



Invasive Lobular Carcinoma of the Breast: Ongoing Trials, Challenges, and Future Directions

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Abstract

Purpose of Review Invasive lobular carcinoma (ILC) is increasingly recognized as a distinct subtype of breast cancer with unique management challenges. We reviewed currently available clinical trials for patients with ILC.

Recent Findings We describe the rationale for and study design of clinical trials for patients with both early stage and metastatic ILC. Molecular alterations specific to or enriched in ILC may serve as treatment targets.

Summary ILC has specific features that may be treatment targets. Clinical trials for ILC are available and being developed.

Keywords Invasive lobular carcinoma · Clinical trials · E-cadherin

Introduction

Breast cancer is the most common malignancy occurring in women, with over 280,000 cases diagnosed annually in the USA [1]. Of these, the second most common subtype after invasive ductal carcinoma (IDC) is invasive lobular carcinoma (ILC), which represents approximately 15% of all new breast cancer diagnoses. Lobular carcinomas arise from the epithelial cells of the terminal duct lobular units of the breast [2]. The defining characteristic of ILC is the absence of the adhesion protein E-cadherin, which results in a number of unique characteristics including a diffuse growth pattern in so-called “single file lines” [3]. The absence of functional E-cadherin in ILC results from alterations in the E-cadherin gene, CDH1. While the majority of ILC tumors have somatic mutations or methylation of CDH1, germline mutations in CDH1 result in the clinical syndrome termed Hereditary Diffuse Gastric Cancer and confer high lifetime risk of both ILC and diffuse gastric cancer [4].

Most ILC tumors are hormone receptor (HR)-positive and human epidermal growth factor-2 (HER2) overexpression negative, with fewer than 10% being either HR negative or HER2 positive [5]. While ILC has been historically viewed as a homogenous tumor type, recent data highlight both the differences between ILC and IDC, and the heterogeneity within ILC [6]. Despite its unique features, few studies focus specifically on this tumor type. In this article, we discuss the distinct features of ILC, challenges to its study, current clinical trials for patients with ILC, and future directions.

Invasive Lobular Carcinoma Is a Distinct Biologic and Clinical Entity

ILC is increasingly recognized as a distinct subtype from the more common IDC in its biologic and clinical features, including its mutational profile, molecular signatures, appearance on imaging studies, response to therapy, and recurrence pattern [7–10]. Nearly all ILC tumors lack E-cadherin expression, which results in a number of consequences including cytosolic translocation of the catenin p120, subsequent activation of the Rho/Rho-associated kinase 1 (ROCK) pathway, and anchorage independent growth in vitro [11]. Additionally, E-cadherin loss appears to result in activation of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt signaling pathway, irrespective of oncogenic mutations in PIK3CA [12]. Somatic mutations in ILC differ from those in IDC, with increased prevalence of mutations in FOXA1, AKT1, PTEN,

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HER2, HER3, and FGFR4 seen in HR-positive, HER2-negative ILC compared to HR-positive, HER2-negative IDC [8, 13, 14]. Within ILC, specific gene expression signatures have recently been described, providing evidence for heterogeneity within this tumor type and potential predictors of response to therapy [7, 15, 16]

Upon clinical presentation, patients with ILC face unique challenges starting with delays in diagnosis and imprecision of clinical staging. Indeed, many standard tools for diagnosing and treating breast cancer show diminished performance in ILC compared to IDC. Imaging tests like mammography, ultrasound, and breast magnetic resonance imaging (MRI) have reduced sensitivity for ILC, resulting in patients with ILC being diagnosed at later stages, with the extent of disease often being underestimated during surgical planning [17]. This, coupled with the diffuse growth pattern seen in ILC, leads to high positive margin rates at surgical excision and the need for more repeat operations, completion mastectomies, and axillary dissections compared to those with IDC [18]. Response rates to standard chemotherapy are lower in ILC, and long-term recurrence risk is equal to or higher than those seen in luminal IDC [19–21]. In the metastatic setting, ILC has a unique pattern of metastasis including diffuse involvement of the gastrointestinal tract, peritoneum, and pleura. Metastatic lobular carcinoma is often radiographically occult, resulting in delayed diagnosis of recurrence and making disease and response assessment challenging [22].

Despite these differences in molecular drivers and clinical presentation between ILC and IDC, current paradigms for breast cancer treatment do not take histologic differences into account, largely based on historic beliefs that ILC required no special therapeutic strategy [23]. However, the appreciation for heterogeneity in breast cancer has allowed for tailoring treatment driven by tumor biology. The recent creation of the Lobular Breast Cancer Alliance, the first national advocacy organization with a focus on advancing research in ILC, reflects the growing need for ILC specific research studies [24].

Unique Challenges Associated with Invasive Lobular Cancer Research

Although increased awareness of and appreciation for the unique features and clinical challenges in ILC have led to the development of some clinical trials specifically for patients with ILC, barriers to research in this field exist. Challenges include difficulties with patient accrual given the relatively lower incidence of ILC compared to IDC, and lack of a robust validated endpoint for treatment response in both the early and late stage settings specifically for lobular histology. In the neoadjuvant setting, pathologic complete response (pCR) after neoadjuvant chemotherapy is a validated early endpoint

that predicts long-term recurrence risk and survival [25–27]. Rates of pCR are low in ILC and HR+ HER2-negative tumors in general, and the prognostic value of pCR is less informative in these subtypes. The Residual Cancer Burden method, which provides a more nuanced reflection of tumor response, may provide more dynamic range to assess response in ILC [28]. In addition, HR+ HER2-negative ILC may benefit more from endocrine-based strategies than chemotherapy. Testing endocrine-based strategies in the neoadjuvant setting is of great interest; however, one of the main limitations in moving this field forward is the lack of a reliable response endpoint for neoadjuvant hormone therapy.

The common use of Response Evaluation Criteria in Solid Tumors (RECIST) to assess efficacy in the metastatic setting makes it particularly difficult for patients with advanced lobular cancer to participate in clinical trials [29]. These trials require patients to have measurable disease based on strict RECIST definitions. Due to the unique non-measurable pattern of metastasis in lobular cancer [22], many patients with widely metastatic ILC do not have measurable disease per RECIST and are often excluded from therapeutic trials. Thus, current clinical trial eligibility criteria may put patients with lobular cancer at a disadvantage, and additional eligibility and response criteria for lobular histology should be considered.

Current Clinical Trials for Patients with Invasive Lobular Carcinoma

There are currently active clinical trials specifically for patients with ILC or E-cadherin-deficient tumors like ILC, and others that include HR-positive tumors with a goal to enrich for patients with lobular histology. These trials are described below and grouped by early stage versus late stage settings. Included trials were identified from clinicaltrials.gov (Table 1).

Trials for Early Stage Disease

Neoadjuvant Study of Targeting ROS1 in Combination with Endocrine Therapy in Invasive Lobular Carcinoma of the Breast (ROSALINE)

Synthetic lethality has been demonstrated in CDH1 mutated breast cancer cells treated with inhibitors of the tyrosine kinase ROS1, suggesting a potential targeted strategy for treating E-cadherin-negative cancers [30]. The ROSALINE study ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04551495) is designed to test ROS1 inhibition in combination with endocrine therapy in the early stage setting [31]. Studying the small molecule entrectinib, which inhibits pan-tropomyosin receptor tyrosine kinase, ROS-1, and anaplastic lymphoma kinase (ALK),

Table 1 Summary of current therapeutic clinical trials for patients with ILC

	Patient population	Intervention	Design	Primary endpoint
Early stage trials				
ROSALINE study	Stage I–III ILC	Entrectinib plus letrozole	Single arm, pre-operative window trial	Residual cancer burden
TBCRC037	Post-menopausal, stage I–III HR-positive ILC	Tamoxifen, aromatase inhibitor, or fulvestrant	Randomized, pre-operative window trial	Change in Ki-67
PELOPS	Stage I–III HR-positive ILC or IDC	Tamoxifen plus palbociclib, or letrozole plus palbociclib	Randomized, pre-operative window trial	Residual cancer burden
Metastatic trials				
GELATO	Stage IV ILC	Carboplatin plus atezolizumab	Single arm, non-randomized phase II	Progression-free survival by RECIST
ROLo study	Stage IV E-cadherin-negative tumors	Crizotinib plus fulvestrant	Single arm, non-randomized	Response rate by RECIST
SUMMIT	Stage IV, solid tumors with activating HER2 mutation	Fulvestrant with or without trastuzumab or neratinib	Basket trial	Response rate by RECIST

ROSALINE is a neoadjuvant, single-arm, non-randomized trial for patients with early stage ILC. Patients will receive 4 months of entrectinib in combination with letrozole followed by surgical treatment, with Residual Cancer Burden being the primary study endpoint [32].

Endocrine Response in Women with Invasive Lobular Breast Cancer, Translational Breast Cancer Research Consortium 037

Randomized trials have shown that the use of adjuvant endocrine therapy in the treatment of early-stage HR-positive breast cancer significantly improves disease free and overall survival [33, 34]. Standard approaches include the use of selective estrogen receptor modulators (e.g., tamoxifen) in the pre-menopausal setting, and aromatase inhibitors in the post-menopausal setting [35]. While aromatase inhibitors result in superior disease-free survival over tamoxifen in postmenopausal women, as well as a subset of higher risk premenopausal women when given in combination with ovarian suppression [36], the differential benefit of aromatase inhibitors over tamoxifen appears relatively larger in patients with ILC compared to those with invasive ductal carcinoma [37]. This finding suggests that endocrine therapy strategies might have differential efficacy in ILC versus invasive ductal tumors.

To study this question, TBCRC037 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02206984) Identifier NCT02206984) is a window trial testing three different endocrine therapy strategies in the pre-operative setting. This trial is enrolling post-menopausal women with early stage ILC. Patients are randomized to either tamoxifen (a selective estrogen receptor modulator), anastrozole (an aromatase inhibitor), or fulvestrant (a selective estrogen receptor degrader) for 21 days pre-operatively. Change in the proliferation marker Ki67 is the primary endpoint.

Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study

Cyclin-dependent kinase-4 (CDK4) and cyclin-dependent kinase-6 (CDK6) regulate cell proliferation and can deactivate the retinoblastoma (RB) protein, resulting in initiation of the S phase of the cell cycle and increased cell proliferation in a number of cancer types [38]. Early work studying CDK4/6 inhibitors in breast cancer cell lines demonstrated growth inhibition in HR-positive cell lines, but not HR-negative cell lines. Additionally, CDK4/6 inhibitors showed synergy with endocrine therapy in growth inhibition. Clinical trials have shown significant improvement in progression-free survival and overall survival using CDK4/6 inhibitors plus endocrine therapy for patients with HR-positive, HER2-negative metastatic breast cancer [39–43]. The role of CDK 4/6 inhibitors in the early-stage setting remains unclear; however, early report from the phase 3 MonarchE trial shows significant improvement in DFS with 2 years of adjuvant abemaciclib in clinically high-risk node-positive women [44].

The majority of ILC tumors show HR-positivity and decreased response to standard chemotherapy [21]. As such, there is great interest in the use of CDK4/6 inhibitors for this tumor type. The PELOPS study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02764541) Identifier: NCT02764541) is a prospective, randomized trial for early stage patients with HR-positive ILC or IDC [45]. In the window phase, patients are randomized to 2 weeks of tamoxifen or letrozole, followed by repeat biopsy and evaluation of change in tumor proliferation as measured by change in Ki-67. In the treatment phase, patients are randomized to either tamoxifen plus the CDK4/6 inhibitor palbociclib, or letrozole plus palbociclib for 24 weeks. The primary endpoint is response to therapy as measured by Residual Cancer Burden [32].

Trials for Metastatic Disease

Assessing Efficacy of Carboplatin and Atezolizumab in Metastatic Lobular Breast Cancer

The expression of programmed death-ligand 1 (PD-L1) on tumor infiltrating immune cells can prevent anti-tumor immune responses by inhibiting T cell response. Conversely, targeting PD-L1 with checkpoint inhibitors can reverse this T cell suppression. The Impassion130 trial showed improved progression-free survival in patients with metastatic triple negative breast cancer treated with the anti PD-L1 monoclonal antibody atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel, leading to accelerated approval of atezolizumab from the US Food and Drug Administration (FDA) [46]. The GELATO study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03147040) Identifier: NCT03147040) is a single arm, non-randomized phase II study enrolling patients with metastatic ILC [47]. Patients will receive treatment with carboplatin and atezolizumab, with the primary endpoint being progression-free survival at 6 months as measured by RECIST [29]. Whether immunotherapy will show benefit in ILC is unknown, as ILC is a largely HR-positive tumor type with fewer tumor infiltrating lymphocytes compared to invasive ductal carcinomas [48]. These features predict lower response rates; however, recently identified gene expression signatures within ILC identify an “immune-related” subset, suggesting the possibility of responders to immune activation within ILC [7, 15].

ROS1 Targeting With Crizotinib in Advanced E-Cadherin-Negative, ER-Positive Lobular Breast Cancer or Diffuse Gastric Cancer Study (ROLo)

The ROLo study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03620643) Identifier NCT03620643) is a non-randomized, phase II study evaluating the use of the ROS1 inhibitor crizotinib in combination with the selective estrogen receptor degrader fulvestrant [49]. Crizotinib is currently approved for use in ROS1-positive non-small-cell lung cancer [50]. Eligible patients include those with a histological diagnosis of metastatic or inoperable E-cadherin-negative tumors: either diffuse gastric cancer or ER-positive HER2-negative ILC. Patients with ILC receive crizotinib in combination with fulvestrant, with the primary study endpoints being response rate as measured by RECIST and safety/tolerability [29].

Neratinib HER Mutation Basket Study (SUMMIT)

Recent studies have shown enrichment of activating HER2 mutations in ILC compared to IDC, with 5.7% of early stage ILC cases having such mutations compared to 1.4% of IDC cases [13]. Rates of HER2 mutations appear

to be even more prevalent in certain subtypes of ILC, with up to 26% of pleomorphic ILC tumors harboring such mutations [51]. SUMMIT ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT019539926) Identifier NCT019539926) is an international, phase 2, basket study for patients with advanced solid tumors and somatic HER2 activating mutations [52]. For the HR-positive breast cancer arm, patients with prior CDK4/6 inhibitor treatment are randomized to either neratinib (an oral pan-HER tyrosine kinase inhibitor), fulvestrant, and trastuzumab vs. fulvestrant and trastuzumab vs. fulvestrant alone. For HR-positive breast cancers without prior CDK4/6 inhibitor treatment, patients receive neratinib, fulvestrant, and trastuzumab. The primary endpoint is objective response rate by RECIST. SUMMIT does not restrict histologic subtype; however, an early report from this study shows that nearly half of the breast cancer cohort has lobular histology which is consistent with the known higher incidence of HER2 activating mutations in metastatic ILC compared to IDC. [53]

Future Directions

Pre-clinical work in cell lines, animal models, and via analyses of large gene expression datasets continue to identify treatment targets that may be particularly relevant for ILC. Several studies now suggest putative treatment strategies that should soon enter clinical testing. Recent data show that high expression of the bromodomain and extraterminal domain (BET) proteins BRD3/BRD4 are associated with worse outcomes in ILC and that resistance to BET inhibition may be driven by tyrosine kinases including fibroblast growth factor receptor (FGFR)-1. Indeed, FGFR-1 is thought to be necessary for tumor cell survival in the setting of endocrine resistance in ILC cell lines and is implicated in recurrent or metastatic ILC [54]. The combination of BET inhibition with FGFR1 inhibition or FGFR1 inhibition alone have therefore been posited as potential treatment strategies for ILC tumors with endocrine resistance [55, 56]. Resistance to BET inhibition may also be related to increased dependence on BCL2, an anti-apoptotic protein. As such, investigators have suggested increasing pro-apoptotic signaling through the use of BH3 mimetics in combination with chemotherapy [57].

While the PI3K pathway is known to be upregulated in many breast cancer subtypes, activating mutations in this signaling pathway are especially common in ILC. PI3K signals in part through the kinase mammalian target of rapamycin (mTOR). Interestingly, investigators recently showed a beneficial effect of mTOR inhibition in a mouse model of ILC, with tumor response being

linked to an intact adaptive immune system in the tumor microenvironment [58].

Studies of tumor stroma identify differences between ILC and IDC, including an increase in the presence of cancer associated fibroblasts in ILC. This may result in increased levels of the metalloproteinase pregnancy-associated plasma protein-A (PAPP-A), leading to increased insulin-like growth factor (IGF)-1 and activation of its signaling pathway, another putative treatment target in ILC [59, 60].

Conclusions

As ILC is increasingly recognized as a unique subtype of breast cancer, clinical trials evaluating targeted treatment strategies for lobular cancers are emerging. Currently, a number of early-stage and metastatic trials testing small molecules that inhibit the tyrosine kinase ROS1, endocrine therapy strategies, CDK4/6 inhibition, immunotherapy with checkpoint inhibition, and inhibition of HER2 in patients with activating HER2-mutations are available for patients with ILC. These trials represent important advances in the personalization of breast cancer management for patients with ILC.

Development of novel imaging tools that are more sensitive for lobular cancer will be critically important. One promising novel imaging tool is fluoro-estradiol positron emission tomography which has been able to detect HR+ lobular metastases not identified by FDG-PET [61–63]. Surgical outcomes for patients with early-stage ILC remain worse than the surgical outcomes for patients with IDC, with higher rates of positive margins and increased need for repeat operations and completion mastectomies. While more sensitive imaging tools should help reduce the incidence of positive margins, the optimal pre-operative and surgical management of this disease requires further investigation. Additionally, it is critical that we increase access to and participation in clinical trials for patients with lobular cancer. Current eligibility criteria and definitions of treatment response do not represent patients with lobular cancer well. Broadening these criteria to reflect the unique biology and clinical course of lobular cancers should be considered. Histologically based differences in potential endpoints need careful attention. For example, while circulating tumor cells are being actively investigated as potential predictors and endpoints in breast cancer trials, a recent study demonstrated that the significance of these cells differs in ILC compared to IDC. This further highlights the importance of including, and enriching for, patients with ILC in studies [64].

As appreciation for the unique features of ILC increases, hopefully treatment options and outcomes will improve for patients with this understudied tumor type.

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