Highlights of the 2022 Joint International ELBCC/Lobsterpot & LBCA Invasive Lobular Carcinoma (ILC) Symposium

Clinical Highlights

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European Lobular Breast Cancer Consortium
LBCA™ Lobular Breast Cancer Alliance
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Clinical Topics from the ILC Symposium

- Epidemiology
- Diagnosis and Treatment
  - Imaging
  - Local Therapy
  - Systemic Therapy
- Early stage and metastatic

Clinical Themes

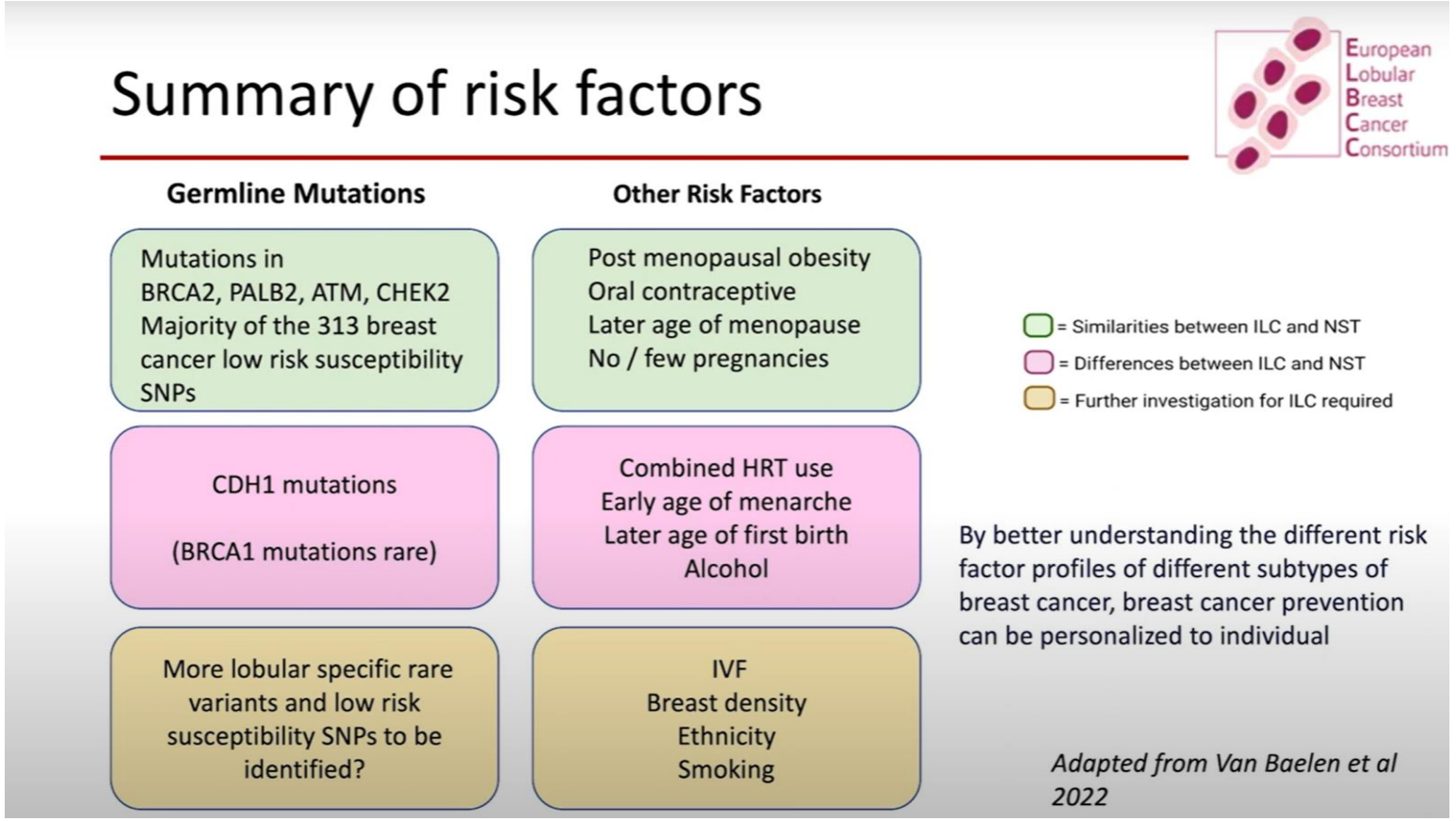
- Important concepts:
  - Discordance of diagnosis on histopathology
    - Recommendation for E-cadherin staining
  - Reduced sensitivity of imaging
  - Increased rates of mastectomy and axillary dissection
  - A subset of patients with ILC benefit from chemotherapy
  - Targeting Receptor tyrosine kinases in trials

Epidemiology: Breast Cancer Risk Factors

- Early menarche, late menopause, nulliparity, late parity (after age 35)
- Lobular carcinoma *in situ*
  - increased lifetime risk of breast cancer, all types but relatively more ILC
- Combined estrogen and progesterone hormone replacement therapy
- Obesity in setting of post-menopausal status increases risk of ER positive breast cancer
- Alcohol increases risk of ILC compared to NST (Li *et al*)

Mammary Gland Development, Renee van Amerongen
Risk factors, clinical diagnosis, and treatment of ILC: Elinor Sawyer

Epidemiology



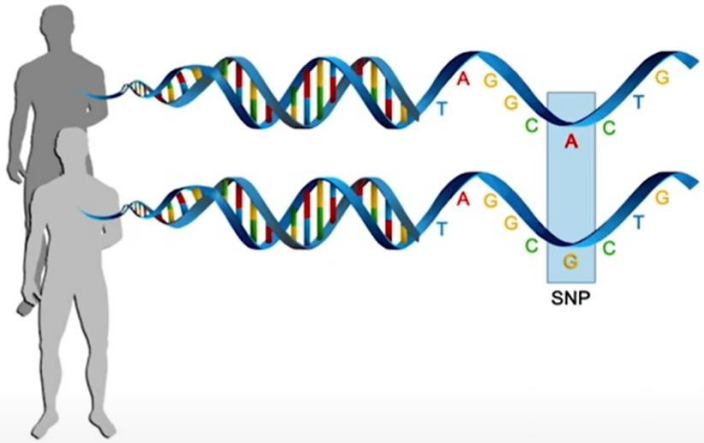
Risk factors, clinical diagnosis, and treatment of ILC: Elinor Sawyer

Polygenic risk score: ILC specific SNP's

Low-penetrance genetic variants & ILC

European Lobular Breast Cancer Consortium

- 313 low penetrance single nucleotide polymorphisms (SNPs) that predispose to breast cancer
- Tend to be located in non-coding regions
- Common in the population
- Majority predispose to breast cancer in general or ER+
- Some SNPs are lobular specific
  - **rs11977670 on chromosome 7q34**
  - rs11249433, at 1p11.2 stronger association with ILC



Elinor Sawyer

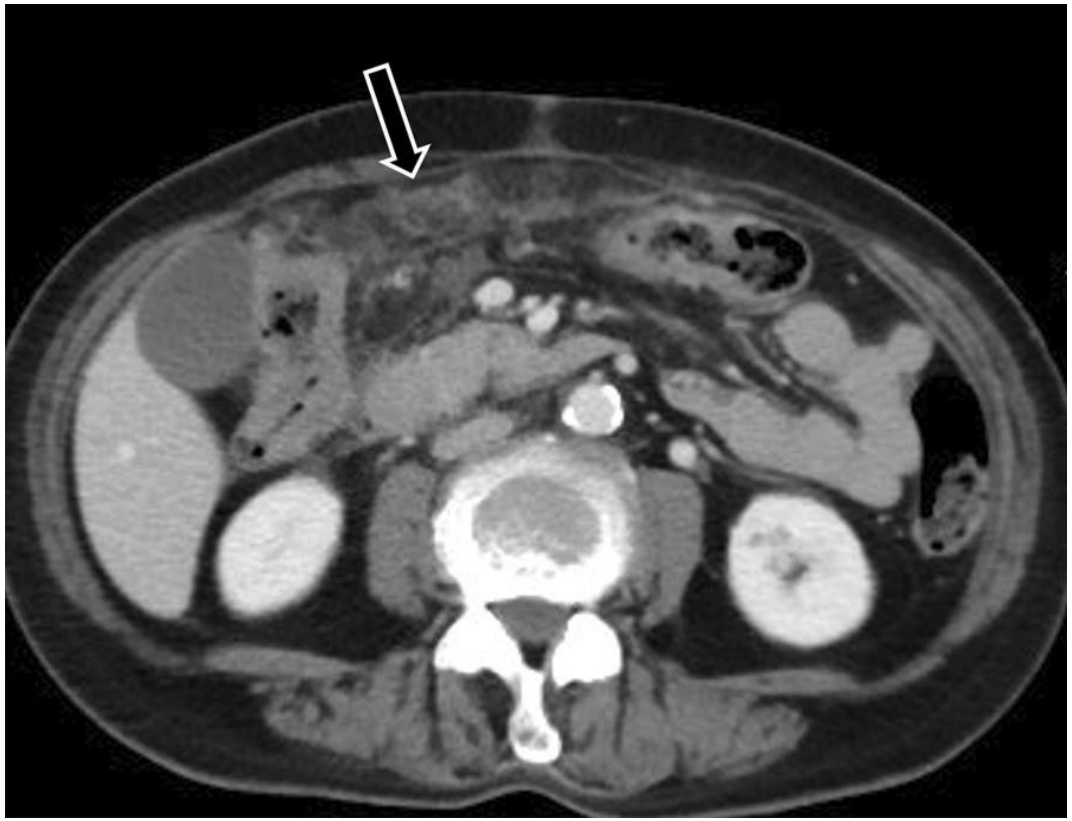
Epidemiology

- Identifying those with elevated risk for ILC could guide screening
  - Mammography has lower sensitivity for ILC
    - Lack of desmoplastic reaction, diffuse growth pattern
- The Great Lakes Breast Cancer Consortium
  - 33,662 patients, of which 3,617 have ILC
  - ILC patients diagnosed at later stages
  - Higher rates of mastectomy use in ILC

Risk factors, clinical diagnosis, and treatment of ILC: Elinor Sawyer
The Great Lakes Breast Cancer Consortium: A comparison of clinicopathologic features between ILC and IDC: Neil Carleton

Diffuse growth pattern impacts stage IV patients as well

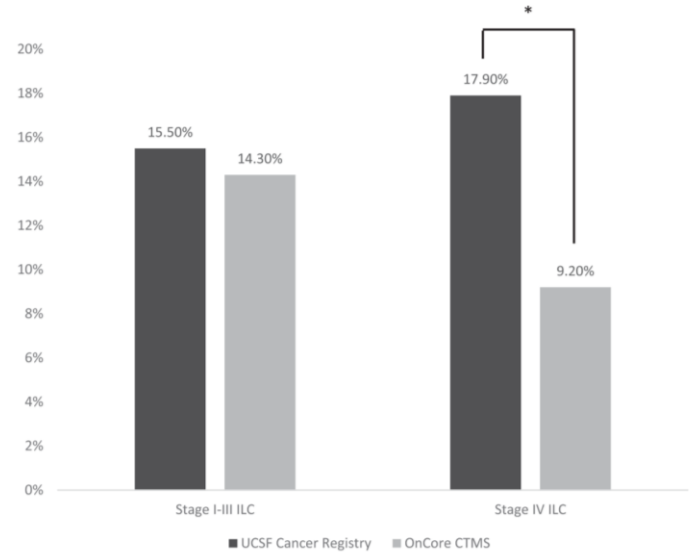
"Unmeasurable" peritoneal involvement of ILC in patient with stage IV disease.



Wong YM et al.11 Infiltrative pattern of metastatic invasive lobular breast carcinoma in the abdomen: a pictorial review
Insights into Imaging volume 12, Article number: 181 (2021)

Need more patients with ILC in clinical trials, especially stage IV

Trial Enrollment Rates



Decreased enrollment in breast cancer trials by histologic subtype: does invasive lobular carcinoma resist RECIST? Abel MK *et al*, npj Breast Cancer 2021

Patients with stage IV ILC were significantly underrepresented in clinical trials (two sample test of proportion $p<0.005$)

UCSF Department of Surgery

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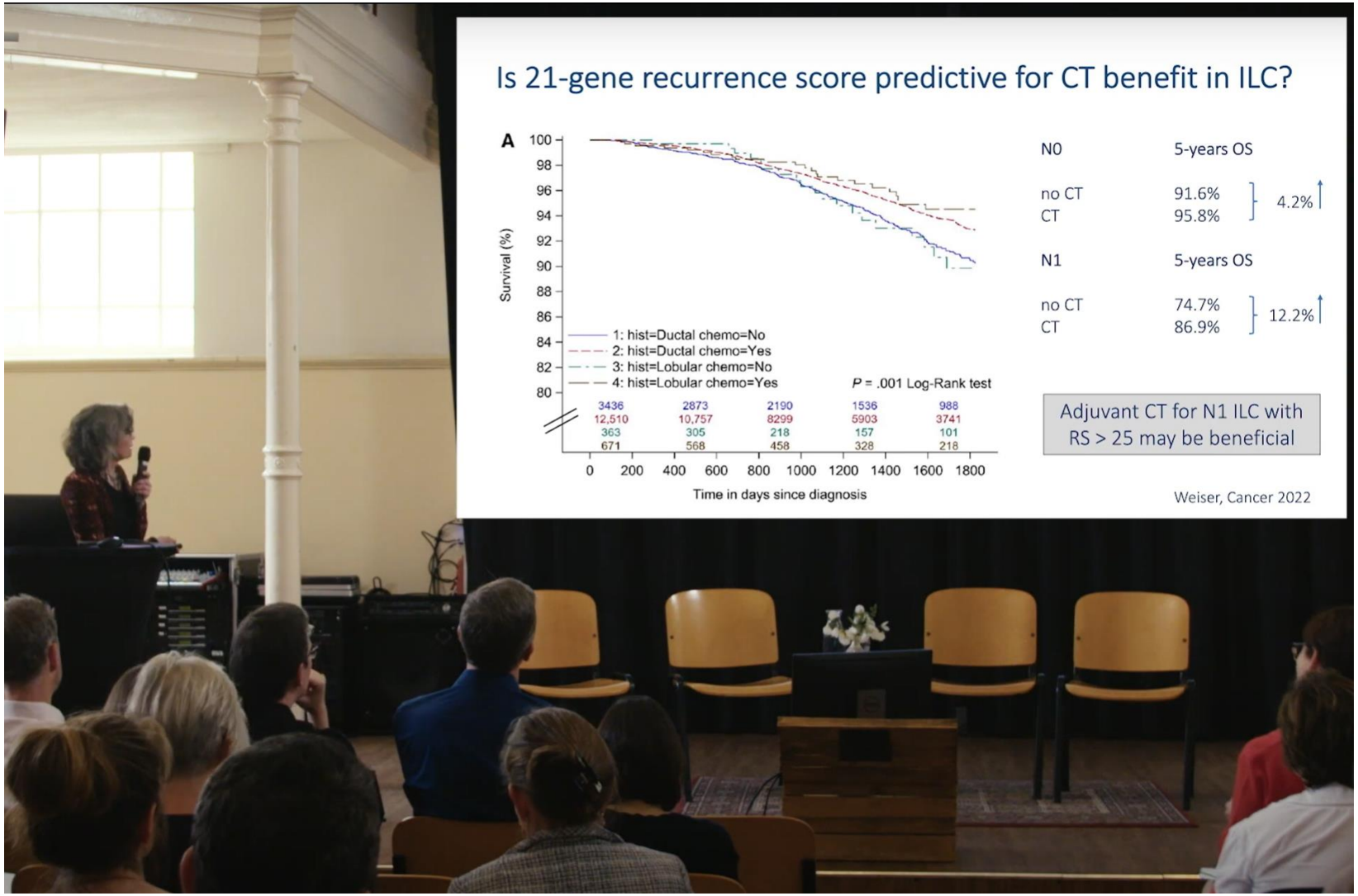
Endocrine Therapy and ILC

- Retrospective analysis of BIG 1-98
  - Relative difference in AI effect versus tamoxifen significantly larger in ILC
- Potential for treatment resistance to tamoxifen in ILC
- In pre-menopausal women with ILC and low clinical risk, tamoxifen likely adequate
- In pre-menopausal women with ILC and high clinical risk, optimal endocrine therapy less clear (OFS/AI?)
- Optimal duration of endocrine therapy needs more study
- ILC specific analyses of SOFT and TEXT trials ongoing

Hormone Receptor Function and Drug Responses in ILC: Otto Metzger

Chemotherapy and ILC

- Molecular assays such as Mammaprint and Oncotype Dx are prognostic in ILC
- A higher proportion of ILC is molecularly low risk than IDC
- However, a subset of patients with ILC benefit from chemotherapy



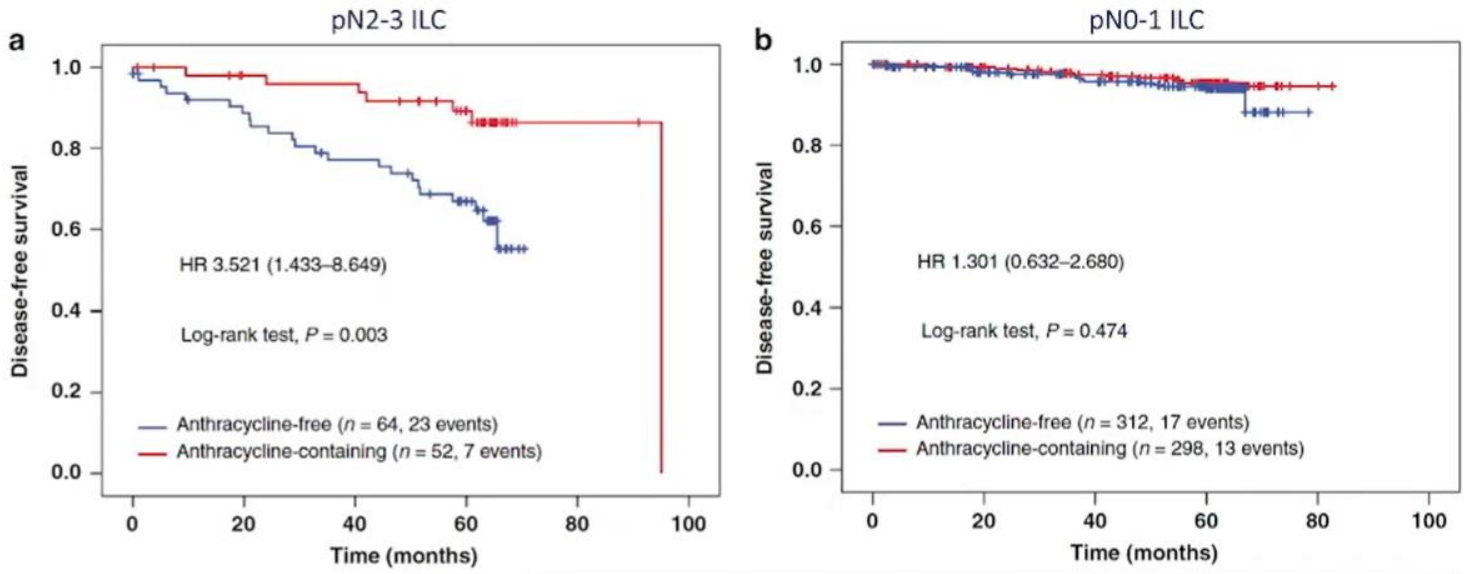
In multivariate analysis, chemotherapy was associated with improved overall survival in patients with node positive ILC with high recurrence score.

Toward Precision Medicine for ILC: Sabine Linn

Chemotherapy and ILC

What type of adjuvant chemotherapy for ILC?

SUCCESS and PlanB RCT: n=5,924 pts, ±50% N+, 40% grade 3, ILC n=726



de Grigorio, Br J Cancer 2022

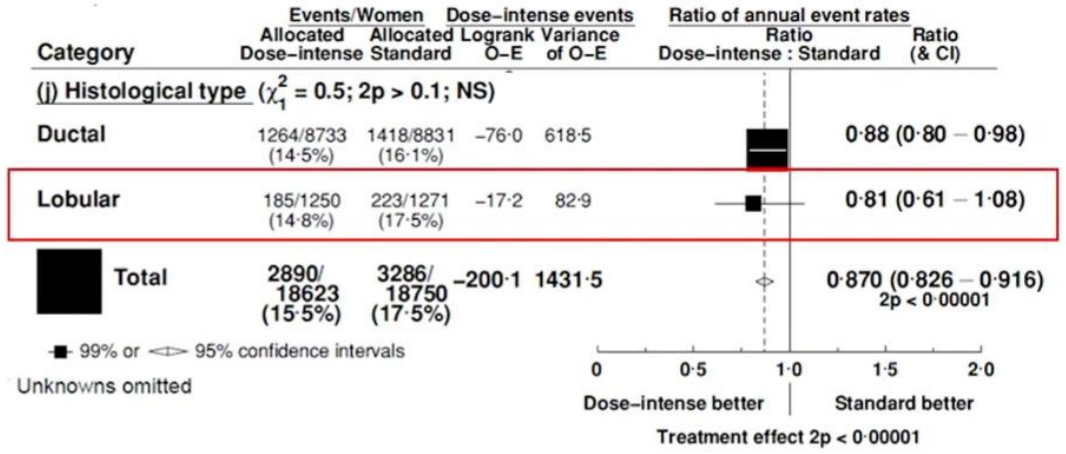
Preferably anthracycline-containing CT for pN2-3 ILC

Analysis of SUCCESS and PlanB trials:

In patients with ILC and 4 or more positive nodes, chemotherapy regimens containing anthracycline were associated with significantly improved DFS compared to non-anthracycline containing regimens.

Chemotherapy and ILC

Dose dense adjuvant chemotherapy for ILC?



19% relative risk reduction to die from ILC with dose-dense chemotherapy

±2500 ILC patients – RR 0.81 for breast cancer specific survival

EBCTCG, Lancet 2019

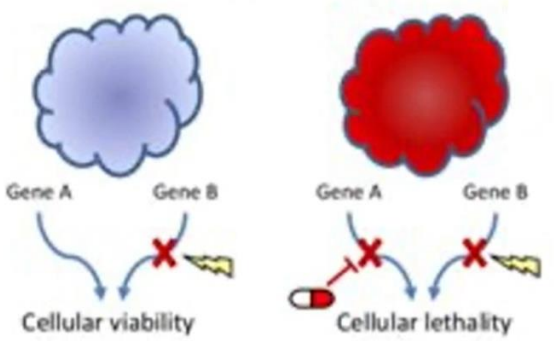
Dose dense chemotherapy associated with improved breast cancer specific survival in ILC

Toward Precision Medicine for ILC: Sabine Linn

Receptor tyrosine kinases in clinical trials

- Several receptor tyrosine kinases have been implicated in ILC and may be targets for therapy
  - ROS1
  - PI3K/AKT/PTEN
  - BET
  - IGF-1R

E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer



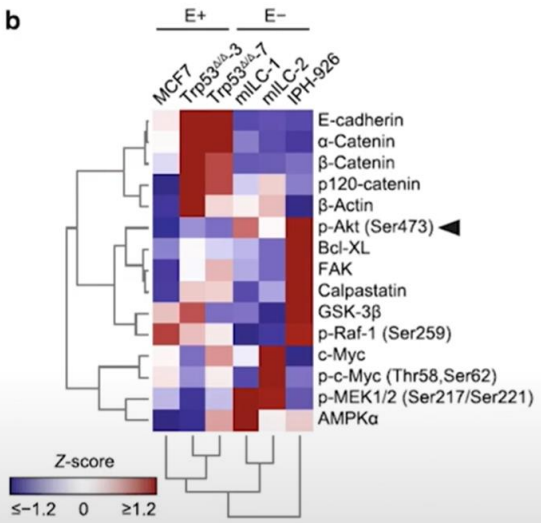
Synthetic lethality arises when a combination of deficiencies in the expression of two or more genes leads to cell death, whereas a deficiency in only one of these genes does not.

Trial	Phase	Design	Patient population	Nr of pts	Treatment	Primary endpoint	Date expected completion enrolment
ROSALINE (NCT04551495)	2	Single arm	Stage I–III ILC	45	Entrectinib + letrozole (+goserelin)	RCB	October 2022
ROLo (NCT03620643)	2	Single arm	Stage IV E-cadherin negative BC	58	crizotinib + fulvestrant	Response rate	May 2023

Bajrami *et al.* Cancer Disc 2018

Ongoing trials of ROS1 inhibitors based on synthetic lethality data

PI3K/AKT activation is independent of *PIK3CA*, *AKT1* or *PTEN* mutations



- Growth factor signals are hyperactivated upon E-cadherin loss, independent of somatic activating mutations in downstream effectors
- **Potential for drugs targeting the PI3K/Akt axis in ILC, irrespective of oncogenic pathway mutations**

Teo *et al.* Sci Rep 2018

- As of yet targeting these pathways shows only modest response and can cause toxicity but still of interest as treatment target
- Potentially test AKT inhibition in combination with IGF1R inhibitor (MEK inhibitor)

Hormone Receptor Function and Drug Responses in ILC: Otto Metzger
Toward Precision Medicine for ILC: Sabine Linn

Conclusions

- Traditional risk factors for breast cancer remain
  - Working towards ILC specific predictors
- Decreased sensitivity of imaging
  - Leads to delay in diagnosis
  - Difficulty with surgical planning and need for more extensive operations
  - Challenges in following disease extent could impact clinical trial enrollment

Conclusions

- Systemic therapy
  - Potentially tamoxifen resistance in some ILC→ongoing work
  - Chemotherapy is beneficial in some ILC
    - Clinically high risk, 4 or more positive nodes→ dose dense anthracycline containing regimen
  - Targeted therapies being tested
- Increasing lobular specific analysis of trial data, development of lobular consortia