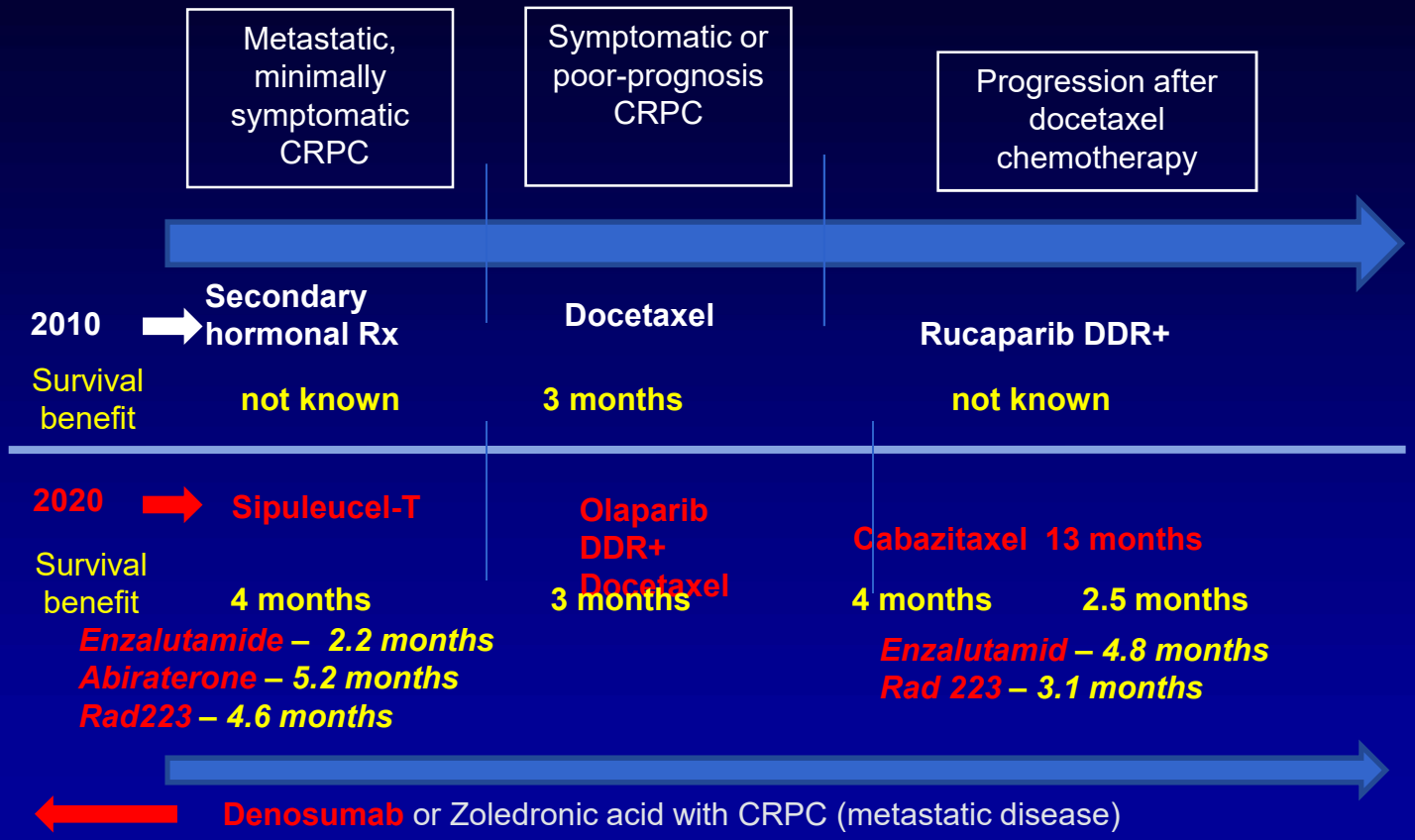
Sequencing mCRPC therapy – 2020



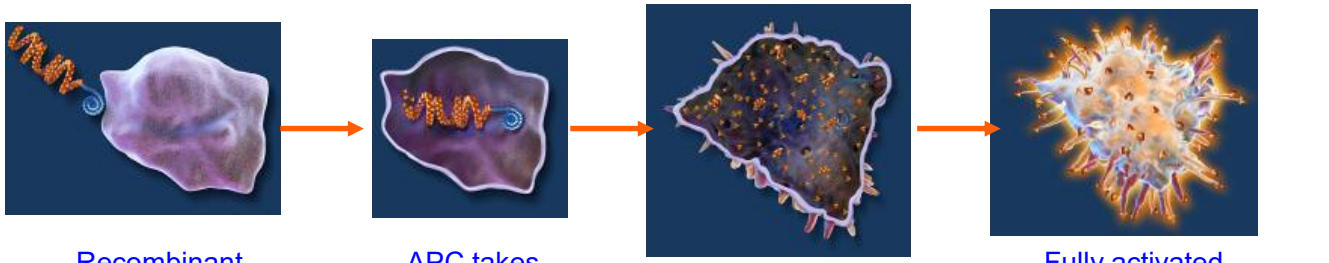
Classes of Agents

- Immunotherapeutic
  - Sipuleucel T
  - Pembrolizumab MSI high
- Hormonal
  - Enzaluamide, Apalutamide, Daralutamide, Abiraterone ,
  - ?Docetaxel
- Cytotoxic
  - Docetaxel, Cabazitaxel
- DNA Damage
  - Rad 223
  - Olaparib, Rucaparib

How do we sequence these agents?

- Clinical Characteristics
  - Symptomatic vs Asymptomatic
  - Visceral vs Non Visceral
  - Pre vs Post Docetaxel
  - HSPCA vs CRPC
- Biological Markers
  - Androgen Receptor
  - DNA Repair
  - MSI

Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein



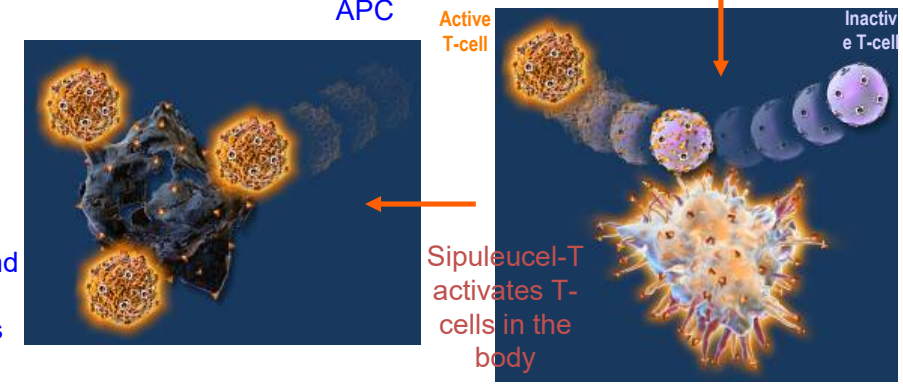
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT

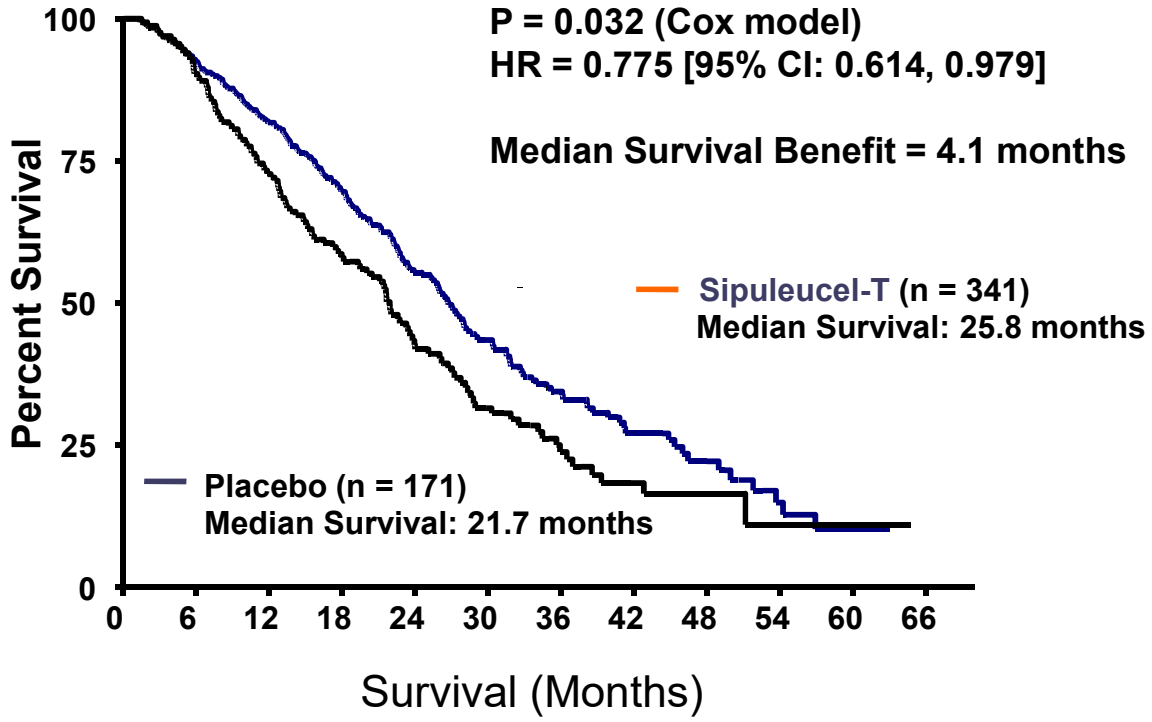


Sipuleucel-T activates T-cells in the body

T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

IMPACT Overall Survival
Intent-to-Treat Population



Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

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Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

Baseline PSA ng/mL	≤22.1 (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, months	**13.0**	**7.1**	**5.4**	**2.8**
HR (95% CI)	(0.31 – 0.85)	(0.47 – 1.17)	(0.52 – 1.24)	0.84 (0.55 – 1.29)

- Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS
- The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively)

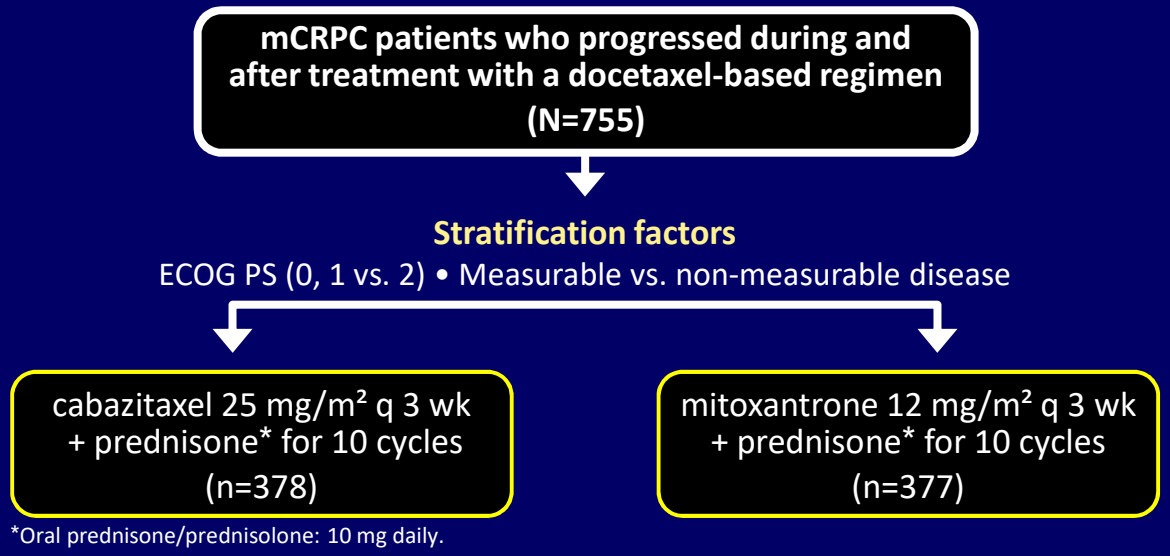
1. Crawford ED et al. AUA 2013. Abstract #960; 2. Schellhammer PF et al. *Urology*. 2013 Jun;81(6):1297-302

MSI in Prostate Cancer

- 1033 patients who had adequate tumor quality for MSI sensor analysis 32 (3.1%) had MSI-H/dMMR prostate cancer.
- 23 of 1033 patients (2.2%) had tumors with high MSI sensor scores, and an additional 9 had indeterminate scores with evidence of dMMR.
- Seven of the 32 MSI-H/dMMR patients (21.9%) had a pathogenic germline mutation in a Lynch syndrome–associated gene.
- Six patients had more than 1 tumor analyzed, 2 of whom displayed an acquired MSI-H phenotype later in their disease course.

Abida et al JAMA Oncol. 2019;5(4):471-478.
doi:10.1001/jamaoncol.2018.5801
Published online December 27, 2018.

TROPIC: Phase III Registration Study
146 Sites in 26 Countries

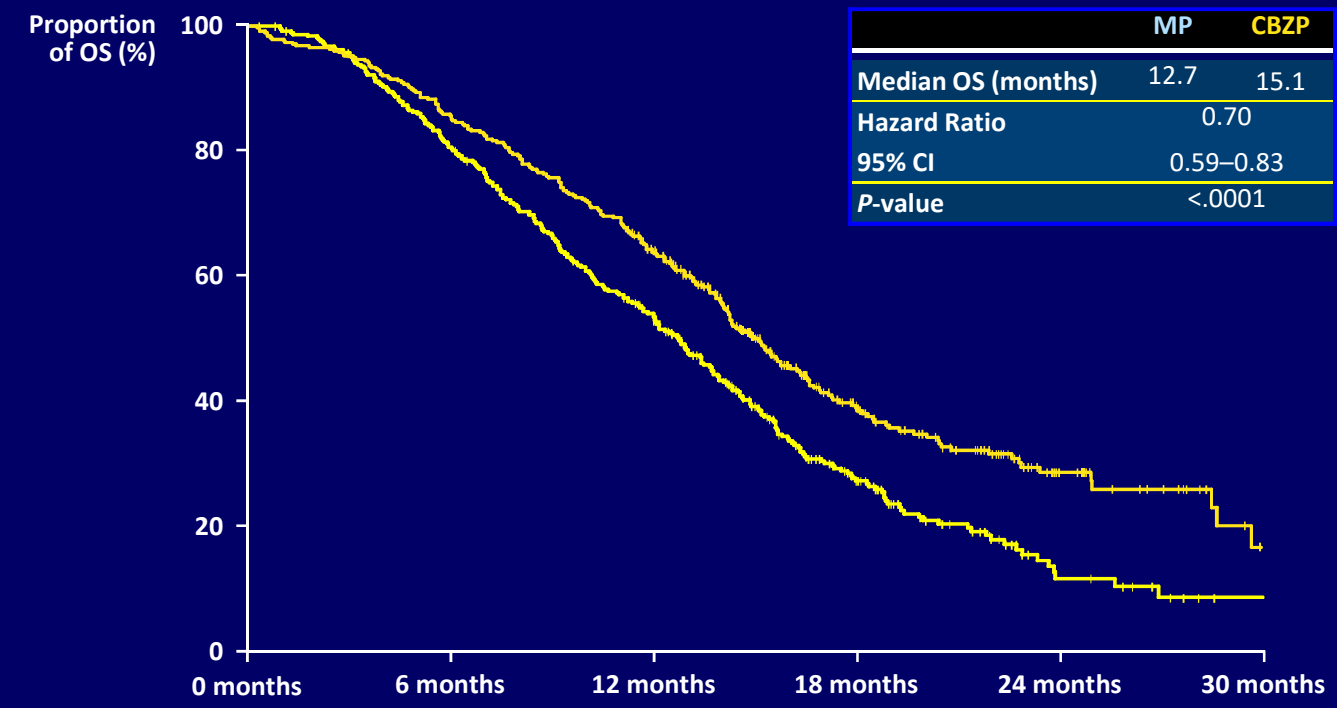


Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

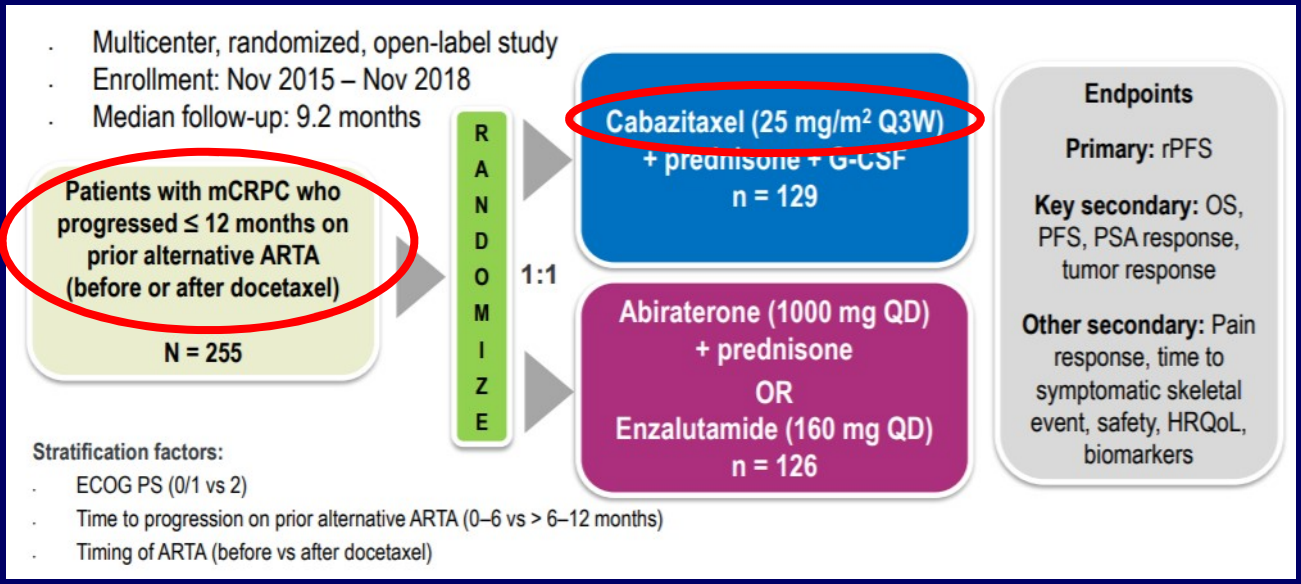
Primary Endpoint: Overall Survival (ITT Analysis)



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

Number at risk	0 months	6 months	12 months	18 months	24 months	30 months
MP	377	300	188	67	11	1
CBZP	378	321	231	90	28	4

Phase IV CARD Trial: Cabazitaxel Versus AR-Targeted Agent—Study Design



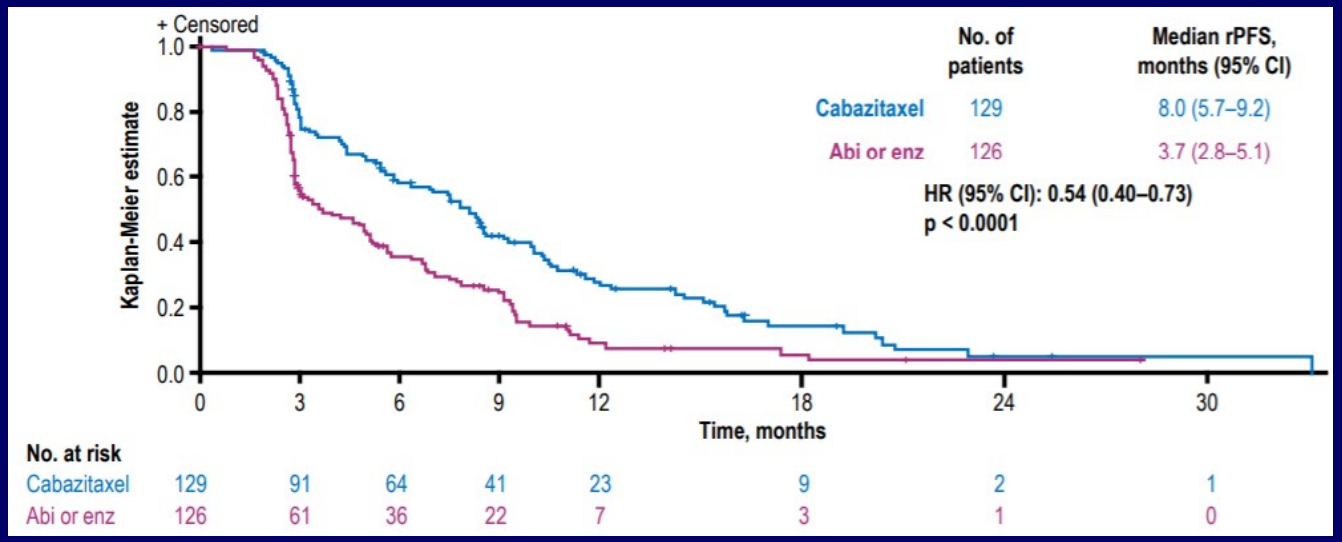
De Wit R, et al. 2019 ESMO. Abstract LBA13.

CARD Trial: Baseline Characteristics

	Cabazitaxel (N = 129)	Abiraterone or enzalutamide (N = 126)
Median age, years (range)	70.0 (46–85)	71.0 (45–88)
≥ 75 years, n (%)	45 (34.9)	34 (27.0)
ECOG PS 0–1, n (%)	123 (95.3)	119 (94.4)
Visceral metastases, n (%)	21 (16.3)	25 (19.8)
Type of progression at study entry, n (%)		
PSA only	11 (8.5)	10 (7.9)
Radiologic (± PSA), no pain	23 (17.8)	16 (12.7)
Pain (± PSA, ± radiologic)	86 (66.7)	90 (71.4)
Gleason 8–10 at diagnosis, n (%)	73 (56.6)	81 (64.3)
M1 disease at diagnosis, n (%)	49 (38.0)	60 (47.6)
Docetaxel/abiraterone in mHSPC, n (%)	14 (10.9)/0	18 (14.3) /1 (0.8)
Prior alternative ARTA, n (%)		
Abiraterone/enzalutamide	56 (43.4)/72 (55.8)	67 (53.2)/59 (46.8)
Received before/after docetaxel	50 (38.8)/79 (61.2)	49 (38.9)/77 (61.1)
Median duration of prior alternative ARTA, months	7.6	8.0

De Wit R, et al. 2019 ESMO. Abstract LBA13.

CARD Trial: Radiographic PFS

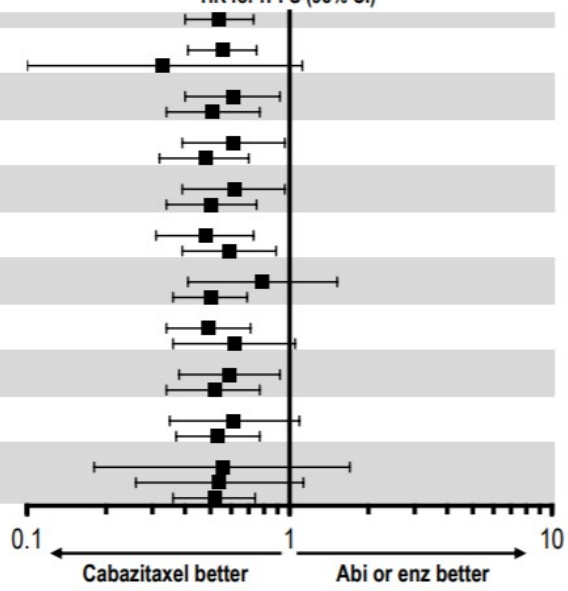


rPFS, radiologic tumor progression (RECIST 1.1) and/or progression of bone lesions (PCWG2) and/or death from any cause.

De Wit R, et al. 2019 ESMO. Abstract LBA13.

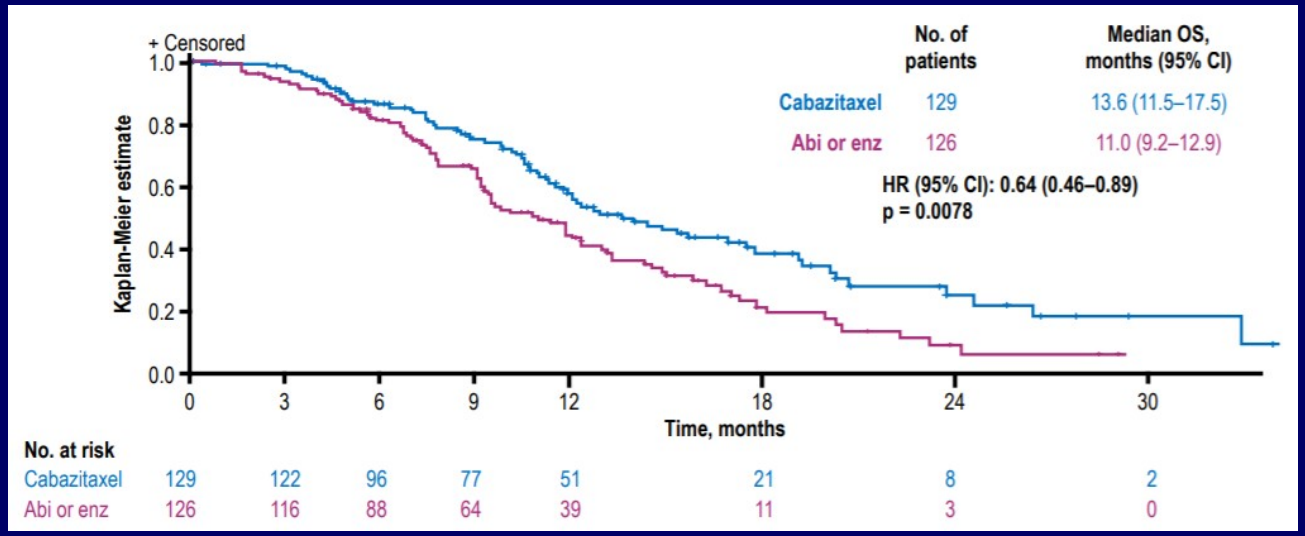
CARD Trial: Radiographic PFS: Preplanned Subgroups

Subgroup	No. of patients	HR for rPFS (95% CI)
All patients	255	0.54 (0.40–0.73)
ECOG PS		
0–1	242	0.56 (0.41–0.75)
2	13	0.33 (0.10–1.12)
Time from prior alternative ARTA initiation to progression		
≤ 6 months	127	0.61 (0.40–0.92)
> 6–12 months	128	0.51 (0.34–0.77)
Timing of prior alternative ARTA		
Before docetaxel	99	0.61 (0.39–0.96)
After docetaxel	156	0.48 (0.32–0.70)
Duration of first androgen deprivation therapy		
< 12 months	113	0.62 (0.39–0.96)
≥ 12 months	140	0.50 (0.34–0.75)
Age		
< 70 years	120	0.48 (0.31–0.73)
≥ 70 years	135	0.59 (0.39–0.89)
Visceral metastases		
Yes	46	0.79 (0.41–1.52)
No	209	0.50 (0.36–0.69)
Gleason 8–10 at diagnosis		
Yes	154	0.49 (0.34–0.71)
No	88	0.62 (0.36–1.05)
M1 disease at diagnosis		
Yes	109	0.59 (0.38–0.92)
No	142	0.52 (0.34–0.77)
Prior therapy with curative intent for localized disease		
Yes	68	0.61 (0.35–1.09)
No	168	0.53 (0.37–0.77)
Type of progression		
PSA only	21	0.56 (0.18–1.70)
Radiologic, no pain	39	0.54 (0.26–1.13)
Pain	176	0.52 (0.36–0.74)



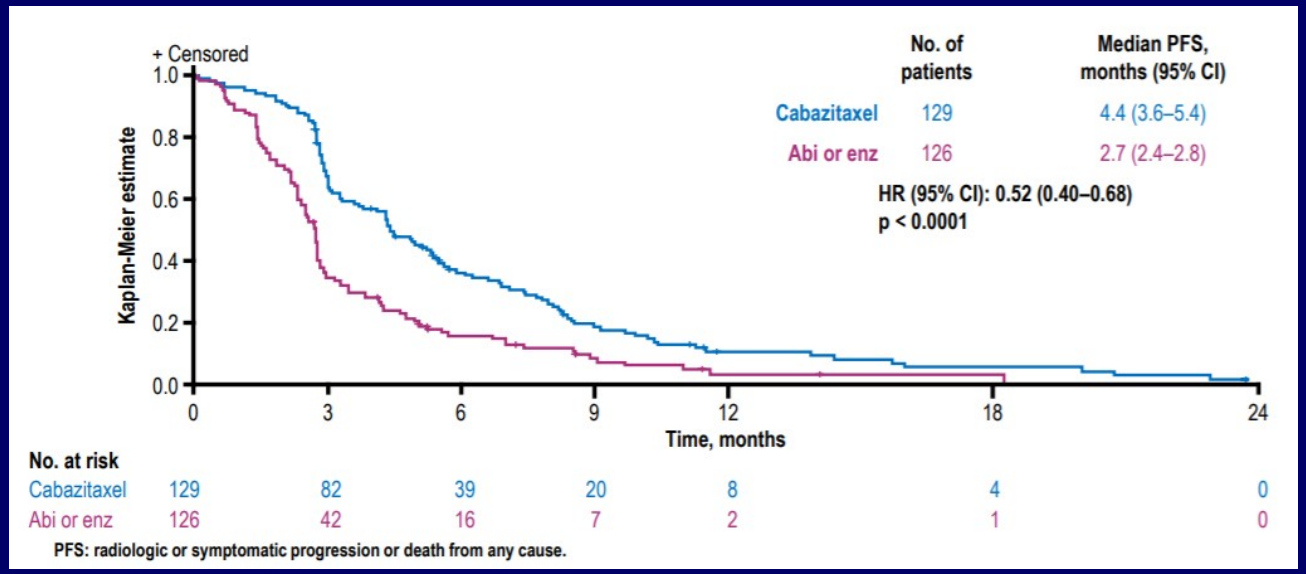
De Wit R, et al. 2019 ESMO. Abstract LBA13.

CARD Trial: Overall Survival



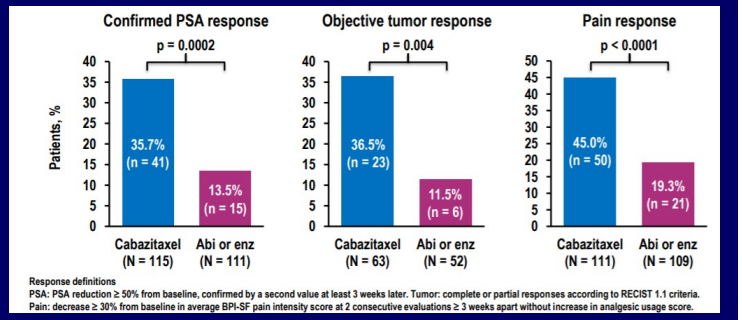
De Wit R, et al. 2019 ESMO. Abstract LBA13.

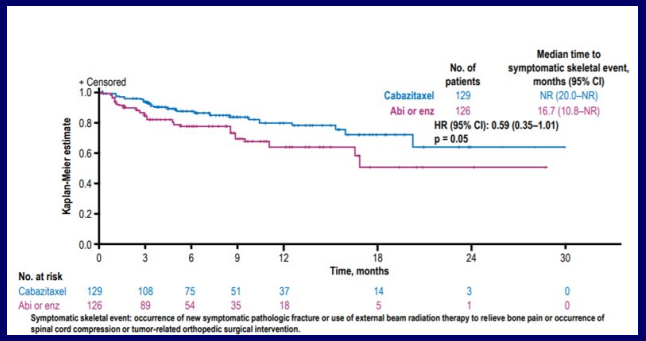
CARD Trial: Progression-Free Survival



De Wit R, et al. 2019 ESMO. Abstract LBA13.

CARD Trial: PSA, Tumor, and Pain Responses





- Preplanned analysis show improvement in pain, time to pain progression, and time to SSEs with cabazitaxel

De Wit R, et al. 2019 ESMO. Abstract LBA13;
Fizazi K, et al. GU Ca Symp 2020. Abstract 16.

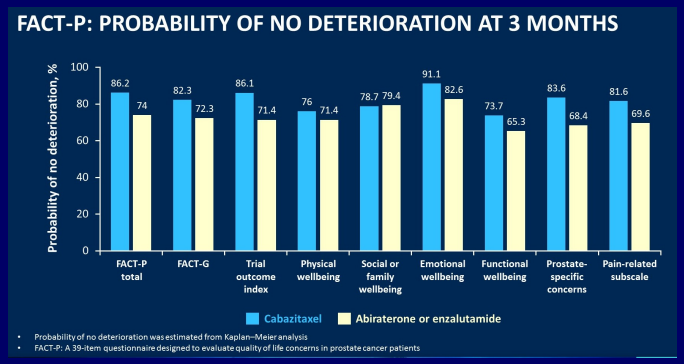
CARD Trial: Safety

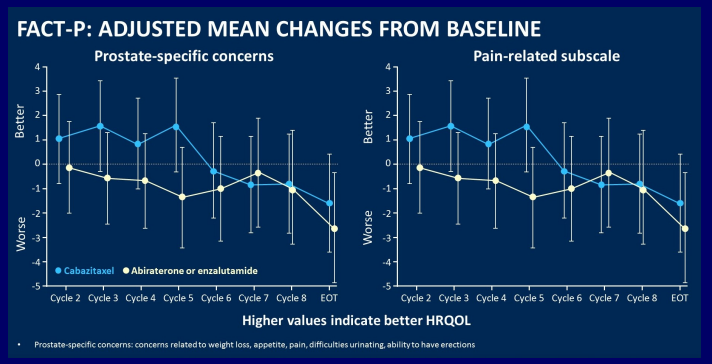
Patients, n (%)	Cabazitaxel (N = 126)	Abiraterone or enzalutamide (N = 124)
Any AE	124 (98.4)	117 (94.4)
Any grade ≥ 3 AE	71 (56.3)	65 (52.4)
Serious AE	49 (38.9)	48 (38.7)
AE leading to treatment discontinuation	25 (19.8)	11 (8.9)
AE leading to death*	7 (5.6)	14 (11.3)

*During treatment emergent AE period (from randomization to 30 days after last treatment administration).

De Wit R, et al. 2019 ESMO. Abstract LBA13.

CARD Trial: Health-Related Quality of Life





Fizazi K, et al. GU Ca Symp 2020. Abstract 16.

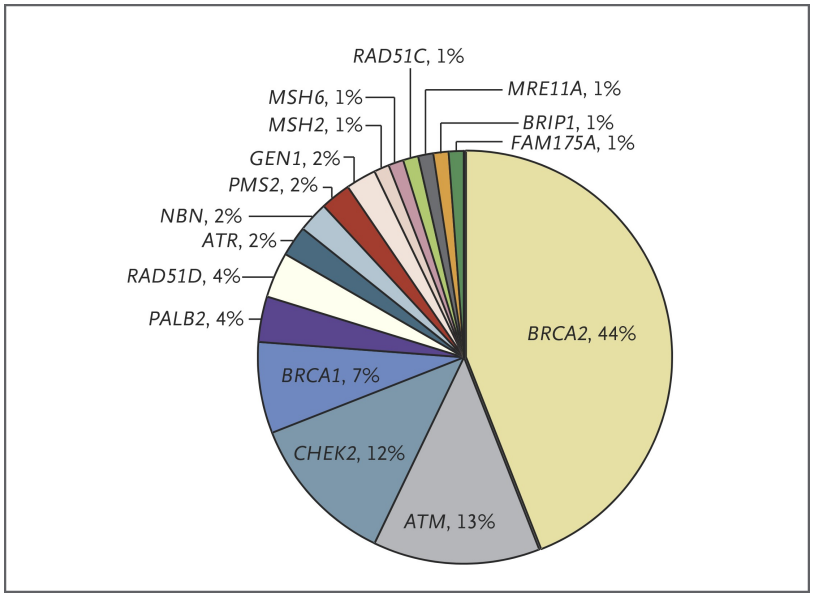


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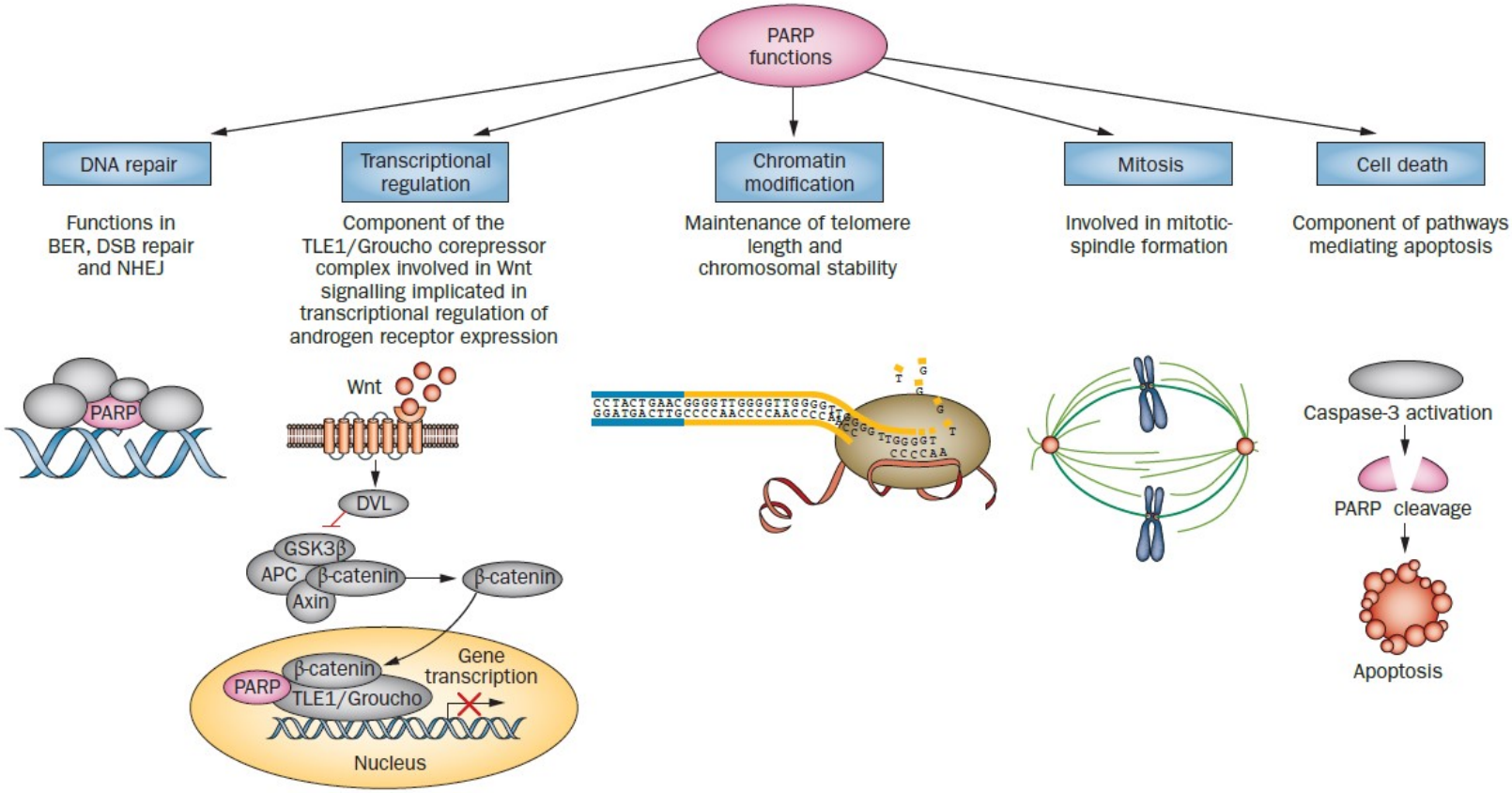
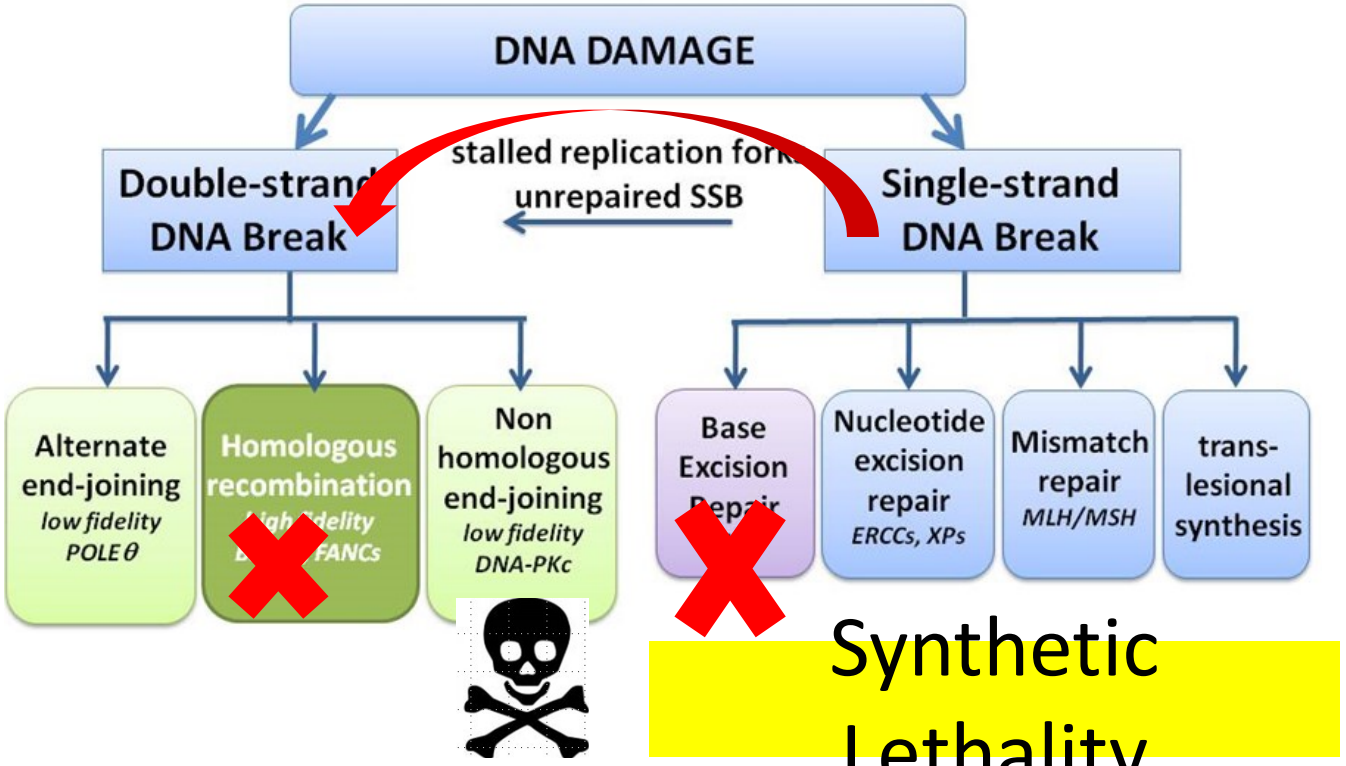
Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)



Sonnenblick. Nature Review 2015

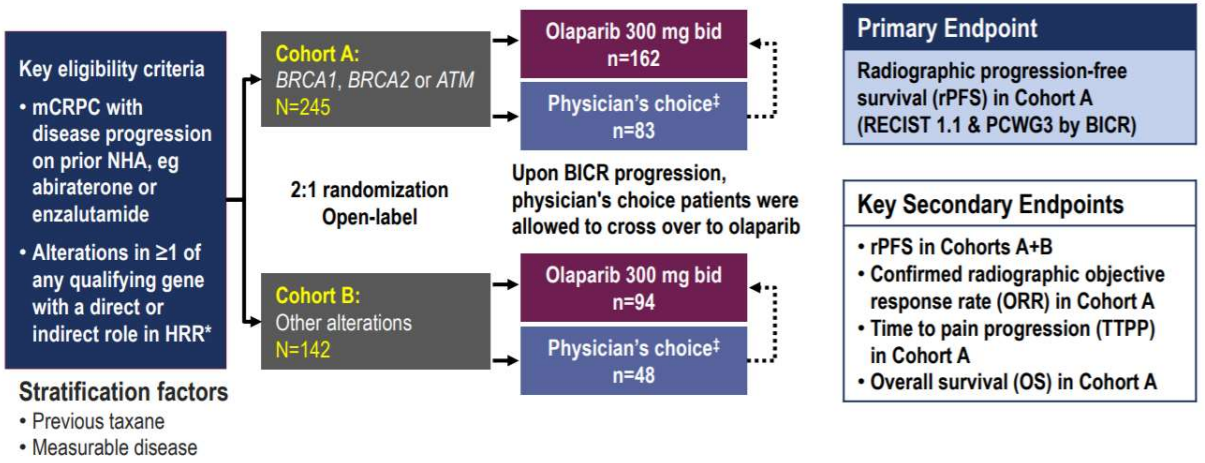
Synthetic Lethality: PARP inhibition in HRD cancer



Olaparib in Prostate Cancer

- **TOPARP study: n=49 patients with mCRPC, who are docetaxel- pre-treated.** (Mateo et al. 2015)
  - **32.7 % (16/49**) response rate in “unselected” mCRPC patients.
  - Genomic Analysis of their prospectively obtained tumor samples:
    - **16 (33%)** had mutations in DNA repair pathway (*ATM, BRCA2* and others*)* (biomarker positive)
      - **14 of these patient responded**
    - **33 (67%)** had no such mutations (biomarker negative)
      - **2 o**f these patients responded.

Phase III PROfound Study: Study Design



*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

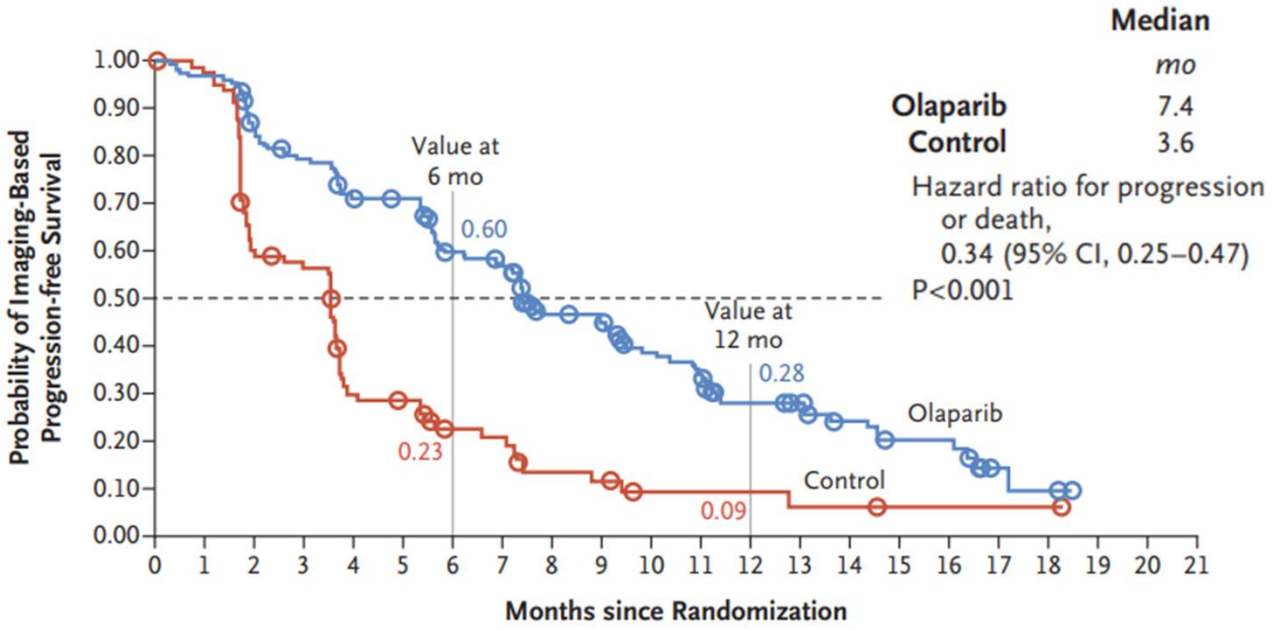
Phase III PROfound Study

Prespecified HRR-Associated Genes

- *BRCA1*
- *BRCA2*
- *ATM*
- *BRIP1*
- *BARD1*
- *CDK12*
- *CHEK1*
- *CHEK2*
- *FANCL*
- *PALB2*
- *PPP2R2A*
- *RAD51B*
- *RAD51C*
- *RAD51D*
- *RAD54L*

Alteration in ≥ 1 of these genes found in 28% (n = 778) of 2792 samples

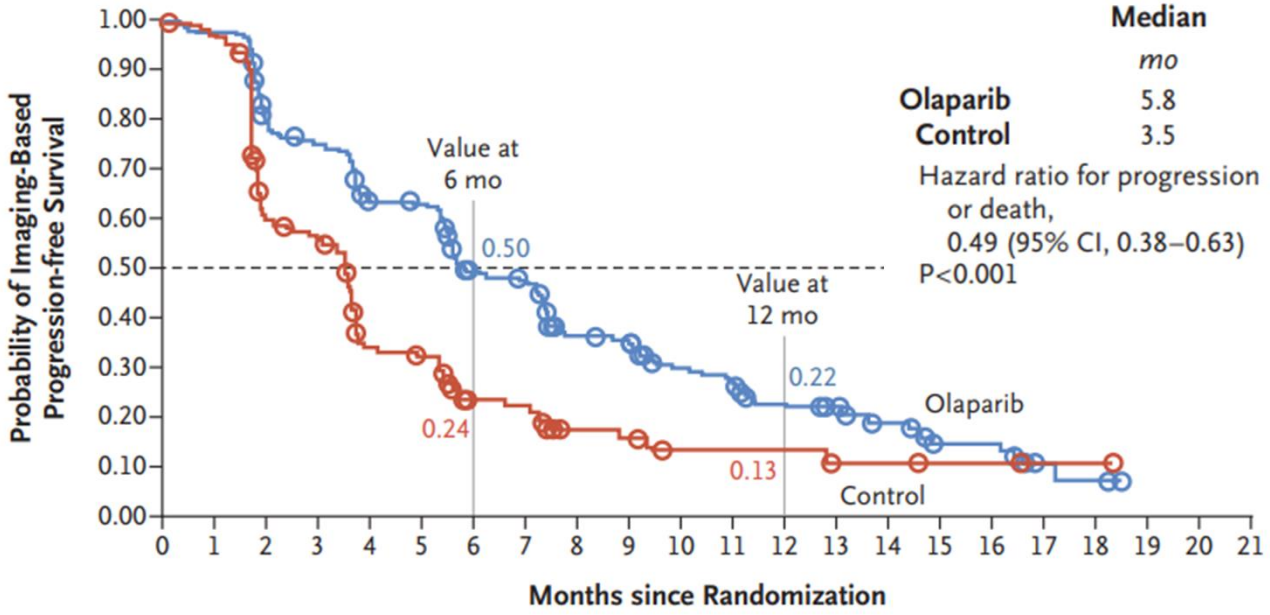
Phase III PROfound Study: rPFS BY BICR in Cohort A (Patients With *BRCA1/2* or *ATM* Alterations)



No. at Risk

Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Control	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

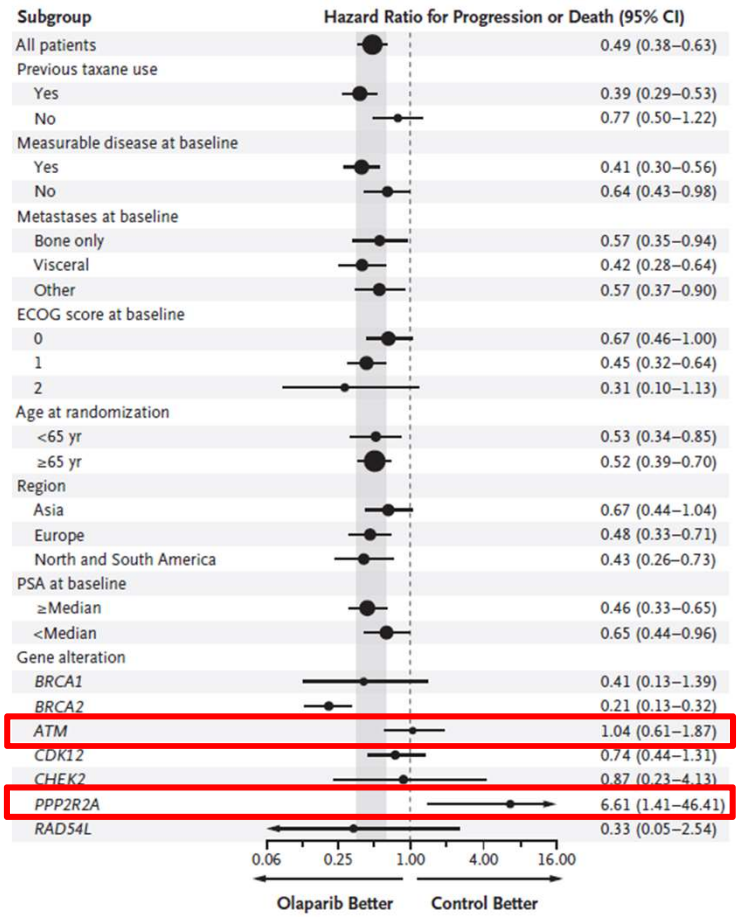
Phase III PROfound Study: rPFS by BICR in Cohorts A + B (Overall Population)



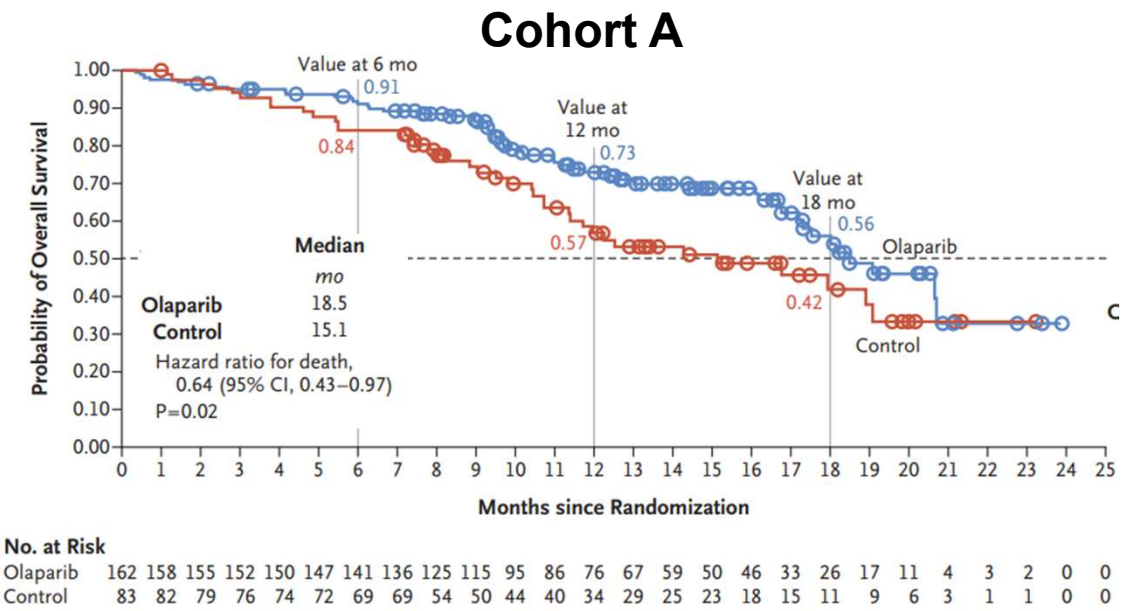
No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

PROfound: PFS by Subgroup (Overall Population)



Phase III PROfound Study: Interim OS



Overall population, median OS: 17.5 mo vs 14.3 mo (HR, 0.67; 95% CI, 0.49-0.93; *P* =.0063)

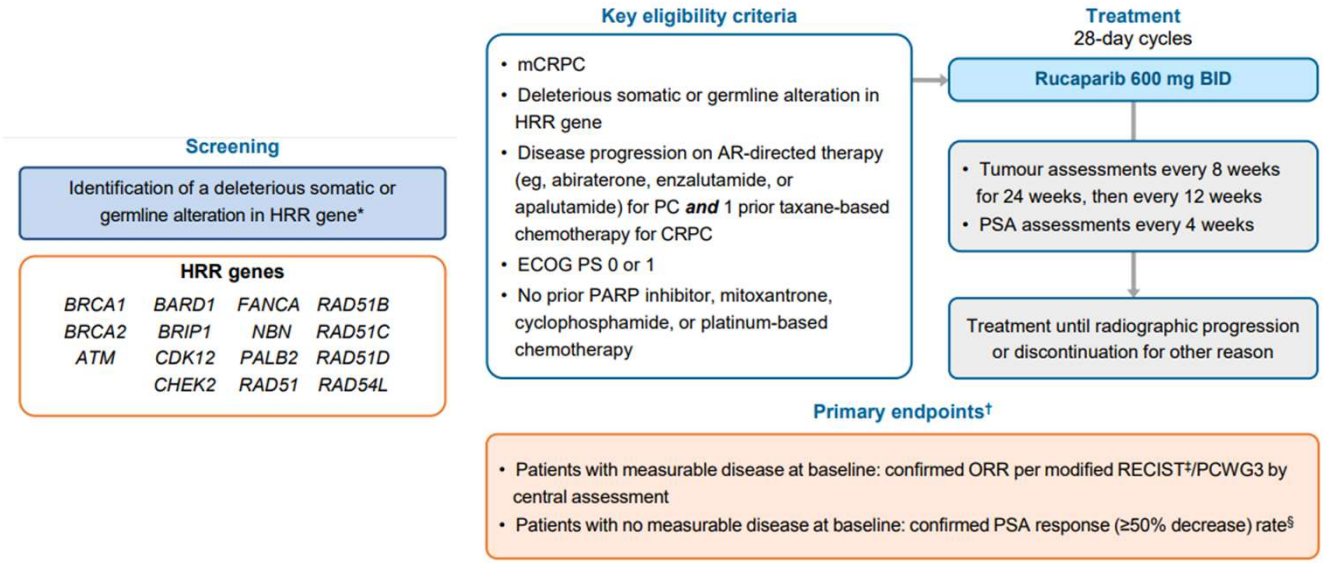
Phase III PROfound Study: Safety Summary

Median treatment duration: Olaparib 7.4 months; Physician's choice 3.9 months

	Olaparib (N=256)	Physician's choice (N=130)
Any AE, n (%)	244 (95.3)	114 (87.7)
Any AE of CTCAE grade 3 or higher, n (%)	130 (50.8)	49 (37.7)
Dose reduction due to AE, n (%)	57 (22.3)	5 (3.8)
Discontinuation due to AE, n (%)	42 (16.4)	11 (8.5)
Death due to AE, n (%)	10 (3.9)	5 (3.8)
Reported to be related to study treatment	1 (0.4)	1 (0.8)

AEs are reported irrespective of attribution, unless otherwise stated

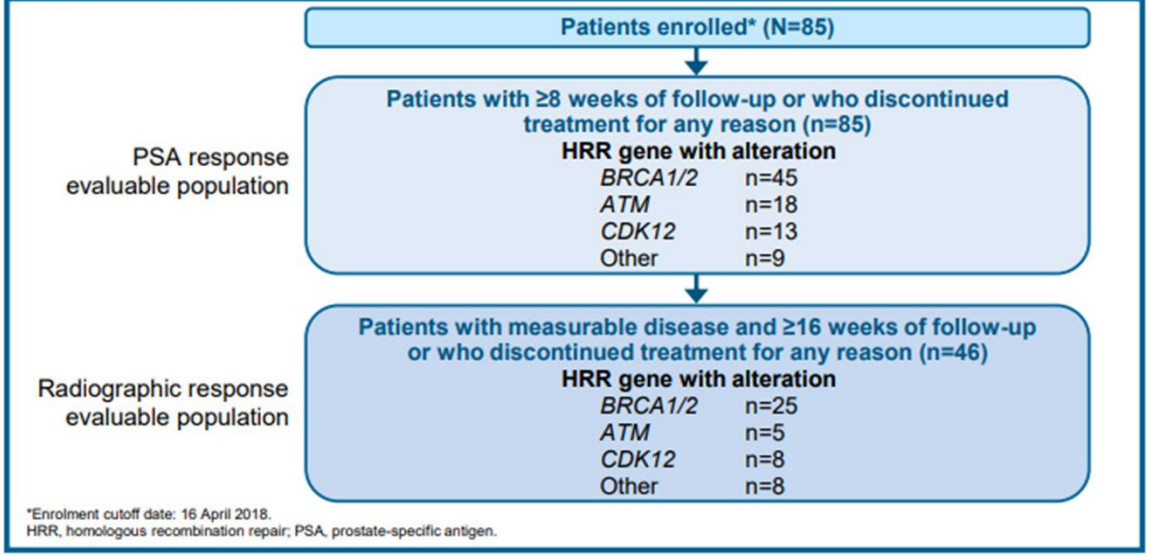
Phase II TRITON2 Trial of Rucaparib for mCRPC: Study Design



Phase II TRITON2: Population

- As of 16 April 2018, 85 patients were enrolled in TRITON2 (**Figure 2**; **Table 1**)
  - At the visit cutoff date (29 June 2018), median duration of follow-up was 5.7 months (range, 2.6–16.4 months)

Figure 2. Efficacy Populations



*Enrolment cutoff date: 16 April 2018.
HRR, homologous recombination repair; PSA, prostate-specific antigen.

Phase II TRITON2: Radiographic Response

Investigator-Confirmed Objective Response in Patients With Measurable Disease
Radiographic Response in Patients With Measurable Disease

- 44% (11/25)
- 1 patient with a *BRIP1* alteration and 1 patient with a *FANCA* alteration

Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

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

Phase II TRITON2: Biochemical Response

Table 3. Confirmed PSA Response Rates

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]
With measurable disease	17/27 (63.0%) [42.4–80.6]	0/5 (0%) [0.0–52.2]	1/8 (12.5%)[a] [0.3–52.7]	2/8 (25.0%)[b] [3.2–65.1]
With no measurable disease	6/18 (33.3%) [13.3–59.0]	0/13 (0%) [0.0–24.7]	0/5 (0%) [0.0–52.2]	0/1 (0%) [0.0–97.5]

Visit cutoff date: 29 June 2018. Includes patients who had ≥ 8 weeks of follow up or who discontinued treatment.
[a]This patient did not demonstrate a confirmed objective radiographic response.
[b]1 patient with a *BRIP1* alteration and with a *FANCA* alteration; both demonstrated a confirmed objective radiographic response.

Phase II TRITON2: Ad Hoc Analysis of non-*BRCA* DDR Gene Alterations (n = 78)—Response

	By DDR gene group			
	ATM **(*n* = 49)**	***CDK12*** **(*n* = 15)**	***CHEK2*** **(*n* = 12)**	**Other[a] (*n* = 14)**
Confirmed investigator-assessed objective response[b]	2/19 (10.5) [1.3–33.1]	0/10 (0) [0.0–30.8]	1/9 (11.1) [0.3–48.2]	4/14 (28.6) [8.4–58.1]
Complete response	0/19 (0.0)	0/10 (0)	0/9 (0)	1/14 (7.1)
Partial response	2/19 (10.5)	0/10 (0)	1/9 (11.1)	3/14 (21.4)
Stable disease	9/19 (47.4)	6/10 (60.0)	6/9 (66.7)	8/14 (57.1)
Progressive disease	7/19 (36.8)	3/10 (30.0)	2/9 (22.2)	1/14 (7.1)
Not evaluable	1/19 (5.3)	1/10 (10.0)	0/9 (0)	1/14 (7.1)
6-month clinical benefit rate[c]	12/42 (28.6) [15.7–44.6]	3/15 (20.0) [4.3–48.1]	3/8 (37.5) [8.5–75.5]	6/11 (54.5) [23.4–83.3]
12-month clinical benefit rate[d]	3/18 (16.7) [3.6–41.4]	1/14 (7.1) [0.2–33.9]	0/5 (0) [0.0–52.2]	3/8 (37.5) [8.5–75.5]
Confirmed PSA response[e]	2/49 (4.1) [0.5–14.0]	1/15 (6.7) [0.2–31.9]	2/12 (16.7) [2.1–48.4]	5/14 (35.7) [12.8–64.9]
Median time to PSA progression, mo (95% CI)	3.1 (2.8–4.6)	3.2 (2.8–4.6)	7.4 (2.8–7.4)	11.1 (3.0–NR)

Phase II TRITON2: Safety

Median Treatment Duration

- Overall safety population, 3.7 mo (range, 0.5-12.9)
- Patients with a *BRCA1/2* alteration, 4.4 mo (range, 0.50-12.0)

Table 4. Summary of TEAEs

	Overall safety population (N=85), n (%)
At least 1 TEAE	81 (95.3%)
At least 1 TEAE grade ≥3	45 (52.9%)
Treatment interruption and/or dose reduction due to TEAE	45 (52.9%)
Treatment interruption due to TEAE	41 (48.2%)
Dose reduction due to TEAE	25 (29.4%)[a]
TEAE leading to discontinuation	5 (5.9%)[b]
Death due to TEAE	1 (1.2%)[c]

Phase II TRITON2: Safety (cont.)

Table 5. Most Common (≥10%) TEAEs of Any Grade in All Patients Regardless of Causality

	Overall safety population (N=85)	
	Any grade, n (%)	Grade ≥3, n (%)
Asthenia/fatigue	38 (44.7%)	4 (4.7%)
Nausea	36 (42.4%)	3 (3.5%)
Anaemia/decreased haemoglobin	24 (28.2%)	13 (15.3%)
Decreased appetite	24 (28.2%)	3 (3.5%)
Constipation	19 (22.4%)	1 (1.2%)
ALT/AST increased	18 (21.2%)	4 (4.7%)
Vomiting	17 (20.0%)	0
Diarrhoea	16 (18.8%)	1 (1.2%)
Arthralgia	11 (12.9%)	1 (1.2%)
Dizziness	11 (12.9%)	0
Back pain	10 (11.8%)	2 (2.4%)
Oedema peripheral	10 (11.8%)	0
Weight decreased	10 (11.8%)	0
Dysgeusia	9 (10.6%)	0
Dyspnoea	9 (10.6%)	0
Haematuria	9 (10.6%)	3 (3.5%)

Visit cutoff date: 29 June 2018.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

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On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology, Inc.) for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

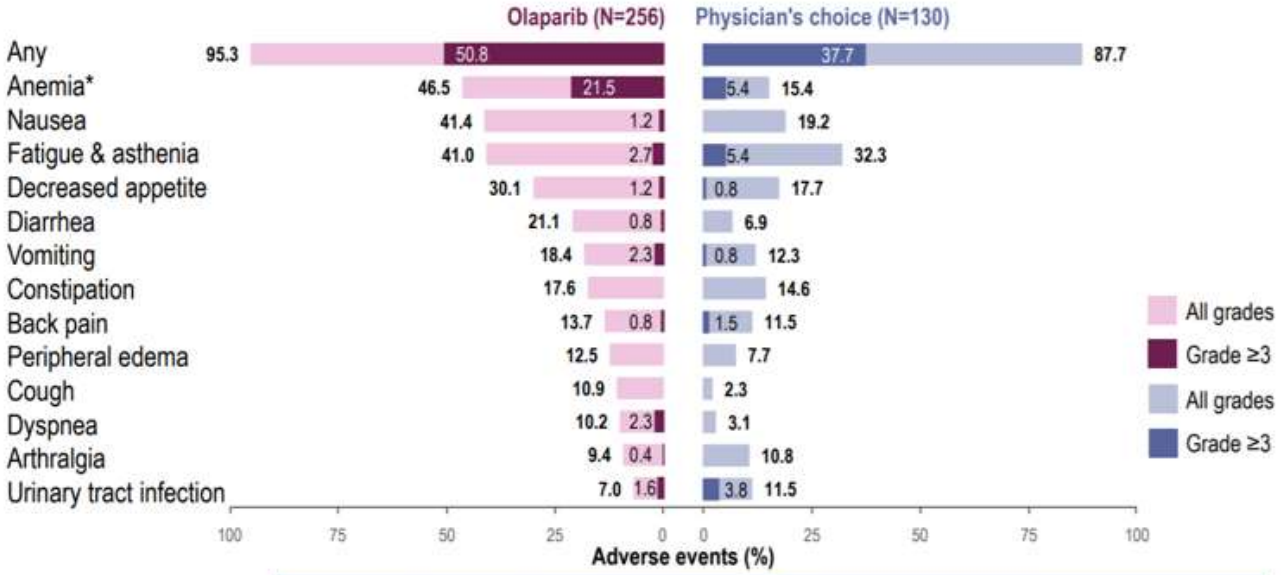
Phase III PROfound Study: Safety Summary

Median treatment duration: Olaparib 7.4 months; Physician's choice 3.9 months

	Olaparib (N=256)	Physician's choice (N=130)
Any AE, n (%)	244 (95.3)	114 (87.7)
Any AE of CTCAE grade 3 or higher, n (%)	130 (50.8)	49 (37.7)
Dose reduction due to AE, n (%)	57 (22.3)	5 (3.8)
Discontinuation due to AE, n (%)	42 (16.4)	11 (8.5)
Death due to AE, n (%)	10 (3.9)	5 (3.8)
Reported to be related to study treatment	1 (0.4)	1 (0.8)

AEs are reported irrespective of attribution, unless otherwise stated

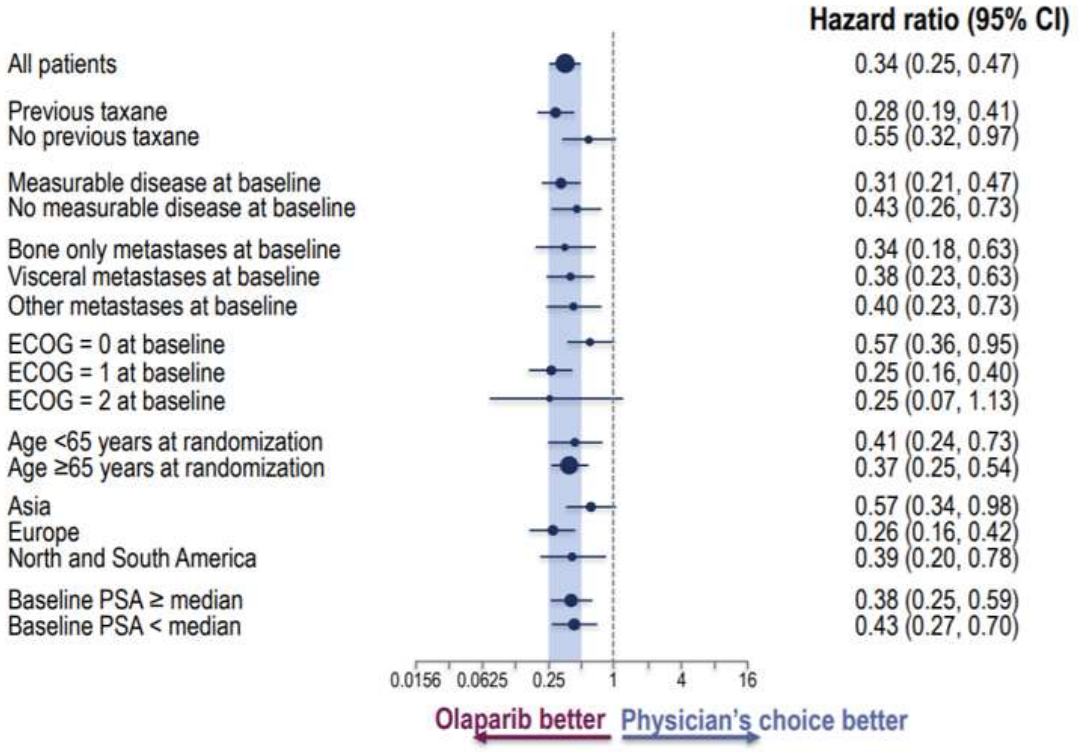
Phase III PROfound Study: Most Common AEs (≥ 10 % of patients in either arm) in Cohorts A+B



- 4.3% pulmonary embolism with olaparib vs 0.8% with physician's choice; **none were fatal**
- No reports of myelodysplastic syndromes or acute myeloid leukemia

*Anemia (46.1%) and decreased Hb (0.4%)

Phase III PROfound Study: Subgroup Analyses of rPFS in Cohort A



OPTIMIZING OUTCOMES IN PROSTATE CANCER
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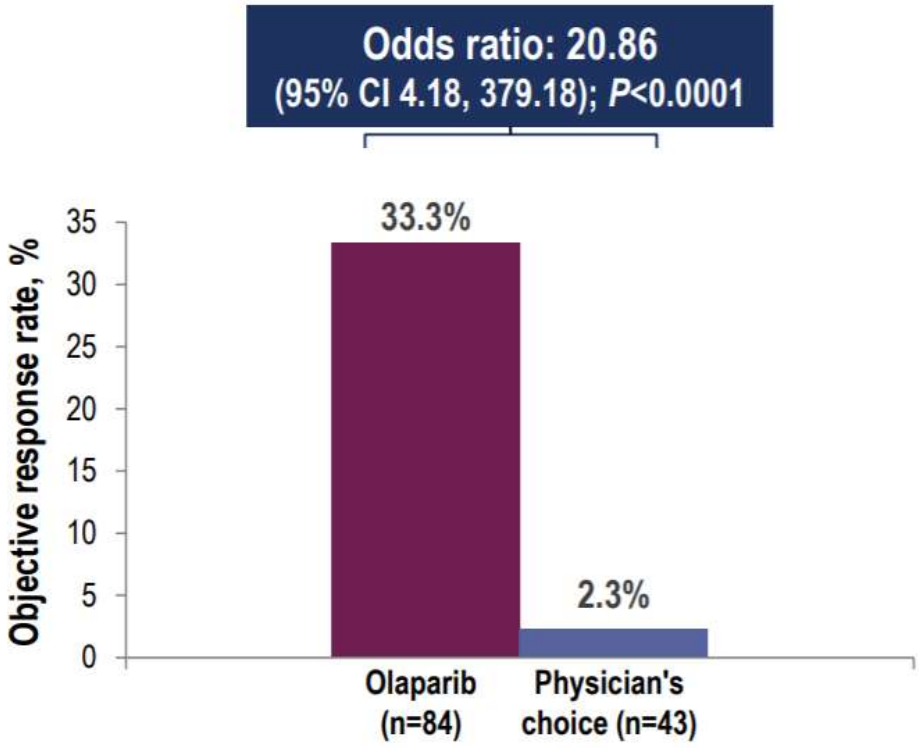
Phase III PROfound Study: confirmed ORR in Cohort A



FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

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On May 19, 2020, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

Today, the FDA also approved FoundationOne CDx (Foundation Medicine, Inc.) for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

Select Ongoing PARPi Combination Trials in Advanced PC

Study	Phase	Est. N	Patient Population	Study Arm(s)	Primary Endpoint(s)
COMRADE[1]	I/II	112	mCRPC with bone mets	**Olaparib** + radium-223 vs radium-223	MTD, rPFS
NCT02893917[2]	II	90	mCRPC with progression on prior tx	**Olaparib** ± cediranib	rPFS
NCT03516812[3]	II	30	Asymptomatic mCRPC with progression on ABI and/or ENZ	**Olaparib** + testosterone	PSA ↓
NCT03810105[4]	II	32	Castration-sensitive PC with biochem recurrence, no mets, + DDR mut	**Olaparib** + durvalumab	Undetectable PSA
NCT03572478[5]	Ib/IIa	60	mCRPC or metastatic/recurrent endometrial cancer	Phase Ib: **rucaparib** + nivolumab Phase IIa: **rucaparib** vs nivolumab vs **rucaparib** + nivolumab	DLT of combo
Javelin PARP Medley[6]	Ib/II	242	Locally advanced or metastatic CRPC and other solid tumors	Phase II: **talazoparib** + avelumab at MTD from phase Ib	Phase Ib: DLT Phase II: ORR
TALAPRO-2[7]	III	872	DRD+ mCRPC	**Talazoparib** + AR-targeted therapy vs PBO + AR-targeted therapy	rPFS

All trials recruiting as of February 2019, except NCT03810105 is new.

1. NCT03317392. 2. NCT02893917. 3. NCT03516812. 4. NCT03810105. 5. NCT03572478. 6. NCT03330405. 7. NCT03395197.

Characteristics of Radioisotopes

	Alpha Particles[1]	Beta Particles[2]
Size		
Definition	Consists of helium nuclei High LET Do not penetrate a sheet of paper	Consists of electrons Relatively low LET May be halted by an aluminum plate
DNA hits to kill cells	1-10	100-1000
Type of DNA Damage	Double-strand breaks (Lethal, more difficult to repair)[3]	Single-strand breaks (More repairable)[3]

LET = linear energy transfer

1. Henriksen G, et al. *J Nucl Med*. 2003;44(2):252-259; 2. Bruland OS, et al. *Clin Cancer Res.* 2006;12(20):6250s–6257s.

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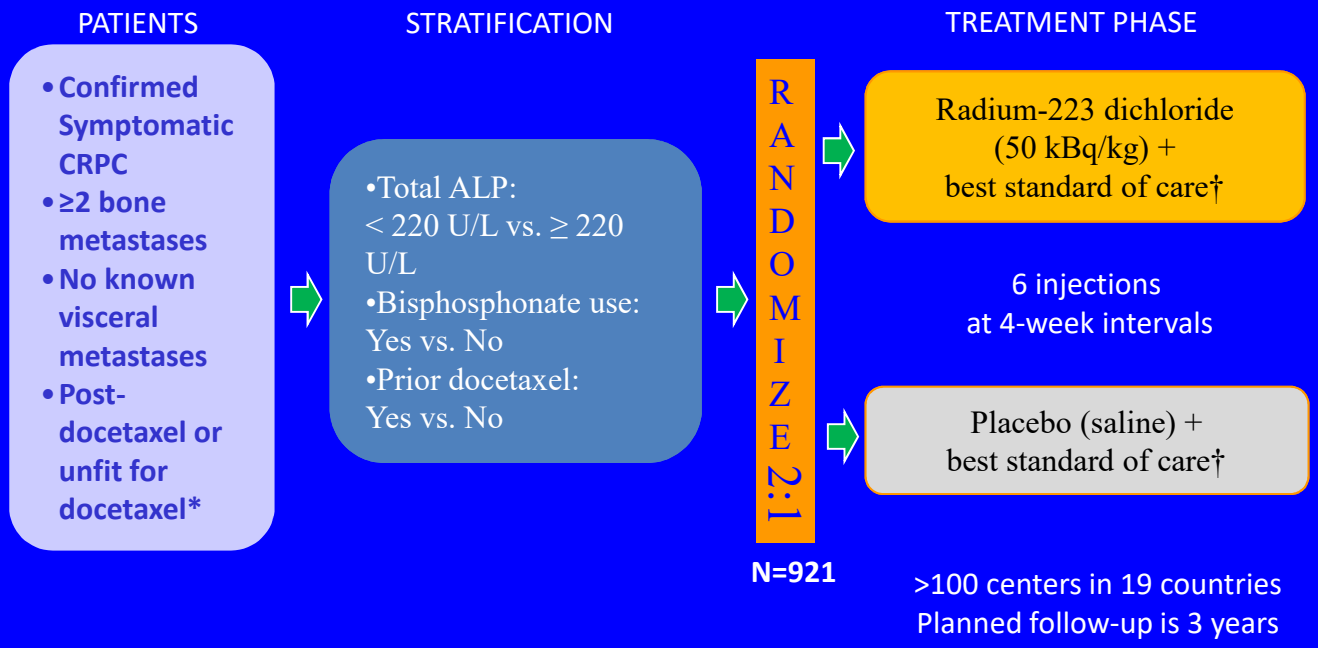
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design[1]



*Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable

†Best standard of care defined as a routine standard of care at each center, eg. local external beam radiotherapy, corticosteroids, anti-androgens, estrogens (e.g., stilbestrol), estramustine, or ketaconazole

Reference: 1. Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

ALSYMPCA : Patient Demographics and Baseline Characteristics

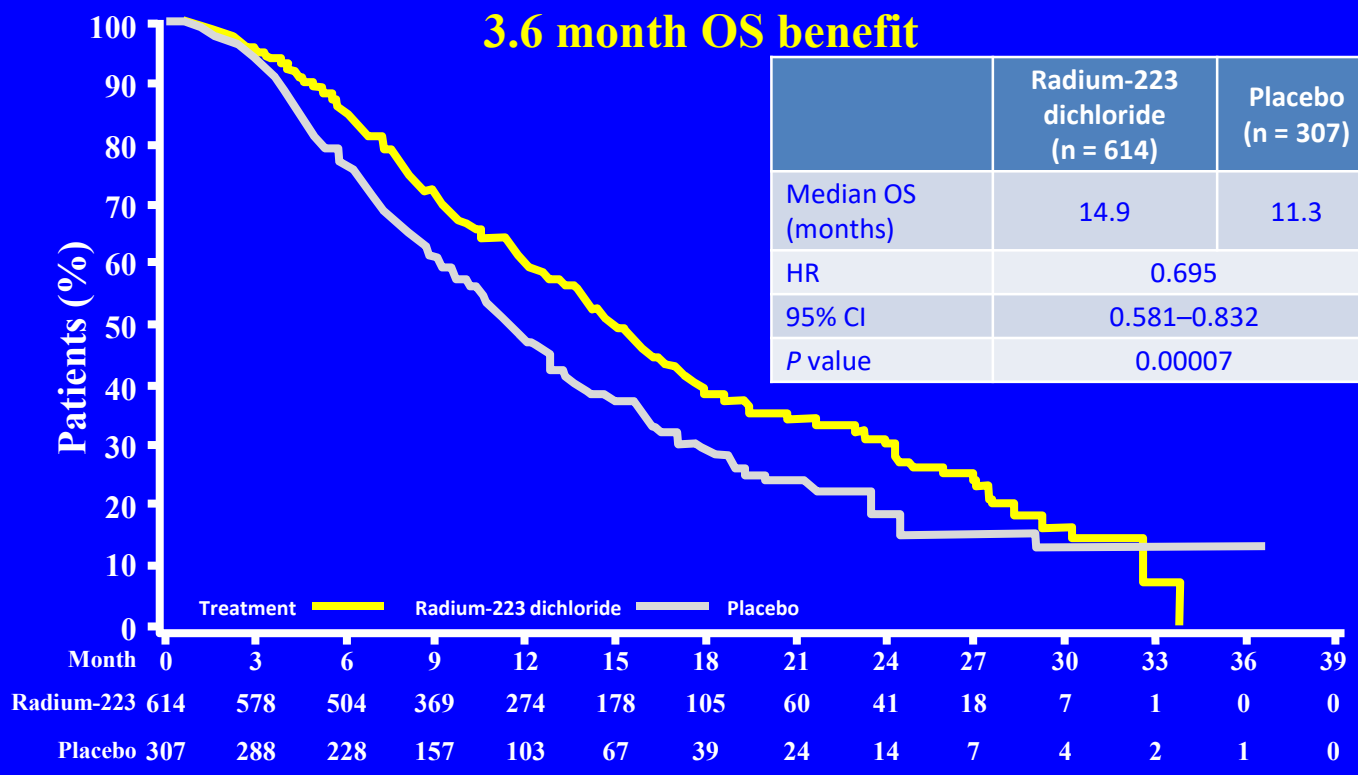
Parameter	Radium-223 dichloride (n = 614)	Placebo (n = 307)
Mean age, y	70.2	70.8
Caucasian, n (%)	575 (94)	290 (95)
Baseline ECOG score, n (%) ≤1 2	 536 (87) 76 (12)	 265 (86) 40 (13)
Extent of disease, n (%) <6 metastases 6–20 metastases >20 metastases/superscan	 100 (16) 262 (43) 249 (41)	 38 (12) 147 (48) 121 (40)
WHO ladder, cancer pain index ≥2, n (%)	345 (56)	168 (55)

ITT group (n = 921)

WHO pain relief ladder:
1 – Non-opioid analgesic ± adjuvant
2 – Opioid for mild to moderate pain ± non-opioid analgesic ± adjuvant
3 – Opioid for moderate to severe pain ± non-opioid analgesic ± adjuvant
Patients may have also received external-beam radiation therapy for pain

Reference: Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

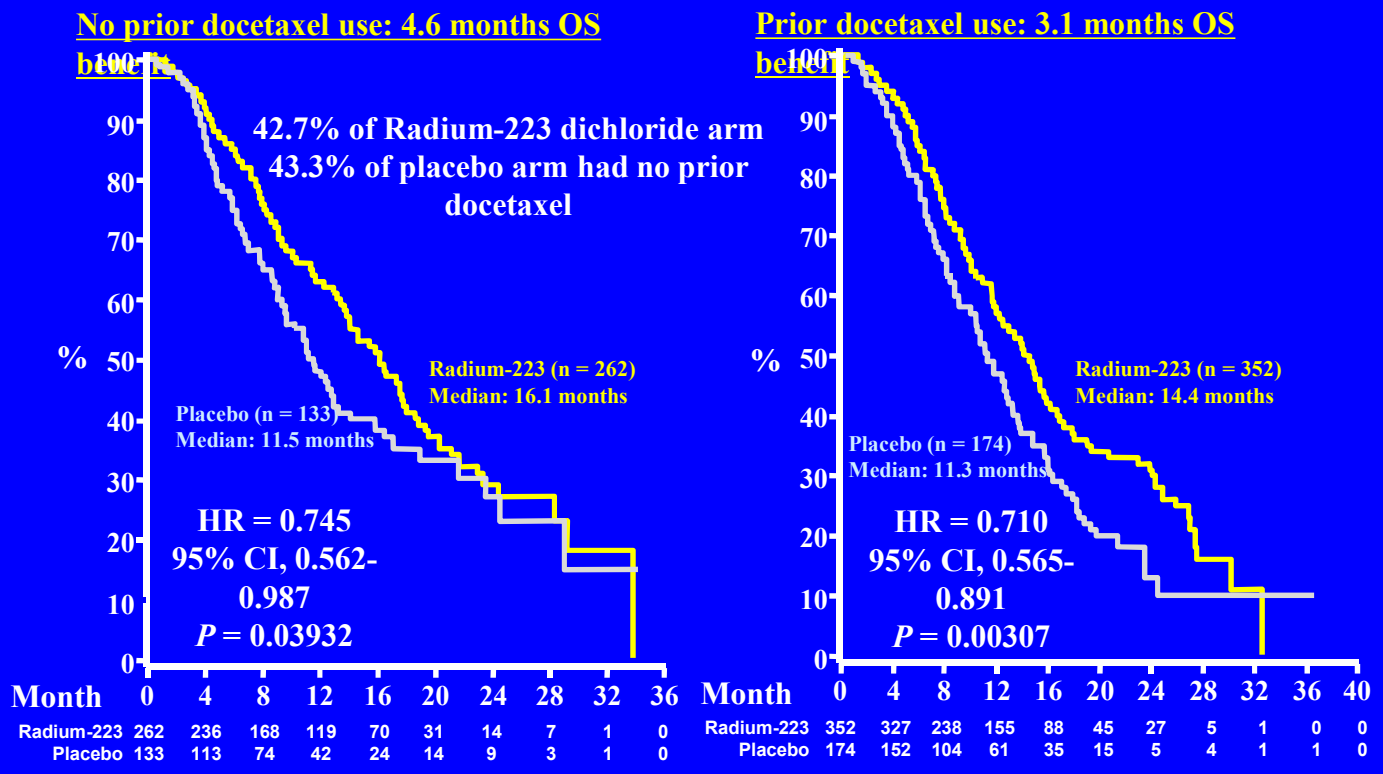
ALSYMPCA Updated Analysis: Overall Survival



	Radium-223 dichloride (n = 614)	Placebo (n = 307)
Median OS (months)	14.9	11.3
HR	0.695	
95% CI	0.581–0.832	
P value	0.00007	

Reference: Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

ALSYMPCA : Overall Survival Stratified by Prior Docetaxel Use



Reference: Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

Conclusions and Clinical Implications

- All patients with CRPC should be evaluated for DNA repair mutations and MSI
- Provenge should be used early in the course of CRPC
- Cabazitaxel improves rPFS and OS when compared to alternative NGAA in CRPC
- Olaparib and Rucaparib are approved for patients with CRPC