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What Is the Latest Real-World Evidence With CDK4/6 Inhibitors in Metastatic HR+ Breast Cancer?

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Dr. Rugo:
Hello, I'm Hope Rugo from the University of California San Francisco's Comprehensive Cancer Center, where I'm a Professor of Medicine and Director of Breast Oncology and Clinical Trials Education. It's a pleasure to talk to you today about the latest real-world evidence with CDK4/6 inhibitors in patients with metastatic hormone receptor positive breast cancer. Now today, I'm going to really just give you a bird's eye view of real-world evidence, and in the use of CDK4/6 inhibitors combined with endocrine therapy in patients with metastatic hormone receptor positive breast cancer, and give you three examples with a three CDK approved CDK4/6 inhibitors in clinical practice.

So first, let's just talk about what we - what real-world evidence is. So we understand randomized clinical trials. This is the evidence we bring to our clinical practices every day and interpret. So the question of a randomized clinical trial is can the drug work? So you select a patient population with strict inclusion and exclusion criteria, the protocol-driven treatment is in an ideal setting that's designed to meet requirements of the regulators first and the payers second. In this type of trial, you're comparing a new treatment to the standard of care. And in this case was CDK4/6 inhibitors, endocrine therapy alone, depending on the class of endocrine therapy, with or without a CDK4/6 inhibitor.

Now, the way we treat patients in clinical practice may not reflect a clinical trial population. We have to carefully select these patients. For example, some trials will control for glucose, will control for measurable disease or not, which is certainly not the majority of our patients in the first line hormone receptor positive metastatic setting. There are other criteria that may play a role, including the access of certain patient populations to clinical trials and their ability to comply with the strict
standards in clinical trials, the sites, the geographic locations, etcetera, where clinical trials are done.

In addition, in a clinical trial, you have your own concierge. So a clinical trial coordinator is able to strictly enforce and standardize the treatment. In real-world evidence, you have diverse and unselected populations. There are - the only exclusion criteria and inclusion that play a role here are what you as a clinician bring to your practice. Now, there are prospective registry studies where patients fit specific criteria, but these are generally very loose compared to clinical trials. This is routine clinical practice. And you have - the comparator is the patients you've chosen to treat with as these, for example, in this setting, endocrine therapy alone. And the discretion intervention for toxicity, doses, etcetera, are at the discretion of the treating physician. And this shows you a little bit about the diversity of patients here.

Now, in order to deal with this diversity, if you're going to evaluate real-world evidence that's been collected prospectively, and you're comparing it to a population of patients who has received endocrine therapy alone, and you're using as your indicator, endocrine therapy plus the CDK4/6 inhibitor, you need to address the inherent bias in these trials. And there are two ways to do that. The inverse probability treatment waiting, IPTW. And that allows us to adjust for differences in the characteristics of study subjects by adjusting the

weighting that's assigned to variables that we know impacts outcome in these patients. So you basically have a pseudo population where patients represent a reference population, you keep all eligible subjects, but you - and you can include more than two comparisons, you can look at different comparisons, even comorbidities, for example, or racial subgroups. And then you can also address the extreme weight issues as well, where you have patients who really have very big differences in populations. And then there's propensity score matching, or PSM. Here, we match patients across treatment groups according to demographic and clinical characteristics. So basically, you're comparing patients who look the same by propensity score, but receive different treatments. So in some ways, you're trying to mimic the randomization and stratification of a randomized clinical trial. And then you can compare the treatments that you've chosen to give patients directly between matched patients. So that's actually very helpful. And really, what we want to do is look at both.

So I think that the best example of real-world evidence study is P-REALITY X, even given the bias that I recently published an update on this data. So this is a called the palbociclib real-world first-line comparative effectiveness study extended. There was an initial publication by Angie DeMichele that I think is an excellent example of use of a real-world evidence database. And here, we use the U.S. Flat Iron Health Analytic database that has a thousands of clinical practices that contribute data prospectively and allows you to go back and access the database to look at a number of different factors. You can actually in the Flat Iron Database even look at gene mutations. So our goal was to evaluate the effectiveness of first-line palbociclib and aromatase inhibitors compared with aromatase inhibitors alone in patients with hormone receptor positive HER2 negative metastatic breast cancer treated in real-world clinical practice in the United States.

Now, the way you do these analyses is you select your population. So because the trials included postmenopausal women, we included postmenopausal women and men who were at least 18 years or older. And we had almost 2,900 patients that fit into this category in the Flat Iron Database. And then you want to set your start and end date in terms of when people started their therapy. So we looked at February 2015 to March of 2020, because you need to have enough time after you close your enrollment to see what happened to those patients over time. So then you have your follow-up data from index date to death, study end, last visit whatever occurred first, and you need to have 6 months follow-up available.

So we looked at patients who received palbociclib in an AI versus an AI alone. And you can see this isn't a randomization; it's just how patients were allocated in the clinical practice. And for this extension of the P-REALITY study called P-REALITY X, we looked at overall survival and then secondarily relooked at real-world

Progression-free survival which was published in that initial paper by Angie DeMichele. So we used sIPTW as the primary analysis to perform baseline demographic and clinical characteristic of balancing. And then PSM is a sensitivity analysis as we talked about. Median survival times are estimated using the Kaplan-Meier method. And then we used the Cox Proportional Hazard Method to compute hazard ratios and the confidence intervals.

So this shows you the data with overall survival before and after the sIPTW and PSM. And I've spelled them out here for you because if you're like me, these abbreviations aren't part of your standard clinical conversation. So you can see the unadjusted analysis, we look at median overall survival from 40.4 to 53.4 months. When we use IPTW, it's 43.2 to 49.1 months with a hazard ratio of 0.76., And this to me, as well as that sensitivity PSM analysis with a hazard ratio of 0.72 is quite compelling because he's hazard ratios are quite similar to what's been seen in the randomized clinical trials and the first-line setting and second-line setting, looking at adding CDK4/6 inhibitors to endocrine therapy.

So here, the median overall survival, and you can see the median follow-up at about 25 months across the board, was longer in patients who received palbociclib and an AI versus AI alone. And I think this contributes nicely given the differences in eligibility and characteristics between the randomized clinical trials that we've seen and the difficulties interpreting the survival data with palbociclib. We also of course, looked at real-world progression-free survival again, as a secondary endpoint. And here you can see also these hazard ratios of about 0.7 across the board after IPTW and PSM. So very encouraging to see this. And there were no unusual or unexpected safety signals.

So what about ribociclib? So this data, I chose the data that was most recently presented at San Antonio 2022. And this is a planned study of 300 patients in 13 sites across Austria, presented by Singer and colleagues; 283 patients were actually eligible and evaluable. And what they looked at patients who receive ribociclib with either an aromatase inhibitor or fulvestrant, in the first-line setting for metastatic hormone receptor positive breast cancer, and they were allowed to have up to one line of chemotherapy for advanced breast cancer. So it's relatively a little bit more of a heterogeneous population, but trying to mimic some of the other trials.

And then they also wanted to look at safety looking at the QT interval before treatment initiation of less than 450 milliseconds as an eligibility and then see what happened to that QT interval because that's something of course, we need to monitor on ribociclib. Their

primary endpoint was progression-free survival. And of course, they have the usual secondary endpoints, an important one here being the safety as well as time to first chemotherapy progression on first-line CDK4/6 inhibitors. And this data is still immature, but I'm showing you I think the key data from the presentation from San Antonio.

So here you can see this is not a comparative population, you have 283 patients, and on the upper left-hand side you can see median progression-free survival of about 30 months. So this is actually quite comparable to what we've seen in the randomized trials. They have overall survival data at 12 And 24 months, it's not yet mature. Patients are doing very well, which is amazing for our patients, 77% surviving at 2 years. And if you look at the treatment modifications for ribociclib, where a lower dose was used in the NATALEE adjuvant trial, 400 milligrams, versus the 600 milligrams that we standardly use in the metastatic setting, you can see that about 54% had a dose interruption and dose reduction after dose interruption occurred in only 14%. And of those patients, you can see that any dose reduction occurred in about 14%. And I think that goes along pretty well with what we see in clinical practice. And the database is really helpful to see that with that very nice PFS.

What about Q TC prolongation? That was seen in 11%. But the grade 3 was only point 4%, and 61% of patients were taking comedications that are known to cause Qt prolongation. And this was managed quite nicely with dose reduction, or delay in the majority of patients. So although this is a small database, and there's a larger prospective style looking at ribociclib in a real-world data population, I thought it was really interesting, updated information just to share with you today.

What about abemaciclib? Well, there's one retrospective study that's published in 2021 that used the Flat Iron Health electronic database. And they included patients who were treated between June of 2016 and August of 2018. It's important to keep in mind that that was all within a period of 21 months of FDA approval of abemaciclib. So they basically included abemaciclib used in any setting. And what you can see here is the majority of patients received abemaciclib and fulvestrant. So that's 70 patients out of their 118. And an aromatase inhibitor in the probably more in the first-line setting was 27 patients. And as you recall, abemaciclib was also - is also approved as a single agent, although we don't use it anymore. And that was just 15 patients, so you get a better idea. And you can see that a lot of the use was in the first- and second-line setting. So if you added up the second-line setting, that's where the majority of use was. And I think that's really just given the approval.

And here's the real-world progression free survival and a little bit more about the database; 50% had visceral mets and a quarter had prior CDK4/6 inhibition. There's an ongoing study actually looking at abemaciclib following the use of a CDK4/6 inhibitor and an aromatase inhibitor in the second-line setting. And I think that's going to provide really important data about the use of continued CDK4/6 inhibitors after progression. So this speaks a little bit to that. They didn't reach the median real-world progression-free survival, but at 12 months, it was 62%, really encouraging in this population with 50% with visceral metastases.

So just a little bird's eye view about real-world studies evaluating CDK4/6 inhibitors in patients with metastatic hormone receptor positive HER2 negative breast cancer. You've seen three different methodologies, that retrospective databases are the most common. And the largest vetted database is Flat Iron where data is collected prospectively and carefully evaluated. It can be done by institution or by groups of institution. But as you can see, you know, it depends on when the drug is approved, you may have smaller numbers, and it may be difficult to accumulate all of your data because you're not - you're looking retrospectively at data that wasn't collected with the study in mind. We saw how you could - you're limited in numbers by how long the drug is available. And the prospective real-world studies that I showed you, that single study in Austria, you generally have numbers - smaller numbers, and longer time to data maturity.

But there are now some studies which are coming to maturity that are looking at several thousand patients in sort of a registry, a prospective study. And this actually has several purposes. Not only does it provide us with real-world data, but it also provides access to patients before a drug approval in many countries.

We know that real-world data provides a heterogeneous population. But this more closely mimics the true population of patients we treat. It clarifies, it confirms efficacy and safety data suggested from phase 3 trials. And it may give us a greater window into safety and what happens with those different doses that are used. And in fact, it may help us educate ourselves as well, because if we see that many are starting at lower doses, it may be that the clinical trials really support starting at the full dose or that in certain populations, this is more preferable and ensures adherence. But clearly it's advantageous for evaluation of small populations and may lead to the ability to add small populations into approval labels as you'll hear about next from my colleague, Dr Adam Brufsky.

Thank you so much for your attention.

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