Deciphering the molecular landscape of metastatic lobular breast cancer

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Invasive lobular carcinoma (ILC) accounts for up to 15\% of all invasive breast cancers and is the second most common type in female breast cancer patients, following invasive breast cancer of no special type (NST).\textsuperscript{1} An increase in the incidence of ILC over the last decade has been linked to advances in diagnosis and increased use of hormone replacement therapy in postmenopausal women.\textsuperscript{2} Compared to NST, ILC has distinct biological and clinical features which challenge diagnosis and treatment management. Despite these unique differences, ILC and NST are currently treated the same way. Furthermore, prognosis in the long term is worse for ILC than NST patients, mainly due to late recurrences. Nevertheless, there are some controversies regarding the outcome differences.\textsuperscript{3,4} One of the hallmarks of ILC is the loss of E-cadherin and a linear growth pattern. Interestingly, the diagnosis of ILC is therefore challenging, and frequently, larger tumors are diagnosed. At the early stage, this leads to higher rates of mastectomies due to larger tumors and greater tumor involvement. Overall, diverse biology and clinical behavior are caused by distinct cells of origin, molecular features, dynamics of disease, growth, and metastasis pattern.

In a recent issue of eBioMedicine, Davis and colleagues\textsuperscript{5} analyzed circulating tumor DNA in a large cohort of breast cancer patients. So far, as the authors correctly state, their analysis provides the largest evidence on ILC circulating tumour DNA (ctDNA) profiles to date. Among the mutations more commonly found in ILC was CDH1. Interestingly, CDH1 was significantly co-mutated with targetable alterations like PIK3CA and ERBB2. Some of these alterations are known predictors for response to drugs; for example, PIK3CA-mutated tumors were shown to derive benefit from alpelisib.\textsuperscript{6} ERBB2 was one of the alterations in the PLASMA-match trial, where clinical benefit could be demonstrated in patients with ERBB2 mutations detected in ctDNA who were then treated with Neratinib.\textsuperscript{7} Also, mutations associated with endocrine resistance, such as ARID1A, NF1, RB1, ESR1, and FGFR2, were more commonly found in ILC. For some of these mutations, novel therapeutic approaches are under investigation. The recently published PADA1 trial highlights a fundamental paradigm shift in how to interpret and handle endocrine resistance. For the first time, the possibility to switch only the endocrine partner while the patients remain on CDK4/6 inhibitors was demonstrated as beneficial.\textsuperscript{8} With novel selective estrogen receptor degraders (SERDs), these findings may gain even more importance. Analog studies are now being performed with ctDNA-based ESR1 testing and a switch from aromatase inhibitors to SERDs while keeping the CDK 4/6 inhibitor.\textsuperscript{9} Such an approach could soon bring ctDNA testing into clinics and may be particularly important for ILC patients. Inactivating NF1 mutations have been recognized as contributors to endocrine resistance, and treatment evaluating trametinib in combination with endocrine treatment may become a therapeutic option.\textsuperscript{10} As Davies et al. have shown, NF1 mutations are also more frequent in ILC.

These mutational profiles and differences between NST and ILC provide important information for basic researchers to establish molecular approaches and evaluate key mechanisms leading to novel treatment strategies. In silico-based analyses can be used to assess resistance alterations and modify these alterations using CRISPR-Cas9-based integration of short nucleotide variants in breast cancer cell lines. These models allow for drug and resistance testing and evaluating novel therapeutic approaches. Thus, an increasing number of novel therapeutic strategies can be expected in coming years, as studies such as the ctDNA analyses by Davis et al. provide additional evidence.

Several mutations particularly described in ILC patients are targetable. As of yet, there is no direct implication of these data on treatment of patients since, in the early-stage disease in particular, mutational profiling does not add any additional treatment option. In metastatic disease, patients in the first lines of treatment receive endocrine treatment combinations either regardless of mutations or independent of histological subtype. However, in second line treatment,

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PI3 kinase inhibitor treatment is dependent on detection of the activating mutation, and data by Davis et al. support more frequent PIK3CA mutations in ILC. Although these studies have not focused on ILC, Davis et al. add this knowledge by showing the frequency of mutations in ILC, thereby defining our clinical expectations.

In the metastatic setting, even fewer data are available to provide insights into the molecular mechanisms of diseases. Thus, the ctDNA characterization of ILC in patients with metastatic breast cancer by Davis et al. adds important evidence to the existing literature and increases insight into ILC. It is almost imperative to suggest, based on this data, that studies specifically addressing ILC of defined genomic profiles should be designed. Meanwhile, we can acknowledge that ILC has distinct molecular features compared to mixed histologies and NST.

Contributors
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Declaration of interests
The authors declare no conflict of interest.

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