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Pulse Points in Prostate Cancer:
Embracing Advances with PARPi Combinations

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Disclosure of Conflicts of Interest

Johann de Bono, MB, ChB FRCP, MSc, PhD, FMedSci reported a financial interest/relationship or affiliation in the form of *Advisory board, Served as a speaker,* and *Contracted research*: AstraZeneca Pharmaceuticals LP; Astellas Pharma US, Inc; Bayer HealthCare, Inc; Bioxcel Therapeutics; Boehringer Ingelheiml Cellcentric; Daiichi Sankyo Company, Ltd; Eisai Inc; Genentech/Roche; Genmab; GlaxoSmithKline; Janssen Oncology; Merck Serano; Merck Sharp & Dohme; Menarini/Silicon Biosystems; Orion; Pfizer, Inc; Qiagen; Sanofi-aventis; Sierra Oncology; Taiho Pharmaceutical Co, Ltd; Terumo; and Vertex Pharmaceuticals. *Research funding to IRC*: AstraZeneca Pharmaceuticals LP; Astellas Pharma US, Inc; Bayer HealthCare, Inc; Cellcentric; Daiichi Sankyo Co, Ltd; Genentech, Inc; Genmab; GlaxoSmithKline; Janssen Oncology; Merck Serano; Merck Sharp & Dohme; Orion; Sanofi-aventis; Sierra Oncology; Taiho Pharmaceutical Co, Ltd; Pfizer, Inc; and Vertex Pharmaceuticals.

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Learning Objectives

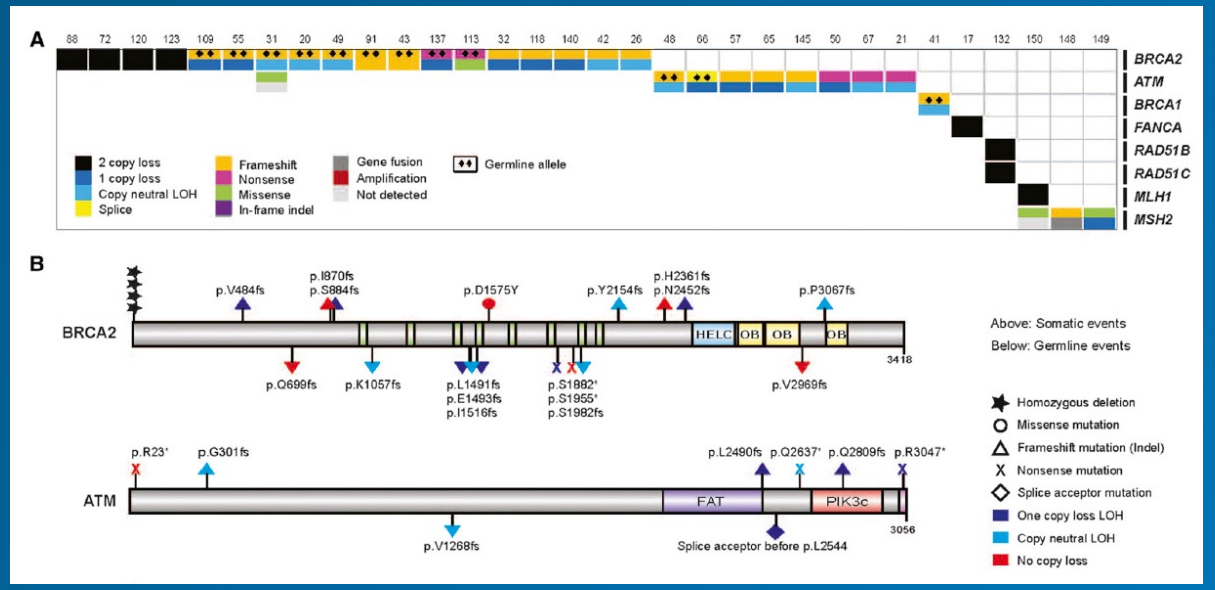
Upon completion of this activity, participants should be better able to:

- Describe the significance of testing for DNA damage repair (DDR) pathway mutations in mCRPC to guide treatment decisions
- Discuss the rationale for combining PARP inhibition with androgen pathway inhibition for the treatment of mCRPC
- Evaluate recent clinical efficacy data and ongoing clinical trials for PARP inhibitor combinations in mCRPC

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer

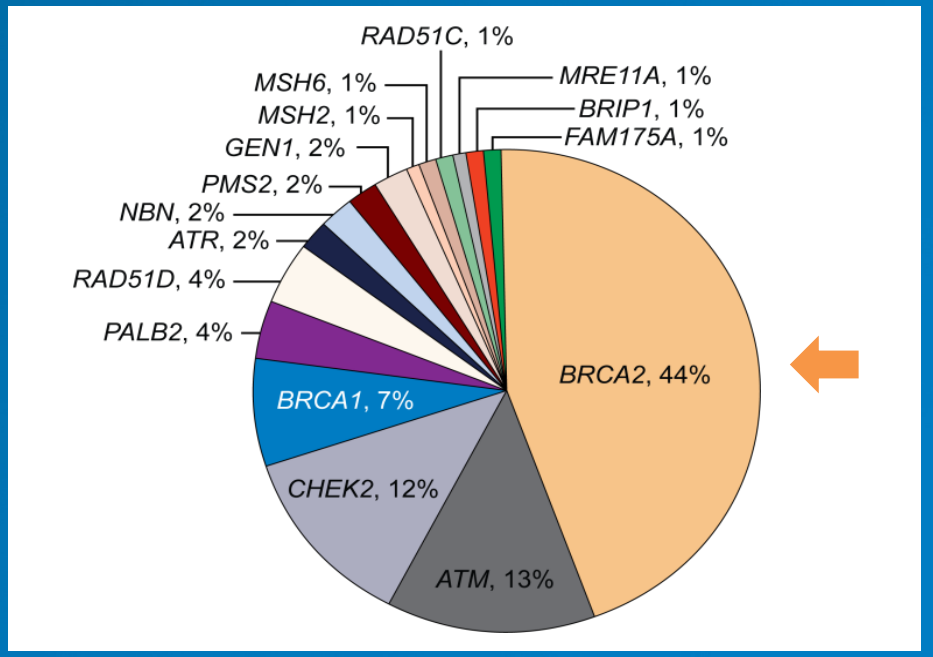
Somatic

- **~23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases with disease progression**



Germline

- **~12%** of men with metastatic prostate cancer have a germline DNA repair defect
- Age and family history do not affect mutation frequency



Robinson et al. *Cell.* 2015;161:1215-1228; adapted from Pritchard et al. *N Engl J Med.* 2016;375:443-453.

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NCCN (V 1.2021) Guidelines for Genetic Testing

Germline Testing	Somatic Tumor Testing

• Germline genetic testing is recommended for patients with prostate cancer and any of the following:
  • High risk, very high risk, regional, or metastatic prostate cancer
  • Ashkenazi Jewish ancestry
  • Family history of high-risk germline mutations (eg, *BRCA1/2,* Lynch syndrome mutation)
  • A positive family history of cancer
	• Recommend evaluating tumor for alterations in homologous recombination DNA repair genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,* and *CDK12,* in patients with metastatic prostate cancer
	• Can be considered in men with regional prostate cancer
	• Testing for MSI-H or dMMR is recommended for patients with metastatic prostate cancer and can be considered for patients with regional or castration-naive

CRPC, castration-resistant prostate cancer; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high.

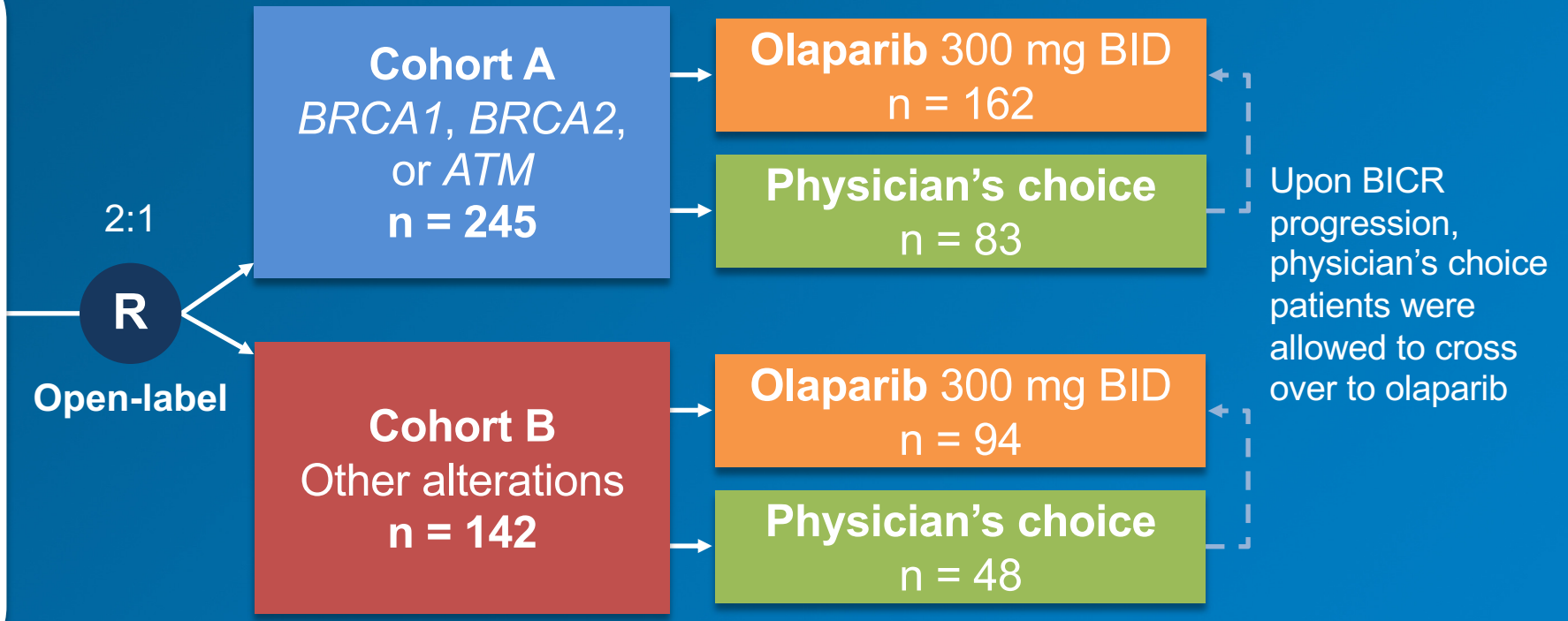
PROfound: Study Design

Key Eligibility Criteria

- mCRPC with disease progression on prior NHA (eg, abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification Factors

- Previous taxane
- Measureable disease



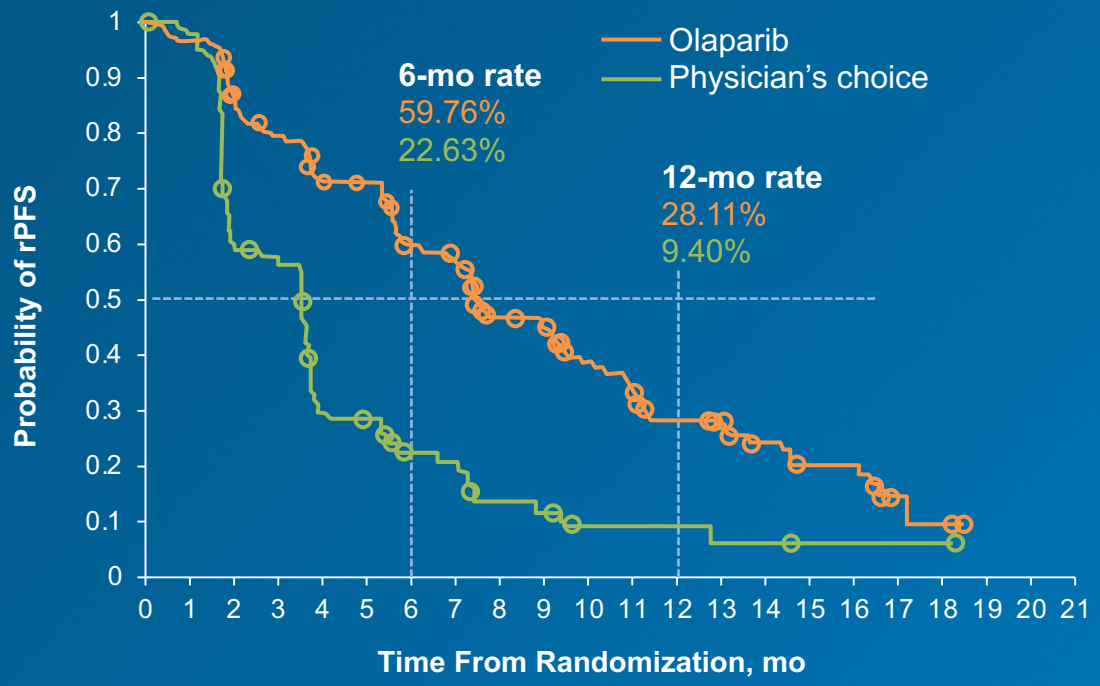
- Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

BICR, blinded independent committee review; BID, twice daily; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; ORR, objective response rate; OS, overall survival; R, randomized; rPFS, radiographic progression-free survival.

de Bono et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound Primary Endpoint: rPFS (Cohort A)

rPFS by BICR in Patients With Alterations in *BRCA1*, *BRCA2*, or *ARM* (Cohort A)



No. at Risk

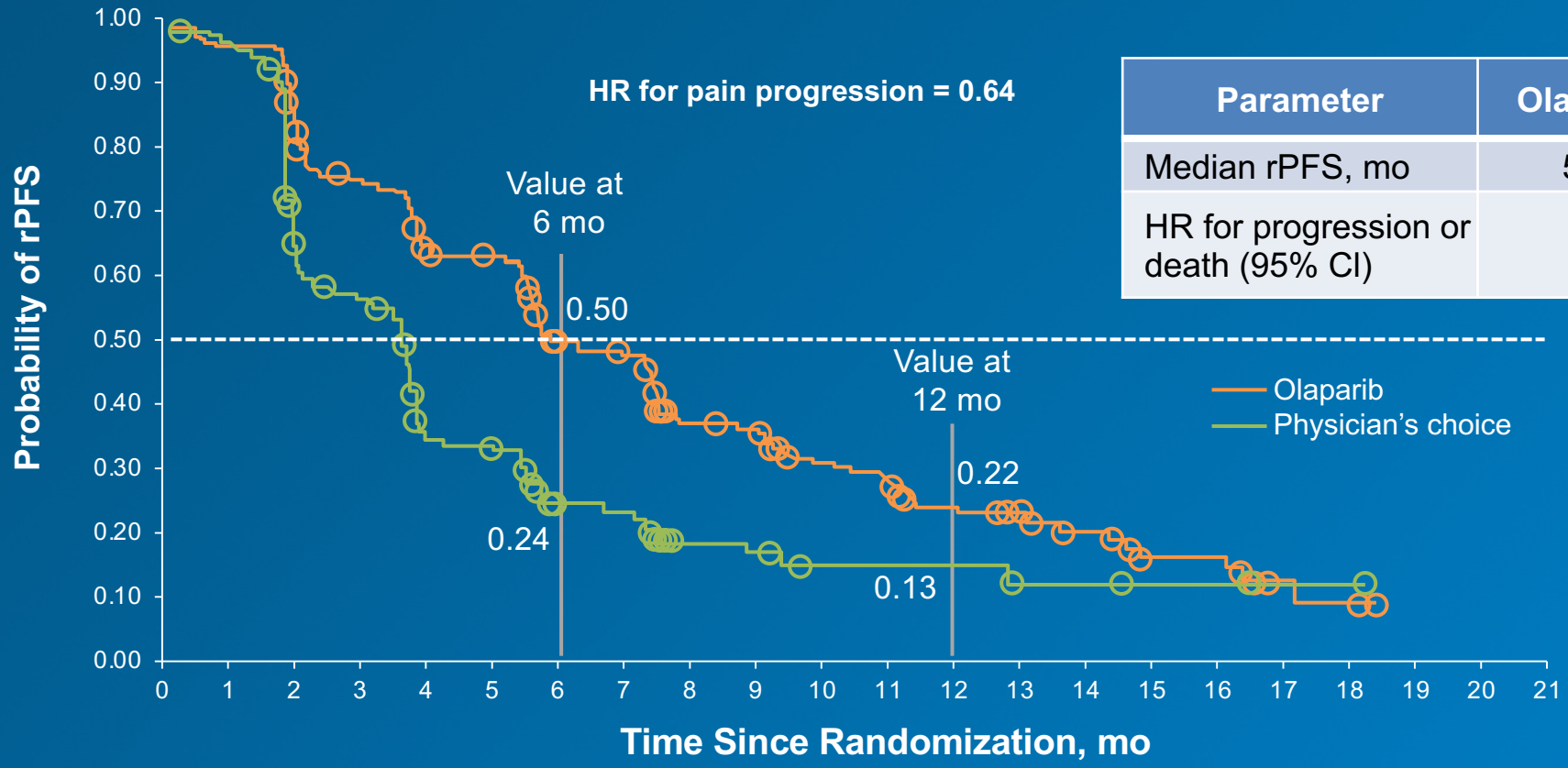
Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

Parameter	Olaparib (N = 162)	Physician's Choice (N = 83)
Events, n (%)	106 (65.4)	68 (81.9)
Median rPFS, mo	7.4	3.6
HR (95% CI)	0.34 (0.25-0.47) *P* < .001	

BICR, blinded independent committee review; rPFS, radiographic progression-free survival.

de Bono et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: rPFS Overall Population (Cohorts A+B)



Parameter	Olaparib	Physician's Choice
Median rPFS, mo	5.8	3.5
HR for progression or death (95% CI)	0.49 (0.38-0.63) $P < .001$	

No. at Risk

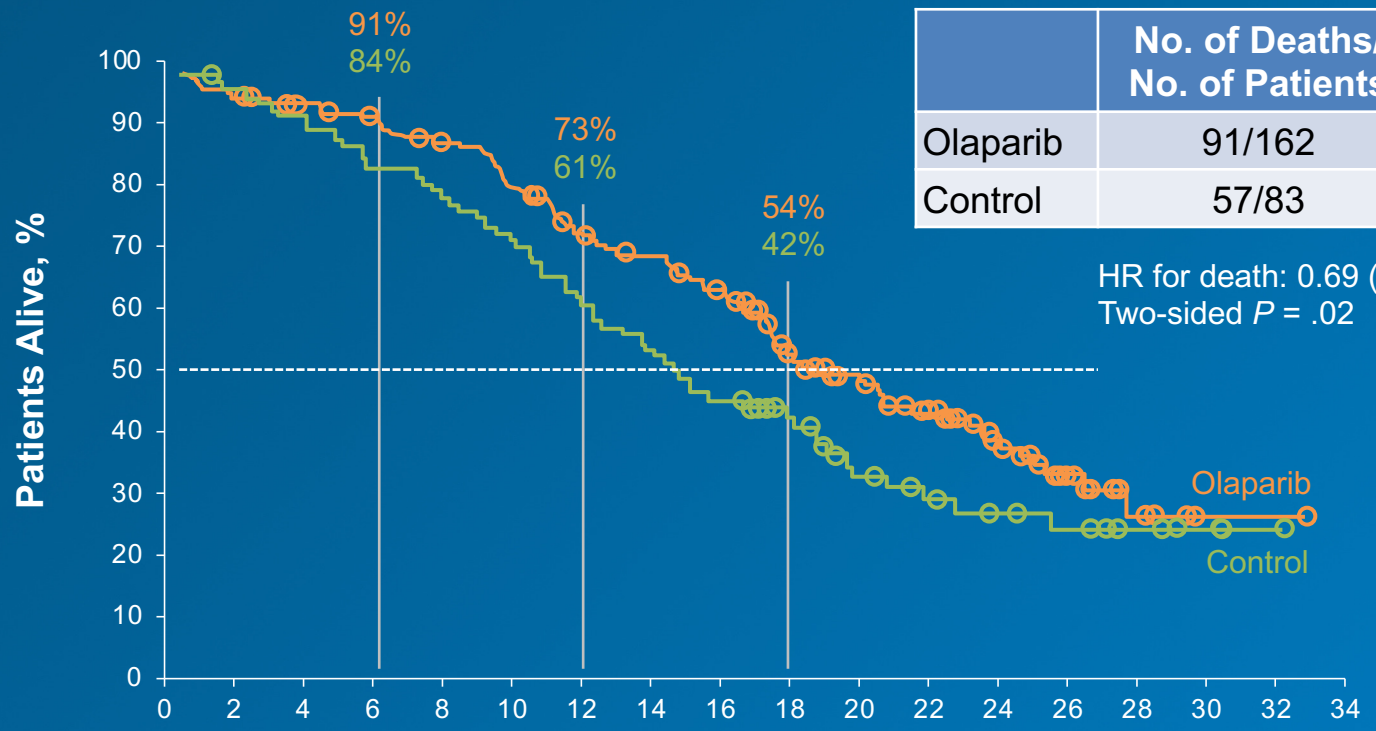
Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

rPFS, radiographic progression-free survival.

de Bono et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: Final Overall Survival

OS in Cohort A[a]



	No. of Deaths/ No. of Patients	Median OS (95% CI), mo
Olaparib	91/162	19.1 (17.4-23.4)
Control	57/83	14.7 (11.9-18.8)

HR for death: 0.69 (95% CI, 0.50-0.97)
Two-sided *P* = .02

No. at Risk																	
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

[a] Median follow-up duration was 21.9 months for the olaparib arm and 21.0 months for the control arm.
OS, overall survival.
Hussain et al. *N Engl J Med*. 2020;383:2345-2357.

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PROfound Safety

Adverse Event	Olaparib (N = 256)		Control (N = 130)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Any	244 (95)	130 (51)	114 (88)	49 (38)
Anemia	119 (46)	55 (21)	20 (15)	7 (5)
Nausea	106 (41)	3 (1)	25 (19)	0
Fatigue or asthenia	105 (41)	7 (3)	42 (32)	7 (5)
Decreased appetite	77 (30)	3 (1)	23 (18)	1 (<1)
Diarrhea	54 (21)	2 (<1)	9 (7)	0
Vomiting	47 (18)	6 (2)	16 (12)	1 (<1)
Constipation	45 (18)	0	19 (15)	0
Back pain	35 (14)	2 (<1)	15 (12)	2 (2)
Peripheral edema	32 (12)	0	10 (8)	0
Cough	28 (11)	0	3 (2)	0
Dyspnea	26 (10)	6 (2)	4 (3)	0
Arthralgia	24 (9)	1 (<1)	14 (11)	0
Urinary tract infection	18 (7)	4 (2)	15 (12)	5 (4)
Interruption of intervention because of adverse event	115 (45)	N/A	24 (18)	N/A
Dose reduction because of adverse event	57 (22)	N/A	5 (4)	N/A
Discontinuation of intervention because of adverse event	46 (18)	N/A	11 (8)	N/A
Death because of adverse event	10 (4)	N/A	5 (4)	N/A

FDA Approval: Olaparib for mCRPC

In May 2020, based on data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic HRR gene-mutated mCRPC, who have experienced disease progression following prior treatment with enzalutamide or abiraterone

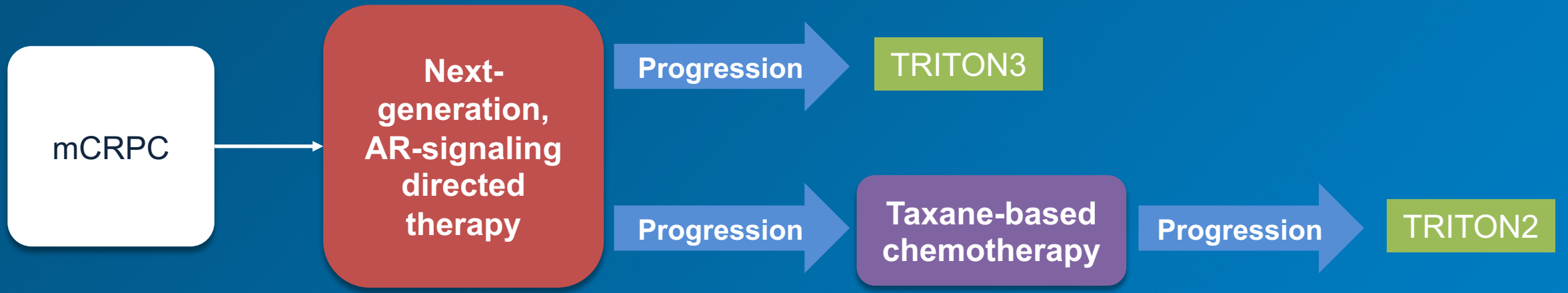
BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.
FDA, US Food & Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer.
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

European Commission Approval: Olaparib for mCRPC

In November 2020, based on data from the PROfound study, the European Commission approved olaparib for the treatment of adult patients with mCRPC and *BRCA1/2* mutations (germline and/or somatic) who have experienced disease progression following prior therapy that included a new hormonal agent

mCRPC, metastatic castration-resistant prostate cancer.
https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/lynparza-approved-in-the-eu-for-prostate-cancer.html

Rucaparib TRITON2 and TRITON3: Study Design



HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*)

AR, androgen receptor; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer.
Abida et al. *Ann Oncol*. 2018:29:viii271-viii302.

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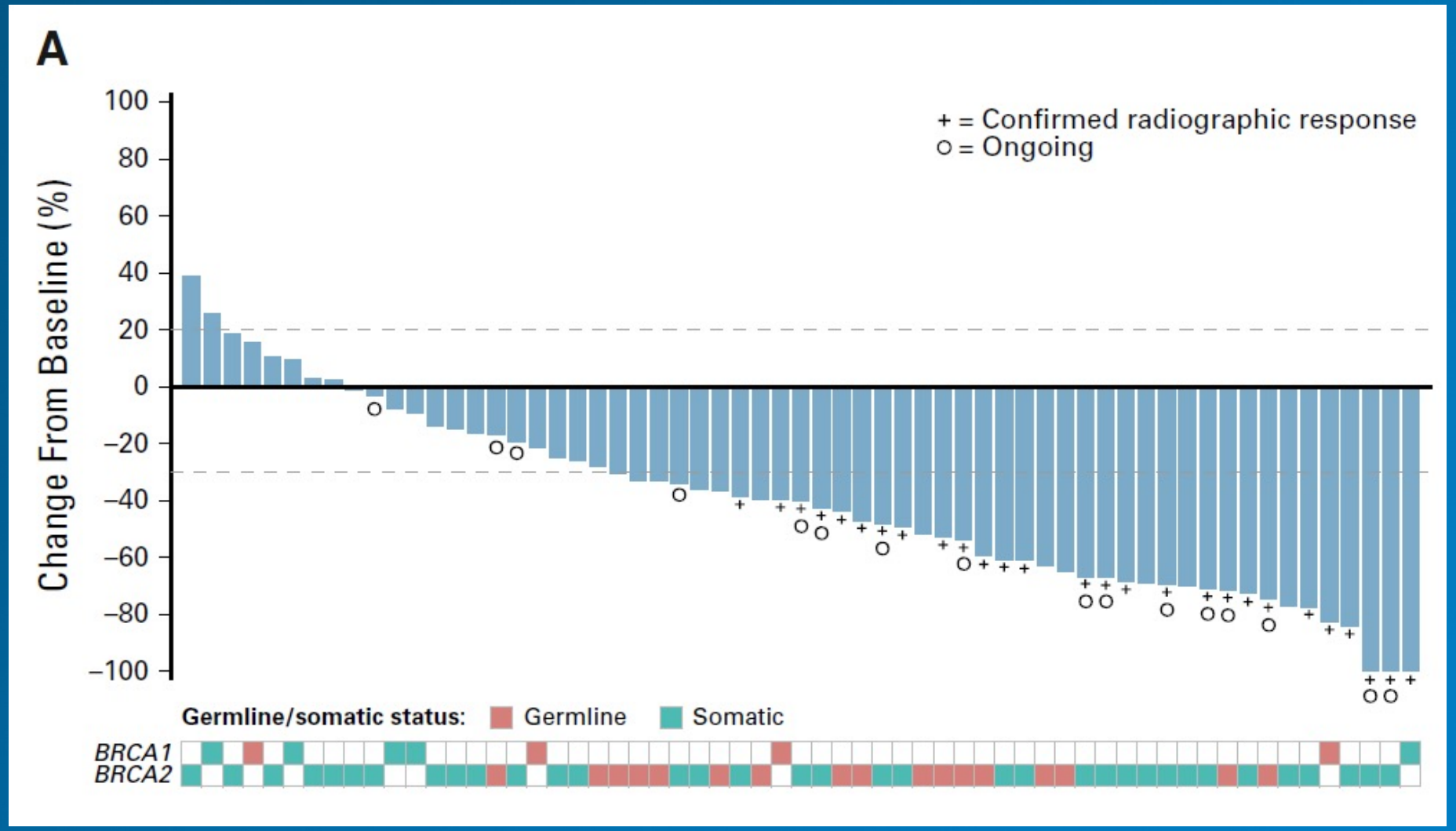
TRITON2: Rate of Response

Response	Investigator-Evaluable Population (N = 65)	IRR-Evaluable Population (N = 62)
Confirmed ORR, n (%)[a]	33 (50.8) 95% CI 38.1-63.4	27 (43.5) 95% CI 31.0-56.7
Complete response	4 (6.2)	7 (11.3)
Partial response	29 (44.6)	20 (32.3)
Stable disease	25 (38.5)	28 (45.2)
Progressive disease	6 (9.2)	6 (9.7)
Not evaluable	1 (1.5)	1 (1.6)
	Overall Efficacy Population (N = 115)	
Confirmed PSA response rate, n (%)	63 (54.8) 95% CI 45.2-64.1	

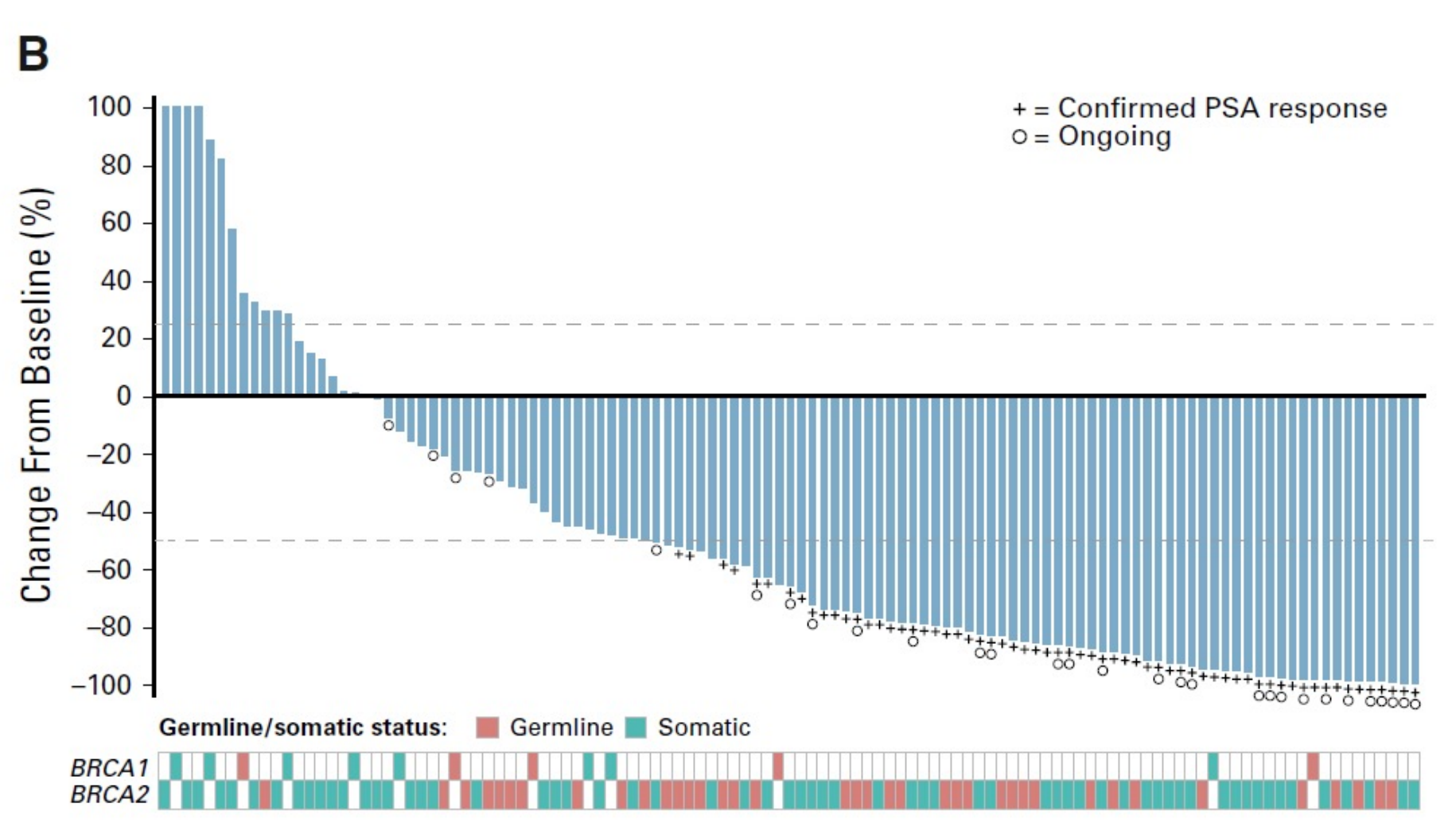
Note. Data presented as No. (%) unless otherwise indicated. Visit cutoff date: December 23, 2019.
IRR, independent radiology review; objective response rate; PSA, prostate-specific antigen.
[a]Per modified RECIST/Prostate Cancer Clinical Trials Working Group 3 criteria.
Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

TRITON2: Objective Responses



Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

TRITON2: PSA Responses



PSA, prostate specific antigen.

Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

TRITON2: Response by Non-*BRCA* DDR Gene Alterations

	By DDR Gene Group			
	ATM (n = 49)	CDK12 (n = 15)	CHEK2 (n = 12)	Other (n = 14)
Confirmed investigator-assessed objective response, n/N (%) CR PR SD PD NE	2/19 (10.5) 95% CI 1.3-33.1 0/19 (0.0) 2/19 (10.5) 9/19 (47.4) 7/19 (36.8) 1/19 (5.3)	0/10 (0) 95% CI 0.0-30.8 0/10 (0) 0/10 (0) 6/10 (60.0) 3/10 (30.0) 1/10 (10.0)	1/9 (11.1) 95% CI 0.3-48.2 0/9 (0) 1/9 (11.1) 6.9 (66.7) 2/9 (22.2) 0/9 (0)	4/14 (28.6) 95% CI 8.4-58.1 1/14 (7.1) 3/14 (21.4) 8/14 (57.1) 1/14 (7.1) 1/14 (7.1)
6-mo clinical benefit rate, n/N (%)	12/42 (28.6) 95% CI 15.7-44.6	3/15 (20.0) 95% CI 4.3-48.1	3/8 (37.5) 95% CI 8.5-75.5	6/11 (54.5) 95% CI 23.4-83.3
12-mo clinical benefit rate, n/N (%)	3/18 (16.7) 95% CI 3.6-41.4	1/14 (7.1) 95% CI 0.2-33.9	0/5 (0) 95% CI 0.0-52.2	3/8 (37.5) 95% CI 8.5-75.5
Confirmed PSA response, n/N (%)	2/49 (4.1) 95% CI 0.5-14.0	1/15 (6.7) 95% CI 0.2-31.9	2/12 (16.7) 95% CI 2.1-48.4	5/14 (35.7) 95% CI 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)	11.0 (3.0-NR)

CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; PSA, prostate specific antigen; SD, stable disease.

Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

TRITON2: Safety

Most Commonly Reported TEAEs (N = 115)

Individual TEAE (preferred terms) Occurring in ≥15% of Patients	Any Grade, n (%)	Grade ≥3, n (%)
Asthenia / fatigue	71 (61.7)	10 (8.7)
Nausea	60 (52.2)	3 (2.6)
Anemia / decreased hemoglobin	50 (43.5)	29 (25.2)
ALT / AST increased	38 (33.0)	6 (5.2)
Decreased appetite	32 (27.8)	2 (1.7)
Constipation	31 (27.0)	1 (0.9)
Thrombocytopenia / decreased platelets	29 (25.2)	11 (9.6)
Vomiting	25 (21.7)	1 (0.9)
Diarrhea	23 (20.0)	0
Dizziness	21 (18.3)	0
Blood creatinine increased	18 (15.7)	1 (0.9)

Note. Data presented as No. (%). Visit cutoff date: September 13, 2019.
TEAEs were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03.
There were no TEAEs for myelodysplastic syndrome or acute myeloid leukemia reported.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

FDA Approval: Rucaparib for mCRPC

In May 2020, based on data from the TRITON2 study, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor–directed therapy and a taxane-based chemotherapy.

The TRITON3 study is underway and recruiting patients with mCRPC and homologous recombination gene deficiency.

mCRPC, metastatic castration-resistant prostate cancer.
https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.
https://clinicaltrials.gov/ct2/show/NCT02975934.

Other PARP Inhibitors Undergoing Evaluation in mCRPC

Niraparib

- Phase 2 GALAHAD
  - Niraparib in previously treated mCRPC patients with biallelic DDR mutations established from an 8-gene ctDNA assay
    - *Niraparib demonstrates clinical activity with durable responses, particularly in biallelic* BRCA1/2 *mutation carriers (ORR 41%)*[1]
- Phase 3 MAGNITUDE
  - Niraparib + abiraterone/prednisone in frontline mCRPC
    - *Trial in progress*[3]

Talazoparib

- Phase 2 TALAPRO-1
  - Talazoparib as monotherapy in men with mCRPC and DDR mutations
    - *Antitumor activity in patients who previously received taxane therapy and NHT, especially in patients with a* BRCA1/2 *alteration (ORR 41.5%)*[2]
- Phase 3 TALAPRO-2
  - Talazoparib + enzalutamide
    - *This combination showed promising signs of efficacy reflected by the reduction in PSA levels from baseline*[4]

DDR, DNA damage repair; mCRPC, metastatic castration-resistant prostate cancer; NHT, nonhormonal therapy; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; PSA, prostate-specific antigen.

1. Smith et al. *Ann Oncol.* 2019;30(suppl 5):v884-v885. 2. de Bono et al. *J Clin Oncol*. 2020;38:5566-5566.
3. Chi et al. *J Clin Oncol*. 2020;38:TPS5588. 4. Agarwal et al. *J Clin Oncol*. 2020;37(15):5076-5076.

ARSI/PARPi Combinations Under Evaluation

- Olaparib + abiraterone: PROpel, BRCAAway
- Talazoparib + enzalutamide: TALAPRO-2
- Rucaparib + enzalutamide: TRITON3, CASPAR
- Niraparib + abiraterone: MAGNITUDE, QUEST
- Veliparib + abiraterone

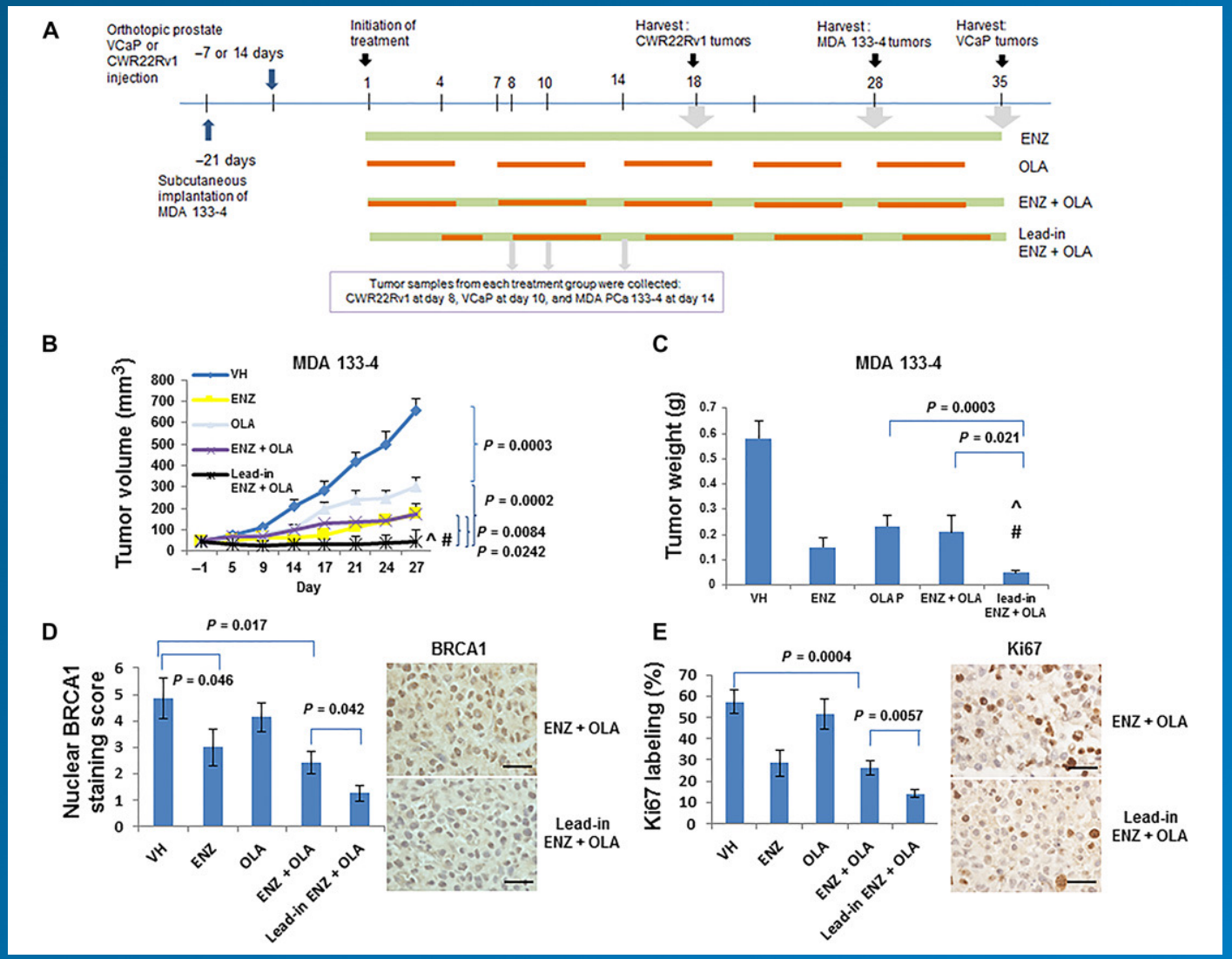
ARSI, androgen receptor signaling inhibitor; PARPi, poly (ADP-ribose) polymerase inhibitor.

ARSIs With PARPi

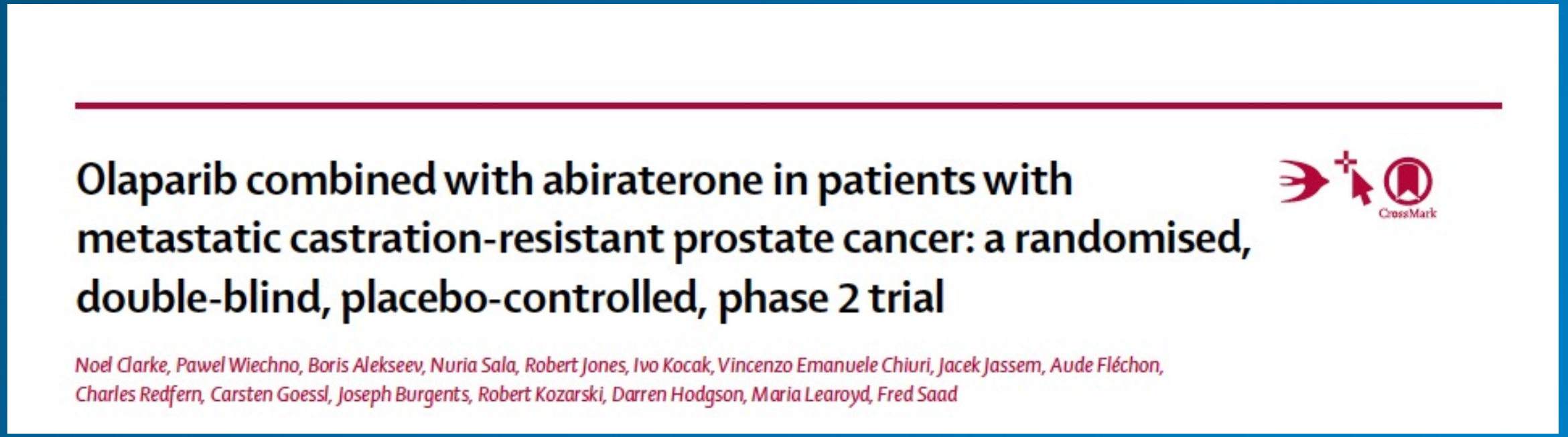
- Pragmatic combination
  - Both drugs utilized in the same therapeutic disease space
  - Likely tolerability of these combinations
- Evidence that PARPi works in DNA repair defective cancers (eg *BRCA1/2, PALB2, ATM* defective tumors) that can also be sensitive to AR targeted drugs
- Some preclinical evidence that PARP inhibition can block androgen receptor transcriptional activity
- Preliminary data suggesting that AR blockade may induce 'BRCAness'
- Hypothesized clearance of endocrine resistant subclones with PARP inhibition due to synthetic lethal interactions with defective DNA repair in resistant subclones

AR, androgen receptor; ARSI, androgen receptor signaling inhibitors; PARPi, poly (ADP-ribose) polymerase inhibitor.

In Vivo Combination Data in MDA PCa 133-4 Model



Olaparib + Abiraterone: Randomized Phase 2



Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial

Noel Clarke, Pawel Wiechno, Boris Alekseev, Nuria Sala, Robert Jones, Ivo Kocak, Vincenzo Emanuele Chiuri, Jacek Jassem, Aude Fléchon, Charles Redfern, Carsten Goessl, Joseph Burgents, Robert Kozarski, Darren Hodgson, Maria Learoyd, Fred Saad

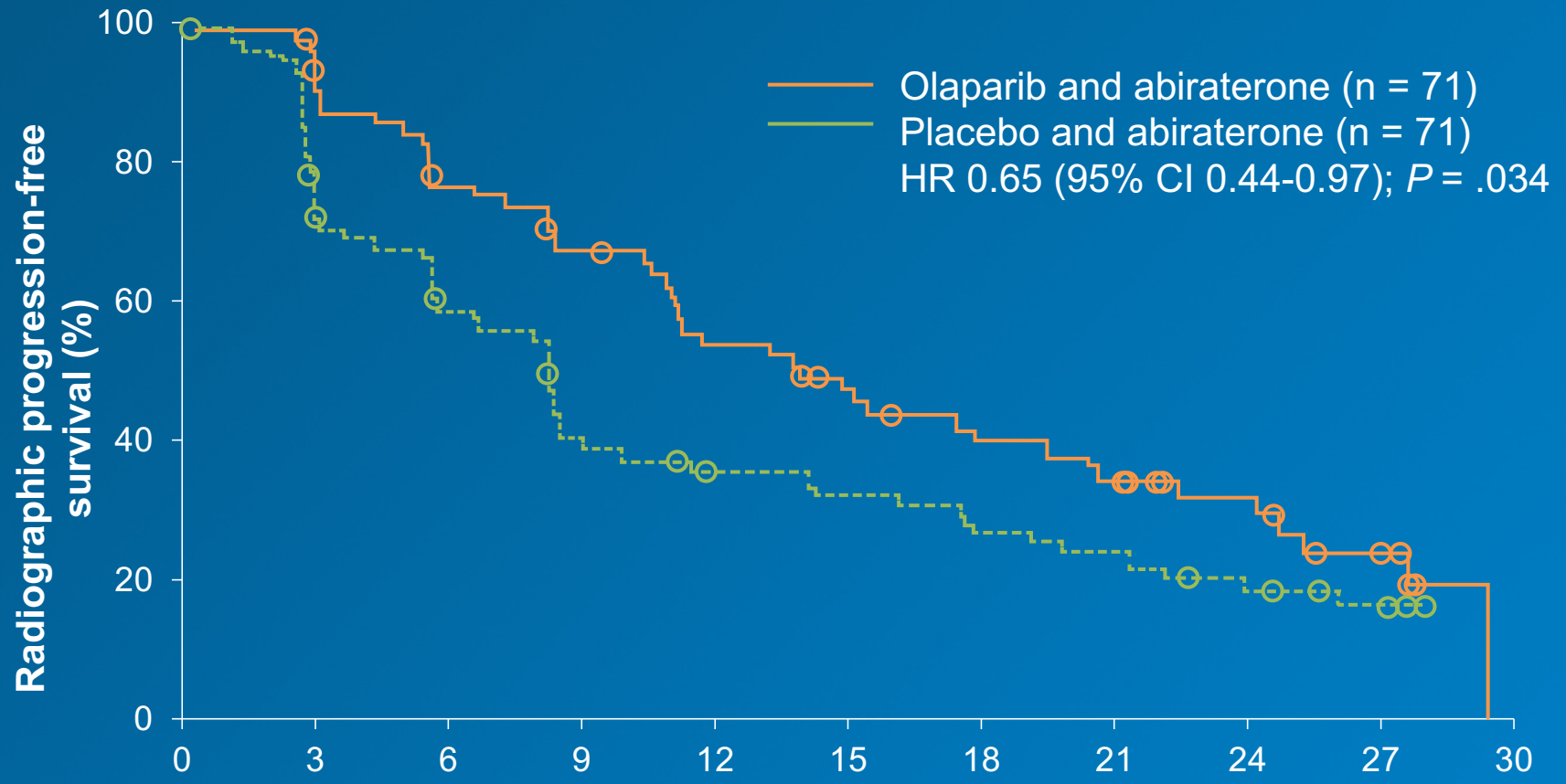
We have most data with this combination

Olaparib + Abiraterone: Randomized Phase 2

- Double-blind, randomized, placebo-controlled, phase 2
- 41 centers; 11 countries; North America and Europe
- Abiraterone 1,000 mg with olaparib 300 mg bid vs abiraterone and placebo
- Primary endpoint: Investigator assessed rPFS (RECIST)
- 142 patients randomly assigned; 71 to each arm
- No molecular patient pre-selection

bid, two times a day; rPFS, radiologic progression-free survival.
Clarke et al. *Lancet Oncol*. 2018;19:975-986.

Olaparib + Abiraterone: Radiographic PFS



No. at Risk (number censored)											
Olaparib and abiraterone	70 (0)	58 (5)	50 (6)	42 (8)	33 (9)	26 (12)	21 (13)	18 (13)	13 (17)	8 (19)	0 (25)
Placebo and abiraterone	70 (0)	48 (3)	39 (4)	25 (5)	21 (7)	19 (7)	16 (7)	14 (7)	10 (8)	7 (10)	0 (17)

PFS, progression-free survival.
Adapted from Clarke et al. *Lancet Oncol*. 2018;19:975-986.

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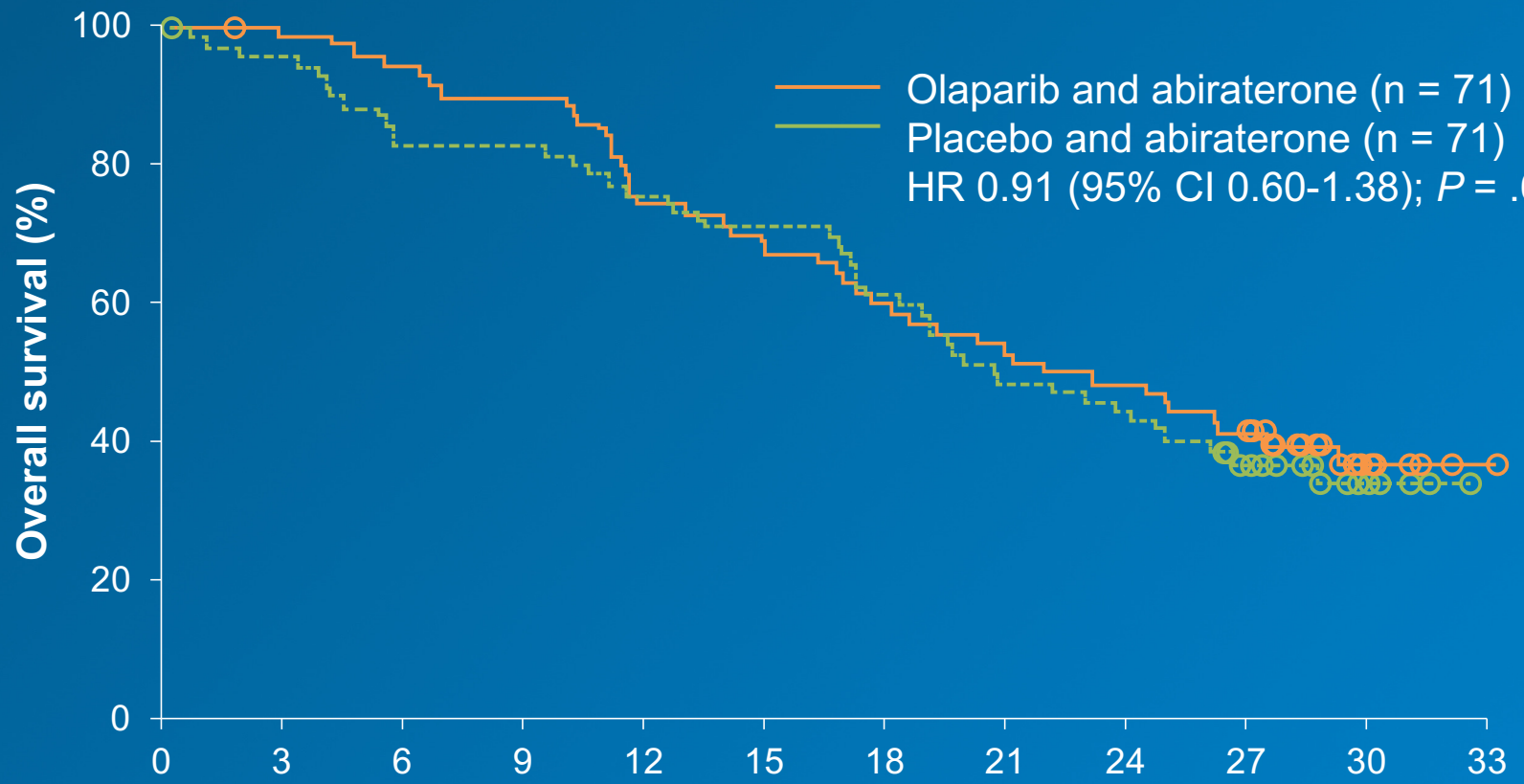
Olaparib + Abiraterone: No Overall Survival Benefit Demonstrated



No. at Risk (number censored)												
Olaparib and abiraterone	71 (0)	69 (1)	66 (1)	63 (1)	52 (1)	49 (1)	42 (1)	38 (1)	34 (1)	29 (1)	9 (19)	1 (27)
Placebo and abiraterone	71 (0)	67 (1)	58 (1)	58 (1)	53 (1)	50 (1)	43 (1)	34 (1)	31 (1)	22 (5)	6 (20)	0 (26)

Adapted from Clarke et al. *Lancet Oncol*. 2018;19:975-986.

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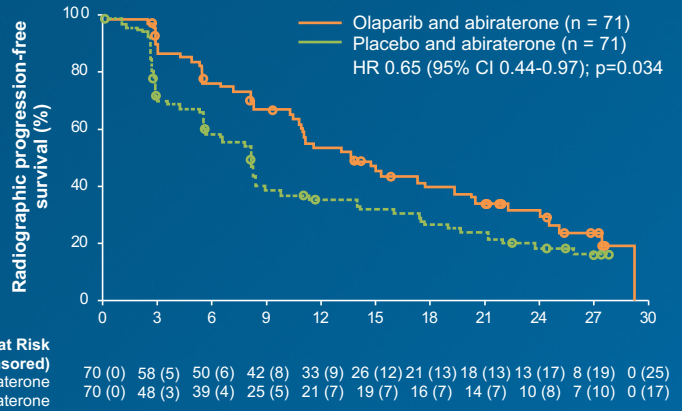
Olaparib + Abiraterone: Adverse Events

Adverse Event	Olaparib and abiraterone (N = 71)				Placebo and abiraterone (N = 71)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
All	28 (39%)	29 (41%)	5 (7%)	4 (6%)	37 (52%)	19 (27%)	0	1 (1%)
Nausea	26 (37%)	1 (1%)	0	0	13 (18%)	2 (3%)	0	0
Constipation	18 (25%)	0	0	0	8 (11%)	0	0	0
Back pain	17 (24%)	1 (1%)	0	0	13 (18%)	1 (1%)	0	0
Fatigue	14 (20%)	1 (1%)	0	0	7 (10%)	2 (3%)	0	0
Asthenia	13 (18%)	3 (4%)	0	0	10 (14%)	0	0	0
Vomiting	13 (18%)	2 (3%)	0	0	8 (11%)	1 (1%)	0	0
Peripheral edema	13 (18%)	0	0	0	8 (11%)	0	0	0
Decreased appetite	12 (17%)	0	0	0	4 (6%)	1 (1%)	0	0
Diarrhea	11 (15%)	0	0	0	7 (10%)	1 (1%)	0	0
Dyspnea	10 (14%)	0	0	0	4 (6%)	1 (1%)	0	0
Pyrexia	10 (14%)	0	0	0	1 (1%)	0	0	0
Cough	9 (13%)	2 (3%)	0	0	2 (3%)	0	0	0
Bone pain	9 (13%)	1 (1%)	0	0	7 (10%)	1 (1%)	0	0
Urinary tract infection	8 (11%)	1 (1%)	0	0	1 (1%)	2 (3%)		
Arthralgia	8 (11%)	0	0	0	3 (4%)	1 (1%)	0	0
Viral upper respiratory tract infection	8 (11%)	0	0	0	3 (4%)	0	0	0
Abdominal pain	8 (11%)	0	0	0	1 (1%)	0	0	0
Anemia	7 (10%)	14 (20%)	1 (1%)	0	1 (1%)	0	0	0
Neutropenia	7 (10%)	1 (1%)	0	0	0	0	0	0
Hypokalemia	4 (6%)	2 (3%)	0	0	4 (6%)	0	0	0
Pneumonia	2 (3%)	2 (3%)	2 (3%)	0	0	3 (4%)	0	0
Musculoskeletal chest pain	1 (1%)	0	0	0	3 (4%)	2 (3%)	0	0
Myocardial infarction	0	4 (6%)	0	0	0	0	0	0

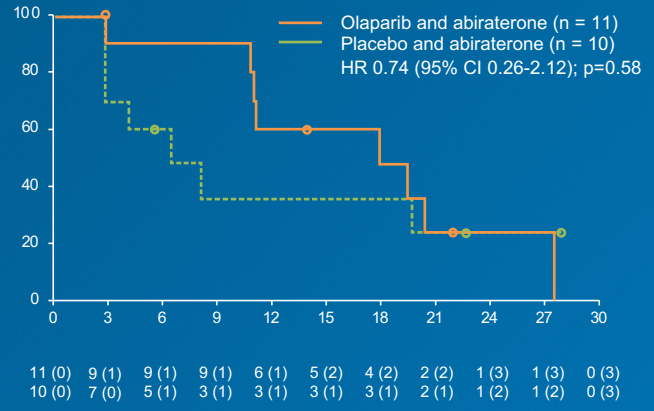
Data are n (%). The table shows grade 1-2 adverse events that occurred in 10% or more patients in either group and grade 3-5 events that occurred in 2% or more patients in either group.
Adapted from Clarke et al. *Lancet Oncol*. 2018;19:975-986.

Olaparib + Abiraterone: rPFS Major Caveats to Reported Sub-Group Analyses

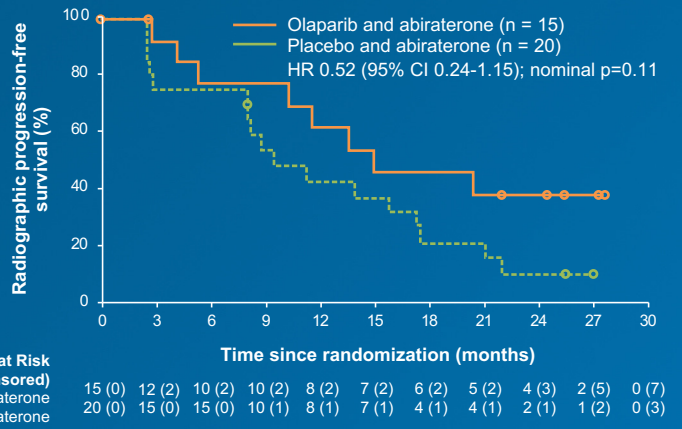
Intention-to-Treat



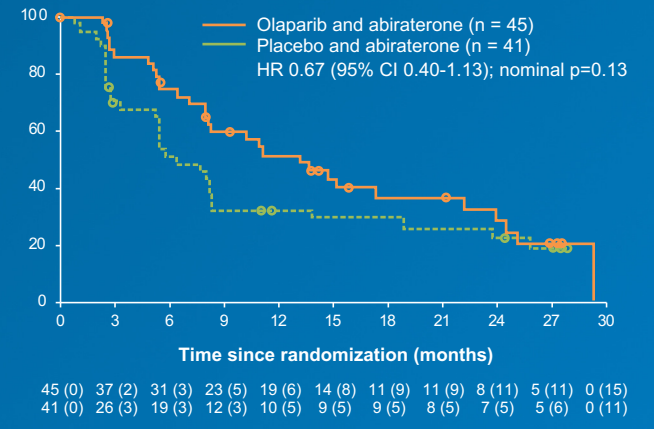
HHR Mutation-Positive



Wild-type



Partially Characterized HRR Status



Subgroup Analyses

- Multiple DNA repair genes ‘lumped’ incorrectly as HRR genes
- Very small numbers in subgroups
- Olaparib and abiraterone group:
  - 3 ATM
  - 2 BRCA2
  - 2 CDK12
  - 2 CHEK2
  - 1 BRIP1
  - 1 CHEK1

HRR, homologous recombination repair; rPFS, radiographic progression-free survival.
Adapted from Clarke et al. *Lancet Oncol*. 2018;19:975-986.

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Multiple Combo Registration Trials Ongoing But Many Major Questions Remain

- Can we justify treating tumors without DNA repair defects that sensitize to PARP inhibition?
- Should the lack of OS benefit in the olaparib/abiraterone randomized phase 2 trial raise concerns?
  - If the phase 3 trials improve rPFS but not OS, what does this prove?
- Is reported cardiac toxicity a real concern?
- Should trials compare combined versus serial treatment?

OS, overall survival; PARP, poly (ADP-ribose) polymerase; rPFS, radiologic progression-free survival.

PARP Inhibitor Combination Therapy Trials in mCRPC

Agent	Trial	Phase	Arms	Setting	Primary Endpoint(s)
Olaparib	PROpel (NCT03732820)	3	Olaparib + abiraterone vs placebo + abiraterone	Chemotherapy and new hormonal agent-naïve	rPFS
	KEYLYNK-010 (NCT03834519)	3	Olaparib + pembrolizumab vs abiraterone or enzalutamide	Prior treatment with 1 next-generation hormonal agent and chemotherapy; Unselected for HRR defects	OS rPFS
	BRCAAway (NCT03012321)	2	Olaparib vs abiraterone vs olaparib + abiraterone	DRD	Objective PFS
Rucaparib	TRITON3 (NCT02975934)	3	Rucaparib vs physician's choice (docetaxel, abiraterone, or enzalutamide)	Disease progression after 1 prior next-generation AR targeted tx; Deleterious mutation in a BRCA1/2 or ATM gene	rFPS
	CASPAR (NCT04455750)	3	Rucaparib + enzalutamide vs placebo + enzalutamide	First-line mCRPC	rPFS OS
Niraparib	MAGNITUDE (NCT03748641)	3	Niraparib + abiraterone + prednisone vs placebo + abiraterone + prednisone	First-line mCRPC Cohort 1: positive for DRD Cohort 2: not positive for DRD	rPFS
	QUEST (NCT03431350)	1/2	Niraparib + cetrelimab; Niraparib + abiraterone + prednisone	mCRPC	Recommended phase 2 dose
Talazoparib	TALAPRO-2 (NCT03395197)	3	Talazoparib + enzalutamide vs placebo + enzalutamide	First-line mCRPC; Unselected pts & pts harboring DDR deficiencies	rPFS
Veliparib	NCT01576172	2	Veliparib + abiraterone + prednisone vs abiraterone + prednisone	mCRPC	Confirmed PSA response rate

AR, androgen receptor; DDR, DNA damage repair; DRD, DNA repair gene defects; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; pts, patients; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; tx, treatment.

Case Study

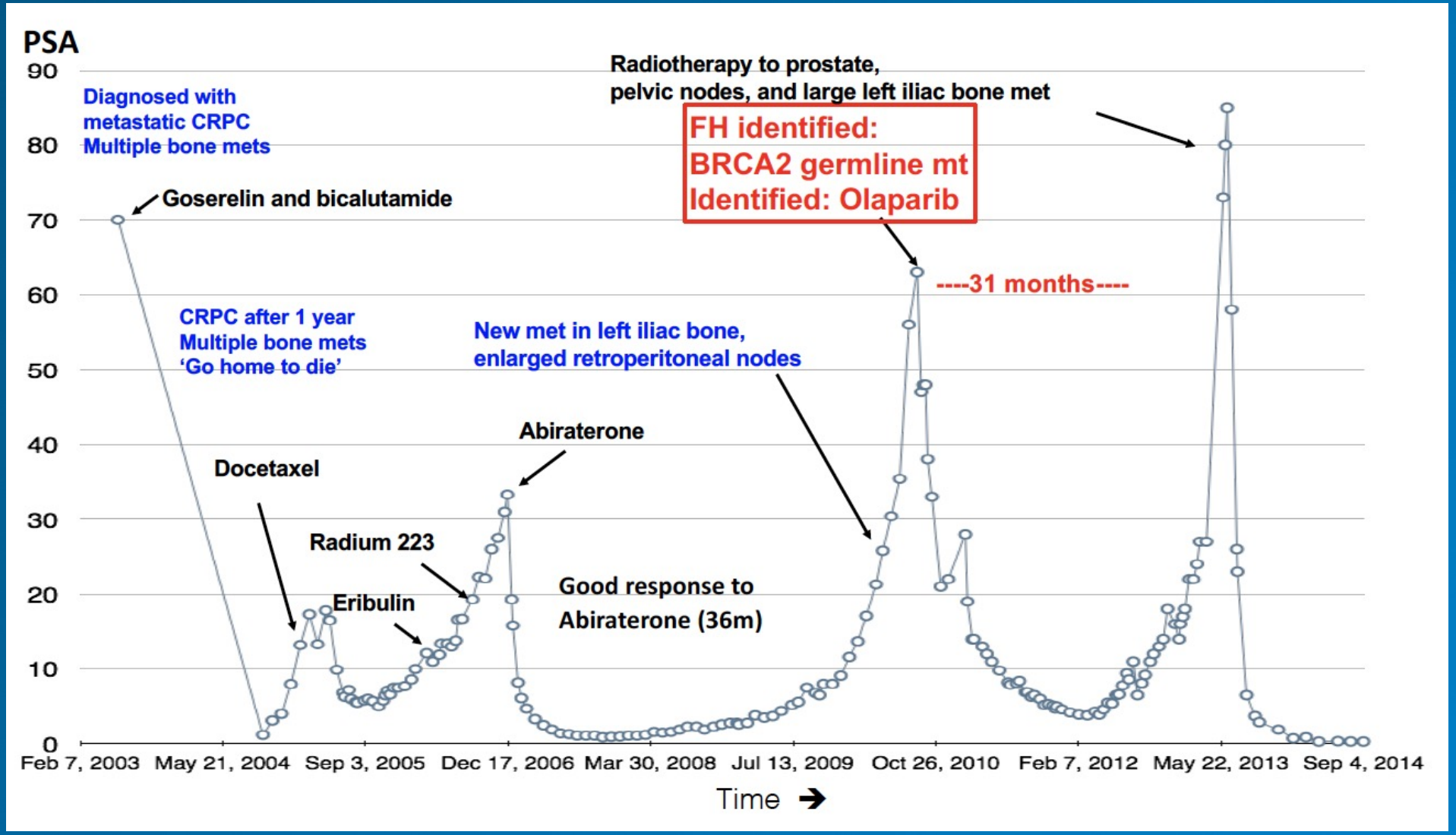
A 48-year-old man was diagnosed with metastatic Gleason 5 + 5 prostate cancer 1 year ago. He has a family history of breast cancer in his mother and aunt. He received leuprolide and docetaxel x 6 cycles for mCRPC and is now has disease progression with new painful bone and liver metastases. He does not respond to enzalutamide.

What do you recommend next?

a) Pembrolizumab
b) Abiraterone/prednisone
c) Radium-223
d) Test for *BRCA* mutations and, if (+) olaparib
e) Sipuleucel-T

mCRPC, metastatic castration-resistant prostate cancer.

Case Study:
Royal Marsden Patient Case



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Pulse Points in Prostate Cancer:
Embracing Advances with PARPi Combinations