LBCA's 2023 Free, Live Streamed Webinar
What's New in Screening and Treatment for Lobular Breast Cancer

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LBCA Scientific Advisory Board Member, Dana-Farber Cancer Institute

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Memorial Sloan Kettering Cancer Center

Tali Amir, MD
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Today’s Agenda

Welcome and Introductions- Laurie Hutcheson
ILC Imaging/Detection- Tali Amir, MD
ILC and Surgery- Anita Mamani, MD, FACS
ILC and Treatment- Rinath Jeselsohn, MD
Q&A - Laurie Hutcheson
Our Panelists

Tali Amir, MD
Anita Mamtani, MD, FACS
Rinath Jeselsohn, MD
Invasive Lobular Breast Carcinoma

• Detection and Surveillance

• September 12, 2023

Tali Amir, MD
Assistant Attending Radiologist
Director of Breast Imaging MSK-Bergen
Invasive Lobular Carcinoma: Detection and Surveillance

- Invasive Lobular Carcinoma (ILC) – Brief Overview
- Best Screening Practices
- Challenges in Detection and Diagnosis
- Surveillance
- Looking into the future
Invasive Lobular Carcinoma: Detection and Surveillance

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Invasive Lobular Carcinoma: An overview

• Second most common type of breast cancer

• Accounts for 10-15% of all breast cancers

• Often diagnosed at a larger tumor size

• More commonly presents as multifocal disease (multiple tumors)

• Tends to recur later (>10 years after initial diagnosis)
Invasive Lobular Carcinoma: Detection and Surveillance

• Invasive Lobular Carcinoma – Brief Overview

• Best Screening Practices

• Challenges in Detection and Diagnosis

• Surveillance

• Looking into the future
Screening & Detection: How do we screen?

Standard of breast cancer screening = Mammography

https://www.mammoguide.com/tomosynthesis.html
Screening & Detection: How do we screen?

[Images of CC and MLO views of the breast, highlighting areas like the nipple, underarm, sternum, and feet.]

Screening & Detection: How do we screen?

**Screening average risk women** (<15% lifetime risk of breast cancer)

- Mammogram starting at age 40
  - 2D (full field digital mammogram)
  - 3D (digital breast tomosynthesis, DBT)
  - Dense breasts
- Ultrasound
  - Supplemental screening in dense breasts
Screening & Detection: How do we screen?

Screening above average risk women
- Intermediate risk: 15-20% lifetime risk
- High risk: >20% lifetime risk

Consider:
- Contrast Enhanced Mammography (CEM)
- Contrast Enhanced Magnetic Resonance Imaging (MRI)

Images courtesy of Dr. Maxine Jochelson
Screening & Detection: Breast Symptoms

• Breast Symptoms
  - Palpable lump
  - Nipple symptoms (discharge, inversion)
  - Skin changes (redness, thickening)

• Imaging Evaluation
  - Mammogram (starting at 30 years old)
  - Ultrasound
  - CEM
  - MRI (problem solving, persistent symptom)
Invasive Lobular Carcinoma: Detection and Surveillance

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- Challenges in Detection and Diagnosis
- Surveillance
- Looking into the future
Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis

Almost entirely fatty
Scattered
Heterogeneously dense
Extremely dense
Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis

- Almost entirely fatty
- Scattered
- Heterogeneously dense
- Extremely dense
Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis

- Can be inconspicuous
- Cells grow “single file”

- Variable appearance
  - Mass
  - Distortion (pulling appearance)
  - Asymmetry (tissue without discrete mass)
Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis

Architectural Distortion
Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis
Invasive Lobular Carcinoma: Defining extent of disease after biopsy

After mammogram and ultrasound, consider:

• CEM
• MRI

• Studies have demonstrated comparable performance of MRI and CEM for evaluating disease extent

• MRI & ILC
  • Preoperative MRI helps identify additional disease in up to 25% of patients
  • Preoperative MRI imaging can impact clinical management

*Balancing potential benefits with potential risk*


ILC: Defining extent of disease after biopsy
ILC: Defining extent of disease with CEM

Left CC  Left CC  Left MLO  Left MLO
ILC: Defining extent of disease after biopsy
ILC: Defining extent of disease with MRI
Invasive Lobular Carcinoma: Detection and Surveillance

• Invasive Lobular Carcinoma – Brief Overview
• Best Screening Practices
• Challenges in Detection and Diagnosis
  • Surveillance
• Looking into the future
ILC Surveillance

• Surveillance in women with a history of ILC

• Consider:
  • 3D Mammogram (DBT)
  • US
  • CEM
  • MRI with and without contrast
Surveillance:

**Contrast Enhanced Mammography**

- CEM has a higher cancer detection rate than 2D mammograms
Screening CEM after lumpectomy
Screening CEM after lumpectomy
Surveillance:

Breast MRI with and without contrast

- Improves the detection of early-stage but biologically aggressive tumors in patients diagnosed at 50 years or younger

Invasive Lobular Carcinoma: Detection and Surveillance

• Invasive Lobular Carcinoma – Brief Overview

• Best Screening Practices

• Challenges in Detection and Diagnosis

• Surveillance

• Looking into the future
Looking into the future

A Role for Artificial Intelligence


Invasive Lobular Carcinoma: Detection and Surveillance

• Take home points

• ILC is not a rare cancer
• ILC can be inconspicuous and present with variable appearance
• 3D Mammography, US, CEM, and MRI are tools we can consider, depending upon a person's personal risk profile
Thank you

• Thank you, Laurie Hutcheson, and LBCA

• Acknowledgements:
  • Dr. Maxine Jochelson and Dr. Victoria Mango
Surgery for Lobular Breast Cancer in 2023

Lobular Breast Cancer Alliance Webinar
September 12th, 2023

Anita Mamtani, MD, FACS
Breast Service, Department of Surgery
Memorial Sloan Kettering Cancer Center
Disclosures

None
Treatment Approach

• Initial evaluation
  • History
  • Physical exam
  • Imaging
  • Pathology: lobular history, receptor subtype

• Not all patients and not all breast cancers are the same

• **Precision medicine**: integrating information about the cancer, the patient, to create an individualized plan
Treatment Approach

• Timeline

  • “Upfront” surgery (surgery first)
    • Early-stage cancers

  • “Neoadjuvant” approach (medicine first, surgery later)
    • More advanced cancers (larger tumors, known to have positive lymph nodes, etc.)
    • Certain subtypes of cancer (HER2+, TN: relatively uncommon in ILC)
Surgery in ILC

• Similar fundamentals as other breast cancer
  • Breast
  • Axilla

Illustration courtesy of American Cancer Society
Surgery in ILC: Breast

- 2 options:
  - Breast-conserving surgery (“lumpectomy”)
  - Mastectomy

**Lumpectomy**

- The tumor is removed with a rim of normal breast tissue.

**Total mastectomy** - no reconstruction

**Skin Sparing Mastectomy** + reconstruction

**Nipple Sparing Mastectomy** + reconstruction
Surgery in ILC: Breast

• 2 options:
  • Breast-conserving surgery ("lumpectomy")
  • Mastectomy

How do we choose?

- Early or advanced cancer
- Tumor size, location, extent
- Patient preference
- Genetics, family history
- Patient factors
Surgery in ILC: Breast

• 2 options:
  • Breast-conserving surgery ("lumpectomy")
  • Mastectomy

• **Survival** after BCT (lumpectomy + radiation) is equivalent to survival after mastectomy for early-stage breast cancers.

• Multiple randomized trials with >25 years of follow-up

• 10-year local recurrence rates of <10% with adjuvant therapy

*Anderson J Clin Oncol, 2009*  *Wapnir J Clin Oncol, 2006*
Surgery in ILC: Breast

• Do lumpectomy and mastectomy result in equivalent survival for patients with ILC as well?

• Yes: if negative margins are achieved.
  • Small studies including early ILC-only population
    N = 235 (treated from 1983-1987)
    Lumpectomy + RT vs. mastectomy
    15-year follow-up
    No difference in breast cancer specific survival

• Subsequently validated

Fodor J Rep Pract Oncol Radiother, 2011
Surgery in ILC: Breast

• Are positive margins more frequent in ILC patients who undergo lumpectomy? Is mastectomy required more frequently in ILC?

• Mixed findings
  • Some studies: no difference (Morrow *Cancer*, 2006)

• Heavily rely on pre-operative workup (particularly imaging) to determine optimal surgical plan
Surgery in ILC: Breast

• Are ILC patients at a higher risk of local recurrence compared to other types of breast cancer?

• **No**: similar risk as other types of breast cancer.
  • After lumpectomy with negative margins: 3.1–5.7%

• Factors predictive of recurrence are similar to other types:
  • Larger tumor size, heavy nodal disease burden, high grade, more aggressive receptor subtypes, omission of adjuvant therapies

Molland J *Breast*, 2004
Braunstein L *Breast Cancer Res Treat*, 2015
Sagara Y *Ann Surg Oncol*, 2015
Surgery in ILC: Breast

- Can ILC patients have breast reconstruction?
  - Yes: no differences in reconstructive options
    - Implant-based
    - Autologous
Surgery in ILC: Axilla

• 2 options:
  • Sentinel lymph node biopsy (SLNB)
  • Axillary lymph node dissection (ALND)
  • None* (select patients: age >70 with stage I HR+/HER2- tumor, significant comorbidities)
Surgery in ILC: Axilla

• Do ILC patients more often have lymph node involvement?

• Mixed findings
  • Some studies: no difference (Wasif ASO, 2010)
  • Others: increased likelihood of positive lymph nodes (Vandorpe Breast Cancer Res Treat, 2011)
Surgery in ILC: Axilla

• Do ILC patients more often need ALND?

• No
  • SLNB is equally feasible in ILC as compared to other breast cancer types
  • SLNB provides equivalent axillary control in ILC patients with negative sentinel nodes
  • Even if positive nodes: lobular histology does not predict need for ALND

Khakpour Am J Surg, 2005
Mamtani Ann Surg Oncol, 2019
Surgery in ILC: Summary

• The fundamentals of surgical management of ILC remain very similar to other breast cancer types

• Breast cancer detection and treatment continues to evolve

• Tailoring our medical treatments is the next frontier: tumor biology is **key**

• Ultimate goals:
  - Individually tailor treatment
  - Decrease the morbidity of surgery
  - Achieve excellent cancer outcomes
  - Improve quality of life
Thank you
Invasive Lobular Breast Cancer:
Current treatment and future directions

Rinath Jeselsohn MD
Director for ER+ Translational and Discovery Research

Breast Oncology Center
Dana Farber Cancer Institute
Incidence of Invasive Lobular Breast Cancer (ILC)

• ILC is the second most common histological type of breast cancer after invasive cancer of no special type (NST)\#.

• Approximately 15% of all breast cancers.

• The incidence of ILC has increased over the past 2 decades.

\#Invasive ductal cancer
ILC is a unique Breast Cancer

- Risk Factors
- Molecular Sub-types
- Clinical Presentation
- Genetics
- Histology
- Epi-Genetics
Risk factors that are more strongly associated with ILC compared to NST (Nurses Health Study)

• Age at 1\textsuperscript{st} menstrual period
• Age at first birth
• Post-menopausal hormone use

(No differences in associations with age, parity, age of menopause, family history of breast cancer or alcohol intake)
Clinical Presentation: ILC vs NST

• Average age at diagnosis of ILC is mildly higher compared to NST (61 vs 57 yrs).

• Presents more often with larger tumors\(^2\) and lymph node\(^3\) involvement (more frequently classified as Stage III and IV; 20.7% vs 10.4%\(^4\)).

• More often presents as multi-focal.

• Difficult to detect by MMG.

\(^{2}\)Pestalozzi BC, JCO 2008, \(^{4}\)Oestrerreich S, JNCI 2022
ILC Unique Histology

• Unique histology of non-cohesive cells with a single file pattern.

• Loss of the cell adhesion protein E-cadherin is a hallmark of ILC (E-cadherin is absent in ~90% of all ILCs).
ILC has several histological variants

- Classic (56%)
- Alveolar (15%)
- Mixed, Non-classical (15%)
- Solid (10%)
- Trabecular (4%)

High grade/ high proliferation
Worse prognosis

Most studies do not differentiate between the variants, even though they have very different outcomes
Molecular Subtypes in ILC

**ILC subtypes by IHC**
- 92% HR+ HER2-
- 2% HER2+ HR+
- 1% HER2+ HR-
- 5% HR- HER2-

**ILC intrinsic subtype by PAM50**
- 92% Luminal A
- 5% Luminal B
- 2% HER2-enriched
- 1% Basal-like

**IDC subtypes by IHC**
- 55% HR+ HER2-
- 18% HER2+ HR+
- 7% HER2+ HR-
- 20% HR- HER2-

**IDC intrinsic subtype by PAM50**
- 42% Luminal A
- 25% Luminal B
- 10% HER2-enriched
- 23% Basal-like

Mouabbi J, Breast Cancer Research and Treat, 2022, Williams LA, CCC 2019
Unique Genetic Landscape of ILC

Frequency of Alterations in ILC

- CDH1 & 16q loss
- PIK3CA
- MYC
- CCNE1
- TBX3
- RUNX1
- FOXA1 7% vs 2%

Frequency of Alterations in IDC

- TP53
- SNV
- amp

Ciriello G, Cell 2015,
Desmedt C, JCO 2016
Michaut M, Scientific Reports 2016
ILC has a Unique Chromatin state driven by FOXA1

Cell line studies

Primary Breast Cancers (TCGA cohort)

Unique FOXA1 binding sites enrich for ILC
Treatment in Early Stage ILC

• Currently there are no specific guidelines for the systemic treatment of ILC
• Treatment includes +/- neo/ adjuvant chemotherapy and endocrine therapies.
• Decisions regarding chemotherapy in early-stage ER+ BC are made based on molecular risk (grade, molecular stratification tools) and tumor burden (size/number of positive lymph nodes, menopausal status.)
Do patients with early-stage ILC benefit from chemotherapy?
Neoadjuvant Chemotherapy is less effective in Early Stage ILC compared to IDC

<table>
<thead>
<tr>
<th>STUDY / Number of Patients</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>outcome</td>
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<tr>
<td>Cocquyt, 2003 (prospective)</td>
<td>CMF or CAF</td>
<td>BCS</td>
</tr>
<tr>
<td>IDC N=102</td>
<td></td>
<td>pCR</td>
</tr>
<tr>
<td>ILC N=26</td>
<td></td>
<td>PFS (5yrs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS (5yrs)</td>
</tr>
<tr>
<td>Cristofanilli, 2005 (retrospective)</td>
<td>All had A, or A+T</td>
<td>pCR</td>
</tr>
<tr>
<td>IDC N=908</td>
<td></td>
<td>RFS (5yrs)</td>
</tr>
<tr>
<td>ILC N=122</td>
<td></td>
<td>OS (5yrs)</td>
</tr>
<tr>
<td>Tubiana-Hulin, 2006 (retrospective)</td>
<td>A or A+T</td>
<td>BCS</td>
</tr>
<tr>
<td>IDC N=742</td>
<td></td>
<td>pCR</td>
</tr>
<tr>
<td>ILC N=118</td>
<td></td>
<td>RFS (5 yrs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS (5 yrs)</td>
</tr>
<tr>
<td>Delpech, 2013 (retrospective)</td>
<td>A+T, A alone, or T alone</td>
<td>BCS</td>
</tr>
<tr>
<td>IDC N=1718</td>
<td></td>
<td>pCR</td>
</tr>
<tr>
<td>ILC N=177</td>
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</tbody>
</table>

*Limitations:
- Mostly retrospective
- Lacking molecular classification data
- Late Recurrence data lacking
# The role of adjuvant chemotherapy in early stage ILC

<table>
<thead>
<tr>
<th>Study/ Number of patients</th>
<th>Treatment</th>
<th>10 YR OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDC</td>
<td>ILC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truin W, 2012</td>
<td>Chemo -&gt;</td>
<td>8,171</td>
</tr>
<tr>
<td>IDC N=19,603 ILC N=3,685</td>
<td>ET</td>
<td>11,438</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>21,323</td>
</tr>
<tr>
<td>Marmor S, 2017</td>
<td>Chemo -&gt;</td>
<td>11,281</td>
</tr>
<tr>
<td>IDC N=32,149 ILC N=4,095</td>
<td>ET</td>
<td>21,323</td>
</tr>
</tbody>
</table>
No benefit to the addition of adjuvant chemotherapy in ILC tumors with an OncotypeDX RS of $\geq 26$ (National Cancer Database 2010-2016)

OncotypeDX $<26$

OncotypeDX $\geq 26$

Yaghi M, Ca Treat and Res Com, 2023
Evidence for Benefit from Adjuvant Chemotherapy in patients with high risk ILC

N= 2318 patient with ILC, ET alone =1485, ET+chemo=823
15 academic French cancer centers between 1990-2014

Factors associated with decreased DFS and OS:

- Age
- Tumor size
- Nodal status
- LVI
- grade

Multi-variate analysis

- Age
- Tumor size
- Nodal status
- LVI

<table>
<thead>
<tr>
<th>DFS</th>
<th>OR</th>
<th>[95% CI]</th>
<th>p values</th>
<th>OS</th>
<th>OR</th>
<th>[95% CI]</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.46</td>
<td>1.21-1.76</td>
<td>&lt;0.001</td>
<td>Age</td>
<td>1.45</td>
<td>1.27-1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.88</td>
<td>1.36-2.59</td>
<td>&lt;0.001</td>
<td>Tumor size</td>
<td>1.87</td>
<td>1.34-2.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodal status</td>
<td>1.40</td>
<td>1.22-1.59</td>
<td>&lt;0.001</td>
<td>Nodal status</td>
<td>1.40</td>
<td>1.31-1.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVI</td>
<td>1.69</td>
<td>1.21-2.35</td>
<td>&lt;0.001</td>
<td>LVI</td>
<td>1.69</td>
<td>1.53-2.76</td>
<td>0.06</td>
</tr>
<tr>
<td>Grade</td>
<td>1.21</td>
<td>0.92-1.58</td>
<td>0.18</td>
<td>Grade</td>
<td>1.24</td>
<td>0.80-1.86</td>
<td>0.26</td>
</tr>
</tbody>
</table>

DFS: disease-free survival, OS: overall survival, OR: odds ratio, CI: confidence interval, LVI: lymphovascular invasion

p = 0.01

p < 0.001
Clinical factors point score identifies a subgroup of ILC patients that benefit from chemotherapy

pN1 (macroscopic) 6 pts
Tumor size (>2cm) 3 pts
LVI 2 pts

Low risk <5
High risk 5-11

de Nonneville, Breast Ca Res and Treat 2019
Oncotype DX RS is mostly low or intermediate in ILC and may high RS may not be prognostic or predictive of response to chemotherapy

- High RS seen ~10% of patients and mostly seen in the pleomorphic variant\(^1\).
- No significant difference with the addition of chemotherapy to ET in ILC patients with high or intermediate RS in the SEER database (N=7316) \(^2\).
- Lobsig is a gene set of 194 genes prognostic of survival in ILC\(^3\).

Endocrine therapy in ILC

• Most ILCs are ER+/ luminal A and adjuvant ET is standard of care.

• Aromatase inhibitors are superior to tamoxifen in ILC and IDC.

• Retrospective study of BIG-1-98 suggested that the magnitude of the difference between AI and tamoxifen was higher in ILC vs IDC\(^1\). This was not confirmed in a meta-analysis from TEAM, ATAC and Big-1-98\(^2\).

Is the ER axis different in ILC vs IDC?
Implications for the optimization of endocrine therapy in ILC

NCT02764541

Palbociclib and Endocrine Therapy for Lobular Breast Cancer Pre-operative study (PELOPS):
Phase II neoadjuvant study

PI: Otto Metzger

N = 180
Eligibility:
Invasive breast cancer that is:
T1 (>1.5 cm only), stage II or stage III
1. ER and/or PR-positive and HER2-negative
2. Invasive ductal carcinoma or invasive lobular carcinoma

Stratification:
1. Initial lymph node status: Positive vs. Negative
2. Pre-treatment tumor size: T1-2 vs. T3
TBCRC037: NCT02206984

• Neoadjuvant study for post-menopausal women with ILC.

• Randomization to tamoxifen, anastrozole and fulvestrant x 21-24 days

• Primary endpoint: change in Ki67
E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer

Ilirjana Bajrami1,2, Rebecca Marlow3, Marieke van de Ven4, Rachel Brough1,2, Helen N. Pemberton1,2, Jessica Frankum1,2, Feifei Song1,2, Rumana Rafiq1,2, Asha Konde1,2, Dragomir B. Krastev1,2, Malini Menon1,2, James Campbell1,2, Aditi Gulati1,2, Rahul Kumar1,2, Stephen J. Pettitt1,2, Mark D. Gurden1, Marta Llorca Cardenosa1,5, Irene Chong1, Patrycja Gazinska3, Fredrik Wallberg6, Elinor J. Sawyer7, Lesley-Ann Martin1, Mitch Dowssett1, Spiros Linardopoulos1,8, Racheal Natrajan1, Calm J. Ryan9, Patrick W.B. Derksen10, Jos Jonkers11, Andrew N.J. Tutt1,12, Alan Ashworth12, and Christopher J. Lord1,12

Cancer Discovery 2018
ROSALINE neoadjuvant trial of the ROS1 inhibitor Entrectinib+letrozole in ILC

N=45
- Stage II A-IIIA ILC
- ER+/HER2-
- T > 2 cm
- Untreated
- Pre- or post-menopausal

Primary endpoint:
Rate of RCB 0/1

Treatment period:
Entrectinib (600 mg) + Letrozole (2.5 mg) +/- Goserelin (3.6 mg)

Surgery
End of treatment visit

Figure 1. ROSALINE study design.
Metastatic ILC

- ILC metastasizes to distinct sites:
  - Leptomeningeal dis.
  - Orbits
  - GI tract
  - Peritoneum/ascites
  - Ovaries
Treatment in Metastatic ER+ Breast Cancer
Similar ILC and IDC (NST)

**Endocrine Therapy (ET) + CDK4/6i**
- Abemaciclib (MONARCH 2 and 3)
- Ribociclib (MONALEESA 2, 3, 7)
- Palbociclib (PALOMA 2 and 3)

**PARPi**
- Olaparib (OLYMPIAD)
- Talazoparib (EMBRACA)

**Alpelisib + ET**
(BYLieve, SOLAR1)

**Everolimus + Exemestane or Fulvestrant**
(Bolero2, PrECOG)

**Fulvestrant + alternative CDK 4/6i (Ribo or abema)**
(MAINTAIN, Wander et al JNCCN 2021)

**Fulvestrant**

**Elacestrant in ESR1 mutant**
(Emerald)

**Standard chemotherapies**

**Second-Line:**
- Trastuzumab Deruxtecan (Destiny Breast-04)
- Sacituzumab Govitecan (TROPICS-02)
Meta-Analyses shows that pts with met. ILC benefit from CDK4/6i comparable to patients with NST

<table>
<thead>
<tr>
<th>Histology*</th>
<th>CIN-dependent kinase inhibitor group, events, n/patients, %</th>
<th>Placebo group, events, n/patients, %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular</td>
<td>33 (89) (4%)</td>
<td>28 (95) (13%)</td>
<td>0.46 (0.20-1.04)</td>
</tr>
<tr>
<td>Ductal</td>
<td>230 (47) (4%)</td>
<td>128 (23) (14%)</td>
<td>0.75 (0.51-0.93)</td>
</tr>
</tbody>
</table>

Table - CIN-dependent kinase inhibitor group vs placebo in patients with met. ILC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CIN-dependent kinase inhibitor group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (events, n/patients, %)</td>
<td>364 (15) (4%)</td>
<td>340 (15) (5%)</td>
<td>0.77 (0.68-0.88)</td>
</tr>
<tr>
<td>Distant metastasis (events, n/patients, %)</td>
<td>14 (4) (3%)</td>
<td>16 (5) (3%)</td>
<td>0.71 (0.58-0.89)</td>
</tr>
<tr>
<td>Locoregional recurrence (events, n/patients, %)</td>
<td>349 (94) (5%)</td>
<td>330 (95) (5%)</td>
<td>0.80 (0.66-0.95)</td>
</tr>
</tbody>
</table>

Gao jj, Lancet Onco 2021
## Multiple Genetic Alterations in met ILC are Potentially targetable

<table>
<thead>
<tr>
<th>Somatic alteration</th>
<th>Primary ILC [12, 42, 58] (%)</th>
<th>Metastatic ILC [12, 42, 58] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>CDH1</em></td>
<td>53–82</td>
<td>62–76</td>
</tr>
<tr>
<td><em>PIK3CA</em></td>
<td>44–57</td>
<td>44–52</td>
</tr>
<tr>
<td><em>ESR1</em></td>
<td>2.0–12.5</td>
<td>15</td>
</tr>
<tr>
<td><strong>ERBB2 (HER2)</strong></td>
<td>2</td>
<td>12.0–15.6</td>
</tr>
<tr>
<td><em>PTEN</em></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><em>FGFR1</em></td>
<td>6–7</td>
<td>6–11</td>
</tr>
<tr>
<td><em>RUNX1</em></td>
<td>3–9</td>
<td>5–6</td>
</tr>
<tr>
<td><em>TBX3</em></td>
<td>10–21</td>
<td>16.0–18.7</td>
</tr>
<tr>
<td><em>TP53</em></td>
<td>9–18</td>
<td>9–20</td>
</tr>
<tr>
<td><em>FOXA1</em></td>
<td>8–15</td>
<td>11–15</td>
</tr>
<tr>
<td><em>ARID1A</em></td>
<td>8–12</td>
<td>11–12</td>
</tr>
<tr>
<td><em>GATA3</em></td>
<td>3–15</td>
<td>7–15</td>
</tr>
<tr>
<td><strong>AKT1</strong></td>
<td>6</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>2–3</td>
<td>6–8</td>
</tr>
</tbody>
</table>

* Have approved drugs that either target the gene or pathway
MutHER part II: Phase II trial of Neratinib in combination with fulvestrant in met. BC with mutated non-amplified HER2

Results: 24 fulvestrant treated 11 fulvetsrant naïve ER-=5 CBR = 38% in fulvetrant treated, 30% in fulvetsrant naïve CBR was positively associated ILC and negatively associated with the HER2 L755 mutation.
ILC and Immunotherapy

- A higher proportion of ILC metastases will have a high tumor mutational burden (TMB, >10 mutations per megabase) than NST metastases¹

- A subset of ILC tumors will have >10% TILs (tumor infiltrating lymphocytes)²

- These findings along with evidence of immunotherapy working synergistically with platinum-based chemotherapy in mouse models of lobular breast cancer gave rationale for the GELATO trial

Completed Trial in Metastatic ILC: Phase II GELATO Trial

- More CBR in ILC that was TNBC vs. ER+ & responses were not durable
- Higher benefit in PDL1+ (not s.s.) and trend toward high TMB
- However - one patient with ER+ ILC had response>1 year and had TME with high sTILs and CD8+ Tcells

First trial dedicated to met. ILC

Future trials should select patients with a higher likelihood to benefit from ICI

The ROLO study (NCT03620643): non-randomized, phase II study evaluating the use of the ROS1 inhibitor crizotinib in combination with the selective estrogen receptor degrader fulvestrant

- Eligible patients: 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 endpoints being response rate & safety/tolerability.
Summary

- ILC is a distinct breast cancer (clinical features and biology)
- Significant progress in understanding the unique biology of ILC
- Ongoing first trials dedicated to ILC
- Pathology consensus on the diagnosis of ILC
- Studies will need to investigate the specific variants of ILC
- We need collaborative efforts between multiple centers for further investigation.
We are grateful for the support from Seagen that helped make the production of this webinar possible.
Thank you for Joining!