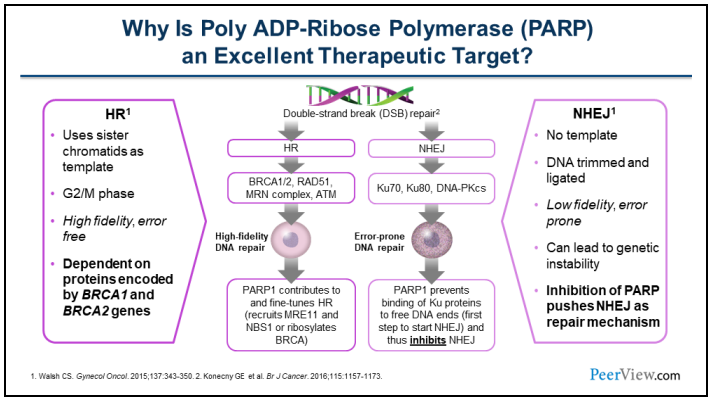
Slide 1

Announcer: Welcome, everyone, to our program. Welcome to "Managed Care Implications of the Expanding Role of PARP Inhibitors in Oncology: Evolving Evidence Base, Current Value Assessment Frameworks and Considerations for Decision-Making in Managed Care Settings." Now I'll turn I'll turn it over to Dr. Kathleen Moore from the University of Oklahoma Health Sciences Center.

Dr. Moore: Well, good day, everybody. It's my great pleasure to be here today to give what is going to be a pretty rapid-fire overview of the use of PARP inhibitors across several solid tumors—ovarian, breast, prostate, and pancreas—and sort of why we think they're so important for their therapeutic benefit to our patients.

PARP Inhibition as a Rational Treatment Strategy in Oncology With Increasing Clinical Importance Across Different Tumor Types: What Managed Care Professionals Need to Know

Slide 2



Dr. Moore: So I like to always start, when we're talking about PARP inhibitors, just to define why we think PARP is an excellent target. Like why did we even start looking at this? So, first of all, just definitions. What's PARP? So PARP is poly ADP-ribose polymerase, and it's a protein that responds to DNA damage and recruits a number of proteins to repair that damage. So it's a very important protein in several of the DNA repair processes.

And this slide seems complex, but it's overly simplified. But it really takes us down the two main pathways of double-strand DNA breaks. So double-strand DNA breaks are the most important because they're the most lethal. And cells that are normal, like our normal cells, really like to use homologous recombination, which is what you see on the left.

So, homologous recombination is the preferred mechanism for double-strand DNA break repair because it's very high fidelity, and it can be high fidelity because it uses a template, it uses the sister chromatid as a template for the repair. It really is predominantly something that takes place in the G2/M phase, and it is dependent on the proteins BRCA1 and BRCA2. And in fact, those proteins are kind of the rate-limiting step for homologous recombination repair.

And you can see in the center two pathways, the one on the left represents homologous recombination. And so here, PARP, the PARP protein, specifically PARP1, will recruit a lot of the DNA repair proteins in addition to BRCA1 and

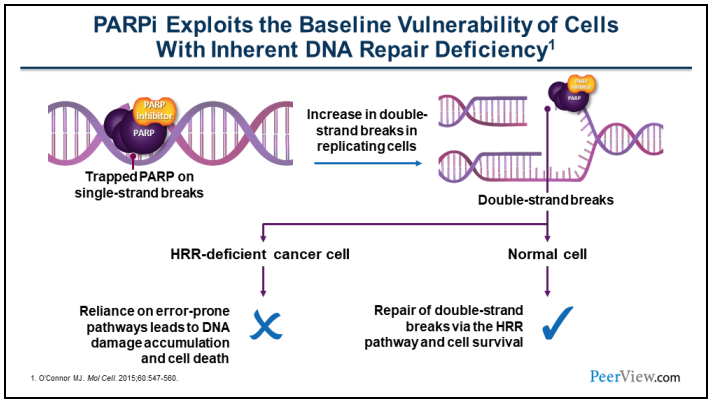
BRCA2 to facilitate homologous recombination. And so if you're a normal cell, you want this to happen, because you want that double-strand break to be repaired so that the daughter cells remain normal.

If we have a cancer cell, of course, a cancer wants to be really good at this, too. It wants to be proficient at homologous recombination, because then it can repair the damage that we induce with therapeutics that are DNA-damaging, such as platinums or radiation or any other number of therapeutics. And so we don't want our cancer cells to be proficient at homologous recombination, so taking out that PARP protein helps dismantle this insensitive tumor. And I'll explain that in a second.

The other pathway that is important in double-stranded DNA repair is nonhomologous end joining. And you see that on the right. So this is also regulated by the PARP protein. So the PARP protein blocks entry into nonhomologous end joining and routes the repair through homologous recombination. So, again, PARP is acting to facilitate homologous recombination, that high-fidelity repair, and blocks entry into nonhomologous end joining.

When nonhomologous end joining is the predominant mode of repair, it's very error-prone, because it doesn't use a template. It just trims the ends of the damaged DNA and fills them in with random nucleotides, and it leads to a lot of genomic instability.

Slide 3



So this is just another little cartoon. So the PARP protein we were just talking about is in purple. The PARP inhibitor is the little glowy orange blob. So PARP also is very facile at fixing single-strand breaks.

And so it binds to the site of the single-stranded breaks. It creates a scaffolding onto which DNA repair proteins will come and bind, at which point the PARP dissociates. The DNA repair proteins do their thing and fix the DNA, and then they all dissociate.

And so the other way we can come at this is, of course, if you block PARP, you block that recruitment of protein. But also, if you block PARP and then prevent its dissociation from the DNA–and this is called PARP trapping–you basically lead to replication for collapse. And you can see that on the right-hand side of your screen.

And so what happens here and this is what I was talking to when I alluded to vulnerable cells. So if you have a cell, a normal cell, or a cancer cell that's really good at fixing its DNA, even though you've caused these double-strand breaks, they're going to have so many redundant systems to repair that they're just going to keep right on living. And we call these tumors homologous recombination proficient.

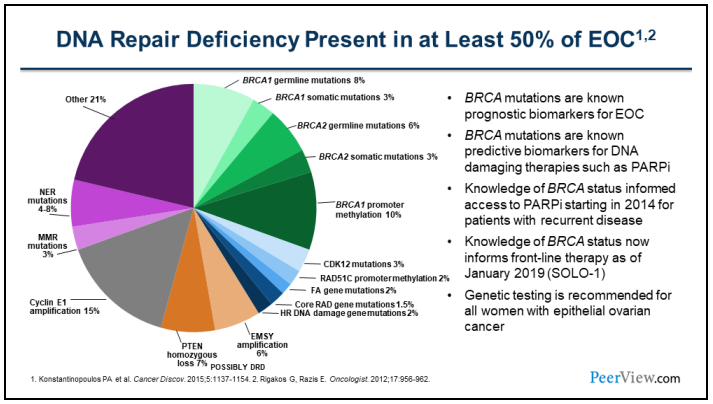
In cancer cells, where we have so much genetic instability, there are situations where there's already an inherent vulnerability to loss of these key proteins of DNA damage response pathways. So, taking out the PARP protein, it works if they already have some inherent vulnerability.

And the poster child for this, of course, is BRCA germline mutation, which leads to the loss of BRCA proteins, which are the rate-limiting step for homologous recombination. But there are many other things that, either epigenetic changes or somatic changes or germline changes, that lead a cancer cell to

be vulnerable to loss of one of its key protein.

So these are called homologous recombination repair-deficient cells, or we can just call them HRD, and these are the cells that are most likely to die when you give them a PARP inhibitor.

Slide 4



So let's talk about the four tumors we're going to talk about. When we talk about ovarian cancer, and specifically high-grade serous ovarian cancer, which is the most common, we think that up to 50% of patients are going to have this state of being homologous recombination deficient.

The most common reason for this is a BRCA alteration, either a germline mutation, and those occur in 15% to 17% of women, or a somatic mutation, so this isn't heritable. It's just something that happens in the tumor mutation rate in about 7% of the population.

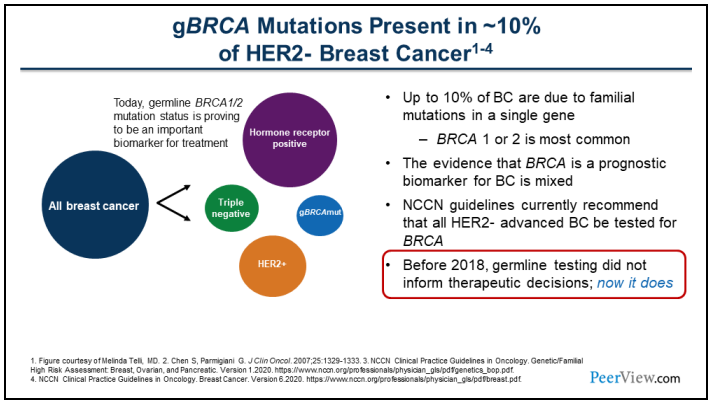
About 10% of women with epithelial ovarian cancer will have epigenetic changes to their BRCA1 gene, so they'll have what's called promoter methylation. So the gene is normal. There's no mutation, but because the promoter is methylated, it doesn't get transcribed. So it's just like having a BRCA mutation. You don't have the protein. So that kind of cumulative piece of the pie is almost 30% of patients with epithelial ovarian cancer, and they are very sensitive to use of PARP inhibitors.

And so with recent approvals in ovarian cancer, for this slide, we now know that knowing a patient's BRCA status did inform the ability to access a PARP inhibitor starting in 2014, and until very recently continued to be quite important for accessing a PARP inhibitor, at least in frontline chemotherapy, increasing knowledge of BRCA in the front line, which is, we think, the best place to use a PARP inhibitor, started informing frontline use of PARP inhibitor maintenance in January of 2019, when SOLO-1 gained approval.

And so because of this, germline testing is recommended for all patients with epithelial ovarian cancer. There's no reference to family history or age at diagnosis or anything. It's probably the easiest genetic recommendation that's out there. If your patient has epithelial ovarian cancer, she should be offered

therapy.

Slide 5

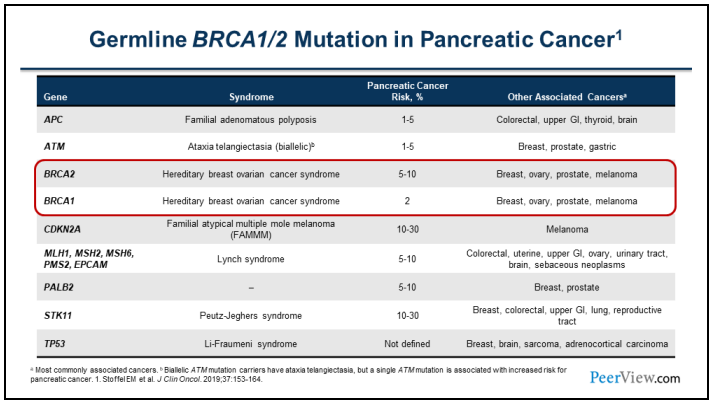


So, a slightly different story for breast cancer. So in breast cancer, which is, of course, so many different diseases, we're really talking about HER2-negative. And you do find germline BRCA mutations in about 10% of HER2-negative breast cancer. And so this has been known for a long time, and it certainly was important in informing cascade testing of family members and prognosis, but it really didn't inform therapy until relatively recently.

And in the past, you looked at all breast cancers. You would determine their hormone receptor positivity. Were they triple-negative? Were they HER2-positive? But now you see in the pink circle, we have to know their germline BRCA status.

So prior to 2018, it didn't really impact, like I said, the therapy, but now it does. It does change how you would treat these women in the recurrent setting and maybe in the front line soon.

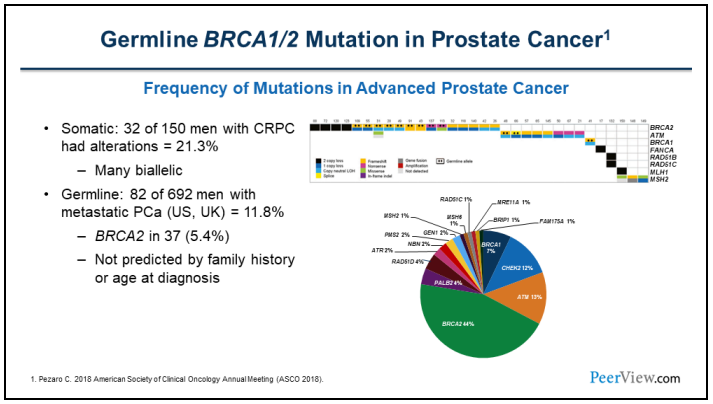
Slide 6



Then when we talk about pancreatic cancer and this is a very recent field. We've known for a long time that BRCA2 more than BRCA1 could be associated with an increased risk of pancreatic cancer, and so when we would identify families that had BRCA2, they would undergo screening, trying to screen for these tumors. And that's still true today.

But it didn't translate into a change in their therapy. It was really just trying a preventive strategy, but it didn't inform therapy. But now it does, and we'll talk about the data from the POLO study. So we think it's probably at most about 12% of patients with pancreatic cancer, probably a little bit less than that, maybe the 10% range, but still definitely worth screening for.

Slide 7

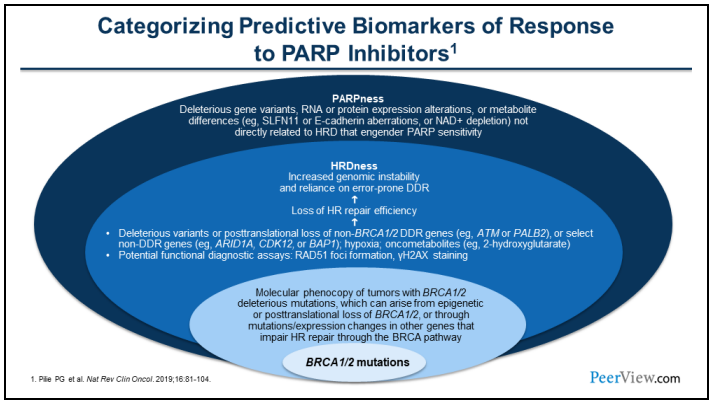


And then prostate cancer, you know, BRCA2 is really the key mutation here. But there are a number of other mutations in DNA damage response pathways, much like I showed you in that pie chart for ovarian cancer. But because ovarian cancer is a rare tumor, we really have focused on BRCA2 or BRCA in looking at predictive capability to predict response to PARP inhibitors and other therapies.

For prostate cancer, you have so many men, unfortunately, diagnosed with prostate cancer that they have been able to amass probably quicker data with some of these other DNA damage response genes, and their capability to predict response to PARP. And so they leapfrogged us a little bit on ovarian cancer as the new approvals have included these, and we'll talk about that.

But here, you see, in castrate-resistant prostate cancer, in this particular study, about 20% had an alteration that could potentially be important. So this isn't super-rare. Only about 11% or so depends on the population you're looking at had a germline mutation. So a lot of these were somatic mutations. And then about 5-ish percent are BRCA2. And it's really not associated, again, like ovary, with family history or age at diagnosis. It's really more associated with pathologic criteria, and we'll talk about that.

Slide 8



And so the other thing we have to think about is that prostate data gets to this a little, but this kind of comes from a DNA damage response paper. If you're ever interested, this is a fantastic resource. It's one of my favorite review articles. But if you look at the bottom of this, you see BRCA1 and BRCA2, which are the poster-child proteins for DNA damage, loss of DNA damage response, and predictive capability of response for PARP.

But then, in the kind of bigger blue, you see those other BRCA alterations, epigenetic changes, somatic mutations that also are very predictive, probably as predictive as a germline mutation.

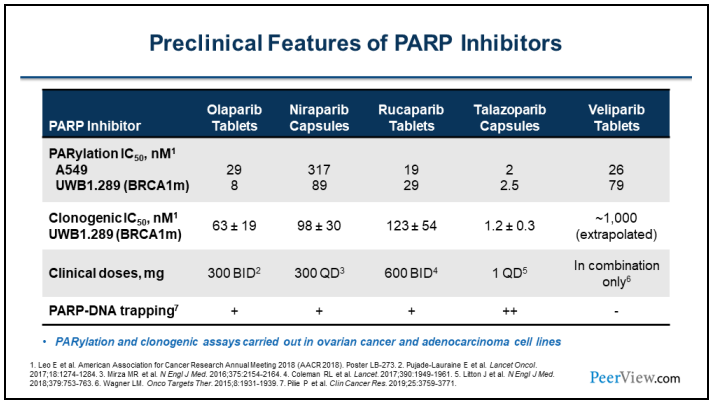
And then in the kind of gray circle inclusive of those two, you have these HRDness, as he calls them homologous recombination-deficient situations, either because you have these low-frequency mutations in the DNA damage response genes, or, again, other epigenetic changes to some of those genes that leads to an overall inherent vulnerability in whatever tumor cell you're talking about to therapies that cause DNA damage.

And that's PARP inhibitors. That's what we're talking about today. But it's a lot of other things, too. It's radiation, platinum-based therapies, anthracyclines, et cetera. Those tumors are going to be more sensitive to those sorts of therapies than not. So they do predict response to PARP.

And then even beyond this is this concept of PARPness, which I think is really fascinating. And we're going to talk about the assays that are available for predicting homologous recombination deficiency a little later in this talk. I'm just going tell you up front, they're not perfect assays, because you have patients who are classified by the assay as homologous recombination proficient, which should mean they're awesome at fixing their DNA and they shouldn't respond at all to PARPs, but some of them do. And so why is that?

Well, it may be that there's other changes, or it must be that there's other changes in the tumor that render it susceptible to PARP that we're not picking up with these HRD tests. And there are some examples here. E-cadherin aberrations, SLFN11 mutations, NAD depletion, many others that we're not picking up on these assays, but may impart responsiveness to PARP that we still need to study. So we're the tip of the iceberg, I think, for really understanding how to predict response to PARP inhibitors in a variety of tumors.

Slide 9



Preclinical Features of PARP Inhibitors

PARP Inhibitor	Olaparib Tablets	Niraparib Capsules	Rucaparib Tablets	Talazoparib Capsules	Veliparib Tablets
PARylation IC_{50}, nM[1]					
A549	29	317	19	2	26
UWB1.289 (BRCA1m)	8	89	29	2.5	79
Clonogenic IC_{50}, nM[1] UWB1.289 (BRCA1m)	63 ± 19	98 ± 30	123 ± 54	1.2 ± 0.3	~1,000 (extrapolated)
Clinical doses, mg	300 BID[2]	300 QD[3]	600 BID[4]	1 QD[5]	In combination only[6]
PARP-DNA trapping[7]	+	+	+	++	-

- *PARylation and clonogenic assays carried out in ovarian cancer and adenocarcinoma cell lines*

1. Leo E et al. American Association for Cancer Research Annual Meeting 2018 (AACR 2018). Poster LB-273. 2. Pujade-Lauraine E et al. *Lancet Oncol.* 2017;18:1274-1284. 3. Mirza MR et al. *N Engl J Med.* 2016;375:2154-2164. 4. Coleman RL et al. *Lancet.* 2017;390:1949-1961. 5. Litton J et al. *N Engl J Med.* 2018;379:753-763. 6. Wagner LM. *Onco Targets Ther.* 2015;8:1931-1939. 7. Pilie P et al. *Clin Cancer Res.* 2019;25:3759-3771.

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Okay. So that sets the stage for sort of the mechanism. Now, let's talk about the PARP inhibitors that are in play in the solid tumors. So there are olaparib, niraparib, rucaparib in ovary and talazoparib in breast. Rucaparib, of course, and olaparib in prostate.

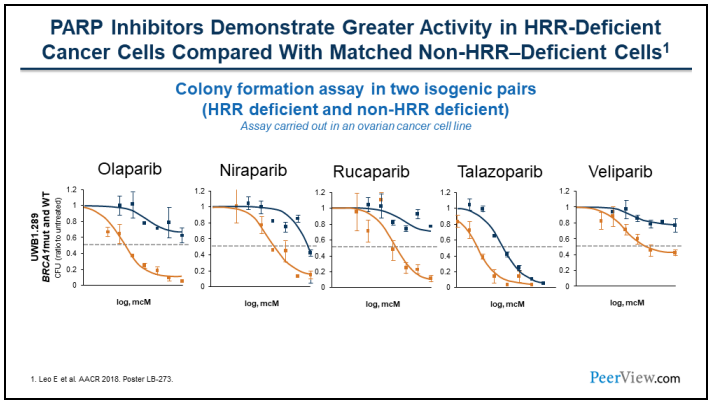
Veliparib I'm not going to talk about too much today. It's been studied in breast and ovary and doesn't have an indication as of yet, so it's not in play as a commercial asset just yet. So we're really going to focus on the, what I call, the big four.

And when we talk about PARP inhibitors, you know, I think we often will say clinically a PARP's a PARP's a PARP. And that may or may not be true, but it's sort of overly true, at least in ovary. But they are different. And so I think it's important to know that.

So you'll see differences in PARylation across the four. The clinical doses are different. The degree of PARP trapping -- and remember, I talked to you about how important that was in single-strand break repair and blockage of single-strand break repair. If you block the PARP protein from recruiting from making its scaffolding and recruiting DNA repair, that's fine. But then if the PARP protein dissociates, another PARP protein can come in and fix it again. But if you trap that PARP protein on there, you cause replication for collapse.

And so talazoparib is probably the most potent PARP trapper out there, and unfortunately, we haven't gotten to use it too much in ovarian cancer yet, so we can't really judge clinically whether it's better than the other three that all have probably equivalent rates of PARP trapping. So they do have some differences pharmacokinetically and pharmacodynamically. Whether this is clinically relevant I think remains to be seen.

Slide 10



PARP Inhibitors Demonstrate Greater Activity in HRR-Deficient Cancer Cells Compared With Matched Non-HRR–Deficient Cells[1]

Colony formation assay in two isogenic pairs (HRR deficient and non-HRR deficient)

Assay carried out in an ovarian cancer cell line

Olaparib | Niraparib | Rucaparib | Talazoparib | Veliparib

UWB1.289 *BRCA1*mut and WT CFU (ratio to untreated)

log, mcM

1. Leo E et al. AACR 2018. Poster LB-273.

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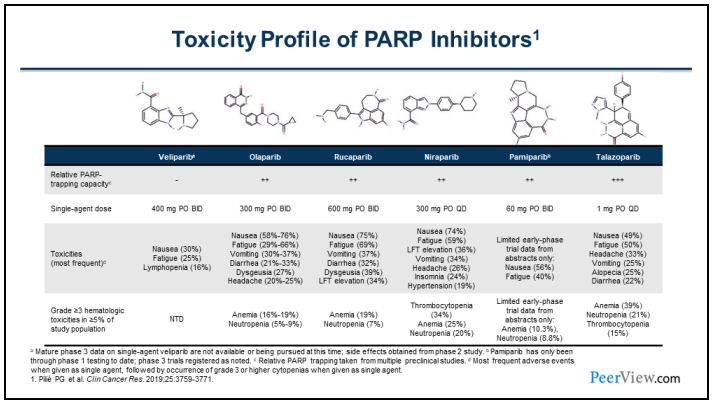
This is just preclinical data in ovary cancer lines, again, with all five, but really just going to focus on the four, looking at the efficacy of each of these drugs in homologous recombination deficient in purple and homologous recombination proficient in gray cell lines.

And so really what you can see here is there are some differences in terms of the amount of inhibition in the deficient cell line. You know, olaparib looks maybe a little bit better, talazoparib probably looks even a little bit better still, for both proficient and deficient.

So this is cell line data that makes us think about whether or not someday we may pick a PARP inhibitor really based on this type of data linked to our patient rather than just empiric selection of a PARP inhibitor. We are not there yet by any stretch of the imagination, so right now we kind of use the PARPs that are available to us, but it's interesting to think about.

Slide 11



The toxicity profiles of PARP inhibitors also differ. Again, we're not going to talk too much about veliparib, but what we'll say is there's class effects for olaparib, rucaparib, niraparib, and talazoparib that are really the same for all four assets.

Very common but low-severity fatigue, nausea and those two. So those are the two most common. 70% of patients. Very common, but usually grade 1 or 2. And managed with dose interruptions, sometimes dose reductions, but usually get away with dose interruptions.

And then you'll see diarrhea and actual emesis in like 20 to 30% of patients with each of these drugs. Those are class effects. Not one of them is better or worse than the other for those side effects.

For anemia, they're all similar. We worry most about grade 3 anemia, because that's where we consider transfusions, and they're all right around the 24% rate for that grade 3 anemia. And then of those, two-thirds may need a transfusion.

Where they differ really is in a couple of things. One is thrombocytopenia, significant-severity thrombocytopenia is much more common with niraparib than olaparib or rucaparib. Now, the 34% rate comes from when they had flat dosing of 300 mg. Now they do what's called individualized dosing based on the patient's starting weight and starting platelet count.

So if the weight is less than 77 kg or the starting platelet counts less than 150,000, you start at 200. If not, you start at 300. And so that has brought down the rate of severe thrombocytopenia to about 13%, but olaparib and rucaparib, it's about 6%. So it's reasonable, but it's still a little bit higher.

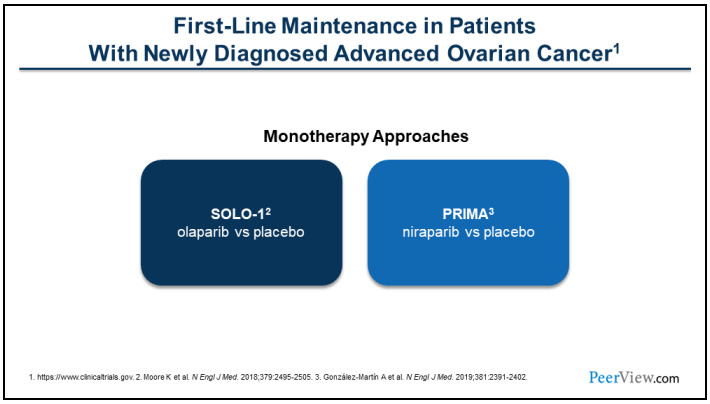
Neutropenia's about the same. Grade 3/4s, like 6%. So we don't see a lot of that. But thrombocytopenia still does characterize niraparib.

So there are some nuances to the PARP inhibitors, some asset-specific toxicities. But then for the most part, they have a class effect that you can sort of use to counsel patients in general about PARP inhibitors.

Slide 12

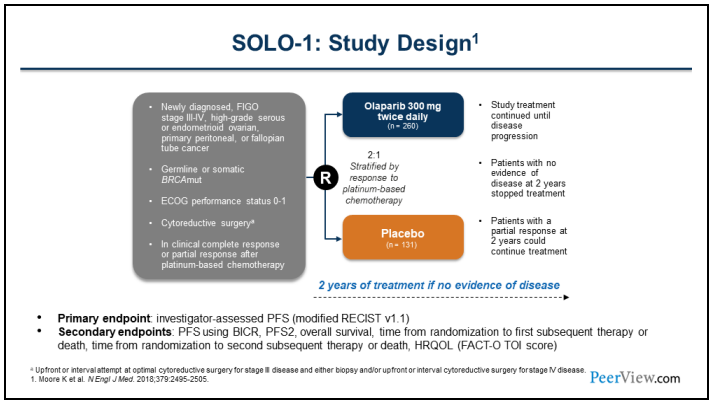
So we'll take the data in each of the four tumors we're going to talk about. So we have the most in ovarian cancer.

Slide 13



And we'll talk about sort of the monotherapy opportunities in front line first.

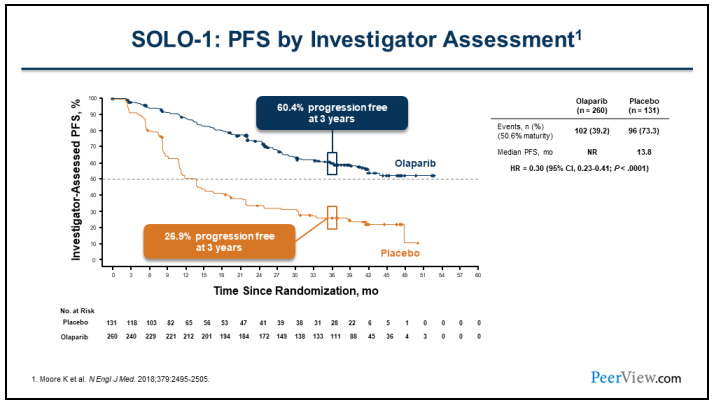
Slide 14



So the first study to come out was SOLO-1. This was designed in 2012 and 2013. It took a long time to result. We presented it in 2018, and it randomized women who had BRCA-associated cancers and had responded to their chemotherapy and surgery in the front line, and then randomized them to olaparib or placebo until progression or toxicity. And if that didn't happen, at 2 years they discontinued their assigned therapy.

And the endpoint was progression-free survival, and there's a number of secondary endpoints that you can see here.

Slide 15

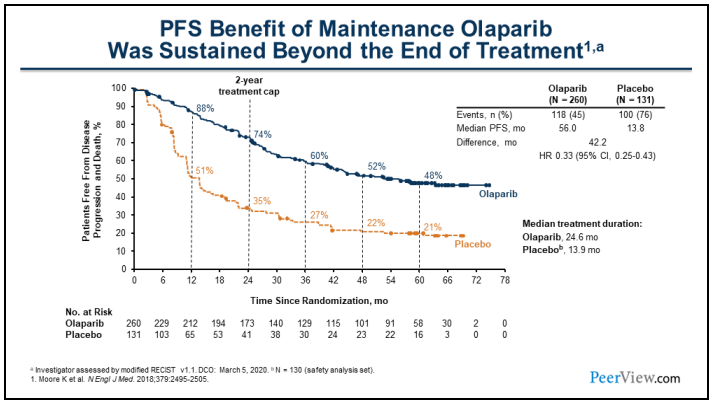


So this was the data we presented at ESMO in 2018, which was so exciting, because we've just never shown this sort of improvement in the front line before. So what we had were a couple of things I want to bring to your attention. Well, let me tell you the data first.

So, first, what we had was a 70% reduction in the hazard of risk of progression of death at every time point along this curve, a 70% reduction in the hazard of progression or death. Just unprecedented improvement in progression-free survival.

At 41 months of follow-up, which is when we reported it in '18, the median progression-free survival for the group randomized to placebo was 13, almost 14 months. That doesn't include the time on chemo, so just at the end, versus not reached for the women randomized to olaparib.

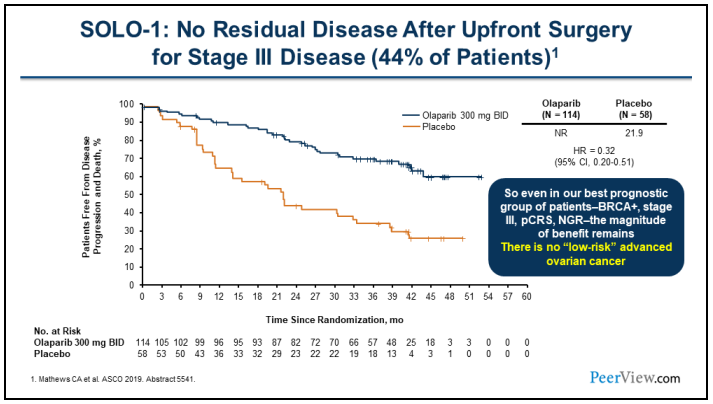
Slide 16



We presented this at ESMO this year. Susana Banerjee presented this. So we don't have overall survival data yet because it's nowhere near mature, but we were able to show 60-month progression and median for progression-free survival, and you still see this plateau holding. So at 5 years, we still have almost 50% of women randomized to olaparib without disease, so long-term disease-free survival. That's the goal.

And so this was incredibly exciting data for us, and it actually gave us a median progression-free survival finally, so 13.8, still of course, for the placebo arm, 56 months for olaparib. Just astonishing, and very exciting, and again, gives us hope that we've converted some of these patients to cure, but time will tell.

Slide 17



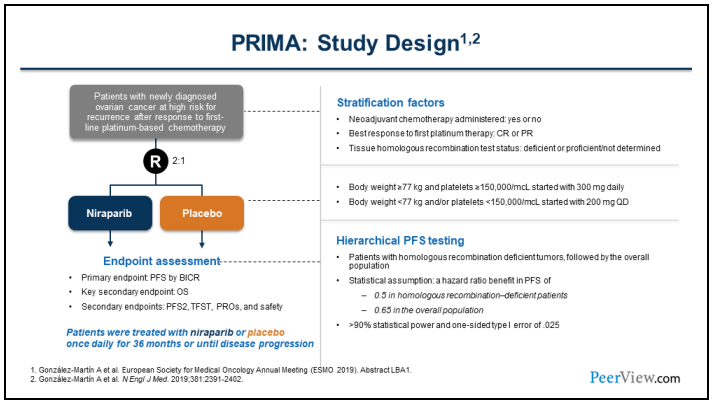
And this is just what I was mentioning to you before, 44% of the patients enrolled on SOLO-1 were called them low-risk patients. I don't think any woman with advanced ovarian cancer is low risk at all. But they are on the lower end of high risk. So they were stage III. They had primary surgery instead of neoadjuvant chemo followed by surgery, and their surgeries were very successful. They had no disease at the end of the surgery that you could see. So those are important prognostic factors.

So that's the best prognostic group of patients you'll ever treat with ovarian cancer in your life. So if anyone's going to be cured, with chemo alone, it's that group. It's this group. And what you can see here, and why I like this study is because this slide looks better than the first slide. The control arm now has a median progression-free survival of almost 22 months as compared to 13. So they do do better. I'm not going to argue that.

But every one of those vertical notches is a patient progressing. So they're cured in large effect. And at least this one is still the 41-month follow-up median, so we can just call it at that kind of 42 bar, where about 25% of patients randomized to placebo are still disease free as compared to 60% randomized to olaparib.

So the benefit is not related to kind of higher-risk patients or lower-risk patients. The benefit is just clear in all patients, and I think this just argues for kind of use of PARP inhibitors in this population as the standard of care, no exceptions. There's no low-risk advanced ovarian cancer. I hate that term.

Slide 18

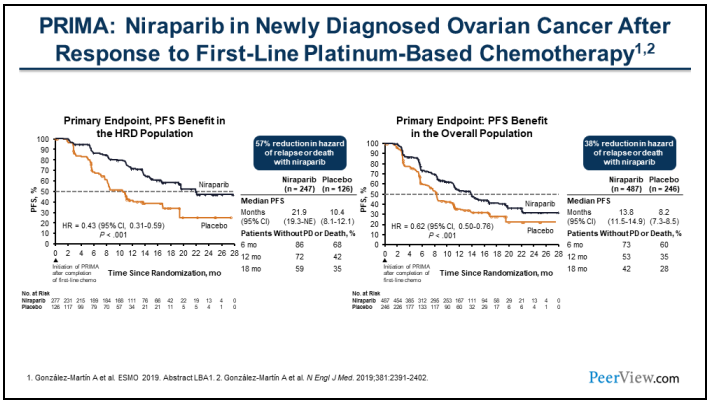


So from that group of patients, lower stratum of high risk, we go to the really high risk. So this is PRIMA. PRIMA is similar to SOLO-1. It enrolled women with newly diagnosed epithelial ovarian cancer, high-grade serous, or high-grade endometrioid.

They did not have to have a BRCA-associated cancer. And at the end of chemotherapy and surgery, they had to either be in a complete or partial response, and then they are randomized to niraparib or placebo until progression or toxicity, or until the 3-year mark, instead of 2 years.

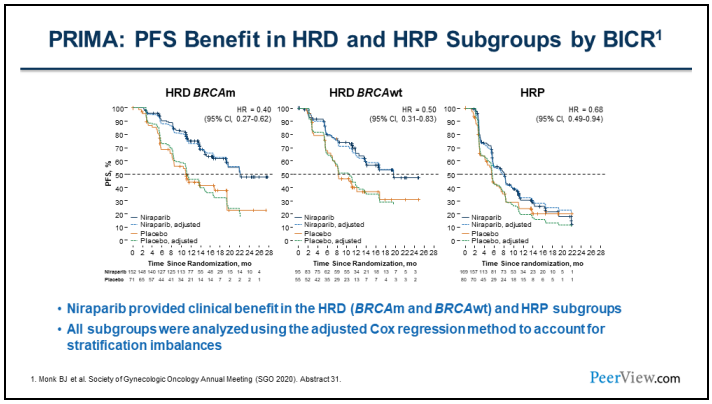
Now, they stratified by homologous recombination deficiency as measured by the Myriad assay. And I'm going to show you that assay in a little bit. And so the primary endpoint was progression-free survival in the entire group, as well as progression-free survival in the homologous recombination-deficient group, and that group would of course include those women with BRCA-assed tumors.

Slide 19

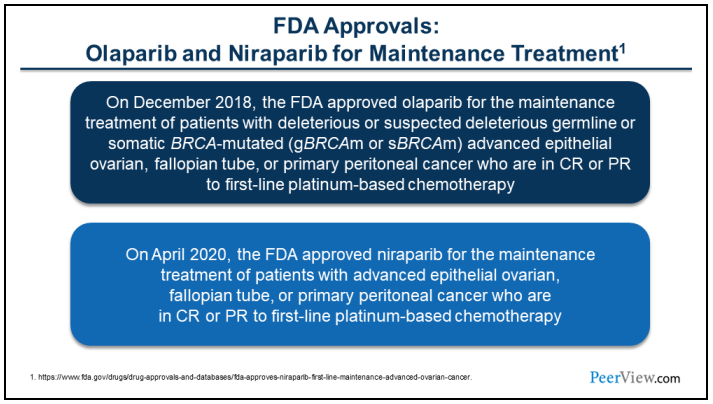


And so here is the primary endpoint in the HRD group on the left, with a hazard ratio of 0.43. So a 57% reduction in hazard of relapse or death. That's significant. And then even in the intent-to-treat group is a 30% reduction in the hazard of relapse or death with niraparib. So both primary endpoints were met.

Slide 20



Slide 21



Interestingly, these are exploratory endpoints, but, you know, we always like to look at them. So on the left, you see the BRCA-associated cancers, with a hazard ratio of 0.4. In the middle, you see those who are BRCA wild-type, but HRD. So homologous recombination deficient. So this is like an additional 20% above the BRCA-associated cancers, and they have a hazard ratio of 0.5.

And then, surprisingly to us all is the group of patients classified as homologous recombination proficient, and this is what I was mentioning to you before. If these tumors were truly proficient in repairing their double-strand breaks, they would not benefit from a PARP. But clearly, the assay is misfiring somewhere, because we do see a statistically and clinically relevant improvement, with a hazard ratio of 0.68.

Now, it does identify a group of patients with poorer prognosis, but they do benefit from PARP, which is why the FDA and now actually the CHMP in the UK have approved niraparib for all comers. So, irrespective of the biomarker, if you're in complete or partial response with advanced ovarian cancer, you can offer niraparib to your patient.

Olaparib monotherapy is just for those with BRCA-associated cancers in this setting.

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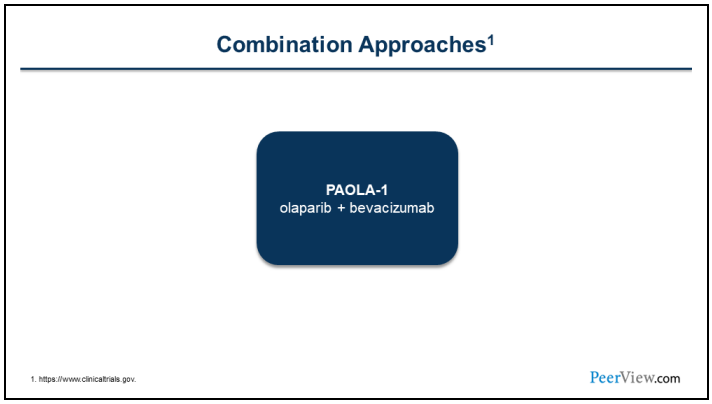

So how about combinations?

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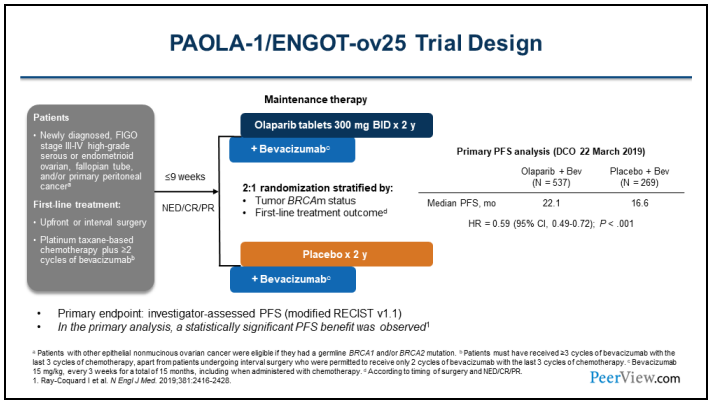

So this is the PAOLA study. So one of the conundrums is that bevacizumab, which is a monoclonal antibody that targets vascular endothelial growth factor, is approved in frontline ovarian cancer. We give it with chemo and to follow.

And you can use it in any setting in the U.S. In other parts of the globe, it is reserved for these higher-risk patients who are stage IV or have a lot of ascites or had not great surgery, like they couldn't get all of the tumor out. And in many parts of the globe, it is the standard of care. It's the only line of therapy in which you can use bevacizumab. And so there was this question of, well, what do you do if you've started bevacizumab in your patient, like can you add a PARP later, and would it benefit them?

So that's what the PAOLA study was investigating. It took patients with high-grade serous and high-grade endometrioid who were in complete or partial response following six cycles of chemo, and then randomized them to continue the bevacizumab plus placebo, or continue the bevacizumab plus olaparib. And the primary endpoint was progression-free survival, and they had a whole group of patients, so it allowed patients with BRCA wild-type and BRCA.

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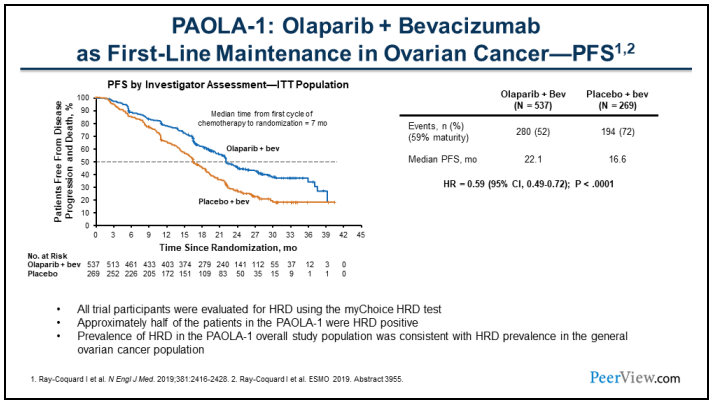

And so here is that result, with a hazard ratio of 0.59. So 41% reduction in the risk of progression or death with use of olaparib with bevacizumab. That's the primary endpoint, and they met it. And so one would think that would be the indication.

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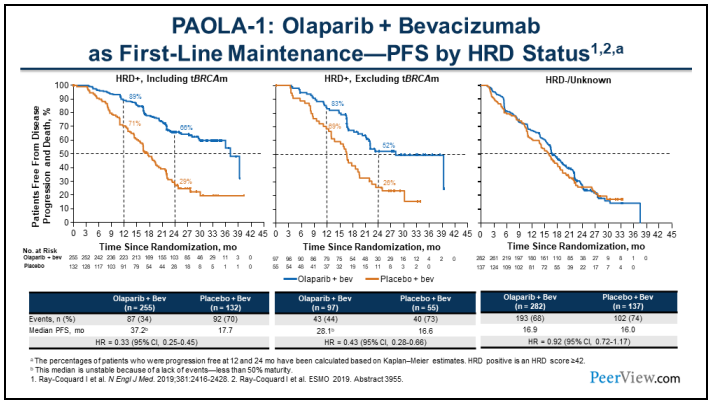

But here are the subgroup analyses, kind of like what I showed you in PRIMA. On the left, you see those with BRCA-associated cancers, with a hazard ratio of 0.33. In the middle, you see BRCA wild-type HRD, with a hazard ratio of 0.43. So a 57% reduction in the risk of progression or death in this group.

But in the homologous recombination-proficient group, there was no benefit over bevacizumab. Remember, the control group here is an active drug. It's bevacizumab, not placebo. So over bevacizumab, addition of olaparib plus bevacizumab did not improve the progression-free survival in that particular patient population.

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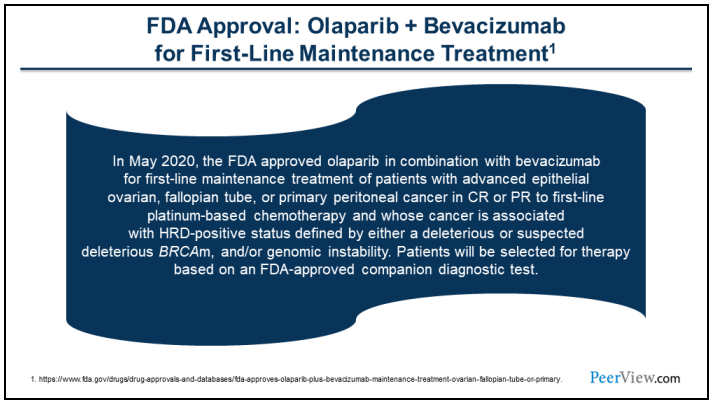

And so the FDA just carved out the approval in patients whose tumors are homogeneous recombination deficient, of course, inclusive of BRCA, but including BRCA wild-type, homologous recombination deficient, and excluding that group who are homologous recombination proficient. So that is the approved indication in the U.S. and also in the EU at this point, and other approvals are pending.

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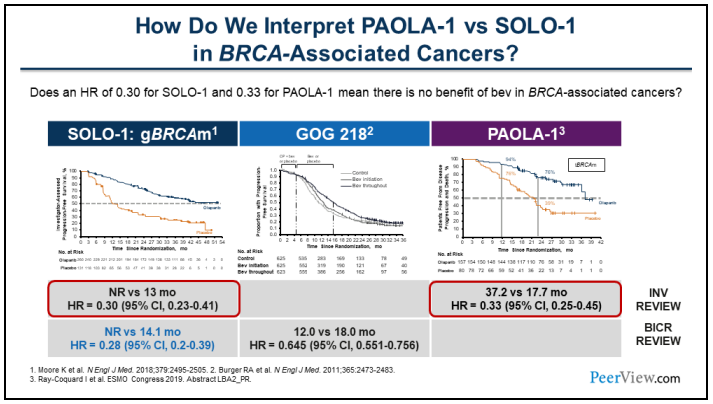

And so there's a number of questions we have to ask. How do you interpret PAOLA-1 and SOLO-1 for BRCA-associated cancers? Are bevacizumab and olaparib the new standard of care for patients with BRCA-associated cancers, or do you have an option of just doing olaparib or niraparib monotherapy at the conclusion of chemo?

And some people would look at these two studies highlighted in red here and they would say, "Well, both have a hazard ratio of 0.3, so the bevacizumab really doesn't add anything in this population, so we don't need it."

So I would caution you with that interpretation because you have to remember, the hazard ratio is a measure of the reduction in risk of your experimental arm versus your control in that particular patient population. And I told you in these three populations, PRIMA's very different than SOLO. PAOLA's kind of in between in terms of risk. And so you can only judge it for the individual trial.

And so you have a hazard ratio of 0.3 for SOLO, 0.33 for PAOLA. All you can say, unprecedented improvement in progression-free survival in both particular groups. Now, how do you compare them?

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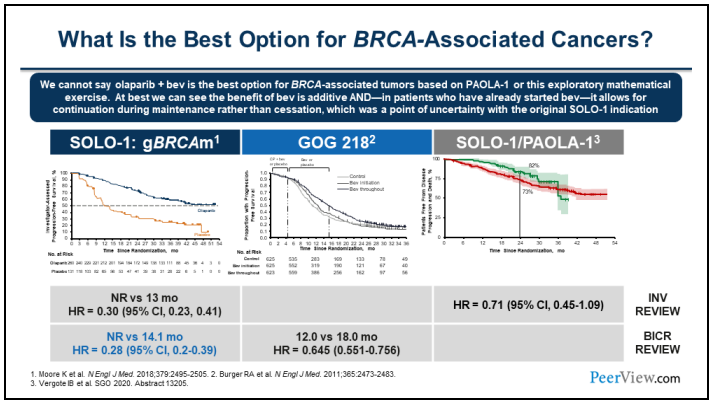

Well, we tried to compare them. The missing arm in PAOLA, of course, is olaparib alone, where you would have stopped the bevacizumab at the end of chemo and just put them on olaparib. So we don't have that arm in PAOLA.

But, because SOLO and PAOLA were the same drug company, we had the individual patient data. So we could take the patients on PAOLA who had BRCA-associated cancers and received bevacizumab and olaparib, and then look in SOLO for the patients who received olaparib of course, they all had BRCA-associated cancers by definition and pick patients who looked similar to the population in PAOLA. So it was called a propensity-weighted match. And then we redid the analysis.

So in green is bev-olaparib from PAOLA, and in orange is monotherapy olaparib, patients matched to be like PAOLA from SOLO, if that makes sense. So you can see these curves do look different. The hazard ratio is 0.71. And so I think what we can say from this is that it's additive, it's likely additive in this population.

And the most important thing here, I think, is that it lets you dissociate your decision about bevacizumab from the PARP. If you think your patient needs bevacizumab in the front line because they have high volume of disease or they have a lot of ascites or they're stage IV, or you just like to use it because it's authorized, that's fine. You can use it while you're testing your patient to see if she has a BRCA mutation.

And if you discover one, you can just layer on the PARP inhibitor on top of the bevacizumab, because stopping bevacizumab makes no sense. The benefit of bevacizumab is with and to follow chemo. This gives you permission and safety data to do this.
But I don't think that it necessarily says, "You must use bevacizumab and olaparib together in this population." If you don't think your patient needs bevacizumab and they have a BRCA mutation, then wait until they're done with chemo, and then start monotherapy PARP. You have both options, and you can dissociate the decision about each of them for the time points at which you're making those decisions.

Bevacizumab decision's been made up front. PARP decision is made at the end of chemotherapy once you've assured a response. So I think this is the nice side of this very exploratory analysis.

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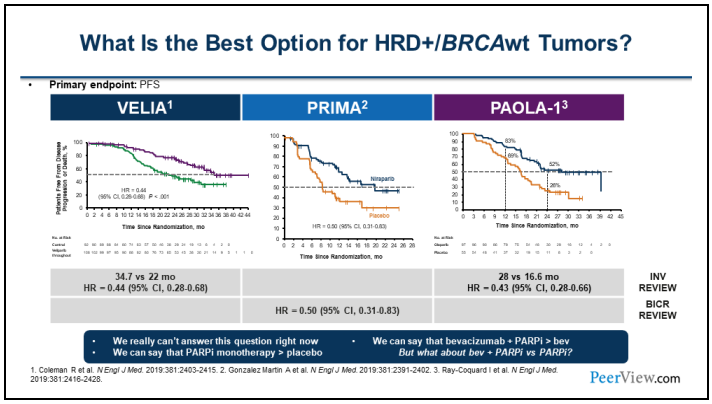

So how about BRCA wild-type tumors who are homologous recombination deficient? So VELIA was a study, and we're not going to talk about veliparib, but this is the data just to kind of show you the curves. They certainly do benefit from PARP inhibitors versus placebo. PRIMA, niraparib versus placebo. And here's PAOLA, bevacizumab-olaparib versus bevacizumab, so versus an active control. So PRIMA, you have a hazard ratio of 0.5, PAOLA 0.43.

So what do you think of these two settings? What's the best situation here? Is it similar to BRCA-associated cancers, where you dissociate the decision of bev and PARP, or is there more rationale to use them together?

Really, the truth of the matter is, we don't know right now, because these are two different drug companies, so we don't have individual data to combine, and PRIMA is a very different patient population. It's a very high-risk patient population, lots of neoadjuvant chemotherapy, 70%. 35% were stage IV. They purposefully selected a very high-risk group of women, and PAOLA-1 didn't do that.

So you can't even overlay the survival curves and try to come up with some cute hypothesis. They're just totally different studies. So we can't answer that question about, is bev plus PARP better than PARP alone? We can say that bev plus PARP is better than bev. PAOLA tells us that, and I think that's compelling, because it removes a little of the clinical equipoise about picking bev or PARP if you know the HRD status, in my mind. But it doesn't tell us bev-PARP versus PARP.

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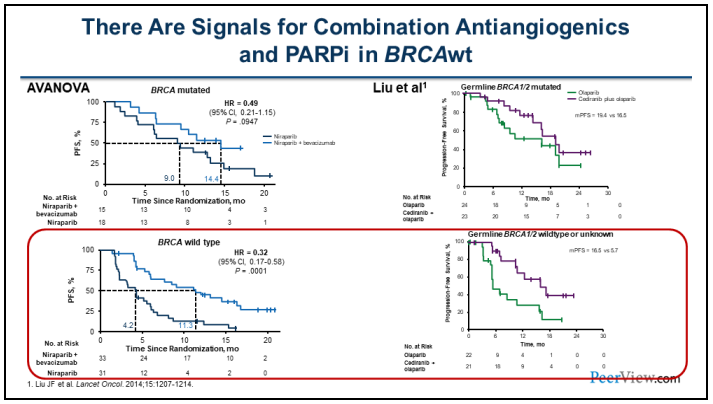

And the reason I bring that up is that there's data in the recurrent platinum-sensitive setting. AVANOVA is one study, which was bevacizumab and niraparib. And Dr. Joyce Liu from Dana-Farber has published on cediranib, which is a tyrosine kinase, and olaparib in both BRCA-mutated on the top row and BRCA wild-type on the bottom row populations.

And their findings are very similar in that, in the BRCA group, the doublet in both settings did improve progression-free survival in this setting, but not a huge amount. It was a little bit.

But in the BRCA wild-type populations in both curves, there was a much more profound synergy between the antiangiogenic and the PARP inhibitor, leading to the hypothesis and this is why PAOLA was developed, that when you use an antiangiogenic agent, you induce some hypoxia in the tumor, and that causes downregulation of DNA repair proteins and leads to this induction of this BRCA-like state where a PARP inhibitor may work better.

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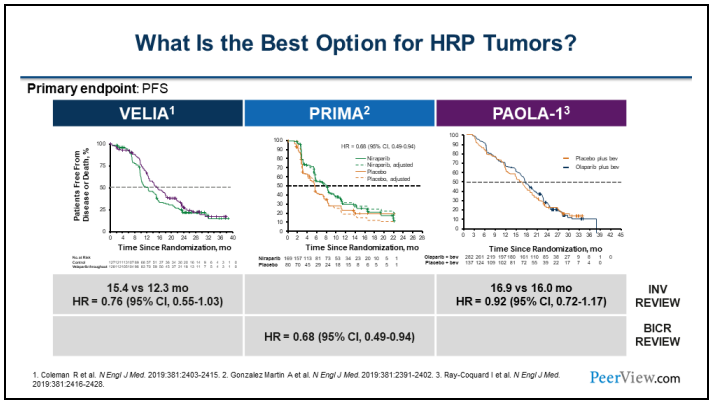

And then the other question, now that we're doing HRD testing, is what is the best option for homologous recombination-proficient tumors as identified by this test? And so what you can see here is that in PAOLA there was no benefit to the PARP plus bevacizumab. PRIMA, there was a significant improvement in progression-free survival, with a hazard ratio of 0.68. And VELIA was a non-significant improvement of about 2 months, but there was a little bump there.

I think what this data shows us most convincingly is that, however accurate the test is, it identifies a group of patients that have a poor prognosis whatever you do. And so we have to do a lot more studies in this population. This is the new high unmet need, in my opinion, for really helping improve outcomes. This is not a small percentage of the population. It's about 40% of high-grade serous and high-grade endometrioid are homologous recombination proficient. So this isn't rare.

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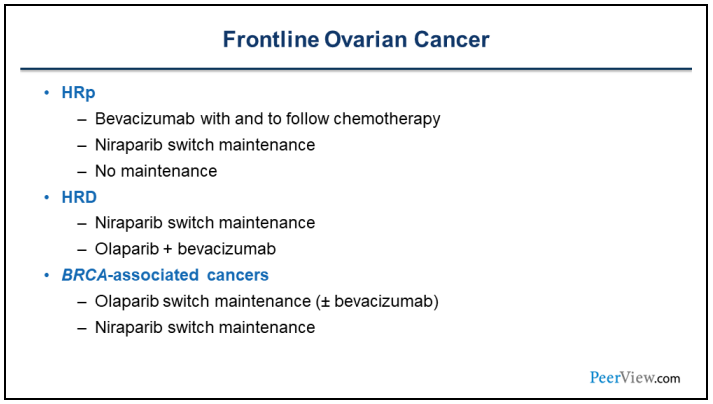

So in frontline ovarian cancer, we have, as I just mentioned, in HRP, you can do bev, you can do niraparib switch maintenance or, you know, if someone's like, "I don't really want to do this. You've identified -- you've told me" though I don't tell patients that they have a poor prognosis, but some do. They may just want a break from you. If the expectation is a median of 6 months, they may not want to do that, and that's okay.

HRD, I really do think PARP makes the most sense here, either PARP plus bev or monotherapy PARP with niraparib. And then for BRCA-associated cancers, kind of the same thing. You have monotherapy, switch maintenance options for niraparib and olaparib or olaparib and bevacizumab based on the PAOLA data. And I think, again, you can dissociate those two decisions based on your patient's tumor characteristics.

So that's the frontline data, and that's all the new data.

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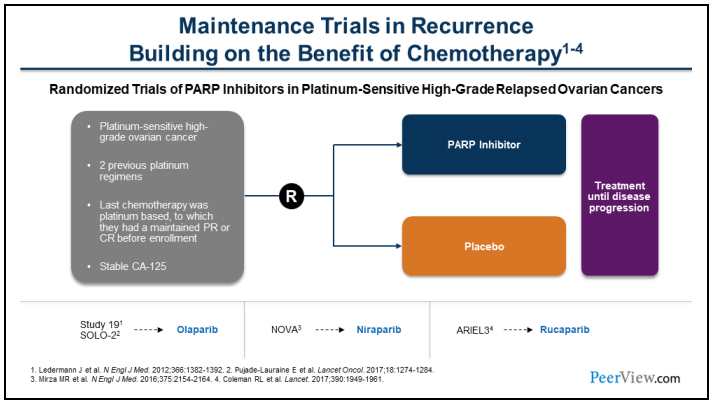

The the originally confirmed approvals, the big phase 3 studies, were in the platinum-sensitive recurrent setting, where these three studies, SOLO-2, NOVA, and ARIEL3, and they're all a little different, but in general, patients had platinum-sensitive disease, meaning they did not recur within the first 6 months following chemo.

They responded to retreatment with platinum, either with a complete or partial response. And then they were randomized to get a PARP inhibitor or placebo until progression, there was no set amount of time. And the primary endpoints were all progression-free survival.

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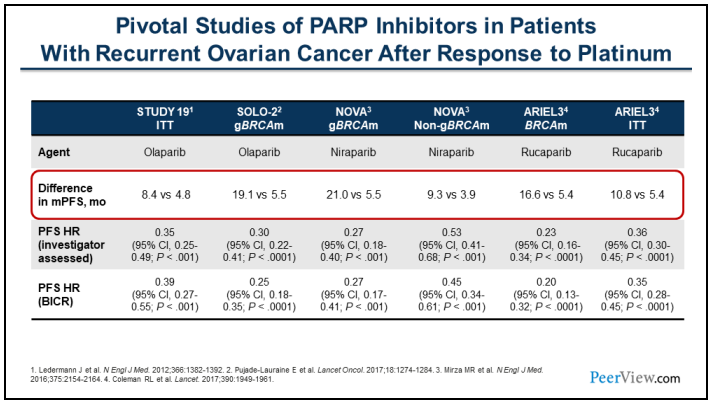


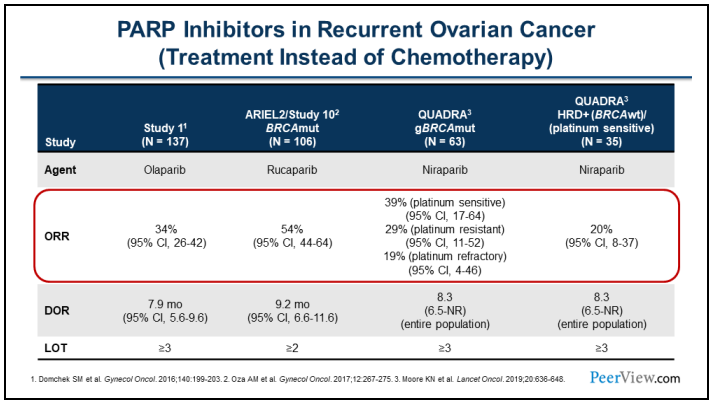
And so if we look at these studies across the board in both BRCA and BRCA wild-type populations, here's the differences in months that you would see in each of the studies and in each of the biomarkers. So of course, those with BRCA-associated tumors benefitted the most. Remember, none of these patients had seen a PARP before. They weren't available. These were all PARP-naïve patients, a situation that won't exist for much longer, so that's an interesting question.

And you can see the hazard ratios here were all markedly positive whatever group you looked at. So it was a very easy decision to see why these all gained approval regardless of biomarker, because there was benefit in all patients. But why is that? You might ask.

It really is a reflection of selection. You have someone who's recurred and has responded to platinum again, so already you know that they have some inherent homologous recombination deficiency because they're responding to their platinum. You've separated out anyone who had stable disease or anyone that recurred quickly. Those patients are all out of the mix.

You've really just isolated it down to this group of patients who have already proven that they have some homologous recombination deficiency, and then you give them a PARP. So of course that's going to work well. And that led to the approvals across the board for all three of these agents.

Slide 35



And so the original kind of work in ovarian cancer was as monotherapy in high-unmet-need populations. So those patients who could no longer receive platinum or they were platinum resistant or had four or five lines of chemotherapy, and these were all judged based on response rates.

And so you can see Study 1, which is olaparib, was in fourth line and beyond, had a 34% response rate. Duration of response was 8 months. That got the first accelerated approval in 2014 for PARP inhibitor use in BRCA-associated cancers fourth line and beyond. That was the only setting you could use it.

Rucaparib showed some similar data in third line and beyond, and so that got approved about a year later. Niraparib was the first to come in with HRD-positive fourth and fifth line, so that got approved actually just last year for both BRCA and HRD-positive. And so we have these accelerated approvals that allow us to use PARP instead of chemotherapy.

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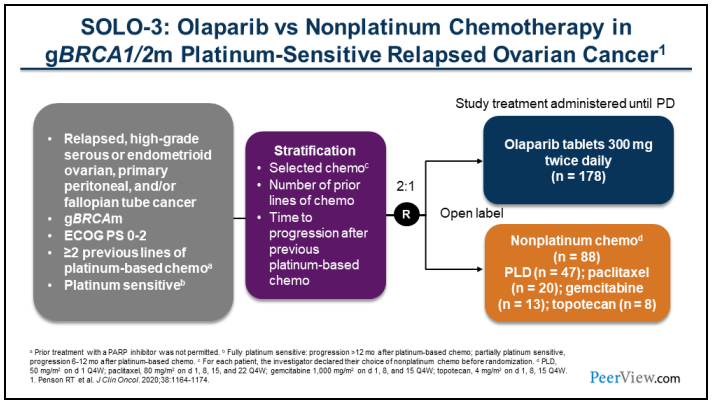

SOLO-3 took patients, who were platinum sensitive and had had at least two lines of platinum, so they were on their third platinum or platinum-sensitive recurrence, and randomized them to olaparib or chemo, but didn't include a platinum, which I still to this day think is kind of odd, but that's how it was designed.

And initially, the endpoint was progression-free survival, but with all of the approvals in patients with BRCA-associated cancers, they had trouble accruing, because you didn't want to not get olaparib if you hadn't had it. So they changed it to a response rate endpoint before the study read out, which is legal.

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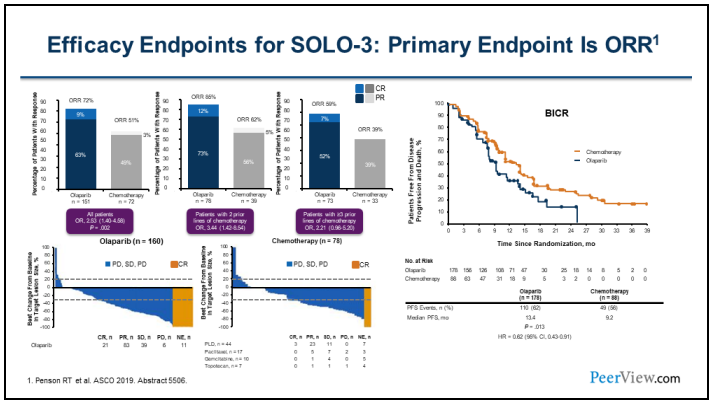

And these are the results. And they're pretty amazing, to be honest. You know, these are 50% of the patients came on fourth line or greater, so relatively heavily pretreated patients, and 72% response to olaparib. That's really high. 9% complete responses.

But look at the chemotherapy arm. It's still 51% with doxo or topotecan or Taxol. So really high response rates in a late line of therapy. And you can see it's even higher in those patients with only two prior lines of chemotherapy, and then it goes a little bit lower with those with three or more prior lines, but still really high response rates, which makes you feel really pretty good about using olaparib.

They were able to look at the progression-free survival with the patients that they had, and it was longer with olaparib as compared to monotherapy non-platinum chemotherapy, with a hazard ratio of 0.62. So this is interesting data.

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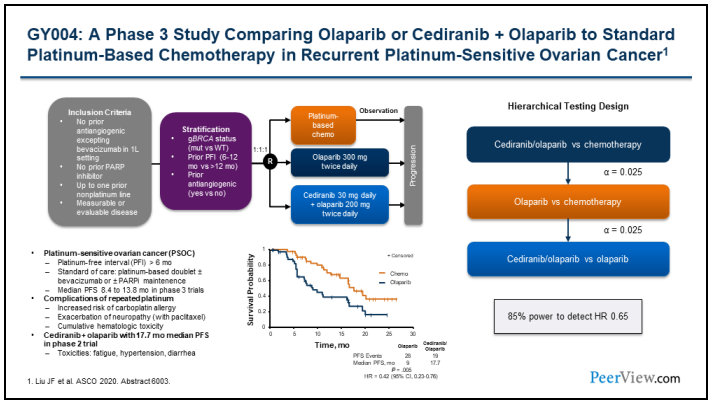

So I showed you in the prior study, SOLO-3, the comparison of PARP inhibitor versus chemo in a platinum-sensitive setting, but without using a platinum. And so in our GY004, which Joyce Liu led for the NCI, really tried to answer the question, is "can you substitute olaparib or in this case, olaparib and Cediranib for chemotherapy in first-line platinum-sensitive recurrence?"

And so they did this randomized phase 3 study comparing those three arms, and this just reported out this year. And while there was no negative effect in any of the subgroups for using olaparib or olaparib-cediranib instead of chemotherapy, so it wasn't inferior, it certainly wasn't superior.

And so at this point, we would call this a negative trial, and I think the question of whether or not you can completely replace platinum with a PARP inhibitor as opposed to platinum followed by a PARP inhibitor remains a little bit unanswered.

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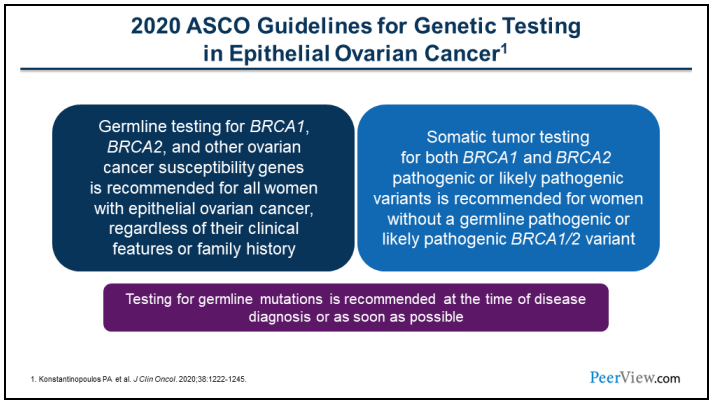

And so these are the ASCO guidelines for genetic testing in epithelial ovarian cancer. I mentioned these earlier. All women should be offered germline testing for BRCA1 and 2 and other ovarian cancer susceptibility genes, such as PALB2, BRIP1, and RAD51C. And it's irrespective of family history or age.

And if that is negative, we recommend somatic tumor testing for BRCA1 and BRCA2 so we can catch that 7% of tumors, 7 to 10% that do have a deleterious mutation just in the tumor, because those patients will really benefit from PARP, as well.

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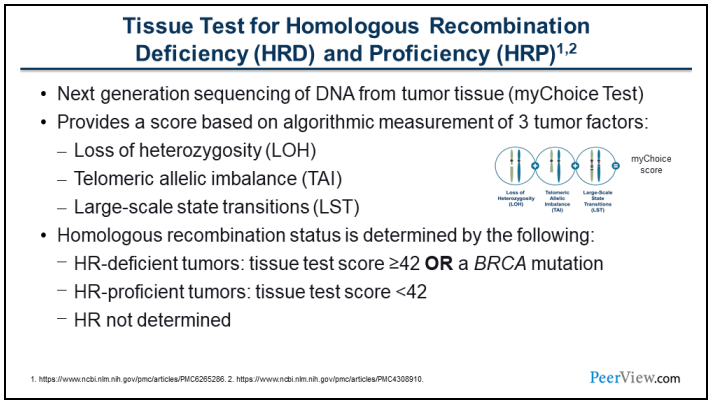

I mentioned the tissue test for homologous recombination. There are two tests. There's one by Myriad that was used in the studies I discussed in front line that is a combination of scores of loss of heterozygosity, telomeric imbalance and large-scale state transitions. You score each of those.

And then an HR-deficient tumor is a genomic instability score of 42 or greater, or if you have a BRCA mutation, you automatically are declared homologous recombination deficient. And then homologous recombination-proficient tumors are genomic instability score less than 42. So that was the test used in the studies I discussed.

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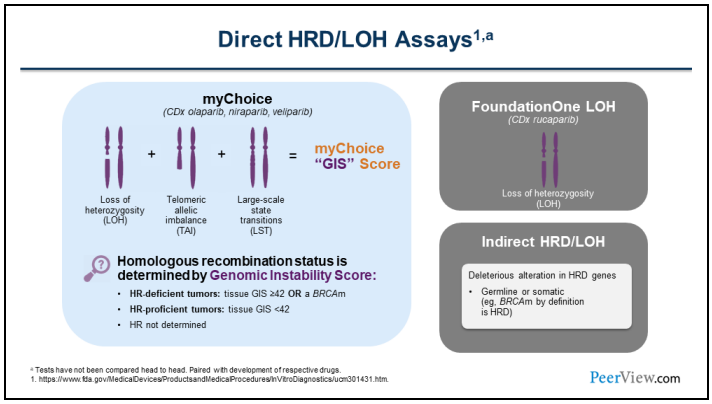

The other test is Foundation Medicine's loss of heterozygosity test. It alone and the LOH test in Foundation One, the methodology is different than the LOH in the myChoice, so it's not like they just are doing one-third of the test. It's a different test.

And here the percentage of the chromosome that has loss of heterozygosity greater than 16% is indicative of someone that has what we would call homologous recombination deficiency, and less than 16% we would call proficient. And these are the two FDA-approved tests that are available for use now.

Slide 42

Okay. So moving on to our other cancers, where we have fewer data. So this will be a little bit quicker, but it's exciting. So we do have two new indications in breast cancer, olaparib and talazoparib. So olaparib, both are only germline BRCA.

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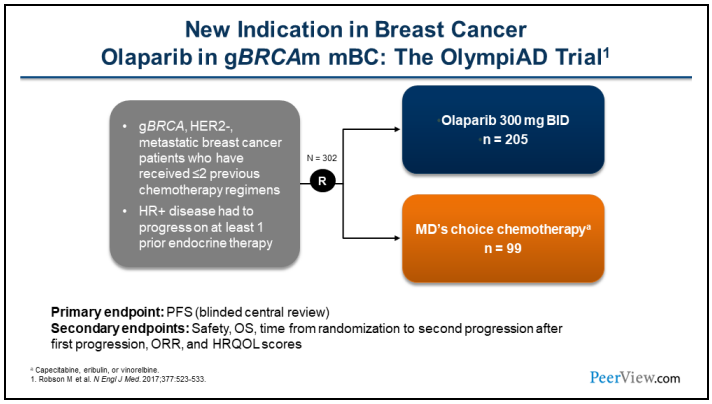

So olaparib, the OlympiAD study was done in women with HER2-negative metastatic breast cancer who had received two or less than two prior lines of chemotherapy, hormone receptor positive, but HER2-negative. And they had to have progressed on at least one prior endocrine therapy. And they were randomized to physician's choice chemo or olaparib.

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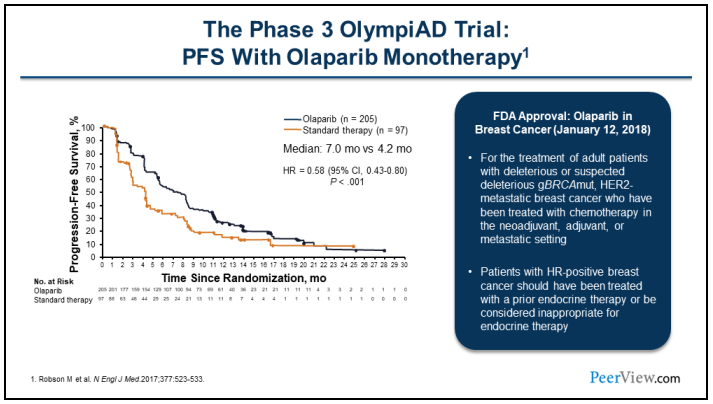
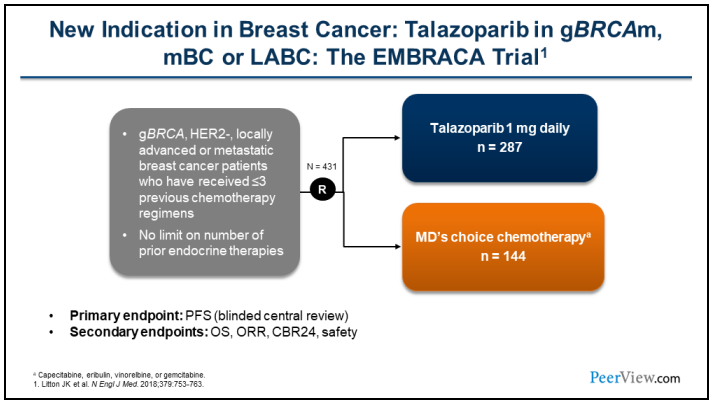


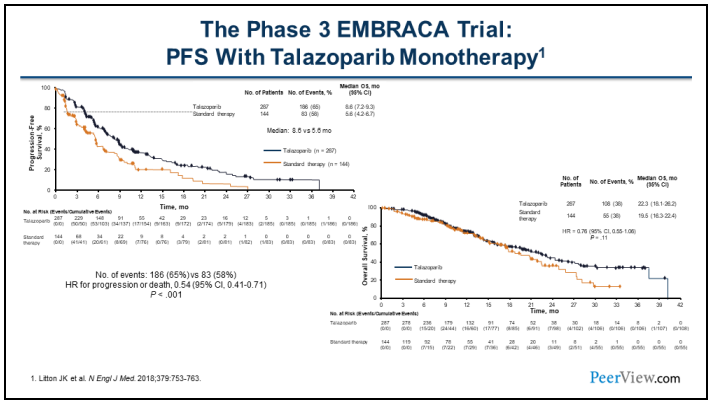
And here's the primary analysis, which was progression-free survival. And it improved progression-free survival with a hazard ratio of 0.58, so a 42% reduction at every point in that curve, and the risk of progression or death with use of olaparib instead of chemo -- an active therapy here -- these are therapeutic trials, not maintenance. So versus standard of care chemo, you did improve by 42% the outcomes for your patients. And that led to FDA approval in January of 2018.

Slide 45



So about the same time was the EMBRACA trial. So this was similar, except that you used talazoparib. Still in germline BRCA-associated HER2-negative locally advanced or metastatic breast cancer. Here, as compared to OlympiAD, where you could only have two or fewer lines of chemotherapy, here you could have three or fewer previous chemotherapy regimens and no limit on number of prior endocrine. And again, they were randomized to either talazoparib 1 mg/day or physician's choice chemotherapy.

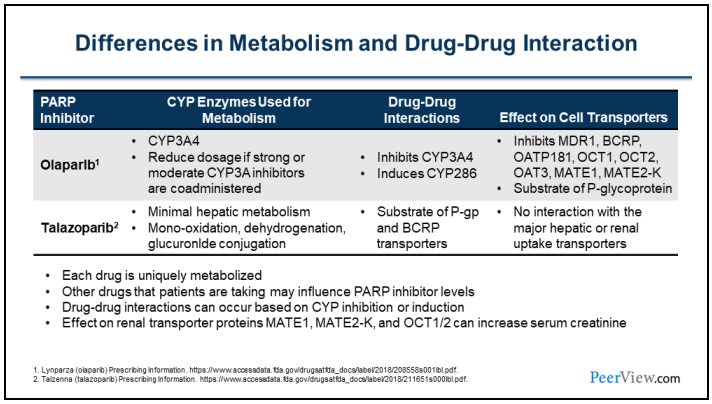
Slide 46



And here are the primary outcomes. Similar to OlympiAD, it's almost an identical hazard ratio. So a 46% reduction in the risk of progression or death with the addition of or the use of talazoparib instead of whatever the investigator's choice chemotherapy was.

Interestingly, they don't show an improvement in overall survival, but they hadn't broken it out by receipt of prior cytotoxics or not, so that may be coming. But this also led to FDA approval of talazoparib in this setting.

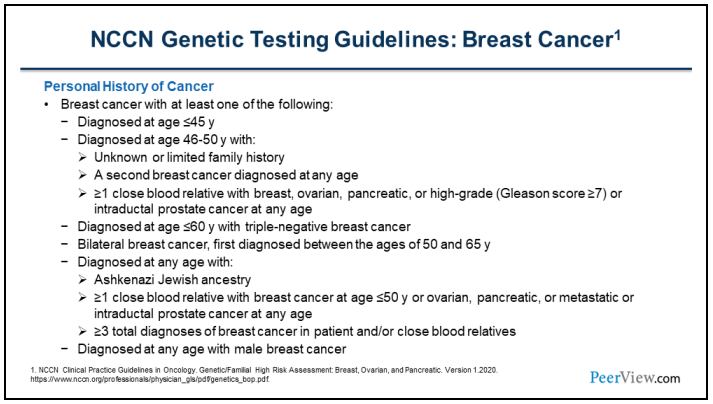
Slide 47



So we have two options in the hormone receptor-positive HER2-negative population, olaparib and talazoparib. And so I just put this comparison slide up for you because, even though the hazard ratios look the same, and clinically, they may behave the same, they are different drugs. So they have different CYP enzymes for metabolism, and so that's important for your clinical pharmacists in terms of watching for drug-drug interactions.

As you'll see in the middle bar, they do have different potential for drug-drug interaction, and they have different effect on cell transporters. Again, I referenced this early with ovarian cancer. You have impacts on creatinine transporters that can bump your creatinine a little bit with olaparib. You don't really see that at all with talazoparib. So there are some subtle differences, but both are really well tolerated and appear effective.

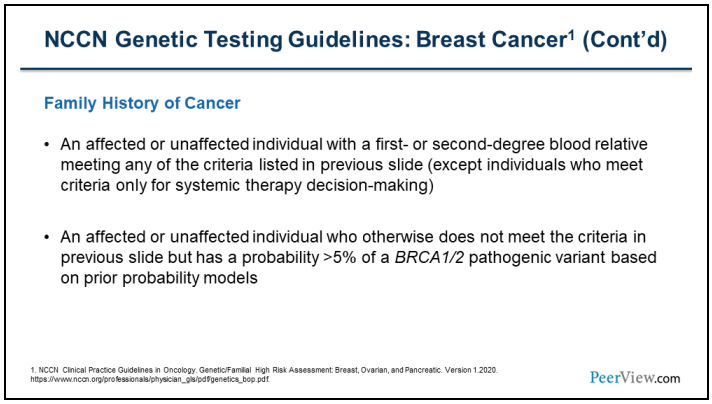
Slide 48



So what you can see here are the NCCN guidelines for genetic testing for breast cancer, and the first big point is, it's very different than ovarian cancer, which is one line, test everybody. Breast cancer is, I wouldn't say complicated, but it's much more detailed and based on age at diagnosis, family history, ethnicity, and histology.

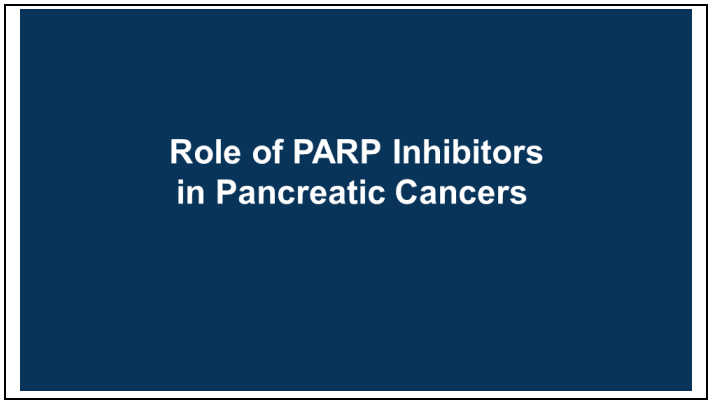
And so you can see here kind of the guidelines for testing in women with a personal history of cancer, and these are, of course, available on the NCCN.

Slide 49



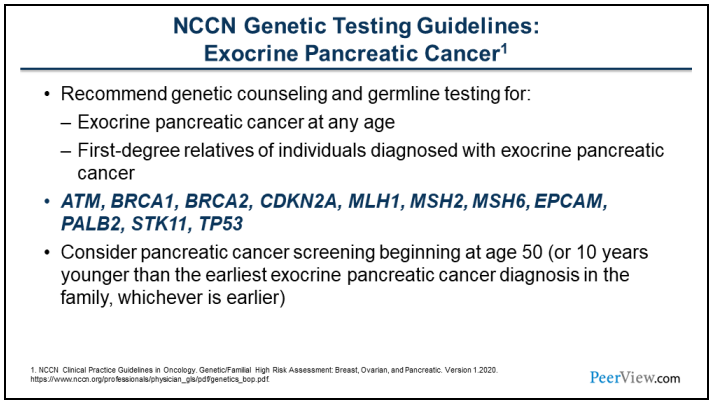
And those with a family history of cancer, how decisions are made regarding who should be referred for genetic counseling and potential genetic testing for BRCA and other high-penetrance genes that are related to breast cancer.

Slide 50



Pancreatic cancer, it's a really short story.

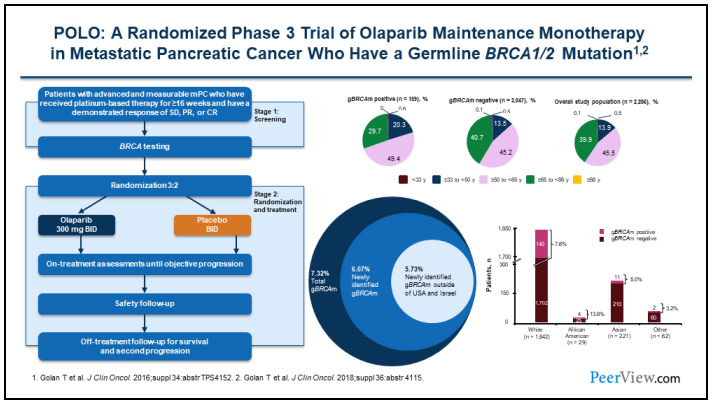
Slide 51



Genetic counseling and germline testing, for everyone, so it's kind of like ovary, for exocrine pancreatic cancer, because we want to find those with BRCA-associated cancers, definitely anyone with a first-degree relative. We're looking at this entire panel, though. So it's not just BRCA.

And then if you identify any of these germline mutations, you want to start screening, and we have a pancreatic cyst monitoring clinic in our cancer center where you start screening either 10 years younger than whoever your relative is or at 50 years, trying to catch things earlier and at a curable state.

Slide 52

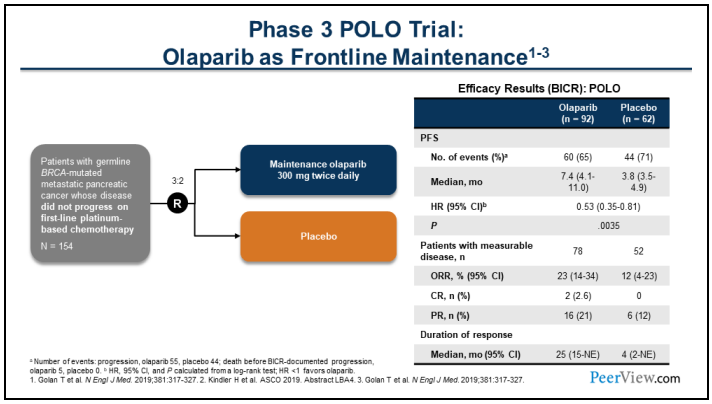


So here we're going to talk about the POLO study. So when we're talking about BRCA mutations in pancreatic cancer, it's really a little bit needle in the haystack. This is the POLO study, where you got registered, and then you tested patients, because it wasn't standard of care, right? All the patients with pancreatic cancer weren't getting tested, like we're now doing in ovary. And so this had to be done on trial.

And so they randomized thousands of patients. You can see that in the lower right-hand side of this graph. You know, of the Caucasians they screened, what is it, 2,102 patients, to find the 140. So it's about 7% of the patients-ish, maybe 10% will have a BRCA mutation, and it's mostly BRCA2.

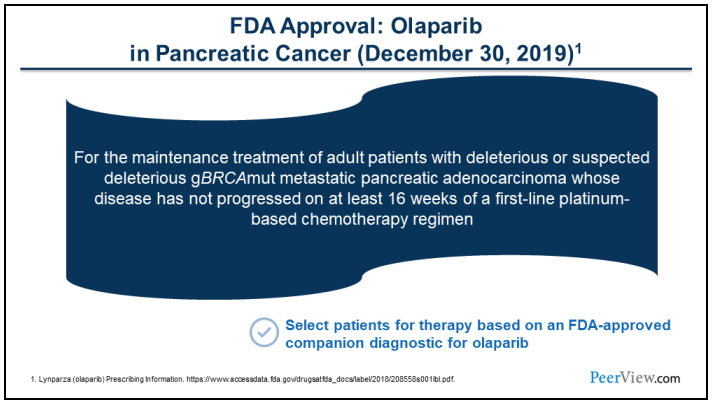
But to find them, you have to test everyone, because the nice thing about these pie charts in the upper right, you can see that of those in the study population, 45% were 50 to 65 years of age, 13% were young, less than 50. But 39% were 65 to 88. So it's not associated with younger age or family history and all of that. It really was random. And so you have to test everybody to find these patients.

Slide 53



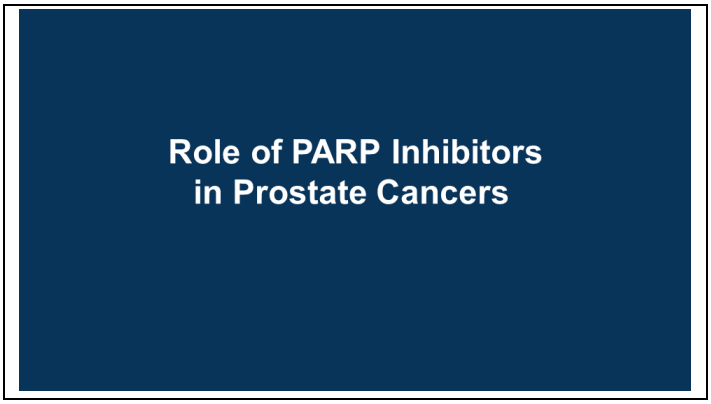
The POLO study looked at patients with a germline BRCA mutation who got first-line chemotherapy and didn't progress. So it's kind of a maintenance idea and randomized them to olaparib or placebo. And the hazard ratio here for progression-free survival was 0.53. So 47% reduction in the hazard of progression or death with use of olaparib as compared to placebo in this population.

Slide 54

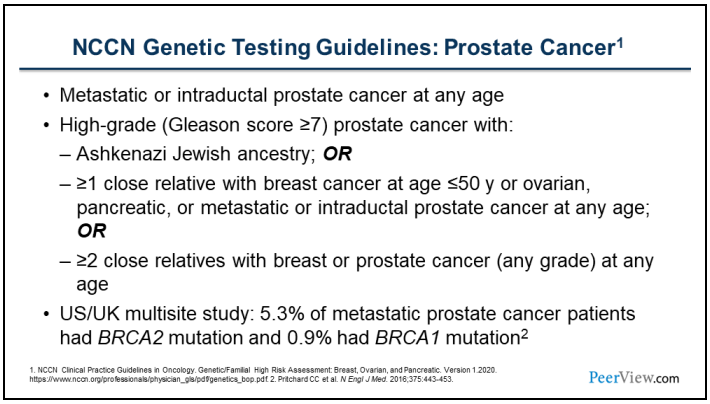


And that led to FDA approval in this setting for maintenance treatment in post-chemo for pancreatic cancer with a germline BRCA mutation whose disease hadn't progressed after at least 4 months of therapy.

Slide 55



Slide 56

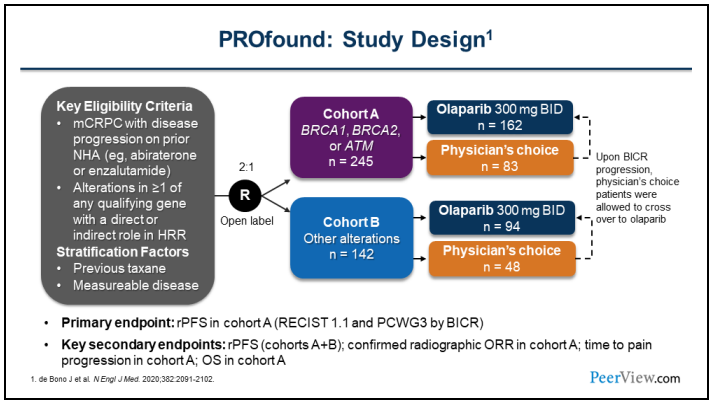


And then for prostate cancer, again, here are the guidelines. We were not testing everybody with prostate cancer. And we're still not testing everybody, but we certainly are testing more.

So metastatic or intraductal prostate cancer at any age, getting tested. High-grade Gleason score greater than or equal to 7 who either are Ashkenazi Jewish ancestry or have one or more close relatives with any of the other genetically associated tumors, or two or more close relatives with breast or prostate at any age, those patients should be offered testing for BRCA mutations.

And you find these in about 5% to 6% of the population with BRCA2, very few, but a few, BRCA1. But mainly you're talking about BRCA2.

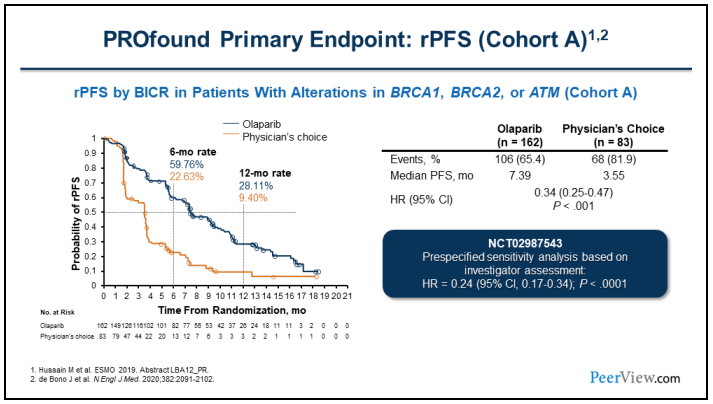
Slide 57



So we do have new indications here. This is the PROfound study. And so again, I mentioned earlier that prostate kind of -- I think they learned, and so they incorporated a lot of homologous recombination genes in addition to BRCA. So this is a study that's metastatic castrate-resistant prostate cancer that had progressed on either abiraterone or enzalutamide, so standard of care. And they had an alteration in one of the identified genes.

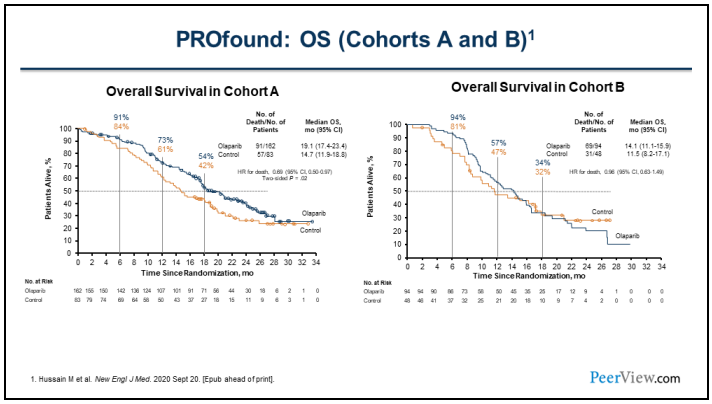
And they were randomized to olaparib or investigator's choice chemotherapy. And there were two cohorts, one with BRCA2, as well as ATM. ATM was and it still is, I think, a little controversial, but it was thought to be important enough to incorporate in cohort A. And then cohort B was any other alteration in homologous recombination genes.

Slide 58



So what you can see here, this is cohort A, and this is the RECIST progression-free survival in patients from cohort A. So the hazard ratio here is 0.34. That's like SOLO-1. So a 66% reduction in the hazard of progression or death with the use of olaparib as compared to investigator's choice chemo in this population of men who have difficult-to-treat prostate cancer. So this was an important finding.

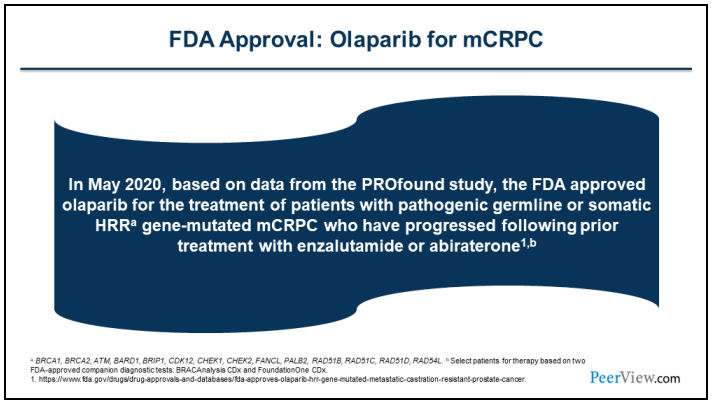
Slide 59



And overall survival was also just reported, and in cohort A there does appear to be an overall survival advantage, with a hazard ratio of 0.69. So a 31% reduction in the hazard for death with the use of olaparib in this setting. This just came out this week, so very exciting. But remember, this is the BRCA1, -2, and ATM.

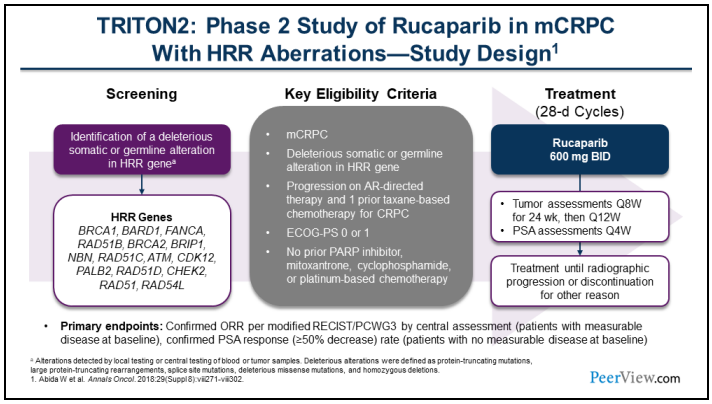
And in cohort B, there does not appear to be that, and so these other DNA damage response genes may be less important, but I think more to come on that, as more data comes out. But certainly, BRCA2 is a driver.

Slide 60



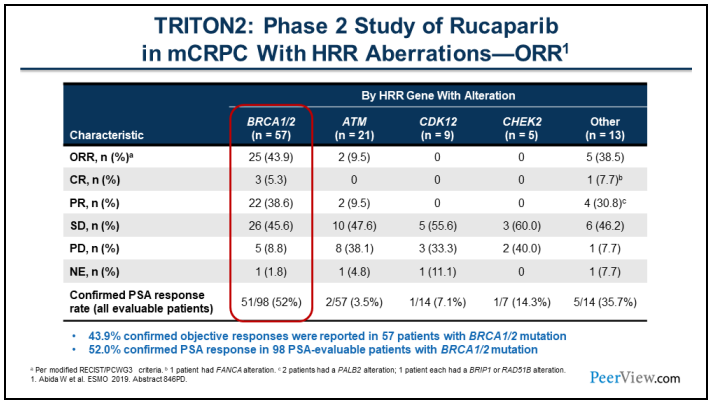
So that led, of course to the FDA approval for olaparib in metastatic castrate-resistant prostate cancer following treatment with enzalutamide or abiraterone.

Slide 61



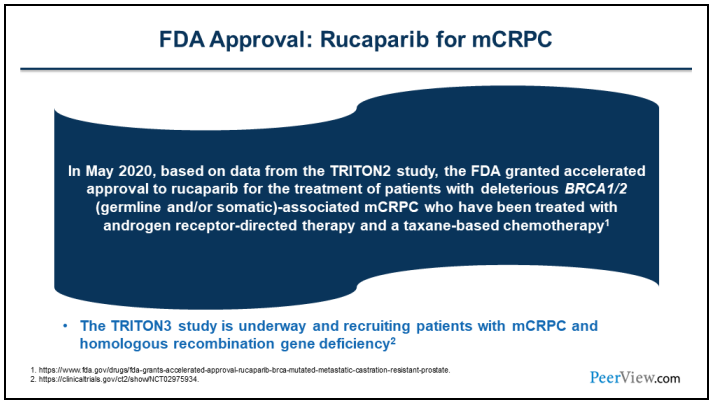
The other study that was important for approval was TRITON2, and this was a phase 2 study of rucaparib in a similar population of metastatic castrate-resistant prostate cancer that have homologous recombination repair aberrations here.

Slide 62



They were looking at overall response rate, and you can see the result by the type of gene alteration here, with the BRCA1 and BRCA2, mainly 2, mutations having a response rate of 43%, which is really quite striking, 38% of those partial responses, and then a smattering of responses amongst the other homologous recombination repair gene alterations.

Slide 63



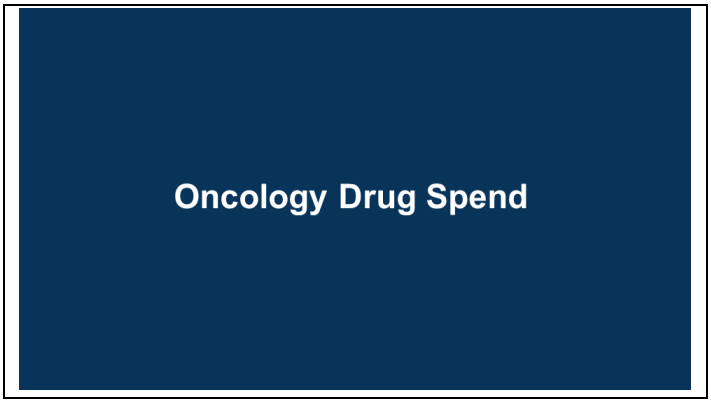
So that led to what we call an accelerated approval for rucaparib in this same population with any of these gene alterations, which was also important.

And with that, I'm going to turn the talk over to my colleague to talk about managed care considerations.

Integrating PARP Inhibitors Into the Oncology Drug Arsenal in Managed Care Settings: Challenges, Practicalities, and Considerations

Kristi Jhangiani, PharmD, BCPS

Slide 1



Dr. Jhangiani: Excellent. Thank you so much, Dr. Moore, for that comprehensive overview of the PARP inhibitors. Let's switch gears now to our discussion on how to integrate PARP inhibitors into the oncology arsenal, with a specific focus on challenges, practicalities, and considerations in managed care settings. We'll start with an overview of oncology spend and trends.

Slide 2

Drug Spend as a Percentage of PMPY in Commercial Plans[1]

2018 Rank	2017 Rank	Therapeutic Class	PMPY Spend	Trend Components		
				Utilization	Unit Cost	Total
1	1	Inflammatory disease	$189.40	-1.9%	14.8%	12.5%
2	2	Diabetes	$157.39	0.7%	8.9%	9.7%
3	4	Oncology	$72.62	-0.9%	14.2%	13.1%
4	3	Multiple sclerosis	$61.87	-9.6%	4.0%	-6.0%
5	6	Asthma/COPD	$59.31	-0.2%	5.7%	5.5%
6	5	Behavioral health	$58.69	-2.9%	-0.4%	-3.3%
7	7	HIV	$42.61	2.1%	8.9%	11.2%
8	9	Blood disorder	$53.39	1.7%	8.7%	10.5%
9	8	High blood pressure	$31.99	-1.1%	-3.8%	-4.9%
10	11	Seizures	$26.58	-0.7%	7.3%	6.5%
		Other therapeutic classes	$342.77	-3.5%	-3.6%	-6.9%
		Total	**$1,078.63**	**-1.5%**	**3.0%**	**1.5%**

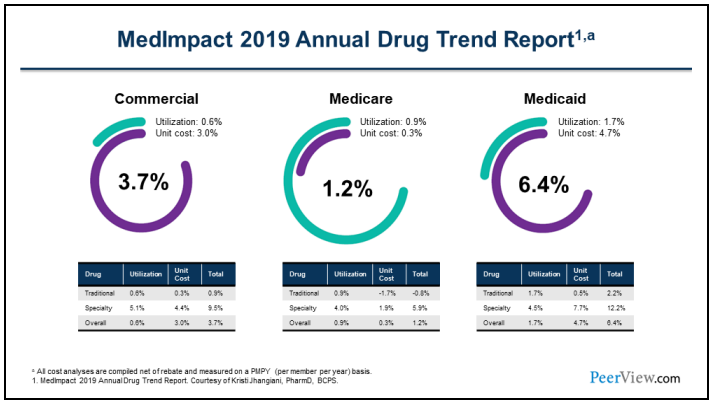
1. MedImpact 2018 Annual Drug Trend Report. Courtesy of Kristi Jhangiani, PharmD, BCPS.

PeerView.com

It should come as no surprise that oncology continues to be in the top ten therapeutic classes of overall drug spend year over year. According to data reported by MedImpact in 2018, Oncology drug spend accounted for just over 13% of the total commercial spend. Oncology was reported as the third-highest category contributing to overall commercial drug spend, which remained consistent with spend patterns from 2017.

Similarly, oncology was also reported to be in the top ten therapeutic categories of total drug spend on the Medicare and Medicaid lines of business.

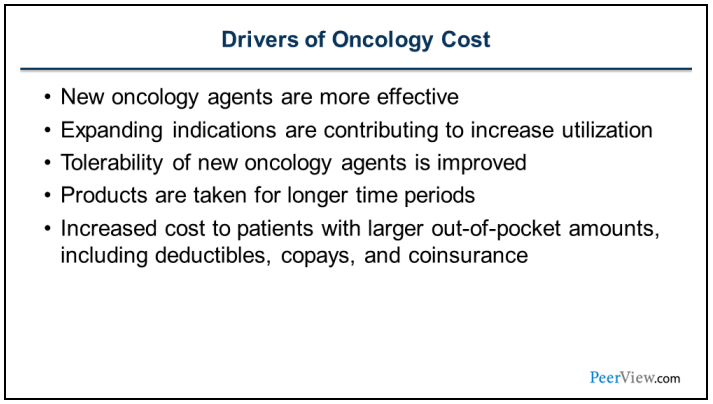
Slide 3



Now let's take a look at overall trend drivers across different lines of business for traditional and specialty drugs. In the commercial specialty space, data show that there was an increase in both utilization and unit cost from 2018 to 2019. And this trend was seen across all lines of business. For non-specialty or traditional drugs, increases in utilize were much lower, with all lines of business seeing less than a 2% increase in 2019.

Similarly, unit cost changes had a slight increase, and even experienced a decrease on the Medicare line of business, as you can see here on this slide.

Slide 4

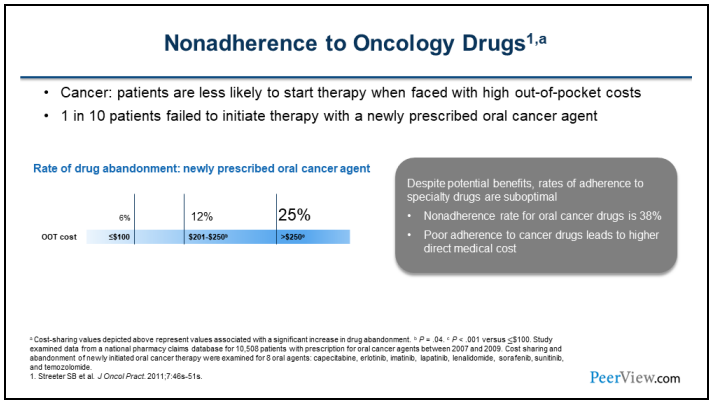


As in years past, oncology continues to be a leading area of drug spend among specialty agents. Regarding cost drivers, newer agents coming to market are generally more effective and more tolerable. Therefore, in many cases, these targeted drugs have more specific indications and are thus used in a particular population. For instance, many new oral oncology agents are targeted for patients with specific get alterations, such as PARP inhibitors targeting those with the BRCA mutation.

But while targeted agents may be more effective, they are also limited in use to that specific population, allowing manufacturers to price agents more competitively. Additionally, with increased effectiveness, products are taken for longer periods of time and will continue to influence drug spend.

On the utilization front, substantial increases in oncology utilization are mainly a result of additional FDA-approved indications which may expand the use of drugs to new tumor types or support use in earlier lines of therapy. The increasing cost of oncology drugs is not only felt by payers, though. It is also felt by the patients in the form of larger out-of-pocket costs, including deductibles, copays, and coinsurance.

Slide 5



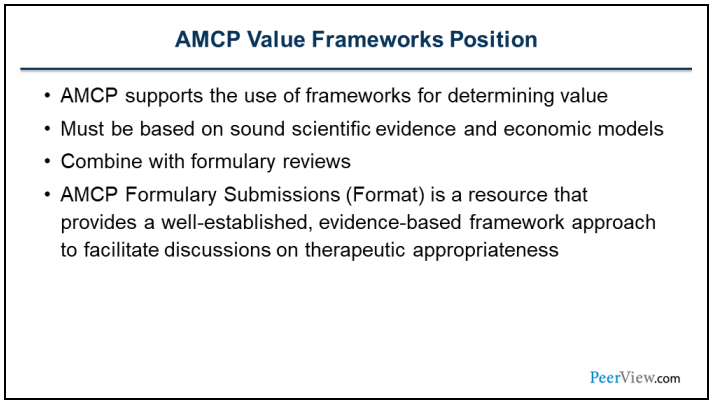
Let's consider for a moment the patient's perspective and their response to the increasing costs of oncology drugs. As out-of-pocket costs increase, patients are less likely to initiate therapy. In fact, one in ten patients fails to begin therapy with a newly prescribed oral oncology agent, and 25% of patients with newly prescribed therapy will not initiate it if their out-of-pocket costs are greater than $500.

However, high out-of-pocket costs are not just a barrier for those who are new to therapy. For all oncology patients, high out-of-pocket costs can lead to poor adherence to medication therapy despite the potential for benefit. Nonadherence rates have been reported to be as high as 38%. Another concern with poor adherence is the potential increase in health care costs, such as in hospitals or other direct medical costs.

Slide 6

Now that we've set the stage with oncology specialty spend, let's review options to assess value of therapy within various oncology value frameworks.

Slide 7

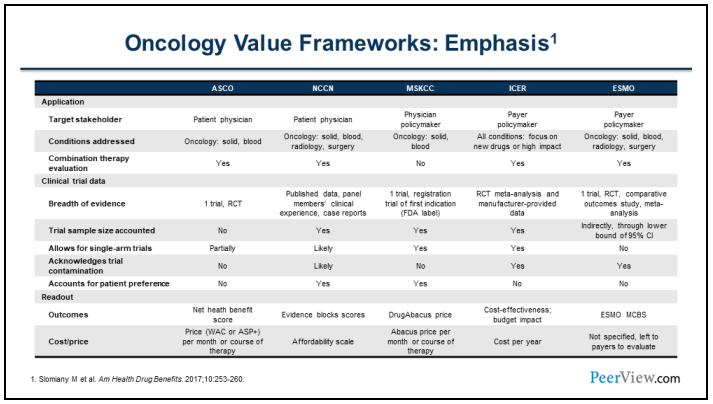


As an organization, AMCP supports the use of value frameworks that are based on sound scientific evidence and reliable models. Value frameworks, however, cannot be used alone. They are only meaningful when used in conjunction with other tools and resources, such as during the formulary review process.

Since the initial release in 2000, AMCP has provided a well-established framework to facilitate discussions on therapeutic appropriateness and value between manufacturers and health care decision-makers via their format for formulary submissions guidance document.

Now, again, in light of the rising health care costs, payers are continuing to search for ways to assess value for their drug spend. To accomplish this, value-based frameworks were developed by various organizations in the oncology space to help compare clinical and economic evidence with the intent to inform health care decision-making across payer, physician and patient groups.

Slide 8



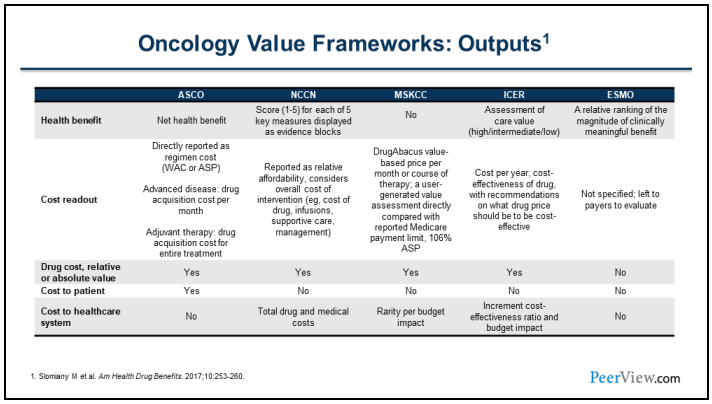
	ASCO	NCCN	MSKCC	ICER	ESMO
Application					
Target stakeholder	Patient physician	Patient physician	Physician policymaker	Payer policymaker	Payer policymaker
Conditions addressed	Oncology: solid, blood	Oncology: solid, blood, radiology, surgery	Oncology: solid, blood	All conditions: focus on new drugs or high impact	Oncology: solid, blood, radiology, surgery
Combination therapy evaluation	Yes	Yes	No	Yes	Yes
Clinical trial data					
Breadth of evidence	1 trial, RCT	Published data, panel members' clinical experience, case reports	1 trial, registration trial of first indication (FDA label)	RCT meta-analysis and manufacturer-provided data	1 trial, RCT, comparative outcomes study, meta-analysis
Trial sample size accounted	No	Yes	Yes	Yes	Indirectly, through lower bound of 95% CI
Allows for single-arm trials	Partially	Likely	Yes	Yes	No
Acknowledges trial contamination	No	Likely	No	Yes	Yes
Accounts for patient preference	No	Yes	Yes	No	No
Readout					
Outcomes	Net heath benefit score	Evidence blocks scores	DrugAbacus price	Cost-effectiveness; budget impact	ESMO MCBS
Cost/price	Price (WAC or ASP+) per month or course of therapy	Affordability scale	Abacus price per month or course of therapy	Cost per year	Not specified, left to payers to evaluate

This slide illustrates some of the key features of the five major oncology frameworks available today. One of the main fields I'd like to highlight is the target stakeholder category. This category is critical to consider, as it directly informs us which audience the value assessment targets. The reason that stakeholder category is so important is because each stakeholder will require different inputs to assess value.

For example, the costs of care, which feeds into the overall value assessment, will be much different for a payer compared to a patient. For a payer, the majority of costs will be incurred from the medication itself, while for a patient, costs to consider are mostly from their out-of-pocket expenses. Ultimately, this difference in costs of care will affect the stakeholders' willingness-to-pay thresholds, thereby affecting the overall value of a given treatment.

While there are five major value frameworks presented here, I will be focusing most of this discussion on the ICER framework, as this one target payers and policymakers and is most often used in the managed care setting.

Slide 9



Oncology Value Frameworks: Outputs[1]

	ASCO	NCCN	MSKCC	ICER	ESMO
Health benefit	Net health benefit	Score (1-5) for each of 5 key measures displayed as evidence blocks	No	Assessment of care value (high/intermediate/low)	A relative ranking of the magnitude of clinically meaningful benefit
Cost readout	Directly reported as regimen cost (WAC or ASP) Advanced disease: drug acquisition cost per month Adjuvant therapy: drug acquisition cost for entire treatment	Reported as relative affordability, considers overall cost of intervention (eg, cost of drug, infusions, supportive care, management)	DrugAbacus value-based price per month or course of therapy; a user-generated value assessment directly compared with reported Medicare payment limit, 106% ASP	Cost per year; cost-effectiveness of drug, with recommendations on what drug price should be to be cost-effective	Not specified; left to payers to evaluate
Drug cost, relative or absolute value	Yes	Yes	Yes	Yes	No
Cost to patient	Yes	No	No	No	No
Cost to healthcare system	No	Total drug and medical costs	Rarity per budget impact	Increment cost-effectiveness ratio and budget impact	No

1. Slomiany M et al. *Am Health Drug Benefits*. 2017;10:253-260.

PeerView.com

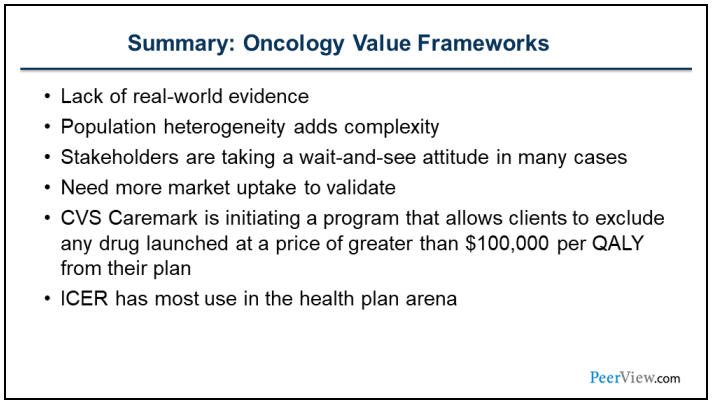
Now, let's dive a little bit deeper into the outputs of each of these value frameworks. In terms of health benefit, ASCO derives its net benefit health score from clinical benefits such as overall survival and progression-free survival report, results that are reported in randomized clinical trials, while NCCN reports its health benefits on a 5-point scale for five different categories, including efficacy, safety, and affordability, to name a few.

But one major drawback of NCCN's affordability block is that for disease states dominated by recently released branded products. In this situation, affordability assessments provide minimal comparative value, since all of the treatments generally score the same. So while ASCO and NCCN value frameworks do have utility, they're usually used to facilitate shared decision-making between patients and providers.

Memorial Sloan-Kettering Cancer Center's Drug Abacus tool is probably the most unique in that it was one of the first tools that allowed users to generate a recommended price based on an oncology agent's evidence and then compared that value to the list price of the agent.

ICER's value assessments, however, are very comprehensive in that ICER considers comparative clinical effectiveness, potential budget impact and incremental cost-effectiveness ratios on a cost per quality adjusted life year or QALY basis. ICER's reports always aim to answer four main questions: How well does the drug work? How much better is the therapy compared to what we already have? How much could it save? And how much could it cost to treat everyone who needs it?

Slide 10



Summary: Oncology Value Frameworks

- Lack of real-world evidence
- Population heterogeneity adds complexity
- Stakeholders are taking a wait-and-see attitude in many cases
- Need more market uptake to validate
- CVS Caremark is initiating a program that allows clients to exclude any drug launched at a price of greater than $100,000 per QALY from their plan
- ICER has most use in the health plan arena

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In summary, value frameworks have the potential to be very powerful tools for all stakeholders in health care. And while valuing cancer treatments based on their health benefits relative to their cost is a step in the right direction. There is not one value framework that fits everyone's needs.

With the current options available, real-world evidence has not been incorporated into the model, which remains a big limitation in value assessments. Because many payers are not consistently using value frameworks in formulary discussions, many stakeholders are taking a wait-and-see approach. And although current value frameworks do have overlapping interests, they are still not completely aligned.

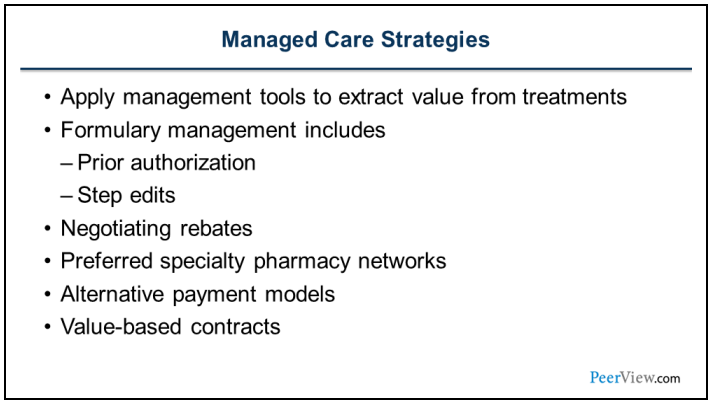
However, despite the limitations of value frameworks, some payers have implemented programs based on ICER's QALY assessments for new drug therapies. It's important to realize that programs based on QALY thresholds set forth by ICER may prevent patients from accessing lifesaving medications. So ultimately, even as payers, we must consider how our decisions affect users of the health care system, our patients, and find a way to balance both cost and access.

In order to strike this balance, we should continue to explore options to assess value while realizing that there's no one-size-fits-all approach to value frameworks.

Slide 11

Let's continue our discussion on value and review current strategies and tools available to managed care industry.

Slide 12



While health plans are key players in managed care, pharmacy benefit managers will likely endure the majority of the costs when it comes to PARP inhibitor coverage. Thus, many of the managed care strategies we will discuss in the remainder of this presentation will be focused on the pharmacy benefit.

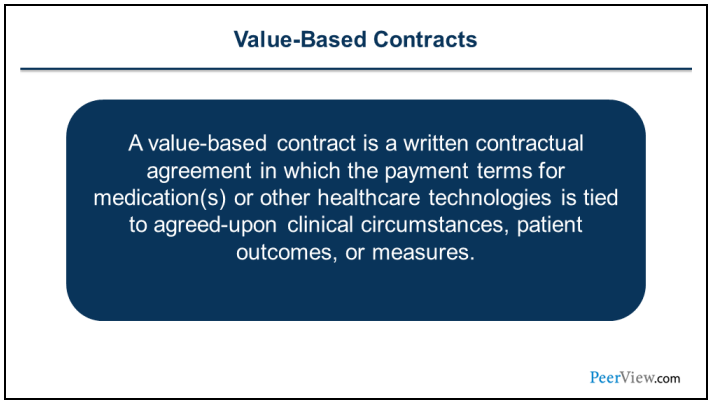
In the case of PARP inhibitors as oral oncology agents, PBMs employ many traditional tools to manage utilization. Formulary management tools such as prior authorization and step therapy may be applied to ensure the appropriateness to ensure the appropriate patients are receiving treatment.

In therapeutic classes where there are multiple agents approved for the same indication, rebate negotiations may also take place to help manage costs. And while PBMs may leverage rebates to reduce net costs, opportunities for rebates may be more limited in the oncology space. For instance, on the Medicare line of business, oncology is considered a protected class. Therefore, application of utilization management tools and discount opportunities are more regulated.

Additionally, with the PARP inhibitors, as Dr. Moore has just reviewed, each of them are ever so slightly different in their indications. With this level of detail, and as we move towards a world in which precision medicine and targeted therapies dominate, treatments in the same therapeutic class will move further and further away from being considered me-too agents.

Outside of formulary management, network structure is an important lever to be considered when further savings opportunities are necessary. Many PBMs consider specialty savings through fulfillment channels which may provide competitive specialty pharmacy rates. We have also presented alternative payment models and value-based contracts as managed care strategies, and we'll discuss these in greater detail in the next few slides.

Slide 13



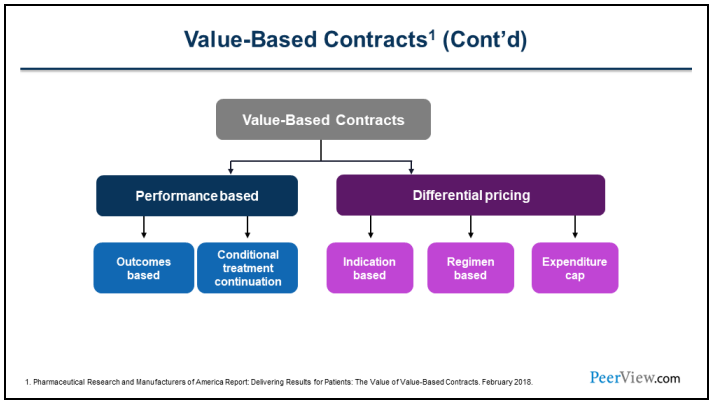
Value-based contracting is an emerging strategy under which payers and manufacturers agree to specific terms that tie payment to results, and in many instances sharing financial risk. A value-based contract is defined as a written contractual agreement in which the payment terms for medication and/or health care technologies is tied to agreed-upon clinical circumstances, patient outcomes, or measures.

Now, there are multiple varieties of these contracts, as detailed on this slide. But the overall objective is to hold manufacturers more accountable for value than other arrangements that tie net prices for drugs to the volume of drugs that are purchased.

Manufacturers in the past would more commonly rely on ongoing sales of chronic disease drugs to large numbers of patients to recoup cost. But in this scenario, manufacturers were able to keep drug prices down due to the high volume.

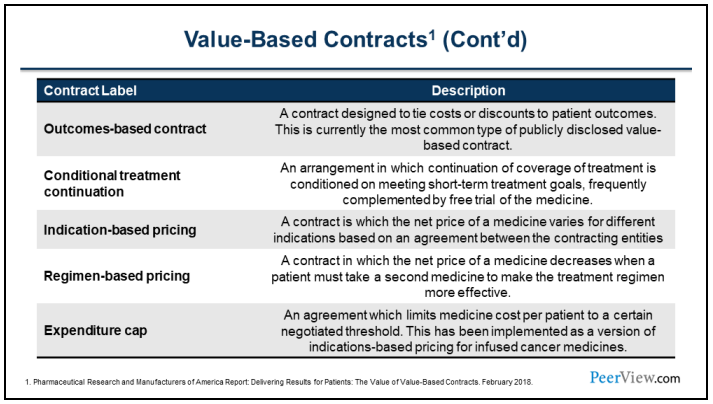
Value-based contracts, therefore, are especially important to manage the rising costs of drugs. These contracts are employed to share the financial risk between manufacturer and payer, to account for the fact that drugs may not work as demonstrated in clinical trials.

Slide 14



There are two main types of value-based contracts, which include performance based and differential pricing based. And in the next slide, we'll review these types of contracts in greater detail. Value-based contracts in effect compensate manufacturers based on obtaining improved outcomes for patients, while utilization of these contracts is evolving.

Slide 15



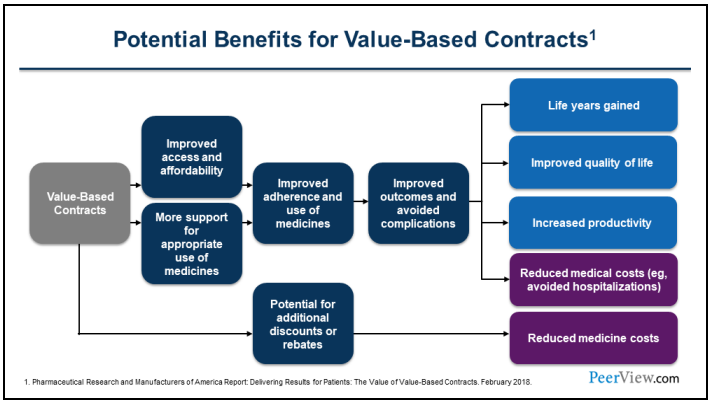
So outcomes-based contracts tie cost or discounts to particular outcomes for patients, such as overall survival or progression-free survival. In oncology, outcomes-based contracts carry many challenges. Therefore, conditional treatment continuation contracts should be explored. These contracts are contingent upon meeting short-term treatment goals.

For PARP inhibitor therapy, where there are multiple drugs with different indications, indication-based contracts could also be considered. Indication-based pricing allows PBMs to pay different net costs for different indications.

Regimen-based contracts can also be explored in oncology, as many cancers require patients to take multiple medications for effective treatment. And finally, we have expenditure cap contracts, in which drug costs are limited to certain negotiated thresholds.

Although value-based contracts will help all stakeholders better understand the value of many cancer drugs, there are few published reports of these contracts being used in the oncology space. So conceivably, these contract arrangements could relieve some cost burden on payers, but they will not themselves solve the overall arching challenge of affordability of high-cost medications for cancer.

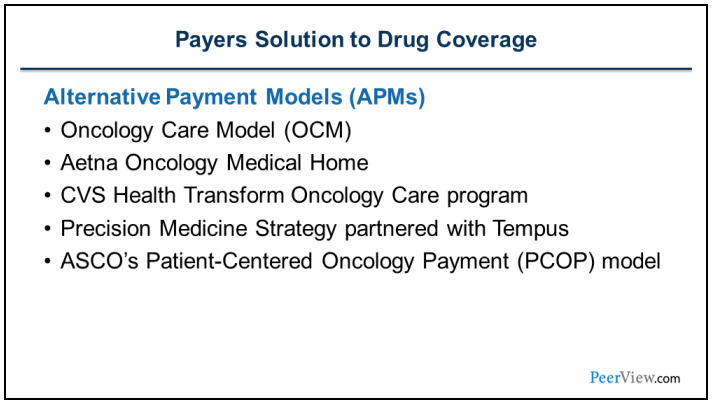
Slide 16



So we've already discussed some of the potential advantages of value-based contracts from the payer perspective. Now let's take a look at some of the benefits from a patient and health care perspective.

Value-based contracts could lead to improved adherence of medications and therefore lead to improved outcomes such as life-years gained, improved quality of life, increased productivity and reduced medical cost from avoided hospitalizations. As illustrated on this slide, these contracts not only help payers manage costs, but the benefit is seen throughout the entire health care ecosystem, from patients to health care delivery centers.

Slide 17



Value-based contracts are not the only innovative tools payers have established. Alternative payment models have also been developed to help manage costs. Alternative payment models were developed as a multi-payer strategy to help coordinate costs and patient care. Multiple alternative payment models have been piloted, including those listed on this slide.

The Oncology Care Model is a multi-payer solution that came out of CMS's Innovation Center. OCM focuses on Medicare fee-for-service beneficiaries receiving chemotherapy treatment and includes the spectrum of care provided to a patient during a 6-month episode. So primary outcomes such as reduction in total cost of care is then evaluated based on these episodes of care. This pilot program began in 2016, and will be ongoing through 2021.

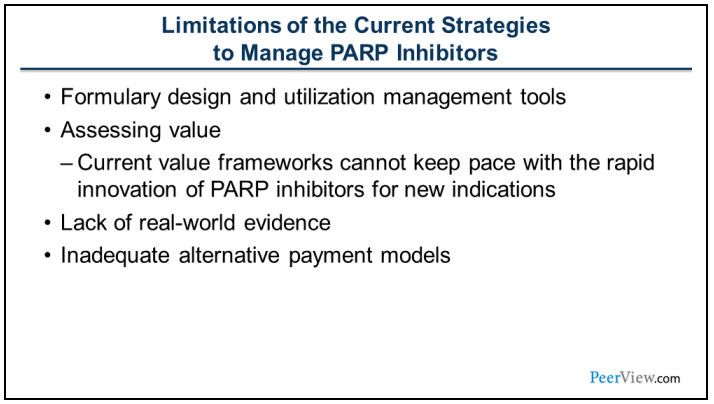
ASCO's patient-centered oncology model is most similar to OCM in that they use this episode-of-care idea to improve outcomes and reduce cost.

Aetna's Oncology Medical Home is currently only being targeted to members of the regional cancer care associates in New Jersey and Maryland, so we won't spend too much time on this one today.

CVS also has an alternative payment model called the Transform Oncology program. Through this program, when therapeutic regimens align with NCCN guidelines and clinical pathways set out by CVS Health, eligible patients can automatically receive prior authorization approvals, which may reduce waiting time to initiate therapy.

And as an extension of this program, CVS developed the precision medicine strategy with their partner, Tempus. As part of their precision medicine initiative, CVS is helping to provide access to broad-panel genomic testing and connect eligible patients with clinical trials.

Slide 18



Now, while these alternative payment models are available, they are currently only being explored for drugs that span both the medical and pharmacy benefit, and are thus limited in their ability to provide benefit for oral cancer therapies that would be paid for by the majority by the specialty pharmacy benefit. Now, of course, there's no doubt that the pace of innovation in the oncology arena is seemingly unmatched by any other therapeutic area, and it continues to accelerate.

Our current formulary design and management tools can aid in ensuring the appropriate patients get access to medications that are most likely to benefit them. However, they are still limited in scope. High costs and targeted indications, therefore, require further evaluations for benefit of therapy, which is where value of therapy becomes an important factor.

Value of a therapy can inform decision-makers on clinical benefit as well as cost effectiveness. However, the value framework tools available today cannot keep pace with the rapidly changing environment, especially in oncology and with PARP inhibitors, where supplemental indications are being approved, most often under the accelerated pathway from the FDA. And even after a value assessment is completed, drugs cost for specialty oncology agents will likely always remain in the top ten therapeutic categories of drug spend.

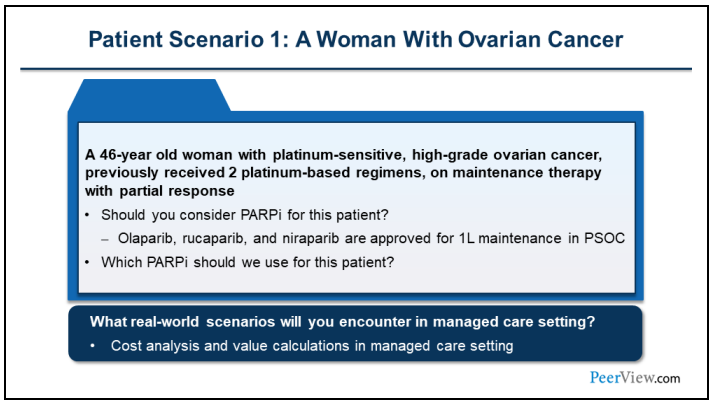
Our alternative payment models do not address this cost barrier for pharmacy benefit administrators only. So now is really the time for patients, providers, pharmaceutical companies and payers to come together to develop more innovative strategies that benefit multiple stakeholders in our health care system.

Now we'll go on to some practical scenarios, and I'll turn it back over to Dr. Moore.

Practical Scenarios: Integrating PARP Inhibitors Into the Oncology Drug Arsenal in Managed Care Settings

Kathleen N. Moore, MD, MS
Kristi Jhangiani, PharmD, BCPS

Slide 1



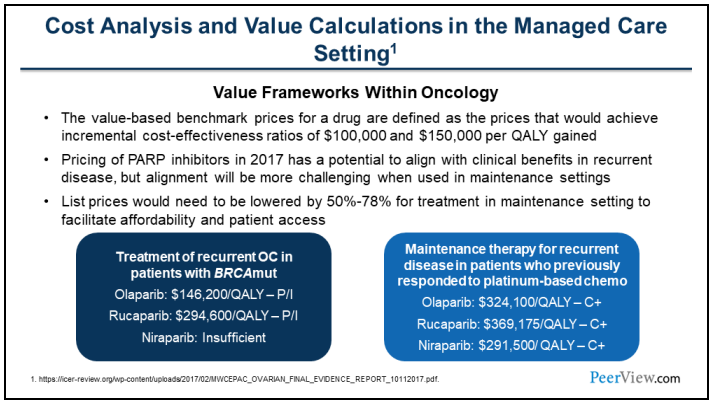
Dr. Moore: Great. So let's just take a case. So this is a patient with ovarian cancer. She's 46. She has recurred and is considered platinum-sensitive, high-grade serious ovarian cancer. She previously received two prior platinum regimens, so she's just finished her first platinum regimen in the recurrent setting. And she has a partial response to that platinum-based therapy.

And so the question here is, should you or would you consider a PARP inhibitor for this patient? You have three options that have been approved, olaparib, rucaparib, and niraparib that are all approved for maintenance in the platinum-sensitive ovarian cancer setting.

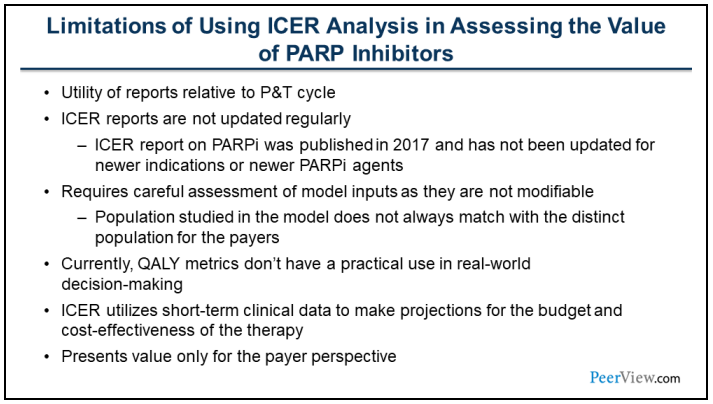
And so to answer the first question, should you consider PARPi for this patient? Yes, especially if she's PARP inhibitor naïve, absolutely, it should be the standard of care, unless there's some rare contraindication or she declines. But this would be what I would offer certainly as standard of care.

Which PARP inhibitor would I use? Honestly, I think that the PARP inhibitor that you should use is the one that you're most comfortable with. Most providers use one or two, and they get really comfortable with them, and their office gets really comfortable with them, so they're very used to assessing the labs, and the side effects that the patients call and ask questions about, and they can respond quickly so that you can maintain dose intensity and compliance. So that's usually my answer for which PARP I would use.

Slide 2



Slide 3



Dr. Jhangiani: So, moving on, let's talk about the value framework. So for this patient's case, let's look at the ICER report that was published in 2017 for PARP inhibitor treatment of ovarian cancer. On the left, we see that the cost per QALY values for current ovarian cancer, and on the right, we have the cost per QALY values for maintenance therapy for recurrent disease. Now, ICER uses a standard value-based benchmark price of $150,000 per QALY. So that is what their threshold is to determine value for a treatment.

Now, here, what we consider is the deviation from this value. In this case, we see that treating recurrent ovarian cancer patients have a better potential to reach that value threshold, but in the maintenance setting, we see that the incremental cost-effectiveness per QALY ratios are so much higher than ICER's recommended threshold of $150,000 per QALY.

So therefore, in the maintenance category, the ICER value or value of this treatment would have to be reduced anywhere from 50 to 78% for the drug cost in order to facilitate affordability for patients.

So our goals do include ensuring member access to the drugs that they need and to provide the highest-value treatment options to allow our client health plan to make the most effective use of their health care dollars. So let me take a moment to go over some of the limitations of the ICER analysis.

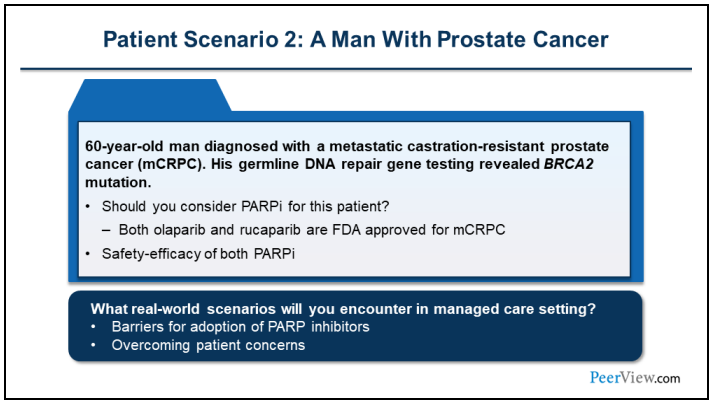
The ICER reports do take time to develop and don't always align with our quarterly P&T cycles. For instance, at my institution, we try to review drugs proactively, which means we review them before they get approval from the FDA. We do so so we have a formulary and UM strategy available at drug launch. But in doing so, also means that we review drugs before many of the ICER reports are published.

So ICER reports are also not updated regularly. As you saw from our PARP inhibitor example, the report was published in 2017 with ICER has no plans to update it. So since then, the PARP inhibitor class has grown significantly with new indications, and there have been new agents that have been approved as well.

So one of the major critiques of the ICER reports from payers is the populations studied in the models does not always match with the distinct populations of certain payers, and the model inputs are not modifiable.

QALY metrics don't have a practical use in real-world decision-making at this time, at least in the United States. So ICER essentially makes decisions from short-term clinical trials and then extrapolates that data for long-term budget and cost-effectiveness projections. So we do still see some limitations, but we do as well use ICER as a guiding body when we have value questions for therapies.

Slide 4

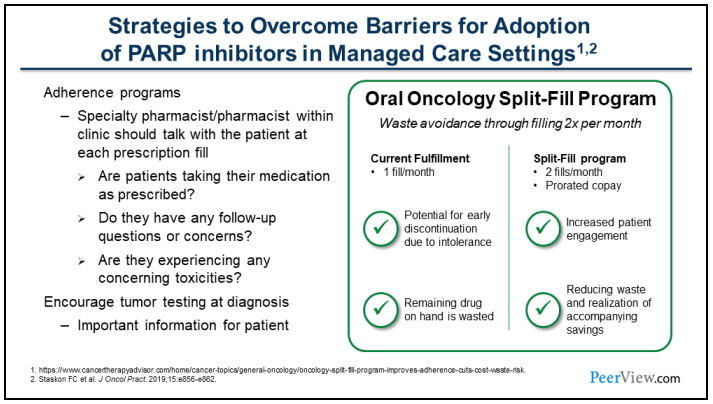


Dr. Moore: Great. It's so complicated, I feel like. So let's do a different scenario. So this is a man with metastatic castrate-resistant prostate cancer. He has a known BRCA2 mutation, and so the question, again, should you consider PARP inhibitor for this patient? You have two approvals now, olaparib and rucaparib, for metastatic castrate-resistant prostate cancer.

And again, I think that the answer here is very clear, given the efficacy improvement with either of these PARP inhibitors in this setting, and there's -- we have an abundance -- and I didn't show it to you just in the interest of time, but the safety profile for PARP inhibitors, really in all solid disease states, but inclusive of prostate cancer, has very manageable, mainly low-severity toxicities that we know well how to manage now with dose interruptions and sometimes reductions.

So the safety/efficacy ratio really benefits -- or really favors the efficacy side and use of PARP inhibitor in this setting. And so I'll turn it back over for implications of managed care.

Slide 5



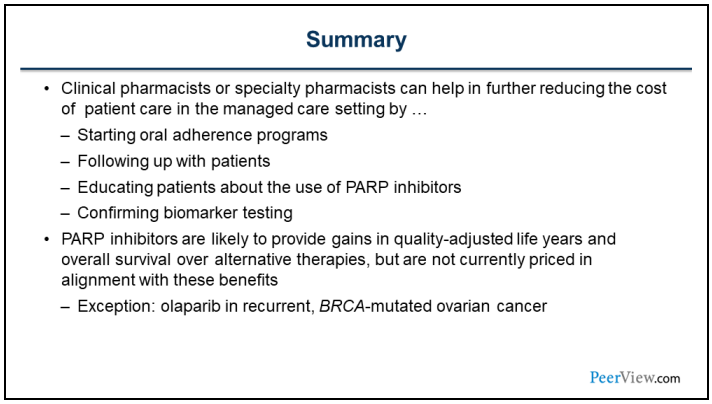
Dr. Jhangiani: Excellent points. Again, thank you, Dr. Moore. So let's talk about adherence programs. For oral oncology agents, this is still a big question. Some patients can be taking therapies for many years. As Dr. Moore mentioned earlier in the program, we did see some really positive clinical impact with the PARP inhibitors when added to therapy and some durable responses.

So earlier in the program, we also addressed the effects of nonadherence. These could be as high as 38%. Adherence programs could reduce this by providing resources to patients to help keep them on track with taking their medication.

Additionally, split-fill programs are available. This is a strategy that many payers use, and they only dispense 2 weeks of the medication instead of a 1-month supply at a time. This would allow patients to have, maybe if they get 1 month of therapy and they need to dose-reduce for whatever reason, for a toxicity, a side effect, and then instead of getting 1 month up front, they can instead get 2 weeks, and then 2 weeks once they know that they can tolerate the therapy.

But in these split-fill programs, you don't always see two copays. So that's the benefit of having a split-fill program available on the payer side.

Slide 6



So in summary, you know, we'd like to just mention, again, utilize your clinical pharmacists or specialty pharmacists, as they can really help in further reducing the cost of patient care. Clinical pharmacists, whether inpatient, outpatient, they can all play a role in education, assessment, and compliance of PARP inhibitor use.

And an alternative to clinical pharmacists is, if that resource is not available to you, is specialty pharmacies. Some specialty pharmacies currently offer programs and personnel to work with patients to improve medication adherence.

Slide 7

With that, Dr. Moore, let's continue our conversation on considerations in clinical practice and managed care. And Dr. Moore, if you can please describe to us some of the main challenges you encounter when treating patients with PARP inhibitor in your clinical practice.

Dr. Moore: Thanks. You know, I think, fortunately, we've been working with PARP inhibitors in the ovarian cancer space for many years now, and so we've figured out sort of a lot of the nuances. But I think there are several things that are pragmatic challenges.

One, you referenced this, is the copays. The copays are pretty high, and so you have for these oral medications the copays can be different than, for whatever reason, patients had with infused agents. So all of a sudden they're being asked to kind of up front give what can be very substantial amounts of money. And, you know, I don't work in a wealthy state. So $500, $1,000 is not doable every month for many of my patients. And so the copays are a challenge.

Now, most of the programs have really nice copay assistance programs, so that has been helpful.

But I think the other area where you get into some cost or financial toxicity for patients and you referenced this. I like the split-dosing idea. Some of these PARP inhibitors, when you dose-reduce, you change the formulation. So, for example, with olaparib, it's 150 mg capsules. But if you have to dose-reduce, then you have to get the 100 mg capsules. And that requires a new prescription and a new copay, which someone may already barely making.

And so with niraparib, that's one of the benefits, is that you don't really have that, because everything's a 100 mg capsule.

So there's little, subtle things like that we've sort of learned

like tricks of the trade. When we're dose-modifying, you know, trying to not change the formulation or dose it in such a way that you kind of keep with the, what they have on hand until they run out, and then change and give them a new prescription. So there are little tricks that we've used to overcome some of these financial challenges.

I think the third thing is that you really have to have staff who are well-versed in triaging the calls from patients so that their concerns can be quickly managed, and that they can maintain their dosing, because we do know from prior studies that a lot of noncompliance, and you brought this up with some of your, your talk today really does impact efficacy.

And so if patients aren't getting their questions answered and they're just stopping until someone calls them back, then that's 2 or 3 days off drug and that intermittent usage isn't as effective as continuous maintenance of drug. And that costs things for practices. So I think those are kind of the three big things.

Dr. Jhangiani: Absolutely. Financial toxicity is a real thing for patients, especially those taking oncology drugs. With regards to some of your concerns about copay, I did bring up the split-fill programs. And I'll answer this in kind of a twofold way.

So from the payer perspective, copays are, you know, of course per client, you know, for the specialty pharmacy that they might be contracting with, what are the negotiated rates? So that's kind of one thing. It is very client-specific.

But I think this, the challenge of copays has also been addressed by policymakers on a national level. Under the essential health benefits through Obamacare for plans that have to be compliant with essential health benefits, at least in California, there is a requirement to put a cap on copays for specialty oral oncology drugs, which caps this amount, you know, at a certain, let's say, $300 amount.

So no matter what the cost of the drug, the patients will always see the same copay, which of course is great for the patients, but on the other hand, then we have to think about, you know, coming from a payer, how is that financial toxicity going to affect the payer?

Another facet is, you mentioned, you know, switching doses for dose toxicity. What manufacturers can do, and some have already done this, is, instead of doing a standard price across the board for every single dose of an agent, manufacturers can instead say, "Okay, well, we can do a differential pricing," so instead of per capsule or per tablet, the price would be per milligram. So if you're taking less, you also have a lower cost.

So those are two different ways that the health care market has approached the pricing, but of course, it's still not enough there. You know, we can always do more, and I think that financial toxicity conversation is true across everyone in the health care industry. So, thank you. Thank you so much for those points.

Dr. Moore, we have another audience question. What PARP inhibitor characteristics inform your decision-making when choosing PARP inhibitors either prostate cancer or breast cancer? Can you tell us a little bit more about that, please?

Dr. Moore: Sure. I mean, I think that when you look across the four disease types right now where we see PARP inhibitor indications, ovarian, we have three approved, olaparib, rucaparib, and niraparib. In breast cancer, we have two, olaparib and talazoparib. And then in prostate, we have two, olaparib and rucaparib. In pancreas we only have one, so you only have one choice. So pancreas is easy. You pick olaparib.

I think honestly, for all of the other settings, the choice is really, one, and I think I said this earlier, about just your individual practice's comfort with managing patients on that particular PARP inhibitor, like what dose do you start? How do you dose-modify? How do you counsel patients? How do you set expectations? And does your staff understand how to respond appropriately to concerns that are called in so you can maintain the dose intensity and compliance that you need for that patient?

The pill burden of all these is relatively low. You know, gone are the days of eight pills twice a day with the original olaparib tablets or capsules. Now it's the tablets. You know, it's two twice a day. So the pill burden is not high with any of them. But you do have both talazoparib and niraparib that are once daily, as the rest are all twice daily.

So that comes into mind, because I do have patients that really struggle to even swallow a Tylenol. And so asking them to take two pills twice a day, there's just people that struggle with that. And so, you know, sometimes I pick just based on reduced pill burden. So there are little nuances that help me pick. But I'm not picking based on efficacy right now. I really do think clinically they look very similar to one another in all disease types that I can tell thus far, so I pick based on tolerability.

Dr. Jhangiani: Excellent. So let me piggyback off of that for the managed care perspective. I think you brought up a really great point about the different nuances between each different PARP inhibitor, and I think it's really interesting, because from a clinical perspective, your version of nuances is looking at the safety and some of the other characteristics such as pill burden.

But from a managed care payer perspective, some of the nuances that we consider are more like the FDA-approved indications. So we'll say, "Well, one PARP inhibitor is approved in the third-line setting. One is approved in the fourth, the second. You know, one requires an FDA-approved diagnostic."

So when we're doing some formulary you know, when we're thinking about formulary management, it becomes a challenge for payers to contribute to the decision as to, well, should we add a step therapy? Should we, you know, for ovarian cancer, where there are multiple options, should we step olaparib through, you know, rucaparib? Which we can't really do because of the nuances within the FDA-approved indication.

So some of the things that we take into consideration when writing the prior authorization is to ensure kind of two things. Firstfold is, you know, making sure we're aligned with the FDA-approved indication, and secondly is keeping up with NCCN guidelines, which could be a challenge, especially with the new data that's, you know, being released ongoing.

Dr. Jhangiani: Well, thank you so much, Dr. Moore, for joining us in that discussion. Thank you, and have a great day.

Announcer: This activity is jointly provided by Medical Learning Institute, Incorporated, and PVI, PeerView Institute for Medical Education.

Abbreviations List

4L: fourth line
AMCP: Academy of Managed Care Pharmacy
AR: androgen receptor
ARID1A: AT-rich interaction domain 1A
ASP: average sales price
BAP1: BRCA1 associated protein 1
BARD1: BRCA1-associated RING domain 1
BC: breast cancer
BCRP: breast cancer resistance protein
bev: bevacizumab
BICR: blinded independent central review
BID: twice a day
BRCA1: breast cancer 1
BRCA2: breast cancer 2
BRCAm: BRCA mutated
BRCAwt: BRCA wild type
BRIP1: BRCA1 interacting protein C-terminal helicase 1
CBR24: clinical benefit rate at 24 weeks
CDK12: cyclin-dependent kinase 12
CDKN2A: cyclin-dependent kinase inhibitor 2A
CDx: companion diagnostic
CHEK2: checkpoint kinase 2
chemo: chemotherapy
COVID-19: coronavirus disease 2019
CR: complete response
CRPC: castrate-resistant prostate cancer
CYP: cytochrome P450
DCO: data cutoff
DCR: disease control rate
DDR: DNA damage response
DNA-PKcs: DNA-dependent protein kinase catalytic subunit
DOR: duration of response
DRD: DNA repair deficient
ECOG-PS: Eastern Cooperative Oncology Group performance status
EOC: epithelial ovarian cancer
EPCAM: epithelial cell adhesion molecule
ER: estrogen receptor
FA: Fanconi anemia
FACT-O TOI: Functional Assessment of Cancer Therapy - Ovarian Trial Outcome Index
FAM175A: family with sequence similarity 175 member A
FANCA: Fanconi anemia complementation group A
FANCL: Fanconi anemia complementation group L
FIGO: International Federation of Gynecology and Obstetrics
FTC: fallopian tube cancer
gBRCAm: germline BRCA-mutated
gBRCAmut: germline BRCA-mutated
HR: homologous recombination
HRQOL: health-related quality of life
HRR: homologous recombination repair
IC_{50}: half maximal inhibitory concentration
LABC: locally advanced breast cancer
LOT: lines of therapy
MATE1: multidrug and toxin extrusion protein 1
MATE2-K: multidrug and toxin extrusion protein 2
mBC: metastatic breast cancer
MCBS: Magnitude of Clinical Benefit Scale
mCRPC: metastatic castrate-resistant prostate cancer
MDR1: multidrug resistance mutation

MLH1: MutL homolog 1
MMR: mismatch repair
mOS: median overall survival
mPFS: median progression-free survival
MRN: MRE11-RAD50-NBS1
MSH2: MutS homolog 2
MSH6: MutS homolog 6
MSKCC: Memorial Sloan Kettering Cancer Center
NAD: nicotinamide adenine dinucleotide
NBN: nibrin
NCCN: National Comprehensive Cancer Center
NCCN: National Comprehensive Cancer Network
NE: not evaluable
NED: no evidence of disease
NER: nucleotide excision repair
NGR: no gross residual disease
NHEJ: nonhomologous end-joining
NR: not reached
NS: not significant
NTD: none to date
OAT3: organic anion transporter 3
OC: ovarian cancer
OCT1: organic cation transporter 1
OCT2: organic cation transporter 2
ORR: objective response rate
P & T: promotion and tenure
PALB2: partner and localizer of BRCA2
PARPi: poly ADP-ribose polymerase inhibitor
PCa: prostate cancer
pCR: pathologic complete response
PCWG3: Prostate Cancer Working Group 3
PD: progressive disease
PD-L1: programmed cell death ligand 1
PFS2: second progression-free survival
PgR: progesterone receptor
PLD: pegylated liposomal doxorubicin
PMPY: per member per year
PPC: primary peritoneal cancer
PPP2R2A: protein phosphatase 2 regulatory subunit B alpha
PR: partial response
PRO: patient-reported outcome
PSA: prostate-specific antigen
PSOC: platinum-sensitive ovarian cancer
PTEN: phosphatase and tensin homolog
Q8W: every 8 weeks
Q4W: every 4 weeks
Q12W: every 12 weeks
QALY: quality-adjusted life year
QD: once daily
RECIST: Response Evaluation Criteria in Solid Tumors
rPFS: radiographic progression-free survival
SD: stable disease
SLFN11: Schlafen family member 11
SOC: standard of care
STK11: serine/threonine kinase 11
TEAE: treatment-emergent adverse event
TFST: time to first subsequent therapy
TP53: tumor protein 53
TPC: treatment of physician's choice
WAC: wholesale acquisition cost
WT: wild type
γH2AX: phosphorylated H2A histone family member X