ADOPTING THE EVOLVING MANAGEMENT OF HR+/HER2-MBC INTO PRACTICE

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BACKGROUND AND SCOPE FOR MANAGEMENT OF PATIENTS WITH HR+/HER2- MBC

HOPE RUGO, MD: Let's start and talk about the background and scope for management of patients with HR+/HER2- mBC. Breast cancer is classified based on the cell of origin, ductal or lobular, and really the pattern on histologic evaluation, as well as immunohistochemical features. Estrogen influences the growth of most breast cells, and we have understood now that even cancers that no longer express the hormone receptors—estrogen and progesterone receptors—are still driven, at some point during their life, by the presence of estrogen. For metastatic disease, the most common sites of metastases for hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) disease are bone, soft tissue, and then visceral organs, such as lung, liver, and brain. Risk factors for breast cancer, of course, are not the same as risk factors for developing metastatic disease, but risk factors for developing breast cancer overall include increasing age, being female, family history, high breast density, and then some reproductive factors play a role as well, such as absent or late childbearing, as well as breastfeeding and then genetic mutations. Of course, germline mutations are really a higher risk category—patients who have germline mutations, breast cancer gene 1 and 2 (BRCA1 and 2). But we've learned to know, with the decreased cost of doing large mutation screening, that there are multiple germline mutations that may increase the risk of breast cancer but are thought to be less penetrant overall because the risks are not as high as BRCA1 and 2. But nonetheless, these have really changed the landscape of understanding risk for breast cancer. The lifetime risk for breast cancer for a patient who inherits a mutation in BRCA1 or 2 is as high as 65% for BRCA1 and up to 50% to 60% for BRCA2.

In the United States, and around the world, breast cancer is the most common cancer in women. Internationally, breast cancer is the most common cause of cancer death, but this is not true in the United States with better treatment and earlier diagnosis. Overall, 13% of all women will be diagnosed with breast cancer at some point during their lifetime and the most common subtype of breast cancer overall is HR+/HER2-, representing about 70% of breast cancers. And interestingly, this incidence rate goes across early and late-stage disease. The median age of diagnosis of breast cancer is 63 years old, and it remains an uncommon diagnosis in very young women, although these rates have been increasing slowly over time. The 5-year relative survival rate for early-stage breast cancer is 91.2%, but you can see that the 5-year relative survival rates, when you have metastatic disease, markedly decrease down to about 35% of patients surviving 5 years who have HR+/HER2- disease.

The subtypes of breast cancer are important to understand as we move forward and talk about treatment options. As I mentioned, HR+/HER2- disease is the most common subset of breast cancer, regardless of stage. These cancers are defined as exhibiting 1 or both hormone receptors, estrogen and progesterone receptors, and not having HER2 gene amplification. Now, there are additional categories that have been defined based on new antibody drug conjugates (ADCs), so-called HER2-low, but these still qualify as HER2- when we're thinking about the up-front treatment for these patients at the present time.

Patients with triple-positive disease have tumors that exhibit both HER2 gene amplification and also hormone receptor positivity and, of course, triple-positive means both estrogen receptor (ER) and progesterone receptor (PR) are positive, but we have grouped together patients who have ER+ and PR- disease into this category quite commonly. HER2+ disease overall is defined regardless of hormone receptor positivity and represents about 15% to sometimes 20% of all breast cancers, and these tumors have amplification of the HER2 gene. But also, that translates into overexpression of HER2 protein on the cell surface. And then the third big category is triple-negative disease where tumors don't have evidence of expression of the ER and PR and they don't meet the criteria for being HER2+. Although some of these tumors may have some expression of HER2, they don't meet the standard criteria for HER2+ disease. Triple-negative tumors represent about 15% of breast cancers.

Sara, when do you look at these receptors in the diagnosis of patients with metastatic disease and how does it influence your next steps?

SARA HURVITZ, MD: I think it's really important for patients to have their tumor biopsied at the time metastatic disease is suspected. I think it's important not to take the imaging results as pure evidence that there is metastatic disease. A biopsy is usually done at the time of metastatic diagnosis and the sample can then be tested for hormone receptors and also molecular testing can be done at that time on the sample. Advances in liquid biopsy looking at circulating tumor DNA (ctDNA), for example, is helping us avoid having to sample the tumor tissue repeatedly with needle biopsies, but at the initial diagnosis of metastatic disease, when possible. I try to get a sample of the tumor through needle biopsy as a definitive way of establishing metastatic disease and rechecking the biomarkers.

MOLECULAR AND TUMOR PROFILING

HOPE RUGO, MD: When a patient presents with metastatic disease, you're going to do a history and physical exam and extensive scanning and I think your decisions about what kind of workup you do have to do with the stage of disease at diagnosis. A patient who presents with metastatic disease, we generally would not do breast imaging primarily. A patient who presents with de novo metastatic disease would have that imaging. Otherwise, your imaging is directed to where you need further definition of disease, and we generally are doing overall computed tomography (CT) scans of chest, abdomen, and pelvis, and many people will use positron emission tomography (PET) CT scans as their initial imaging procedure. You need laboratory studies to understand the impact on

organ function and then diagnostic tissue, as we talked about. I think that there's really been a shift in when we do biomarkers, when we do the next generation sequencing (NGS). We have to get ER, PR, and HER2 which are the biomarkers, and then the germline genetic testing, if it hasn't been done before, I think is a critical part of this evaluation, if it's appropriate. Women who are diagnosed with breast cancer the first time when they're elderly and have no family that would be impacted and no family history, this may not be an up-front type of testing that you need to pursue.

Sara, has recent data changed anything about when you do NGS when a patient presents with metastatic disease?

SARA HURVITZ, MD: I think the approval of inavolisib in the first-line setting for HR+/HER2- metastatic breast cancer (mBC) and availability of that agent in patients with endocrine-resistant *PI3* kinase mutated breast cancers prompted me to be testing at that first-line setting now, whereas in the past, I would wait until the second-line setting.

HOPE RUGO, MD: Let's talk about the definition of HER2+ disease simply because I think that might have become a little bit more confusing over time as we've had ADCs that appear to be quite effective in tumors that don't meet criteria for HER2 positivity for treatment with HER2-targeted agents but are HER2-low where these HER2 trastuzumab ADCs have been quite effective. If the immunohistochemistry (IHC) is 3+, showing extensive staining, complete, intense and in greater than 10% of cells, that's HER2+ and I think an aromatase inhibitor (AI) will play a big role here because there's always been some question about what part of the tumor you're looking at and what you do with significant heterogeneity where 1 part of the tumor is strongly positive and another may be completely negative. IHC 2+ is weak to moderate complete membrane staining observed in more than 10% of cells and that's called equivocal. We learned from the very original studies with HER2-targeted therapy and that should reflex looking at gene amplification with in situ hybridization (ISH) where we look at both copy number for HER2 and the ratio with centromere 17, and if that's positive, the tumor is HER2+.

Very few IHC 1+ are HER2+ by gene amplification. It's vanishingly low and there you have incomplete membrane staining that you cannot see as well, but it's still more than 10%. That's called HER2- definitively. IHC 2+ without gene amplification is HER2- and then IHC 0 is that category that's a moving target at the moment because of these HER2-low and ultra-low studies with ADCs, but here you have no membrane staining that's really zero. But then you have the HER2 ultra-low group now where you have ≤10% with very little staining and how much you need, whether you need 1 cell in a thousand, less than 1%, does that really count, we don't know yet, and additional studies are looking at this. About 70% of patients with breast cancer will have HR+/HER2- disease. I also mentioned that this is quite heterogeneous. In older women, the tumors are more likely to be low grade with low proliferation, measured by Ki-67 and often quite endocrine sensitive with long durations of response to endocrine therapy now in combination with targeted agents. But there are subsets, both in older and younger women, that are high grade, more proliferative, less endocrine sensitive and develop rapid resistance and even subtypes where, under the pressure of treatment, the receptor is rapidly lost so that when you rebiopsy, ER is negative or low. And some, you have to not be fooled because although it is more common in older women to have these low-grade, low-proliferative tumors, you can see them in young women, and you can see the high-grade, more-proliferative tumors in older women. It's just more common to see that second subset in younger women.

When we think about the treatment for patients with HR+/HER2- disease, we are thinking first about targeting estrogen, and that can be done with selective estrogen receptor modulators (SERMs), like tamoxifen, and there are others that are being tested now. And then selective estrogen receptor degraders (SERDs) or down-regulators of which we've had fulvestrant, but now there are a number of agents that are SERDs that seem to work better than fulvestrant, in patients who have mutations in estrogen receptor 1 (*ESR1)* that affect binding and we have 1 approved drug and a second positive phase 3 trial. But then there's the AIs which really have changed the way we treat breast cancer that's HR+ in the first-line setting and also in early stage disease. AIs block the production of estrogen by blocking the aromatase enzyme, presumably in the cancer cell more than, as well as systemically. They just don't work in the ovary. If you want to use an AI and a patient is producing estrogen from their ovaries, then you have to suppress the ovaries. Otherwise, you end up with an escalation of the estrogen levels and the AI isn't doing anything because it doesn't block the receptor itself. That's why the combination is used in premenopausal women, regardless of stage. And then you can see this really remarkable pathway that has been associated with more endocrine resistance and more highly proliferative disease with *PI3* kinase, *AKT*, mTOR. There's also the MAP kinase pathway and then cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, which I think have been the most important advance over the last 10 years in the treatment of HR+ disease where CDK 4/6 inhibitors have shown improved outcome in the metastatic setting, as well as in high-risk early-stage disease by blocking this enzyme and proliferation, in concert with endocrine therapy.

One of the key factors now—and it's really changed so completely from having new endocrine agents, even though we have new endocrine agents coming out now—is understanding the genetics that drive resistance and really could be tools for allowing us to develop new agents and target those specific pathways for better outcomes for our patients. And a huge advance has also been how we detect these somatic, genomic alterations. These aren't germline genomic alterations or mutations, loss of genes. These are acquired in the tumor, and some of them may be acquired over time, which is also important. Tissue biopsies are the only way we now have for measuring ER, PR and HER2. That also helps us with additional markers through IHC that can tell us that the cancer is most likely from a breast origin or from another tumor, and that's one of the

reasons why biopsy is so important when patients are diagnosed with metastatic disease because occasionally a tumor will not be breast cancer. You definitely want to have that confirmation. But tissues can also allow NGS and that's how that started. And some mutations are only found in tissue, large deletions are hard to see in ctDNA by liquid biopsy now and that really could affect BRCA and *PTEN* primarily, the tumor suppressor gene.

The other thing we sometimes see, and this can be seen in very low proliferative bone, limited bone-only lobular cancers, for example, where I see it the most, sometimes ductal, where the ctDNA fraction in the blood, so the variant allele fraction is less than 1%, and you just can't find anything there, then tissue may help you. But often these patients have bone-only disease and it may be hard to do NGS in bone as well, due to the decalcification, so you might need to use an aspiration with special handling. Liquid biopsy has become the preferred way to look for acquired genomic alterations in tumor, even at first diagnosis of metastatic disease, because we get the results faster than scheduling a biopsy and getting the results back. But because there are mutations which are acquired under the pressure of treatment, most notably *ESR1*, that's why ctDNA is now the preferred way of looking for acquired mutations after initial diagnosis.

How do we detect these targetable mutations in HR+/HER2- metastatic disease? The most common pathway that's altered in HR+/HER2- breast cancer involves the *PIK3/AKT* pathway. This is a mutation which is conserved and clonal, so generally you have the mutation throughout the course of your breast cancer. It may be seen in early-stage disease. It's maybe a little more frequent in the metastatic setting because these tumors may have relative resistance to endocrine therapies in the metastatic setting, although there's data suggesting they respond even better to endocrine therapy in early-stage disease. And when we've looked at this over time, the data is not perfect, but there appears to be a small, less than 10%, acquisition of these pathway alterations over the course of metastatic disease. In contrast, *ESR1* mutations are very rare at initial diagnosis unless the patient is developing recurrent disease while on endocrine therapy, generally at less than 5%. And then increase up to 40% under the pressure of treatment and over the course of treatment, by the third line. A gradual increase in *ESR1* mutations over time.

Tissue biopsy is better than liquid biopsy for detection of *PTEN* loss, the tumor suppressor gene part of the *PIK3/AKT* pathway, and that's really because of the occasional large deletions that aren't picked up by ctDNA. Hopefully, that will improve over time as new techniques are being looked at to try and improve the detection of large deletions and circulating tumor DNA.

The most common alteration seen in HR+ breast cancer is in the *PIK3/AKT/PTEN* pathway. It's actually overall in breast cancer, but it occurs in up to 40% of patients with HR+ disease and you can see *PTEN* as the tumor suppressor gene that can be lost in about 5% of breast cancers. *AKT* mutations are less common than *PIK3*, occurring in 5%, maybe somewhat higher in some cases. Whereas *PIK3* mutations occur overall in somewhere between 30% to 40%.

Interestingly, although in the metastatic setting, alterations in this pathway have been associated with relatively shorter progression-free survival (PFS) to various endocrine therapies. The alterations in the pathway don't affect the benefit to CDK4/6 inhibitors. The hazard ratios are similar regardless of whether or not you have alterations in this pathway when CDK4/6 inhibitors are added to endocrine therapy. That's certainly encouraging for how we make our decisions in treatment of patients with these mutations who don't fit into the rapid relapsing category where we would now treat with a triplet of inavolisib, palbociclib, and fulvestrant.

There are less common mutations. Some of these mutations may not be activating and that generally comes out in your report where you get a little bit better idea of what the mutation means in terms of selection of treatment. Just a brief mention about mTOR. mTOR mutations are very uncommon and we haven't found a specific biomarker that predicts benefit from the mTOR inhibitor, everolimus, where it appeared that the benefit occurred across mutation categories, unless there were many mutations where generally patients have more endocrine-resistant disease.

I was just thinking about the initial guidelines we made with the American Society of Clinical Oncology (ASCO), that I worked on with Hal Burstein, to look at what kind of mutations you should be looking for with NGS when it was quite new. And although we knew that *ESR1* mutations could predict relative resistance to AI, there was really no value in doing this because it occurred under the pressure of treatment, on an AI, and you only had fulvestrant to give with or without a targeted agent. But now, we have the oral SERDs, as I mentioned earlier, that have really changed our treatment decisions. And there are many oral SERDs and on the pathway we're going to see a flourishing number of options in this setting. So, the prevalence, of course, as I mentioned earlier, depends on the time of testing and about 40% of patients who've been exposed to an AI will eventually have an *ESR1* mutation or several, but this increases over time. You have a big jump from first- to second-line treatment. When somebody is developing progressive disease on first-line treatment with an AI and CDK4/6 inhibitor, we always will do ctDNA to look for an *ESR1* mutation because it would impact, potentially, our decision about an endocrine agent. And then, after the second-line setting, again you see an increase in the percentage of patients who have *ESR1* mutations. Interestingly, on effective therapy, the mutations will go away in testing as well. These mutations affect binding and the mutant ER won't bind and so you can't use drugs that are reducing estrogen because the receptor is constitutively activated and doesn't need estrogen anymore to stimulate proliferation.

The other interesting thing about *ESR1* mutations is that this has been that it only affects your response to the type of endocrine therapy. When you're thinking about doing NGS, you already know if you've had an alteration in the *PIK3* pathway. You're testing for *ESR1* because you're thinking about hormone therapy. But once you're no

longer thinking about hormone therapy, this doesn't impact your decisions.

How have we been using ctDNA to look for acquired *ESR1* mutations? Remember, these are acquired under the pressure of treatment. The EMERALD trial was the first trial that really changed our thinking about whether we should be testing for *ESR1* mutations. The oral SERD, elacestrant, was tested vs standard of care in patients who'd had 1, 2, or even 3 lines of endocrine therapy in the metastatic setting and also a small percentage of patients that received chemotherapy. You could receive fulvestrant or an AI, but if you progressed on one of those agents, you couldn't receive them. The majority of patients received fulvestrant. The *ESR1* mutation rate was about 48% and there was a marked improvement in PFS in patients who received elacestrant vs. standard of care that was seen more, notably in patients who'd been on endocrine therapy and a CDK4/6 inhibitor for at least a year. This trial required everybody to receive a CDK4/6 inhibitor, which is not true of any of the other trials, although the rate is increasing continuously as it becomes more of a standard of care internationally and available to patients. You see that very short PFS, 2.8 months, and about almost 40% of patients had progressed on their first scan because they were more heavily pretreated and had endocrine-resistant disease. If you use the surrogate marker of duration of prior endocrine therapy and CDK4/6 inhibitor or endocrine sensitivity, patients who were on for at least a year had a really dramatic improvement in PFS with elacestrant vs standard of care endocrine therapy, even when it was just fulvestrant.

The PADA-1 trial is a fascinating study. This trial actually looked at whether or not changing treatment based on emergence of the *ESR1* mutations while a patient is on first-line therapy, without evidence of radiographic progression, could change PFS and overall outcome. Patients were on an AI and palbociclib as their first-line treatment and then they tested *ESR1* mutations every 2 months. Patients who had rising *ESR1* mutation with no radiographic progression were then randomized to continue their current therapy or switch the AI to fulvestrant and they continued the palbociclib. There also could be a second switch over. If you were on the arm that continued on AI and palbociclib, you could switch to fulvestrant and palbociclib on progression. Their *ESR1* mutation rate at baseline was very low, 2%, as you would expect. And over time, there was an increase in percentage of patients who had *ESR1* mutations, it was still small. They saw a significant improvement in PFS if you switched vs staying on the same endocrine therapy, which was expected, because if you switch early, you're going to have a longer PFS. But then they saw an improvement in PFS2 which I think was the most compelling results from PADA-1, although they couldn't control subsequent therapy, and this is going to be an issue for all of these trials based on where the patients are enrolled since there's enormous disparity around the world in terms of access to next-line therapy. There are no overall survival (OS) results.

It stimulated SERENA-6 and this is the press release from SERENA-6. This is a trial that really had the same approach as PADA-1 except that the switch was not to fulvestrant. It was to the oral SERD, camizestrant, and we know these oral SERDs, at least elacestrant and with recently presented data and published data with imlunestrant, are superior to fulvestrant in patients with *ESR1* mutations. In a patient population who has a developing *ESR1* mutation on an AI and CDK4/6 inhibitors, patients were randomized to camizestrant vs continued AI. The PFS, based on the press release, was significantly improved, as expected with switching to camizestrant. There were no new safety concerns, and these results will be presented at an upcoming meeting. But I think that it's going to be interesting to see how this is interpreted. This was the primary endpoint, but I think that PFS2 is going to be very important in understanding what treatment options patients had. Sara, what was your take on SERENA-6 and the press release?

SARA HURVITZ, MD: I think it's really exciting that we may actually have another agent available to us that's an oral SERD and I'd like to see the data, and to see it in combination with a CDK4/6 inhibitor which is what I think we've all been waiting for. The use of single-agent SERDs doesn't lead to much in the way of a very long PFS, so I think we've all been really eager to see it in combination.

HOPE RUGO, MD: We want to look at tissue for ER/PR and HER2 and then follow ctDNA as long as it's going to influence your treatment decisions. It's important that patients have comprehensive germline testing at some point if it's going to affect your treatment course or screening for the family as well in the metastatic setting. Actionable biomarkers include activating mutations in *PIK3CA* as well as mutations within the *PIK3* pathway and *ESR1* mutations. We now have agents that target the alpha subunit of *PIK3CA*, which is particularly important in efficacy as well as the *AKT* inhibitor that can impact patients whose tumors have abnormalities throughout the *PIK3* pathway.

The key concepts really have to do with evaluating the latest evidence and clinical implications of biomarkers. We talked about biomarker testing recommendations where you might do tissue testing up-front, but then you would follow patients with ctDNA using liquid biopsies that will help guide therapy and understand endocrine resistance. And we're moving more and more towards personalized treatments tailored to individual patient profiles and biomarker results to enhance both patient outcome as well as managing their quality of life.

NAVIGATING THROUGH THE CURRENT TREATMENT OF PATIENTS WITH HR+/HER2- MBC

SARA HURVITZ, MD: When we are considering a patient who has mBC, it's important for us to look at several features to help us determine the best therapy. We look at a patient's signs and symptoms, how symptomatic are they, what are their laboratory results tell us about their liver and kidney function, how fast their disease is growing, what is their menopausal status and what prior therapy did they receive and how much benefit did they derive from the prior therapy received in the adjuvant setting or metastatic setting. It's also critical for us to talk to our patients about their goals

of therapy, what side effects they're willing to manage and deal with, whether or not they're willing to come into the infusion room or would prefer to try oral medications and then, finally, looking at the disease biology, not only the HR and HER2 status, but now we have to consider genomic features of the tumor, including things like *PIK3CA* mutations, *AKT* mutations, *ESR1* mutations, germline BRCA mutation status, and less common mutations that may be clinically impactful, including ERBB2 or HER2 mutations in the tumor.

For women who have functioning ovaries and have been diagnosed with HR+ mBC, one of the ways that we can address the disease is by maximally suppressing ovarian production of estrogen. In the past, the best way to do this was by removing the ovaries, although we now have new agents that can help us achieve that endpoint without actually removing the ovaries or radiating the ovaries. Luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin or leuprolide, may be used as an injection to turn off the ovaries. It is important to note that many of our clinical trials that have guided the way that we prescribe standard of care therapy have not enrolled younger, premenopausal women, so the level of evidence available for managing patients who are younger is lower than it is for postmenopausal patients. The National Comprehensive Cancer Network (NCCN) guidelines recommend that we treat patients who are younger as though they are postmenopausal but utilize ovarian suppression as a form of therapy to render them postmenopausal.

A number of treatment options are available for our patients now with HR+/HER2- breast cancer. AIs, including anastrozole, letrozole, and exemestane, function by lowering estrogen production in somebody who is not producing estrogen with their ovaries. SERDs, including fulvestrant, which is an IM-delivered injection, or elacestrant, which is the first approved oral SERD, are now available with many that are under evaluation and may be available in the coming months and years. SERMs, including tamoxifen, are estrogen receptor blockers that do have estrogen receptor agonist activity in some tissues as well. CDK4/6 inhibitors, including abemaciclib, palbociclib, and ribociclib, are now available. *PIK3* inhibitors, including alpelisib and inavolisib, *AKT* inhibitors, such as capivasertib, and an mTOR inhibitor, everolimus, are all available for our patients with HR+ mBC. Deciding among these agents requires a sophisticated and somewhat nuanced approach to understanding the literature and the clinical trials that have been done evaluating each of these agents for metastatic disease.

Currently, the standard first-line therapy that we recommend utilizing for patients with HR+/HER2- mBC is a CDK4/6 inhibitor plus endocrine therapy. Recently, we saw the approval of inavolisib combined with a CDK4/6 inhibitor, palbociclib, plus fulvestrant, a SERD, for patients who experienced disease recurrence on or within 12 months of completing adjuvant AI therapy.

Subsequent lines of therapy include a CDK4/6 inhibitor combined with fulvestrant, primarily for patients who haven't received a CDK4/6 inhibitor previously, although we do have some evidence now that use of abemaciclib in this setting combined with fulvestrant after a patient has experienced disease progression on palbociclib may be of benefit. Everolimus with endocrine therapy is indicated for patients who do not have a *PIK3* pathway mutation and then we have targeted therapies available that include *PIK3* inhibitors, *AKT* inhibitors for patients who have mutation in that pathway. We have an oral SERD now available for patients who have an *ESR1* mutation, as well as other endocrine monotherapy available for our patients.

Hope, in the first-line setting we now have the use of inavolisib as an approved therapy. Can you just briefly touch on which patients you would consider for the use of this triplet regimen in the front-line setting?

HOPE RUGO, MD: I'm hoping that we'll see more data on this that expands the patient population who might benefit, but at the moment, the INAVO 120 trial really looked at a relatively narrow population of patients who either relapsed while on or within 1 year of their adjuvant AI treatment. In addition, a very small number, less than 5%, had received an adjuvant CDK4/6 inhibitor. I think it's going to be very interesting as we look forward to seeing which patients might qualify. These patients also need to have a *PIK3* mutation, and the triplet with palbociclib is the only triplet that has big data.

SARA HURVITZ, MD: I fully agree with you, and I think this is a very exciting time, given the number of agents we have available for this particular disease category of breast cancer. Our goal is, of course, to optimize patient outcomes and improve their quality of life.

THERAPEUTIC APPROACHES FOR THE TREATMENT OF PATIENTS WITH HER+/HER2- MBC

SARA HURVITZ, MD: For HR+/HER2- advanced breast cancer, current standard of care is to use CDK4/6 inhibitor plus endocrine therapy for the vast majority of patients. Although some patients may not be able to tolerate a CDK4/6 inhibitor for other reasons, for example comorbidities, for the vast majority of patients, even those with symptomatic visceral metastases, a CDK4/6 inhibitor and endocrine therapy should be considered as the standard of care.

A number of clinical trials have been conducted that are large, phase 3, randomized studies evaluating the benefits of adding a CDK4/6 inhibitor to endocrine therapy in the front-line setting in combination with an AI. PALOMA-2 was the first study to report out, looking at palbociclib with letrozole vs placebo/letrozole. And this study showed a highly statistically significant improvement in PFS by using palbociclib in combination with endocrine therapy. Several other studies, including MONARCH-3 evaluating the use of abemaciclib, and MONALEESA-2 and MONALEESA-7, evaluating the use of ribociclib, have indicated similar improvements in PFS, all with strikingly similar hazard ratios of around 0.5. It is interesting to note that only 2 of the clinical trials mentioned showed a statistically significant improvement in OS by adding a CDK4/6 inhibitor to endocrine therapy, and those 2 studies were MONALEESA-2 and MONALEESA-7 which were evaluating ribociclib combinations. That

said, the MONARCH-3 study did show a very interesting 13-month, nonstatistically significant improvement in OS and with palbociclib, a trend toward improvement in OS by adding palbociclib to endocrine therapy.

Hope, how do you approach the choice of CDK4/6 inhibitor in the front-line setting with studies like these showing such a compelling improvement in terms of PFS but slightly different side effect profiles among the 3 agents and OS benefits that aren't similar across the various clinical trials?

HOPE RUGO, MD: It was so surprising to see all this data, particularly because we know that PFS on subsequent agents isn't significantly impacted by the use of a CDK4/6 inhibitor in the first-line setting. There's a lot of heterogeneity across randomized, phase 3 trials. They were done at different times. Some heterogeneity in markers you didn't even know you were supposed to check, could impact OS. We've done a lot of studies looking at real-world data with palbociclib and we just recently published a paper in the European Society for Medical Oncology's *ESMO Open* looking at real-world survival data from the Flatiron database. Now, it does suffer a little bit from the fact that most of the patients received palbociclib, but we did sensitivity analyses looking at starting at 2017 when ribociclib and then abemaciclib were approved. And we saw that the OS was similar between all of the arms. I think that we're generally really compelled by phase 3 data, so I think that most people are using ribociclib up-front to avoid the diarrhea of abemaciclib. The lack of survival benefit in MONARCH-3 is probably numeric and who knows why PALOMA-2, they had a big dropout of patients over time. And then we use side effect profile because there are toxicities of note, of ribociclib and abemaciclib that don't occur with palbociclib. We often will give it to patients who are older and have other comorbidities, because it's easier to manage.

SARA HURVITZ, MD: I think you're highlighting the importance of shared decision-making and taking into account the whole patient as we make these decisions. It's not just about 1 data point from these clinical trials.

The majority of the data are in the second-line setting, after a patient experienced disease progression on endocrine therapy, although the MONALEESA-3 study did have a cohort of patients who were treated in the first-line setting. These data, which evaluated palbociclib, abemaciclib, or ribociclib, in combination with fulvestrant, again showed a similar striking improvement in PFS that was statistically significant for all of these agents, again somewhere around 0.5 or so.

OS was also statistically significantly improved with abemaciclib in the MONARCH-2 and ribociclib in the MONALEESA-3 clinical trials, but similar to the PALOMA-3 study did not end up showing statistically significant differences in OS. Again, the reason that OS wasn't met in this trial is not entirely clear. It could be the level of pretreatment that patients on PALOMA-3 had, the under-powering of the trial, or it could be that palbociclib is not as potent an agent as the other 2 and does not yield that long-term benefit. This is still a matter of some debate.

Once a patient has experienced disease progression on a CDK4/6 inhibitor, we utilize genomic testing on the tumor to help us understand the best treatment options available for the patients. For those patients whose tumor has a *PIK3CA* mutation, we have available alpelisib or inavolisib. For those with an *AKT* mutation or *PIK3* pathway mutation, we have capivasertib. Patients who have a tumor *ESR1* mutation are eligible to receive elacestrant and those who do not have any *PIK3* pathway mutation, we can use endocrine therapy with everolimus. We can also consider switching CDK4/6 inhibitors, for example palbociclib to abemaciclib, based on the post MONARCH study and utilizing fulvestrant. We are using ctDNA analyses to evaluate for tumor mutations like these, but if ctDNA is negative, one may consider reflex testing tumor tissue.

The SOLAR-1 study was the first clinical trial to evaluate a *PIK3* inhibitor and show statistically significant improvements in those patients with a *PIK3CA* mutation who received alpelisib in combination with fulvestrant. In this study, which was a double-blind, phase 3 clinical trial, alpelisib was given at 300 mg daily with standard fulvestrant injections. The study did show over a 5-month improvement in median PFS by using alpelisib in patients whose tumors had a *PIK3CA* mutation. There was no benefit for alpelisib in the cohort of patients without a *PIK3CA* mutation, which is why this drug is only approved for patients with tumor *PIK3CA* mutations. The overall response rate was also improved with alpelisib, and given the *PIK3* pathway's importance in glucose metabolism, an on-target side effect of hyperglycemia was seen in about a third of patients. Patients also experienced rash on this clinical trial which can be mitigated by using an oral non-sedating antihistamine from day one of treatment. And diarrhea was also seen in patients treated with alpelisib.

The INAVO 120 study was a uniquely designed trial to look at a triplet combination of a CDK4/6 inhibitor, palbociclib, in combination with fulvestrant, a SERD, plus a *PIK3* pathway inhibitor, inavolisib, in patients whose tumors had a *PIK3CA* mutation and in patients who had experienced a disease recurrence during or within 12 months of adjuvant endocrine therapy completion. It's important to note that in order to be eligible, patients who were enrolled had to have fasting plasma glucose less than 126 mg/dL and a glycated hemoglobin (A1c) less than 6%. This entry criteria is important to note as we begin to use this triplet regimen in the clinical setting because *PIK3* pathway inhibitors can lead to significant hyperglycemia. In this study, inavolisib was given at 9 mg daily with standard dosing for palbociclib and fulvestrant. And the median PFS was more than 7 months improved in the inavolisib arm with a hazard ratio of 0.43. At the original reporting, the OS was not statistically significantly improved, although there was a strong trend. There was a press release in January 2025 that OS was also met. The FDA approved inavolisib in October 2024 for patients with endocrine-resistant, *PIK3CA* mutated, HR+/HER2- mBC after adjuvant endocrine therapy. I would just highlight the importance of

checking your patients' glucose parameters prior to deciding to use this regimen.

The CAPItello-291 trial is the study that led to the FDA approval of capivasertib in patients who have a *PIK3* pathway mutation. In this study, the *AKT* inhibitor, capivasertib, was given at 400 mg twice daily for 4 days in a row, followed by 3 days off, plus standard of care fulvestrant. In this study, which was a double-blind, phase 3 clinical trial, patients who received capivasertib had about a 4-month improvement in their median PFS if they had an *AKT* pathway alteration with a hazard ratio of 0.5. The overall population also had a significantly improved PFS, but the FDA approval of capivasertib in November 2023 was restricted to patients who have a *PIK3*, *AKT* pathway alteration. This can include a *PIK3CA* mutation, *AKT* mutation, or loss of *PTEN.* Diarrhea is a common side effect experienced with these agents, as well as rash, nausea, fatigue, stomatitis, and hyperglycemia. The grade 3 or greater hyperglycemia incidence for alpelisib was quite high, but again we were on the early part of the learning curve and how to manage hyperglycemia when alpelisib was approved. Capivasertib and inavolisib have lower rates of hyperglycemia, but we are using tactics, such as keto diets, at the run-in, and careful patient selection when using these agents and that may account for the lower rates of glucose alterations.

Fulvestrant is the original SERD available to our patients and it has been shown to be more effective in patients who have an *ESR1* mutation than AI. There were 2 phase 3, randomized trials evaluating fulvestrant vs exemestane in patients who had baseline *ESR1* mutated breast cancer. In these studies, *ESR1* mutations were detected in 30% of the samples. When the PFS is compared between the endocrine therapies, patients who had an *ESR1* mutation did better with fulvestrant than with exemestane, but those with wild type *ESR1* seemed to do similarly with the 2 agents.

The EMERALD clinical trial was the first study to lead to an FDA approval of an oral SERD. In this study, 477 postmenopausal women and men who were on second or later line therapy for their HR+/HER2- mBC were enrolled and they were stratified based on tumor *ESR1* mutation status. Patients were randomly assigned to elacestrant or standard of care, which could include fulvestrant or an AI, based on physician's choice. In the intent-to-treat population, the PFS was improved with elacestrant, but improvement seemed to be most significant for patients whose tumors had an *ESR1* mutation. The FDA ultimately did approve elacestrant as a single agent in January 2023 for patients who have *ESR1* mutated ER+ breast cancer after disease progression on at least one endocrine therapy.

As we've gone over, we have a dizzying array of therapies available to our patients who have HR+/HER2- mBC. While we would all agree that the first-line therapy should be a CDK4/6 inhibitor plus endocrine therapy, once a patient experiences progression of disease, deciding among these agents is based on patient comorbidities, as well as patients' goals of care and looking at features of the tumor behavior, including how long their disease benefitted from first-line therapy with a CDK4/6 inhibitor using 12 months as a cut-off and then looking at tumor mutation status to help guide what therapeutic options are optimal for our patients.

Patients who have benefit from a CDK4/6 inhibitor lasting 12 months or greater might be considered for single-agent endocrine therapy with elacestrant if their tumor has an *ESR1* mutation. One could also consider a PARP inhibitor if they're found to have a BRCA mutation. Looking at other factors, such as *PIK3* pathway mutation status, will help us guide therapy among agents, including alpelisib, capivasertib and, in the front-line setting of endocrine resistant disease, inavolisib. Everolimus is also available to our patients with or without PI3K pathway mutations.

For patients who have HR+ mBC who are premenopausal, ovarian suppression should be added to whatever hormonally directed therapy we are giving them. In patients whose tumors display endocrine resistance based on relapsing within 12 months or while on adjuvant endocrine therapy, we have the availability of inavolisib combined with palbociclib and fulvestrant if their tumor has a *PIK3CA* mutation. And then, at the time of disease progression, one can consider a variety of options based on the pace of the tumor's progression, as well as genomic factors, such as *ESR1* mutation, HER2 mutation, and other rarer mutations. For patients who experience disease progression while on or within 12 months of adjuvant endocrine therapy, if they have a *PIK3CA* wild type tumor, we can look at factors such as disease pace, as well as comorbidities and patient goals of care, but for the most part, I would select fulvestrant with a CDK4/6 inhibitor and then base subsequent therapy options on disease pace and tumor genomic status.

At this time, we have a variety of evidence-based guidelines available to us to select among the various agents that we have available for HR+ mBC. We try to exhaust all endocrine-based options for patients before switching to chemotherapy or ADCs. In all, it is very important for us to keep an eye on patient goals of care and to implement shared decision-making as we choose among the variety of agents we have available for these patients.

Hope, we have so many options available to our patients today, but we also have a variety of ongoing clinical trials looking at novel combinations and new agents. What are you most excited about in the near future for our patients?

HOPE RUGO, MD: You know, the near future is always a challenge. But I think in the HR+/HER2- mBC space, I think being able to more carefully personalize therapy for our patients and use combinations, when appropriate. It's not clear that the triplet with *PIK3* inhibitor will be better in patients who have longer time to relapse and more endocrine sensitive disease because when you add drugs, you add toxicity. On the other hand, identifying the patients who are going to be better targeted would be very helpful. We have a whole host of new drugs that are targeting the *PIK3* pathway, some that appear in early phase trials to have less toxicity, although I have to say that for all of these drugs in post-marketing, hyperglycemia is an issue and diabetic ketoacidosis. We really have to manage our patients carefully, but I think we're already making big advances. The oral

SERDs, I think, are changing the whole course of management. There are trials moving the oral SERDs into the first-line setting. I'm not sure that that's going to be the best approach, but it will be

interesting to see because there won't be any *ESR1* mutation yet. And there is some GI toxicity with a little nausea with those drugs.

We'll see what happens with those trials, but the concept of changing based on emerging mutations is fascinating. And if we can really see that that's something we should be incorporating into practice, then moving that into the early-stage setting, which I think is the most exciting thing in patients with minimal residual disease, maybe someday we could prevent recurrence in patients who are at very high risk based on ctDNA.

SARA HURVITZ, MD: I fully agree with you. It's going to be a very interesting future for our patients and many more options for us to grapple with. And once we begin implementing these novel agents in the earlier line setting, that's going to have clear implications on the later line disease setting and what our options are.