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Interdisciplinary Strategies for BRCA-Mutated EBC: Testing, Targeting, and Team-Based Care

Announcer:

Welcome to CE on ReachMD. This activity, titled Interdisciplinary Strategies for BRCA-Mutated EBC: Testing, Targeting, and Team-Based Care is provided by AstraZeneca Pharmaceuticals and Merck, Sharp & Dhome.

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Chapter 1

So, this first part is called BRCA Testing in High-risk Early Breast Cancer: Some practical guidance.

So, the NCCN guidelines suggest that for localized breast cancer, and that's patients who have invasive, non-inflammatory, non-metastatic breast cancer, genetic counseling and testing in the patient's at risk for hereditary breast cancer is important. This is particularly critical for patients with any stage of triple-negative breast cancer or if they might be a candidate for adjuvant olaparib. And we'll talk more about who is a candidate for adjuvant olaparib, but this often encompasses most of our patients who have ER-positive breast cancer and almost anyone with triple-negative disease.

And then, ASCO and SSO take it a little bit further and they say BRCA mutational testing should be offered to all newly diagnosed patients with breast cancer under 65 and then select patients over 65 based on personal history, family history, and eligibility for PARP inhibitor therapy. And I do agree with those sort of broader ASCO guidelines. I think, this testing and these test results can make a difference for almost any patient. And, knowledge is power and knowing about it, even if it doesn't directly affect exactly what you're going to do from a breast cancer treatment standpoint, might be useful for understanding your own cancer risk going forward, and certainly for impacting and helping your family. So, these are just some things to keep in mind as you think to yourself about which of my patients might be eligible for germline mutational testing.

In the real world, how are we doing with this? So, a total of 2,373 U.S. patients who were diagnosed with HER2-negative early breast cancer between January 2021 and February 2024 were studied, so three years of following this patient population. What was found was that less than half of these patients received a germline BRCA test. There were lower testing rates in patients with hormone-positive disease than triple-negative disease. About 44% of the hormone-positive patients were tested and 73% of the triple-negative. And a substantial portion of patients who had been eligible, including those less than 50 years old, who had high-risk hormone positive early breast cancer, or those with high-risk triple negative breast cancer, had unknown or untested status.

This is an abstract that was presented at San Antonio in 2024. While, of course, this is just a small subset of the US population, it speaks to the fact that we don't have the uptake we would like to be seeing in terms of germline testing for these patients.

So, what are some of the problems behind this? We'll talk more about this, but I think some of it is that we aren't always doing this in our own clinical practices. It can be hard to get patients in with genetic counselors, and therefore patients sometimes don't do just that one more thing if they're already needing to have surgery and think about chemo and anti-estrogen therapy, so sometimes it's just not feasible to make it to a genetic counselor. And sometimes also we don't have the tools that we need to be able to counsel patients on

this.

The point of this slide is that point-of-care germline BRCA testing is feasible. Patients have breast cancer, they come into your clinic, you identify that the patient needs testing, and often as physicians, we are qualified to do the pre-test consenting and counseling for germline testing. We can then obtain a sample, which sometimes is blood, but sometimes can just be a saliva sample, and send the sample to the lab and get the results. And often what we do is we refer the patient to the genetics team if more discussion is required. This kind of takes that bottleneck of seeing the genetic counselor out of the picture. It allows you to get your genetics results early because many patients that you test will be negative and that will be reassuring. But for those who are positive, we are increasingly able to counsel patients on what they need to do from a treatment of the cancer standpoint. And then from a future risk standpoint, that's where bringing a genetic counselor in on a sort of urgent and timely manner, but not so much of an emergency as we've got to get this testing done now, can happen.

So, if no germline BRCA mutation is identified, that's one thing. If you find a germline BRCA mutation, then of course we're going to counsel patients and also send them to genetics. And then if a variant of uncertain significance is detected, then we can often reassure those patients.

But of course, make sure that those patients are then continuing to be followed so that if that variant becomes significant at some time point, we're able to counsel them on what to do.

So, a team approach, I think, is key. We all work in multidisciplinary teams. I think breast cancer, you can't treat this disease alone, and your multidisciplinary team may include a genetic counselor, medical oncologist, surgical oncologist, gynecologist, social worker. Of course, many other people too. I mean, your radiation doctors, your pathologists are all key as part of this, and often your other team members such as cardiology and psychiatry, as well.

So, the multidisciplinary team approach brings together lots of various specialists to deliver this coordinated and comprehensive care. As far as genetics goes, we all are really working together to assess patients' risk, determine the need for genetic testing, and then of course counsel patients about that because patients often will come to the table with certain fears about what they might have inherited, what this might mean for their family, for their insurance, all sorts of things. So, being prepared to talk to patients about all those questions I think is really key.

And with bringing all these different perspectives to the table, the multidisciplinary team can address these needs for patients and make sure that patients get the information that they need to make the best decisions about their care.

Racial disparities, I think, are important to mention. This is different in different parts of the country, depending on the populations that you're treating. But racial disparities in breast cancer outcomes are well-described, of course, and screening strategies need to be risk-based, but also race-based. We know that young black women have often a higher risk of early onset triple negative breast cancer compared to the rest of the population, and we need to be testing these patients. I think sometimes there are misconceptions that if you're not Ashkenazi Jewish, you're not from Eastern Europe, maybe you don't need BRCA testing. But we do see these mutations in black and Hispanic populations as well, and it's important to be counseling these patients on the importance of genetic testing and performing that testing for them.

I think early risk assessment and identification of these patients is very important. And that they make sure that we're educating not just patients, but also healthcare providers about the need to do this testing in these populations is really, really important. And I think studying this is also key because we want to make sure that we're giving patients the most evidence-based and up-to-date recommendations.

Chapter 2

So, evolving evidence in adjuvant therapy for high-risk germline BRCA mutation associated early breast cancer. I think this is really key as well to discuss because it used to be that we did germline testing to say, what is your risk of getting breast cancer and should you potentially be considering risk-reducing mastectomies or oophorectomies? But it wasn't until more recently that we actually had treatment options for patients who had BRCA mutations. I think this really has highlighted the need to do this testing, but also has allowed us to say to patients, if we find out this information, it might actually allow us to optimize your treatment and give you a higher chance of cure. That's a powerful thing to be able to say.

So, a lot of that started with this Phase 3 OlympiA trial that I'll present to you now. This may be data that you're familiar with, but if not, I will tell you about it. And if so, we'll just re-familiarize you.

So, this was a group of patients that had germline pathogenic BRCA1 and 2 mutations. They had HER2-negative early stage breast

cancer. This had to be either a stage two or three breast cancer or lack of pCR with neoadjuvant chemotherapy. So, they divided patients into the neoadjuvant group and then the adjuvant group. So, if you'd gotten neoadjuvant chemotherapy and you had triple negative breast cancer and a non-pCR, you were eligible. If you were hormone-positive and you'd had a non-pCR to neoadjuvant chemotherapy, they did this thing called a CPS EG score. This is a little bit complex and probably not necessary to explain exactly how to do that right now, but just to note that if you had an ER-positive patient who got neoadjuvant chemotherapy and didn't get to pCR, you would do this calculation to see if the patient was eligible to enroll in the trial.

For the adjuvant patients, these were patients with triple-negative breast cancer that was either greater than 2-centimeters or node-positive. And if they were ER positive and had not gotten neoadjuvant, they had to have at least four positive lymph nodes, so a high-risk group of patients.

These patients all were randomized 1-to-1 to either receive placebo twice daily for a year, along with endocrine therapy, of course, if these patients were ER positive, or olaparib 300 milligrams twice daily for one year. And that could be given along with endocrine therapy if the patient was ER-positive.

The primary endpoint was invasive disease-free survival, and then we looked at things like distant disease-free survival and overall survival as well. They also looked at incidents of other BRCA1 and 2 associated cancers, and then, of course, health-related quality of life.

So, this is a description of the patients who enrolled in this study. There were a little over 900 patients in each arm. A young group of patients, which is to be expected given the mutation criteria to entry, with the average age being 42 to 43. About 70% of patients were BRCA1, about 30% of patients or a little fewer than that were BRCA2. There was a handful of patients that had both mutations. And then, the majority of patients, a little over 60%, were premenopausal.

Seventy-five percent of patients roughly had mastectomies. About a quarter had conservative surgery only. And in terms of hormone receptor status, a little over 80% were triple-negative, a little under 20% were hormone positive. All these patients got chemotherapy, about 50% neoadjuvant, and then the rest adjuvant. Most patients had anthracycline and taxane-based regimen.

And then, for the hormone-positive patients, a large proportion received concurrent endocrine therapy as well, Ninety-three percent of the placebo patients and 87% of the olaparib patients.

And then, here is the invasive disease-free survival data, so the primary endpoint. These patients have now been followed out quite a ways, and you can see that at 6 years, the invasive disease-free survival difference is pretty stark with a 9.4% improvement in the patients who received olaparib compared to the patients who received placebo for that last year. And if you look at the different subgroups, you can see that the analysis clearly favors olaparib in all the patient populations, regardless of which BRCA mutation you had, whether you were hormone positive or triple-negative, although we see far more patients with TNBC in this trial. Whether you had prior platinum-based chemotherapy or not. Because olaparib is sort of similar to platinum in its action, there was some concern of you know could this be something that's less effective in the patients who'd received platinum? It was a smaller number of patients, but the data still favored olaparib in this patient group. And it didn't matter whether you received the chemotherapy neoadjuvantly or adjuvantly So, all in favor of the year of added olaparib.

This just divides things out into triple-negative and ER-positive. Obviously, a smaller number of ER-positive breast cancer patients and slightly different biology there, but still at that 5- to 6-year time frame of follow-up favoring the olaparib in both groups.

And then, looking at distant disease-free survival, which was a secondary endpoint, but obviously clinically really important, at 6 years. That was 7.8% better in the patients who received olaparib, and they had an 83.5% chance of being free from distant recurrence at 6 years versus only 75% of patients who met that criteria who received placebo.

So, clear that the olaparib really does have benefit here. And then, if you look at the distant disease-free survival in those same subgroups, you can see again that this favors olaparib across the board.

What about deaths? So, this is obviously very important. The total number of deaths. There were 107 deaths in the olaparib population, 143 deaths in the placebo population. In terms of primary cause of death, there was breast cancer recurrence in 10.2% of the patients with 94 of the 107in the olaparib group, and then 128 out of 143 in the placebo group. So, you're seeing that not only are there longer time to progression, but potentially also fewer progressions and fewer patients dying from breast cancer.

You can see that in the olaparib group, there was one patient who had pancreatic cancer, three patients who had AML, and we'll talk a little bit more about that. And then the placebo group, there were two patients who had ovarian cancer, one with pancreatic cancer, and then also three with leukemia.

So, leukemia is one of those things that with olaparib, sometimes you can see secondary AML and secondary MDS, not typically after one year. And it's important to note that in this study, you didn't see an increased risk of AML in the olaparib group.

This is looking at overall survival, and you can see again, at 6 years, there is a difference of 4.4%. It does seem like those curves potentially are widening. By subgroup, again, the survival data favors the olaparib.

So, all this is to say that this is an effective medication and is now a standard of care for patients who met criteria for this trial. And then, if you look at adverse events of special interest, you can see, as we talked about, that the MDS AML risk was not higher in the olaparib patient population. The pneumonitis risk also was the same. And then, new primary malignancies were actually higher, 7.5% of the placebo group numerically compared to 4.9% in the olaparib group. So, you wonder whether that adjuvant olaparib is maybe preventing things like ovarian cancer or pancreatic cancer down the line.

I think more studies and potentially real-world data will be needed to bear out that potential hypothesis, but certainly patients did not do worse when you incorporated the olaparib.

So, I think all that data really just serves to hammer home the important point that if you get BRCA testing and you find the mutation, then you can potentially offer patients this life-saving treatment after they finish the rest of their neoadjuvant and adjuvant therapy that doesn't add a lot in terms of toxicity and potentially add significant benefit. So, it’s very important to integrate this testing into treatment planning.

Chapter 3

For patients with hormone-positive, HER2-negative breast cancer, if they're node positive after neoadjuvant therapy or have any disease left over, then you're thinking about adjuvant endocrine therapy, of course. And then if they're germline mutated, you would think about adding olaparib to endocrine therapy. You could also consider adding adjuvant abemaciclib or ribociclib to this high-risk population. And we'll talk a little bit in future slides about the MONARCHE and NATALEE trials, which led to those recommendations. We'll also talk a little bit about how you sequence those because you don't want to give all three pills at once.

And then, for triple-negative breast cancer, for these patients who don't get to pCR after neoadjuvant, you're giving adjuvant pembrolizumab as things stand. And then also adjuvant olaparib. There's this question of whether you should be giving adjuvant capecitabine, and we'll talk about this some in the case studies. So, my typical practice in a germline BRCA patient who doesn't get to pCR with chemo is to give adjuvant olaparib along with the pembrolizumab, usually incorporating the olaparib after radiation is done. And then, if patients are able and want to, you could consider adjuvant capecitabine after that. But for many patients, the adjuvant olaparib may be sufficient.

So, talking about hormone-positive, HER2-negative breast cancer with germline BRCA mutations how do you classify these patients and what do you do to treat them? I think there's definitely a difference between clinical stage 1 and 2, versus those who have stage 2 to 3 disease where you might be thinking about neoadjuvant. So, if you've got a higher stage disease over on the right, and you're thinking about neoadjuvant chemotherapy followed by surgery, then you're really dividing those patients after their neoadjuvant chemotherapy into whether they get to pCR or whether they don't.

So, if they get to pCR, they're going to get endocrine therapy alone afterwards. A lot of these patients don't get to pCR, of course, and we always counsel patients that pCR is less of a meaningful predictor in patients with ER-positive breast cancer But if they get there, then we give them endocrine therapy alone and– don’t consider olaparib. If they don't get to pCR, but their nodes are negative, then they also would receive endocrine therapy alone. If patients have node-positive disease after neoadjuvant, that's where we might consider endocrine therapy along with olaparib, and then after that year of olaparib is over, potentially considering sequential CDK 4/6 inhibitor therapy.

For patients who have stage 1 to 2 disease that is operable and go to surgery up front, certainly if they have node-negative disease, some patients might receive chemotherapy based on their Oncotype score or other genomic assay. They're all going to receive endocrine therapy, of course. If these patients have positive nodes at surgery, then they likely will get chemotherapy, especially if premenopausal, then you might also consider olaparib with endocrine therapy afterwards, or you could consider abemaciclib with endocrine therapy afterwards, depending on their disease characteristics and, of course, personal preferences.

And if they have lots of nodal disease, so N2 or N3, that's where we would really be thinking about chemotherapy for sure, and then olaparib endocrine therapy and probably pushing for sequential abemaciclib just to give patients the optimal chance of cure if they can handle all that therapy. It's a really nice way of laying it out.

Chapter 4

So, where do these CDK 4/6 inhibitor recommendations come from? So, the Phase 3 monarchE trial was a trial that looked at adjuvant abemaciclib and endocrine therapy versus endocrine therapy alone in patients with hormone-positive, HER2-negative, high-risk, early-stage breast cancer. So, now we're moving sort of away from the germline BRCA cohort explicitly to talk about patients with just high-risk, early-stage, ER-positive breast cancer.

So, these were patients with very high-risk disease. They either had to have had 4 or more positive lymph nodes, or could have had 1 to 3 positive nodes in at least either grade 3 disease, a tumor greater than 5 centimeters, or have a high Ki-67 index. So, this is a very high-risk group of node-positive patients.

They were enrolled after receiving appropriate chemotherapy, surgery, radiation, and then one-to-one were randomized to receive either endocrine therapy alone or endocrine therapy plus abemaciclib 150 milligrams twice daily. These patients were then followed. The abemaciclib was given for 2 years, so the study period where patients were actively on treatment was 2 years. And then, they were followed after that as clinically appropriate.

The primary objective was invasive disease-free survival, and then there were a number of different secondary objectives.

And then, here are the results. 84-month primary endpoint of invasive disease-free survival. You can see that these curves started to separate really early on at 24 months, where you saw a 2.8% benefit in favor of the abemaciclib and that was really like right at the end of the treatment period. But then, as patients go on over time, you can see that those curves separate more and the overall benefit, the improvement in invasive disease-free survival, now looking at 84-months, is a 6.5% benefit, so 70.9% of patients in the placebo arm, the endocrine-only arm, were disease-free at an 84-month time point versus 77% of patients who received the abemaciclib for that 2-year time frame. So, really impressive data that's both statistically and clinically significant.

And if you look at overall survival, this is an endpoint that is very hard to reach in trials of early-stage, ER-positive breast cancer, because not that many of these patients recur, thankfully, and when they do recur, they live for long periods of time. But you're starting to see, now that we're going out past 5 years, a slight separation of curves that will need to be continued to follow. So, definitely important to think about. And then, if you look at the statistical significance here, technically this was a statistically significant hazard ratio, not crossing 1, so technically, an overall survival benefit Clinically, it's a small number, 1.8% difference, but something that we do expect may continue to widen over time as we continue to follow patients.

This is looking at distant recurrence-free survival, that same trial, with those same endpoints. And you can see that distant recurrence-free survival has also improved at 84 months by 5.1% in patients who received abemaciclib for 2 years.

And then, what about adverse events? Obviously something to think about. This is looking at patients on the abemaciclib arm on the left, the endocrine therapy alone on the right. And these were really consistent with the safety results from prior analyses of this drug. There were no relevant differences between treatment arms and causes of death due to adverse events. Certainly more diarrhea and cytopenias were seen in patients who received abemaciclib, but this was felt to be a cost that was worth it for most patients who were on the study.

And then, what about NATALEE? So, NATALEE is another Phase 3 trial of adjuvant CDK 4/6 inhibitors. This was a trial that looked at ribociclib plus endocrine therapy as opposed to abemaciclib. The main differences in this study, other than the different CDK 4/6 inhibitor, was that this trial looked at 3 years of the CDK 4/6 inhibitor intervention as opposed to 2 years. It also allowed a slightly less high-risk patient population.

These patients had either stage 2 or stage 3 disease, but could be T2 and 0. If they were T2 and 0, they had to have either high-risk Oncotype score, a higher Ki-67 index, or be a grade 3. So, these patients had to have some high-risk criteria, but could be node-negative, as opposed to the abemaciclib study where they were all node-positive. The other thing to note is that this study allowed patients to have already started their endocrine therapy up to one year ago, whereas in the trial of abemaciclib, they only were allowed to have had 3 months on their endocrine therapy before going on the study.

This is a more stringent criteria in the previous study, but this study also was a positive study, which I'll show you. They looked at a 3-year intervention, also a one-to-one randomization. And then, the invasive disease-free survival data that we have so far, looking out at the 5-year mark, 60 months, is a 4.5% difference in favor of the ribociclib arm. So, 81% of patients disease-free at 5 years. And the patients who received placebo or no ribociclib, as it was. But 85% of the patients who were on ribociclib are disease-free at that time point. So, both clinically and statistically significant.

Overall survival, this hazard ratio, as you can see, does technically cross 1, but it is very possible that as we follow these patients further out beyond 5 years, we may too start to see a small overall survival benefit in this patient population.

This slide here, is looking at distant disease-free survival and also distant recurrence-free survival, and you can see that these endpoints also were positive in favor of continuing the ribociclib.

What about deaths and safety assessments? There were 5 deaths due to adverse events, but these were not considered related to study treatment. You can see the list here of what happened in each of these individual patients. The proportion of patients who developed second primary malignancies was also similar in both arms. So, no new safety assessments. This is a drug that we've all been using in the metastatic setting for quite some time. It performed very similarly in terms of how patients tolerated it in the upfront setting.

Chapter 5

So, what about pembrolizumab for patients with ER-positive early-stage breast cancer? We know that from KEYNOTE-522 that pembrolizumab, works very, very well in patients with triple-negative breast cancer and that has become a standard of care of what we give to our early-stage patients. And we give it along with 24 weeks of chemotherapy, neoadjuvantly, followed by an adjuvant course.

And then, what about these hormone-positive patients with high-risk disease? So, KEYNOTE-756 looked at patients who had either T1C or T2 disease that was also node-positive, or T3 to 4 disease that had any nodal status. These patients had to have had grade 3 ER-positive breast cancer, and be treatment naive. They were then randomized one-to-one prior to surgery to receive either a very similar regimen to what was received in the KEYNOTE-522 trial, which was chemotherapy along with paclitaxel and then also, epirubicin or doxorubicin plus cyclophosphamide, with either placebo every 3 weeks or with pembrolizumab. Patients all then went to surgery and then, similarly to the KEYNOTE-522 trial received pembrolizumab afterwards for 6 months plus endocrine therapy or placebo plus endocrine therapy. pCR and event-free survival were dual primary endpoints of this study.

You can see here, the primary endpoint, looking at pCR rates, higher certainly, in the patients who received the pembrolizumab, 8.5% difference with 24.3% of patients who received the pembrolizumab getting to pCR versus just 15.6% in the placebo arm. And then these other pCR definitions, you can see that there are different ways to define pCR. Do you include DCIS or do you not? But you can see that all of these clearly did favor the pembrolizumab in this patient population.

In terms of immune-related adverse events, we obviously saw more of these in the pembrolizumab arm than in the placebo arm, with most of these being hypothyroidism and thankfully most of these being low-grade. And I think the challenge of the pCR is that that's not always the best predictor of prognosis in these patients with ER-positive disease, although maybe a better predictor of prognosis in patients who are exclusively grade 3, as this population was, so it does beg the question of should we be using this? It is not standard of care in this patient population, but definitely is something that I think we need to follow closely.

Chapter 6

So, for patients with germline BRCA-mutated, triple-negative breast cancer, how are we thinking about this patient population? This is a little bit easier, I think, than thinking about the patients with ER-positive disease because there's so many moving parts in terms of how we interpret pCR and then what we do with regards to CDK 4/6 inhibitors. But here's how we look at those TNBC patients.

So, for most clinical stage 1 patients, they're going to go straight to surgery. If they are truly node-negative at the time of surgery, and truly stage 1, then they'll receive adjuvant chemotherapy. If they have more than stage 1 disease, if they are either node-positive or turn out to have more than 2 centimeters of disease, they can get chemotherapy and also receive a year of adjuvant olaparib.

I think it's rarer that we come up with these patients just because so many triple-negative breast cancer patients are getting neoadjuvant chemotherapy these days. But if that does happen, that your patient goes to surgery and you find out, oh, hey, they're germline BRCA mutated and they also have a tumor that's greater than 2 centimeters or node-positive but we didn't realize, they are actually olaparib candidates. So, I think that is an important pearl to remember.

And then, the more common scenario, if patients have a stage 2 or 3 disease and they're receiving neoadjuvant chemotherapy with immunotherapy, then we're really dividing them after that into pCR versus non-PCR. If they get to pCR, then they're completing 1 year of adjuvant immunotherapy or enrolling in a trial, like optimized pCR, that potentially allows them to omit that immunotherapy. If they don't get to pCR, then, assuming they don't have a clinical trial to enroll in, they would be receiving a year of adjuvant olaparib plus or minus immunotherapy.

So, important just to know where that olaparib comes in.

So, the 522 trial I've mentioned already. This was the pivotal trial that led to the incorporation of chemo along with immunotherapy in patients with earlier stage triple-negative breast cancer. This was not just germline BRCA mutation carriers, but all triple negative breast cancer patients with stage 2 or 3 disease.

Patients were randomized in this study in a 2-to-1 fashion to receive either 12 weeks of platinum with paclitaxel, followed by anthracycline plus cyclophosphamide, and then patients either received placebo along with that 24-week course or pembrolizumab every 3 weeks along with that 24-week course.

Patients then went to surgery and the patients who received pembrolizumab pre-op also received pembrolizumab post-op. The patients who did not receive pembrolizumab received placebo afterwards.

So, a complex trial with a lot of therapy. But what we found is that the addition of the pembrolizumab improved event-free survival and overall survival in this patient population. So, if you'll get 5-year event-free survival data, you can see there's almost a 10% improvement for the patients who received pembrolizumab. And then 5-year overall survival data is also bearing that out because unlike with ER-positive breast cancer, these patients do tend to succumb to their disease earlier, so you see those overall survival curves separating more quickly and also more meaningfully.

Looking at adverse events, most of the adverse events that were more significant in the pembro arm were the immune-related adverse events, so mostly things like hypothyroidism, some skin reactions, dermatologic issues, occasionally gastritis. We didn't see a whole lot of other major adverse events. There was a little bit of adrenal insufficiency but most of these patients had grade 1 or 2 adrenal insufficiency, and it was only 2.6% of the population. And the rest of the side effects that patients experience were really more related to the chemotherapy. So, nausea seen in about 60% in both groups, alopecia in about 60% in both groups, and then of course, the cytopenias and fatigue that you would expect with chemotherapy.

This trial is looking at the OlympiaN trial, so not OlympiA, but OlympiaN. This is looking at neoadjuvant olaparib plus or minus durvalumab in HER2-negative early breast cancer patients who had BRCA mutations. So, a very different patient population than KEYNOTE-522. These were patients who had germline BRCA mutations.

They were ER-negative or ER-low. They could be less than 10% ER-positive. They were also HER2-negative. And then, these patients had either tumors that were stage 1 but would have been eligible for neoadjuvant chemotherapy, or could be TN1, so a tumor that was less than 2 centimeters but had a positive node, or could be T2N0, so 2 to 5 centimeters but node-negative.

They were then divided into risk cohorts, so the earlier stage, stage 1 patients, were felt to be lower risk. The patients who were early stage 2s, either T1N1 or T2N0, were felt to be a little higher risk.

These patients then received olaparib, continuously in the lower risk category, and then olaparib plus durvalumab in the higher risk category. All patients then went to surgery. The primary endpoint was pCR, and then afterwards they could receive treatment as per local practice.

So, patients could receive adjuvant olaparib if they got to pCR with neoadjuvant olaparib, but certainly chemotherapy and other medicines could be given. So, really interesting study.

So, if you look here at the results, so for cohort A, those patients with stage 1 disease who received olaparib, 68% got to pCR. Small number. There were only 25 patients in each arm, but this does show the value and the activity of this drug in a pretty impressive way.

And then, if you look at the cohort B, this is patients who received olaparib, durvalumab. You get an 80% pCR rate in those patients. And then, if you look at RCB class 0 to 1, so patients who had a little bit of residual disease, that was 84% of the patient population who really had quite a little bit of cancer left behind.

So, it definitely shows good efficacy in small numbers of patients. Maybe not ready for prime time yet, but definitely worthy of greater study. And I think in those patients who can't tolerate chemotherapy, this would be something I would consider pushing for. It definitely shows the activity of the drug.

So, in terms of adverse events, we could see that most of these adverse events were things like anemia a little bit of diarrhea, things like that. The diarrhea was much more often seen in the patients who received durvalumab. But again, was still only 4% of patients.

There was one patient in the durvalumab cohorts that had diabetes that was felt to be possibly related to the immunotherapy. But patients mostly did quite, quite well. There were no adverse events leading to death, thankfully, and then very few serious adverse events. So, these patients did quite well and also tolerate the treatment beautifully.

Chapter 7

So, moving from treatment to shared decision-making. I think now that we have so many options for patients, it is really important for patients to understand what you're talking about, and also have the opportunity to express buy-in. So, shared decision-making occurs when the healthcare providers, us, and their patients work together to make healthcare decisions that are best for patients.

I think optimal decision making does take into account, of course, the evidence, which we all know well, our experience with drugs and with trials, and also the patient's values and preferences. I think it's really important, I feel, before we even go into a discussion of what are we recommending for you, to kind of understand where patients are coming from. I'll often ask questions like, after I've taken a full history, what else should I know about you in order to help you make good decisions? And I might also ask questions like, what do you know so far about what the treatment might look like for this cancer? I'd just like to know where you're coming from, so I can kind of meet you where you are.

But often those kind of more open-ended questions, both A; show that you care about who they are as a person, and then B; allow you to get really important information about what they think they do know so far, and what their feelings are about things like chemotherapy or genetic testing, or what in their own life might make things particularly hard for them or challenging about the treatment plan you're about to embark upon.

So, how to best do this. The SHARE approach is this 5-step process that I think – and these processes always feel a little bit stilted when you describe them, but I think you can definitely modify them to fit what feels most natural for you. But basically takes these 5 steps to explore and compare the risks and benefits of each option, and then talk to patients about what matters most to them.

So, the S is for seek your patient's participation. You want to bring them into the dialogue and make them know that they value and you value what they have to say. You want to help them explore and compare treatment options. And I think it is nice and important to present, there's not just one way to do this, here are the multiple ways. Here's why I might choose what I would choose if you kind of asked for that guidance But really assess – that's the third one, the assess – your patient's values and preferences. You then reach a decision with your patient after discussion, and then have opportunities to evaluate your patient's decision with them. You also want to make sure that they know that any decision they make is not usually irreversible. They can continue to talk that through with you. If they start a chemotherapy regimen and they really don't tolerate it, there are always opportunities to sort of backtrack or take a different approach as time goes on and to be flexible.

Data shows that patients and their families who are engaged in this shared decision-making are more likely to get to a treatment decision that works best for all of them and more likely to be able to sort of motivate to get through these complex treatments that we are now recommending.

Chapter 8

So, some team-based practical strategies and surveillance and management of adverse events. We've talked a little bit about adverse events already, and this is just a slide looking at olaparib versus placebo in the OlympiA trial, that initial trial that looked at the year of adjuvant olaparib compared to placebo in patients who already received appropriate care for their breast cancer. You see that nausea and fatigue were much more significant in patients who received olaparib than patients who received placebo. Most of this was low-grade, but nausea and fatigue, even at low grade, can be really impactful in terms of everyday life.

Anemia is also a thing, and with anemia, of course, comes more fatigue. And then other side effects were pretty similar, headaches 19% versus 16%, decreased appetite was a little bit more prominent in the olaparib arm. But most of these side effects patients did feel were manageable.

So, I think it's important to sort of think about these things and make sure that you're preparing your patients for what they might experience on these medications, and of course, be following them closely to make sure that if side effects do come up, you can address them in ways that feel safe and helpful.

So, nausea and fatigue are two of the most common side effects associated with PARP inhibitors. We're talking about non-hematologic side effects just because these are the ones that tend to affect patients' quality of life the most. So, this is just a little bit of a baseline guideline for how to manage these things. If patients have low-grade symptoms, you don't want to replace a vomited dose, but you do want to take the next dose at the scheduled time. And then, you can consider prophylactic medications such as metoclopramide 30 to 60 minutes before patients take a PARP inhibitor, so that things are moving through appropriately.

We often will prescribe things like ondansetron as well to help with symptom management. And then, patients can consider taking the pill later in the day for twice-daily dosing, or at night before bed if patients are taking the medication daily. And then for fatigue, this is a harder thing to medicate, of course. We often can optimize sleep management with our patients. We can treat depression. We can optimize nutrition and exercise. Typically, I don't recommend stimulants for patients who have fatigue on PARP inhibitors because it's one of those things where we're not really sure that the stimulant is going to make that better, or if it does, it may come at some cost. So, there's really more lifestyle management, and then if fatigue is overwhelming, considering a dose reduction.

For anemia, neutropenia, and thrombocytopenia, these things are a little bit less gray because they are very well-defined by what the

numbers look like. And you can see that for many patients, you do want to investigate, especially with anemia first, whether they could have a nutritional deficiency contributing or hypothyroidism. But certainly, if symptoms are higher grade or for these other cytopenias, you're probably going to end up doing some drug holds, some rechecking of labs before you get back to a dose that works for the patient.

And I think interprofessional collaboration is really important. So, we want to be managing these toxicities together, making sure that we do utilize dose delays and dose reductions to help patients understand that we can help them feel better, that they don't have to stay on the full dose, and that we can have some be better than none. And then, we have to develop practical strategies to ensure that patients are feeling safe and that they are able to adhere to their treatment.

The other thing we didn't talk about yet is financial toxicity, but that certainly can be an issue too. Some insurance companies cover this more completely and patients may fall into like, donut holes of prescription drug coverage where the cost of the medication can be concerning. I think I find that it's so variable and sometimes patients don't want to talk about that stuff, and so I do say to people, really with any specialty drug, if we prescribe this pill and it's cost prohibitive, definitely let us know because we may not even know. And if you tell us, there may be things we can do about it, talking to the company, getting coupons, those kinds of things.

Chapter 9

So, the first case is a 55-year-old woman. She has a family history of ovarian cancer and her sister at age 47. She herself is now presenting with a left breast mass. Her biopsy shows grade 3 adenocarcinoma. She's ER 50%, PR 30%, Ki-67 of 30%.

She has genetic testing and has a BRCA2 mutation that's found. Because of this, she opts to go with bilateral total mastectomy and left axillary dissection. She's found to have a 2-centimeter ER-positive, HER2-negative breast cancer with 4 out of 14 lymph nodes positive, so she meets the criteria for the OlympiA trial with those four positive nodes.

She receives post-mastectomy radiation, but then you're thinking through with her, what do you want to do next?

So, other than anastrozole for at least 5 years, what else would you offer this patient? Would you offer her no further therapy, capecitabine for 6 months, abemaciclib for 2 years or ribociclib for 3 years, olaparib for 1 year, or olaparib for 1 year, then abemaciclib for 2 years, or ribociclib for 3 years, or would you do something else? And remember, this is a patient with 4 out of 14 positive lymph nodes, ER-positive breast cancer, and a BRCA2 mutation.

So, I think yeah, this kind of does highlight all the options that patients now have and also the importance of shared decision-making. So, this is a patient who's going to benefit from the anastrozole for at least 5 years for sure. I would not say no further therapy because she has so many other options. I also would not say capecitabine for 6 months because that would be really more for a patient with triple-negative disease and probably someone without a germline BRCA mutation, because for those mutation carriers, you're going to be thinking about olaparib.

For this patient, I definitely would want to give her olaparib for a year. With those four positive lymph nodes, she meets criteria for the OlympiA trial, and we have a clear benefit in these patients in terms of disease-free survival, distant disease-free survival, and even overall survival with the olaparib. And I think after the olaparib, it's really about pacing yourself. In patients with BRCA2 mutations and ER-positive disease and those four positive nodes, I do worry about recurrence. I do want to do everything I can within reason to reduce her risk of recurrence. So, I would probably start with the one year of olaparib along with endocrine therapy and after that, if the patient feels well enough and is ready for something more, that's where I would consider either the abemaciclib for 2 years or the ribociclib for 3.

She meets criteria for abemaciclib, and I think 2 years of treatment is often easier for patients than 3 years of additional, so I probably would start with the abemaciclib in her if she was willing to do a CDK4/6 inhibitor. But if diarrhea or something like that became prohibitive, she could always switch to the ribociclib.

I think, psychologically for patients, this can feel like a lot. It's a lot of pills, it's a lot of specialty drugs, a lot of potential side effects and lab draws.

Chapter 10

Dr. Meisel: So, moving on to some of the key takeaways. Every newly diagnosed early breast cancer patient these days will likely receive a germline BRCA test, particularly if they're HER2-negative and per ASCO if they're under 65, regardless. High-risk patients with BRCA-mutated, HER2-negative early breast cancer derive a benefit from adjuvant olaparib, not only in terms of progression-free survival, but also in terms of how long they live. We literally can cure more patients with this drug.

Invasive disease-free survival benefit is seen with adjuvant CDK4/6 inhibitors in patients who have hormone-positive, early-stage breast cancer. There's an overall survival benefit now that we see that's statistically significant with adjuvant abemaciclib. The adjuvant ribociclib trial was not powered for overall survival, so we have to be careful as we continue to interpret that data going forward.

We know that pCR rates are improved by neoadjuvant pembrolizumab in hormone-positive, HER2-negative early breast cancer. We still don't quite know how that correlates with event-free survival and actual outcomes, so we're not really using neoadjuvant pembro yet in hormone-positive disease, but we know that early-stage triple-negative breast cancer patients do benefit from receiving pembrolizumab in the neoadjuvant and adjuvant setting.

How do we choose adjuvant therapy for patients with early-stage breast cancer who have BRCA mutations? We know that for hormone-positive breast cancer, olaparib can be given for a year prior to CDK4/6 inhibitors if residual disease is present after neoadjuvant chemotherapy. And for triple-negative, we can give olaparib with pembrolizumab if there's any residual disease after neoadjuvant chemoimmunotherapy.

I think it's very possible that biomarkers in the future may be able to help us determine the optimal treatments for individual patients.

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