Transcript Details

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Biomarker-Guided Treatment in ER+, HER2- Metastatic Breast Cancer

ReachMD Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:
Welcome to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ryan Quigley, and joining me to discuss biomarker-informed personalized treatment strategies for ER-positive, HER2-negative metastatic breast cancer is Dr. Maxwell Lloyd. He's a Clinical Fellow in hematology and oncology at the Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Dr. Lloyd, thanks so much for being here today.

Dr. Lloyd:
Thank you, Ryan. I really appreciate the opportunity to come on the program and talk about this topic.

Ryan Quigley:
Absolutely, yeah. So, Dr. Lloyd, to kick things off, can you walk us through how biomarker testing has evolved in ER-positive, HER2-negative metastatic breast cancer over the last decade?

Dr. Lloyd:
Absolutely. Over the last decade, biomarker testing has evolved substantially with the advent of next generation sequencing, really making tumor genomic profiling feasible for individual patients and helping to refine our understanding of breast cancer biology and our treatment paradigms.

Using tumor tissue or liquid biopsy specimens, these approaches allow us to identify molecular changes in DNA and RNA, providing insight into signaling pathway dependencies and therapeutic vulnerabilities in breast tumors.

In metastatic breast cancer, commercially available, next-generation sequencing assays are now routinely used to identify genomic alterations. When paired with clinical characteristics and tumor receptor status, these findings can increasingly guide targeted therapy selection and help us understand some of the mechanisms of treatment resistance that might emerge.

A prominent example of this is *ESR1* mutations. *ESR1* encodes the estrogen receptor and is rarely mutated at diagnosis, but mutations commonly emerge as an acquired resistance mechanism to aromatase inhibitors. These mutations promote ligand-independent estrogen receptor signaling, limiting the effectiveness of an estrogen deprivation strategy. Investigators have developed next generation orally bioavailable selective estrogen receptor degraders and other novel endocrine therapies, which are entering clinical practice and have shown improved activity against *ESR1* mutant disease.

Another example is alterations in the PI3K-AKT signaling pathway, including *PIK3CA*, *AKT1,* and *PTEN*, which can drive oncogenic tumor growth. Several *PI3K* and *AKT* inhibitors are now approved for this biomarker-defined population, with many more next-generation agents in active development.

BRCA mutations also inform underlying tumor biology, causing impaired DNA repair and conferring sensitivity to PARP inhibitor therapy, and with a number of therapeutics now having biomarker-approved labels for use in estrogen receptor-positive, HER2-negative metastatic breast cancer, we see evidence in shifting practice patterns for the routine management of advanced disease.

Ryan Quigley:
Now, with all that in mind, how do you approach biomarker testing when a patient first presents with metastatic disease and how does

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that strategy evolve as the disease progresses?

Dr. Lloyd:
That's a great question. In terms of the approach to biomarker testing, we can really think about testing tumor tissue or using ctDNA, and there are advantages and limitations to each approach.

With tissue testing, it requires an invasive biopsy, but it can provide important pathology information. In addition to next generation sequencing, IHC testing of tumor tissue can assess ER, PR, HER2, PD-L1 status, and there are often opportunities where we can actually test archival tissue specimens rather than needing to obtain a fresh biopsy.

Tissue specimens can be limited in terms of insight into tumor heterogeneity just because we are sampling one area of one site.

On the other hand, liquid biopsy is a non-invasive blood test which can assess circulating tumor DNA in the blood, and often provide sequencing information more in real time. While ctDNA cannot yet reliably assess receptor status, newer methods incorporating methylation profiling are looking into this question.

And additionally, ctDNA tends to better reflect tumor heterogeneity and global mutational burden, though it can be less reliable for detecting certain alterations—for example, low level copy number changes.

At metastatic diagnosis for a patient, we would ideally obtain both tissue and ctDNA sequencing. Then, as patients progress on lines of therapy for metastatic disease, repeat genomic sequencing becomes important to identify mutations which may emerge under therapeutic pressure and drive drug resistance. In practice, this often involves repeat ctDNA testing at times of disease progression before changing therapies to identify any new actionable biomarkers.

Ryan Quigley:
And once you have those biomarker results, how do they inform your treatment decisions and what kind of key factors shape how you tailor therapy based on those findings?

Dr. Lloyd:
In the first-line setting, a CDK4/6 inhibitor with anti-estrogen therapy really remains the preferred upfront approach for most patients—irrespective of the biomarker status—given the survival benefit we've seen with this approach, particularly with ribociclib or abemaciclib combined with endocrine therapy.

There are select high-risk patients with *PIK3CA*-mutant breast cancer who relapse on or shortly after adjuvant endocrine therapy for whom triplet therapy with fulvestrant, palbociclib, and inavolisib, which is a PI3K inhibitor, might be preferred, because we did see an overall survival benefit in the INAVO120 trial with this regimen for this high-risk population in the first-line setting.

But as we move into the second-line and third-line setting, genomic biomarkers more often directly inform treatment selection. For example, in patients with an acquired *ESR1* mutation, oral SERD monotherapy is an option.

Elacestrant and imlunestrant are two such agents, which are currently approved in this population, and other next-generation endocrine therapies are emerging clinically. As one example, we recently saw positive phase III data for the PROTAC vepdegestrant, which has a unique mechanism of action in *ESR1*- mutant disease when compared against fulvestrant.

Another example is tumors harboring *PIK3CA, AKT1,* or *PTEN* alterations where a biomarker-approved option is the AKT inhibitor capivasertib combined with fulvestrant. And in patients with *PIK3CA*-mutant disease, the PI3K inhibitor alpelisib is another option, though it can be a little more challenging than capivasertib to tolerate from a side effect perspective, and there are several next-generation *PI3K* pathway-targeted agents that are in development with the potential for improved efficacy and improved safety, including less hyperglycemia with *PI3K* mutant selected inhibitors that are being developed.

In *BRCA*-mutant breast cancers, PARP inhibitor therapy with olaparib is also an effective strategy, and then, in later-line disease that has become endocrine resistant, requiring a transition to an antibody drug conjugate or chemotherapy, HER2-low status—as we mentioned—is used as a biomarker to guide treatment decisions around the use of T-DXd, which, based on the results from the DESTINY- Breast09 trial, is generally preferred over a standard single-agent chemotherapy strategy in this population.

Ryan Quigley:
And for those just tuning in, you are listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Maxwell Lloyd about the evolving role of biomarkers in guiding treatment decisions for ER-positive, HER2-negative metastatic breast cancer.

So, Dr. Lloyd, while the potential of biomarker driven care is exciting, putting it into practice isn't always straightforward, of course. So,

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what challenges or limitations do you see in translating this data into treatment decisions?

Dr. Lloyd:
That is a great question. With multiple biomarker-approved treatment options, one of the most difficult decisions in clinic is selecting the right treatment for the right patient at the right time. While having many different effective regimens is great, it can also create some uncertainties around how to best individualize care and how to best sequence these therapies to optimize outcomes like progression-free survival, overall survival, and quality of life.

Additionally, many of these regimens will never be compared head-to-head in large trials. So combining insights from prospective clinical trial data and real-world evidence from routine practice is key to help address these sequencing questions and equip oncologists with data and information to navigate situations where multiple reasonable treatment options might exist.

Another limitation of biomarker-driven care is the imperfect nature of our diagnostic tools. Tissue biopsies may miss some underlying tumor heterogeneity, while liquid biopsies could underrepresent certain metastatic sites that may have less tumor shedding and could be driven by alternative signaling pathways not detected in the ctDNA sequencing results that the oncologist receives. And this could result in incomplete or suboptimal treatment of a patient's disease, and in some cases, lead to early disease progression.

And beyond just the technical limitations, identifying actionable biomarkers and targeting them can also introduce financial toxicity and logistical challenges for patients. I'm fortunate to practice in a well-resourced, academic cancer center with streamlined access to sequencing technologies. However, in many practice settings, both within the United States and outside of the United States, biomarker-driven care may be less accessible and potentially limit opportunities for personalized treatment for patients.

Ryan Quigley:
So let's look ahead for a moment now. I'm curious, how do you see biomarker informed treatment strategies evolving over the next five to 10 years?

Dr. Lloyd:
There are many emerging biomarker-informed strategies and diagnostic tools on the horizon that are likely to help shape clinical practice.

In the near future, I believe we will see more combination regimens that target multiple genomic alterations simultaneously. For example, pairing a next generation oral SERD with a PI3K or AKT inhibitor or tumors with concurrent *ESR1* and *PIK3CA* mutations. We saw some data from the MORPHEUS trial, which includes an arm evaluating giradestrant, which is an oral SERD, with inavolisib, which is PI3K inhibitor in hormone receptor-positive metastatic breast cancer after progression on a CDK4/6 inhibitor. This regimen showed an impressive 77 percent objective response rate in patients with tumors harboring both *ESR1* and PIK3CA alterations.

At the same time, next-generation PI3K pathway targeted therapies are emerging with more favorable safety profiles and better efficacy, potentially making them better suited for these types of combination strategies with other targeted therapies from an overall safety perspective in a regimen that can be tolerated with multiple agents.

Another exciting, evolving paradigm is the earlier identification in targeting of molecular resistance mechanisms ahead of overt clinical progression. While questions still remain about the overall benefits and logistical implementation of this approach in routine practice—including what is the optimal timing of therapy sequencing and what are the financial and logistical implications of obtaining serial ctDNA monitoring in patients—SERENA-6 nicely illustrates the potential impact of intervening on molecular progression before clinical progression, with the goal of targeting underlying resistance clones in order to prolong disease control using just an endocrine therapy strategy and delaying time to cytotoxic chemotherapy exposure.

Ryan Quigley:
Dr. Lloyd, before we wrap up here, do you have any final thoughts that you'd like to leave with our audience?

Dr. Lloyd:
I believe that continuing to pursue a goal of using the right treatment for the right patient at the right time is paramount to improving the lives of patients with breast cancer. Ongoing advances in diagnostic technologies and targeted therapies are a critical part of making that a reality, and I really want to thank you so much for having me on the program. It was a privilege to join you and be able to discuss this topic.

Ryan Quigley:
Likewise. It was a pleasure to have you on, and with those closing comments in mind, I do want to thank my guest, Dr. Maxwell Lloyd, for joining me to discuss how biomarker testing is shaping personalized care in ER-positive, HER2-negative metastatic breast cancer. Dr. Lloyd, again, thank you so much for doing this. Really appreciate you coming on with us.

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Dr. Lloyd:
Thanks so much. Really appreciate it.

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