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Assessing Atirmociclib Plus Letrozole in HR+/HER2- Metastatic Breast Cancer

Announcer:
You're listening to Project Oncology on ReachMD. This episode is brought to you in partnership with AstraZeneca and First Ascent Biomedical. Here's your host, Dr. Pavani Chalasani.

Dr. Chalasani:
This is *Project Oncology* on ReachMD, and I am Dr. Pavani Chalasani. Today, I am joined by Dr. Antonio Giordano to discuss a recent clinical trial on the safety and efficacy of first-line atirmociclib combined with letrozole for the patients with hormone receptor-positive, HER2-negative metastatic breast cancer.

Dr. Giordano is a medical oncologist and clinical investigator in the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, Massachusetts, as well as the Clinical Director of the Center for Cancer Therapeutic Innovation and the Medical Director of Breast Cancer Pathways. He's also a co-author of the study we'll be discussing today, which he presented at the 2025 ESMO Congress.

Dr. Giordano, welcome to the program.

Dr. Giordano:
Thank you so much, Dr. Chalasani. And thank you, everybody, for being here today.

Dr. Chalasani:
So, let's kick things off, Dr. Giordano, with some background on atirmociclib. What sets this apart pharmacologically from the CDK4/6 inhibitors we currently use, and why do you think it's important to study such new therapies now in combination with aromatase inhibitors?

Dr. Giordano:
Yes, thank you for the question. So atirmociclib is a selective CDK4 inhibitor. So, we know that the current landscape for first-line and also recently, in the adjuvant setting, for hormone receptor-positive, HER2-negative breast cancer, has been the approval of the three CDK4/6 inhibitors, such as palbociclib, abemaciclib, and ribociclib, the latter two also being approved for the adjuvant setting. They are the main stem of the treatment of estrogen receptor-positive, HER2-negative breast cancer in combination with endocrine therapy.

Atirmociclib is a selective CDK4 inhibitor, so it leaves off CDK6 and the possible side effects and toxicity that may come from inhibition of CDK 6, such as, for example, myelotoxicity. And specifically blocking CDK4 alone is able to achieve a better cell cycle control and more apoptosis and cancer cell killing, specifically when combined with endocrine therapy.

Dr. Chalasani:
With that being said, can you tell us how this trial was designed, like patient selection to dosing strategy considerations?

Dr. Giordano:
So this was a classic Phase 1 study where atirmociclib was first tested as a single agent to identify a safe dose. And then, subsequently, we were combining it with endocrine therapy such as fulvestrant and intramuscular SERD and/or letrozole—that is an aromatase inhibitor—in patients where they were very heavily pre-treated in the metastatic setting.

The specific cohort that we presented at ESMO annual meeting in Berlin this year was the cohort of the Phase 1 study where atirmociclib was combined with letrozole for patients with HR-positive, HER2-negative metastatic breast cancer that had not received prior treatment in the advanced setting.

So it kind of simulates almost a first-line scenario, where a patient will receive the CDK4 selective inhibitor in combination with an aromatase inhibitor as letrozole.

Dr. Chalasani:
So, with that in mind, I would like to talk about the efficacy of this combination. I think the presentation focused on the 33 patients who had measurable disease at baseline. Confirmed overall response rate was around 70 percent, with the clinical benefit rate was around 94 percent. So how would you interpret that in the context of our current first-line treatment standards?

Dr. Giordano:
These compare pretty similarly with the clinical trial that has led to the approval of the CDK4/6 inhibitor in the first-line setting. The drug, while it showed a very safe profile—very favorable in terms of myelotoxicity and of GI side effects—we saw the drug moving to the first-line setting here to test in a naive population to see if the results were comparable to these case studies, and to eventually bring us to open the Phase 3 randomized study of atirmociclib with letrozole that compared these novel CDK4 selectives to the prior approved CDK4/6 inhibitors.

Dr. Chalasani:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Antonio Giordano about the efficacy and safety profile of atirmociclib plus letrozole as an initial treatment for HR-positive, HER2-negative metastatic breast cancer.

So as you were mentioning about the safety, and compared to the heavily pre-treated versus the first-line, we would expect some difference in the safety profile. So coming out to that, what were the most common treatment-related adverse events that were noted?

Dr. Giordano:
So in the phase one portion, atirmociclib as a single agent and also, in combination with endocrine therapy, was dosed actually at 300 milligrams twice a day in a continuous dosing. So some of the FDA-approved CDK4/6s actually have a weak interruption to recover from some of the toxicity such as palbociclib and ribociclib, while atirmociclib we are able to dose the molecule continuously for 28 days.

Once tested at this dose of 300 milligrams twice a day, we found that neutropenia was still the most frequent treatment-related adverse event. But the grade 3 neutropenia at this dose was about 26.5 percent, and the drug intensity that we achieved during the treatment of this population was actually pretty high, more than 90 percent. So, we were able to continuously dose the patient at least with the 300 milligram dosage without dose interruption or dose reduction.

Dr. Chalasani:
Okay, so on the trial—I know it was a small study with 33 patients, especially in this treatment-naive group, but overall, how was the tolerability given these side effects in terms of dose interruptions or reductions?

Dr. Giordano:
Atirmociclib is a very well-tolerated drug. The patients we have treated on this clinical trial really did not feel the burden of taking the medication. And other than some neutrophil count drops that led to quick dose interruptions, we didn't have major toxicity for which the patient had to seek for medical attention or return to a clinic or an emergency department for these treatment-related adverse events.

The amazing thing, though, with atirmociclib, is that, in line with the previously approved CDK4/6 inhibitor, it really allows patients to preserve their quality of life and their daily activity as usual, delaying that time to chemotherapy that may affect a patient's lifestyle for sure. So we were gladly seeing that the tox profile of this drug was able to maintain the quality of life and the dose intensity to achieve that dose reduction, tumor volume reduction, and very outstanding median progression-free survival that was right about two years that is in line with the prior CDK4/6 inhibitor in the naive population.

Dr. Chalasani:
That's really good to know. We can always improve on our toxicities and the quality of life for patients. Looking ahead, a Phase 3 trial is now underway, so is there anything that you're hoping to see as that trial unfolds?

Dr. Giordano:
The Phase 3 trial is already open, and so atirmociclib in combination with letrozole has been tested right now head-to-head with the prior approved CDK4/6 inhibitor: so a CDK4/6 of physician choice. Patients will be randomized one-to-one to get a novel selective CDK4/6 inhibitor, such as atirmociclib, in combination with letrozole, versus a prior-approved CDK4/6 inhibitor plus letrozole.

Randomization is one-to-one, and the trial is aiming to enroll patients that never received treatment in the advanced metastatic breast cancer that are hormone receptor-positive, HER2 negative.

Dr. Chalasani:
As we come to the end of our program, Dr. Giordano, what should clinicians take away from this data set when considering future treatment decisions for hormone receptor-positive, HER2-negative metastatic breast cancer?

Dr. Giordano:
I think this sets a nice stage for patients with metastatic breast cancer for treatments that are, at the same time, highly impacting the tumor control and disease controlling with improvement of overall survival, and at the same time, preserving their quality of life.

I think having more oral agents that target cell cycle and endocrine therapy at the same time is, really, a big frontier for the hormone receptor-positive, HER2-negative breast cancer patients that will allow them to continue to extend the survival, even with stage four disease and at the same time, preserve their quality of life.

Dr. Chalasani:
With those important insights in mind, I want to thank my guest, Dr. Antonio Giordano, for joining me to discuss the combination of atirmociclib and letrozole as a first-line treatment option for hormone receptor-positive, HER2-negative metastatic breast cancer. Dr. Giordano, it was great having you on the program.

Dr. Giordano:
Thank you so much, Dr. Chalasani.

Announcer:
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