2026 ASCO® ANNUAL MEETING

Evidence and Exceptions in Systemic Therapy for Invasive Lobular Carcinoma

RINATH JESELSOHN, MD

Key Takeaway Points

1

ILC is a **clinically and biologically** distinct breast cancer subtype, with a unique ER axis, a distinct genomic landscape and ecosystem indicating the need for an ILC **dedicated approach**

2

Currently, there **are no specific ILC systemic treatment** recommendations and overall treatments mirror NST-BC (invasive ductal carcinoma)

3

Multiple studies (mostly retrospective) indicate decreased response to chemotherapy in early-stage ILC and we are lacking **molecular tools** to predict benefit from chemotherapy in ILC

4

The past decade ILC research has advanced substantially. We now have more biologic insight, rationally designed clinical trials with correlative science, that are starting to push ILC toward **precision medicine.**

ILC is Important

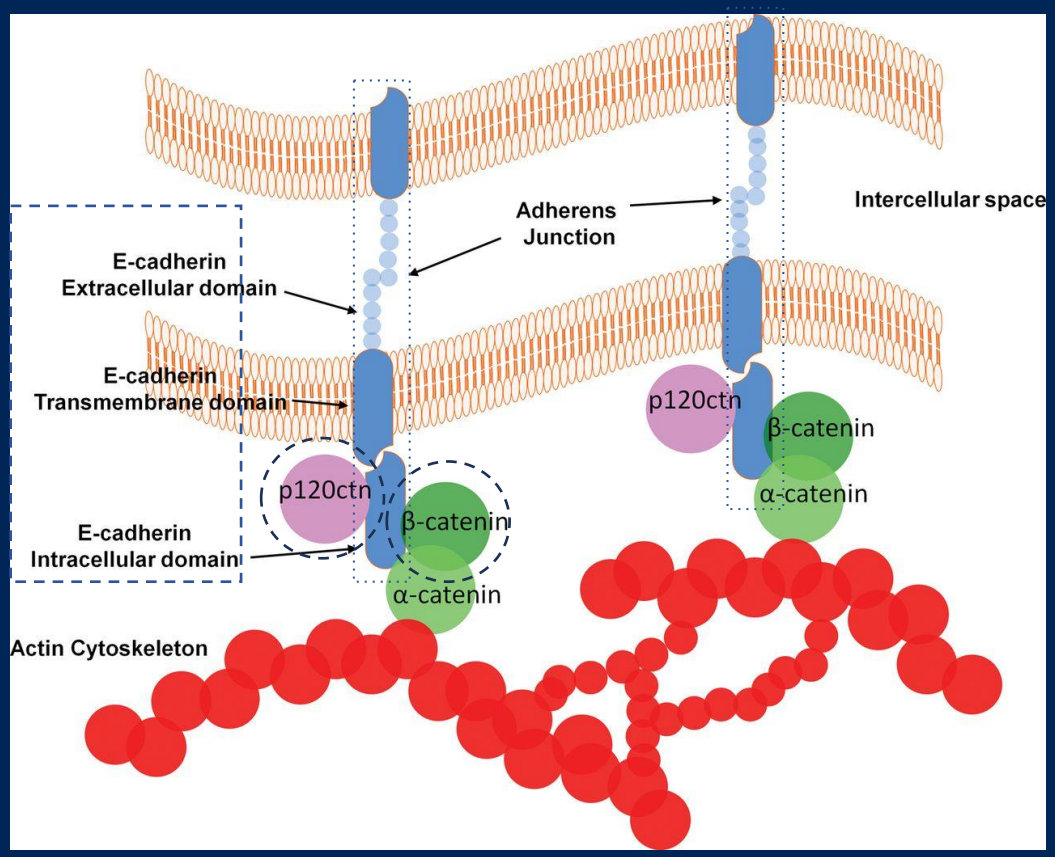
The **most common** special subtype of breast cancer

Accounts for **10-15%** of all breast cancers

In the US alone **33,600 new cases projected** in 2025

Between **2012-2021**, incidence rates increased more steeply in ILC (2.8%) compared to other breast cancers (0.8%).

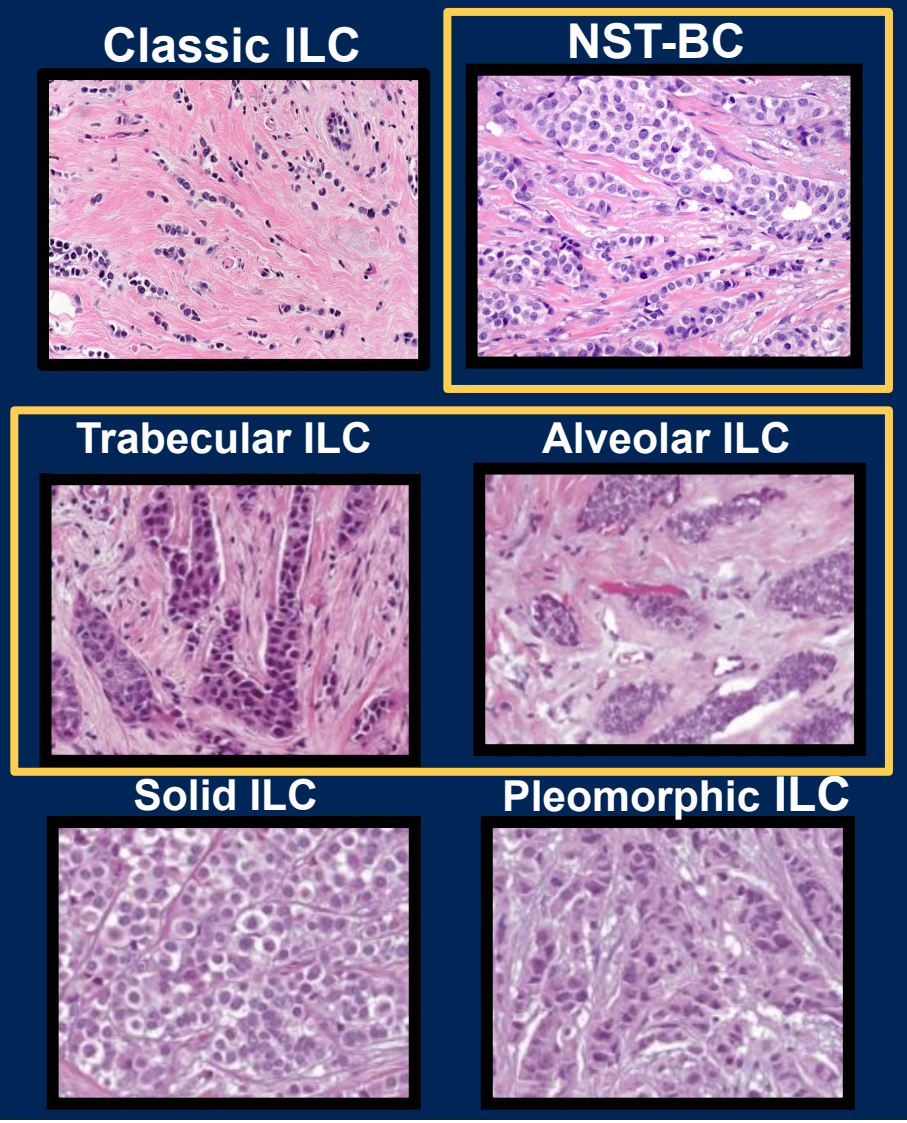
Loss of E-cadherin is Found in ~90% of ILCs and is the Hallmark of ILC



Gall TMH, J Clin Pathol 2013

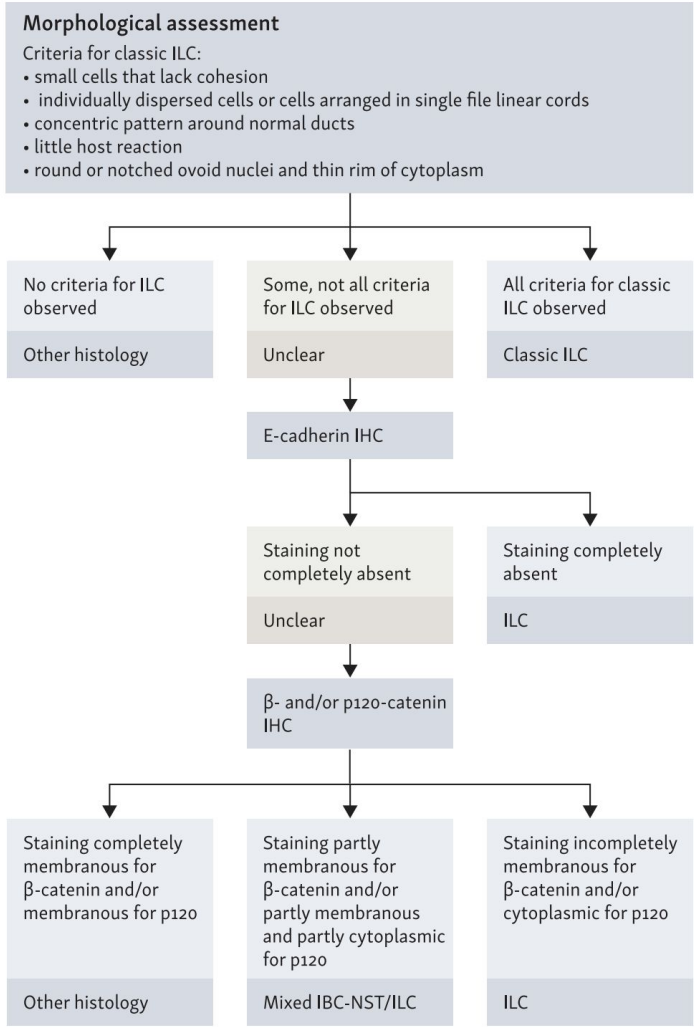
Challenges in the Pathologic Diagnosis of ILC

- **There are also non-classic ILCs that have special architectural patterns and cytological features**
- ILC can be **mixed** containing both classic and mixed non-classic patterns
- Can be **challenging to distinguish** ILC from NST-BC, particularly when there are special architectural patterns, such as trabecular, and alveolar



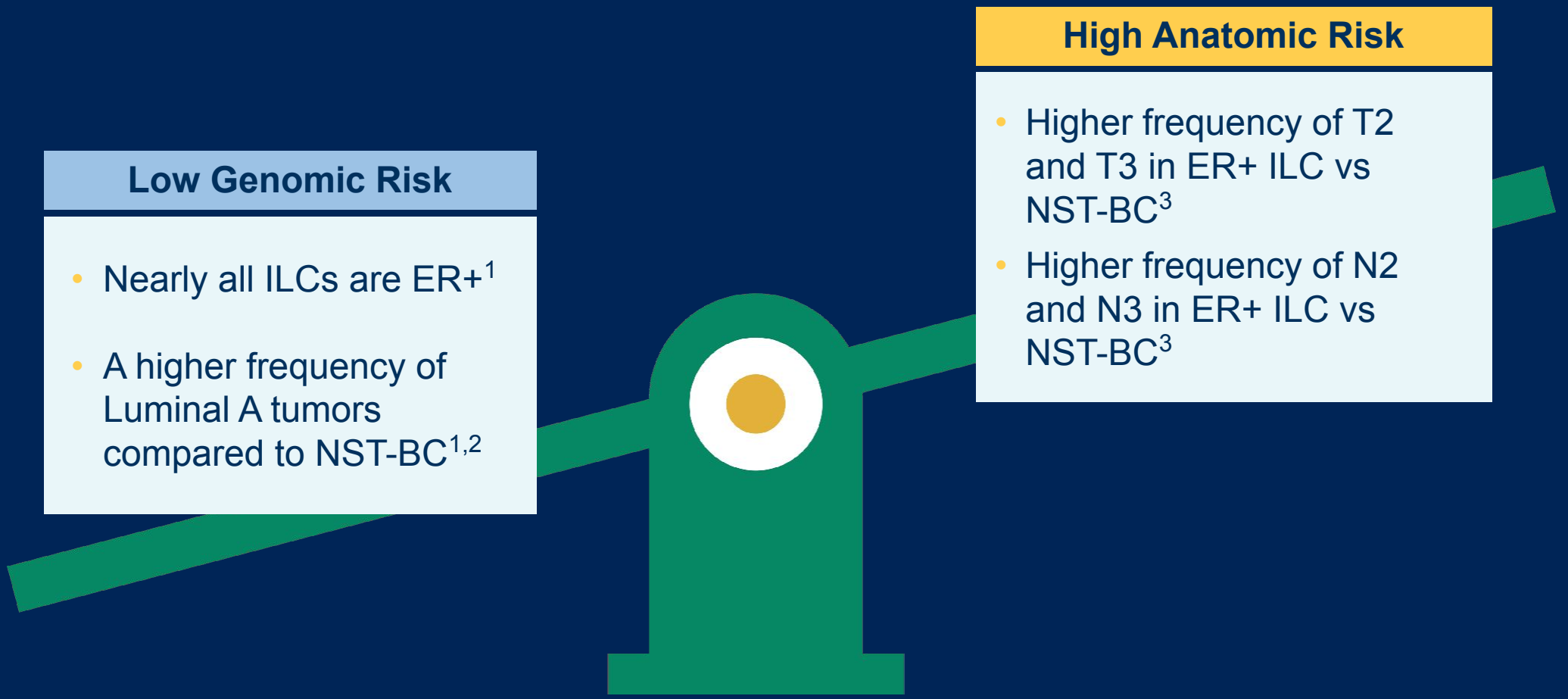
Progress in Improving Pathologic Diagnosis

- The **European Lobular Breast Cancer Consortium pathology** working group developed recommendations for pathologic diagnosis of ILC incorporating E-cad and P120/b-catenin IHC in unclear cases[1]
- **Deep learning models are being developed to support** the diagnosis of ILC and have shown promising results[2,3]



1.De Schepper, Mod Pathology 2024 2. Han Z, Sci Report 2017
3.Pareja F, Cancer Research 2024

Anatomical-Genomic Disconnect in ILC



Low Genomic Risk

- Nearly all ILCs are ER+[1]
- A higher frequency of Luminal A tumors compared to NST-BC[1,2]

High Anatomic Risk

- Higher frequency of T2 and T3 in ER+ ILC vs NST-BC[3]
- Higher frequency of N2 and N3 in ER+ ILC vs NST-BC[3]

1. Williams LA, Ca Causes Cont 2019, Ciriello G, Cell 2015 3. Oesterreich S, JNCI 2022

Anatomical-genomic Disconnect in ILC

	ILC (n = 1497)	NST (n = 5902)	P Value
Concordant risk, n (%)	**797 (53.2%)**	**3715 (62.9%)**	
Anatomical low/Genomic low	552 (36.9%)	2305 (39.1%)	
Anatomical high/Genomic high	245 (16.4%)	1410 (23.9%)	
Discordant risk, n (%)	**700 (46.8%)**	**2187 (37.1%)**	**<0.001**
Anatomical low/Genomic high	167 (11.2%)	1057 (17.9%)	
Anatomical high/Genomic low	533 (35.6%)	1130 (19.2%)	**<0.001**

National Cancer Database, genomic risk based on MammaPrint

Molecular Risk Stratification Tools Were Not Designed for ILC

The majority of ILCs have low-intermediate molecular risk scores (high risk score are found in **~10% -30%** depending on the assay)[1]

High risk scores in ILC are predominantly in non-classic subtypes (pleomorphic subtype is mostly classified as high risk)[2]

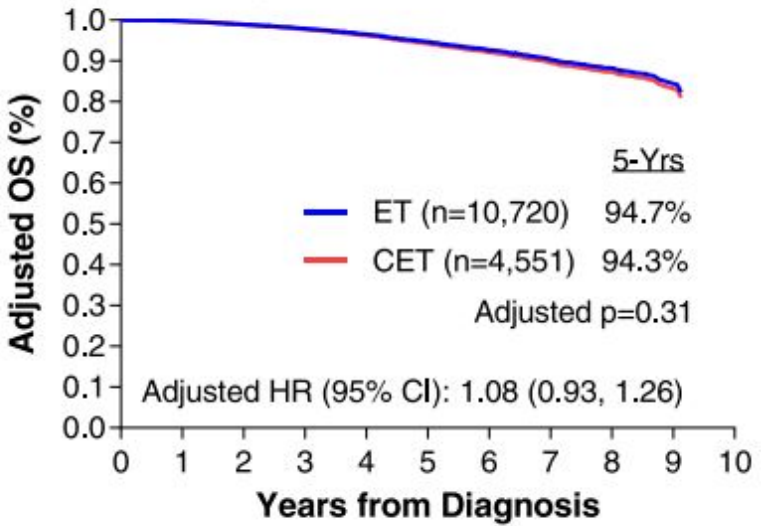
Although prognostic in ILC, there are limited data regarding their ability to predict benefit from chemotherapy in ILC[1,2,3,4,5]

LobSig is the only ILC unique **prognostic signature** but requires validation and its predictive value is unknown[5]

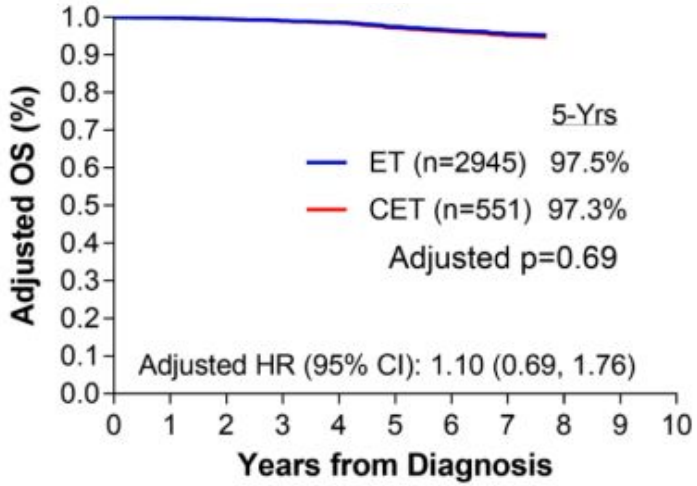
1.Kizy S, Breast Can Res Treat 2017 2. Metzger OF, European J of Cancer 3. Makower D NPJ Breast 2022
4. Yaghi M, Ca Treat and Res Com, 2023 5. McCart R AE, NPJ Breast 2019

OncotypeDX Score of ≥ 26 was Not Predictive of Chemotherapy Benefit

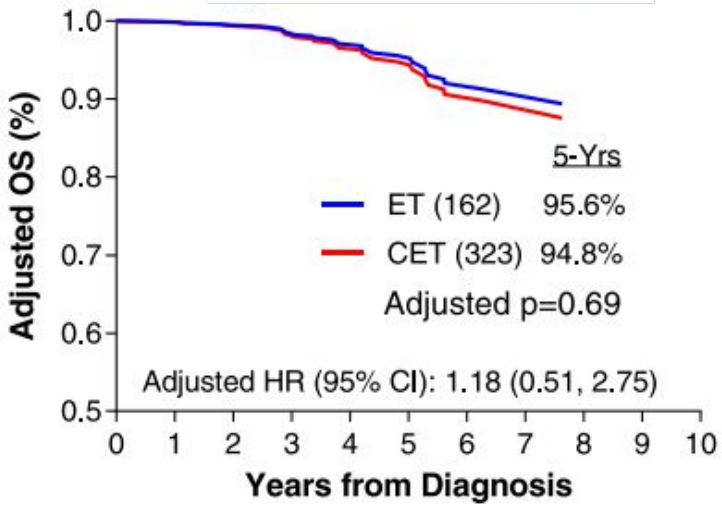
All ILC



ILC oncotype <26



ILC oncotype ≥26



ET: endocrine therapy

CET: chemotherapy and endocrine therapy

National Cancer Database, overall ILC (Classical ILC and MIXED ILC/ IDC) N=15,271 ILC pts with OncotypeDX score N=5561

Yaghi M, Ca Treat & Res Com 2023

Yaghi M, Ca Treat & Res Com 2023

Clinicopathologic Features Identify ER+/HER2− ILC Patients who Benefit from Adjuvant Chemotherapy

Retrospective evidence suggests chemotherapy benefit in a subgroup of patients with high-risk clinicopathological features in ILC. However, there are currently no molecular tools to personalize chemotherapy decisions for ILC, and in practice treatment decisions still largely mirror those used for NST-BC.

Neoadjuvant Chemotherapy in HR+/HER2- ILC

Neoadjuvant Endocrine Therapy

Given the lower rates of BCS and pCR observed with chemotherapy in ILC, neoadjuvant chemotherapy should be reserved for selected high-risk patients (e.g., high-grade or non-classic ILC). **Neoadjuvant endocrine therapy can achieve downstaging in ~30% of patients and is a reasonable option when appropriate.**

How Can We Improve Neoadjuvant (and adjuvant) Treatment in ILC?

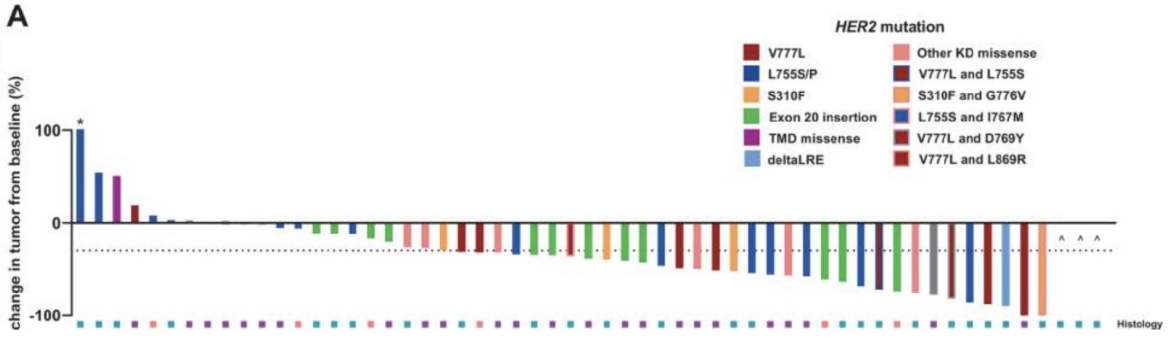
Adapted from: Ciriello G, Cell 2015 and Desmedt C, JCO 2016

LOBSTER (GBG 118): Phase II Randomized Neoadjuvant Study of Capivasertib Plus Fulvestrant VS Fulvestrant in High-risk Lobular Breast Cancer

PRESENTED BY: RINATH JESELSOHN, MD

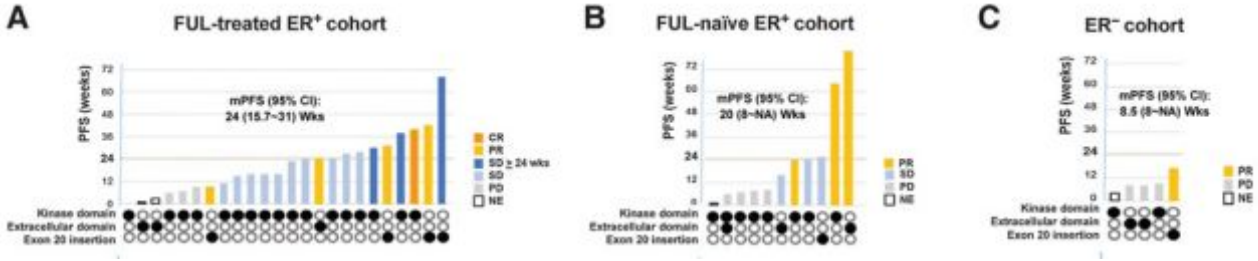
Neratinib is an Effective Treatment For *ERBB2* Mutant Metastatic ER+/HER2- Breast Cancer

SUMMIT Basket Study: ER+/HER2-neg metastatic BC, *ERBB2* activating mutation, post CDK4/6i [1]



Neratinib+Fulvetsrant+Trastuzumab N=57
ORR (confirmed/unconfirmed) 51% Median PFS 8.3M

Phase II MutHER Study: ER+/HER2-neg + ER-/ HER2-neg arm metastatic BC, *ERBB2* activating mutation[2]



CBR in fulvestrant-treated 38% (N=21) CBR in fulvestrant-naïve 30% (N=10) CBR in ER-neg 25% (N=4)

DESTINY-PanTumor01[3]:

Trastuzumab deruxtecan in solid tumors with ERBB2 activating mutations

Breast cancer (HER2-neg)
N=20 ORR= 50%

PRESENTED BY: RINATH JESELSOHN, MD

1.Jhaveri K, Annals of Oncology 2024 2. Ma CX, Clin Cancer Research 2022
3. Li BT, Lancet Onc, 2024

Phase II Neoadjuvant Study of Neratinib in Stage I-III *ERBB2*-Mutated Lobular Breast Cancer

PI: Laura Kennedy

NCT05919108

Key eligibility:

- ER+/ HER2- **ILC**
- Stage I-III (≥1.5cm)
- *ERBB2* activating mutation based on NGS

N=30

Post-menopausal: AI

Pre-Menopausal: AI+ GNRH agonist

Lead-in window

ET* x4 weeks

ET*+Neratinib x4 weeks

Diagnostic biopsy

Research biopsy

Neoadjuvant ET*+ Neratinib x20 weeks

SURGERY

Primary endpoint:

- PEPI score at surgery

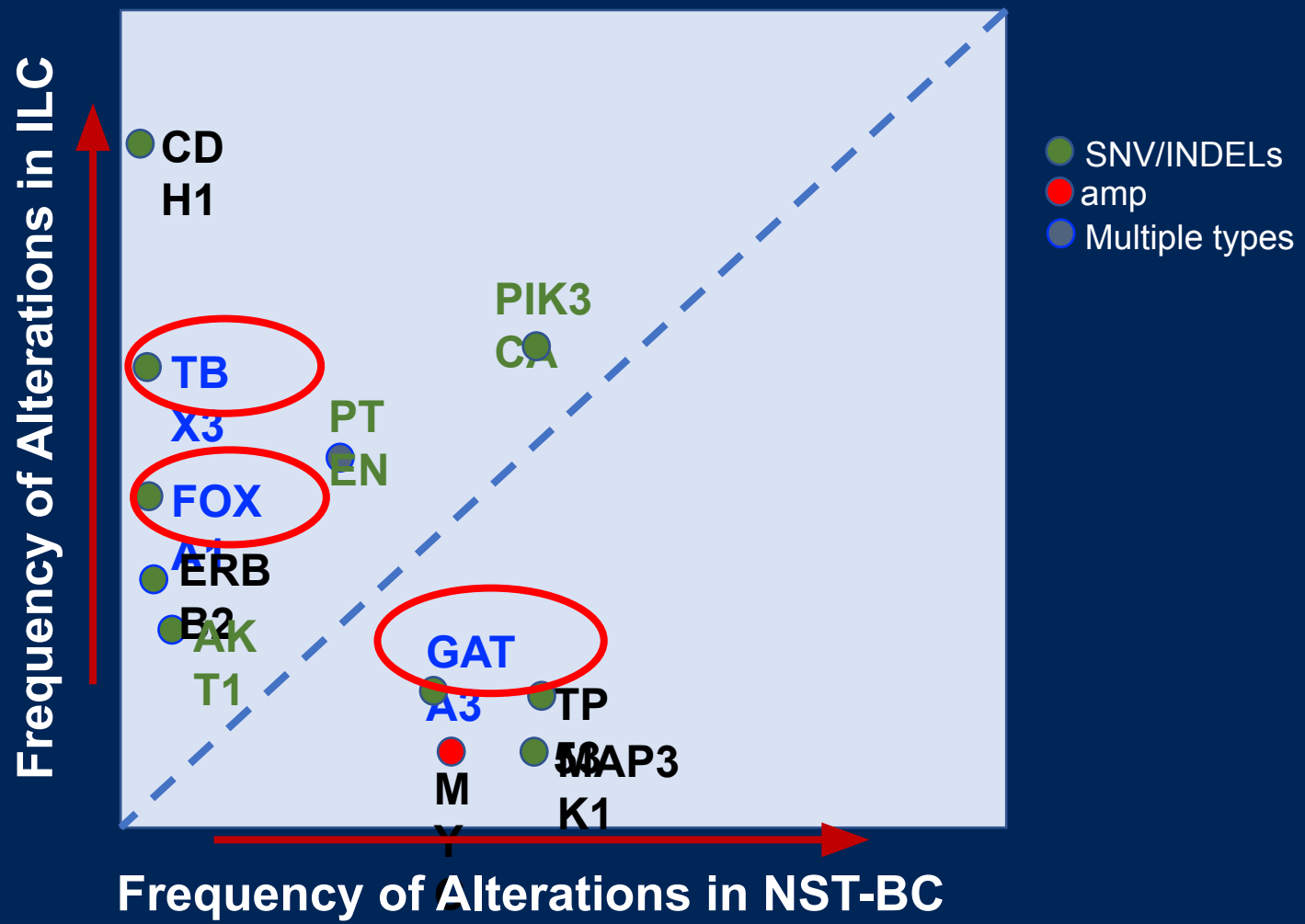
Secondary endpoints:

- Change in Ki67 after lead-in window
- pCR rate
- RCB index
- Rates of Breast Conservation Surgery
- Safety

In a Pre-clinical Study ROS1 Inhibitors were Synthetically Lethal with E-cadherin Loss

Bajrami I, Cancer Discovery 2018 Lobo-Martins S, ESMO Breast Cancer 2025

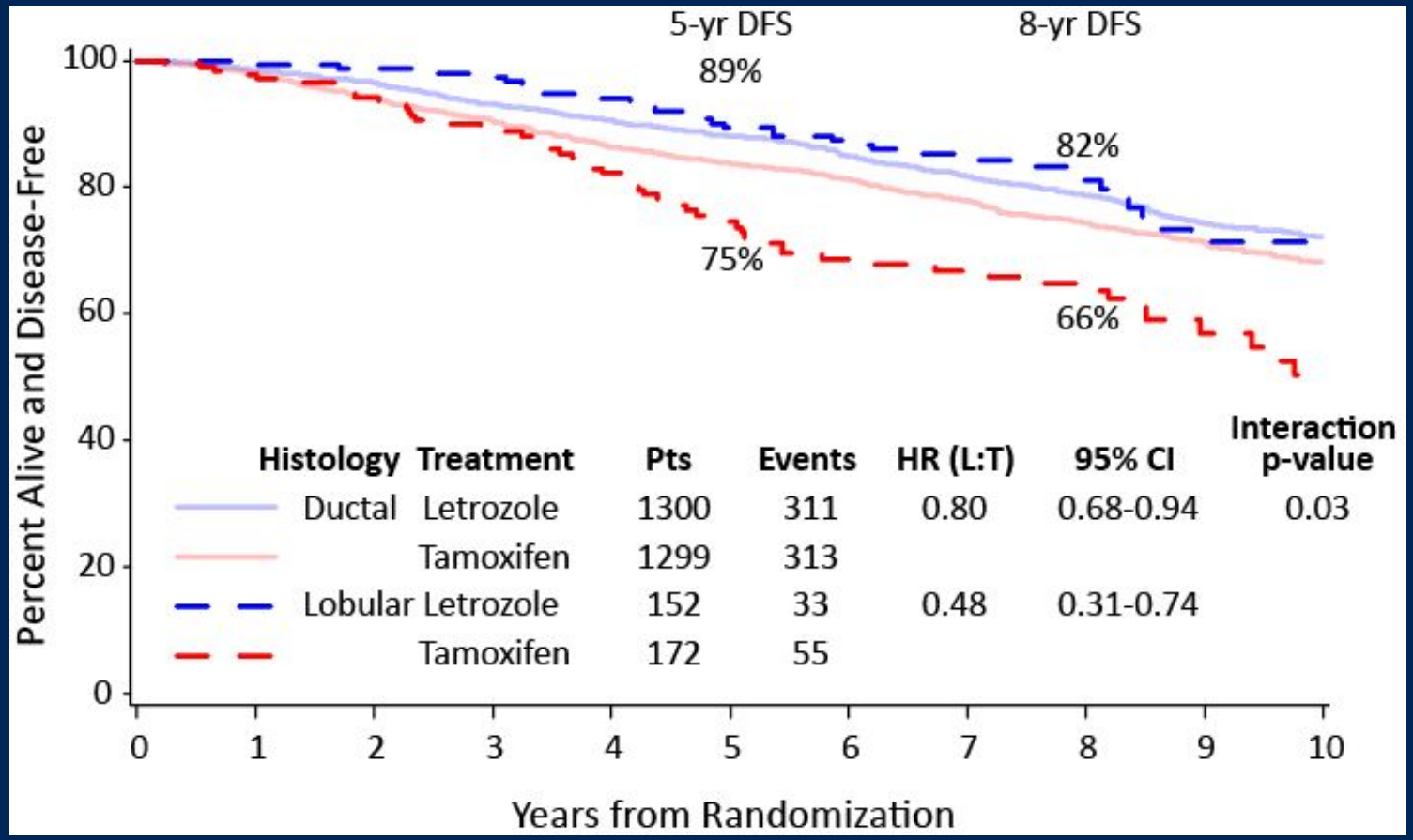
Evidence of an ILC Unique ER Axis



Adapted from: Ciriello G, Cell 2015 and Desmedt C, JCO 2016. Nardone A, Cancer Research 2022

Clinical Evidence for a Unique ER Axis in ILC

Divergent Response to Endocrine Treatment in ILC: In the BIG 1-98 Trial the Magnitude of the Difference between Adjuvant Tamoxifen Compared to AI was greater in ILC versus NST-BC



Metzger O et al , JCO 2015

The Relative Resistance to Tamoxifen in ILC Compared to NST-BC is Controversial

1090 **Adjuvant endocrine therapy for premenopausal invasive lobular carcinoma (ILC): Results from SOFT and TEXT phase III studies**

O. Metzger[1], Y. Ren[2], J. Huober[3], R. Kammler[4], P. Dell'Orto[5], L. Russo[6], G.F. Fleming[7], P.A. Francis[8], O. Pagani[9], B.A. Walley[10], S. Loi[11], M.A. Colleoni[12], B.J.K. Thuerlimann[13], G. Viale[14], M.M. Regan[15]

[1]Breast Oncology Department, Dana-Farber Cancer Institute - Longwood Center, Boston, MA, USA; [2]Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Breast Center, Kantonsspital St. Gallen, St. Gallen, Switzerland; [4]Translational Research Coordination Department, ETOP IBCSG Partners Foundation, Bern, Switzerland; [5]Pathology, European Institute of Oncology, Milan, Italy; [6]Department of Pathology, European Institute of Oncology, Milan, Italy; [7]Section of Hematology/Oncology, University of Chicago Department of Medicine, Chicago, IL, USA; [8]Medical Oncology Department, Peter MacCallum Cancer Center, Melbourne, VIC, Australia; [9]The Interdisciplinary Cancer Service, HRC - Hopital Riviera-Chablais - Site de Rennaz, Rennaz, Switzerland; [10]Medical Oncology, University of Calgary - Oncology, Calgary, AB, Canada; [11]Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Division of Medical Senology, IEO - Istituto Europeo di Oncologia IRCCS, Milan, Italy; [13]Swiss Breast Care, Bethanienspital, Zurich, Switzerland; [14]Pathology Department, IEO - Istituto Europeo di Oncologia, Milan, Italy; [15]Division of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA

GENERAL SESSION ABSTRACTS | MAY 01 2015

Abstract S2-06: Survival advantage of anastrozol compared to tamoxifen for lobular breast cancer in the ABCSG-8 study

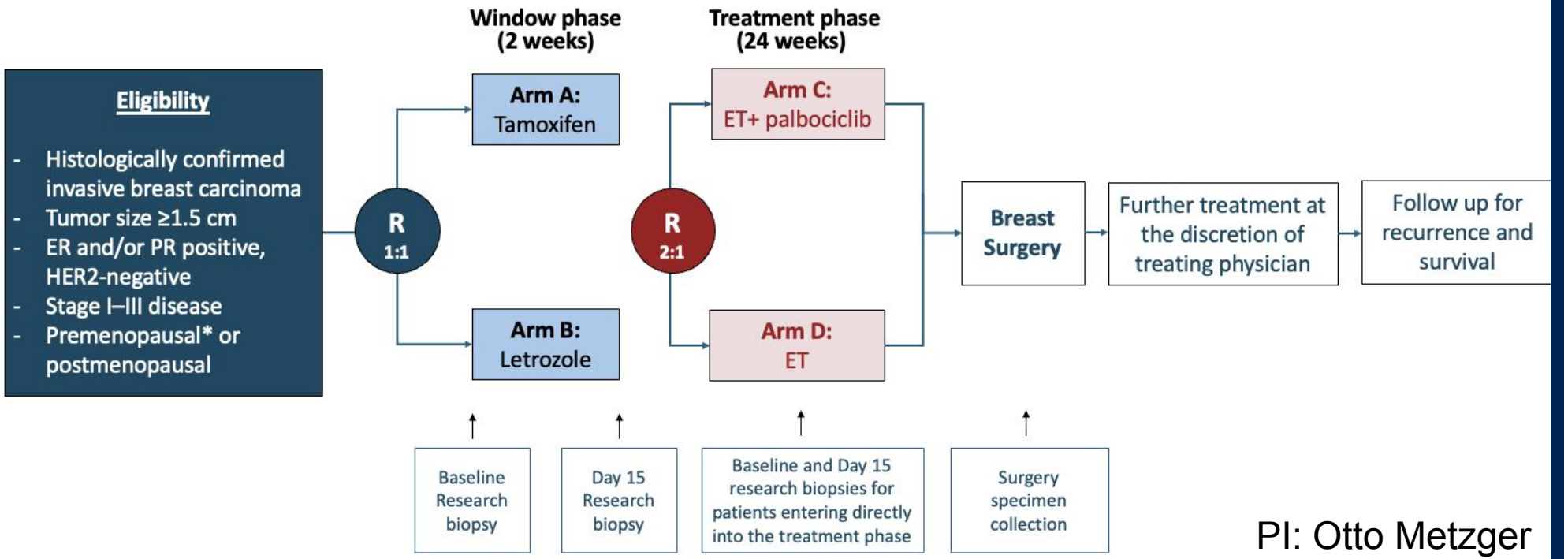
Michael Knauer; Christine Gruber; Otto Dietze; Richard Greil; Herbert Stöger; Margaretha Rudas; Zsuzsanna Bago-Horvath; Brigitte Mlineritsch; Werner Kwasny; Christian Singer; Peter Dubsky; Raimund Jakesz; Florian Fitzal; Günther Steger; Rupert Bartsch; Martin Filipits; Christian Fesl; Michael Gnant

POSTER SPOTLIGHT SESSION ABSTRACTS | FEBRUARY 15 2022

Abstract PD14-08: Effectiveness of aromatase inhibitors versus tamoxifen in lobular compared to ductal carcinoma: Individual patient data meta-analysis of 9328 women with central histopathology, and 7654 women with e-Cadherin status

Robert K Hills; Steffi Oesterreich; Otto Metzger; David Dabbs; Hongchao Pan; Jeremy Braybrooke; Richard Gray; Richard Peto; Rosie Bradley; Ewan Straiton; Richard Berry; Daniel Rea; David Cameron; Jack Cuzick; Meredith Regan; Mitch Dowsett; Ivana Sestak; Jonas Bergh; Sandra M Swain; John Bartlett; Early Breast Cancer Trialists' Collaborative Group

PELOPS: Randomized Phase II Study Of Neoadjuvant Palbociclib +/- ET for BC Patients with ILC OR NST-BC



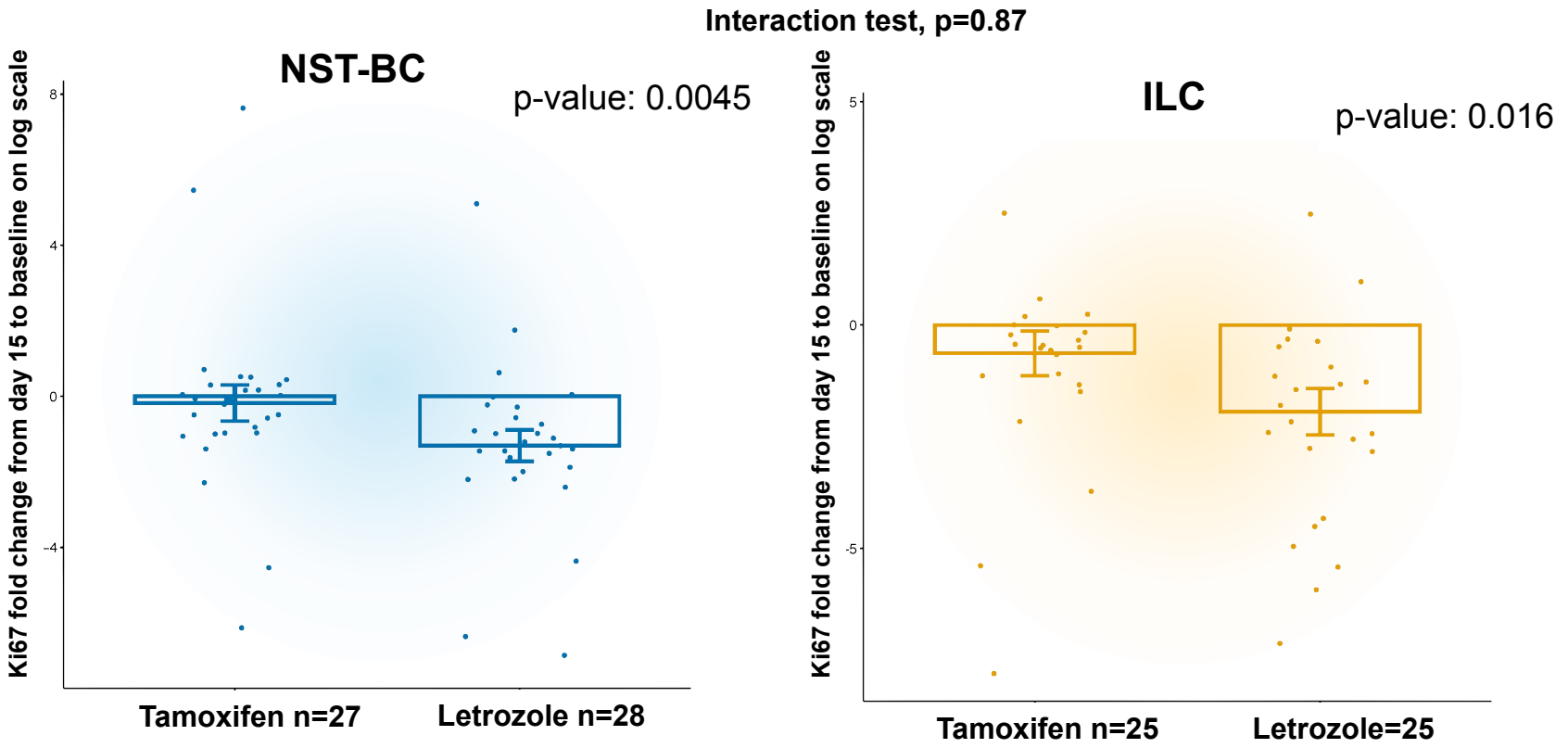
PI: Otto Metzger

Primary Endpoints:

Window Phase: Change in tumor proliferation measured by Ki67 from baseline to day 15 of ET in ILC and NST-BC (Ki67 index)

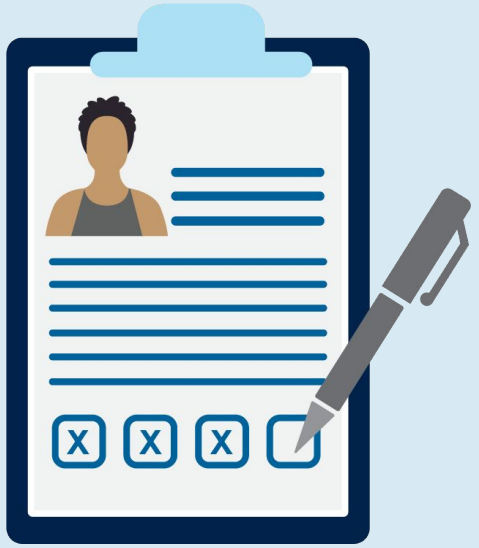
Treatment Phase: Residual cancer burden at the time of surgery

Primary Endpoint Results from the Window Phase



TBCRC 037: Randomized Window Trial Comparing SERD VS AI VS Tamoxifen In ILC

We are observing differences in Ki67 responses across distinct classes of endocrine therapy in two clinical trials, consistent with patterns seen in NST-BC

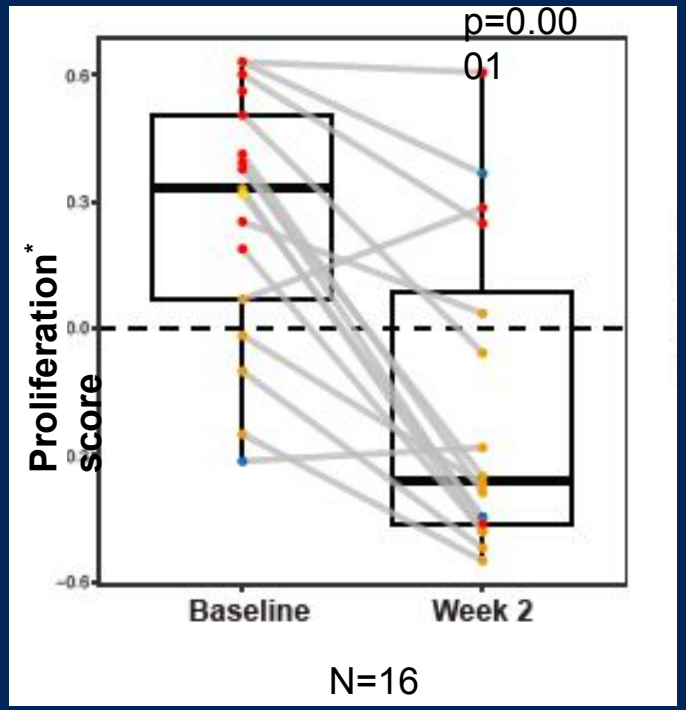


Ki67 vs RNA-seq Proliferation Pathway Analysis

Ki67 MEASUREMENT	RNA-seq PROLIFERATION PATHWAY
Single protein assessed by IHC at a single time, point provides a limited view of the cell cycle	Multi-gene transcriptomic analysis can capture the entire cell cycle programs and provides a broader representation of the proliferative state of the tumor

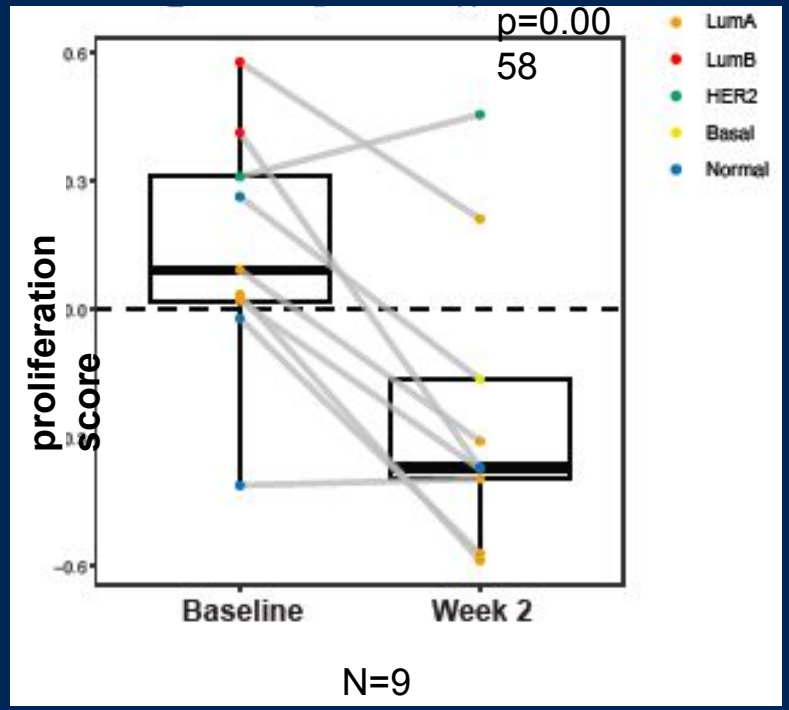
RNA-seq Proliferation Changes with Letrozole are Similar in ILC and NST-BC

NST-BC



N=16

ILC

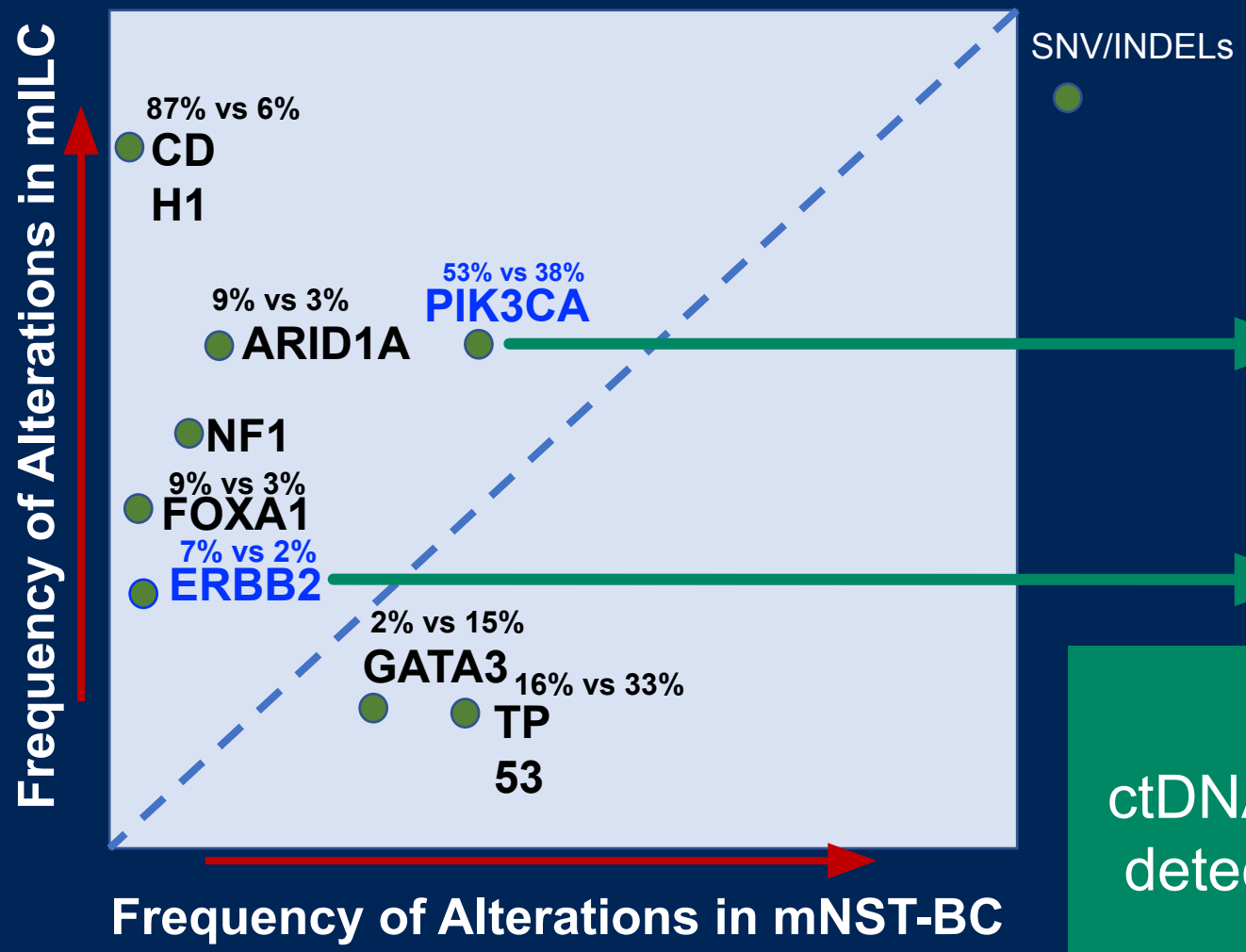


N=9

RNA-seq Proliferation Changes with Tamoxifen are Different in ILC and NST-BC

Clinical data indicating differences between the transcriptional effects of tamoxifen in ILC versus NST-BC supports a distinct ER axis, but does not establish a corresponding difference in long term outcomes

Metastatic ILC has a Unique Genomic Landscape



Alpelisib
Capivasertib
Inavolisib

Neratinib
T-DXd

ctDNA testing in mILC is important for the detection of potential therapeutic targets

Key Takeaways

ILC is **a common and clinically important** breast cancer subtype

Although most ILCs are HR-positive, it is a biologically and clinically distinct breast cancer subtype, that requires **an ILC dedicated approach**

Multiple studies, albeit mostly retrospective, suggest **decreased response to chemotherapy in early-stage ILC**

Currently, **we are lacking molecular tools to predict which subgroup of patients with ILC benefit from chemotherapy** and decisions regarding chemotherapy in early-stage disease overall mirror NST-BC

Ongoing and future pre-clinical research, rationally designed clinical trials testing ILC specific targets and correlative science **are expected to drive precision medicine in ILC and improve patient outcomes**

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BOC, DFCI

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Harold Burnstein

ILC Research Community and Patient Advocates

Lobular Breast Cancer Alliance

THANK YOU

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