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Released: 02/10/2023
Valid until: 02/10/2024
Time needed to complete: 43m

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Interpretation and Application of RWE to Inform Shared Decision-Making in Metastatic HR+ Breast Cancer

Announcer:
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Dr. Rugo:
Hello, and welcome to our panel: Interpretation and Application of Real-World Evidence to Inform Shared Decision-Making in the Treatment of Patients with Metastatic Hormone Receptor Positive Breast Cancer. I'm Hope Rugo, a Professor of Medicine at the University of California, San Francisco's Comprehensive Cancer Center, and I'm joined by my colleague and friend, Dr. Adam Brufsky, a Professor of Medicine, Co-Director of the Comprehensive Breast Cancer Center at the University of Pittsburgh. Welcome, Adam.

Dr. Brufsky:
Thanks, Hope.

Dr. Rugo:
So today, we're going to discuss a little bit about real-world evidence and how we use this data in our clinical practices. To define real-world evidence, we're talking about the ability to take information from real clinical practice, and understand how novel agents apply to real-world patients. So instead of a prospective clinical trial, or, for example, even a registry study, in general, real-world evidence databases take information that's been collected and interpreted based on the kinds of patients that are being treated. And because of the enrollment criteria in clinical trials, also, when clinical trials are being done before drugs are approved, we really get a very select population and a select set of data.

Real-world data tries to overcome this by looking at patients that we treat every day in our practices. There are several ways that we can look at real-world data. I mentioned that registry studies are a little bit different. But these have been used to collect real-world data in a prospective way, usually in a group of centers, but also looking retrospectively, either a data that was collected, not intentionally for trials, or from the U.S. Flat Iron Database, where data is collected prospectively, we're able to look at individual characteristics of patients in these real-world databases.

Adam, when you're looking at real-world data that's either presented or published, what are the key factors that you're looking at in order to understand how these apply to clinical practice?

Dr. Brufsky:
Yeah, it's a really important question. I mean, I think that you mentioned it before, just before we get onto that, that, you know, randomized clinical trials have changed oncology practice. I mean, us in breast cancer in particular, with the NSABP, now NRG, and all the cooperative groups in the last 50 years, really have changed - I think changed the way we practice breast oncology. But as you said before, randomized clinical trials do have limitations. Specifically, they take a long time to do in breast cancer, because people live so long. And as a result, the standard of care changes as the trial goes on. And I think it's really important for us to have other sources of

information, trying to understand the efficacy of our drugs compared to the standard of care, especially when you do something that may be more expensive or more cumbersome. And so that's where we're kind of observational data and a real-world data come in.

And so the kinds of things I look at, I mean, I think the biggest issue with observational data and real-world evidence is bias. I mean, I think we, as physicians, tend to treat people, for example, with the newest therapies who are sick. And so as a result, you know, if you don't control for that, and when you kind of start doing these analyses, you'll find that sometimes that patient will do worse with the new therapy. And I think that what I look at more than anything, is have they tried to control for sources of bias, have they done, say, a variety of statistical techniques such as propensity score matching. That's something I look at almost immediately.

The other things I tend to look at are, obviously, real-world data is limited. I mean, what we decide to put in a medical chart may not necessarily reflect what was done in the clinical trial. And so their data elements are often missing. And so I look for kind of how much data is really missing.

And so really, the two things I look at initially are what the comparison of two, usually these are two groups are being compared in a real-world analysis. And I'll look to see, they'll have a table of the matched patients. So I'll look at the characteristics of the matched patients, make sure they're as equivalent as it can be. And then also, I'll look for the missing data. How much missing data they have of elements that are really important to me?

One big one, for example, is race. We oftentimes look at the these, and race was not recorded in like 30 or 40% of the patients, or performance status isn't recorded in 30 or 40% of patients. And so as a result, you know, we have to kind of then take some of that data with a grain of salt.

I also, one last thing to kind of talk about is I look for internal consistency. So one thing I'll look at is are there randomized data in this particular disease entity? And if there are, are there endpoints that kind of match, so was there progression-free survival? Is the progression-free survival in the observational real-world data similar to the progression-free survival in the clinical trial. And if they're kind of similar, if the hazard ratios are roughly the same, then I'm more comfortable extrapolating to some other endpoints, understanding that these are all still exploratory. You know, without a randomized clinical trial, it's hard to know whether they're real or not, but at least I have a little more comfort in understanding some of those other endpoints.

So that's kind of the things that I look at what I tend to look at some real-world data.

Dr. Rugo:
And I think you bring up some really important points. One is the patching and weighting of trying to understand the bias potentially in patients who aren't, you know, randomized and stratified by specific characteristics that we know impact outcome and tolerance of therapy.

And there are, as I was mentioning earlier, some real differences in the way real-world data is collected. So for example, there might be a prospective trial where they just track everybody who's getting a new therapy to see how that patient population does. And that has its limitations. Because as you pointed out, you don't have the comparison group. There are these unique datasets like Flat Iron, where you can look at patients who were selected for treatment with your treatment of interest versus this previous or ongoing standard of care that doesn't include your targeted agent. So treatment X versus X plus Y, in this case, really where we have the data is with CDK4/6 inhibitors. And I think that that has a specific value that's different from the prospective studies, looking at just how we treat patients in the community. But those prospective studies are also useful.

Then there's the retrospective analysis where you go back and just collect data. And that's probably the weakest type of real-world evidence data because you haven't collected the information prospectively. And there, I think there can be more bias, and you really can't weight that information.

One of the things that I think we learn about that you mentioned that's very important, is the application of novel agents. Again, in this case, using hormone therapy plus CDK4/6 inhibitors in populations that aren't well represented in clinical trials. So patients with significant comorbidities, we treat in clinical practice, but they don't go on clinical trials; they could have any number that you mentioned, of comorbidities. Also, I think ethnic and racial minorities, for example, even you mentioned black patients, male patients, for example, and other minority groups that we might be able to obtain. But I have to say that even then we still have small numbers in our large databases. But it really gives us a little bit of a window.

And then lastly, I think some of the information that we might be sharing with our patients and bringing to the table from real0world evidence is toxicity information. So what are the common toxicities? How often do patients dose reduce or hold doses? That's probably data that's best achieved in a prospective registry-like database? How do you bring out of that kind of data to your discussion with

patients and to your patient management strategies?

Dr. Brufsky:
Yeah, it's really important. I mean, I think that I feel more comfortable giving full dose, for example, of palbociclib to older women. Just as one example, I maybe give ribociclib or abemaciclib, but, based on some of the real-world data, I'm okay with that. I mean, you know, we have data that shows in the real world that it doesn't really affect patient's activities of daily living in patients over 70 given a CDK4/6 inhibitor. So that helps me, give me more comfort. I mean, literally about half an hour ago, I just saw a woman 84 years old, who is doing very well on palbociclib. And I think that this real-world data, the data that's been developed in a variety of settings, again, understanding that it's not a prospective clinical trial, but understanding it is a sum total of real-world experience with the agent, it gives me a lot more comfort that the toxicities are acceptable in that patient population.

Dr. Rugo:
Now, and that's great. And sometimes I think we can learn, for example, there was a combined analysis of the clinical trials where the FDA actually and NCI together looked at toxicities and saw that there were more toxicities in older women but they actually stayed on drug, it seemed like the benefit in terms of PFS was the same. But then looking at this in the real-world population where you didn't sort of like handpick the patients to go on, I mean, that's such an important point that you bring up is that comfort level. And also, maybe the real-world data understands the patients where you might start at a slightly lower dose because they do have a lot of, you know, comorbid conditions that might make you a little bit concerned about starting at the full dose. So that's helpful as well. I think really interesting way of taking that data back to the clinic for our patients and also using our own information and moving forward as well.

I think that one thing that is important in terms of our clinical practices is this shared decision-making. And it does seem that having more real-world evidence helps us with those decision-making processes, and also discussing the drugs with our patients. Do you find that you bring that information to your clinical population, Adam?

Dr. Brufsky:
Yeah, but not in a way like saying, oh, I don't say it's real-world data that's done, it's more, you know, a patient will, you know, if you talk to the patient about this, and in shared decision-making, the patient may ask, well, you know, 'Am I someone that was on the trial?' I mean, patients kind of ask in a different way, you know. But on the other hand, I do that, when I go, 'Listen, you know, we have data on patients like you who received this drug, and they did pretty well. And it wasn't that toxic to them.' Because that's the question a lot of people ask, 'Well, you know, I'm kind of – I'm 80, you know, it looks like everybody was 60 in the trial. And are you sure this is going to, you know, help me out?' You know, and so in that way, it was very helpful and that's sort of shared decision-making. I think that especially as you said, Hope, beforehand in the toxicity discussions, it makes just me a lot more comfortable when I talk to somebody about the toxicity of a new agent, for example. It helps to have data in a particular population and help with that decision-making that we do together.

Dr. Rugo:
Yes, and I know that I - in our own presentations as part of this program, that you're going to talk about how real-world data can be used to even lead to expansion of drug approval to rare populations of patients. So it's been really a great talking to you, Adam, about this. I think it's such an interesting topic, hearing your perspectives, and talking together about how we both use this data in our clinical practices.

Thank you to the audience for listening to us. I'm Hope Rugo from UCSF, joined by Adam Brufsky from the University of Pittsburgh, and have a wonderful day.

Dr. Brufsky:
Thank you very much.

Announcer:
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