Thank you to LBCA for the opportunity to go to SABCS 2023! This year's SABCS (my 4th in person) for me was by far the busiest and most fun I have had. The more times I go, the more people I know, and the more I understand the science.

This year for the first time there was a main stage Lobular Breast Cancer Educational session which I am sure you will be hearing more about in the coming months. Besides the Lobular Session, another reason this year's SABCS was the best so far is that each educational session had an advocate on the panel for the first time. Many of the advocates are friends of mine and our compatriot, Siobhan Freeney from Lobular Ireland was the patient advocate for the ILC session and did an amazing job!
Her are my takeaways and summaries of the lobular sessions and my poster picks, as well as my general impressions of SABCS23.

1. Lobular Educational Session:

Dr. Christine Desmedt: Biological peculiarities of lobular breast cancer

• ILC is generally described a loss of the e-cadherin protein that causes discohesive cells. (cells that don't stick together) ILC is Primarily ER+ Her2-, (up to 95%), Her2+ 3-13%, TNBC 2-9%
• **Pathology** is not the same worldwide and there is currently an effort to create guidelines to harmonize ILC diagnosis.
• Non-classical ILC's have a worse prognosis than Classic ILC. i.e Pleomorphic
• **Mutations in ILC:** (approximate %) based on 3 studies.
  • **Primary ILC:** CDH1, PI3K*, FOXA1 **(**endocrine resistance**),** Her2*,AKT, PTEN, BRCA 2*
  • **Metastatic ILC:** CDH1, Pi3K, ERBB2 (Her2 pathway), AKT*, PTEN*, FGFR2, NF1, High TMB* (Tumor Mutational Burden)*
  • **Markers of Endocrine Resistance:** ESR1*,PTEN*,ARID1A, NF1, RB1,(CDK4/6 resistance) FGFR2
  (Greater than 50% of ILC's harbor resistant mutations)

** Targetable Treatments available in this setting (-added by author(JL)*

• **Leptomeningeal metastasis**: One study showed greater than 1/2 of LM were ILC, (Cerebral Spinal fluid (CSF) showed twice as many mutations than liquid biopsy. (*Fitzpatrick et al.)*
• **Rapid Autopsy Programs:** Create unique opportunities to study, disease progression, treatment resistance, liquid biopsies etc. (i.e.Uptider (Leuven, Belgium), Hope for Others (UPMC)

Dr. Tari King: The Challenges of ILC

• **Primary ILC:**
  • Rates of local recurrence after breast-conserving therapy or mastectomy are similar between ILC and IDC.
  • Regional recurrence is more common in IDC, whereas recurrence in bone and distant recurrencaes are more frequent in ILC.
  • Despite tendency towards increased use of MRI in patients with ILC there is no measured improvement in surgical outcomes.
  • **LCIS** is a risk factor for subsequent development of ILC. Chemoprevention with a selective ER modulator or aromatase inhibitor can reduce the risk of breast cancer after LCIS by 50%.
  •ASCO/ASTRO/SSO Consensus: Negative Margin Defined as "no ink on tumor" should be used for ILC.
  • Low rates of Pathologic Complete Response (pCR) with neo-adjuvant chemotherapy is not associated with inferior survival.
  • **Genomic assays** (Mammaprint, OncotypeDX, Endo-predict all showed prognostic value)*
  (*additional studies are needed to guide optimal systemic therapy and individual differences in subtype, pre- vs post-menopausal etc.)
  • **Future directions**: LobSig a new assay being studied in Australia is prognostic for ILC.

Dr Jason Mouabbi: Innovative approaches at the diagnosis and treatment of invasive lobular carcinoma

Imaging:
  • Contrast Enhanced Mammography (CEM) is promising in Primary ILC.
  • In dense breasts the sensitivity of mammography at detecting ILC is only 11%
  • FDG-avidity of ILC is lower than that of IDC
  • The sensitivity of CT scans has been reported to be as low as 25% In ILC patients with Peritoneal disease.
  • Stark Differences between previous imaging and autopsies in ILC. Many more metastases seen in autopsies.

Staging and Metastatic Imaging in ILC:

- **FDG -PET** avidity is lower in ILC than IDC
- **FES-PET** (Fluoroestrodial tracer) a Clinical trial: NCT04883814 in ILC is showing that measuring estrogen avidity in ILC might be superior to standard of care imaging for both the initial staging of locally advanced and metastatic ER+ disease (FES is approved for use in metastatic disease)*

(there are limitations and can be dependant on location of metastatses, treatment washout periods and the individual)*

- **Promising Staging Modalities of ILC in Trials**– Fluciclovine-PET, PSMA-PET, FAPIPet (68Ga–fibroblast activation protein inhibitor. (FAPI) PET/CT is targeting cancer-associated fibroblasts (CAF) in the tumor microenvironment which are present in abundance in ILC.

Treatments in Metastatic ILC based on mutations:

- 63-71% of ILCs exhibit an activating mutation in the PTEN-PI3K-AKT pathway.(40% are in Pi3k)

(**Capiversitib that targets all three of these mutations was approved in November 2023)**

- 7-10% of early-stage ILC have ERBB2 (Her2) mutations **(Neratinib is an FDA approved Treatment)**

In Trials:

- **Targeting Ros1 mutations:** Rosaline and Rolo **(Europe)**
- **Targeting the IL6/STAT3 Pathway**: Phase 1b/2 Study of TTI-101 (STAT3 inhibitor) in Combination for Patients with Metastatic Hormone Receptor-Positive and HER2-Negative Breast Cancer (NCT05384119)

Immunotherapy:

- **KEYNOTE-028** trial for patients with metastatic PD-L1+ ER+ breast cancer, 2/3 of responders were patients with ILC. **(Keytruda)**
- **Gelato** trial showed only a very small % of ILC patients benefited from immunotherapy.

Future Directions: Targeting ILC with Parp inhibitors and the IL-6/STAT3 pathway and Tumor Micro-environment (TME) with immunotherapy and angiogenesis inhibitors. (Sottnick et al.)

2. General Session Dr. Fresia Pareja: Novel Mechanisms of CDH1 Inactivation in Breast Invasive Lobular Carcinoma Unveiled by the Integration of Artificial Intelligence and Genomics

Dr Fresia Pareja discussed a study using novel mechanisms of discovering CDH1 inactivation by using an artificial intelligence-based system built to detect and diagnose lobular carcinoma. This was done by integrating Genomics and AI to predict the presence of CDH1 in studies that did not show CDH1 mutations on pathology. By applying an AI-based model they were able to identify alternative epigenetic and genetic molecular mechanisms of CDH1 inactivation in ILCs, including novel CDH1 genetic alterations and a new inactivating CDH1 fusion gene. These findings indicate that molecular mechanisms can be unveiled by the integration of AI and genomics. Overall, AI identified alternative/novel mechanisms of CDH1 inactivation in 74% (25/34) cases analyzed demonstrating promising research in diagnosing ILC.

3. ILC Posters: There were 25 - 30 ILC posters this year! Impossible to see all of them

These two in particular stuck out for me as they both represent extremely unmet needs in less common forms of ILC's and I attended GRASP sessions for each so really got to delve into the science of both of them.

(PO5-06-14) Genomic Landscape and Clinical Outcomes of Triple-Negative Invasive Lobular Carcinoma

Hemali Batra-Sharma *(1)* ***Smruthy Sivakumar*** *(2)* ***Prashanth Ashok Kumar*** *(3)* ***Ethan Sokol*** *(4)* ***Rebecca Shatsky*** *(5)* ***Jeffrey Ross*** *(2) (1) University of California San Diego Moores Cancer Center;(2) Foundation Medicine Inc.;(3) SUNY Upstate Medical University, Syracuse, New York, United States;(4) Foundation Medicine Inc;(5) University of California at San Diego*

Triple Negative Breast Cancer (TNBC) comprises only 2% pf ILC's and is rarely studied. TN ILC is associated with more pleomorphism, higher nuclear grade, older patient age, and worse disease-related outcomes compared to estrogen receptor-positive (ER+) ILC. This prompted investigation of the genomic landscape and clinical management of TN ILC to provide insight into potential therapeutic approaches. 20 patients were included in the study. Using a Foundation One database they studied the Genomics of TN ILC's. The most common mutations were in CDH1, TP53 and Pi3k. There were also 3 case studies. Currently the therapeutic management of TN ILC is extrapolated from that of TN IDC, however the patients did not respond to chemoimmunotherapy. Studies with larger sample sizes of TN ILC are needed for molecular profiling and assessment of outcomes with specific therapeutic approaches. (*Lay summary by Julia Levine*)

(PS11-03) Comparison of next-generation sequencing (NGS) results from the cerebrospinal fluid, peripheral blood, and systemic metastatic tumor tissue of patients with metastatic breast cancer (MBC) and leptomeningeal disease (LMD) ***Laura Huppert*** *(1)* ***Lindy Her*** *(2)* ***Christine Hodgdon*** *(3)* ***Susie Brain*** *(4)* ***Carol Simmons*** *(4)* ***Jo Chien*** *(2)* ***Melanie Majure*** *(2)* ***Hope Rugo*** *(5)* ***Mark Jesus Magbanua*** *(6)* ***Ron Balassanian*** *(2)* ***Michelle Melisko*** *(7)* *(1) University of California, San Francisco, Oakland, California, United States;(2) University of California, San Francisco;(3) GRASP - Guiding Researchers & Advocates To Scientific Partnerships, Baltimore, Maryland, United States;(4) I-SPY 2 Advocacy Group;(5) Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States;(6) University of California San Francisco, San Francisco, California, United States;(7) University of California at San Francisco, San Francisco, California, United States*

Although not a Lobular Poster per se: 4 out of 7 ER+ patients enrolled in this study had ILC. This corresponds with previous studies showing up to 40%-50% of ER+ Leptomeningeal metastases are of ILC in origin. (Fitzpatrick et al. referenced above)

Leptomeningeal disease (LMD) is a devastating complication of advanced malignancies and occurs in 5-15% of patients (pts) with metastatic breast cancer (MBC). Metastatic tumors to the central nervous system (CNS) are not routinely assessed for the presence of actionable mutations, so the frequency and concordance of actionable mutations centrally vs. peripherally is not well characterized. 16 pts with MBC were enrolled who had suspected or confirmed LMD in a non-therapeutic prospective study and collected CSF, peripheral blood, and archival systemic tumor samples from each pt. The study demonstrated that Next generation sequencing (NGS) can detect actionable mutations in the CSF of pts with MBC and LMD. They observed concordance and heterogeneity in the status of actionable mutations between the CSF, peripheral blood, and systemic metastatic tumor tissue. Larger studies are needed to assess the clinical utility of these observations, particularly with the development of several novel targeted agents that are CNS-penetrant. Patients with LMD represent a vital and unmet clinical need.
(*A previous poster by this same author at ASCO 2023 showed that there appeared to be an over-representation of pts with lobular cancer and those with de novo metastatic disease. (Lay Summary by Julia Levine)*

The other great part of SABCS is meeting and socializing with researchers and other advocates. I enjoyed meeting and spending time with the other scholarship recipients and LBCA staff. LBCA had a booth for the very first time and I think it was very successful for letting people know about LBCA. The MBCA dinner, of which I am the metastatic representative had a dinner and a panel discussing the Inflation Reduction Act and how it may affect medical billing for MBC patients. GRASP had its always enjoyable cocktail hour, and members of LBCA staff and advocates gathered at the Beautiful San Antonio riverwalk for dinner.

Finally, the most wonderful and poignant thing was to go to Deb Mueller's family's house for dinner with SAB members, other scholarship recipients and ILC researchers. Deb was the LBCA Board chair briefly and passed away suddenly from metastatic ILC a year or so after her primary diagnosis and only 2 months after her metastatic diagnosis. Deb's husband. John graciously opened his beautiful house up again even while he and his family are still deeply grieving. He let me read an unbelievable piece of writing that Deb's high school daughter wrote about grief. What happened to Deb makes me so angry. This should NOT happen, and this is why we do what we do at LBCA and what I do as a metastatic lobular advocate.