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Understanding Crossover and Endpoints in ASCENT-03 and -04

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Gilead Sciences, Inc. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Today, I'm joined by Dr. Neil Iyengar to discuss the impact of crossover on efficacy endpoints and the ASCENT-03 and -04 trials, which evaluated sacituzumab govitecan in patients with metastatic triple negative breast cancer.

Dr. Iyengar is an Associate Professor of Medicine and the Co-Director of Breast Medical Oncology at the Emory Winship Cancer Institute in Atlanta, Georgia. Dr. Iyengar, welcome to the program.

Dr. Iyengar:
Thank you for having me.

Dr. Caudle:
Of course. So I'd like to start by talking about the rationale for crossover in metastatic triple negative breast cancer trials.

What's the ethical and scientific thinking behind allowing patients in the control arm to receive the investigational therapy after progression?

Dr. Iyengar:
So crossover is a very important ethical consideration as you've pointed out, and this is particularly important when we are testing novel treatment strategies using agents that are already available and shown to be efficacious for our patients. So, for example, if there is a therapeutic that is already approved for patients with advanced disease but it is being tested in the more upfront setting, crossover is important because it allows patients to otherwise access what would be considered standard of care in more advanced lines of therapy.

The last thing that we want to do when enrolling patients on a clinical trial is expose them to subpar therapy. So allowing for crossover allows for patients to go on and receive the standard-of-care therapy without compromising their overall clinical treatment or strategic treatment, while still allowing patients to participate in clinical trials and advancing the knowledge, science, and treatment for our patients.

Dr. Caudle:
With that in mind, let's turn to the ASCENT-03 and -04 trials, which allowed control arm patients to access sacituzumab govitecan after progression. Given that, why might overall survival, or OS, underrepresent the true impact of the therapy?

Well, the ASCENT-03 and -04 trials are exactly proof of principle in terms of the discussion we were just having about the ethical considerations of crossover. In ASCENT-03 and ASCENT-04, patients who were randomized to the control arm were allowed to cross over and receive sacituzumab govitecan in a subsequent line of therapy.

Dr. Iyengar:
Now, as a reminder, ASCENT-03 and ASCENT-04 tested sacituzumab govitecan with or without immunotherapy depending on the PD-L1 status of the tumor in the first-line treatment setting for metastatic triple negative breast cancer. Now, if sacituzumab govitecan was not already shown to be efficacious and already approved in the second line and beyond setting, this crossover issue wouldn't be a problem.

Patients would go on to receive other treatments, even if they were in the control arm for the ASCENT-03 and -04 trials. However, we do know that sacituzumab govitecan is efficacious for the treatment of metastatic triple negative breast cancer in the second line setting and beyond.

So I see this as a benefit or a positive design for the ASCENT-03 and -04 trials where patients were allowed to go on and receive sacituzumab govitecan if they were randomized to the control arm. I think if this was not allowed, that would be an unethical trial design.

So, first and foremost, ASCENT-03 and -04,were designed ethically. Now, scientifically speaking, this introduces challenges in terms of how we interpret overall survival, that long-term endpoint, because, essentially, patients in the control arm are going on to receive the investigational treatment that patients who were in the investigational arm received in the first line setting.

So when we look at overall survival, we need to keep in mind crossover as we're interpreting it, because patients received sacituzumab govitecan even if they were in the control arm. They had just received it in a subsequent line of therapy. This is where shorter-term endpoints, or surrogate endpoints like progression-free survival and PFS2 become important.

Dr. Caudle:
With those limitations in mind, how should we weigh progression-free survival and second progression-free survival, also known as PFS and PFS2 respectively, when assessing sacituzumab govitecan's efficacy in these trials?

Dr. Iyengar:
So let's first think about the traditional development or design of clinical trials. In an era when we did not have many treatment options available for metastatic breast cancer, overall survival was and still is the gold standard endpoint for evaluating the efficacy of new treatments.

However, fortunately, we now have newer therapies that are very efficacious, and when we think about how the new treatments are developed, we typically develop new treatments in the metastatic setting in later lines of therapy. So after patients have been exposed to multiple standard-of-care regimens, we will then typically introduce a trial with a novel agent.

Once that agent has been shown or proven to be efficacious, the next step often is then to test whether or not it is efficacious to move that new therapy into an earlier line of therapy, either the upfront setting, like the first-line setting, or even into early-stage disease.

Now, the issue with that approach or that strategy, especially when that therapy has already been approved for use in later lines of therapy, is that we do not want to withhold an efficacious treatment for our patients just because they participated in a clinical trial and were randomized to the control arm.

So getting back to our discussion on ethical design of clinical trials in that setting, it is important that we allow for crossover, as the ASCENT-03 and -04 trials commendably did. But this blurs the overall survival endpoint, scientifically speaking. This is where PFS and PFS2 become very important.

PFS was traditionally considered to be a surrogate endpoint to give us an early look at an overall survival endpoint, because it tells us the more immediate efficacy of a novel agent. PFS2, however, gives us more insight into the longer-term efficacy or durability of benefit by telling us how patients do with subsequent lines of therapy after being exposed to the investigational strategy more upfront.

So, in my mind, when I have PFS and PFS2 data available, I no longer think of these exclusively as surrogate endpoints, but these are more endpoints that give me insight into the immediate benefit of a novel therapeutic strategy and the durability of that benefit. So when we are in a situation where we've done the right thing by our patients, and we've ethically allowed crossover, but scientifically, it makes it challenging to interpret the overall survival endpoint, it allows us to rely on PFS and PFS2 to understand the efficacy and the durability of that efficacy for more upfront treatment of a novel strategy.

Dr. Caudle:
Thank you for that. And for those of you who are just tuning in, you are listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Neil Iyengar about optimizing endpoint interpretation and crossover permitted trials for metastatic triple negative breast cancer.

So, Dr. Iyengar, now that we've discussed the role of OS, PFS, and PFS2 in ASCENT-03 and -04, let's look at the bigger picture.

What frameworks or best practices can clinicians use to best interpret these endpoints together when evaluating a therapy's efficacy?

Dr. Iyengar:
Well, I think for a long time, we've debated in breast cancer therapy whether we should save our most efficacious agents as salvage treatment, if you will, for later lines of therapy, or if we should be using them upfront. And now we've seen, proven over and over again

for multiple different agents in multiple different settings, like the hormone-receptor positive setting and now the triple-negative setting, that it is better to use our most efficacious agents upfront and not save them for later down the road.

And I think this is particularly relevant to triple-negative breast cancer, where, unfortunately, the long-term outcomes in the metastatic setting are still poor. Many of our patients, unfortunately, do not make it to later lines of therapy. This is even more reason for using our most efficacious treatments upfront. And ASCENT-03 and -04 both showed us a PFS and a PFS2 benefit with the use of sacituzumab govitecan with or without immunotherapy in that first-line setting. So if I put all of this together, these data tell me that we should be using this efficacious approach upfront for our patients.

Dr. Caudle:
And as a follow up to that, how can we apply this totality of evidence to guide real world treatment decisions in frontline metastatic triple negative breast cancer?

Dr. Iyengar:
It's certainly been an exciting time in the development of new therapies for metastatic breast cancer, including metastatic triple-negative breast cancer. And it's really helpful, of course, to have treatment options for our patients. I think it allows us to engage in mutual decision making and to include practical considerations in addition to efficacy endpoints. We know that the various treatment options have different schedules, different adverse effects, and different routes of administration, and so we can discuss all of this with our patients and really select the treatment option that's not only the most efficacious, but that also is the most congruent with the patient's life and the patient's desires and wishes.

So if I put all of this together, I would really emphasize that ASCENT-03 and -04 have shown us the importance of using our most efficacious agents upfront in the first-line setting. And, ultimately, when we look at the totality of the treatment landscape for metastatic triple negative breast cancer, we still, despite improvements, see that many patients do not make it to later lines of therapies, even further emphasizing the need to use our most efficacious ADCs upfront.

Dr. Caudle:
Before we wrap up our program, do you have any final takeaways you'd like to leave with our audience?

Dr. Iyengar:
Well, I think that we are in a very exciting time for the development of breast cancer therapeutics. There are many agents that are in the pipeline, but we also have to remember that we already have efficacious agents that are recently approved in triple-negative breast cancer, specifically the antibody drug conjugates.

And what we're learning now is how best to sequence these. I wanna go back to my point about using our most efficacious therapies upfront. I think is the most important thing that we need to offer to our patients, and we'll have data soon to help us understand how we can sequence efficacious therapies in subsequent lines.

Dr. Caudle:
Well, that's a great comment for us to think on as we come to the end of today's program. I'd like to thank my guest, Dr. Neil Iyengar, for joining me to discuss how crossover can influence endpoint interpretation in metastatic triple-negative breast cancer trials. Dr. Iyengar, it was great having you on the program today.

Dr. Iyengar:
Thank you so much for having me.

Announcer:
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