Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/better-early-than-late-cdk46-inhibition-in-hr-her2-early-breast-cancer/15094/

Released: 04/19/2023
Valid until: 06/28/2024
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Better Early Than Late: CDK4/6 Inhibition in HR+, HER2- Early Breast Cancer

Announcer:
Welcome to CME on ReachMD. This activity, titled **"Better Early Than Late: CDK4/6 Inhibition in HR-positive, HER2-negative Early Breast Cancer"** is provided by **AGILE**.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

[CHAPTER 1]

Dr. Rugo:
Hormone receptor [HR]-positive, HER2-negative breast cancer accounts for approximately 70% of early breast cancer. The CDK4/6 inhibitor abemaciclib has been approved in the United States and internationally for the treatment of these patients. Do you know how to evaluate the use of CDK4/6 inhibitors and effectively use them in your practice?

This is CME on ReachMD, and I'm Dr. Hope Rugo. Here with me today is Dr. Peter Schmid.

Dr. Schmid:
Hello, everyone. It's a pleasure being here with you today.

Dr. Rugo:
Let's get started. Dr. Schmid, to set the stage for this chapterized course, can you discuss the importance of risk stratification and assessment of risk of recurrence in HR-positive, HER2-negative early breast cancer?

Dr. Schmid:
Yes, it's a really important point for our treatment decisions. I always say to patients we look at essentially 2 main things. One is stage, and stage means the size of the cancer in the breast and where it has got to, and that includes, of course, the involvement of axillary lymph nodes. And the second factor we look at is what I always describe as the biology or the behavior of the cancer, and that's defined by a number of points. There is obviously the receptor status – not just the estrogen receptor, but also the progesterone receptor – that's tumor grade; that's whether we have evidence of lymphovascular invasion. Really important point is what we often describe as Ki-67, and that's a marker that tells us how proliferative the cancer is, is it a fast-growing cancer or not, and is also linked with whether it's a luminal A or luminal B type cancer. And finally and increasingly over recent years, we've also incorporated gene expression profiles, which is a novel and an independent way of assessing the behavior or biology of cancers. But it comes down to those 2 points being put together, the stage and the biology of the cancer.

Dr. Rugo:
That's so interesting, and I think that these factors are really important, of understanding biology, and I think they help us understand which patients should get hormone therapy alone, chemotherapy and hormone therapy, and now also discussing which patient should receive the CDK4/6 inhibitor abemaciclib. So do you find that getting Ki-67 is important in making those decisions?

Dr. Schmid:

I think Ki-67 is one of the important markers, and I think we've all known for many years, if you have a cancer that has a very low rate of proliferation, we are less anxious about the aggressiveness of the cancer compared to in a hormone receptor-positive cancer with a proliferation index Ki-67 of 40% or 50%. Now in terms of a use of abemaciclib there's obviously an additional criterion assigned to Ki-67 that was extra cohort in the large registrational study. That cohort showed, consistent with other risk cohorts, that patients benefit from the treatment with CDK4/6 inhibitors and abemaciclib in the adjuvant setting. But it is a distinct and is a different and an extra marker, which therefore has to be part of our routine assessment, in my opinion, because it defines an extra group of patients that are otherwise not offered endocrine therapy with CDK4/6 inhibitors in this setting.

Dr. Rugo:
That's a really good point. And do you use gene expression profiles to decide about chemotherapy use and abemaciclib use in patients with early-stage HR-positive, HER2-negative breast cancer?

Dr. Schmid:
It's a brilliant question. Obviously the genomic expression profiles are routine care in most countries as well, including the UK, for deciding whether a patient may be offered adjuvant chemotherapy or not, and as in keeping with the data in other countries as well, we probably spare about a third of patients from having chemotherapy based on a favorable genomic profile.

What we don't do at the moment, because we haven't got the data from the, for example, monarchE study, is use, for example, a higher risk genomic assay in a patient who would otherwise not meet the criteria as per the registrational study for abemaciclib. But it is very tempting, isn't it? If a patient has a Ki-67 of 18% and has 2 lymph nodes as a tumor of 3.5 cm, it's grade 2, but you have a high-risk genomic assay. I think we all would agree that it's very tempting to extrapolate the data because the behavior is very likely the same as for patients who were treated in monarchE trial. But I think the rules and regulations in different countries may not allow us to do this. Biologically, I would say that clearly could make sense.

Dr. Rugo:
Yeah, that's a really good point, and I think it is quite tempting at the moment, because we know those patients have higher risk. And I think it brings up a really important point as well, which is that the Ki-67 that we get from our pathologists and the genomic assays may not always be concordant.

So we do see heterogeneity. You know, sometimes a tumor that has a high Ki-67 has a low score, or the reverse, so it can be quite complicated to decide. I don't know that we use lymphovascular invasion as a final decision point for treatment options. I think that this has been really interesting, talking to you about this area, and I think it gives us a nice background to go on and talk about the use of CDK4/6 inhibitors with endocrine therapy in HR-positive, HER2-negative breast cancer.

That will be Chapter 2. Please stay tuned.

[CHAPTER 2]

Dr. Rugo:
Welcome back. We were just talking about risk stratification in HR-positive, HER2-negative early breast cancer. We're now turning to the use of CDK4/6 inhibitors in these patients.

Dr. Schmid, can you start us off by discussion the PENELOPE-B and PALLAS trials in HR-positive, HER2-negative early breast cancer?

Dr. Schmid:
Thank you very much. These are 2 important phase 3 trials where we've had the primary endpoint data. The PENELOPE-B trial – both trials used the CDK4/6 inhibitor palbociclib in an adjuvant setting in patients who had otherwise completed their chemotherapy and their local therapy for hormone receptor-positive, HER2-negative or HER2-low breast cancer. There's subtle differences between the trials. PENELOPE-B trial used a concept that's actually very effective in HER2-positive disease and in triple-negative disease by offering treatment to those patients who had neoadjuvant preoperative chemotherapy, haven't had an optimal response, had residual cancer, and therefore classified as higher-risk patients. Patients in the PENELOPE-B trial were then offered treatment with the CDK4/6 inhibitor palbociclib, which is given 3 weeks on, 1 week off, together with endocrine therapy. PALLAS trial used a slightly different strategy and, again, is patients with certain risk factors who had completed their early disease management – local management as well as chemotherapy, and then offered them endocrine therapy with or without palbociclib for over 2 years.

Now the results for both trials, unfortunately, were disappointing. There was no benefit from adding palbociclib in either of those trials to standard endocrine therapy in terms of reducing the risk of recurrences.

Dr. Rugo:
Thanks very much. That was a great overview of these 2 trials and indeed disappointing. It's fascinating to me, because monarchE, that I'll talk about now, really worked hard on trying to enroll patients who had a high risk of early recurrence. So we think about hormone receptor-positive disease as being a cancer with a very long natural history, with recurrences out to 20+ years, and about 50% of the recurrences occurring after 5 years. But we know there's a lot of heterogeneity, as we discussed in Chapter 1, and monarchE was designed to really capture those patients who had their highest risk in the first 5 years, based on data from other trials, including data from the cooperative group HICAM.

So patients were enrolled – 5,637 patients – who had specific risk features. Almost all of the patients, 91%, were in Cohort 1 – 4 or more positive axillary nodes, or 1-3 positive nodes and at least grade 3 disease or a tumor size of 5 cm or greater. And because, you know, we've had this longstanding interest in Ki-67, there was a second cohort representing 9% of the population that had 1-3 positive nodes, none of the other factors. So grade 1-2 and tumor size less than 5 cm, but essentially confirmed Ki-67 of 20% or greater. And these patients took standard endocrine therapy for 5 years and were randomized to get abemaciclib for 2 years, 150 mg twice daily with their endocrine therapy or endocrine therapy alone. And I think we learned from the metastatic setting that we can't blind patients, since the side effects from these agents are so clear.

So the most recent follow-up for this study is quite striking. The median follow-up was 42 months, and there's a 4-year landmark analyses, and compared to the first 2 presentations that led to the first approval of abemaciclib in this setting, all of the patients are now off of abemaciclib, which I think is really important. And what's really striking about this new data is that in the overall patient population, not only is there an improvement in invasive disease-free survival [IDFS] and distant recurrence-free survival, but the difference appears to be widening over time. So if you think about the fact that, you know, you have 2 more years in this landmark analysis, so everybody's off abemaciclib. If you compare the difference – so 2.8% at 2 years, 4.8% at 3 years, now 6.4% for IDFS at 4 years – and the same is true for the most important endpoint, I think for oncologists, which is distant recurrence-free survival, where the difference is now 5.9% compared to 2.5 and 4.1% at 2 and 3 years. So really remarkable.

And in the prespecified subgroups there were really no difference in terms of the benefit from abemaciclib when you looked at patients across tumor grade, tumor size. Importantly pre- and postmenopausal women and older and younger women seem to benefit as much. And even if you looked at the earlier stage versus later stage, there were a reasonable number of patients who were of Asian descent, and those patients benefited as well as the Caucasian patients – an important thing because toxicity might differ between different ethnic and racial subgroups. And similarly, the hazard ratio was improving as you went from the first 2 years – year 2-3 – and year 3+ which was evaluated now. Of course, there's interest in overall survival in this trial, but it's still quite immature, and that's the natural history, thankfully, of hormone receptor-positive disease, where even when you develop metastatic disease, we have a lot now, increasing number of treatments to offer, that improve survival. But in an interesting analysis, in the last update of monarchE at San Antonio in 2022, there were fewer patients with metastatic disease in the abemaciclib arm. So really interesting – just the patients who were alive, living with metastatic disease – remarkably less patients, you know 100 patients less in the patients who received abemaciclib. So really interesting.

There was a big issue with the FDA about the initial approval. So the US FDA approved abemaciclib only in patients who had a Ki-67 of 20% or greater, something that none of the consensus guideline groups agreed with, because it seemed like the benefit was across the whole trial. And Cohort 1, 91% of the patients were not eligible because of Ki-67 but because of tumor characteristics.

So what was shown at the most recent update is really important. Ki-67 is clearly prognostic. This is the best data we've had ever, in the current day, that Ki-67 is prognostic. But it's not predictive of abemaciclib benefit. There was benefit in patients who had a low Ki-67 or a high Ki-67, almost equally, which is really important, and it shows us that that's not the right sole criteria for selecting patients. So based on this updated information, the US FDA actually changed the indication for abemaciclib by expanding it, so it's now approved in combination with tamoxifen or an aromatase inhibitor for adjuvant treatment of patients with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk for recurrence, given for 2 years. High risk defined per protocol, and they removed the requirement for a Ki-67 of 20% or greater. This new expansion now aligns with the ASCO guidelines, the ESMO guidelines, and everybody's recommendations – NCCN guidelines, which use the protocol. I will say the FDA didn't make it clear that if you didn't meet the tumor characteristics but have a Ki-67 of 20% or greater – so 1-3 positive nodes and a Ki-67 of 20% or greater – you are still eligible to get abemaciclib.

I think the last thing, really, to just cover is the safety. There were no additional safety events in patients who are off abemaciclib, which is really encouraging. It's important to keep in mind there's an increase in venous thromboembolism if you combine abemaciclib with tamoxifen, so caution should be exercised, and that the increase with aromatase inhibitors is much smaller. Diarrhea is the most common toxicity. It occurs early and decreases over time as patients are dose-reduced and learn how to manage it. And there's a slight

increase in transaminases. But that is usually easily controlled and wasn't a reason for discontinuing this therapy. So really very nice data to see, exciting to see this difference as well.

Dr. Schmid, do you have anything to add to that?

Dr. Schmid:
I think there's very little to add to this comprehensive overview. I think we – well, what I found particularly interesting and impressive is the fact that the absolute benefit seems to be increasing over time. The third point you mentioned around safety – again, with the real-world experience and all of us using this combination now increasingly in clinical practice, it is clear that despite the distinct safety profile, actually patients do cope relatively well with this treatment, and many of the side effects may, in fact, get better over time. For example, look at the gastrointestinal side effects you mentioned. We see often that after a period, our patients adjust in terms of lifestyle, in terms of co-medications. We often see an improvement, and after 3, 6, 12 months, in our experience, the incidence of gastrointestinal side effect goes down substantially.

Dr. Rugo:
Yeah, it is really exciting, this data.

Could you briefly describe to us the one ongoing trial that we're waiting for results from, the NATALEE trial?

Dr. Schmid:
The trial focuses predominantly on stage 2 patients with additional risk factors, again, in terms of grading or stage 3 patients. It's, again, a roughly 4,000-patient trial. We have to wait for the results quite a bit longer.

Dr. Rugo:
Yeah, I think that's really interesting, and the major difference between NATALEE and the other 3 trials is that ribociclib is being given for 3 years. I think the important takeaway from that is that if we see a benefit early on, which we expect – we'll see what happens. We're going to have to follow these patients for a very long time to see if there's any differences in outcome based on duration of CDK4/6 inhibitor therapy. It is really exciting to have this additional option for therapy in our patients with high-risk, early-stage HR-positive, HER2-negative breast cancer and to have it widely approved in multiple countries.

In Chapter 3, we'll be discussing the selection of adjuvant therapy in HR-positive, HER2-negative early breast cancer. Stay tuned.

[CHAPTER 3]

Dr. Rugo:
Welcome back. We just covered the use of CDK4/6 inhibitors in HR-positive, HER2-negative early breast cancer. Now we're going to discuss how to select adjuvant therapy in these patients. I'll get us started by quickly reviewing some of the clinical guidelines.

We have a number of different international organizations that provide guidelines, which are very helpful – essentially pathways for choice of therapy for patients with both early- and late-stage breast cancer. ASCO [American Society of Clinical Oncology], the NCCN [National Comprehensive Cancer Network], and ESMO [European Society for Medical Oncology] provide guidelines for HR-positive, HER2-negative early breast cancer related to CDK4/6 inhibitors. ASCO, NCCN, and ESMO essentially agree that using the criteria for eligibility for the monarchE phase 3 trial, as we reviewed in Chapter 2, are the best criteria to select eligibility. So essentially, we're using the patient's node status, tumor size, grade, and Ki-67 all together, to really decide which patients are the best candidates for abemaciclib in combination with endocrine therapy. These guidelines also note the increase in risk of venous thromboembolism when abemaciclib is combined with tamoxifen, and we can talk about that a little bit more when we review our case, but it's certainly something to be aware of, if you're going to combine abemaciclib with tamoxifen.

But I think this does give us a clear path for selecting the patients who are the best candidates for abemaciclib – patients who have 1-3 positive nodes, a tumor size greater than 5 cm, or a grade 3 histology, or a Ki-67 of 20% or greater, or patients who have 4 or more axillary lymph nodes.

Let's go through a case, and then discuss guideline recommendations for treating this patient.

This is a 44-year-old woman who presents with a left breast mass and palpable axillary nodes. On core biopsy, the invasive ductal tumor is grade 3, ER/PR highly positive, and HER2 1+ negative by IHC [immunohistochemistry]. A Ki-67 is 30%, and a fine-needle aspiration of the axillary node is positive for carcinoma. She has a 70-gene MammaPrint score, and this is high risk. She then receives neoadjuvant chemotherapy with a clinical response on examination and imaging and undergoes breast-conserving surgery with axillary node sampling. This shows 2 cm of residual carcinoma, with a cellularity of 20%. Two out of six nodes are positive for carcinoma, with evidence of treatment effect.

Peter, along with radiation, ovarian function suppression, and an aromatase inhibitor, what would you do for this patient who sees you now in the postoperative setting?

Dr. Schmid:
This is an excellent case that's really coming straight out of the clinic. I think this is a treatment case where we have much better options now than we used to have 3, 4 years ago. The patient has grade 3 disease and has clearly at least 2 lymph nodes involved. That's after neoadjuvant therapy, could have been more before neoadjuvant chemotherapy. So even without the Ki-67 of 30%, the patient already meets the criteria of the monarchE trial and therefore, in my opinion, should very clearly be offered a treatment with abemaciclib alongside ovarian function suppression and aromatase inhibitors. The Ki-67 just enhances that message, but as I said, we would have offered abemaciclib in this situation regardless of this. We would also consider, in this group of patients with ovarian function suppression, an aromatase inhibitor, use of biphosphanates, and, again, bone-targeted therapy has shown to provide an additional risk reduction of about 17%. And I think that's important because we're not looking just at the major improvements by a single treatment modality. It's the small, incremental benefits we have from each treatment modality – chemotherapy, endocrine therapy, ovarian function suppression, and an aromatase inhibitor plus abemaciclib plus zoledronic acid. If you take all of that together, you have a much better outcome, fortunately, than we would have seen, let's say, 10 years ago.

Dr. Rugo:
Yeah, I think that's so important. We really have improved outcome for patients with early-stage, high-risk, hormone receptor-positive, HER2-negative breast cancer.

And as we briefly discussed in Chapter 1, one of the challenges for us moving forward is how to improve outcome for patients who look like they have lower-risk disease but still develop metastases over time. And because these metastases occur quite late, we need to understand whether or not there's anything else we should be doing. And there are, of course, a number of studies that are looking at this now, looking at circulating tumor DNA and particular risk factors to try and extend out, add endocrine therapy and even change or add to endocrine therapy over time. But that, of course, remains for the future.

I think the overview you gave, Peter, is really helpful, and one of the other things that's really important when we're thinking about treating these patients is coordination of care. And this patient of mine from clinical practice really is a good example of how important coordination of care really is between the oncologist, the surgeon, the pathologist, and the radiation oncologist, and then a number of other people as well. Our infusion staff, for example, our nurse practitioners or physician's assistants and then our social work and other supportive care services. Because a diagnosis of early-stage breast cancer can be quite difficult in managing it in your life. You know, how you manage the care of children, your work, your family, and even just transportation can be quite difficult, so our social workers play a really important role as well in helping support our patients.

We have a setup, because we give a lot of neoadjuvant therapy, where we work very closely with our breast surgeons. We're actually in the same physical space with our breast surgeons, and that allows us to discuss patients carefully and coordinate care in terms of which patients are the best candidates for neoadjuvant therapy versus going to surgery first. And I think that's really the first path of most importance in terms of our coordination of care. And then, the next step is really when you've treated patients, working with your surgeon to time the surgery and then seeing the patients after surgery. We work closely with our pathologists as well, in reviewing the pathology, understanding the cellularity – which I find very helpful – the extent of disease or a presence of disease in the lymph nodes, and any change in markers and how we should be able to evaluate that. And then we, also, we all have our multidisciplinary tumor boards, which are so incredibly important, where we review these patients and talk about questions over time. And our radiation oncologists, we work with as well. I would say on the medical oncology and surgery side, we think they might be radiating too much right at the moment, and there are a number of trials which might help us understand which patients who have a great response to neoadjuvant therapy still need extensive radiation or not. But in this case, the patient had residual lymph nodes, and I think where we're collaborating with our radiation oncologists and surgeons also, is trying to reduce the number of lymph nodes that we take out at the time of surgery and allow patients to go through breast-conserving surgery if at all possible, depending on a number of different risk factors and patient preference.

We also work closely with our psychologists and psychiatrists, since this is a very stressful time for anyone diagnosed with early-stage breast cancer and trying to manage over time. And we want to have everybody be on the same page so that we give the same expectations for every patient.

So I think you also probably have a big area where you're working with this at your institution. But of course, when you're working with a pathologist, one area that you work on, Peter, is trying to understand the different markers that we get and Ki-67, we talked about earlier in our earlier chapters, a really important assessment. So can you describe to us how you work with Ki-67 and the use of adjuvant CDK4/6 inhibitors in HR-positive, HER2-negative early breast cancer? And then, sort of as you extend that, we talked a little bit in

Chapter 2 about adverse events, but how do look for those, educate your patients and staff, and how do you monitor your patients?

Dr. Schmid:
So I think in terms of Ki-67 assessment, it is well established that this can be quite heterogenous throughout the cancer. And if you look at old data, and some of the data there were the concordance of different Ki-67 assessments, I think, if you look at the more recent literature, Ki-67 is a highly reproducible marker, if the appropriate guidelines for assessment are being followed, where sometimes different results can come from if you take different biopsies of the cancer. So one of the areas that's, for us, important is if we see the cancer itself, once it has been taken out, is quite heterogenous, then it is sometimes important to us – sometimes a consideration worthwhile, repeating a Ki-67 assessment that has just been done on the biopsy. But is has become routine care. I have, in the past, found it already a helpful marker, because it did give us additional insight in whether patients may benefit from chemotherapy or not. Now it has become an essential marker in selecting optimal endocrine strategy and advising us on the use of abemaciclib.

In terms of the safety monitoring you mentioned, Hope, I think it's a learning curve for most teams. We obviously all have substantial experience in managing patients with metastatic breast cancer who are on CDK4/6 inhibitors, but again, these patients are traditionally seen very frequently in clinics. And we took that same setup and moved this into an early breast cancer setup, where I would still see the patients on a monthly basis and make sure we monitor possible adverse events very well and give patients, ideally, optimal guidance on how to manage them. And our experience is that if you do this well at the beginning, that we can actually decrease the frequency of visits over time, because most patients settle – if I may use that word – settle well into the therapy within 2 or 3 months, and the frequency but also the grading of side effects goes down as patients stay on these therapies. So we don't see cumulative side effects in the majority of patients. In fact, we see actually a better tolerability over time in the early disease setting, and we are adjusting patient pathways accordingly.

Dr. Rugo:
That's such an important point, you know, when we're trying to give patients new therapies that improve outcome, of course, if they don't take the medicine or they can't tolerate it, we're not getting any improvement in outcome, and quality of life is really important. We've talked to a lot of patients about taking half of their antidiarrheal medication, you know, especially if they eat a big, leafy green salad, or, you know, if they're going to go on a big hike or things like that where, you know, you really want to be preventing diarrhea, you're out with a bunch of people, et cetera. And people are always interested in the fact that they can take a half a pill, so, you know, working with the patients early on makes a big difference. I totally agree with you that over time the tolerance improves tremendously, and it's just really an early event that we're working on in those first 8 to 12 weeks.

So really an interesting conversation, both talking about the pathology, how we decide on treatment in the early-stage setting, applying abemaciclib to the treatment of our patients with early-stage breast cancer, understanding Ki-67 and what role it plays with the expanded FDA guidelines, as well as other guidelines that are available for our use. And I think really emphasizing that we now have a treatment, along with the therapies available, that can improve outcome and reduce distant recurrences in our patients with high-risk, early-stage breast cancer. We're looking excitedly to the future with the next study as well as further survival endpoints for monarchE, understanding the optimal duration of CDK4/6 inhibitors as well, though I think that's going to take us a few years.

So it's really been nice talking with you this morning, Peter. It's all the time we have today. I want to thank you, the audience, for listening in, and thank you, Dr. Peter Schmid, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Schmid:
Thank you. It was a pleasure, as always.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by **AGILE**.

To receive your free CME credit, or to download this activity, go to ReachMD.com/**AGILE**. Thank you for listening.