CME

Targeting DNA Repair Defects Through PARP Inhibition in Prostate Cancer: Rationale, Evidence, and Clinical Implications

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Activity Information

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Activity Description
In this activity, Emmanuel S. Antonarakis, MD, discusses the rationale for targeting DNA repair defects through PARP inhibition and reviews recent safety and efficacy evidence with PARP inhibitors in patients with prostate cancer. He also highlights guidelines for genetic testing that is used to identify patients who might benefit from PARP inhibitor therapy and explores using PARP inhibitors in the urology clinic.

Target Audience
This activity has been designed to meet the educational needs of urologists, oncologists, physician's assistants, nurse practitioners, and other health care professionals involved in the management of patients with prostate cancer.

Educational Objectives
Upon completion of this activity, participants should be better able to:
- Describe the rationale for therapeutic targeting of DNA repair defects and the mechanism of PARP inhibition in managing *BRCA*-mutant prostate cancer
- Review companion diagnostic tests that detect germline and somatic mutations within the DNA repair pathways
- Discuss the latest evidence with PARP inhibitors in advanced prostate cancer harboring DNA repair defects
- Identify patients with prostate cancer who may be candidates for clinical trial based therapeutic approaches, including studies testing combination regimens with PARP inhibitor components

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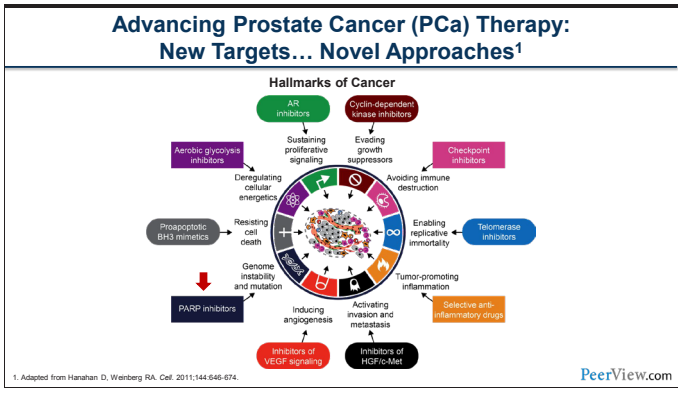
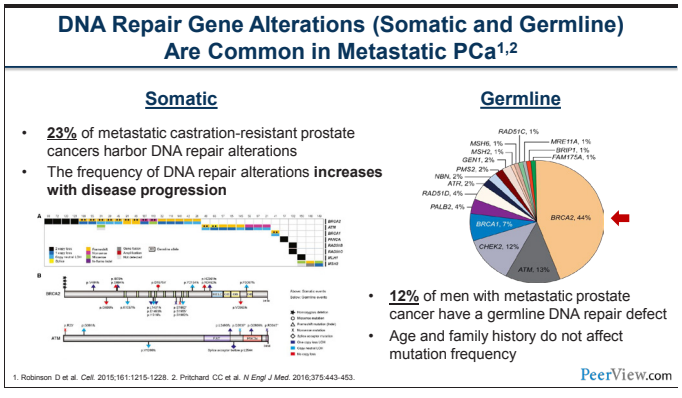
The Rationale for PARP Inhibition in Prostate Cancer

Dr. Antonarakis: Hello, my name is Dr. Emmanuel Antonarakis, and I'm professor of oncology and urology at the Johns Hopkins University School of Medicine and Sidney Kimmel Comprehensive Cancer Center.

Welcome to this educational activity entitled Targeting DNA Repair Defects Through PARP Inhibition in Prostate Cancer, designed to improve the management of patients with advanced prostate cancer. So let's move right into the talk here.



On the first slide, what I'm showing is the classic Weinberg and Hanahan Hallmarks of Cancer figure. And this goes to show that there are many targetable pathways that a cancer cell is dependent on for its growth. And the PARP inhibitors focus on the genomic instability and the mutability, the high mutation rate that is present in many cancers, and this will be the focus of this presentation.

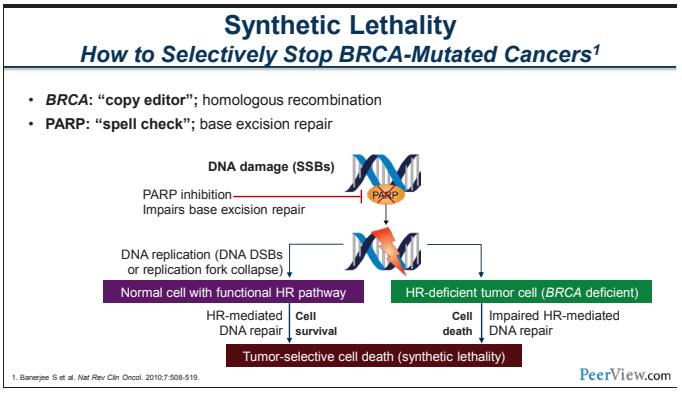


So first of all, how common are these so-called DNA repair gene mutations in prostate cancer and why are they relevant? And this was quite an unexpected discovery that was made about 4 or 5 years ago now, and there are many publications and this slide shows two of the key publications.

On the left side, I'm showing the somatic DNA repair mutations, in other words, the ones that are found inside the prostate cancer cell, and on the right side, I'm showing the germline mutations, which are the inherent mutations that are found in patients who subsequently develop prostate cancer. And the punchline is that approximately one-quarter of all prostate cancers have a somatic DNA repair gene mutation. Of those 23%, the most prevalent mutation is *BRCA2*, followed by *ATM*.

What was perhaps a bit more surprising is that there are many, many germline mutations in prostate cancer. And we have known for a long time that these were present in breast and ovarian cancer, but recent data suggest that 12% of men with metastatic prostate cancer have one or more germline mutations, meaning inherited mutations in one of these DNA repair genes, and that is shown in the pie chart on the right. *BRCA2* is the most commonly mutated germline gene, followed by *ATM*, followed by some other rare genes.

And this is important in the context of PARP inhibition because these DNA repair mutations can become a liability and they can make drugs like PARP inhibitors work in cancers that have these homologous recombination gene mutations or in patients who have inherited germline homologous recombination mutations.



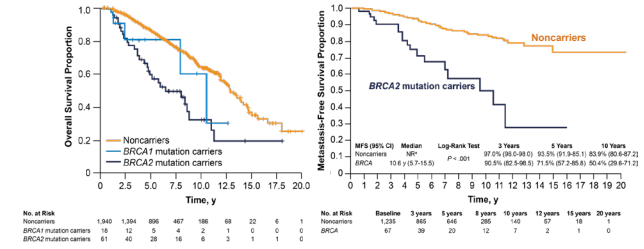
And the way in which these PARP inhibitors work is a term called synthetic lethality. Let me just explain that for a second because it's quite important for understanding the way PARP inhibitors work. There are two ways that any cell, including a cancer cell, can fix DNA damage. The first is to fix one strand at a time, a single-strand

DNA repair. The second is to fix both strands of the double helix at once; that is called a double-strand repair.

The main protein or enzyme that is responsible for double-strand breaks are the homologous recombination genes, of which the most famous is *BRCA1* and *BRCA2*. However, the single-strand DNA repair is fixed primarily by PARP1, and synthetic lethality means that both the single-strand repair pathway and the double-strand repair pathway need to be crippled or inactivated in order for the cell to die.

In the case of a cancer that has a *BRCA2* mutation, or a patient who has an inherited *BRCA2* mutation, that cancer has an inactivation of homologous recombination because of a genetic mutation that is found. And in that context, blocking PARP1 with a drug, a PARP inhibitor, then subsequently wipes out that cell's ability to fix single-strand damage. So now this cell has both double-strand and a single-strand DNA damage, which leads to catastrophic DNA damage and subsequent cell death. So this is what is known as synthetic lethality and this is the broad mechanism by which PARP inhibitors work.

BRCA2 Carriers With PCa Have Worse Prognosis[1,2]



[a] Median survival not reached after a median of 64-mo follow-up.
1. Castro E et al. *J Clin Oncol.* 2013;31:1748-1757. 2. Castro E et al. *Eur Urol.* 2015;68:186-193.

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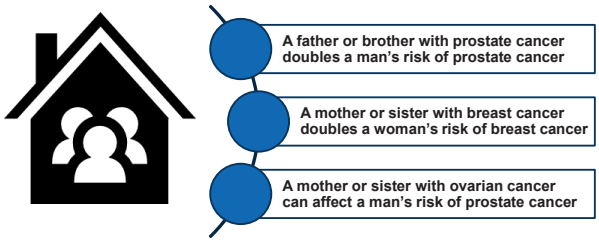
One of the interesting early findings in patients that had germline *BRCA2* mutations is that those men with germline *BRCA2* mutations who developed prostate cancer tended to have worse outcomes, as shown on this slide. Not only did they have generally younger age of onset of their cancer and generally higher Gleason scores, but they also had a shorter metastasis-free survival and shorter overall survival if they had a germline *BRCA2* mutation compared with no *BRCA2* mutation.

The *BRCA1* mutations in prostate cancer are relatively more rare, but their outcomes are sort of intermediate between the wild type patients and the *BRCA2*-positive patients.

Family History Is a Real Risk Factor



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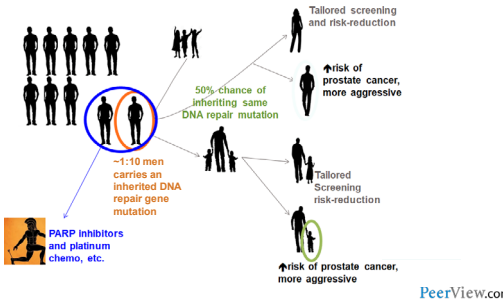
And this is where the discussion about family history is very, very important. And a lot of us, including myself, we used to always ask about family history of prostate cancer in our clinics but we weren't very good, at least I wasn't, at asking about family history of breast cancer or ovarian cancer. And it turns out that this was a big mistake because the same genes that predispose to breast cancer and ovarian cancer in females are one and the same that also predispose to prostate cancer in men.

So of course, we should still be asking every patient "Do you have a father or a brother or a son with prostate cancer," but beyond that we should be asking the second question which is, "Do you have a mother or a sister or a daughter with breast cancer or ovarian cancer?" And by asking this more broad question, instead of focusing only on the prostate cancer family history, we might capture a larger number of these genetically-inherited forms of prostate cancer.

Cascading Impact



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This has implications not just for the patient but also for the patient's family members. This is what is called the cascade effect, also known as cascade testing. So if a man with prostate cancer is himself diagnosed with a germline DNA repair gene mutation such as *BRCA2*, then each of his first-degree relatives of both sexes, meaning parents, siblings, and children, have a 50% chance of also inheriting the same DNA repair gene mutation.

This is important in the case of *BRCA1* and *BRCA2* because, of course, in males these gene mutations can predispose to prostate cancer, but in females, these genes can predispose to breast and

ovarian cancer. And in the case of *BRCA2*, can also predispose to melanoma and also pancreatic cancer in both sexes.

So, on the one hand, while finding a *BRCA2* germline mutation in a male with prostate cancer can potentially help to prioritize that patient for PARP inhibitor therapy or maybe even platinum therapy, there are also family implications for this gentleman's first-degree relatives, meaning parents, siblings, and children.

NCCN (V 2.2020) Guidelines for Genetic Testing[1]

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 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 in patients with metastatic CRPC, and should be considered in patients with regional or castration-naïve metastatic prostate cancer

1. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

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The NCCN guidelines have been very quick to adopt guidelines both for germline testing and somatic testing, as I'm showing on this slide. And about two years ago, this wasn't even discussed on the panel and in the current version, which is version 2.2020, which was issued in May of 2020, there are now very well-developed guidelines both for germline testing, as shown on the left, and somatic testing, as shown on the right.

So the current NCCN prostate cancer guidelines recommend germline testing for every patient with prostate cancer who has high-risk, localized disease or very high-risk localized disease, or patients who have a regional spread, meaning a lymph node-positive prostate cancer, or patients that have metastatic prostate cancer. If you turn that on its head, it's basically everyone except for the low-risk and very low-risk.

In addition to that, anyone that has an Ashkenazi Jewish ancestry, regardless of the risk, even if they are low-risk or very low-risk, they are recommended to undergo germline testing. And in addition, anyone who has a known family history of a *BRCA1*, *BRCA2*, or a mismatch repair mutation, in other words the Lynch syndrome, and anyone who has a strong positive family history, not just of prostate cancer but other cancers as well, such as breast, ovarian, and pancreatic cancer, should also undergo testing.

So when you actually sum it all up, virtually every patient according to NCCN guidelines, with very few exceptions, is recommended to undergo germline testing, typically at the time of the first diagnosis.

Moving over to somatic testing, in other words, tumor testing. Because of the FDA approval of PARP inhibitors and because of the availability of pembrolizumab as well for the MMR-deficient prostate cancers, now the panel recommends somatic testing in all patients with metastatic disease, and it should also be considered in patients with regional prostate cancer - again, meaning those that have positive lymph nodes. So again, this is virtually every patient that a medical oncologist sees and most patients that a urologist will see in his clinic.

Latest Evidence of PARP Inhibitors in Prostate Cancer Treatment

Many PARP Inhibitors Are Being Tested in PCa[1]

Properties of PARP Inhibitors

	Olaparib	Veliparib	Talazoparib	Niraparib	Rucaparib
MW	434.5	244.3	380.8	320.4	323.4
PARP1 IC_{50}	5 nM	1.2 nM	0.56 nM	3.8 nM	0.65 nM
PARP2 IC_{50}	1 nM	0.41 nM	0.15 nM	2.1 nM	0.08 nM
Trapping	++	+	++++	+++	++

1. Carney B et al. *Nat Commun*. 2018;9:176.

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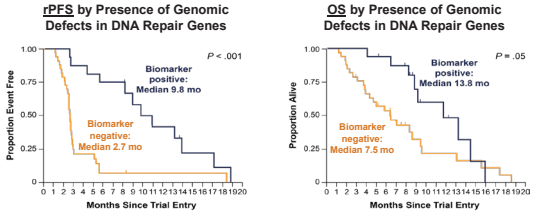
Let's now move on to the second part of the talk, which is to review the data of at least four PARP inhibitors that have been tested in prostate cancer, and at least two of them have already transformed the treatment landscape based on the May 15, 2020 FDA approval of rucaparib, and the May 19, 2020 FDA approval of olaparib. So in an unprecedented move within the span of one week, the FDA has now approved two PARP inhibitors for advanced prostate cancer. We're going to review the data in more detail.

There are many, many PARP inhibitors out there already and I'm showing five in this particular slide. They are all relatively similar in some respects but they do have some differences. There are two main ways in which PARP inhibitors work. One is they inhibit the enzymatic activity of the PARP1 and PARP2 enzymes, and the second is that they trap PARP on the DNA and they prevent PARP from detaching or ungluing itself from the DNA. And it is thought that stronger PARP1 and PARP2 enzymatic inhibition, as well as stronger PARP trapping, or the combination of the two might be required for maximum activity.

So I'm going to go through some of these agents just to make the point that some of these, such as talazoparib, are more potent PARP trappers, while other agents, such as rucaparib, are very potent PARP1 and PARP2 enzymatic inhibitors.

TOPARP-A: Olaparib and Superior Outcomes in mCRPC Patients With DNA Repair Gene Alterations[1]



- Overall response rate of 32.7%; median duration of response ~9 months
- 14 of 16 patients (88%) with a DNA repair alteration had a response
- 2 of 33 patients (6%) without a DNA repair alteration had a response

1. Mateo J et al. *N Engl J Med*. 2015;373:1697-1708.

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So let's start with olaparib, and this is the one that really was the first in the field to be tested in prostate cancer in any systematic way. And this paper that I'm showing here is *The New England Journal of Medicine* paper from 2015. This was the first study of olaparib in approximately 49 patients with advanced metastatic castration-resistant prostate cancer, and this was an unselected population, meaning that patients with, as well as without, DNA repair gene mutations were allowed to enroll.

And after the study was fully enrolled, the investigators then went back retrospectively and looked to see which patients benefit most from this class of therapies. And what they found was patients who had at least one or more DNA repair gene mutation, specifically those in the homologous recombination pathway such as *BRCA2*, derived the greatest benefit.

So if you look at these Kaplan-Meier curves showing progression-free survival on the left and overall survival on the right, in both cases the biomarker-positive patients, meaning those that had one or more DNA repair gene mutations, were the ones that had the greatest sensitivity. Interestingly, when they looked at response rates, if the patient had a DNA repair mutation, there was an 88% chance of a response, and if the patient didn't have a DNA repair mutation, there was only a 6% chance of a response. This was the TOPARP-A study.

TOPARP-B: Phase 2 Olaparib Trial in mCRPC Patients Positive for DNA Repair Gene Alterations[1]

Median follow-up: 20.5 mo

Endpoint	Overall (n = 92)	By DNA Repair Gene Alteration, n (%)				
		BRCA1/2 (n = 30)	*ATM* (n = 19)	*PALB2* (n = 7)	*CDK12* (n = 20)	Other (n = 20)[a]
Confirmed composite response	400-mg cohort: 54% (95% CI, 39-69.1) 300-mg cohort: 39% (95% CI, 25.1-54.6)	25 (83%)	7 (37%)	4 (57%)	5 (25%)	4 (20%)
RECIST/PSA response	400-mg cohort: 41% (95% CI, 27-56.8) 300-mg cohort: 28% (95% CI, 16-43.5)	24 (80%)	2 (10.5%)	4 (57%)	0%	2 (10%)
Median PFS, mo (Evaluable N)	400-mg cohort: 5.6 300-mg cohort: 5.5	8.3 (N = 32)	5.8 (N = 21)	5.3 (N = 7)	2.9 (N = 20)	2.8 (N = 18)

[a] *ATRX, CHEK1, CHEK2, FANCA, FANCF, FANCG, FANCI, FANCM, RAD50, WRN.*
1. Mateo J et al. *Lancet Oncol*. 2020;21:162-174.

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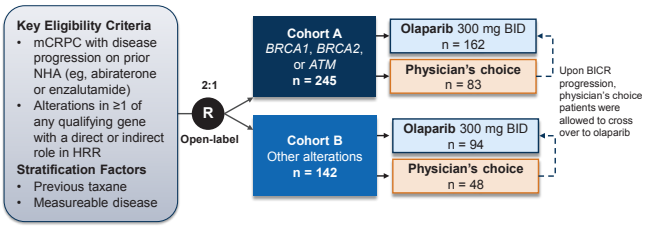
Based on this genomically unselected study, the same investigators followed up with a second trial called the TOPARP-B study. And here what they did was they tested olaparib at two different doses in only the biomarker-positive patients, in other words, only patients that had one or more of the homologous recombination gene mutations.

And the long story short is that this agent, olaparib, continued to show very promising activity in many of these genes, but the most pronounced activity, by far, actually was in patients who had *BRCA1* and *BRCA2* mutations. And the responses were far less impressive in patients who had other mutations, such as *ATM*, *PALB2*, or *CDK12*.

PROfound: Study Design[1]



- 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

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

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This ultimately led to the phase 3 registrational study that was called PROfound, published in *The New England Journal of Medicine* in May of 2020, and subsequently leading to the FDA approval of olaparib in prostate cancer. Let's go through the eligibility because this actually informed the FDA's label.

So these patients were metastatic castration-resistant prostate cancer patients. They had to have received either enzalutamide or abiraterone or both, and they were allowed to have received one taxane chemotherapy, such as docetaxel, but it was not required, so a taxane was not mandatory but it was permitted. And then they were randomized to either receive olaparib or their physician's choice of enzalutamide or abiraterone.

There were two cohorts. The primary statistical analysis was based on cohort A, which only included patients with either *BRCA1*, *BRCA2*, or *ATM* mutations. That cohort comprised 245 patients, who were then randomized 2:1 to receive either olaparib or physician's choice of novel hormone therapy.

There was then a second cohort, and in the second cohort they considered patients with genetic mutations in one of 12 other DNA repair genes other than *BRCA1*, *BRCA2*, or *ATM*. That cohort comprised 142 patients, and in this cohort patients were also randomized 2:1 either to receive olaparib or physician's choice of hormonal therapy. The primary endpoint was radiographic progression-free survival for cohort A, and the secondary endpoint was radiographic progression-free survival for cohort A plus B combined.

PROfound: Patient Characteristics[1]

Characteristics	Cohort A		Cohorts A and B	
	Olaparib (n = 162)	Control (n = 83)	Olaparib (n = 256)	Control (n = 131)
Median age at randomization, y (range)	68 (47-86)	67 (49-86)	69 (47-91)	69 (49-87)
Age ≥65 y at randomization, n (%)	108 (67)	60 (72)	174 (68)	97 (74)
Metastatic disease at initial diagnosis, n (%)	38 (23)	19 (23)	66 (26)	25 (19)
Missing data	7 (4)	4 (5)	11 (4)	7 (5)
Gleason score ≥ 8, n/total n (%)	105/157 (67)	54/80 (67)	183/251 (73)	95/127 (75)
Patients with alterations in a single gene, n (%)				
BRCA1	8 (5)	5 (6)	8 (3)	5 (4)
BRCA2	80 (49)	47 (57)	81 (32)	47 (36)
ATM	60 (37)	24 (29)	62 (24)	24 (18)
CDK12	N/A	N/A	61 (24)	28 (21)
Median PSA at baseline (IQR), mcg/L	62.2 (21.9-280.4)	112.9 (34.3-317.1)	68.2 (24.1-294.4)	106.5 (37.2-326.6)
Measurable disease at baseline, n (%)	95 (59)	46 (55)	149 (58)	72 (55)

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

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The baseline characteristics of the patients receiving olaparib and the patients receiving the control therapy were generally matched. The most common gene mutation was *BRCA2*. The second-most common was *ATM*, and then in the cohort that included the non-*BRCA1*/2 and *ATM* mutations, the most common gene alteration in that cohort was in *CDK12*.

PROfound Patient Characteristics[1] (Cont'd)

Characteristic	Cohort A		Cohorts A and B	
	Olaparib (n = 162)	Control (n = 83)	Olaparib (n = 256)	Control (n = 131)
Metastases at baseline, n (%)				
Bone only	57 (35)	23 (28)	86 (34)	38 (29)
Visceral: lung or liver	46 (28)	32 (39)	68 (27)	44 (34)
Other	49 (30)	23 (28)	88 (34)	41 (31)
ECOG performance status, n (%)				
0	84 (52)	34 (41)	131 (51)	55 (42)
1	67 (41)	46 (55)	112 (44)	71 (54)
2	11 (7)	3 (4)	13 (5)	4 (3)
Missing data	0	0	0	1 (1)
Previous new hormonal agent, n (%)				
Enzalutamide only	68 (42)	40 (48)	105 (41)	54 (41)
Abiraterone only	62 (38)	29 (35)	100 (39)	54 (41)
Enzalutamide and abiraterone	32 (20)	14 (17)	51 (20)	23 (18)
Previous taxane use, n (%)	106 (65)	52 (63)	170 (66)	84 (64)
Docetaxel only	74 (46)	32 (49)	115 (45)	58 (44)
Cabazitaxel only	2 (1)	0	3 (1)	0
Docetaxel and cabazitaxel	29 (18)	20 (24)	51 (20)	26 (20)
Paclitaxel only	1 (<1)	0	1 (<1)	0

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

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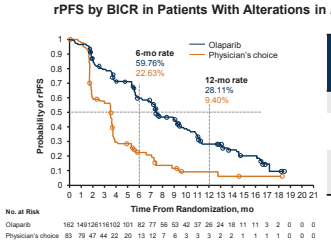
About 65% of patients in all cohorts had previously received at least one chemotherapy agent, so about one-third were chemotherapy-naïve and two-thirds were chemotherapy-treated. All patients had received either enzalutamide or abiraterone, and approximately 20% in both groups had received both enzalutamide and abiraterone. The groups were also well-balanced with respect to ECOG score and other baseline characteristics.

PROfound Primary Endpoint: rPFS (Cohort A)[1,2]



	Olaparib (n = 162)	Physician's Choice (n = 83)
Events, %	106 (65.4)	68 (81.9)
Median PFS, mo	7.39	3.55
HR (95% CI)	0.34 (0.25-0.47) *P* < .001	

1. Hussain M et al. European Society for Medical Oncology Congress 2019 (ESMO 2019). Abstract LBA12_PR. 2. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

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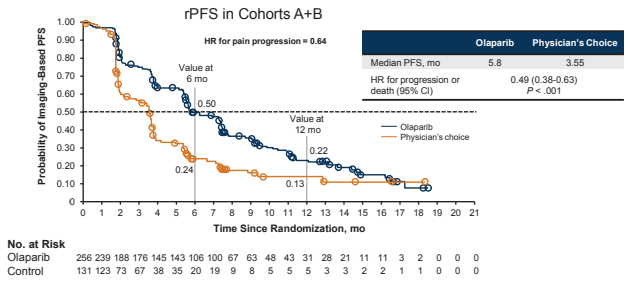
This slide shows the primary endpoint of radiographic progression-free survival comparing olaparib versus physician's choice of abiraterone or enzalutamide in cohort A, again including patients with *BRCA1*, *BRCA2*, or *ATM* mutations. This shows a big difference favoring olaparib, with a hazard ratio of 0.34, showing almost a 70% risk reduction of radiographic progression or death in patients receiving olaparib as opposed to enzalutamide or abiraterone.

PROfound: rPFS Overall Population (Cohorts A+B)[1]



	Olaparib	Physician's Choice
Median PFS, mo	5.8	3.55
HR for progression or death (95% CI)	0.49 (0.38-0.63) P < .001	

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

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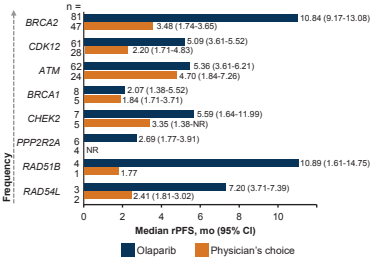
On this slide, I'm showing the prespecified secondary analysis, which comprises radiographic PFS in the entire population of patients, cohort A plus B, so this includes all 15 genes that were included in the eligibility criteria. And what you can see here is that there is also a big difference in radiographic progression-free survival also favoring the olaparib arm over the abiraterone or enzalutamide control arm, and here there's about a 50% relative risk reduction in the chance of developing radiographic metastasis or death.

PROfound: Exploratory Gene-by-Gene rPFS Analysis[1]

- 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)
- 97% of patients were randomized based on alterations in 8/15 single genes
- There is evidence of clinical activity of olaparib in patients with alterations in genes other than *BRCA1* or *BRCA2*
- Gene-level analysis is complex and exploratory, and comparisons may be confounded by multiple factors



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

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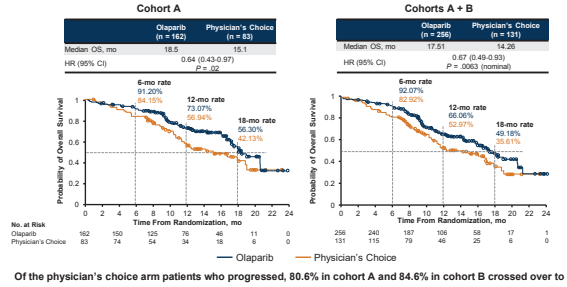
An exploratory gene-by-gene analysis was also reported, and I find this interesting but it should be considered hypothesis-generating at this point. And what this graph on this figure shows is the radiographic progression-free survival in the olaparib group, shown in blue, versus the abiraterone or enzalutamide group, shown in orange. And this is shown on a gene-by-gene basis. So for example, in patients specifically with *BRCA2* mutations, radiographic PFS with olaparib was 10.8 months and radiographic PFS with abiraterone or enzalutamide was 3.5 months.

There are no statistics here because these are not meant to be compared. But what this figure, at least to me, shows is that the majority of the benefit here was derived in the *BRCA2* patients, although there do seem to be some numerical improvements in progression-free survival for some of the other genes as well, potentially *CDK12* and *CHEK2*.

There are also some individually rare genes like *RAD51B* and *RAD54L*, where there does seem to be a very robust, at least numerical, improvement in PFS with olaparib. But these genes are so individually rare that not much can be made of this at this moment.

PROfound: Interim OS[1,2]



Of the physician's choice arm patients who progressed, 80.6% in cohort A and 84.6% in cohort B crossed over to olaparib

1. Hussain M et al. ESMO 2019. Abstract LBA12_PR. 2. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

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This slide shows the overall survival. This is an interim analysis; this is not the mature overall survival analysis. But interestingly, both in cohort A, which is the *BRCA1*, *BRCA2*, *ATM* cohort, and in cohorts A plus B, which are all 15 genes, there is a strong trend favoring the overall survival in the olaparib group versus the abiraterone, enzalutamide group.

Subsequent to this data release, there was a press release reporting data which has not been published yet, saying that in cohort A the overall survival statistical significance has now been met. So perhaps with further follow-up and with that publication being released, we might also see a statistically significant difference in survival, as well as geographic progression-free survival. So again suggesting that maybe not just in the *BRCA1*, *BRCA2*, and *ATM* cohort, but maybe the entire cohort, all 15 genes involved, there might be a PFS advantage and also an OS advantage.

PROfound Safety[1]

Adverse Event[a]	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[b]	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

[a] Any grade AE (≥10% of pts) according to CTCAE and irrespective of attribution, and dose modifications and discontinuations because of AEs.
[b] Includes anemia, decreased Hb level, decreased red cell count, decreased Hct level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia; anemia reported in 46% of patients, and decreased Hb level reported in <1%.
1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

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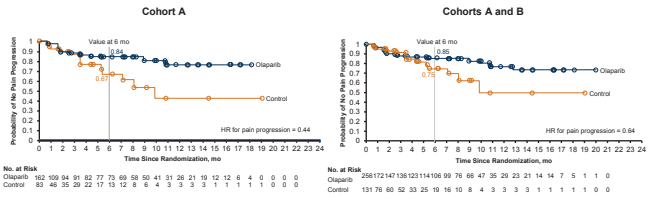
Side effects of PARP inhibitors and of olaparib specifically are notable for anemia, occurring in about half of patients; 20% of those are grade 3. Fatigue is quite common. A decreased appetite or anorexia is quite common and constipation is common. Those are the ones that appear to be more prevalent in the olaparib group compared with the control group.

PROfound Time to Pain Progression[1]



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

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What were some additional quality-of-life endpoints? Firstly, the time to pain progression was prolonged in patients receiving olaparib versus physician's choice. And also, the time to first opioid was also prolonged.

PROfound (Cohorts A + B): Burden of Pain[1]

Time to Pain Progression and First Opiate Use[a]

	Agent	Events, n (%)	6-Month Event-Free Rate, %	12-Month Event-Free Rate, %	Median, m	HR (95% CI)	*P*
Time to progression in worst pain	Olaparib (n = 256)	32 (12.5)	85.2	76.3	NR	0.64 (0.35, 1.21)	.149
	pcNHA (n = 131)	16 (12.2)	74.7	50.5	NR		
Time to progression in pain severity	Olaparib (n = 256)	24 (9.4)	88.7	81.0	NR	0.71 (0.35, 1.54)	.411
	pcNHA (n = 131)	11 (8.4)	81.5	65.2	NR		
Time to first opiate use[b]	Olaparib (n = 175)	65 (37.1)	74.8	58.8	18.0	0.67 (0.46, 0.99)	.023
	pcNHA (n = 92)	44 (47.8)	61.0	47.7	9.0		

[a] Overall questionnaire compliance rate: 92.6% olaparib; 93.1 physician's choice of new hormonal agent (pcNHA). [b] Patients not on opiates at baseline.
1. Saad F et al. 2020 American Society of Clinical Oncology Annual Meeting (ASCO 2020). Abstract 5538.

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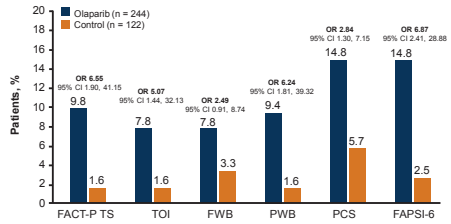
At the ASCO 2020 meeting, there was an ASCO abstract about the burden of pain, in this case primarily bone pain, and this abstract shows that the time to worse pain progression, the time to increasing pain severity, and the time to first opiate use were all numerically and sometimes statistically better in the olaparib arm compared with the physician's choice control arm.

PROfound (Cohorts A + B): HRQoL[1]



A higher proportion of patients in the olaparib arm reported improvement in HRQoL

1. Thiery-Vuillemin A et al. ASCO 2020. Abstract 5539.

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In addition, a second abstract from ASCO 2020 is focusing on the health-related quality of life, and using the classic FACT-P instrument, as well as a number of other quality-of-life instruments. There seems to be consistent advantage of olaparib over abiraterone or enzalutamide in various quality-of-life metrics, again suggesting that not only are patients living longer, but potentially they are also living better.

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[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]

[a] *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*.
[b] Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.
1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

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This phase 3 PROfound study led to the FDA's approval of olaparib for metastatic castration-resistant prostate cancer on May 19, 2020. And this is important because the FDA approval of this agent is slightly different from the FDA approval of rucaparib. And for olaparib, this was approved for patients that had a germline or somatic mutation in one of those HRR genes; it was not specifically for *BRCA1*, 2, and *ATM*; it was for the entire gene panel. So it's a broad FDA approval for all HRR-mutated metastatic prostate cancers.

And in terms of the disease state, these patients do have to have mCRPC and they have to have received one prior line of therapy with either enzalutamide or abiraterone and they don't have to have received the taxane, so this is not an FDA approval that specifically states post-taxane. They could have received the taxane, but it's really not necessary for the FDA label. So any HRR gene mutation and they have to have received either enzalutamide or abiraterone, and they could have received also a taxane, but that is not mandatory for the approval.

Common Side Effects of Olaparib

- Anemia
- Fatigue
- Nausea (vomiting rare)
- Decreased appetite
- Diarrhea
- Thrombocytopenia
- Creatinine elevation
- Cough and dyspnea

Rare but serious: MDS/AML; pneumonitis; PE/thromboembolism

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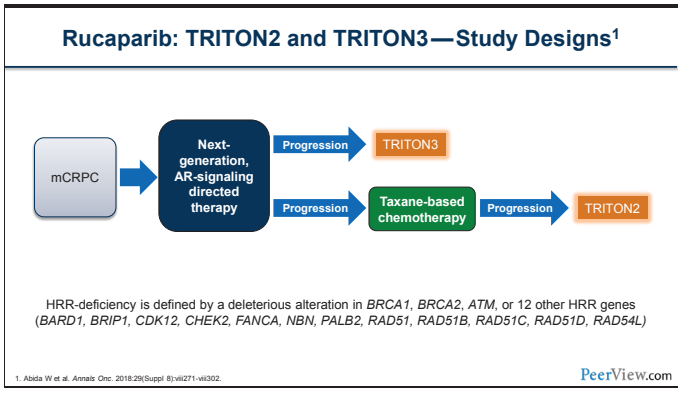
Just to recap, the common side effects of olaparib for treating physicians, like myself. Anemia is quite common, fatigue can be reported, nausea is frequent, but vomiting is rare. The nausea tends to be self-limiting and typically gets better within the second and third month. Decreased appetite or anorexia can sometimes occur.

Diarrhea is common with olaparib, but it's relatively mild. And we see some cytopenia in addition to anemia. Thrombocytopenia can also occur. There's also a class effect with all PARP inhibitors that can slightly raise the creatinine level.

Something that is a little bit unique to olaparib and has not really been seen as much with the other PARP inhibitors is a dry cough and also a subjective feeling of breathlessness or dyspnea. This occurs in about 5% of people. And there's also a rare but serious complication, which is pneumonitis, that has been reported with olaparib. Other rare but serious complications are theoretical risk of MDS or AML, acute myeloid leukemia, and myelodysplastic syndrome, as well as a 7% risk in the PROfound study of a thromboembolic event, either a DVT or a PE or both.

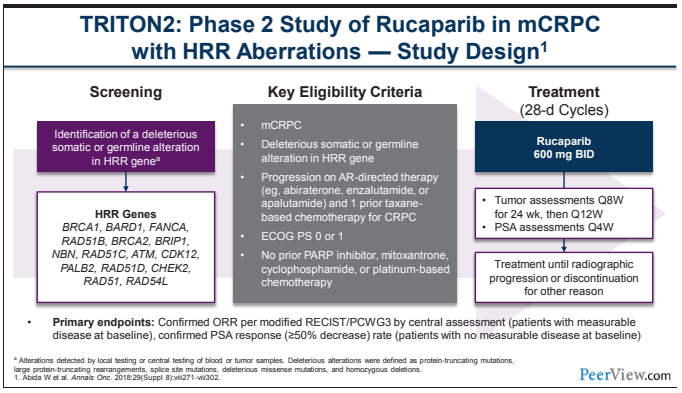


I now want to shift our attention to discuss the second PARP inhibitor that has received FDA approval for prostate cancer, that is rucaparib. And rucaparib has been approved based on a series of trials called the TRITON trials, TRITON2 is the phase 2 trial that led to the FDA approval and TRITON3 is the ongoing trial, which will lead to full approval following the initial accelerated approval.

TRITON2 was a third-line CRPC study, meaning that patients had to have metastatic castration-resistant prostate cancer. They had to have failed at least one AR-signaling therapy, and at least one taxane therapy. I'll talk about the details in a second.

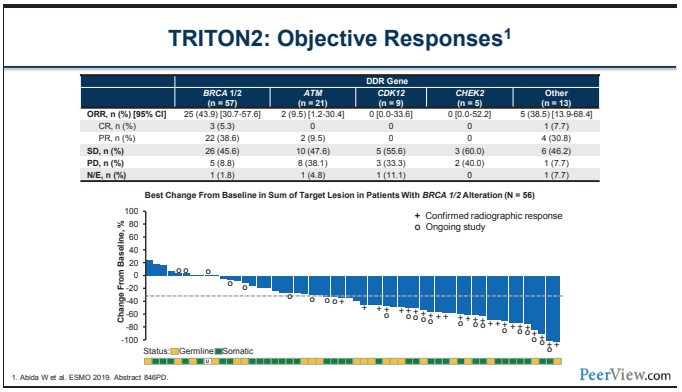
TRITON3, which is the ongoing study, is a second-line study, so it's one step earlier in the disease course, and this study is for patients that have received at least one AR-targeting agent but are chemotherapy-naïve.

The panel of genes that was used for inclusion into the TRITON2 and 3 studies was overlapping but partially different from those genes included in the olaparib PROfound studies. Of course, *BRCA1*, *BRCA2*, and *ATM* were included, but some of the other 12 genes were largely overlapping but not completely identical.



This slide shows the design of the TRITON2 study. Now, this is very important because this was a nonrandomized study; it had a single arm, and quite surprisingly but encouragingly, it did lead to accelerated FDA approval even without having a control arm.

So patients had to have one or more of those DNA repair gene mutations listed in the box on the left. And as I mentioned before, these were post-abiraterone or enzalutamide and also had to be post-taxane. They received rucaparib at a dose of 600 mg twice a day, and the primary endpoint was a composite of either objective response rate or PSA response rate.

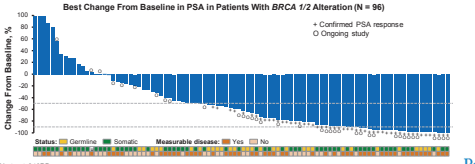


This slide shows objective response rates, in other words, RECIST responses in patients on the TRITON2 study. The table on the top shows objective response rates on a gene-by-gene basis, comparing *BRCA1/2* versus *ATM* versus *CDK12* versus *CHEK2* versus the other rare genes. And what this table shows is that the objective response rate was much, much higher in patients that had *BRCA1/2* mutations compared with the other genes.

The waterfall plot specifically shows objective response rates only in the patients with *BRCA1* and *BRCA2*; these are the patients that led to the FDA approval. And what you can see there by just eyeballing that waterfall plot is that the majority of patients had at least some degree of tumor shrinkage, and approximately 44% had a technical RECIST partial or complete response.

TRITON2: PSA Responses[1]

	DDR Gene				
	BRCA1/2	*ATM*	*CDK12*	*CHEK2*	Other
PSA response rate, n/N (%) [95% CI]					
All evaluable patients	51/98 (52.0) [41.7-62.2]	2/57 (3.5) [0.4-12.1]	1/14 (7.1) [0.2-33.9]	1/7 (14.3) [0.4-57.9]	5/14 (35.7) [12.8-64.9]
With measurable disease	34/57 (59.6) [45.8-72.4]	2/21 (9.5) [1.2-30.4]	1/9 (11.1) [0.3-48.2]	1/5 (20.0) [0.5-71.6]	5/13 (38.5) [13.9-68.4]
With no measurable disease	17/41 (41.5) [26.3-57.9]	0/36 (0) [0.0-9.7]	0/5 (0) [0.0-52.2]	0/2 (0) [0.0-84.2]	0/1 (0) [0-97.5]
Median time to PSA progression, mo [95% CI]	6.5 [5.7-7.5]	3.1 [2.8-3.7]	3.5 [2.8-4.6]	5.6 [2.8-NR]	5.8 [2.8-NR]



1. Abida W et al. ESMO 2019. Abstract 846PD.

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This slide focuses on PSA responses from the TRITON2 study. Again, the table at the top shows PSA responses on a gene-by-gene basis, again showing *BRCA1/2* patients had a much higher chance of a PSA response than patients with other gene mutations. And on the bottom, the waterfall plot shows best PSA response and again, the majority of patients had at least some degree of PSA reduction, and approximately 50% of patients had a confirmed PSA response. Again, the waterfall plot shows only the *BRCA1* and *BRCA2* patients.

TRITON2: Response by Non-*BRCA* DDR Gene Alterations[1,a]

	By DDR Gene Group			
	ATM (n = 49)	CDK12 (n = 15)	CHEK2 (n = 12)	Other[b] (n = 14)
Confirmed investigator-assessed objective response[c]	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)
CR	0/19 (0.0)	0/10 (0)	0/9 (0)	1/14 (7.1)
PR	2/19 (10.5)	0/10 (0)	1/9 (11.1)	3/14 (21.4)
SD	9/19 (47.4)	6/10 (60.0)	6.9 (66.7)	8/14 (57.1)
PD	7/19 (36.8)	3/10 (30.0)	2/9 (22.2)	1/14 (7.1)
NE	1/19 (5.3)	1/10 (10.0)	0/9 (0)	1/14 (7.1)
6-month clinical benefit rate[d]	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[e]	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[f]	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)	11.0 (3.0-NR)

[a] Visit cutoff date: April 29, 2019. Data are *n/N* (%) (95% CI) unless stated otherwise. [b] Includes patients with an alteration in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n =2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1). [c] Per modified RECIST/PCWG3 criteria; includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up. [d] Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 6 months. [e] Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 12 months. [f] Defined as ≥50% reduction in PSA from baseline; includes patients who had ≥16 weeks of follow-up.
1. Abida W et al. *Clin Cancer Res*. 2020 Feb 21 [Epub ahead of print].

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The TRITON2 study has already published the non-*BRCA* cohort. Surprisingly, they published the non-*BRCA* cohort before they published the *BRCA1* and *BRCA2* cohort, and in fact, the *BRCA1* and *BRCA2* cohort is still not published to date. And the *BRCA1* and *BRCA2* cohort is the one that led to the FDA approval.

The FDA approval of rucaparib, as I will discuss in a second, does not cover the genes shown on this slide. It does not cover *ATM*, *CDK12* or *CHEK2*, unlike the FDA approval of olaparib, which does.

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.[1]

The TRITON3 study is underway and recruiting patients with mCRPC and homologous recombination gene deficiency.[2]

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

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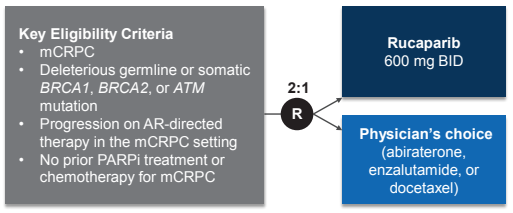
So on May 15, 2020, the FDA approved rucaparib based on the single-arm, uncontrolled study of TRITON2. The difference compared with olaparib being that here the indication was a bit narrower; it was only for patients with germline or somatic *BRCA1* or *BRCA2* mutations, specifically. And this was a third-line mCRPC approval, meaning that for this drug, patients have to have received and progressed after an androgen receptor-directed therapy and a taxane-based chemotherapy. So two main differences between rucaparib and olaparib are olaparib is approved for all HRR gene mutations, rucaparib is only approved for *BRCA1/2*, and olaparib does not require a taxane-based chemotherapy previously but rucaparib does require that.

And the TRITON3 study is the trial that will convert the accelerated approval, which is what rucaparib has right now, into a full approval. And the next slide shows the trial design of the TRITON3, which is the randomized registrational phase 3 study.

TRITON3: Study Design[1]



- **Primary endpoint:** radiographic PFS

1. https://clinicaltrials.gov/ct2/show/NCT02975934.

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So in this trial, patients with metastatic castration-resistant prostate cancer with a *BRCA1*, *BRCA2*, or *ATM* mutation, so a narrower genomic population, who has received at least one AR-directed therapy but has not previously received chemotherapy or a PARP inhibitor will be randomized in a 2:1 fashion to either receive oral rucaparib or a physician's choice of one of three agents, either abiraterone or enzalutamide or actually even docetaxel chemotherapy.

The primary endpoint here is radiographic progression-free survival. This study is ongoing, and if this study is positive, the

FDA will convert the accelerated approval of rucaparib into full approval.

Common Side Effects of Rucaparib

- Anemia
- Fatigue, asthenia
- Nausea (vomiting rare)
- Decreased appetite
- Diarrhea or constipation
- Thrombocytopenia
- Increased AST/ALT and/or creatinine
- Rash
- *Rare but serious*: MDS/AML; fetal teratogenicity

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This slide shows the common side effects of rucaparib. These are partially overlapping but not identical with those of olaparib. So anemia is common, usually grade 1 or grade 2. Fatigue or asthenia can be seen. Nausea again is quite common and self-limiting after the second or third month. Anorexia or decreased appetite can be seen. Either diarrhea or constipation have been noted. Again, cytopenias, including mild thrombocytopenia should be looked for.

And this drug, rucaparib can also cause AST/ALT elevations, typically grade 1. Unlike olaparib, this one also has a little bit higher incidence of a rash. But unlike olaparib, rucaparib has not really been shown to be associated with the pulmonary complications, like the cough or the pneumonitis, nor has it really been associated with venous thromboembolic events. A theoretical risk of myelodysplastic syndrome and acute myeloid leukemia is still there for this one, as well as the potential risk of teratogenicity to a fetus as well.

Phase 2 GALAHAD: Niraparib in Previously Treated mCRPC With *Biallelic* DDR Mutations[1]

Biomarker evaluation (prescreening) → **Screening phase (28 d)** → **Treatment phase (niraparib 300 mg/d)** → **Follow-up phase**

28-d cycle until end of treatment[a]

Every 3 mo after end of treatment

Key Eligibility Criteria
- mCRPC
- Biomarker positive for **biallelic** DRD mutation
- Progressed on ≥1 ARSI therapy and ≥1 taxane-based chemo
- No prior PARP inhibitor or platinum-based chemo
- No prior MDS/AML

Primary Endpoint

ORR of soft tissue (visceral or nodal disease), as defined by RECIST 1.1[b] with no evidence of bone progression according to PCWG3 criteria in patients with **biallelic** *BRCA* mutations

Secondary endpoints
- ORR
- CTC response
- OS
- rPFS
- DOR
- Safety

Composite response rate, derived from the secondary endpoints and the exploratory endpoint of CTC conversion, was defined as ORR by RESIST 1.1, or conversion CTC from ≥5/7.5 mL to <5/7.5 mL of blood, or ≥50% decline in PSA level.

[a] Treatment continued until disease progression, unacceptable toxicity, or death. [b] Investigator assessed.
1. https://clinicaltrials.gov/ct2/show/NCT02854436.

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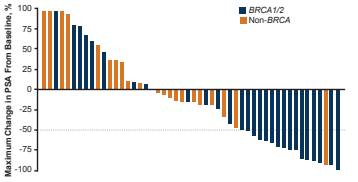
I now quickly want to review some preliminary unpublished data on two additional PARP inhibitors. The first is niraparib and the second is talazoparib. So the niraparib program is called the GALAHAD study, and the GALAHAD is a phase 2 trial looking at patients that have one or more DNA repair gene mutations, again.

The interesting thing about the GALAHAD study, which sets it apart from the other two, is that in this trial they are using a liquid biopsy, in other words, a circulating tumor DNA analysis. That's the first difference. The second difference is that this study requires a biallelic inactivation of the gene, biallelic meaning that both copies of the gene, both alleles need to be mutated or inactivated or lost.

So this restricts the population a little bit more, because if you have a *BRCA2* mutation but you have a *BRCA2* mutation in only one allele and the second alleles is wild type, theoretically that person would not be allowed to enroll in this study. And the drug, of course, as I mentioned is niraparib, which was 300 mg daily. Primary endpoint here was objective response rate and then the secondary endpoint is a composite involving objective response rate, PSA response rate and CTC reduction.

Phase 2 GALAHAD: ORR, PSA Response, CTC response[1]

n/N % (95% CI)	All Biallelic DND (N = 50)	
	BRCA1/2 (n = 29)	Non-*BRCA1/2*[a] (n = 21)
Composite RR	18/29 62.1 (42.3-79.3)	5/21 23.8 (8.2-47.2)
Objective RR[b]	6/16 37.5 (15.2-64.6)	2/15 13.3 (1.7-40.5)
≥50% decline in PSA	15/29 51.7 (32.5-70.6)	1/21 4.8 (0.1-23.8)
CTC conversion (<5/7.5 mL blood)	12/29 41.4 (23.5-61.1)	4/21 19.0 (5.5-41.9)
CTC response	6/29 20.7 (8.0-39.7)	2/21 9.5 (1.2-30.4)



[a] *ATM, FANCA, PALB2, CHEK2, BRIP1,* or *HDAC2* assayed, not all represented in non-BRCA patients. [b] Investigator-assessed.
1. Smith MR et al. *J Clin Oncol.* 2019;37(Suppl7):202.

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This slide shows objective response rates in the *BRCA1/2* patients versus the non-*BRCA1/2* patients. And as shown before, the responses are more pronounced in those that have the *BRCA1* and *BRCA2* mutations. In the waterfall plot, the black bars show the *BRCA1* and *BRCA2* mutations and the blue bars show the non-*BRCA* mutations, again showing that the majority of the most profound responses are, again, in patients with the *BRCA1/2*. Different PARP inhibitor, same story: *BRCA1* and *BRCA2* are the main sensitivity genes, the other genes not so much, although there can be occasional patients with rare responses.

TALAPRO-1: Talazoparib in mCRPC With DDRm[1]

Eligibility criteria
- Age ≥18 y
- Progressive mCRPC
- Measurable soft tissue disease
- 1-2 previous chemotherapy regimens (≥1 taxane-based regimen) for mCRPC
- Progressed on ≥1 NHT[a] for mCRPC
- DDRm[b] likely to sensitize to PARPi

N = ~100

→ **Talazoparib 1 mg daily** (0.75 mg, if moderate renal impairment) → Until radiographic progression, unacceptable toxicity, consent withdrawal, or death

Primary endpoint: ORR

Secondary endpoints: Time to OR, DOR, PSA decrease ≥50%, CTC count conversion (to CTC = 0 and <5 per 7.5 mL blood) time to PSA progression, rPFS, OS, safety

[a] Enzalutamide/abiraterone acetate. [b] DDRm are defined as known/likely pathogenic variants or homozygous deletions in: *ATM, ATR, BRCA1/2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C.*
1. https://meetinglibrary.asco.org/record/188251/abstract.

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And finally, talazoparib, which is the fourth in line. This was investigated in the TALAPRO study, recently presented at ASCO 2020. These were, again, genomically selected patients with at least one or more DNA repair gene mutations. And again, objective

response rate was the primary endpoint, a number of secondary endpoints, as discussed above. These trials have similar types of endpoints.

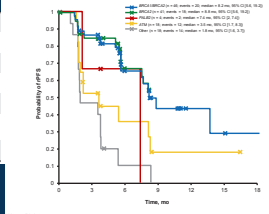
TALAPRO-1: Efficacy and Safety Results[1]

% (response/n)	*BRCA1/2* (n = 46)	*BRCA2* (n = 41)	*PALB2* (n = 4)	*ATM* (n = 18)	Other (n = 18)	Total (N = 86)
Composite Response	71.7 (33/46)	75.6 (31/41)	50.0 (2/4)	22.2 (4/18)	11.1 (2/18)	47.7 (41/86)
ORR	41.5 (17/41)	40.5 (15/37)	33.3 (1/3)	11.8 (2/17)	0 (0/14)	26.7 (20/75)
Confirmed CR	4.9 (2/41)	5.4 (2/37)	0 (0/3)	5.9 (1/17)	0 (0/14)	4.0 (3/75)
Confirmed PR	36.6 (15/41)	35.1 (13/37)	33.3 (1/3)	5.9 (1/17)	0 (0/14)	22.7 (17/75)
SD ≥6 mo	2.4 (1/41)	2.7 (1/37)	0 (0/3)	11.8 (2/17)	0 (0/14)	4.0 (3/75)
PSA decline ≥50% from baseline	60.9 (28/46)	63.4 (26/41)	50.0 (2/4)	5.6 (1/18)	5.6 (1/18)	37.2 (32/86)
CTC conversion ≥5 to <5	93.8 (15/16)	93.8 (15/16)	0 (0/1)	50.0 (3/6)	25.0 (1/4)	70.4 (19/27)

In this interim analysis (Dec 2019) of TALAPRO-1, talazoparib monotherapy demonstrated antitumor activity in mCRPC patients with DDR alterations who have previously received taxane therapy and NHT with a confirmed overall ORR of 26.7%. Efficacy was most notable in the subset of patients with mCRPC whose tumors harbored *BRCA1/2* alterations, who had a confirmed ORR of 41.5%.

Talazoparib monotherapy was generally well tolerated. No new safety signals were observed in this patient population compared with the known safety profile of talazoparib.

rPFS by DDR Alteration by BICR[a]



[a] DDR-deficient population (N = 86) includes DDR patients who received treatment for ≥16 weeks.
1. de Bono J et al. ASCO 2020. Abstract 5566.

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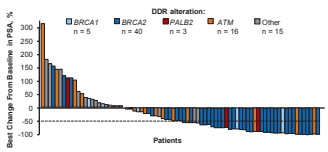
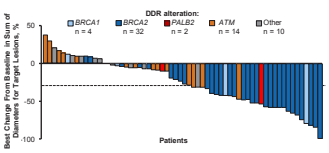
And here it just makes the point that not all genes respond equivalently to talazoparib. For *BRCA1* and *BRCA2*, there are very high response rates, approaching 41%. For the other genes, there are much lower response rates, between 10% and 30%. And the Kaplan-Meier curve on the right shows radiographic progression-free survival, suggesting that the green and the blue, which are *BRCA1* and *BRCA2*, have the longest-term responses, whereas the orange and the gray, which are *ATM* and other genes, have fewer responses.

TALAPRO-1: Efficacy and Safety Results[1]

Best Change From Baseline in PSA[a]



Best Change From Baseline in RESIST[a]



[a] DDR-deficient population includes DDR patients who received treatments for ≥16 weeks; PSA, n = 79 and RECIST, n = 62.
1. de Bono J et al. ASCO 2020. Abstract 5566.

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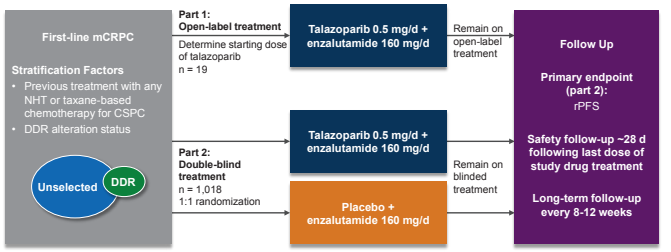
These are the waterfall plots for best PSA responses on the left, and best objective responses on the right. The bars shown in light blue and dark blue are *BRCA1* and *BRCA2*, respectively, and the bars shown in other colors are the other genes.

This again shows that the greatest chance of having a PSA response or an objective response to talazoparib is for those patients who have a *BRCA1* and *BRCA2* mutation, but there are also occasional responses, sometimes pronounced responses in patients that have non-*BRCA* mutations as well.

TALAPRO-2: Study Design[1]



1. https://clinicaltrials.gov/ct2/show/NCT03395197.

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This will lead to the ongoing TALAPRO-2 study, and this is a trial that is a combination of talazoparib plus enzalutamide. I want to point your attention to the fact that the dose of talazoparib is half of the dose used in other cancers like breast cancer, it's 0.5 mg rather than 1 mg, and that's because there was a drug-drug interaction within talazoparib. So in this study, the design was the full dose of enzalutamide, which is 160 mg daily, plus the half-dose of talazoparib, which is 0.5 mg daily.

This study has two cohorts, a genomically unselected cohort, in other words an all-comers cohort, and then a separate DNA damaged response mutation-positive cohort. In each cohort, there's a randomization against enzalutamide plus placebo or enzalutamide plus talazoparib. The question here is whether the addition of talazoparib to enzalutamide will prolong radiographic progression-free survival and overall survival.

Ongoing Studies of Novel Hormonal Agents in Combination With PARP Inhibitors in PCa

- NCT03732820: Phase 3 Study of Olaparib + Abiraterone vs Abiraterone in mCRPC **(PROpel)**
- NCT03748641: Phase 3 Study of Niraparib + Abiraterone vs Abiraterone in mCRPC **(MAGNITUDE)**
- NCT03395197: Phase 3 Study of Talazoparib + Enzalutamide vs Enzalutamide in mCRPC **(TALAPRO-2)**

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Based on the promising single-agent activity of these various PARP inhibitors, a number of combination strategies are now being pursued. The first type of combination is the combination of PARP inhibitors with novel hormone agents, including abiraterone and enzalutamide, as shown on this slide. And the three key ongoing trials to point out are the PROpel study, the MAGNITUDE study and the TALAPRO-2 study.

Ongoing Studies of PD-1/PD-L1 Inhibitors in Combination With PARP Inhibitors in PCa

- NCT03338790: Phase 2 Study of Nivolumab in Combination With Rucaparib, Docetaxel, or Enzalutamide in mCRPC **(CheckMate -9KD)**
- NCT03330405: Phase 2 Study of Avelumab Plus Talazoparib in Locally Advanced or Metastatic Solid Tumors **(JAVELIN PARP Medley)**
- NCT03834519: Phase 3 Study of Pembrolizumab + Olaparib vs Abiraterone or Enzalutamide in mCRPC **(KEYLYNK-010)**

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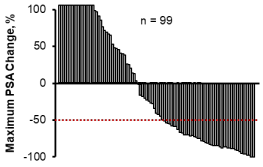
Of course, there are other investigational agents that can also be combined with PARP inhibitors and this slide here shows the combination of PARP inhibitors with immunotherapy, specifically, PD-1 or PD-L1 agents. This list here is incomplete and there are many other trials that are ongoing combining PARP inhibitors with other investigational agents, but the combination specifically with immune checkpoint inhibitors is of particular interest to the field and also to patients.

Phase 2 LuPSMA Trial: Tumor Response and PSA Response With ^{177}Lu-PSMA-617 in mCRPC[1,2]

Maximum % PSA Change From Baseline Over Total Follow-Up Period (PSA increase >100% cropped for simplification)



Imaging Response at 3 Months After Last Cycle of Lu-PSMA Received

Response n (%)	Bone Scintigraphy	Soft-Tissue Lesions (Nodal and Visceral[a]; n = 17)	PSMA-PET	FDG-PET[b]
CR	N/A	5 (29)	3 (10)	6 (20)
PR	N/A	9 (53)	9 (30)	4 (13)
SD	11 (37)[c]	0	0	1 (3)
PD	9 (30)	2 (12)	8 (27)	8 (27)
Not performed (clinical progression or death)	9 (3)	0	9 (30)	10 (33)
Not performed (death from other cause)	1 (3)	1 (6)	1 (3)	1 (3)

[a] As assessed by RECIST 1.1 with PCWG2 caveats. [b] FDG-PET refers to metabolic responses. [c] Nonprogressive disease on bone scintigraphy includes patients with CR, PR, or SD.

1. Rahbar K et al. *J Nucl Med*. 2017;58:85-90. 2. Hofman MS et al. *Lancet Oncol*. 2018;19:825-833.

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There has also been great enthusiasm in potentially combining PARP inhibitors with the lutetium-PSMA. This is radioligand therapy which is a PSMA-targeted beta radiation particle called lutetium-177. And this slide shows very favorable PSA responses and also objective responses when using lutetium-PSMA-617 in patients with metastatic castration-resistant prostate cancer, with a positive PSMA PET scan.

Of course, the theory here is that the beta particles are causing the DNA damage, and the rationale to combine a beta particle, radioligand therapy such as lutetium-PSMA with a PARP inhibitor is that the DNA damage that is caused by the radioligand will not be repaired in the context of a PARP inhibition, and so there might be catastrophic accumulation of DNA damage that goes unrepaired, leading to cell death.

LuPARP Trial: ^{177}Lu-PSMA-617 + Olaparib[1]

- mCRPC
- Progressed after second-generation AR-targeted agent
- Post–taxane chemotherapy

↓

PSMA + FDG-PET/CT

↓

^{177}Lu-PSMA-617 Q6W, 4 cycles 7.4 GBq **+** **Olaparib days 2-15** 3+3 dose-escalation design 500 mg to 300 mg BID (6 levels of increment)

1. https://clinicaltrials.gov/ct2/show/NCT03874884.

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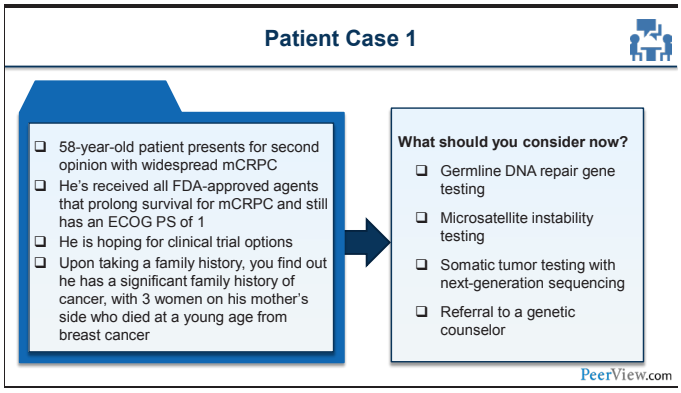
This hypothesis has led to the LuPARP trial, which is a combination of lutetium-PSMA-617, which is the PSMA-targeted beta-emitting radionuclide, plus olaparib. And this study is being led by Australian investigators. These are all patients that have a positive PSMA PET scan and they are then given the lutetium-PSMA-617 plus various doses of olaparib. And this study, I think, is very, very interesting but, of course, we have no clinical data reported thus far.

Applying PARP Inhibitors in the Clinic: Implications for the Urology Practice



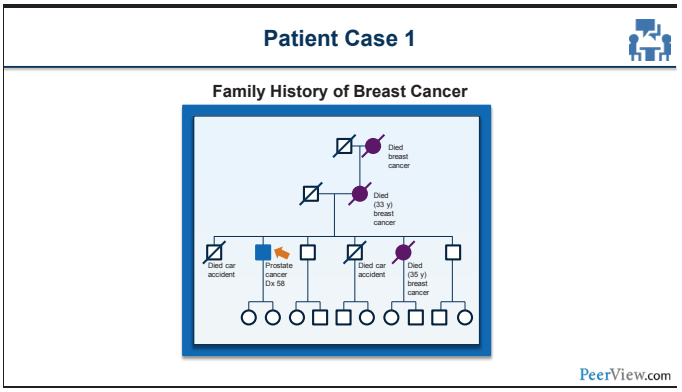
I now want to spend a few minutes talking about some practical implications in the clinic, in the urology clinic and the oncology clinic, and give some particular examples of patient scenarios that we might encounter in our clinics. So I'll start with Patient Case 1. This is a 58-year-old patient who presents for a second opinion. He has metastatic castration-resistant prostate cancer. He has previously received all the life-prolonging therapies, abiraterone and enzalutamide, both of the taxane agents. He still has a good performance status of at least 1. He's interested in novel options or clinical trial participation.

When you take a family history, you find out that he has a very strong family history of breast cancer, so three women in his family were diagnosed and also passed away from breast cancer, his mother, sister, and daughter. So when you encountered this type of patient in the past, this might have been someone that we may have missed if we just asked about prostate cancer history only; and now only by asking about breast and ovarian cancer history this important family history is brought to light.

So some of the considerations for a patient like this would be, should germline genetic testing be performed at this time, when would that be done, and using what type of sample? Should this patient be tested for a somatic tumor DNA mutation by taking either a new metastatic biopsy or an archival biopsy? Should this patient undergo microsatellite instability testing? When or if the patient undergoes germline testing, should this person be referred for genetic counseling ahead of time or after the fact?

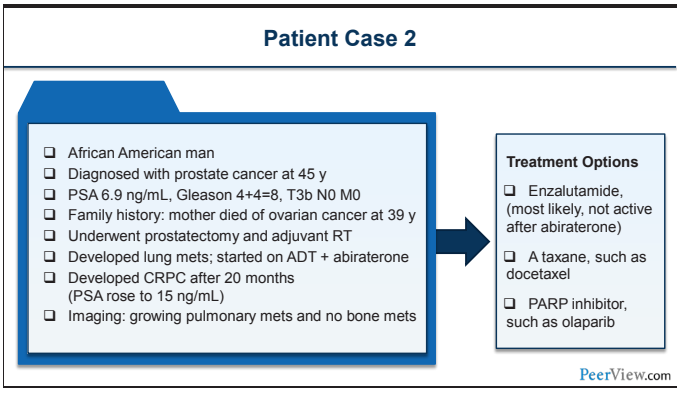
And, there are a lot of differences in practice patterns across the country and even between physicians. I would say that based on the fact that this patient has metastatic prostate cancer, the NCCN guidelines currently would strongly and immediately recommend both germline testing from a saliva sample or a blood sample, as well as somatic testing from either a new metastatic biopsy or from some archival biopsy.

Microsatellite instability testing, I think in this patient, makes a little bit less sense because he doesn't have a family history of the Lynch syndrome, which is hereditary nonpolyposis colorectal cancer and that might be the one thing that is less relevant here. But, of course, pembrolizumab would be an FDA approved-option if he was found to have microsatellite instability as well.



So this shows a family tree. So the orange arrow shows the prostate cancer patient in question, and the purple dots show that the patient's grandmother, mother, and sister all had breast cancer in their 30s, and subsequently, died from it. So with this type of family history, we would all definitely recommend germline genetic testing.

I think that the point to make here is even in the absence of any family history, just simply because he has metastatic prostate cancer, this patient would have statistically a 12% chance of having a DNA repair gene mutation anyway. Based on this family history, his chance of having a DNA repair mutation in the germline would probably be 25% or 30%, but I've seen many patients like this in my clinic who do test negative for a germline mutation. And part of the reason for that is that we have not yet identified all of these rare genes or rare variants that could have a very strong penetrance, in other words, they run in families, but the gene is not one of the classic genes that we are used to testing for.



And now moving to the second case, and we're going to discuss treatment options for these patients. This was a patient from my clinic that I have seen in the last 18 months. African American man

diagnosed with prostate cancer himself at a very young age, mid-40s. At the time of diagnosis, he had nonmetastatic disease, PSA of 6.9. Biopsy showed a Gleason score of 8, and he had clinical stage T3b disease, meaning extracapsular extension, seminal vesicle invasion. No lymph nodes, no metastases.

Upon taking a family history, he reported that his mother had been diagnosed and died from advanced ovarian cancer in her 30s. I believe she was diagnosed in her mid-30s and passed away in her late-30s. This patient appropriately opted for radical prostatectomy as a primary treatment modality, had a subsequent PSA recurrence and received adjuvant radiotherapy very quickly after the prostatectomy.

Unfortunately, within one year, this patient had developed pulmonary metastases, was appropriately placed on a combination of androgen deprivation plus abiraterone. And this was highly effective, but only for about 20 months, and approximately a year and a half after beginning the combination androgen deprivation therapy plus abiraterone, he was developing a rising PSA, reaching 15. And a new CT scan and bone scan at that time showed enlarging pulmonary metastases, but remarkably still no evidence of bone metastases as well.

So here we have a patient now with metastatic CRPC. He has received abiraterone. He has pulmonary metastases, his PSA is 15, no evidence of bone mets, and a very suggestive family history based on a mother with ovarian cancer in her 30s.

Patient Case 2: Germline Testing

Hereditary Cancer Risk Test

A pathogenic mutation was identified in the *BRCA2* gene.

DETAILS

A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function. A pathogenic mutation is also referred to as a mutation in this report.

GENE	MUTATION	CLASSIFICATION
BRCA2	c.1813delA (p.Ile605Tyrfs*9) *Alternate name(s): chr13.GRCh37:g.32907428delA, 2041delA* *Transcript: ENST00000544455* *Zygosity: Heterozygous*	Pathogenic

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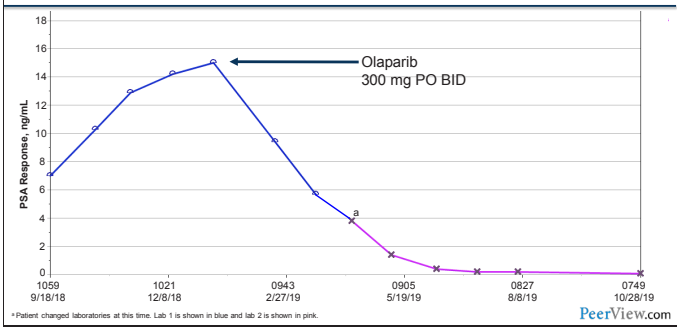
So I ordered the germline testing. In those days, I was using genomics, and this shows his report; it's de-identified so you cannot tell who the patient is. But as you can see in the red bar in the middle, it says a pathogenic mutation was identified in *BRCA2*. If you are more interested in the actual mutation, you can see that this is a frameshift mutation. Frameshift means that it results in a truncated protein product, so this is unequivocally a pathogenic mutation. This almost certainly came from the patient's mother. We don't know that for a fact because she was never tested and subsequently passed away. So now we have a patient with metastatic castration-resistant prostate cancer who has progressed after abiraterone and has a pathogenic *BRCA2* gene mutation.

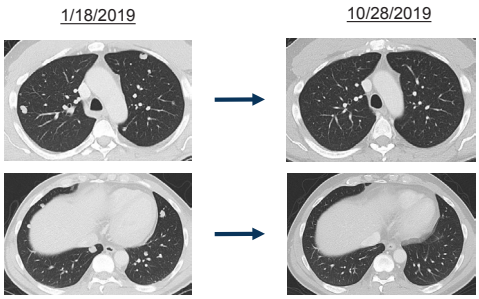
So options for this patient, of course, would include enzalutamide, although enzalutamide would not have such high activity after abiraterone. A taxane would certainly be appropriate, such as docetaxel. He does not have bone metastases, so drugs like radium-223 would not be indicated. But of course, in this case, I decided to treat the patient with olaparib.

Patient Case 2: PSA Response (ng/mL)



As you can see there, at the end of 2018—this is a real graph—I treated the patient with olaparib. His PSA dropped down to undetectable within the course of about 9 months. Interestingly, it did not drop immediately; it was a gradual and consistent decline. And this patient was recently in my clinic in May 2020 with a persistently undetectable PSA, so this gentleman has had an 18-month complete biochemical response using olaparib.

Patient Case 2: Objective Response (CR)



And this slide shows the CT scan with the pulmonary metastases on the left and the scan on the right, which was taken 9 months after the olaparib was started, showing complete disappearance of all of the pulmonary metastases, so complete PSA response and a complete objective response by CT criteria. Just to remind you, this patient did not have bone metastases, so his bone scan remained clear during this time.

He tolerated the drug quite well. He had very little, if any, comorbidities. He got some nausea for the first month; it disappeared by the second month. He had a little bit of anorexia and appetite suppression; he lost about 5 pounds in the first month and then his weight stabilized. And other than the slight anorexia, slight nausea, and the mild weight loss, this person is doing

extremely well, hasn't had any of the other major toxicities, such as the cytopenias. So this is, clearly an extreme example of a success case, but this is the type of response that you may expect to see in patients that have *BRCA2* mutations who receive olaparib.

Clinical Take-Homes

- Men carrying inherited *BRCA2* mutations and diagnosed with prostate cancer have a more aggressive disease
- Somatic and germline testing are recommended for all patients with metastatic prostate cancer, and for some with locally advanced or high-risk localized prostate cancer
- Two PARP inhibitors have been FDA approved for mCRPC: olaparib (HRR mutations) and rucaparib (*BRCA1/2* mutations)
- Side effects of PARP inhibitors include: fatigue, nausea, anorexia, cytopenias, diarrhea, and risk of MDS/AML
- Novel combinations of PARP inhibitors and other agents are on the horizon and may lead to further success

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I would like to finish by mentioning some take-home points. First, men carrying inherited *BRCA2* mutations are typically diagnosed at younger ages with more aggressive disease and typically have more rapid metastasis and death from their disease. Fortunately, these patients now have a novel therapy option, meaning PARP inhibitor treatment. This is certainly true of *BRCA2* mutation carriers and might also be true of *BRCA1* mutation carriers, although the data there are a little bit more sparse.

According to current NCCN guidelines and other guideline groups as well, somatic and germline testing are now recommended for every patient with metastatic prostate cancer and also, for the majority of patients with locally-advanced, as well as high-risk localized prostate cancer.

As of May 2020, we now have two FDA-approved PARP inhibitors for metastatic castration-resistant prostate cancer. Olaparib is approved for any HRR gene mutation in patients who have received abiraterone or enzalutamide, and rucaparib is approved specifically for *BRCA1* and *BRCA2* mutations for men that have received at least one androgen receptor therapy and one taxane therapy.

Common side effects of the class of PARP inhibitors are fatigue, nausea, anorexia, cytopenias, specifically anemia and thrombocytopenia, and diarrhea, as well as a small but dangerous risk of myelodysplastic syndrome or acute myeloid leukemia.

And I just want to leave you with the notion that these PARP inhibitors are now being combined with many other standard and nonstandard agents for the treatment of prostate cancer and there is a lot of excitement in this field in the years to come.

I hope that you have found today's presentation to be enjoyable and helpful. We've covered a lot of information and concepts regarding the use of PARP inhibitors in prostate cancer management that I hope will be useful for your clinical practice. Thank you for your time and attention.

Narrator: This activity has been jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

CME

Targeting DNA Repair Defects Through PARP Inhibition in Prostate Cancer: Rationale, Evidence, and Clinical Implications

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This activity is supported by independent educational grants from AstraZeneca, Clovis Oncology, Inc., and Merck & Co., Inc.

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