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Double Take: Pivotal Data Evaluating PI3K Inhibitor/Endocrine Therapy Regimens in mBC

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Dr. Kalinsky:
Hi, this is CE on ReachMD. I'm Kevin Kalinsky, and we're going to talk about the approval of alpelisib for patients who have PI3K or PIK3CA mutations, who have metastatic hormone receptor-positive, HER2-negative disease.

So why don't we even take a step back and then acknowledge that the first agent in this pathway that we had an approval for was everolimus based upon the BOLERO-2 data. And that was regardless of the presence or absence of PIK3CA mutations.

Alpelisib was the first approved PI3K inhibitor in metastatic hormone receptor-positive, HER2-negative disease. This is based upon the SOLAR-1 study that was published in The New England Journal of Medicine. And so one of the things that's important to know in the design is that there was a population of patients who had PIK3CA mutations, so around like 300 or so patients, or a little over 300 patients. And then, there were also patients who had PIK3CA wild-type disease, which was around like 200, 250 patients.

The benefit was exclusively seen in patients with PIK3CA mutations. So just to define the randomization, it essentially was looking at giving fulvestrant with or without alpelisib. In alpelisib, there was a randomized, placebo-controlled trial. The benefit, again, of fulvestrant/alpelisib was exclusively in those patients with PIK3CA mutations, which we've defined in an earlier episode. We've seen about 30% to 40% of patients with metastatic hormone receptor-positive, HER2-negative disease. So what was that benefit? That benefit showed an improvement in progression-free survival. There was a difference at about 5 1/2 months to around 11 months for those patients who received fulvestrant plus alpelisib.

One important thing to know about the population in SOLAR-1, it was a small population of patients who had received prior CDK4/6 inhibitors.Just think about the time in which the study was enrolled and reported. This was before we had the approval of our CDK4/6 inhibitors in the metastatic setting and for sure before we had the approval in the early-stage setting.

Subsequent to that, there were some smaller studies, smaller cohorts in the study, the BYLieve study, which really looked at patients who have had prior CDK4/6 inhibitors. And in that population, there were different cohorts in there that gave different endocrine therapies, including aromatase inhibitors, and the take-home point was that the median progression-free survival of giving endocrine therapy plus alpelisib in a post-CDK4/6 inhibitor world was really about 6 months or so.

Alpelisib, it is important to note, does have some associated toxicities; that includes hyperglycemia. They have pretty strict criteria in

terms of patients who were able to enroll to that, including having to have an appropriate hemoglobin A1c and glucose, like patients who are on insulin were not eligible for that. And that does have implications when we think about utilization of alpelisib in the real world, because as somebody who practices in the state of Georgia, not everybody has perfect glucose control. It also can cause rash. And one of the things that we've since learned is that prophylactic utilization of antihistamines could really decrease that risk.

So their main toxicity that we saw was hyperglycemia. There was also rash, and then there are other gastrointestinal issues, like nausea or diarrhea, and some fatigue.

And so it was an available drug. It's still available and available worldwide. I would say that its utilization in clinic has been subsequently impacted from the approval of capivasertib, which also is approved along with fulvestrant, and also is approved for patients with AKT mutations or P10 alterations and also doesn't have the same sort of rate of hyperglycemia.

So alpelisib is a potential agent that's given along with fulvestrant. We've seen data from SOLAR-1 as well as BYLieve in the post CDK4/6 inhibitor setting. Its use has been somewhat decreased because of some of the toxicities, though it is widely available. I would also say that we are entering a world where we're evaluating either more specific PI3K inhibitors that we'll be talking about in other sessions. But this was very much a proof-of-principle study where we saw that its benefit was specifically in those with PI3K inhibitors. Also to mention that in this particular study, we did not see an overall survival benefit with alpelisib.

Thank you for your attention, and we'll have other topics on other episodes as well.

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