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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Evaluating Post-CDK4/6 Therapy in *PIK3CA*-Mutated Metastatic Breast Cancer

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

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss a study that focused on real-world clinical outcomes for *PIK3CA*-mutated metastatic breast cancer following CDK4/6 inhibitor therapy is Dr. Maxwell Lloyd. He's a Clinical Fellow in Hematology/Oncology at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. He also recently presented this research as a poster at the 2025 San Antonio Breast Cancer Symposium. Dr. Lloyd, it's great to have you here today.

Dr. Lloyd:
Thank you so much for having me. I really appreciate the opportunity to come on and chat with the team and share some of our work.

Dr. Caudle:
Well, we're excited that you're here. So why don't we start with some background— what was the motivation behind this study? And why is the post-CDK4/6 setting such a pivotal decision point for patients with *PIK3CA*-mutated metastatic breast cancer?

Dr. Lloyd:
Great question. For first-line treatment of hormone receptor-positive, HER2-negative metastatic breast cancer, a CDK4/6 inhibitor regimen improves progression-free survival and overall survival. However, the optimal treatment selection following progression on a CDK4/6 inhibitor remains unclear. We now have multiple biomarker-guided and biomarker-agnostic therapeutic regimens approved in this setting, making the post-CDK4/6 inhibitor treatment landscape increasingly complex and important to study.

In our work, we specifically evaluated patients with *PIK3CA*-mutant metastatic breast cancer, which represents a substantial population and accounts for roughly 40 percent of hormone receptor-positive metastatic breast cancer cases. For these patients, there are several approved therapies which target *PIK3CA* or downstream components of the PI3K pathway like AKT, which can potentially be utilized for treatment.

Our study evaluated real-world data to better understand how treatment decisions are being made for these patients in routine practice after CDK4/6 inhibitor progression. We looked at treatment selections, clinical outcomes, and concurrent genomic alterations detected in ctDNA profiling. With emerging targeted therapeutics against *PIK3CA* and *ESR1* mutations, real-world evidence is becoming increasingly important to better understand how therapies are being utilized and sequenced for patients, and to identify clinical and genomic biomarkers that could be leveraged to help improve outcomes and hopefully minimize unnecessary toxicities.

Dr. Caudle:
Now, let's zero in on the study's design for a moment. How did the GuardantINFORM dataset and the use of ctDNA testing shape your approach?

Dr. Lloyd:
We leveraged GuardantINFORM for this study, which is a large real-world clinical genomic data set that integrates de-identified ctDNA sequencing results with real-world claims data. This dataset allows us to evaluate treatment selections and clinical outcomes that are linked with genomic biomarkers.

So, in this context, we used GuardantINFORM to take a close look at how providers are managing *PIK3CA*-mutant metastatic tumors in

modern practice by including patients with ctDNA testing from November 2023 onward, which was the time that the FDA approved capivasertib in combination with fulvestrant.

In our study, we included only patients who progressed on a line of CDK4/6 inhibitor therapy who had a ctDNA-detected *PIK3CA* mutation detected before starting the next line of therapy. So this approach allowed us to accurately assess therapy choices and associated genomic profiles in this population following progression on a CDK4/6 inhibitor. Clinical outcomes on these next-line therapies were then evaluated using time to next treatment or time to treatment discontinuation, which are well-described surrogate outcomes for progression-free survival, using real-world claims data.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Maxwell Lloyd about real-world outcomes in *PIK3CA*-mutated metastatic breast cancer following progression on a CDK4/6 inhibitor.

So, Dr. Lloyd, now that we have some background on the study, let's take a look at the findings. Capivasertib emerged as the most commonly used therapy after CDK4/6 inhibitor progression, with 25 percent of patients receiving it. Can you walk us through what stood out about its use in this real-world setting?

Dr. Lloyd:
It's a great question. As you highlight here, in this cohort with *PIK3CA*-mutant tumors following progression on a CDK4/6 inhibitor, we found that in routine practice, capivasertib was more frequently selected than other therapy options, including the *PIK3CA* inhibitor alpelisib, CDK4/6 inhibitor rechallenge, or chemotherapy.

These data demonstrate shifting practice patterns in the current management of hormone receptor-positive metastatic breast cancer and an increasing adoption of precision therapeutic strategies based on genomically identified biomarkers and ctDNA.

Compared to alpelisib, we found that the time to treatment discontinuation was slightly longer with capivasertib, though these data, along with our time to next treatment and overall survival data, are still maturing. Our goal is to conduct an updated analysis sometime next year with more mature data to better identify potential differences in clinical outcomes between these agents in practice.

Notably, not captured in our current study are differences in toxicity between these therapies. In general, capivasertib has a more favorable safety profile compared to alpelisib, which likely plays a role in providers more frequently using capivasertib in routine practice.

Dr. Caudle:
As a follow-up to that, in your post-treatment analysis of patients receiving capivasertib, you found increased frequencies of alterations like *FGFR1*, *CCND1*, and *KRAS* compared to baseline. What do these shifts suggest about potential resistance mechanisms, and how might that influence future research efforts?

Dr. Lloyd:
Great question. In this study, we compared genomic alterations detected in baseline and post-progression ctDNA among patients treated with capivasertib. So we limited the post-progression ctDNA analysis to be within 90 days of stopping therapy in order to better model the genomic profile of these tumors at or around the time of progression. And what we found was that the alterations in these three genes—*FGFR1*, *KRAS*, and cyclin D1—were potentially enriched in the post-capivasertib samples compared to baseline, with a two- to three-fold greater alteration frequency after progression. Enrichment was not seen in the other genes that we assessed. While this study evaluated small sample sizes, overall, these data hint at potential acquired resistance mechanisms to AKT inhibitor therapy. Dysregulated signaling mediated by these genes in downstream pathways could diminish sensitivity to AKT blockade and drive tumor progression.

These findings are hypothesis-generating and require additional clinical and preclinical validation, but these data could serve to inform the design of future precision clinical trials, for example, with exploring combination therapies targeting these genes or downstream pathway components in order to overcome resistance and potentially resensitize tumors to a targeted therapeutic approach.

Dr. Caudle:
Now, among patients with both *PIK3CA* and *ESR1* mutations, elacestrant was the preferred option, with 40 percent of patients receiving it. What does that tell you about how clinicians are approaching treatment selection based on mutational profiles in the real world?

Dr. Lloyd:
Yeah, this is a really important population where we have a lot of interesting questions right now emerging in practice. So *ESR1* mutations are a well-described, commonly acquired mechanism of resistance to aromatase inhibitor therapy in metastatic breast cancer. And after progression on a first-line CDK4/6 inhibitor and endocrine therapy, studies estimate that about 20 percent or more of

patients could have tumors that harbor alterations in both *PIK3CA* and *ESR1*. This is particularly relevant because there are multiple biomarker-guided therapies that are approved for alterations in each of these genes. And in patients with dual-mutant disease, the optimal treatment selections and sequencing of these agents remain uncertain.

As you mentioned, in real-world practice, we found that 40 percent of patients with ctDNA-detected *PIK3CA* and *ESR1* mutations received elacestrant after progression on a CDK4/6 inhibitor, while the next most common therapy given was capivasertib at 17 percent. These data suggest increasing utilization of mutation-guided treatment selection in routine practice, and they also reflect that providers are individualizing treatment decisions for patients with multiple biomarker-based therapy options at times of progression. In clinical practice, the optimal sequence of therapies is not well established, and treatment decisions are often individualized based on factors like duration of response to prior therapies, the overall burden of disease and presence of visceral metastases, associated symptoms, potential side effects of therapy, and patient preference.

Elacestrant was the most commonly employed next-line therapy in our patient cohort within this dual-mutant subgroup; elacestrant generally has a favorable safety profile as an endocrine monotherapy, and prior evidence also suggests that it retains efficacy in tumors with concurrent *PIK3CA* mutations. However, there are certain circumstances in certain patient populations or tumor characteristics where clinicians would favor using an agent like capivasertib with fulvestrant or even a biomarker-agnostic approach with medicines like an antibody-drug conjugate or even chemotherapy. And the variations we found in subsequent therapies for this dual-mutant disease population illustrates the need for additional clinical and genomic biomarker validation to really help guide these real-world care decisions in situations where multiple treatment options are approved.

Dr. Caudle:
And as we come to the end of our program, Dr. Lloyd, how do you see these findings shaping next steps, whether in clinical trials or everyday practice?

Dr. Lloyd:
These data help support the general shift we are seeing toward biomarker-informed approaches to treatment selection after progression on a CDK4/6 inhibitor for patients with metastatic breast cancer.

Our results here illustrate real-world practice patterns and identify potential biomarkers of acquired resistance to AKT inhibitor therapy, though these findings need prospective and laboratory validation to potentially inform treatment decisions. We envision a potential role for tracking of emerging resistance mediators with tools like serial ctDNA, which are being incorporated more and more into modern clinical trial designs.

Our data also highlight the need for additional clinical and genomic biomarkers to help clinicians with decisions about optimal treatment selection in situations where multiple therapies are approved concurrently.

Dr. Caudle:
That's a great comment for us to think on as we wrap up today's program. And I'd like to thank my guest, Dr. Maxwell Lloyd, for giving us a real-world look at *PIK3CA*-mutated metastatic breast cancer treatment post-CDK4/6 inhibitor therapy. Dr. Lloyd, thank you so much for being here today.

Dr. Lloyd:
Thank you so much. I really appreciate the opportunity.

Dr. Caudle:
Thank you.

Announcer:
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