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Genomic Profile of ER+ HER2- Metastatic Invasive Lobular Carcinoma

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. Pavani Chalasani.

Dr. Chalasani:
This is *Project Oncology* on ReachMD, and I'm Dr. Pavani Chalasani. Today, we'll be discussing a recent analysis presented at the 2025 San Antonio Breast Cancer Symposium, where the authors presented the genomic landscape of ER-positive, HER2-negative metastatic invasive lobular carcinoma and how it compares to that of invasive carcinoma of no special types or other subtypes.

Joining me for this conversation is Dr. Christina Fanucci, who's a co-author on this study, an instructor in medicine at Harvard Medical School, and an oncologist at Dana-Farber Cancer Institute in Boston.

Dr. Fanucci, it's great to have you here today.

Dr. Fanucci:
Thank you for having me.

Dr. Chalasani:
To start us off, Dr. Fanucci, can you walk us through how invasive lobular cancer differs from the invasive carcinoma of no special type and why those differences might matter?

Dr. Fanucci:
Sure. So invasive lobular carcinoma, or ILC, is the second most common subtype of breast cancer after invasive carcinoma of no special type, or NST, which we also commonly call invasive ductal carcinoma, or IDC. And ILC makes up about 10 to 15 percent of all breast cancers. This means that ILC is more common in women than cancers of the ovary, pancreas, brain, kidney, or liver, with about 47,000 patients diagnosed with ILC each year in the United States. But we have a lot less research and understanding of ILC compared to NST.

Lobular carcinoma has unique pathologic features that are generally characterized by its loss of this cell adhesion molecule E-cadherin, which leads to tumors with diffuse infiltrating patterns rather than discrete mass formation. And this can cause a growth pattern that can impact its ability to be well seen on some imaging modalities and that can underestimate the extent of disease.

Lobular breast cancers also have unique patterns of metastatic spread, including a proclivity for sites like the omentum, peritoneum, and pleura, which can lead to different complications that come along with the cancer.

And despite all these really meaningful differences, ILC treatment doesn't differ from the treatment for NST.

Dr. Chalasani:
With that background in mind, let's dive into the study's results. What were the most notable genomic alterations you were able to find in the metastatic invasive lobular carcinoma group, and what stood out to you about these patterns, especially when compared to the non-invasive lobular or invasive carcinoma of no special type subgroup?

Dr. Fanucci:
So we used a cohort of patients from our institutional database who had metastatic hormone receptor-positive, HER2-negative breast cancer, who were seen here between 2001 and 2022, and who had a tumor tissue sample that had our genomic panel, OncoPanel,

completed on it. And basically, the questions we were asking in our analysis were, what are the most common mutations we see in this cohort? And then, comparing samples from patients with ILC to samples from patients with NST, what are the differences we see in terms of the genomic landscape?

So, in our analysis, we found that the most commonly mutated genes in ILC were *CDH1*, which was mutated in 76 percent of the samples; *PIK3CA*, which was mutated in 58 percent of samples; *TP53*, which was mutated in 14 percent of samples; *ESR1* in 10 percent; *P10* in six percent; *NF1* in six percent; *MAP3K1* in six percent; *ERBB2* in six percent; and *AKT* in five percent. And then we also saw amplifications in *CCND1* in 16 percent of samples and *FGFR1* in seven percent of samples.

And then, when we compared the rates of these alterations between ILC and NST, we found that alterations in *CDH1*, *PIK3CA*, *ERBB2*, and *FOXA1* were more common in ILC, while mutations in *GATA3* and *P53* were more common in samples from patients with NST.

And I think that this unique genomic landscape highlights potential targets for treatments that are specific to patients with ILC, some of which are already being explored, but many of which still have a long way to go before being actionable in the clinic.

So this most common alteration that we see, *CDH1*, is not thought to be directly druggable, but it does increase dependence on other pathways for proliferation like SRC, and that is a druggable target. SRC is inhibited by the tyrosine kinase, bosutinib. And early phase trials of bosutinib in combination with fulvestrant and palbociclib showed potential benefit of the combination in pre-treated patients and will potentially be explored in other clinical trials in the future.

And then with this protein that's encoded by *CDH1*, e-cadherin, when we have cells that lack e-cadherin, the cells lose spatial orientation and regulation of tumor cell growth, in part because of loss of regulation of P10 expression, which is an important protein in that PI3kinase *AKT/P10* pathway.

And so loss of P10 expression can result in increased activation of the PI3-kinase pathway, providing a rationale of potential increased benefit of inhibiting that pathway in patients with ILC. Right now, we have medications that target that pathway, like capivasertib, which we have approval for in patients who have *PIK3CA* or *AKT* pathway alterations. But there's potential benefit in patients with ILC who even lack alteration based on this increased activation of the pathway. And so I think another future, exciting, potential route for investigation would be drugs that target that pathway in patients with ILC, regardless of their mutation status—all things that are being explored and exciting for potential future clinical trials.

Dr. Chalasani:
When you looked at the timings of recurrence, there were differences in genomic profiles between early versus late relapse. Can you walk us through those findings and their potential implications?

Dr. Fanucci:
Yeah, sure. So, we were interested to see if there were any associations with different clinical variables of some of these genomic alterations. And one that particularly stood out was that we found that *ERBB2* alteration, the gene that encodes the HER2 protein, was associated with early recurrence. So patients who recurred within the first five years after their initial diagnosis of early-stage breast cancer were more likely to have an *ERBB2* alteration. I think that where this is potentially interesting in a clinical context is that this could be investigated as a biomarker that could help identify patients with more aggressive disease subtypes and then, potentially, in patients who have *ERBB2* mutation, escalate treatment in some way in the neoadjuvant or adjuvant setting, hoping to increase the rates of cure in this population. But I think all of those things will need to be investigated in future trials.

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. Christina Fanucci about the genomic profile of ER-positive, HER2-negative metastatic invasive lobular carcinoma.

Now, let's talk about the treatment response results, Dr. Fanucci. Despite the genomic differences you mentioned about ILC, especially when compared to the invasive carcinoma of no special type, there were no significant differences in the median time to next treatment or in the overall survival. How do you interpret these outcomes in the light of those distinct genomic landscapes?

Dr. Fanucci:
So we were reassured to see that in our cohort of patients, which included about 100 patients with lobular breast cancer and 350 patients with NST, who we had survival outcomes for, we did not see significant differences in terms of how well these patients did. So we looked at patients who were treated with first-line endocrine therapy plus CDK4/6 inhibitor—our current standard of care of first-line treatment in this population—and regardless of histology, patients had similar median time to next treatment.

So in patients with lobular breast cancer, we saw a median time to next treatment of 18 months, compared to 21 months for patients with NST, and that wasn't significantly different. And we were also reassured to see that the median overall survival between these two

groups was also similar.

I think this is just an encouraging indicator that these genomic differences we're seeing don't result in significantly different treatment outcomes with the current regimens that we're using.

Dr. Chalasani:
The last finding I would like to get your thoughts are on the link between *ERBB2* alterations and liver metastases. What do you think those findings mean and how do they impact clinical practice?

Dr. Fanucci:
Sure. Our numbers were small, but we did see that *ERBB2* alteration was more common in patients with liver mets. The reason for this is unknown, but it's possible that the increased cell motility that we see with *ERBB2* mutation coupled together with the loss of cell adhesion that comes along with *CDH1* alteration could increase this propensity for mets to the liver. Many analyses of patients with metastasis to liver have shown shorter overall survival compared to patients without liver mets. And disease in the liver has been shown to be particularly insensitive to some treatments, maybe because of this unique immune environment that's present in the liver. But I think that the finding of increased *ERBB2* alteration in disease with liver mets could suggest benefit from medicines that target HER2 in this population.

There have been trials that looked at investigating combinations of HER2-targeting medicines with estrogen receptor-targeting medicines in patients who have hormone receptor-positive disease with *ERBB2* alteration. The SUMMIT trial looked at the combination of neratinib with fulvestrant and trastuzumab in patients with pretreated hormone receptor-positive, HER2-negative metastatic breast cancer that had activating HER2 mutation and found a clinically meaningful progression-free survival about eight months in those patients.

And then we also have the medication trastuzumab-deruxtecan that's available in patients with HER2 alteration, based on the DESTINY-PanTumor01 trial that enrolled patients with solid tumors with activating HER2 mutations. That trial included patients with breast cancer and also found a potential benefit in progression-free survival in these populations.

So I think it really just highlights another targeted treatment that's available for patients with *ERBB2* alteration.

Dr. Chalasani:
As we come to the end of our program, Dr. Fanucci, what would you say are some of the important takeaways for oncologists treating patients with metastatic invasive lobular carcinoma?

Dr. Fanucci:
I think there are two important takeaways. The first is that in this metastatic cohort of patients, we found that ILC has this unique genomic landscape that creates opportunities for development of histology-specific treatments. There are lots of exciting lobular-specific clinical trials that are opening, and the goal is to open more trials that are either ILC-specific or more inclusive of patients with ILC, so that we can learn more about what treatments are most effective in patients with this unique histology.

And I think the other important takeaway from this cohort is that we saw similar outcomes for patients with ILC to those with NST. So, while our available therapies aren't specific for patients with ILC, they are effective against this disease.

Chalasani:
With that key takeaway in mind, I want to thank my guest, Dr. Christina Fanucci, for sharing this research on genomic differences between ER-positive, HER2-negative metastatic invasive lobular carcinoma compared with invasive carcinoma of no special type.

Dr. Fanucci, thanks for joining us today.

Dr. Fanucci:
Thank you for having me.

Announcer:
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