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Keeping Pace in Women's Cancer: The Role of PARP Inhibitors in Ovarian Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace: The Role of PARP Inhibitors in Ovarian Cancer” is provided by Prova Education and is supported by an independent educational grant from GSK.

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Dr. Huh:
This is CME on ReachMD, and I’m Dr. Warner Huh. Joining me to discuss the advances of PARP inhibitors are Dr. Robert Coleman and Dr. Deborah Armstrong.

Welcome, Dr. Coleman and Dr. Armstrong.

Dr. Coleman:
Thanks for having us.

Dr. Armstrong:
Thank you.

Dr. Huh:
Okay, so to get us started: As you’re well aware, Dr. Armstrong, we have 3 FDA-approved PARP inhibitors for advanced ovarian cancer. Can you walk us through the rationale of using PARP inhibitors in advanced ovarian cancer? And more importantly, how do we decide what the right PARP inhibitor is for each patient?

Dr. Armstrong:
Thank you.

PARP inhibitors function by inhibiting single-strand DNA repair, and what happens when those single-strand breaks move along the replication fork, they become double-strand breaks. In normal cells where the BRCA is proficient, that gets repaired, but in tumor cells that are deficient in BRCA, that double-strand break cannot be repaired. This is what we call synthetic lethality, and it’s really the difference between the sensitivity of normal cells and cells with a BRCA deficit, and that, in terms of laboratory data, is about 2 logs of sensitivity, so we have a really large therapeutic window. And that inability to repair double-strand DNA breaks leads to death in the tumor cells, so it really exploits the differences between the tumor cells and the normal cells, a real optimal target for therapy in ovarian cancer.

With regard to the PARP inhibitors, as you said, there are 3 FDA-approved PARP inhibitors—niraparib, olaparib, and rucaparib. We also have data with veliparib, which is not FDA-approved. We now use these in many settings, and what we’re going to be talking about mostly today is in maintenance in the upfront setting. The data are that—really across the studies—the use of PARP inhibitors in patients who responded to upfront therapy improves outcomes.

What we do know is that the patients who have the greatest benefit are those who have BRCA mutations, whether that's somatic or germline. That's about 15% of our patients with germline mutations and another 5 to 10% with somatic BRCA mutations. Another 25% of patients have some deficit in homologous recombination, and that's our biggest challenge today because our tools for measuring homologous recombination deficiency are pretty inexact.

Dr. Huh:
So now, Dr. Coleman, over the last 2 years, we've had several truly pivotal phase III studies that have been published in the area of PARP inhibition in the frontline setting, and we're clearly looking at a major paradigm shift with this class of drug, specifically in the frontline setting. Which PARP inhibitors do you think are emerging as frontline or maintenance treatment?

Dr. Coleman:
Yeah, so, as you mentioned, right now there are 2 that are approved, olaparib and niraparib, and we have 1 combination that's approved, and that's olaparib and bevacizumab, and these came from pivotal trials that were presented at ESMO this last year and were published subsequently along with VELIA/GOG-3005, which was looking at the role of veliparib in combination with chemotherapy followed by veliparib maintenance. These 3 trials really were attempting to explore the efficacy of PARP in the frontline setting knowing that we already had data which was confirming the hypothesis that Deb presented regarding mechanisms of action, and that's the role of PARP in patients who have BRCA-mutated ovarian cancer. That study, SOLO-1, demonstrated a significant benefit that was truly revolutionary, I think, almost in the way we look at how we've managed patients with this disease.

The subsequent trials were broadening the patient population and reported each in their own right that there was benefit across a broad spectrum of patients with primary disease. In the PRIMA trial, we looked at the role of niraparib in patients who had responded to a platinum-based therapy in the frontline setting and then were randomized to the PARP inhibitor niraparib versus placebo, and it showed a benefit across its 3 patient populations that were ultimately approved by the FDA just this past month. PAOLA-1 was taking patients who were started on paclitaxel, carboplatin, and bevacizumab and then randomizing them at the completion of their chemotherapy combination to the addition of olaparib or placebo, and so, again, this demonstrated a benefit across the intent-to-treat cohort, which was one of its primary endpoints. When the subgroups were analyzed, there seemed to be less of a strong effect of the doublet versus bevacizumab in the homologous recombination-proficient patient cohort, and so the FDA, within this past month, allowed a—or enabled an approval based on a companion diagnostic that assessed for HR deficiency. And VELIA, the third of those 3 trials, has yet to be opined on by the FDA, but this particular trial looked at the role of adding a PARP inhibitor during chemotherapy in the frontline setting and then randomized patients to continuance of that PARP versus placebo in the maintenance phase, and it also showed a benefit across all patient cohorts.

So, very interesting expansion of the indications for the use of PARP in the frontline setting and obviously now provides us with more options and more questions about how we approach this group of patients.

Dr. Huh:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Warner Huh, and I'm joined by Dr. Robert Coleman and Dr. Deborah Armstrong. We're discussing novel PARP inhibitors and how they apply to frontline treatment setting for advanced ovarian cancer.

So, Dr. Coleman, switching from frontline therapy to recurrent therapy, can you comment how this has changed our approach to where PARP inhibitors belong in the overall sequencing of therapy in advanced, recurrent ovarian cancer?

Dr. Coleman:
Yeah, and this is a really important question now because much of our development of PARP inhibitors in the recurrent space has been in patients with either a documented mutation or was given as a maintenance therapy in patients who had platinum-sensitive recurrent disease who responded to chemotherapy, but all of these trials in this development space in the recurrent setting were done in a PARP-naïve space. In other words, none of these patients were allowed to participate in these trials if they had previous exposure to a PARP inhibitor. So, if we look at that through the lens of what I just mentioned about the primary setting, we'll see that we'll be re-addressing these questions about the role of PARP in the recurrent space in a group of patients that will be increasingly exposed to PARP in the frontline space. And so when we think about how we address that, we have to go back to the biology again to understand what's going on in the tumor microenvironment that would enable us to have confidence in using PARP again in certain cohorts of patients based on their potential prior exposure. And so that's kind of like an active place of investigation, and it's led us to start to investigate various combinations with a PARP inhibitor in that recurrent ovarian cancer space.

Some of these trials that have been done to look at these combinations as part of an exploratory evaluation have done so in patients who have proficient tumors, so we're very excited now that we have a large number of studies ongoing now that are looking at combinations of various different strategies that are trying to either augment a response in patients that we know would respond to

overcome potential resistance that may have emerged because of prior exposure or those patients who have proficient tumors who you wouldn't expect a response. And so our preliminary data are starting to emerge saying that, yes, there is a signal here, and because of that, we've taken that strategy and moved it into the frontline setting. And so there are now a number of trials, 4 of them, which are looking at PARP combinations that are being done in the frontline setting with the idea of potentially improving the outcomes of patients even in that setting, so lots of exciting work.

Dr. Huh:
And, Dr. Armstrong, as many of us have these patients who, unfortunately, progress on a PARP inhibitor, what are your thoughts in terms of mechanisms or strategies to overcome PARP resistance? And what do we do when a patient has disease progression after initially being treated with a PARP inhibitor?

Dr. Armstrong:
I look at PARP inhibitor resistance in sort of a number of ways. Probably one of the first mechanisms we recognize for PARP inhibitor resistance was secondary mutations in patients with a BRCA mutation that restored the reading frame and basically restored the ability of the tumor to make a functional BRCA protein. That's probably not an area that we can really target for reversing resistance.

The other sort of 2 main areas that we are looking at are combinations of PARP inhibitors with angiogenesis inhibitors and combinations that are looking at other agents that can either increase DNA damage by decreasing—by using DNA damage repair inhibitors or inducing a state of homologous recombination deficiency. The angiogenesis inhibitors we have actually the most data, a number of studies looking at the combination of the oral VEGF TKI cediranib with PARP inhibitors and use of bevacizumab with niraparib, including the updates from the AVANOVA study that were presented at ASCO, and these clearly show at least additive efficacy when angiogenesis inhibitors are used.

We have a long list of drugs that are being studied, and this is a very active area of both preclinical and clinical research, and a number of trials looking at combinations of PARP inhibitors with WEE1 inhibitors, BET inhibitors, MEK inhibitors, ATK inhibitors, mTOR inhibitors, PI3 kinase inhibitors—the list is really quite long right now—with the thought that if these can inhibit DNA damage or induce a homologous recombination-deficiency state, that the use of those in combination with PARP inhibitors will be able to expand our use of these, particularly in patients who previously had PARP inhibitors. And as we've been talking about, probably the majority of patients with newly diagnosed disease will get a PARP inhibitor as maintenance therapy, and so we'll have a pretty large group of patients we will have who have previously had PARP inhibitors.

The combinations though, I think, except for with the angiogenesis inhibitors, really remain investigational at this time, but there are lots of ongoing studies, and it's a pretty exciting area of investigation at this point.

Dr. Huh:
I totally agree with you. Well, this has certainly been a valuable conversation. Before we wrap up, can you both share with our audience the one take-home message you'd want them to remember from our discussion? Dr. Coleman, I'll let you go first.

Dr. Coleman:
Thank you. Yes, thanks for having me as well to participate. I think that the world of the treatment for ovarian cancer has changed dramatically. I think we owe a great amount of debt to our patients and the investigators who are trying to define this space in improving outcomes. It's been a very frustrating time up until this point in time that we have had effective tools to start to really pivot the expectations for outcomes in this disease, so it's been amazingly exciting to be involved in this particular environment where we're starting to see some real fruit from this labor. I think that as time goes on we'll continue to explore and expand in space, and it's a very exciting time for our patients.

Dr. Huh:
Dr. Armstrong?

Dr. Armstrong:
Thank you. I would agree with Rob. I think it's an exciting time. We have data now that these improvements in progression-free survival are starting to potentially be translated into an overall survival benefit for our patients, and that's really what they want. I think we have kind of—it's kind of a brave new world for us. We have lots of tools now. We have to figure out how to use the tools that we have, what order to use them in, and which patients will get the greatest benefit, but that's a good problem to have.

Dr. Huh:
I think that's great. I love both of your perspectives on this, and I couldn't agree more. And I guess from my vantage point, I think the biggest takeaways from today is that in 5 to 10 years, the management of advanced ovarian cancer is going to look entirely different, and I think what's going to be fascinating is we're going to have trainees in the future that are going to look back on how we managed

advanced ovarian cancer preceding PARP inhibition and they're going to be, "Wow, this has really taken off." And you're going to see a marked change, and so it's really, perhaps, one of the most exciting times to be in the field of ovarian cancer management.

Unfortunately, that's all the time we have for today, so I want to thank our audience for your participation and thank you, Dr. Coleman and Dr. Armstrong, for joining me and for sharing all of your valuable insights. It was absolutely great speaking with you today.

Dr. Coleman:
Thank you very much.

Dr. Armstrong:
Thank you.

Anouncer:
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