Current and Emerging Role of PARP Inhibitors in Breast Cancer

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Dates of certification: *July 31, 2017, to July 31, 2018*
Medium: *Print with online posttest, evaluation, and request for credit*

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Disclosure: *Grant/Research Support: Calithera, Pfizer, Novartis, Janssen, Genentech; Consultant: Pfizer, Calithera, Novartis*

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Overview
This activity is designed to inform physicians about the current and developing strategies in using PARP inhibitors to treat patients with breast cancer.

Target Audience
This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with breast cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other health care providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:

- Describe the biologic function of PARP, its role in DNA repair, and the rationale behind targeted inhibition in breast cancer
- Explain the developmental history of PARP inhibitors to date, including recently published clinical data
- Discuss emerging treatment options and ongoing trials of PARP inhibitors

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Introduction

Breast cancer is the most frequently diagnosed cancer in women.[1,2] In 2017, an estimated 252,710 cases of breast cancer will be diagnosed in the United States, accounting for 15.0% of all new cancer cases.[1,2] Breast cancer is most common in older women, with a median age at diagnosis of 62 years.[2] However, about 32% of patients are aged less than 55 years at diagnosis.

Over the past 40 years, the incidence rate for breast cancer has generally remained the same. The 5-year survival rate, however, has increased more than 15%, to about 89.7%.[1,2] Still, it is estimated that 40,610 women will die of breast cancer this year, accounting for 6.8% of all cancer-related deaths.[2] The median age at death is 68 years. It is estimated that there are currently about 155,000 women alive with metastatic breast cancer in the United States.[3] Overall, 12.4% of women will develop breast cancer at some point in their lifetime.[2]

Standard therapies for breast cancer are dependent on estrogen receptor (ER) and progesterone receptor status (collectively referred to as hormone receptor status); human epidermal growth factor receptor 2 (*HER2*) status; and grade and stage. Treatment for nonmetastatic breast cancer can include a combination of chemotherapy, targeted therapy, and radiation therapy across the adjuvant and neoadjuvant settings, as well as surgical resection.[1] Metastatic disease, which remains incurable, typically requires ongoing treatment with serial systemic therapies, due to the inevitable development of resistance.

DNA Repair Pathways

The cellular reaction to DNA damage is a complex process tailored to the type of damage that occurs.[4] Proper repair of DNA damage is essential for preservation of the genetic information encoded by DNA, and it ensures accurate transmission to subsequent generations of cells. Interruptions of DNA repair mechanisms have been associated with an increased susceptibility to cancer.[5]

The cell has 5 main pathways to repair DNA damage, each of which corresponds to certain types of damage. Base excision repair, in which small, non–helix-distorting errors are removed and replaced, is used to repair damage to base pairs caused by oxidation, alkylation, deamination, or single-strand breaks (SSBs).[6] A similar pathway, nucleotide excision repair, in which bulky additions are removed and replaced, while conserving the overall structure of the DNA strand, is used to repair damage caused by UV light. Mismatch repair is a strand-specific repair mechanism to correct errors from replication; these include adenine-guanine and thymine-cytosine mismatch, as well as insertions and deletions (indels). Finally, double-stranded breaks (DSBs) are repaired by 1 of 2 mechanisms: homologous recombination (HR), in which the sister chromatid is used as a template to correct errant nucleotide sequencing; or nonhomologous end joining (NHEJ), in which blunt ends of DSBs are stitched together, disregarding original sequence. NHEJ is more prone to errors. The specific repair mechanism utilized is cell cycle–dependent. HR dominates throughout the S and G2 phases; NHEJ is present throughout the cell cycle.[6]

BRCA1 and *BRCA2* are critical elements in HR-based repair of DNA DSBs. When *BRCA1* and *BRCA2* genes are mutated in patients with breast cancer, cancer cells rely on alternative methods of DNA repair. By targeting and further inhibiting these alternative DNA repair mechanisms, synthetic lethality can be induced in cancer cells, inducing a second DNA repair defect, leading to cell death.[7]

One such target is the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) family of proteins, which comprise 17 different enzymes. PARP plays a role in numerous cellular functions, ranging from DNA transcription/repair to genomic stability, cell cycle regulation, cell signaling, and programmed cell death.[8,9] PARP-1 and PARP-2 are the most extensively studied members of the PARP family, specifically for their role in the repair of SSBs.[8] PARP-1 detects SSBs, binds to DNA, catalyzes the polymerization of PARP to itself and other substrates, and recruits DNA repair proteins to the site of damage.[6]

PARP inhibitors bind PARP-1 and PARP-2 to the sites of DNA damage, "trapping" them and thereby preventing DNA repair, replication, or transcription.[10] This trapping of PARP to DNA induces a secondary DSB, a cytotoxic event for the cell. PARP itself is necessary for the cytotoxicity of PARP inhibitors: In other words, depletion of PARP proteins in the cell, or independent inactivation without DNA binding, is a nonlethal event.[11]

An enhanced understanding of the role of PARP has led to investigations of PARP inhibitors in the clinical setting.[9] While the development of PARP inhibitors has primarily focused on targeting tumors with *BRCA1* or *BRCA2* mutations, studies are also investigating the efficacy of PARP inhibition in non–*BRCA*-mutated tumors that harbor other DNA damage repair abnormalities.[9]

PARP Inhibitors

Olaparib

Olaparib is an oral PARP inhibitor shown to have antitumor activity in HER2-negative metastatic breast cancer with a germline *BRCA* mutation.[12] Following results from a proof-of-concept phase II trial, the phase III, open-label, randomized, controlled, multicenter OlympiAD trial (NCT02000622) compared olaparib monotherapy with standard chemotherapy in patients with germ-line *BRCA*-mutated, HER2-negative, metastatic breast cancer who had received fewer than 3 previous chemotherapy regimens and had not progressed on platinum-based chemotherapy.[13]

A total of 205 patients were randomized to receive 300 mg of olaparib twice daily, while 97 were randomized to standard

chemotherapy of physician's choice, consisting of either capecitabine, eribulin, or vinorelbine at standard doses. The primary endpoint of median progression-free survival (PFS) was significantly longer in patients receiving olaparib monotherapy than in patients receiving chemotherapy (7.0 months versus 4.2 months, respectively), resulting in a 0.58 hazard ratio for disease progression or death (95% CI, 0.43-0.80; *P* <.001). An overall response rate (ORR) of 59.9% was observed in the olaparib group versus 28.8% in patients receiving standard therapy.[13]

Among secondary endpoints, median time from randomization to second progression or death following first progression was 13.2 months for patients receiving olaparib compared with 9.3 months for patients receiving chemotherapy (hazard ratio, 0.57; 95% CI, 0.40-0.83; *P* = .003). The median duration of response was 6.4 months in the olaparib group and 7.1 months in patients receiving chemotherapy.[13]

Overall survival (OS) was another secondary endpoint. At the time of primary analysis, 54.1% of patients receiving olaparib compared with 52.6% of patients receiving chemotherapy were still alive. Median time to death was 19.3 months compared with 19.6 months in the olaparib and chemotherapy groups, respectively. The difference in OS was not statistically significant between the 2 groups, with a hazard ratio for death of 0.90 (95% CI, 0.63-1.29; *P* = 0.57), though these results were not yet mature due to the relatively short follow-up.[13]

The most common adverse events (AEs) in patients receiving olaparib were anemia, nausea, vomiting, fatigue, headaches, and cough. In patients receiving chemotherapy, AEs including neutropenia and palmar-plantar erythrodysesthesia (hand-foot syndrome) were more common than in patients receiving olaparib. The rate of grade 3 or higher AEs was lower in the olaparib group (36.6%) than in the chemotherapy group (50.5%). Anemia was the most common cause of dose reduction in patients receiving olaparib (13.7% of patients), and that led to discontinuation of treatment in 2.0% of patients receiving olaparib.[13] A summary of outcome measures can be seen in the **Table**.

TABLE. Summary of Primary and Secondary Outcome Measures From a Phase III Trial Comparing Olaparib With Standard Chemotherapy in Patients With HER2-Negative, Germline BRCA-Mutated, Metastatic Breast Cancer[12]

	PFS (months)	ORR (%)	Median Duration of Response (months)	Secondary Progression (months)	Grade ≥3 AEs (%)
Olaparib	7.0	59.9	6.4	13.2	36.6
Chemotherapy	4.2	28.8	7.1	9.3	50.5

AE indicates adverse event; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

A phase III trial investigating olaparib as an adjuvant therapy for patients with germline *BRCA*-mutated, HER2-negative, primary breast cancer (OlympiA, NCT02032823) is currently active and recruiting participants.[14]

Veliparib

Veliparib is another PARP inhibitor that has shown success in phase II trials in combination with chemotherapy. The ongoing phase II I-SPY 2 trial (NCT01042379) randomized patients with stage II or stage III breast cancer with ER-positive/Mamma-Print-high or triple-negative subtypes to veliparib in combination with carboplatin and paclitaxel versus paclitaxel alone followed by doxorubicin and cyclophosphamide.[15] This adaptively randomized trial is designed to evaluate potential for success in a subsequent phase III evaluation; the primary endpoint is pathological complete response (pCR). In triple-negative patients receiving the veliparib/carboplatin combination, the predicted probability of pCR was 51% (95% Bayesian probability interval [PI], 36%-66%) versus 26% (95% PI, 9%-43%) for patients in the control group, resulting in an estimated phase III success of 88%.[15]

These promising results led to the randomized, placebo-controlled, double-blind phase III Brightness trial (NCT02032277), which also evaluated veliparib and carboplatin in the neoadjuvant setting for patients with triple-negative breast cancer, regardless of *BRCA* status.[16] Patients were randomized 2:1:1 among 3 arms: veliparib plus carboplatin plus paclitaxel (arm A), placebo plus carboplatin plus paclitaxel (arm B), and placebo plus placebo plus paclitaxel (arm C). No significant difference was observed in pCR between arms A and B (53.2% and 57.5%, respectively); however, both arms were markedly improved over arm C, which had a pCR of 31.0% (*P* <.001). High-grade AEs were observed in both arms containing carboplatin (86% of patients in arm A and 85% of patients in arm B, versus 45% of patients in arm C). Veliparib did not significantly impact toxicity. Common AEs included neutropenia, thrombocytopenia, anemia, nausea, and vomiting.[16]

Other evaluations of veliparib in combination with carboplatin have been performed in the metastatic setting, including the phase II, randomized BROCADE trial (NCT01506609). In this trial, patients with germline *BRCA*-mutated metastatic breast cancer were randomized to receive either veliparib plus carboplatin plus paclitaxel, placebo plus carboplatin plus paclitaxel, or veliparib plus temozolomide.[17,18] For the veliparib/carboplatin/paclitaxel arm, the primary endpoint of PFS was 14.1 months and demonstrated a numerical improvement compared with 12.3 months in the placebo/carboplatin/paclitaxel arm. OS

was 28.3 months versus 25.9 months respectively. The ORR was 77.8% compared with 61.3%, reaching statistical significance. No significant increases in toxicity were observed.[17,18]

Results from the phase II trial prompted a phase III investigation, Brocade 3 (NCT02163694), which is currently active and recruiting participants. This trial contains 2 arms, veliparib plus carboplatin plus paclitaxel, and placebo plus carboplatin plus paclitaxel. The primary outcome measurement is PFS.[19]

Talazoparib

Talazoparib is a dual-mechanism PARP inhibitor that actively traps PARP on DNA.[20] The 2-stage, 2-cohort phase II ABRAZO trial (NCT02034916) evaluated talazoparib in patients with germline *BRCA*-mutations and previously treated metastatic breast cancer. Forty-nine patients had previously been exposed to platinum-based chemotherapy (cohort 1) and 35 patients had been previously treated with 3 or more platinum-free cytotoxic regimens (cohort 2). Overall response rates of 21% and 37% were observed in patients in cohorts 1 and 2, respectively.[20] Following the success of ABRAZO, the phase III EMBRACA trial (NCT01945775) is evaluating talazoparib versus physician's choice in patients with unresectable locally advanced or metastatic breast cancer. The primary outcome of EMBRACA is PFS. This trial is currently active and recruiting patients.[21]

Niraparib and Rucaparib

Niraparib is another PARP inhibitor that has shown clinical benefit in germline *BRCA*-mutated recurrent ovarian cancer and is currently approved for that indication.[22,23] BRAVO, a randomized, open-label, multicenter phase III trial (NCT01905592) is currently investigating niraparib in germline *BRCA*-mutated, HER2-negative breast cancer.[24] Patients are randomized 2:1 to either receive 100 mg of niraparib once daily or physician's choice of chemotherapy. The primary outcome measure of this trial is PFS. Secondary outcomes include OS and quality-of-life measurements. This study is ongoing, but not actively recruiting.[24]

Like niraparib and olaparib, rucaparib is also approved in *BRCA*-mutated advanced ovarian cancer. RUBY, a single-arm, open-label phase II trial (NCT02505048), is currently investigating rucaparib in patients with a BRCA-like genomic signature.[25] Patient will receive 600 mg of rucaparib daily, over 28-day cycles. The primary outcome measure is clinical benefit rate, and secondary outcome measures include PFS, OS, and AE measurements. This study is ongoing and actively recruiting.[25]

For more information on the current and emerging use of PARP inhibitors in the treatment of breast cancer, see our interview with Dr DeMichele below.

Angela DeMichele, MD, MSCE, is a professor of medicine and epidemiology and holds the Jill and Alan Miller Endowed Chair in Breast Cancer Excellence at the Perelman School of Medicine at the University of Pennsylvania. Dr DeMichele is also the co-leader of the Breast Cancer Research Program at Penn Medicine's Abramson Cancer Center.

What makes *BRCA*-positive or "BRCA-like" breast cancer particularly susceptible to PARP inhibition? Are there differences in susceptibility for patients with germline or somatic *BRCA* mutations?

Dr DeMichele: This is really an important question. Essentially, there are 5 major mechanisms of DNA repair that cells can use to repair the DNA damage that naturally occurs in our cells because of day-to-day wear and tear, exposure to things like UV light, and other toxins in our environment. Cells that are mutated in *BRCA1* or *BRCA2* have very specific defects in 1 such mechanism, homologous recombination. Tumors that have mutations in this particular mechanism of DNA repair have been very instructive to us in understanding carcinogenesis. It is from this understanding that the PARP inhibitors were developed as a way to take advantage of cells that already had 1 DNA damage repair mechanism knocked out. If we could then knock out others, then we could impair the cells from being able to survive.

The fact that a cell already has an intrinsic deficiency or impairment in the ability to repair its DNA is what makes it susceptible to PARP inhibition. Now, the difference between a *BRCA*-mutated cell and one that just has "BRCA-like" qualities is that cells are able to develop impairments in these mechanisms for reasons other than *BRCA1* or *BRCA2* mutations. If we could identify other mechanisms by which homologous recombination is impaired in cells, either through other mutations or by loss of heterozygosity, we could identify other tumors that would be sensitive to PARP inhibition.

Still, because these are different from *BRCA*-mutant tumors, we don't know if they're going to have the same sensitivity to PARP inhibitors that *BRCA*-mutant tumors have. Simply put, we don't yet know if drugs in the PARP inhibitor family will also be effective in tumors that have impairments in DNA repair other than *BRCA1/2*.

Olaparib has been approved for use in ovarian cancer since December 2014. At ASCO this year, results from the phase III OlympiAD trial investigating olaparib in metastatic breast cancer were presented. Can you talk about the results and key takeaways from this trial?

This was a practice-changing study in the sense that it really showed definitive benefit of PARP inhibitors, olaparib specifically, in patients who harbor a germline *BRCA1/2* mutation, over and above the benefits those patients would have received from chemotherapy. This trial was in a group of patients who had metastatic disease, but were also identified solely by the fact that they had germline *BRCA1* or *BRCA2* mutations. It was really agnostic about the subtype of breast cancer—it had to be *HER2*-negative, but it could be ER-positive or ER-negative. I think that

including both of those patient groups was a strength of this study. Importantly, in order to be eligible, patients could not have progressed on a prior platinum therapy. This is incredibly important because we don't yet know the relationship between sensitivity to platinum and sensitivity to PARP inhibitors. In many ways, these therapies operate similarly in terms of synthetic lethality in cells that have impaired DNA repair; thus, resistance to one may result in resistance to the other.

Patients were randomized to single-agent olaparib versus physician's choice standard chemotherapy, a design which really now looks to be common for trials in this space. The results were quite impressive. There was a significantly longer median PFS in the patients in the olaparib group compared with the patients in the standard therapy group, which was 7 months versus 4.2 months. The hazard ratio for disease progression was also impressive at 0.58.

I think what this trial tells us is that these drugs have single-agent activity in tumors that are *BRCA1/2*-mutant regardless of whether they're estrogen-receptor–positive or –negative. One other impressive result was that PARP inhibitor treatment was well tolerated and patients had a preserved quality of life. Especially given that the current standard of care here is single-agent chemotherapy—capecitabine, eribulin, or vinorelbine—which have substantial toxicities. The oral, well-tolerated drug olaparib, clearly shows benefit in terms of PFS, preserved quality of life, and tolerability.

Olaparib as another option for patients who have metastatic breast cancer, a currently incurable disease, is meeting a major unmet need in our field. This drug is giving people more time. This is giving us another treatment option in the armamentarium that is well tolerated, that allows patients to live their lives, to do the activities they like to do, and to really be able to live better with this disease. I think this was really groundbreaking and I think it bodes very well for the other PARP inhibitors that are being tested in a similar way. I anticipate that this will lead to FDA approval of the drug for this indication, and I think this was really a major breakthrough in this area.

What are some of the next steps following the results from this trial?

The results that were presented will likely lead the FDA to consider this drug for approval in breast cancer. As clinicians, we would really like to have access to this option for patients, and I hope that in the coming months that will occur. I also think that this should help bolster the enrollment in other clinical trials of PARP inhibitors in *BRCA*-mutation carriers, because we now have demonstrated proof of principle. Further, there are ongoing trials in the adjuvant setting, particularly the OlympiAD trial, investigating if the drug is this effective in early-stage disease. We hope that PARP inhibition will actually be effective in this setting and potentially prevent a greater proportion of patients from ever becoming metastatic.

To recap, getting FDA approval for this drug so that it's available to patients, providing the proof of concept to support the other clinical trials of other PARP inhibitors that are being tested similarly, and ultimately to be able to try to bring this earlier into the treatment trajectory to help prevent recurrence are all important consequences of these trial results.

Talazoparib has been shown to reduce tumor size in early-stage breast cancer and is currently being investigated in the phase III EMBRACA study. Does talazoparib have a role in the future of breast cancer treatment and what might we expect from this study?

Talazoparib is another promising agent in this space. Talazoparib is also targeting the trapping of PARP, and may even have enhanced trapping abilities. It was very exciting to see the neoadjuvant data presented at ESMO where, after 8 weeks of single-agent talazoparib, all patients in the study had tumor shrinkage, with an average of about 78%.[26] This trial is another proof of concept that we're seeing activity of this agent in actually shrinking tumors. The ABRAZO trial in metastatic patients, which was presented at ASCO, also showed response rates that were also very encouraging, with a 21% ORR in patients who had previously demonstrated platinum sensitivity.[20]

So I think that these 2 trials, one in the neoadjuvant setting, one in the metastatic setting, provide us with some of the preliminary evidence that the EMBRACA trial may similarly show activity and potentially benefit patients. Whether the magnitude of that benefit will exceed the standard-of-care chemotherapy in that trial remains to be seen. I think it's difficult to extrapolate from the data we have so far what the magnitude of the benefit will be. Certainly the OlympiAD data are encouraging, so if we have a drug that's as efficacious as olaparib in this setting, my hope is that this will be a positive trial as well.

Veliparib has been shown to be highly responsive in combination with chemotherapy in the phase II BROCADE trial and had a high predicted probability of phase III success in the phase II I-SPY 2 trial. Can you comment on the role veliparib may have in the future of breast cancer treatment and what we may expect from the phase III Brightness and BROCADE 3 trials?

I think we can learn a lot from the neoadjuvant and metastatic settings. In the neoadjuvant setting, the data are somewhat mixed. In the I-SPY 2 trial, the comparison was between veliparib/carboplatin plus paclitaxel versus paclitaxel alone, followed by doxorubicin and cyclophosphamide. I-SPY 2 did not separate testing veliparib versus carboplatin versus the combination. As seen in the published data, there was a very high predictive probability of success for the triplet in a subsequent phase III trial, as well as a high predictive probability of an improvement of pathological complete response [pCR] over standard treatment, both of which were metrics of success in the I-SPY 2 trial.

Again, by its design, I-SPY 2 didn't address whether the benefit was coming from the veliparib, from the carboplatin, or both. As I

said earlier, we have these questions about this interaction between PARP inhibitor activity and platinum activity and whether they are targeting the same processes. A potential answer to this was the phase III BROCADE trial in metastatic patients. In the BROCADE trial we have veliparib plus carboplatin plus paclitaxel compared with placebo plus carboplatin plus paclitaxel, and then the third arm being veliparib plus temozolomide.

Putting the temozolomide aside, if we simply look at this comparison of veliparib/carboplatin/paclitaxel versus placebo/carboplatin/paclitaxel, we saw a higher response rate to the veliparib-containing arm, 77% versus 61%, and a very small increase in PFS of 14.1 months versus 12.3 months. This was not statistically significant.

There is concern that perhaps we aren't getting independent activity from veliparib and carboplatin—that giving carboplatin alone may be just as good, or close to as good, as giving it in combination with veliparib, potentially with less toxicity. We need to think about this in the context of the other trials. Many of the trials being done do not allow patients who have progressed on platinum before, for registration purposes. So the BROCADE trial is trying to separate out this issue, and I think it has given us food for thought about whether the PARP inhibitors will give us something independent of platinum. I don't think we know that yet, but there may be an answer to the question in the Brightness trial.

In the Brightness trial, we see that they've broken it down even further. This trial compared veliparib/carboplatin/paclitaxel with placebo/carboplatin/paclitaxel or placebo/placebo/paclitaxel. This trial really helps us compare the effects of paclitaxel alone, paclitaxel with carboplatin, and paclitaxel with carboplatin and veliparib. In this trial, we really saw no difference between the veliparib/carboplatin/paclitaxel and the placebo/carboplatin/paclitaxel arms. It's a similar situation to the BROCADE trial, but is now in the neoadjuvant setting. When we look at the pCR rates, we saw it was about 53.2% for veliparib/carboplatin/paclitaxel and 57.5% for placebo/carboplatin/paclitaxel. Again, this is not a large difference in terms of the addition of veliparib. But when you look at the paclitaxel alone without either drug, there was a pCR rate of only 31%. So, clearly, you're getting more for the addition of the carboplatin or the veliparib, but it's not clear that you're getting more for the addition of both.

Niraparib and rucaparib are both approved for use in ovarian cancer. Is there a role for either of these agents for patients with breast cancer? What can we expect from the phase III BRAVO trial investigating niraparib in patients with germline *BRCA*-positive breast cancer?

Let's take niraparib first. There were some nice data in phase I, *BRCA1/2*-mutated breast cancers, showing a response rate of 50%. So that was quite compelling in terms of thinking that this drug may have some activity in *BRCA*-mutation carriers. This ultimately led to the design of the BRAVO trial, which is very similar in design to the OlympiAD trial in that it is looking at single-agent niraparib versus physician's choice chemotherapy. It also has the same caveat that it is only allowing prior platinum if the patients were sensitive and not allowing patients who have platinum-resistant cancer. We're all very excited about seeing the results of the BRAVO trial and wondering if this drug also will have similar activity to olaparib as the results seen in OlympiAD. Moving to rucaparib, I think that this is a slightly different drug. It blocks PARP1, 2, and 3 and right now is being tested in the phase II RUBY trial, which is for metastatic disease, enrolling patients who have the BRCA-ness profile. This trial is really looking at the group of tumors that may have some other DNA damage repair abnormalities, not patients who are mutation carriers. I think that this is another agent that looks potentially very interesting, and I think we'll need to wait for those results to see if we can identify another group of noncarriers who may be particularly susceptible to PARP inhibitors.

Is there a role for PARP inhibitors as adjuvant therapy in breast cancer? What can we anticipate from the phase III OlympiAD trial?

Certainly when we see activity in the metastatic setting as impressive as what we saw with the OlympiAD trial, for any agent, we're really anxious to look at whether that agent will actually have an effect in preventing patients with early-stage disease from recurring. It's only natural that we would want to bring that agent forward into the adjuvant setting. Of course, primary tumors are, to some degree, biologically different than metastatic tumors, and the ability to eliminate micrometastatic disease and ultimately improve cure rates is certainly a very different bar to clear. It's not a slam-dunk to assume efficacious drugs in the metastatic setting will provide event-free survival advantage in the adjuvant setting. It is essential to design trials to ask that question and, if they are successful, they will have a major impact on the prevention of a currently incurable disease—metastatic breast cancer.

I think it will also be very interesting to see whether we see reduction in additional primary breast cancers in patients with *BRCA* mutations who do not have a prophylactic mastectomy. It's hard to look at this question because so many patients who are mutation carriers elect to have a bilateral mastectomy during primary treatment. We don't know if PARP inhibitors have any primary preventative effect. To be able to look at whether there are any effects on local invasive recurrences will also be important. This is an incredibly important trial. It is focused on the highest-risk patients, those who are node-positive, and that's important because those are the patients who have the most to gain. These patients have the highest risk of recurrence and it will help us get answers sooner than if a group of lower-risk patients had been included.

Are *BRCA*-mutation status or "BRCA-like" traits indicative of response to PARP inhibitor treatment? Is there a second-generation biomarker that better predicts susceptibility to treatment that accounts for germline *BRCA*-positive patients who do not respond to treatment?

I think this remains an open question. There have certainly been some interesting biomarker data to come out of some of these trials. From the I-SPY 2 trial, in the veliparib/carboplatin arm, there's the PARPi 7 gene expression profile that further identified the group that was enriched for response to neoadjuvant veliparib in combination with carboplatin. These kinds of data can be very helpful in trying to understand somatic tumor changes that might be able to predict who will respond. Really very few trials, with the exception of the RUBY trial, have focused on that group. There are a few other trials that are focusing on other groups that may have BRCA-like changes that aren't somatic. I think that we just need to wait to see.

Additional tests have been developed. On one hand, the question is whether there are there any other germline mutations that might be predictive. There are some data to suggest that *RAD51*, *ATM*, or *ATR* could have germline mutations that would predict response. Then, of course, things like loss of heterozygosity profiles and gene expression profiles will need to be tested. I think that it would be a shame to not take advantage of all of the knowledge we've gained from patients who have *BRCA*-mutated breast cancer to really try to find a broader group of patients who will respond even though they don't have a germline mutation.

And then how can we understand the germline patients who don't respond to treatment? I think that's trickier. In general, we have considered germline *BRCA1* or *BRCA2* mutations to be drivers. By this I mean that in those patients, it is the loss of *BRCA1* and *BRCA2* that is solely driving tumor growth, and if you can exploit that, you will kill the tumors. It's possible that there are other drivers in these tumors and that only targeting DNA damage repair is not enough to keep these tumors from growing. That led to some of the combination trials that are going on, looking at combining PARP inhibitors with other targeted therapies, for example with the PI3 kinase inhibitors, with HSP90 inhibitors, or even with immunotherapy.

Resistance really is a problem. Even patients who respond to PARP inhibitors ultimately become resistant, for the most part. Developing ways to get around that resistance by understanding those resistance mechanisms is incredibly important. Some of these trials are trying to address this. And so I think that these are very exciting avenues of inquiry in which we may be able to not only build on some of the successes, but also expand the group of patients who respond to PARP inhibition, and potentially be able to delay the time to development of resistance.

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