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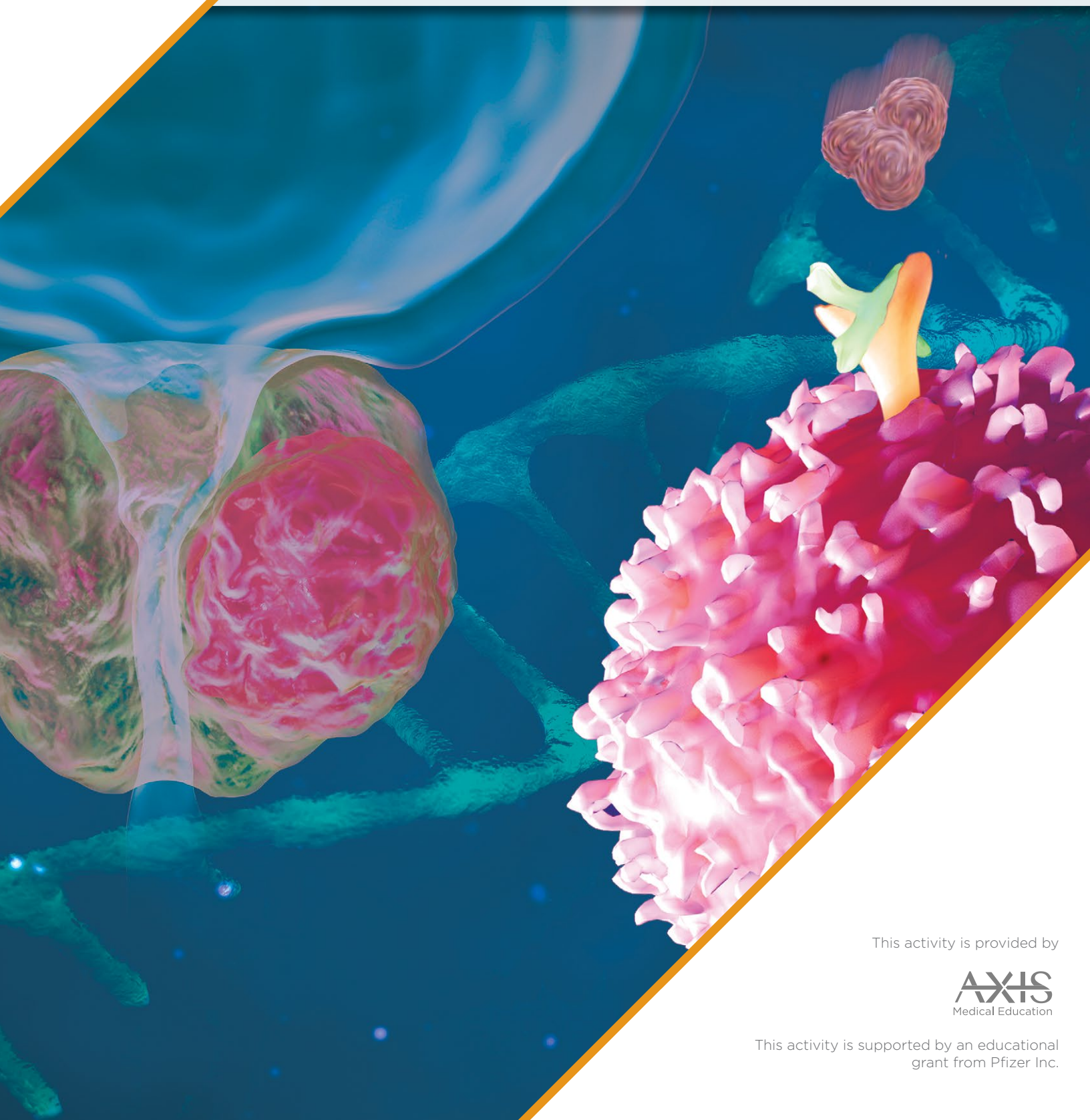
Pulse Points in Prostate Cancer:
Embracing Advances with PARPi Combinations

This transcript has been edited for style and clarity and includes all slides from the presentation.



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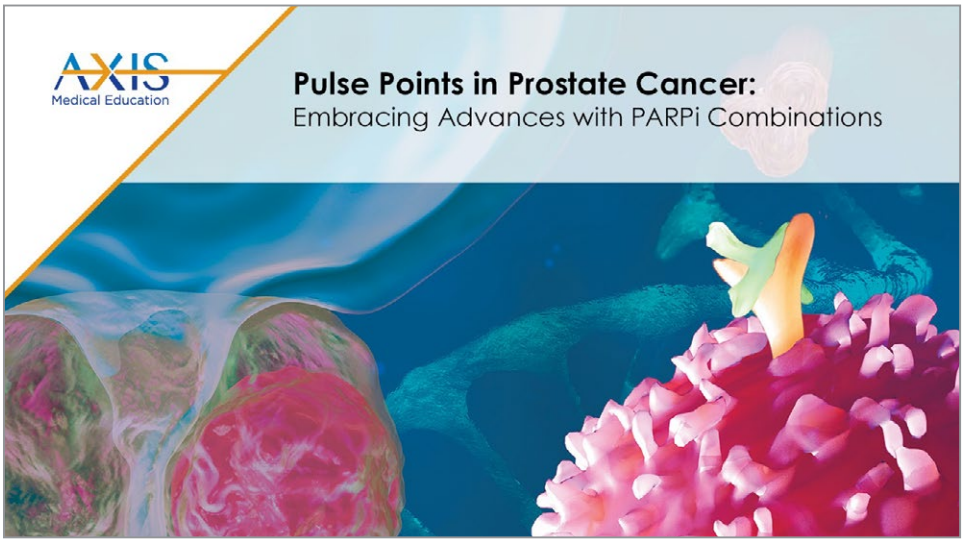
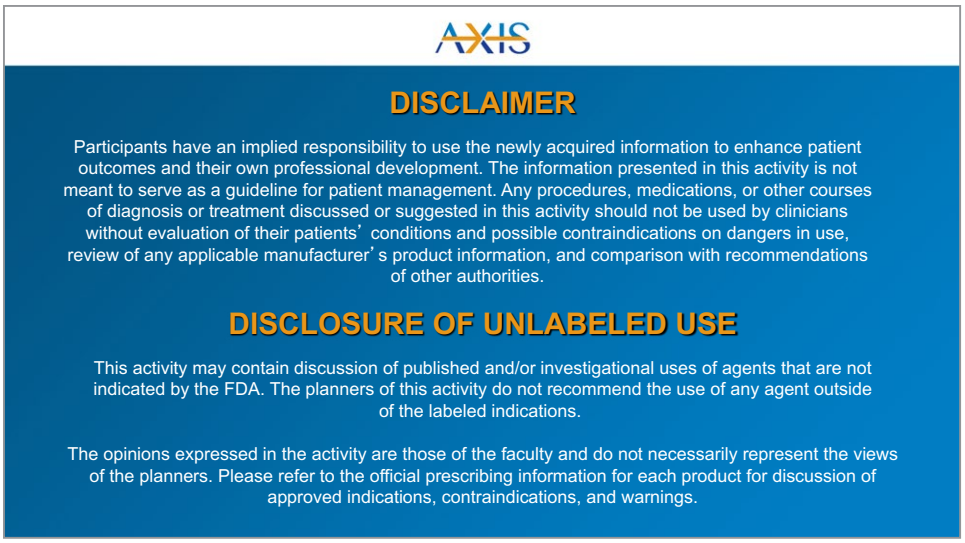
Pulse Points in Prostate Cancer: Embracing Advances with PARPi Combinations

Robert Mocharnuk, MD, Neeraj Agarwal, MD and Johan de Bono, MB, ChB FRCP, MSc, PhD, FMedSci



Robert Mocharnuk, MD: Hello and welcome to this educational activity titled, *Pulse Points in Prostate Cancer: Embracing Advances with PARPi Combinations.*

I am Dr. Robert Mocharnuk, professor of clinical medicine at Southern Illinois University. I am joined today by Dr. Johan de Bono from the Institute of Cancer Research and the Royal Marsden Hospital in the United Kingdom and Dr. Neeraj Agarwal from Huntsman Cancer Institute at the University of Utah in Salt Lake City, Utah.



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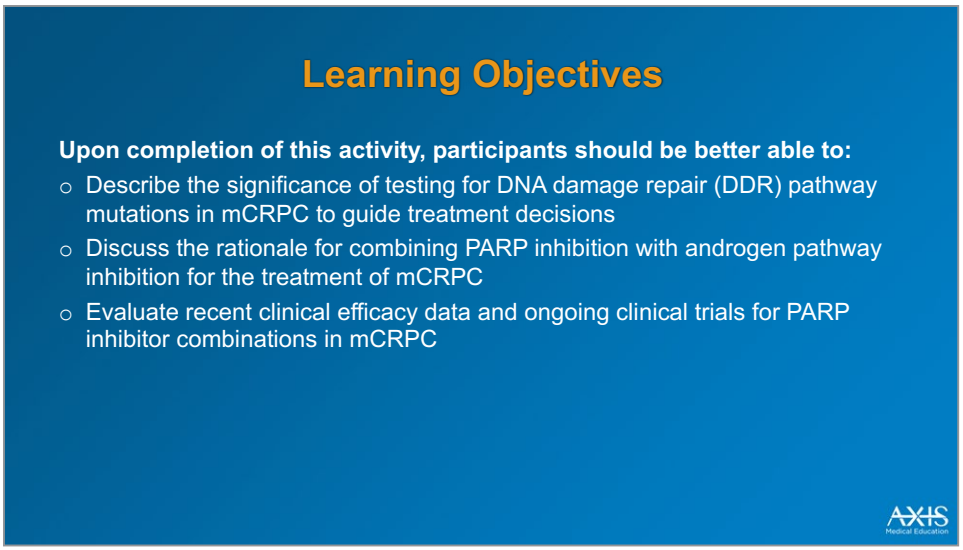
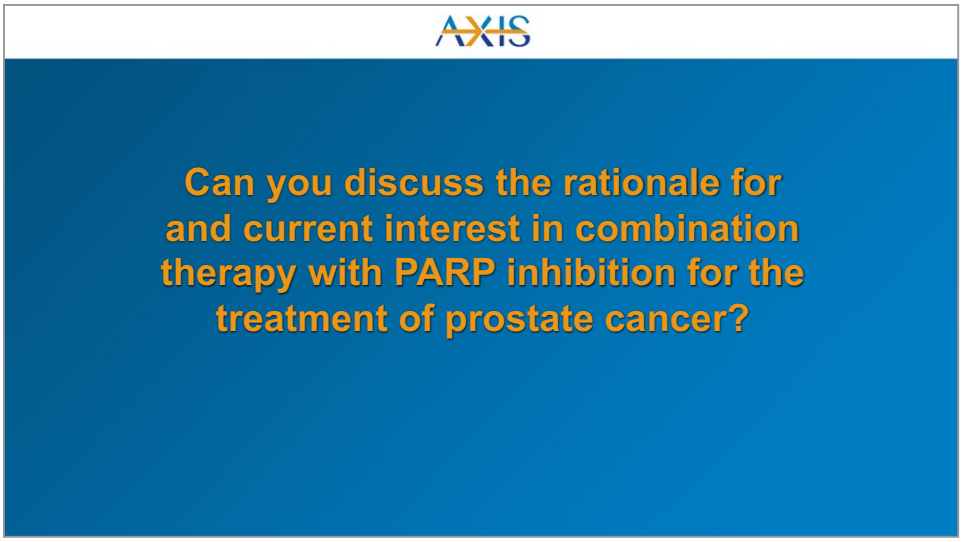


- Here are the learning objectives for this activity.

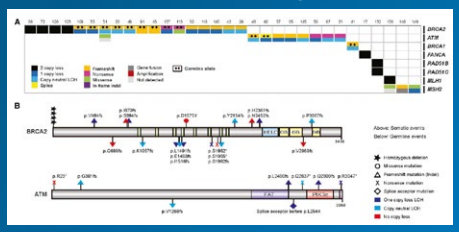


- Dr. Agarwal, can you discuss the rationale for and current interest in combination therapy with PARP inhibition for the treatment of prostate cancer?

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer

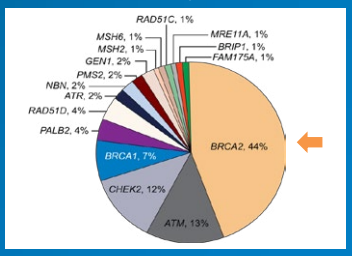
Somatic

- **~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.

Neeraj Agarwal, MD: Approximately 23% of patients with metastatic castration-resistant prostate cancer harbor somatic mutations in DNA repair genes with the vast majority of these being in either *BRCA2* or *ATM* genes.

If you just look at the germline DNA, 12% of men with metastatic castration-resistant prostate cancer harbor germline mutations in their DNA repair genes with greater than 44% of them being in *BRCA2* gene alone.

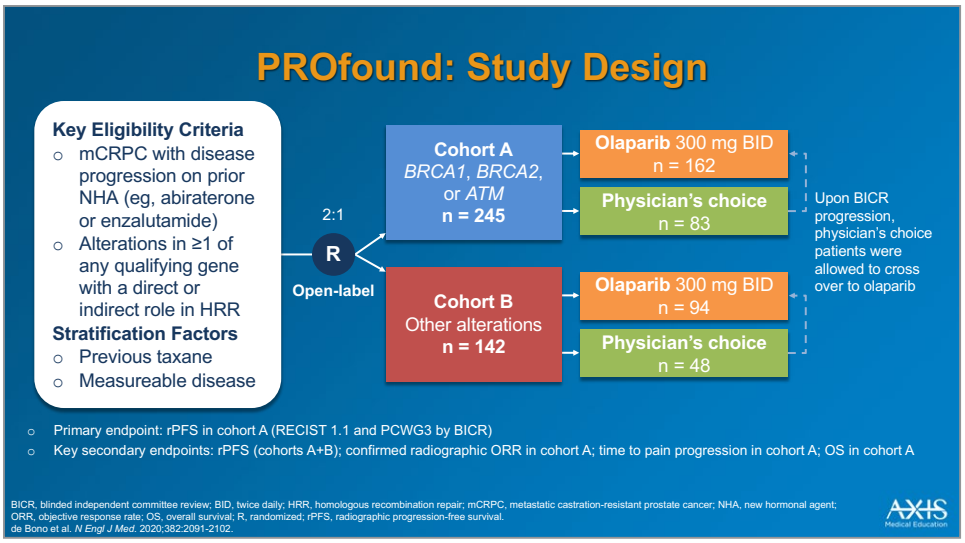
NCCN (V 1.2021) Guidelines for Genetic Testing

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

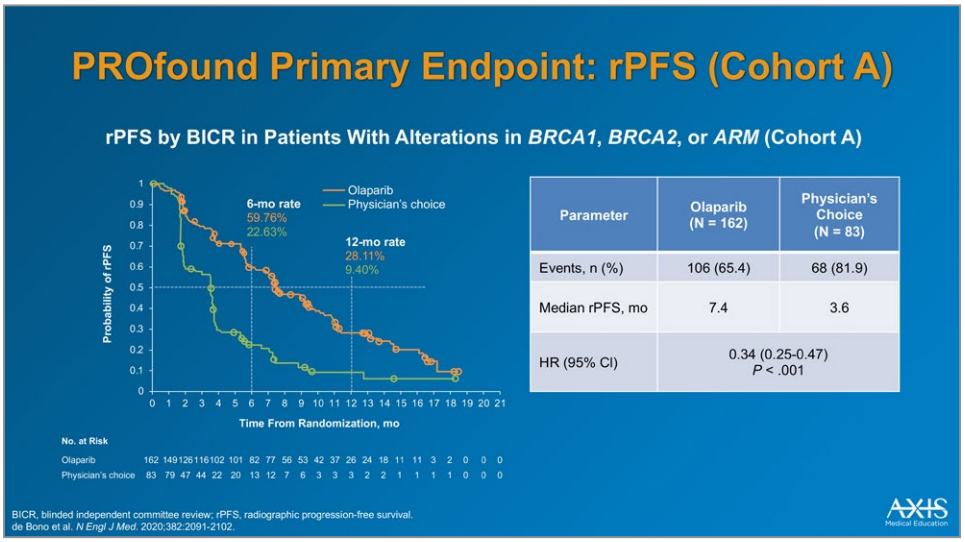
CRPC, castration-resistant prostate cancer; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high.
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate cancer. Version 1.2021. ©2021 National Comprehensive Cancer Network, Inc.
https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

The most recent NCCN Guidelines recommended germline testing for patients with prostate cancer who are at a high risk for rapid progression or have metastatic disease. Testing for somatic mutations in the homologous recombination repair genes is recommended only for patients with metastatic disease. Additional details are shown in this table that has been put together by the expert panel of the NCCN Guidelines for genetic testing.



Let's start with the PROfound trial, which lead to approval of olaparib, the first PARP inhibitor ever approved for patients with metastatic castration-resistant prostate cancer. In the PROfound trial, 387 men with metastatic castration-resistant prostate cancer (CRPC) were assigned to either cohort A or cohort B based on the presence of mutations in one of the genes belonging to the homologous recombination repair pathway. And this schema is showing those two cohorts here.

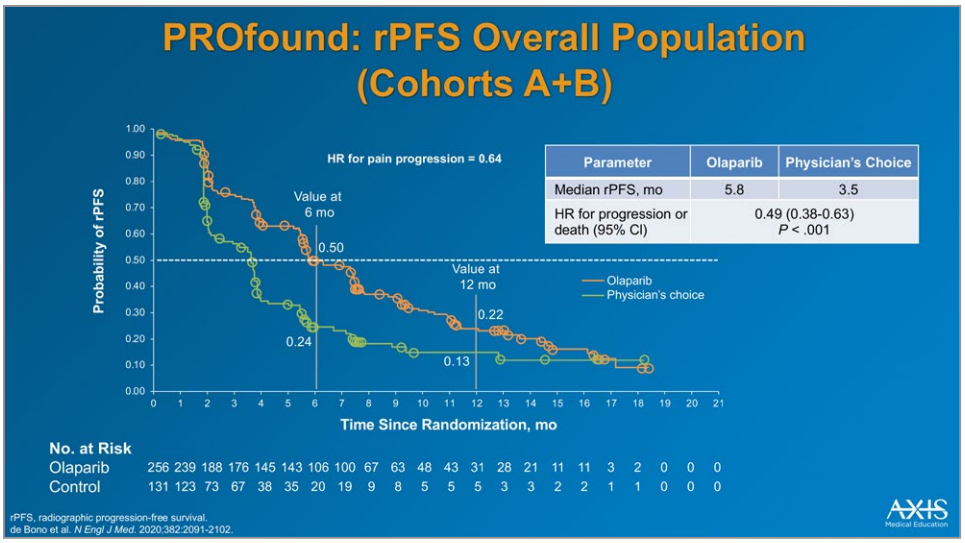
Cohort 1 included *BRCA1, BRCA2*, and *ATM* genes. Cohort B has multiple other alternations that were included. Following assignment to either one of these cohorts, these men were randomized 2:1 to either olaparib or physician choice of enzalutamide or abiraterone.



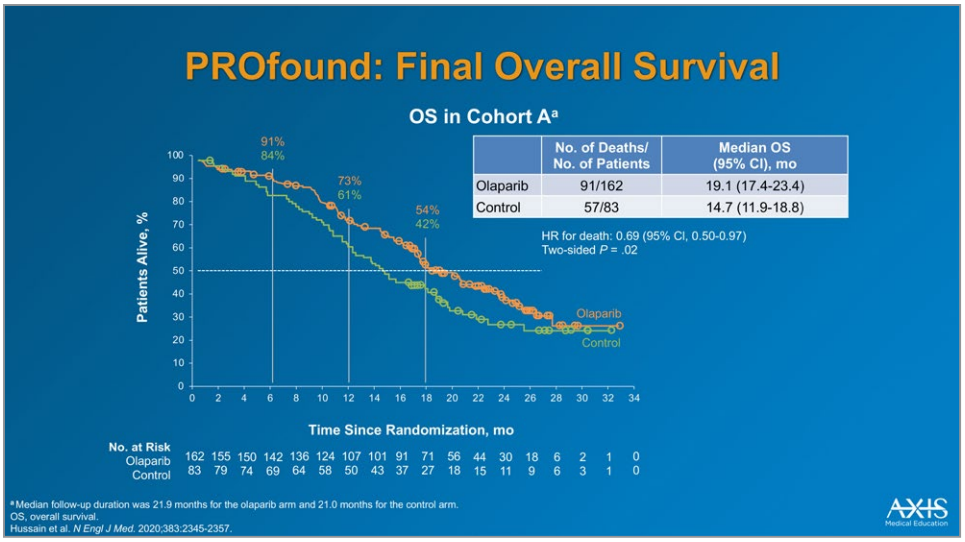
The primary endpoint was radiographic progression-free survival. Prior treatment with a novel hormonal agent was allowed, and stratification was based on whether patients had received prior taxane chemotherapy or if they had measurable disease. Please note that the PROfound trial was the first positive randomized control trial in metastatic prostate cancer where patients were selected based on biomarker.

Analysis of the primary endpoint was performed after 174 of 245 patients in cohort A experienced radiographic disease progression by independent radiology assessment or had died. Median radiographic progression-free survival was significantly longer in the olaparib group compared to the control group at 7.4 months with olaparib versus 3.6 months with the control treatment.

The hazard ratio for disease progression or death favoring olaparib was 0.34. This translates into 65% reduction in the risk of progression or death on treatment with olaparib.



- In the overall population, the median radiographic progression-free survival by independent radiology assessment was also significantly longer in the olaparib group compared to the control group at 5.8 months versus 3.5 months.



- At the time of final analysis of the overall survival, 148 patients of 245 patients originally enrolled—that is 60% of the patients in cohort A—had died, which triggered the analysis for overall survival that was also a prespecified endpoint. The median duration of overall survival was 19.1 months with olaparib and 14.7 months with control therapy with a hazard ratio of 0.69, favoring olaparib. This translates into a 30% reduction in risk for death on treatment with olaparib compared to control.

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

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- There were not many significant grade 3 or 4 adverse events. As we can see here, most adverse events were grade 1 and 2. In fact, if you look at the grade 3 events in the olaparib arm versus control arm, pretty much all grade 3 adverse events were similar except anemia, which was higher with olaparib. And it is a known class effect of PARP inhibitor therapy.

  For the sake of discussion, the most common adverse events regardless of grades were anemia, nausea, and fatigue with olaparib and fatigue with the control arm. There were no reports of myelodysplasia or acute myeloid leukemia seen in the olaparib arm in this elderly patient population.

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.

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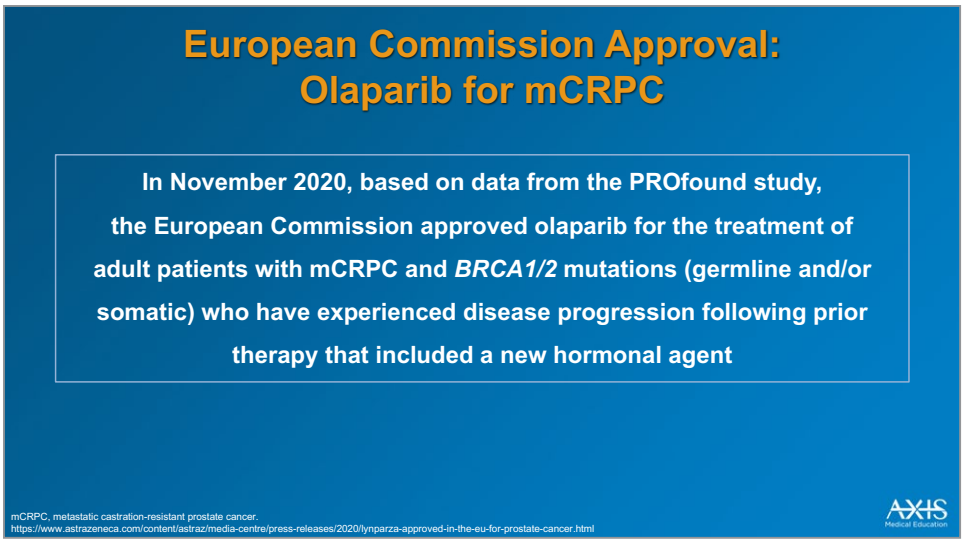
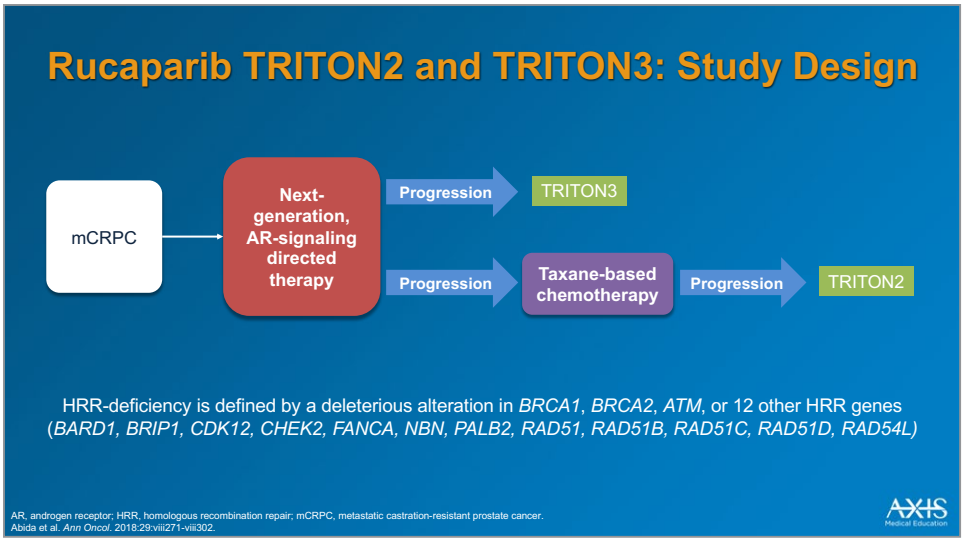
- In May 2020, based on the results of the PROfound trial, the FDA approved the first ever biomarker-based systemic therapy for men with metastatic castration-resistant prostate cancer after progression on a novel hormonal therapy and without requirement for prior exposure to chemotherapy with taxane.

  This was a very welcome step for patients with metastatic castration-resistant prostate cancer who are harboring these mutations in their homologous recombination repair pathway.



- Based on the same findings from the PROfound trial, the European Commission also approved olaparib for *BRCA1*- and *BRCA2*-mutated tumors. So, in men who are harboring these *BRCA1*- and *BRCA2*-mutated tumors and have had disease progression on novel hormonal therapy also have access to olaparib in the European Union.



- So, let's now move on to the next PARP inhibitor, which is rucaparib. Rucaparib was the second PARP inhibitor to be approved for patients with prostate cancer. So, in the TRITON trial, men with deleterious germline or somatic alternations in *BRCA1, BRCA2*, or one of the other prespecified homologous recombination repair pathway genes were included.

  Patients who experienced disease progression on one or two lines of novel hormonal therapy with enzalutamide or abiraterone and one prior line of taxane-based chemotherapy for metastatic castration-resistant prostate cancer were eligible.

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.

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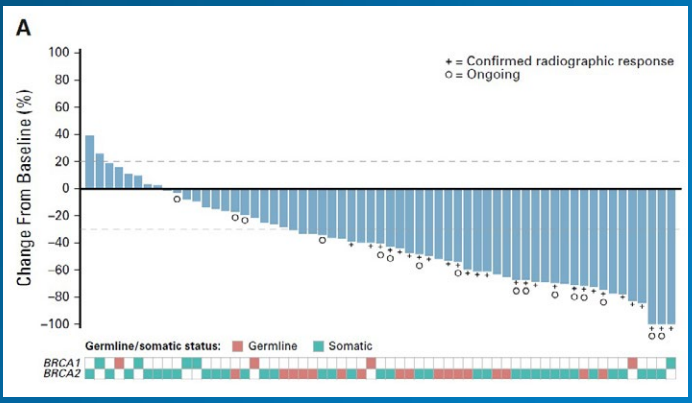
- The primary endpoint here was centrally assessed confirmed objective responses per RECIST 1.1 or per PCWG3 for patients with measurable disease and confirmed PSA responses of 50% or more for patients without measurable disease. So, this trial uniquely incorporated endpoints based on either measurable disease responses or PSA responses. The confirmed objective responses per independent radiology review of the evaluable population was 43%, and the confirmed objective responses for investigator assessed review as 50%. Disease control rate, which includes stable disease and objective responses, was 88.7% per independent radiology review. This is very encouraging news for our patients.

TRITON2: Objective Responses



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

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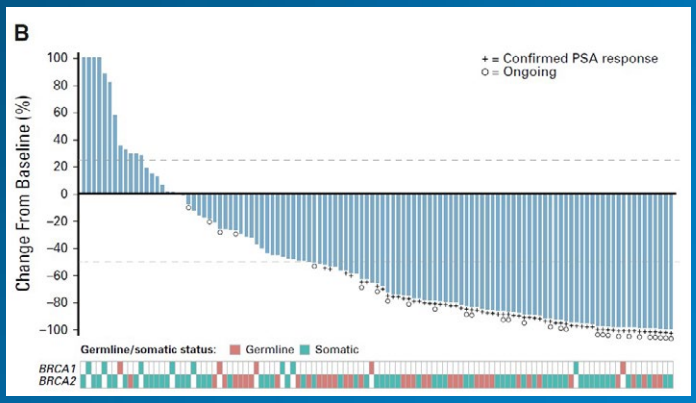
- This waterfall plot shows objective responses, and we see that the majority of patients are achieving some shrinkage of the measurable disease. And 60% of patients demonstrate a more than 30% reduction in the target lesion from the baseline.

TRITON2: PSA Responses



PSA, prostate specific antigen.
Abida et al. *J Clin Oncol*. 2020;38:3763-3772.

- In this waterfall plot showing PSA responses, we see that 60% of patients demonstrate a single best PSA reduction of 50% or more from the baseline.

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 (%) 95% CI 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 (%) 95% CI	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 (%) 95% CI	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 (%) 95% CI	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.

- The confirmed investigator assessed objective responses were low for genes other than *BRCA1* and *BRCA2*. For example, we didn't see a lot of responses in patients with *ATM*, *CDK12*, or *CHEK2* mutations.

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.

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- If you look at the treatment-related adverse event of any grade, they occurred in 99% patients, and grade 3 or more frequent emergent adverse events were reported in 60% or 61% of patients. The most frequent grade 3 or more treatment emergent adverse events were anemia at 25% followed by thrombocytopenia at 10%. It was followed by fatigue in 9% of patients. Overall, 28% of patients received more than one transfusion of packed red blood cells.

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.

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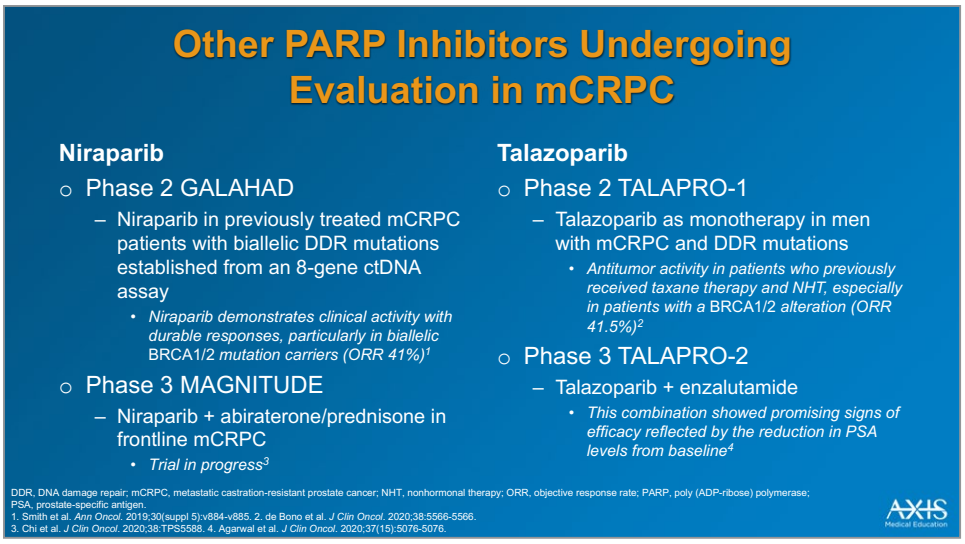
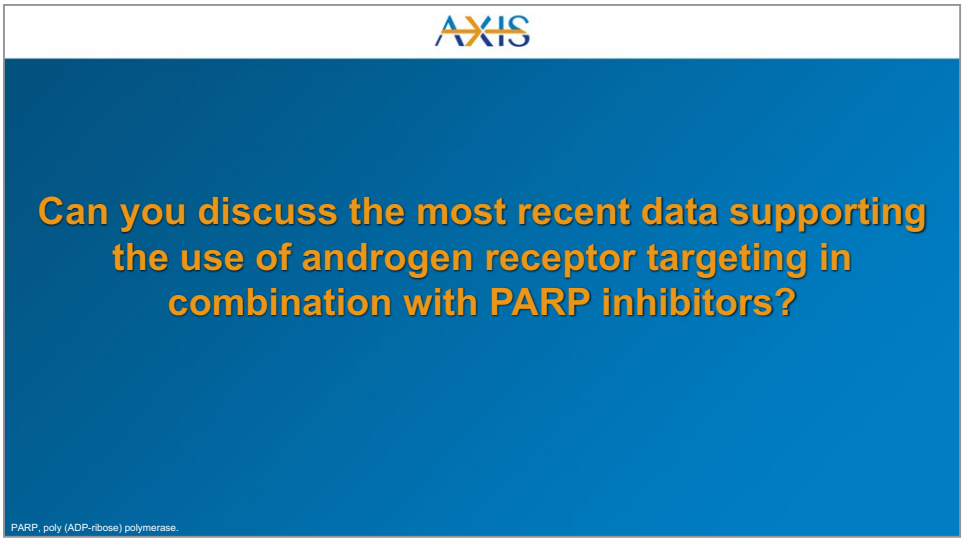
- In May 2020, based on the results of this TRITON2 trial, the FDA approved rucaparib for men with metastatic castration-resistant prostate cancer harboring mutations in *BRCA1* and *BRCA2* genes only. These men have to have disease progression on a novel hormonal therapy with abiraterone or enzalutamide and a taxane therapy. So, approval is different for olaparib versus rucaparib. Approval for olaparib is for men who have *BRCA1, BRCA2*, and many other mutations including *CHEK2, RAD5, ATM*, and so on. And these patients do not have to have prior therapy with taxane for metastatic castrate-resistant prostate cancer.

  For rucaparib, it is only approved for men with *BRCA1* and *BRCA2* mutations, and these patients have to have prior exposure to a novel hormonal therapy and a taxane in metastatic castration-resistant prostate cancer setting.

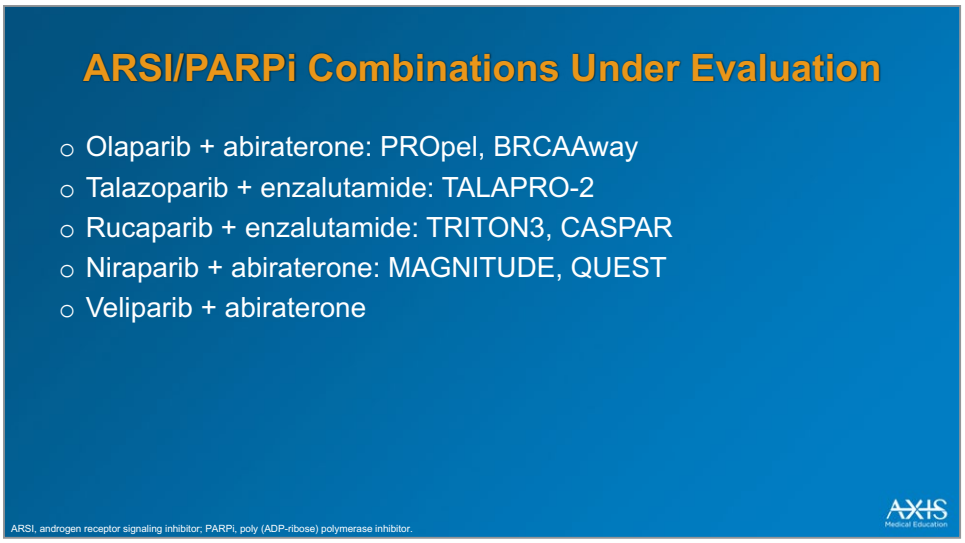


- We also know that results from two other phase 2 trials evaluating monotherapy with niraparib or talazoparib showed clinical activity with an approximate objective response of 41%. Additionally, two phase 3 trials evaluating combinations of a PARP inhibitor with either abiraterone or enzalutamide in the MAGNITUDE and TALAPRO trials, respectively.

  So, we are going to see the results of these phase 3 trials where these PARP inhibitors are being combined with novel hormonal therapy in the first-line castration-resistant prostate cancer setting.

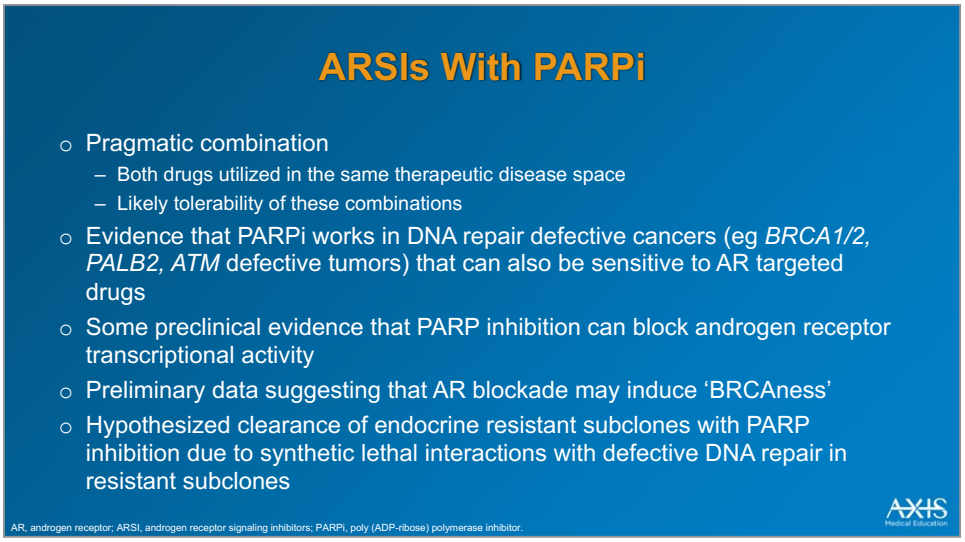


- **Dr. Mocharnuk:** Thank you, Dr. Agarwal. Dr. de Bono, can you discuss the most recent data supporting the use of androgen receptor targeting in combination with PARP inhibition?



Johan de Bono, MB, ChB FRCP, MSc, PhD, FMedSci: There are multiple ongoing trials studying PARP inhibition with next-generation hormonal agents. These include combination olaparib with abiraterone, rucaparib and enzalutamide, niraparib and abiraterone, talazoparib with enzalutamide, and even veliparib and abiraterone.

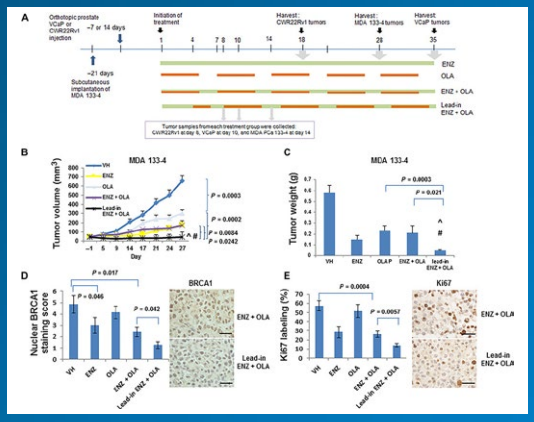
However, I think that we really have to wait on the outcomes of these trials—some of which are pragmatic combinations trying to get the PARP inhibitors into earlier lines of therapy, which makes a lot of sense, because if we give these drugs early, we may get longer benefits.



There is some evidence that PARP inhibition can sensitize disease to targeting agents. There are some data published about that, and indeed, there's evidence that PARP inhibition can block androgen receptor (AR) transcriptional activity; although I think these data will indicate primarily that the effects of PARP inhibition are not tumor cell kill but actually more cytostasis—tumor cell cycle arrest.

There is some evidence as well that AR blockade may induce BRCAness; however, I think this is controversial and more evidence is required. What is particularly interesting is that there is some evidence that when you get resistance to AR-targeted agents, you get alterations in the DNA of these tumors that actually result in sensitivity to PARP inhibition—so a new acquired vulnerability in the tumor cell to PARP inhibition that may reverse AR antagonist resistance.

In Vivo Combination Data in MDA PCa 133-4 Model



- This is some of the published data regarding these studies. You see that in vivo combination in the MD Anderson prostate cancer model 133-4 suggests that if you combine enzalutamide with olaparib, you get increased antitumor activity. And you can refer to this important paper, in *Science Signaling* from 2017, that argues the case for this drug combination.

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

- There are, obviously, multiple ongoing phase 2 trials, but the only data we have supporting the combination in a randomized study is from a placebo-controlled randomized phase 2 study led by Noel Clarke, a urologist in Manchester in the United Kingdom. This was a randomized trial of olaparib combined with abiraterone versus abiraterone alone in metastatic first-line CRPC treatment as a randomizable blind placebo-controlled trial.

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.

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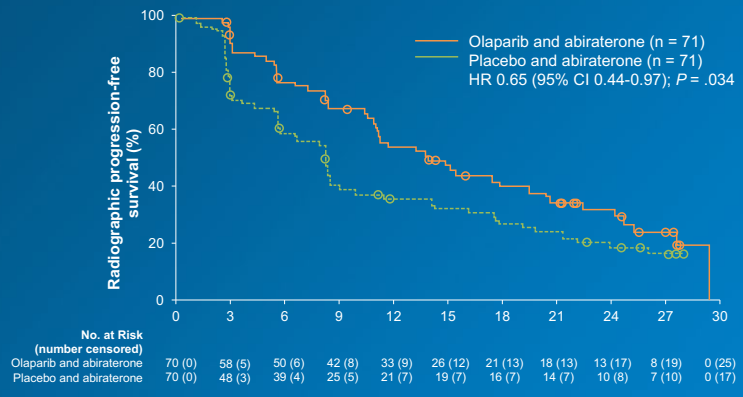
- This trial was a 41-center, 11-country study in North America and Europe. Abiraterone was standard dose and olaparib was given at 300 mg twice a day. The primary endpoint was investigator-assessed radiographic progression-free survival based on RECIST. And 142 patients were randomly assigned—71 to each arm—with no molecular tumor genomics preselection.

Olaparib + Abiraterone: Radiographic PFS



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

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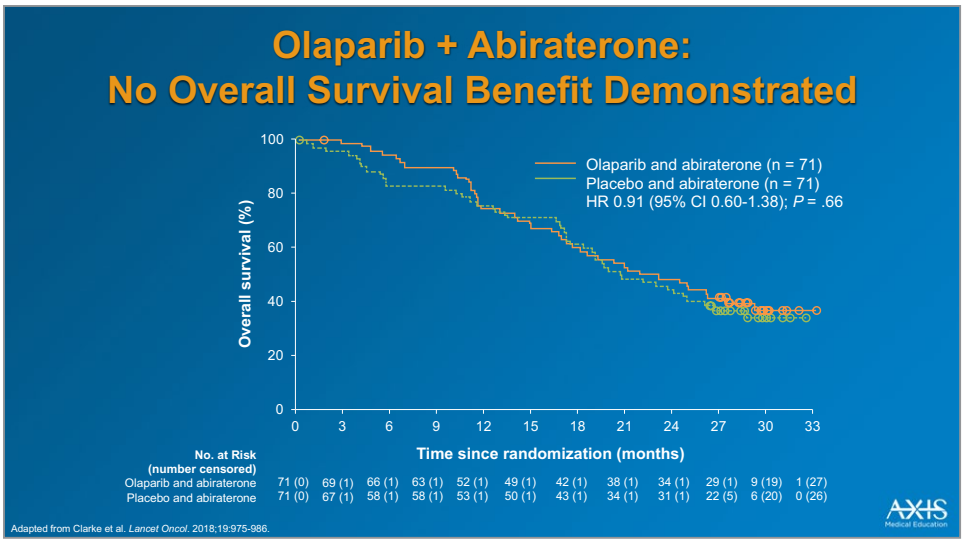
- The trial did show an improved radiographic progression-free survival, which is shown here. This was published in *Lancet Oncology* by Clarke et al with a hazard ratio of 0.65—a 35% decrease in risk for progression—and 95% CI, 0.44 to 0.97; *P* = .34.



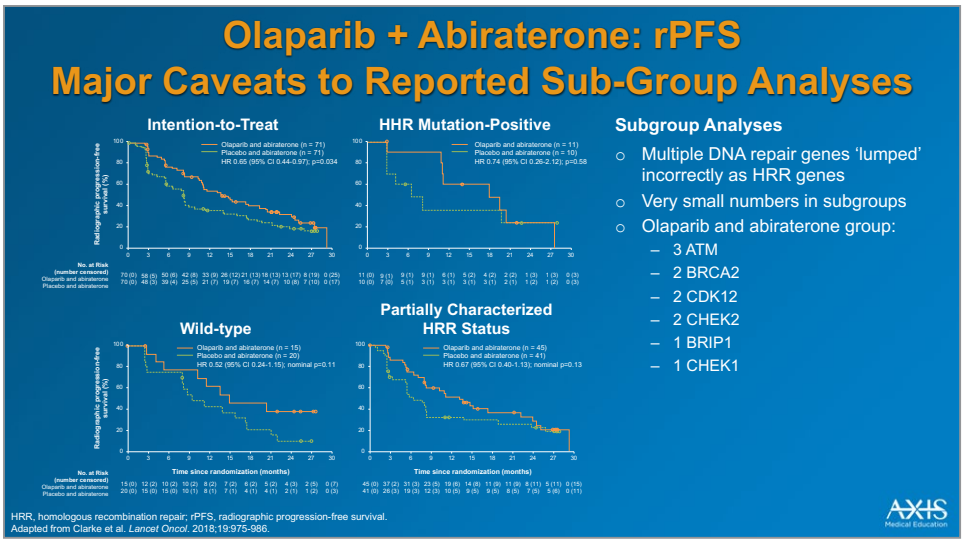
- However, the study showed that there was no overall survival benefit. My concern is that the radiographic progression-free survival benefit from this trial was primarily from the patients with a *BRCA* or DNA repair defect.

Olaparib + Abiraterone: Adverse Events

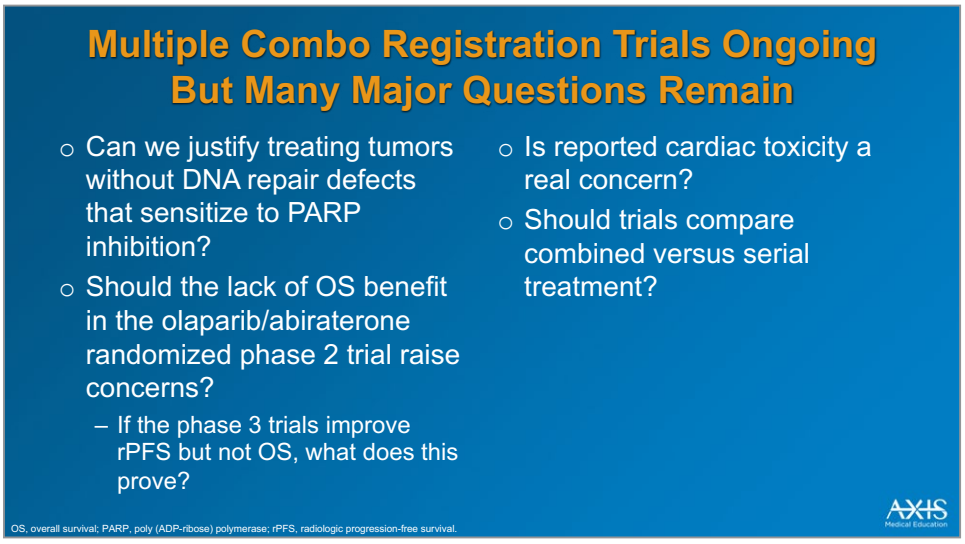
Adverse Event	Olaparib and abiraterone (N = 71)				Placebo and abiraterone (N = 71)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
All	28 (39%)	29 (41%)	5 (7%)	4 (6%)	37 (52%)	19 (27%)	0	1 (1%)
Nausea	26 (37%)	1 (1%)	0	0	13 (18%)	2 (3%)	0	0
Constipation	18 (25%)	0	0	0	8 (11%)	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.

- The trial did show that there was largely no surprise regarding tolerability. Although there was some concern when these data were presented, at ASCO, about an increase in myocardial infarctions in the combination arm, which we haven't really seen with PARP inhibition before in single-agent trials.

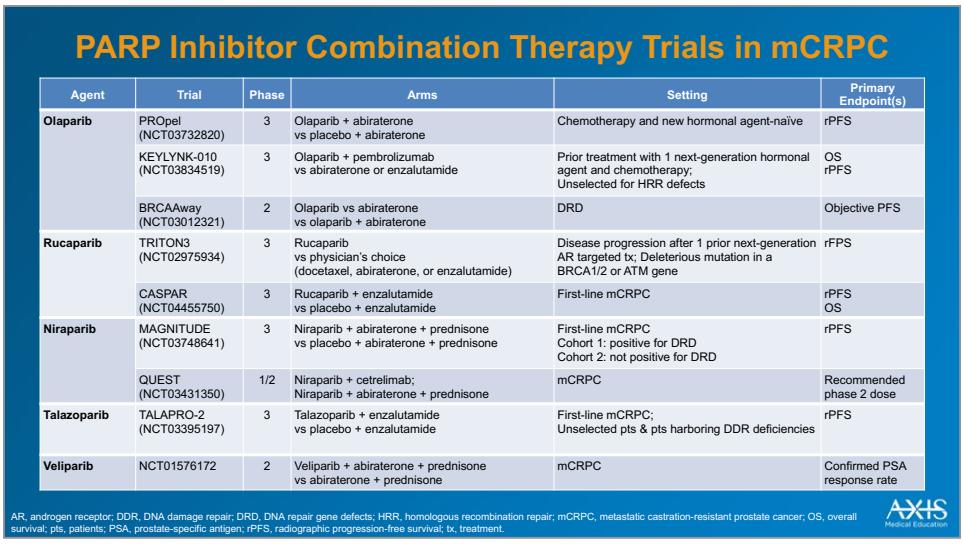


- The trial did try and break down the benefits in the DNA repair defect group. This subset study was not well enough powered for any comment to be made here and was largely post hoc.



- The key question that remains is can we really justify treating patients whose tumors do not have DNA repair defects? I think we need more data to actually make this assumption. I think at present the likely benefit from these combinations are primarily in the DNA repair defective group. But we'll have to see. If the combination studies show an overall survival benefit, then I would personally be convinced that the combination is better than the single agent. But we'll have to see benefit in the subgroups based on DNA-repair defects; not only for the overall population, but also for DNA repair defects, in particular, *BRCA* and the remaining other groups with no DNA repair defects.

  Is reported cardiac toxicity a real concern? It is definitely a concern that will require more assessment. I hope this will not be a major concern but really more data to clearly state what this really means for our patients that we serve. And it is going to be quite interesting to see how these trials evolve.



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.

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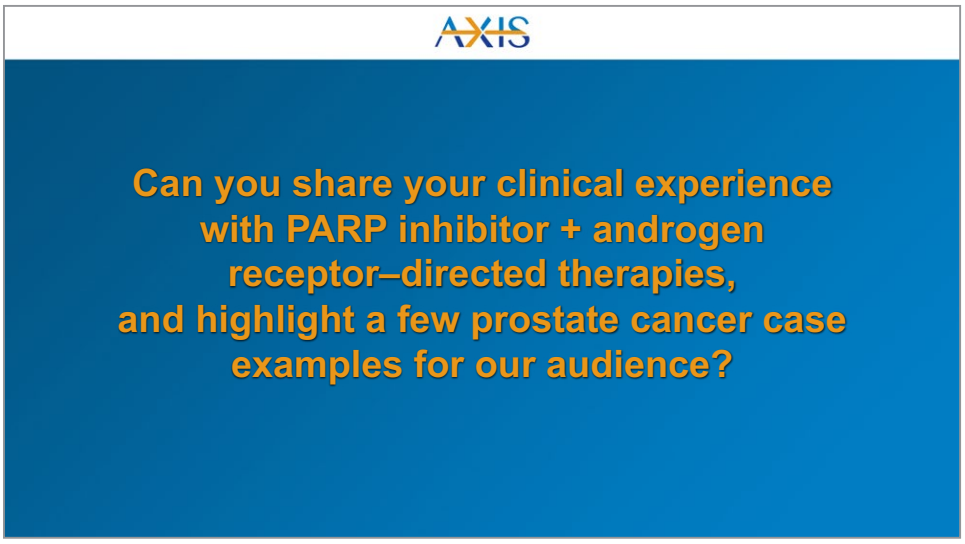
- Clearly, a number of these trials will readout in the near future—PROpel for olaparib/abiraterone. But there's also other combinations. For example, olaparib/pembrolizumab—a trial that's ongoing that I'm involved with, which has some justification based on olaparib causing double-strand DNA breaks, cytosolic DNA, STING pathway activation. Potentially, that may sensitize to immune checkpoint inhibition. And this is partially based on work that has been previously generated by the group at the NCI lead by Professor James Gulley.

  The other combinations we can talk about today are the rucaparib combination; for example, TRITON3 as well as CASPAR; the niraparib studies, MAGNITUDE and QUEST; the talazoparib studies, TALAPRO2; and the veliparib trial, which is depicted in this slide.



- **Dr. Mocharnuk:** Thank you for that. Now, can you both share your clinical experience with PARP inhibitor and androgen receptor–directed therapies and highlight a few prostate cancer case examples for our audience?

Case Study: Dr. Agarwal

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.

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Dr. Agarwal: The case of a 48-year-old man who was diagnosed with metastatic prostate cancer a year ago. The Gleason score was 5 + 5. He also had a family history of breast cancer in his mother and an aunt. He received leuprolide and docetaxel for 6 cycles for the diagnosis of de novo metastatic castration-sensitive prostate cancer and now has disease progression with new painful bone metastasis and liver metastasis. He was started on enzalutamide but did not have any response to enzalutamide. In fact, there was a PSA decline for maybe a month, and then PSA starts to rise again very quickly. So, literally no response to enzalutamide. What do you recommend next?

So, these are the options: pembrolizumab; abiraterone plus prednisone; radium-223; test for *BRCA* mutations, and if positive, start him on olaparib; and sipuleucel-T. And I will just go through them one by one.

Pembrolizumab is not approved for prostate cancer except a very small number of patients who have MSI-high prostate cancer. This is not the case clearly in this patient. At least we have not been told that.

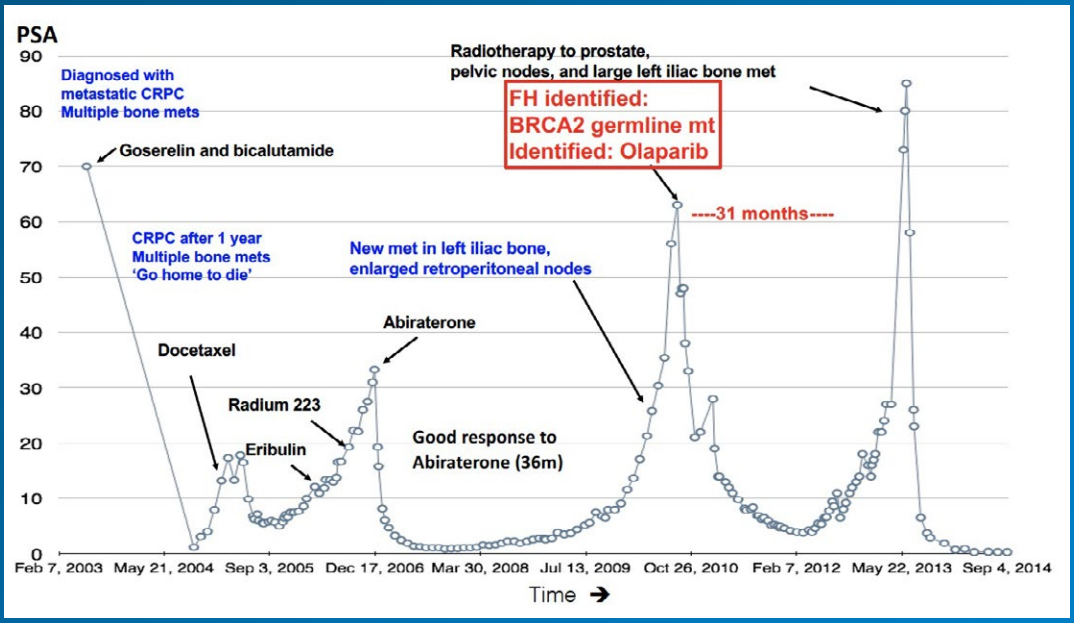
Abiraterone is clearly not an answer here because the patient did not have relevant response to a novel hormonal therapy, enzalutamide. Radium-223 and sipuleucel-T both would be contraindicated in this patient because of the visceral metastasis and also because of the overall rapid increase in the PSA or rapidly progressive prostate cancer.

So, obviously, I'm going to pick up tests for *BRCA* mutations, and if positive, pick up olaparib.

Now, this may take some time. This may take 2 or 3 weeks, up to 6 weeks or 8 weeks. And in this patient who has a rapidly progressive disease, I would keep a close eye. I would definitely have my nurse call the patient every 15 days and probably see the patient in the clinic at least once a month while I'm working on getting the preauthorization for olaparib and getting the test results of comprehensive genomic profiling of this patient.

Having said that, I think the most appropriate therapy for this patient if the patient has a *BRCA1, BRCA2*, or other DNA-repair approved homologous recombination repair gene mutation would be olaparib.

Case Study: Dr. DeBono
Royal Marsden Patient Case



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Dr. de Bono: I would like to talk about a patient who did have a *BRCA* mutation. This patient was under my care for quite a long time. And he was diagnosed in 2003 with M1 with multiple bone metastases at diagnosis. He had androgen deprivation therapy (ADT), which was the standard of care at that time with a relatively short—1 year or so—progression-free interval and then experienced disease progression quite quickly in just over 1 year of starting ADT with bicalutamide.

He then went on to get docetaxel and did not get much of a duration of benefit with that. He progressed soon after starting docetaxel. He came to my team, and I gave him a clinical trial of a drug that was then known as a halichondrin B analogue and is now known as eribulin on a phase 2 study of that agent. He did not respond on that agent. And he then got radium-223 because he only had bone metastasis. This was again on a clinical trial. Clearly, this was in 2007/2008 before radium was approved.

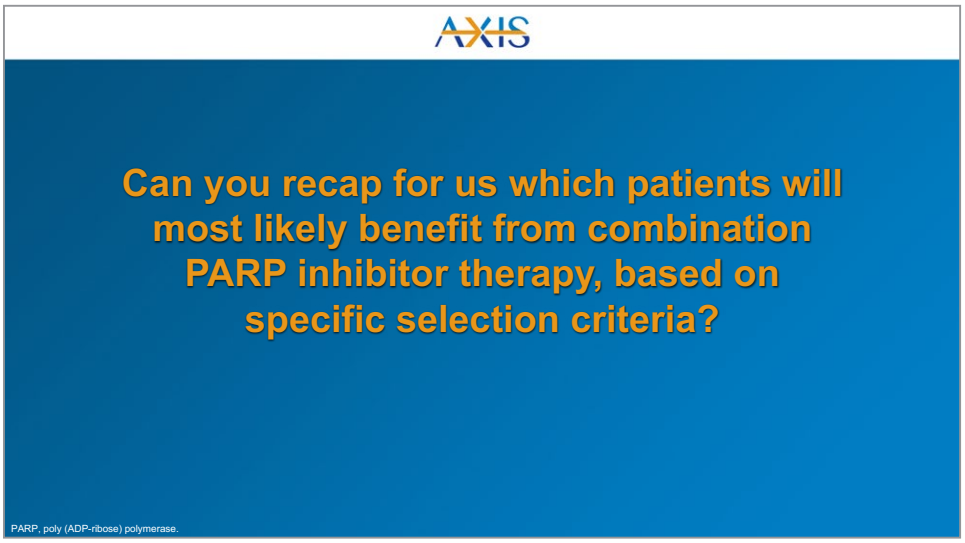
What is quite interesting here is that in 2008 when he experienced disease progression on radium we gave him abiraterone, and he then had a 3-year period of disease control, which really is pretty good for this kind of patient, although not unusual. The disease then progressed. He mentioned to my nurse that he had returned from a funeral of one of his cousins who had died of prostate cancer.

Now, this is way back in 2010. But at this juncture, germline defects are getting interesting. We sequenced his tumor in my laboratory and found he had a *BRCA2* germline mutation 11 years ago. And we started him on olaparib.

And what you see here is that he had a super response to olaparib. His PSA fell quite nicely. He was on olaparib for about 3 years or so. At the end of which, he had disease progression only in the pelvis—in the prostate, some small pelvic nodes, and one solitary left iliac bone metastasis, which we irradiated. Interestingly, after that radiation therapy, his PSA normalized and really pretty much fell down to zero. And then, he continued to have a good duration of disease benefit.

Now, why do I mention this? I think it's important to note that this man with a *BRCA2* mutation really did quite poorly initially with regards to presenting with very aggressive disease, metastatic at diagnosis, and a fairly short duration on ADT before disease progressed. But actually, he had a pretty good response to abiraterone and a fairly good period of disease control with olaparib.

We need to know whether giving olaparib better done together or serially, as in this patient, a better way forward for these men? The answer to that will come from the trials that are now running. So, you know, I think that there's been much progress, overall, for serving these men with advanced prostate cancer with new drugs and particularly these new AR and PARP inhibitor agents. But many questions remain.



Dr. Mocharnuk: And, doctors, can you recap for us which patients will most likely benefit from combination PARP inhibition therapy based on specific selection criteria?

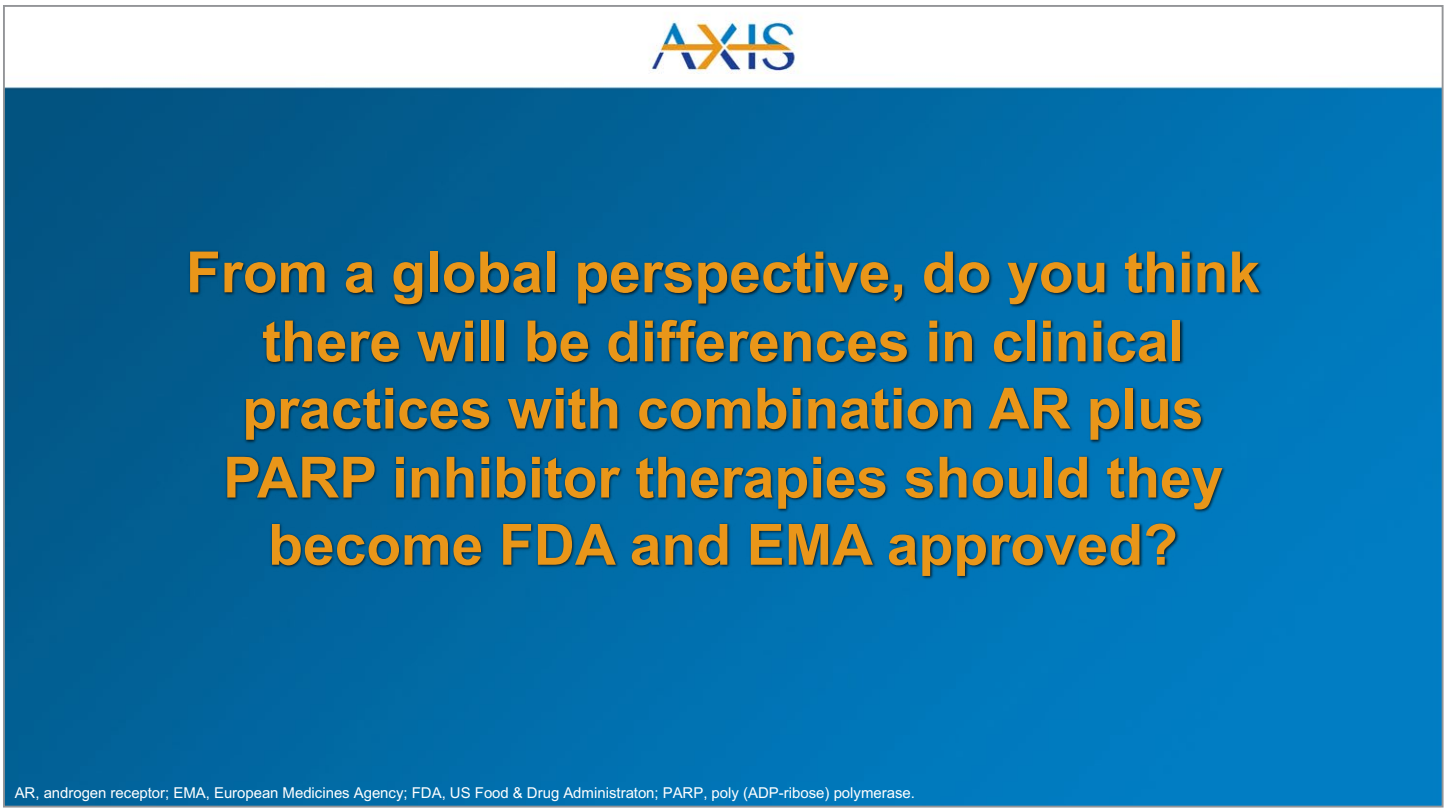
Dr. Agarwal: This is a great question, Dr. Mocharnuk. As we know, we do not have any approval for combination therapies with PARP inhibitors for our patients. Of course, there are clinical trials going on combining PARP inhibitors with enzalutamide such as the TALAPRO2 trial or combining the PARP inhibitor olaparib with abiraterone in the PROpel trial. But we do not have the results on efficacy or safety of these trials.

I think these combinations are quite safe because phase 3 trials are already happening, but we do not have the data yet. Please also note that many of these large trials include selected and unselected patients, meaning these trials also include patients who are not selected necessarily for one of the homologous recombination repair mutations. So it is possible that these trials may show that the combination of androgen receptor inhibitor enzalutamide plus talazoparib may be effective in patients who do not have these mutations. But we do not have that information yet.

My answer would be to wait for the results of those trials. And if those trials are positive, of course, I'll be very happy to use the combination of novel hormonal therapy with a PARP inhibitor in patients with newly diagnosed metastatic castrate resistant prostate cancer. That's where these combinations are being tested right now.

Dr. de Bono: From my perspective, patients with *BRCA2* are the ones who benefit most. I think that's going to be the case for both the single agent and the combination. There is definitely benefit for some patients with *ATM* loss, but I do think for *ATM* we have to probably focus on protein IHC complete loss to see sensitization. And it's likely that this benefit is less than what you see with the *BRCA*s. The *PALB2, RAD51, FANCA* with biallelic loss does sensitize to PARP inhibition and some other genes. And again, it's like that for the combinations. These are probably going to be the patients that benefit most from the combination.

There are clearly differences arising between Europe and the United States. And in some ways, I wish that we could find a common ground whereby we had approval that was maybe a bit less broad in the United States and a bit broader in the Europe. We should not forget carboplatin. If the patient cannot access PARP inhibition—maybe in Europe because he can't have a PARP inhibitor yet because it's not approved for say FANCA or PALB2 or ATM complete loss—I do think that these patients can benefit— with carboplatin probably single agent, AUC 5 or 6 based on the EDTA. And this can really be quite beneficial for patients.

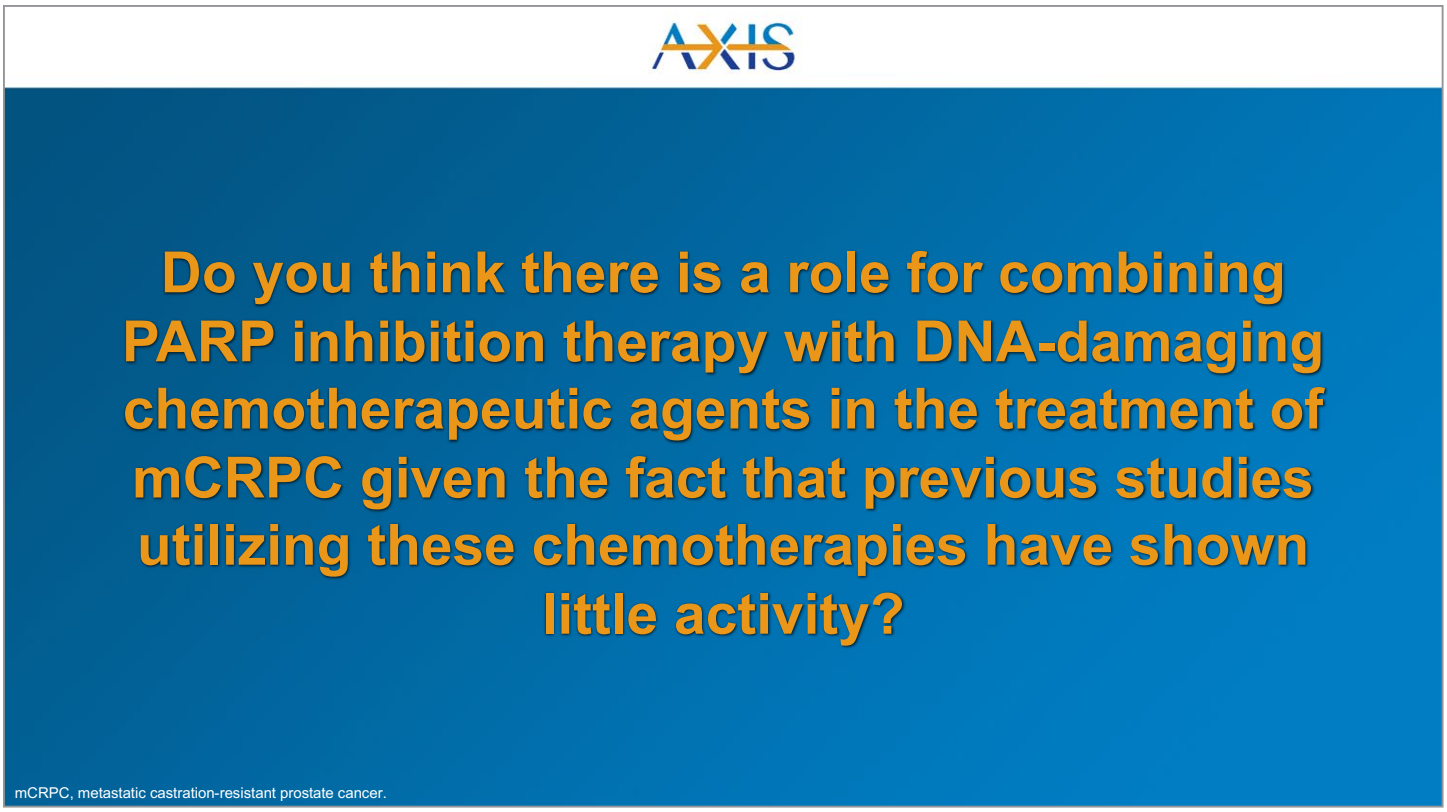


Dr. Mocharnuk: From a global perspective, do you think there will be differences in clinical practices with combination androgen receptor PARP inhibition therapies should they become FDA and EMA approved?

Dr. Agarwal: We already know that there is global variance in the practice patterns despite drugs being approved, which are already approved for patients with advanced prostate cancer. We know that in castration-sensitive metastatic prostate cancer in many countries their health system cannot afford these oral novel hormonal therapies for the majority of the patients. And in those countries, docetaxel is used more often in hormone sensitive or castration-sensitive metastatic prostate cancer.

Radium-223, for example, is not even approved in many countries while it is approved and is used widely in the United States. So, I think it will all depend upon, first of all, the results on the efficacy of these trials – how strongly efficacious they are? How strongly positive they are? What are the side effects? And do the side effects of these combinations justify the use of the drug? Are they efficacious enough to clearly outweigh the side effects of these combinations and the cost of these combinations?

I think all of those factors will network or interact with each other in ultimately deciding how these combinations are going to be approved and used in various countries. It's very hard to predict upfront at this point in time. But I really hope that these combinations are beneficial because that will allow PARP inhibitors to move to the first-line metastatic CRPC setting, which is not the case right now.



Dr. Mocharnuk: Do you think there is a role for combining PARP inhibition therapy with DNA-damaging chemotherapeutic agents in the treatment of metastatic castrate resistant prostate cancer given the fact that previous studies utilizing these chemotherapies have shown little activity?

Dr. Agarwal: My short answer is no. These chemotherapy agents have never been tested, at least in my knowledge, in large trials in combination with PARP inhibitors. We know that at least some of those agents which are used—especially platinum-based therapies—in these patients are also associated with significant toxicities including marrow toxicities in this elderly patient population.

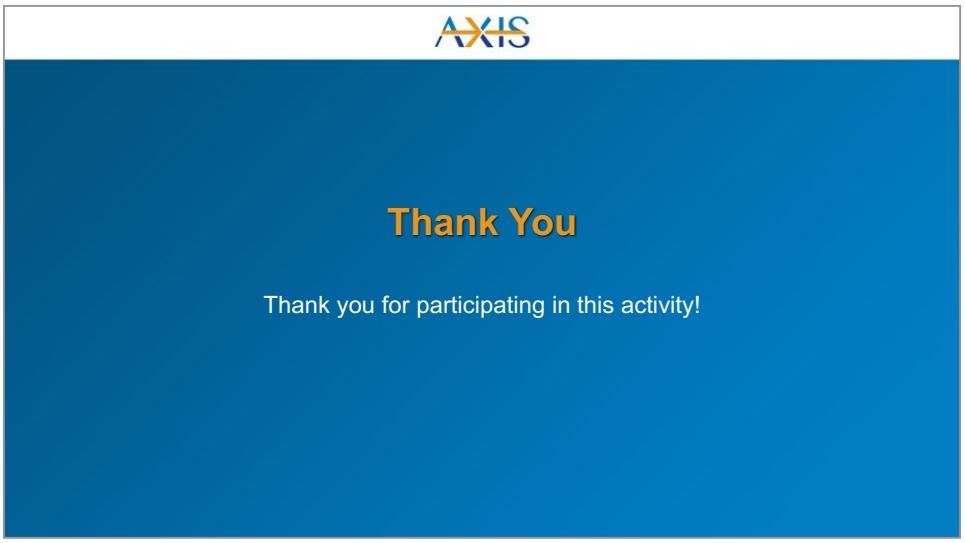
We also know that PARP inhibitors as a class are associated with anemia. We saw anemia to be a common side effect with olaparib and thrombocytopenia a common side effect of rucaparib.

And now, if you throw in chemotherapy in this mix, I personally think we are looking at really intolerable side effects in our patients, elderly patients, the prostate cancer patient population.

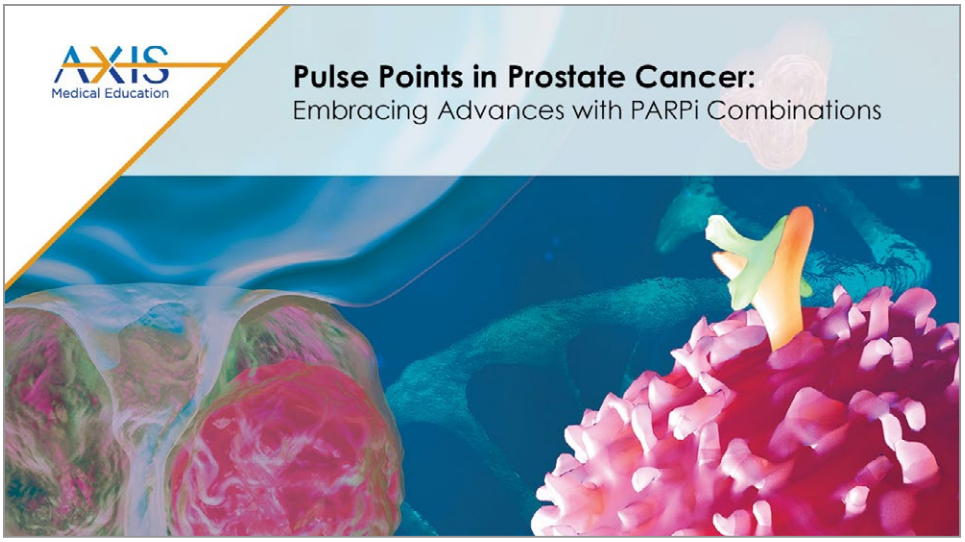
So, I do not think that there's any role for combining these chemotherapies with PARP inhibitors. And with the approval of PARP inhibitors, I have these agents available in my clinic. And beyond anemia, probably that is the only relevant remarkable side effect I can think of with PARP inhibitors compared to these chemotherapy agents that have side effects way beyond anemia.

We see anemia, febrile neutropenia, severe nausea, vomiting, and just so many other side effects that are known to be associated with agents like carboplatin especially in the elderly patient population. So, at this point in time, I'm happy that PARP inhibitors are approved for my patients in my clinic, and I'll continue to offer to them and not use any chemotherapy agents unless there's a problem with access or affordability.

Dr. de Bono: There's been a lot of work combining PARP inhibitors with chemotherapy like carboplatin, topoisomerase I inhibitors, maybe even topoisomerase II inhibitors, mitoxantrone, could come to mind. My concern here is that this sensitized not only the tumor to that chemotherapy but also normal bone marrow in, for example, the gut. In my experience, certainly carboplatin combinations are really tough with PARP inhibitors. There may also be some merit in PARP inhibition with radiation therapy, which might be of interest downstream. And, obviously, there's the pembrolizumab, you know, PD-1/PD-L1 trial combinations ongoing, which will be of interest, although we'll have to see what those trials show.



- **Dr. Mocharnuk:** Thank you, Dr. Agarwal and Dr. de Bono, for sharing your thoughts. And thank you for participating in this activity today.



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About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

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