SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Invasive Lobular Carcinoma

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Boston
March 29, 2022

Thesis

- ILC represents a unique breast cancer subtype deserving special attention
  - clinical presentation
  - responsiveness to therapies
  - pattern of disease dissemination
  - unique genomic features

Challenge: Limited clinical data and inherent challenges to the interpretation of subgroup analyses

A Rare Form of Mammary Cancer

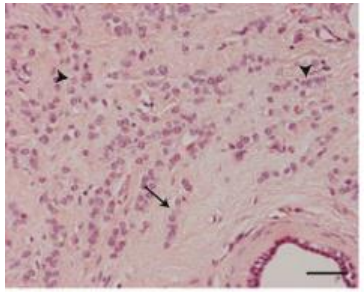
Frank W. Foote, Jr., M.D., and Fred W. Stewart, M.D.
(*From the Pathological Laboratories of the Memorial Hospital, New York, N.Y.*)

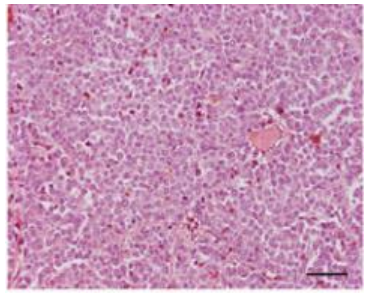
“ *It is apparent, however, that this type of mammary cancer,* i.e., cancer originating in lobules and terminal ducts, is more common than this incidence would appear to indicate, for, when the tumor infiltrates, it is apt to do so in a peculiar fashion *which permits one, after some experience, to recognize the high probability of such origin even though it is impossible actually to trace it* ”

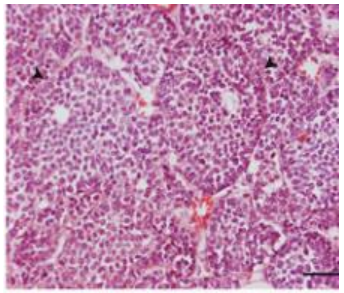
Foote FW Jr, Stewart FW. Am J Pathol 1941

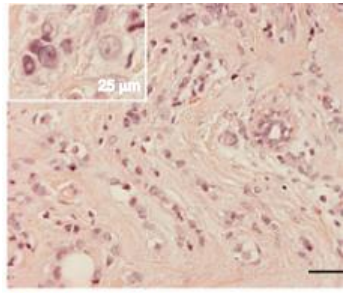
Background

- Classic ILC is the most common subtype
- Other variants: solid, tubulo-lobular, alveolar and pleomorphic


Classic ILC


Solid ILC

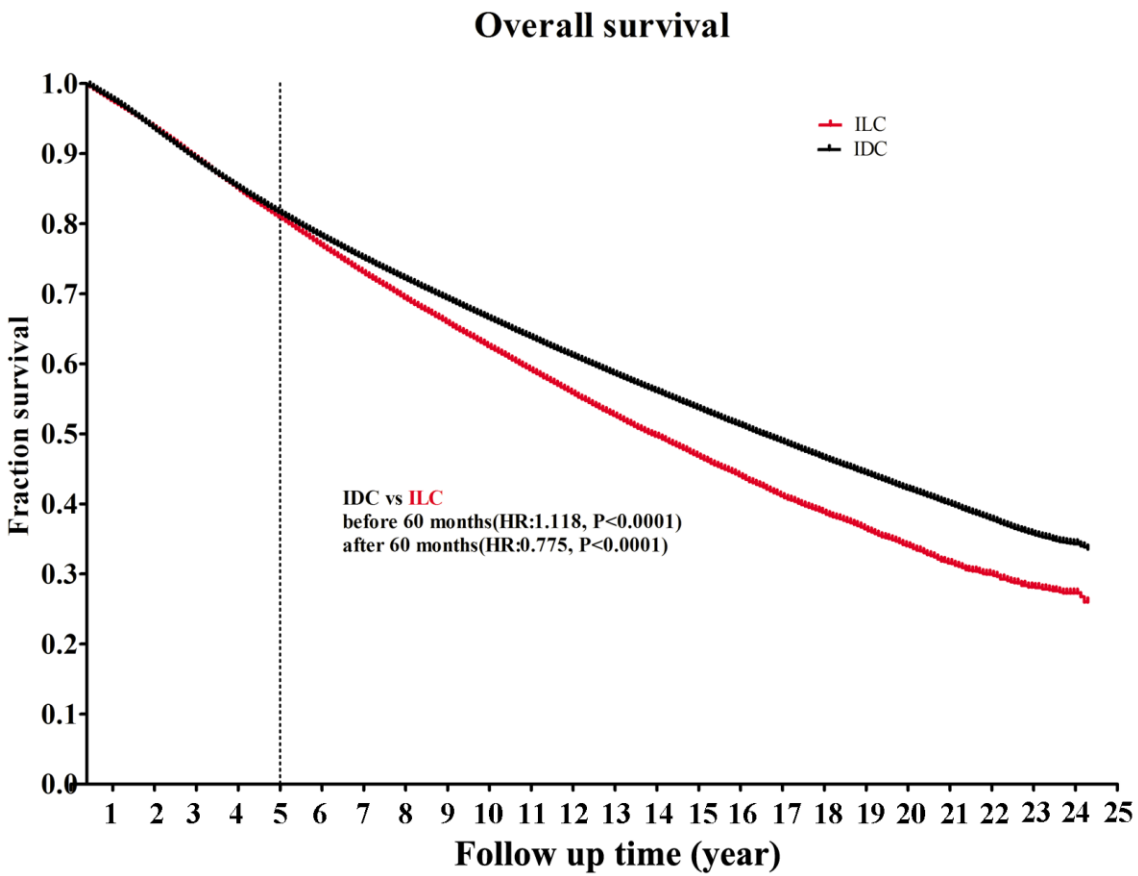

Alveolar ILC

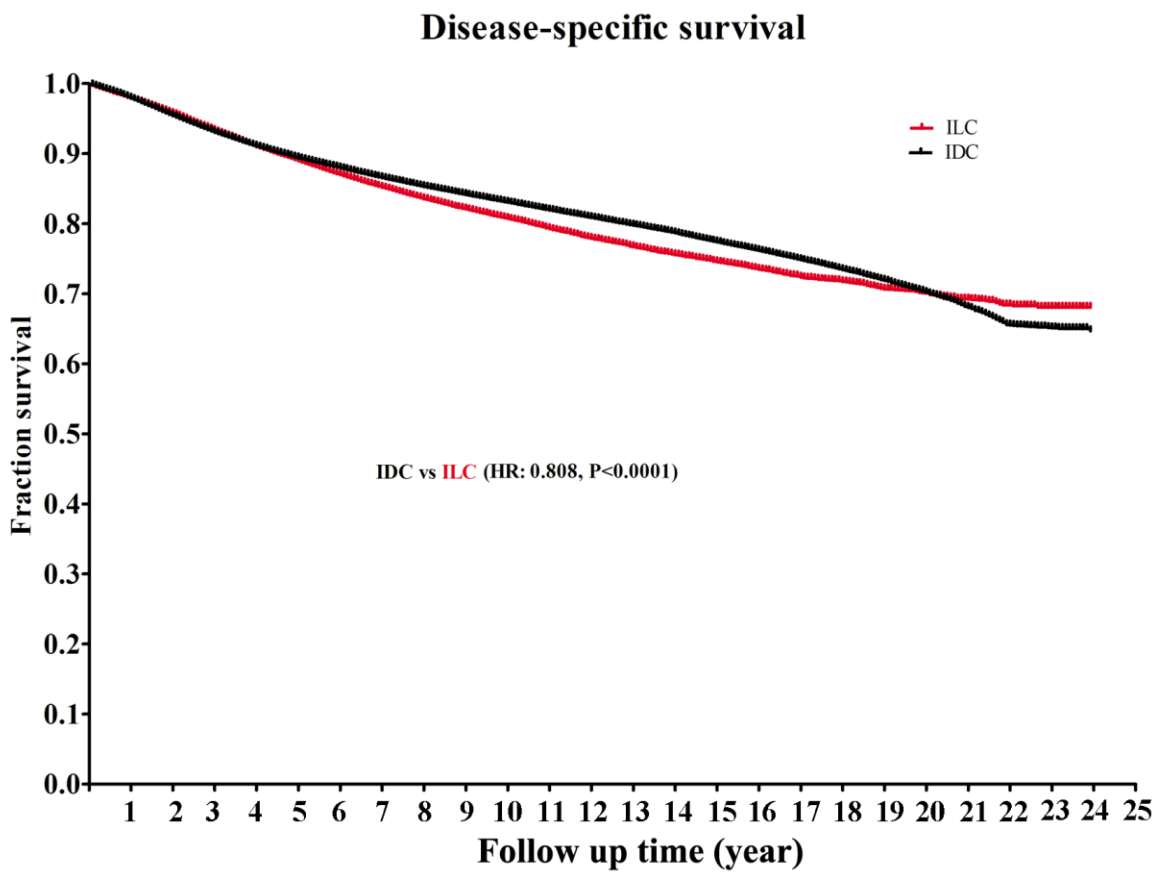


Pleomorphic ILC

Sinn H-PP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition\Breast Care. 2013;8:149–154.
Figure adapted from Vlug E, et al. Lobular breast cancer: pathology, biology, and options for clinical intervention. Arch Immunol Ther Exp (Warsz) 2014;62:7–21.

Comparison of overall survival and disease-specific survival rates of IDC and ILC



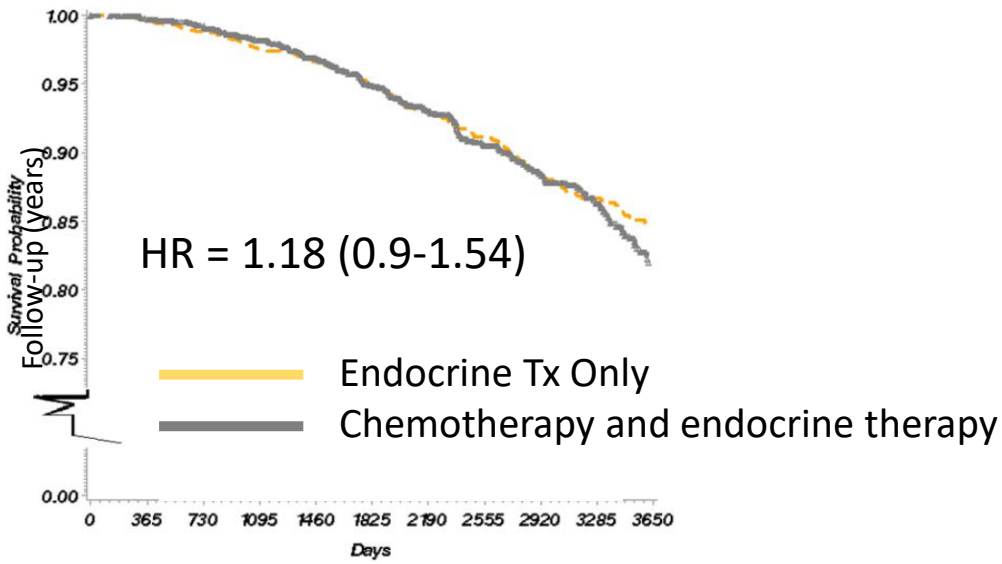


Chen Z, Yang J, Li S, Lv M, Shen Y, et al. (2017) Invasive lobular carcinoma of the breast: A special histological type compared with invasive ductal carcinoma. PLOS ONE 12(9): e0182397. https://doi.org/10.1371/journal.pone.0182397 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0182397

Adjuvant Chemotherapy

Is the lack of Treatment Effect Consistent Across Subgroups?

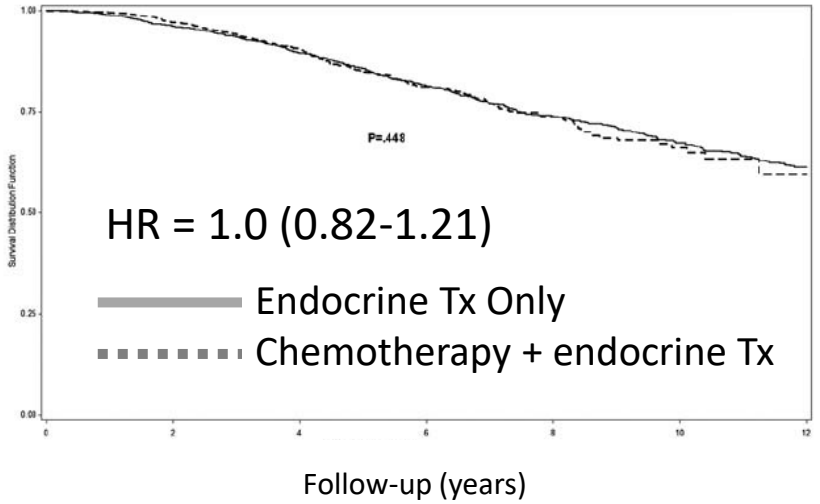
California Cancer Registry



N= 4095 ILC

- 11% Histologic Grade 3
- HG3 vs HG1: HR = 1.49 (1.01-2.19) p = 0.04

Netherlands Cancer Registry

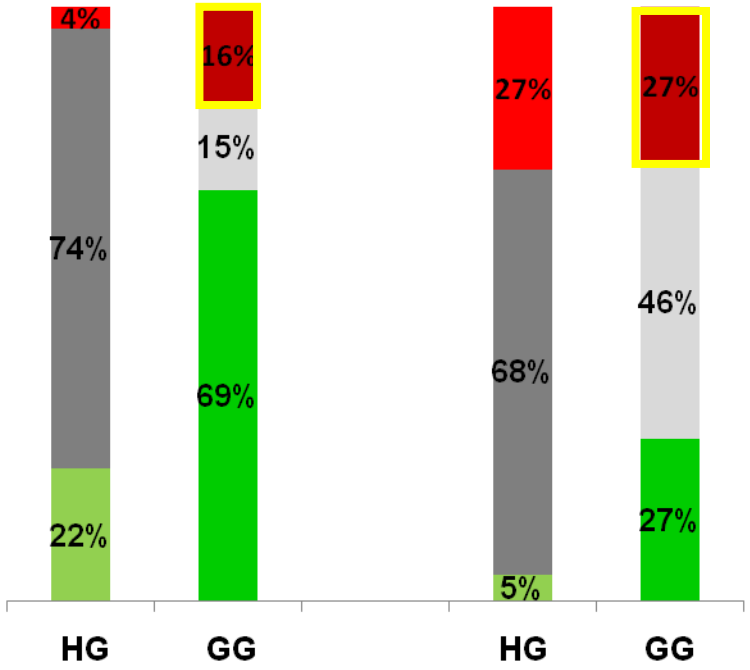


N= 3685 ILC

- 11% Histologic Grade 3
- HG3 vs HG1: HR = 1.54 (1.07-2.22) p = 0.021

Are we missing a small subgroup of ILC that could potentially benefit from adjuvant chemotherapy?

Genomic Grade Index

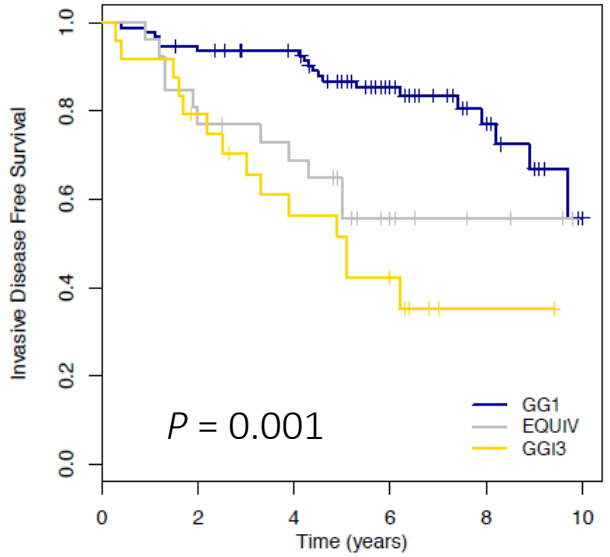


Classic ILC
N = 144

Pleomorphic ILC
N = 22

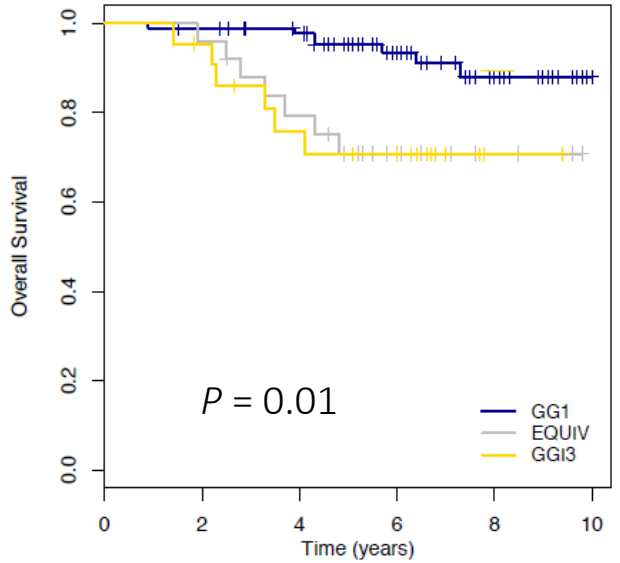
HG3 GG3
HG2 Equivocal
HG1 GG1

IDFS



No. At Risk						
GG1	95	89	84	48	20	3
EQUIV	26	21	18	9	5	1
GGI3	24	19	13	7	2	1

OS



No. At Risk						
GG1	90	89	83	49	21	3
EQUIV	25	25	20	10	5	1
GGI3	22	21	16	12	4	1

Metzger Filho et al. Ann Oncol 2012

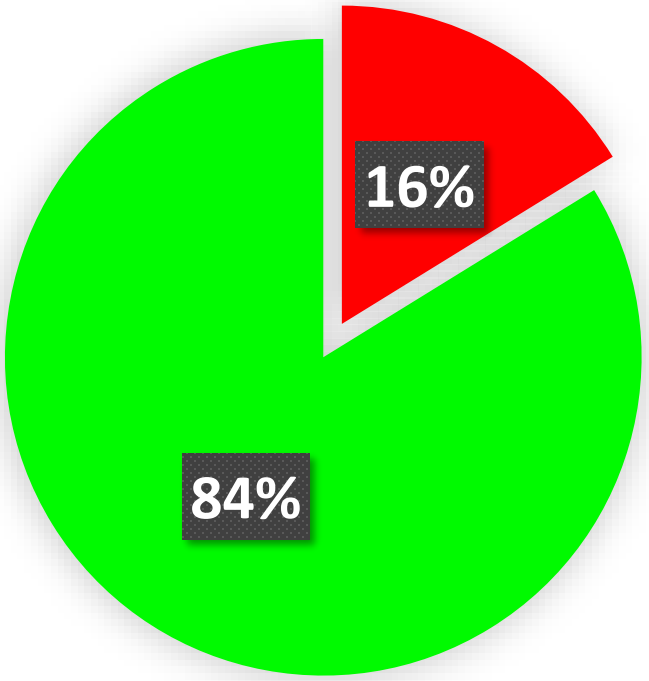
EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Clinical Utility of MammaPrint testing in Invasive Lobular Carcinoma: Results from the MINDACT phase III trial

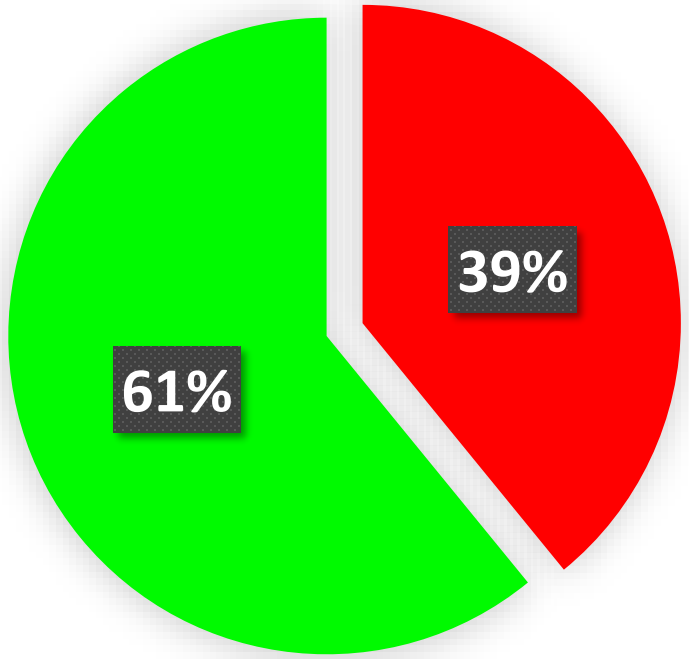
Otto Metzger, Fatima Cardoso, Coralie Poncet, Christine Desmedt, Sabine Linn, Jelle Wesseling, Florentine Hilbers, Kim Aalders, Mauro Di Lorenzi, Suzette Delaloge, Jean-Yves Pierga, Etienne Brain, Suzan Vrijaldenhoven, PA Neijenhuis, Emiel Rutgers, Martine Piccart, Laura Van't Veer and Giuseppe Viale

Results: MammaPrint Risk Classification

Invasive Lobular Carcinoma
N = 487



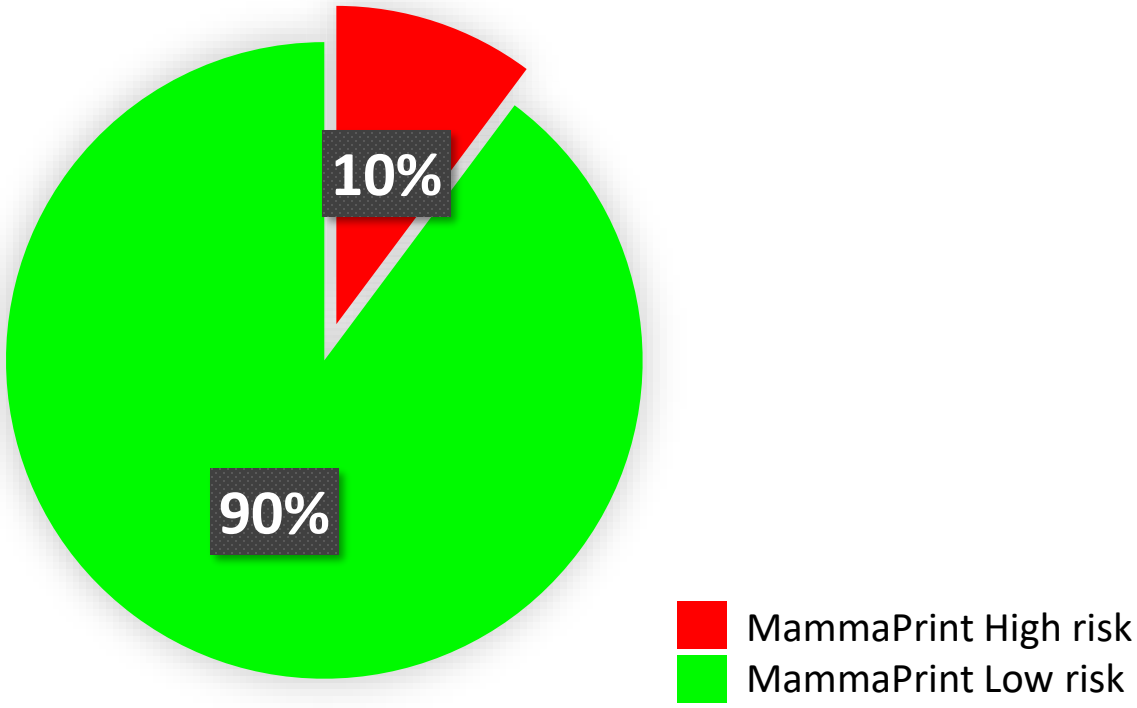
Invasive Ductal Carcinoma
N = 4826



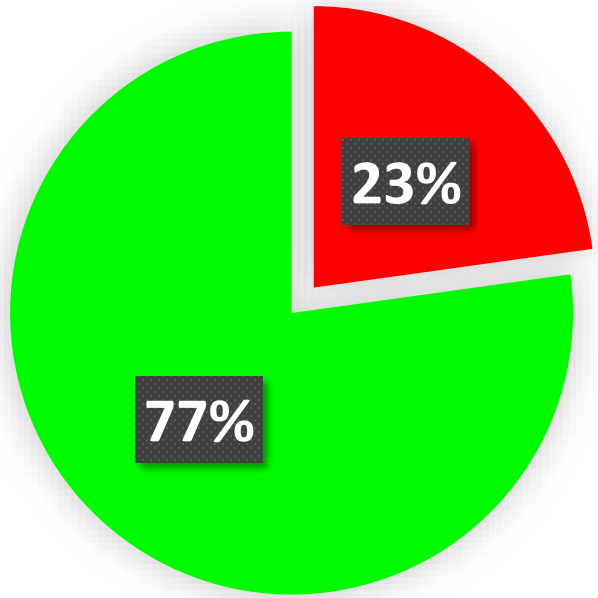
MammaPrint High risk
MammaPrint Low risk

Results: MammaPrint Risk Classification

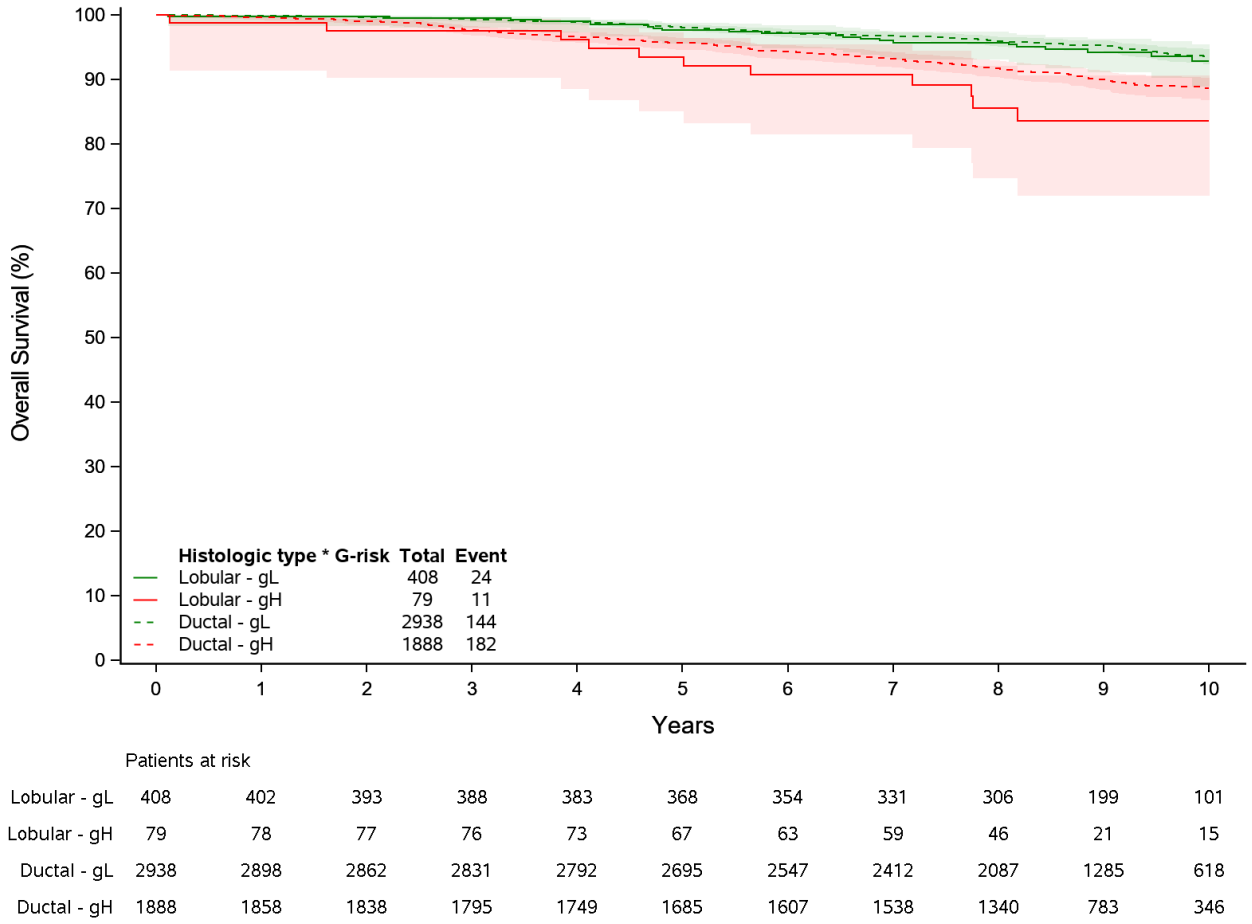
Classic Invasive Lobular Carcinoma
N = 255



Non-classic variants of Invasive Lobular Carcinoma
N = 232



Results: OS by histology and genomic risk



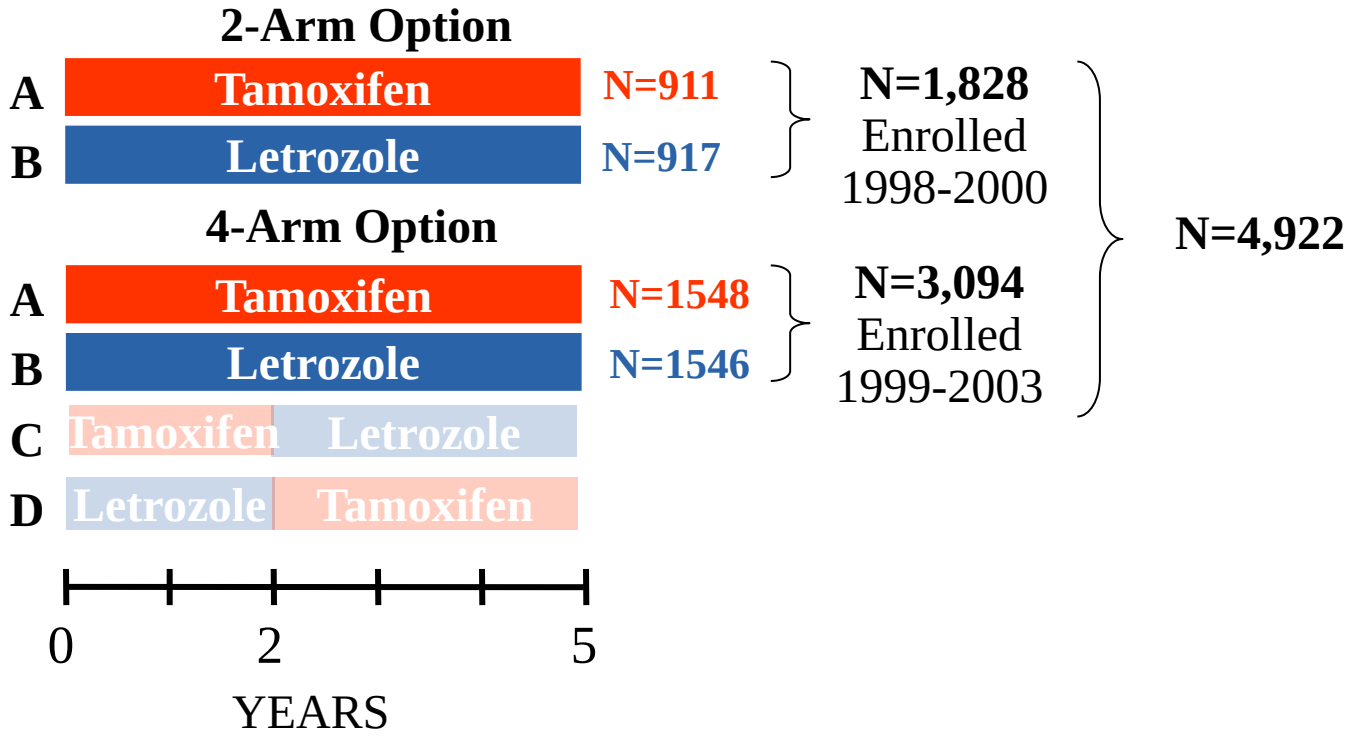
Genomic Risk	Survival Estimates (95% CI)KM
Ductal - gL	5 years: 98.1 (97.5-98.5%)
	8 years: 95.9 (95.1-96.6%)
Lobular - gL	5 years: 97.7 (95.6-98.8%)
	8 years: 95.7 (93.1-97.4%)
Ductal - gH	5 years: 95.6 (94.6-96.5%)
	8 years: 91.7 (90.3-92.9%)
Lobular - gH	5 years: 93.5 (85.0-97.2%)
	8 years: 85.6 (74.7-92.0%)

Median FU: 8.7 years

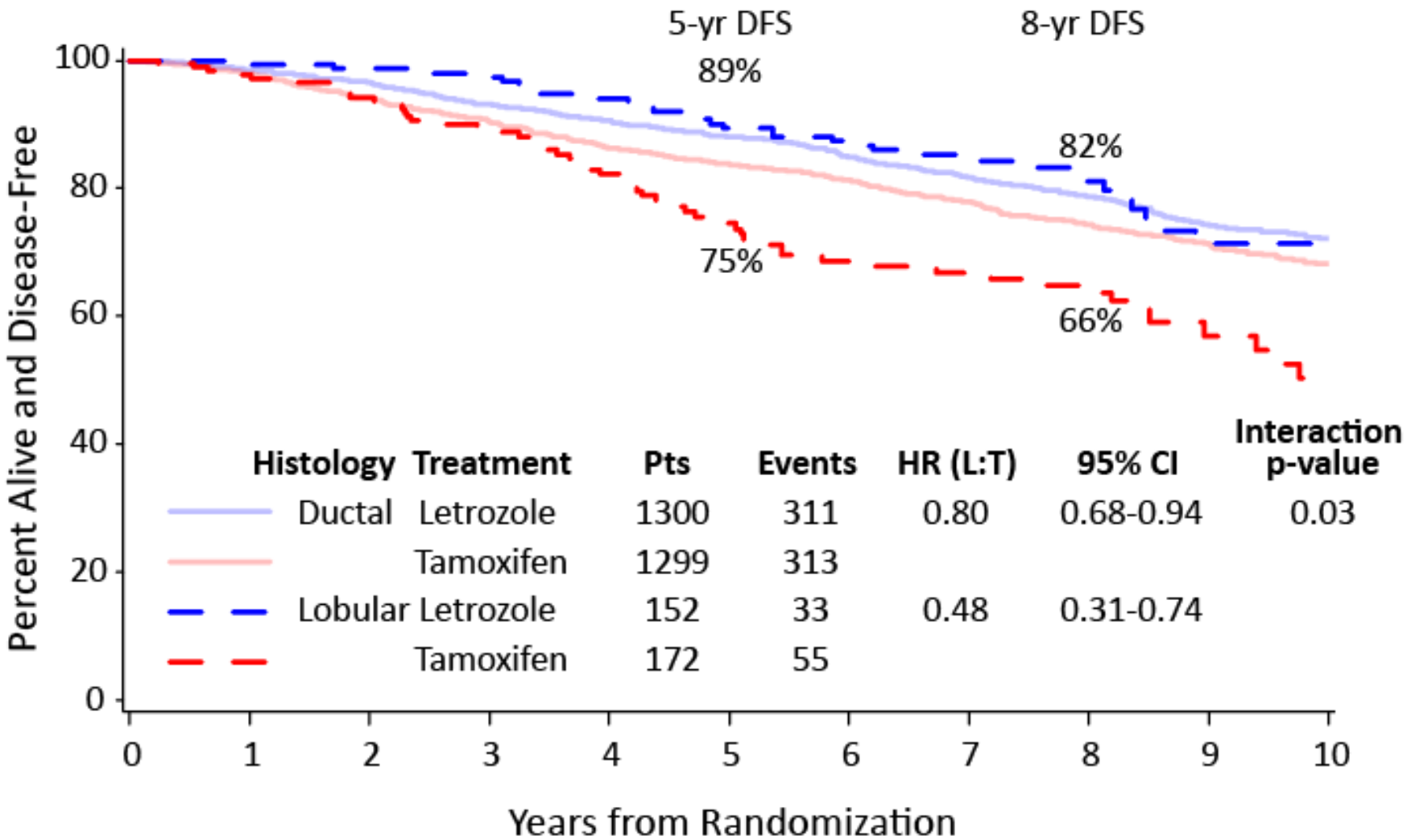
Adjuvant Endocrine Therapy

Endocrine Therapy Recommendations for ILC

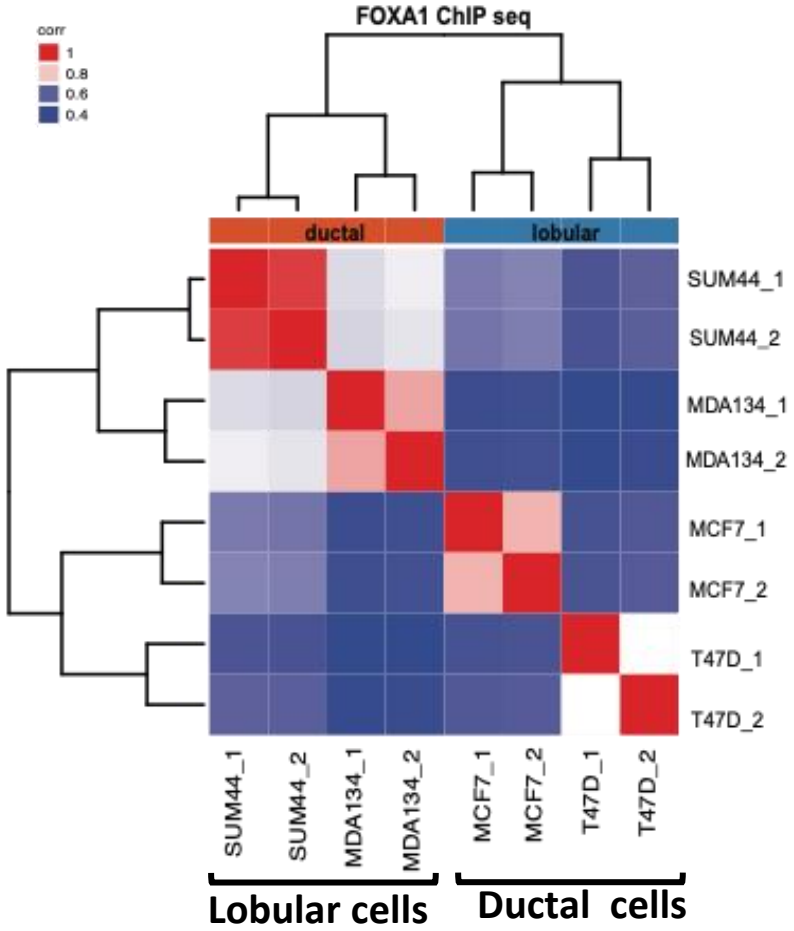
- BIG 1-98 Analytic Cohort
- 12-year updated

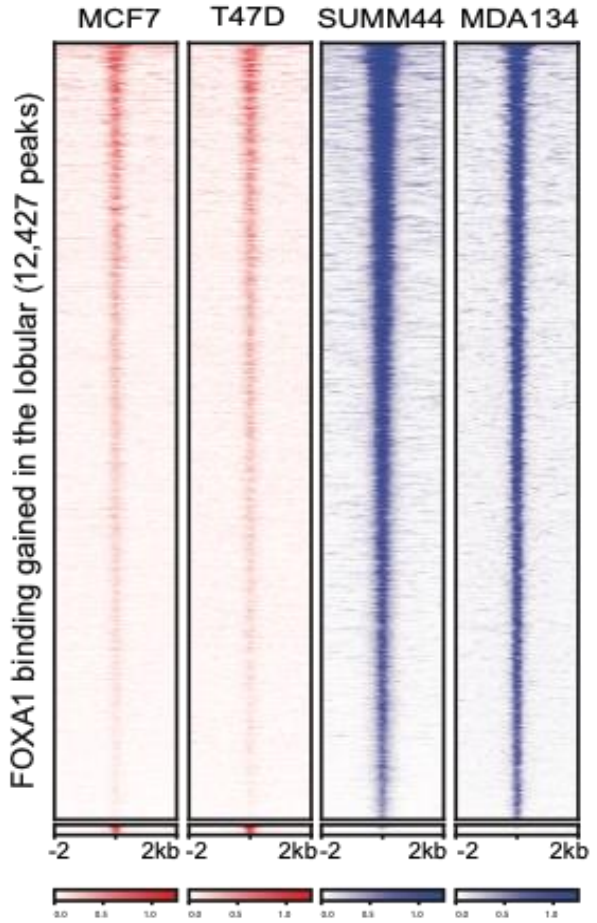


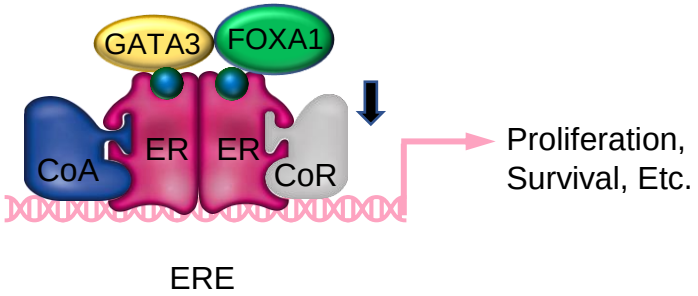
Disease-free survival



ILC has a Unique Chromatin State Shaped by FOXA1 Gained Binding that Dictates a Unique ER Axis and Resistance to Tamoxifen



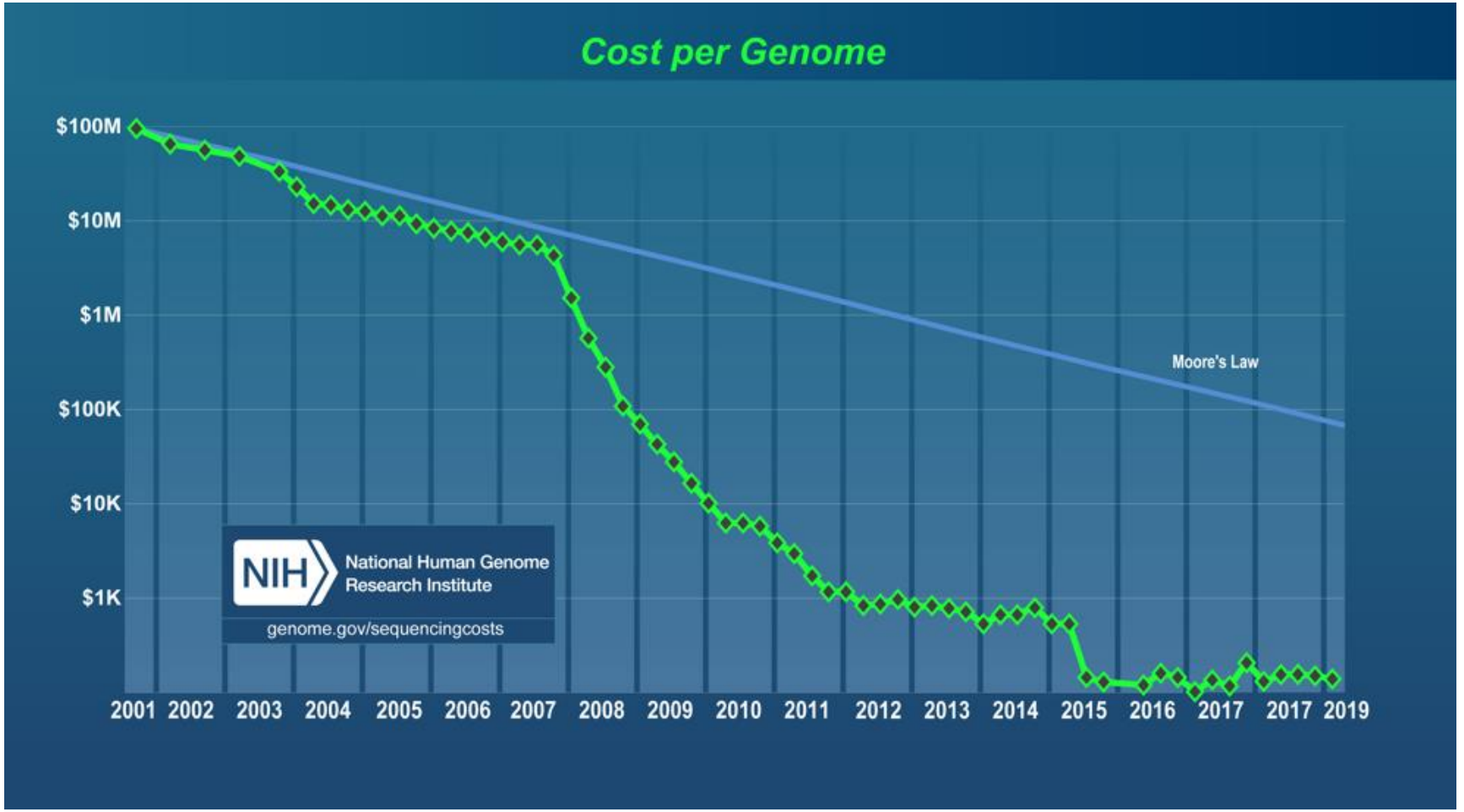




Manuscript in Review

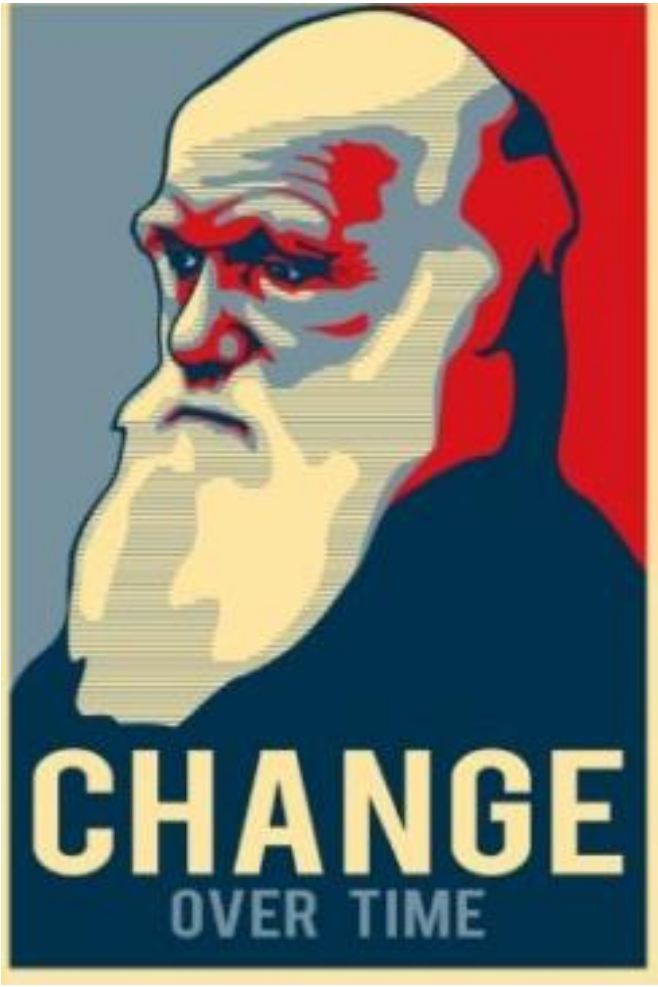
Translating all knowledge towards tailored treatment for patients diagnosed with advanced breast cancer

Genomics: Falling Cost is Driving Change



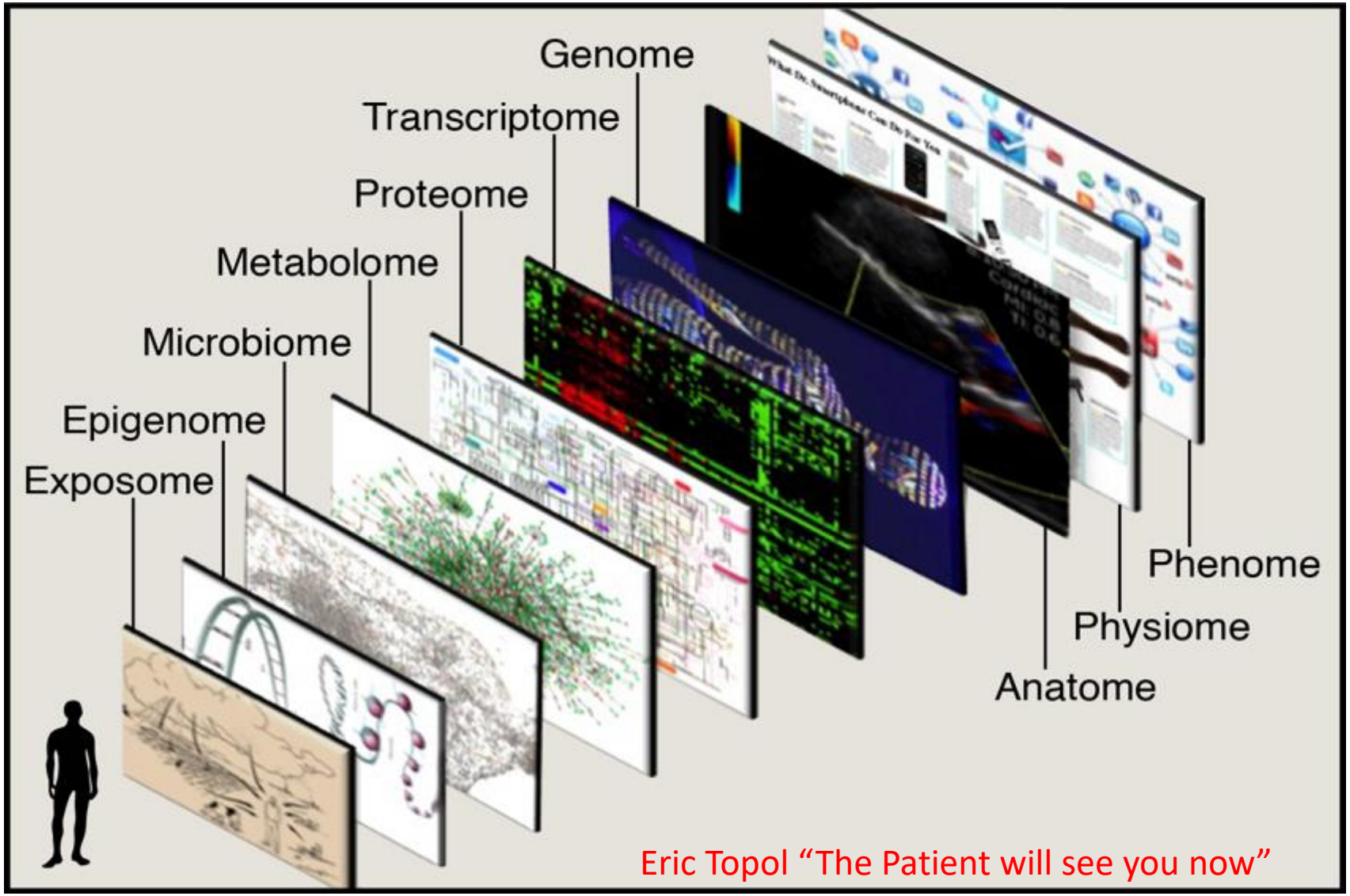
Genomics-Based Approaches

- Diagnostic (adjunct to imaging)
- Adjuvant/Neoadjuvant (early micrometastatic)
- Surveillance (later micrometastatic)
- Metastatic (overt)



Adapted from Prof. Sledge

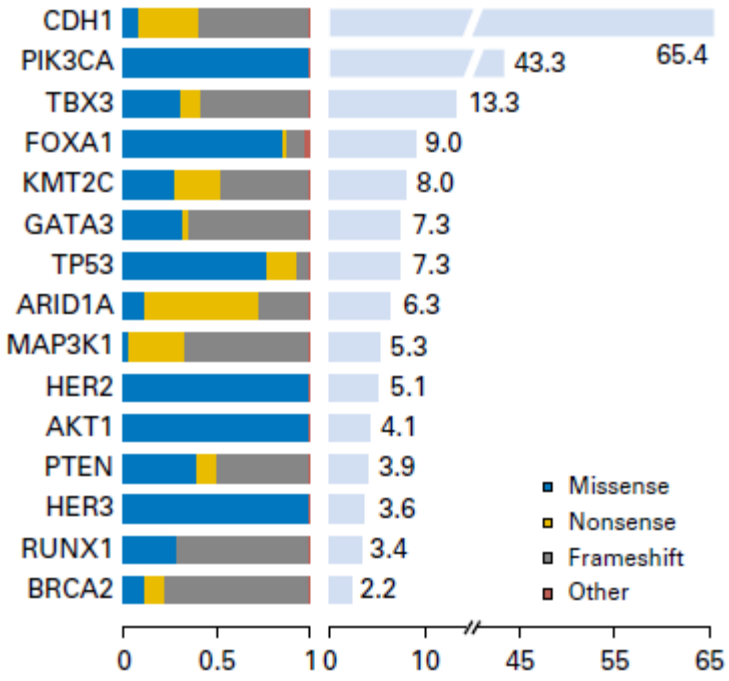
Human “GIS”



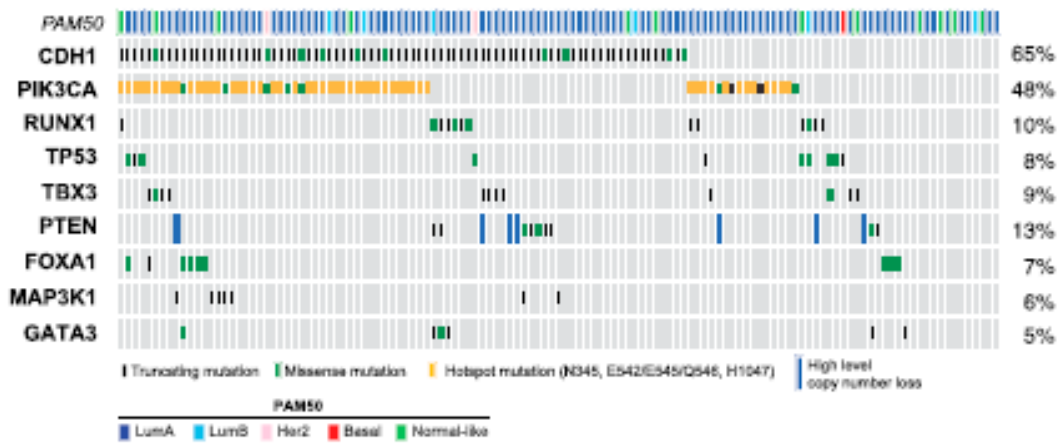
Eric Topol “The Patient will see you now”

Genomic Landscape of ILC tumors

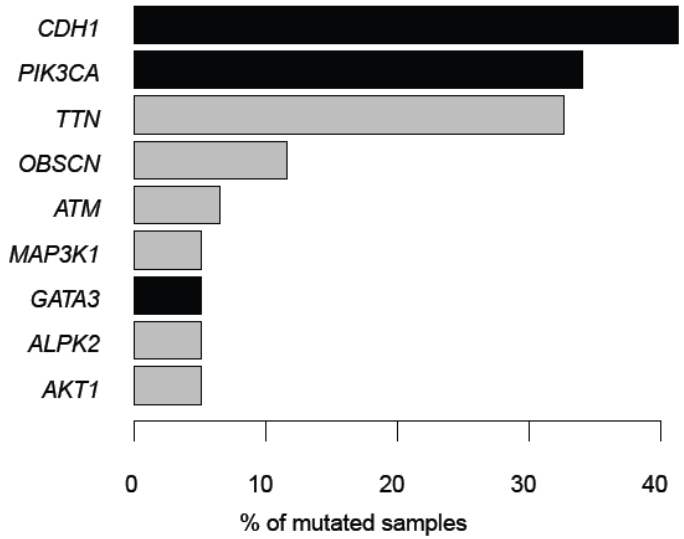
Desmedt et al. **n=414**



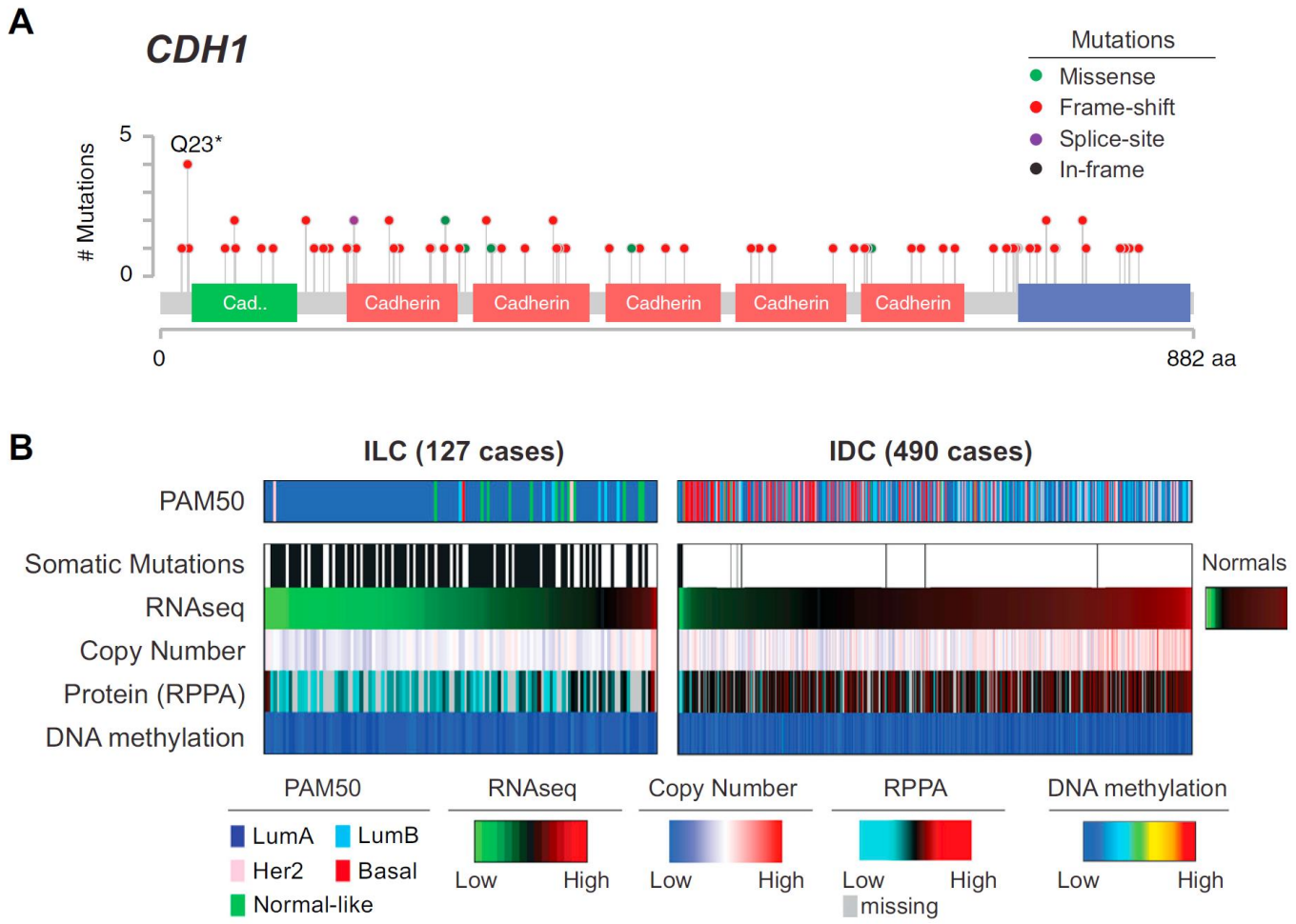
Ciriello et al. **n=127**



Michaut et al. **n=138**

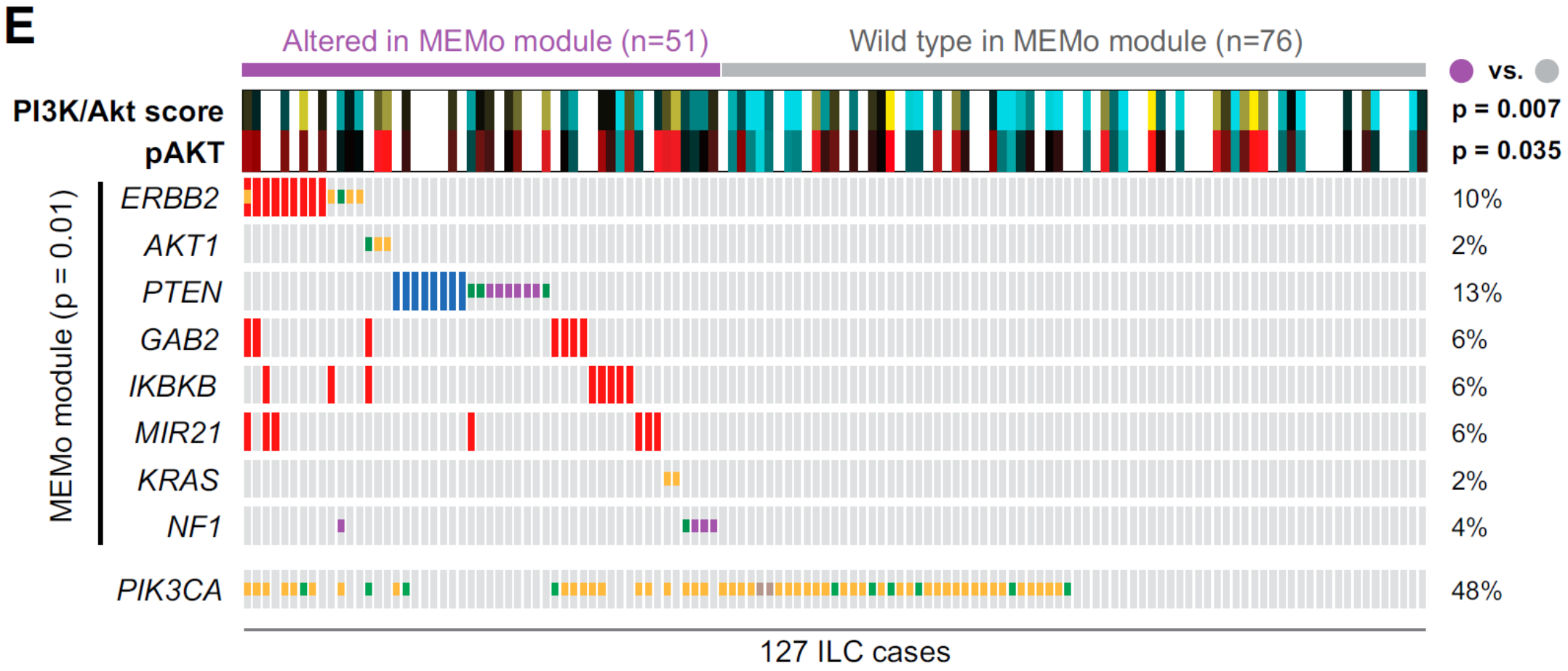


CDH1 (E-cadherin) alterations



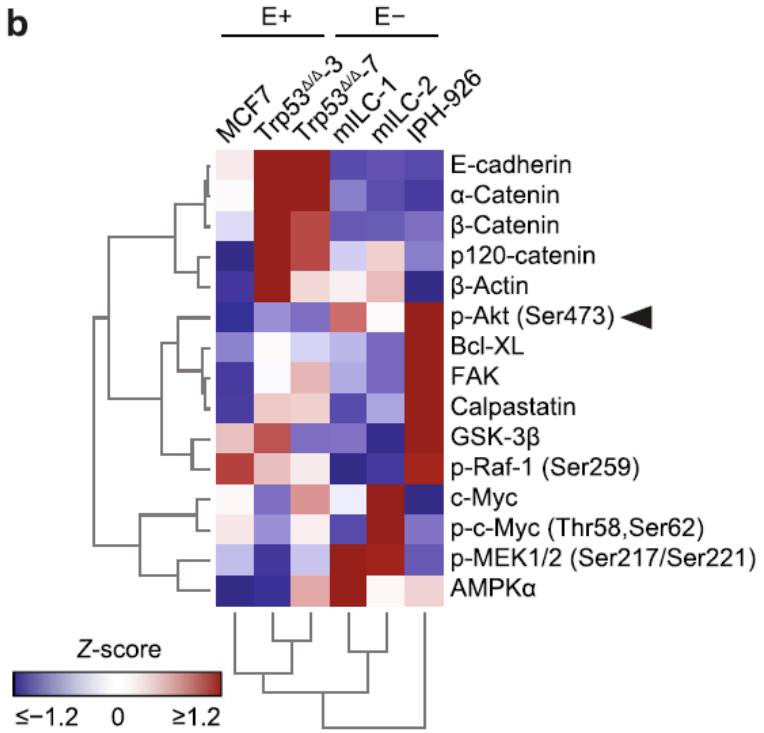
Ciriello *et al.* Cell 2015

40% of ILC have an alteration converging to AKT activation



Ciriello *et al.* Cell 2015

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

2018 Nobel Laureates
Jim Allison and Tasuko Honjo

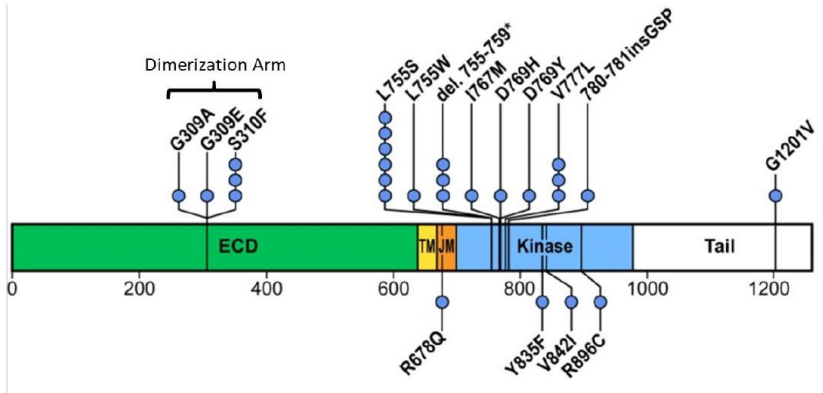
Hypermutated breast cancers according to pathological characteristics

Characteristics	# of Patients	N = 78 (Hypermutated)	% of hypermutated tumors	Median TMB
Tumor histology				
- IDC	2513	39	1.6	14.96
- ILC	448	24	5.4	15.25
- Others	493	2	0.4	20.9
- Mixed	183	7	3.8	14.12
- Unknown	367	6	1.6	13.9
Sample type				
- Metastatic	1709	52	3.1	14.69
- Primary	2188	26	1.2	15.61
Tumor Subtype				
- HR+/HER2-	741	19	2.6	17.59
- HER2+	184	5	2.7	15.41
- TNBC	193	8	4.2	16.07
- Unknown	2886	46	1.6	14.12

Barroso et al. ASCO 2018

HER2 mutations

HER2 mutations across 1,500 breast cancer patients

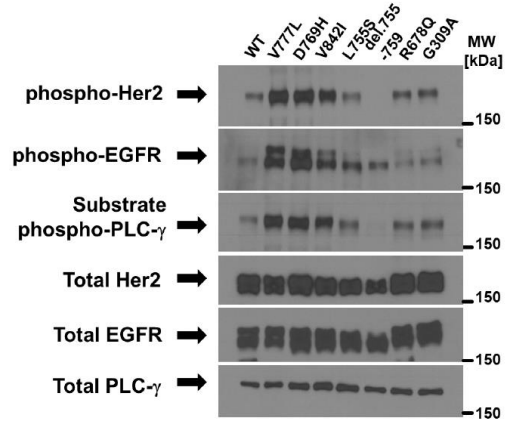


Mutation frequency:

- Newly diagnosed patients = 1.6%. → 4,000 pts annually.
- Metastatic breast cancer = 2-2.5% → 4,000 – 5,000 MBC cases
- Invasive lobular breast cancer = 5-7%

Incidence/prevalence

Bose et al., Cancer Discovery, 2013
Ma et al., ASCO 2016
Desmedt et al., JCO 2016



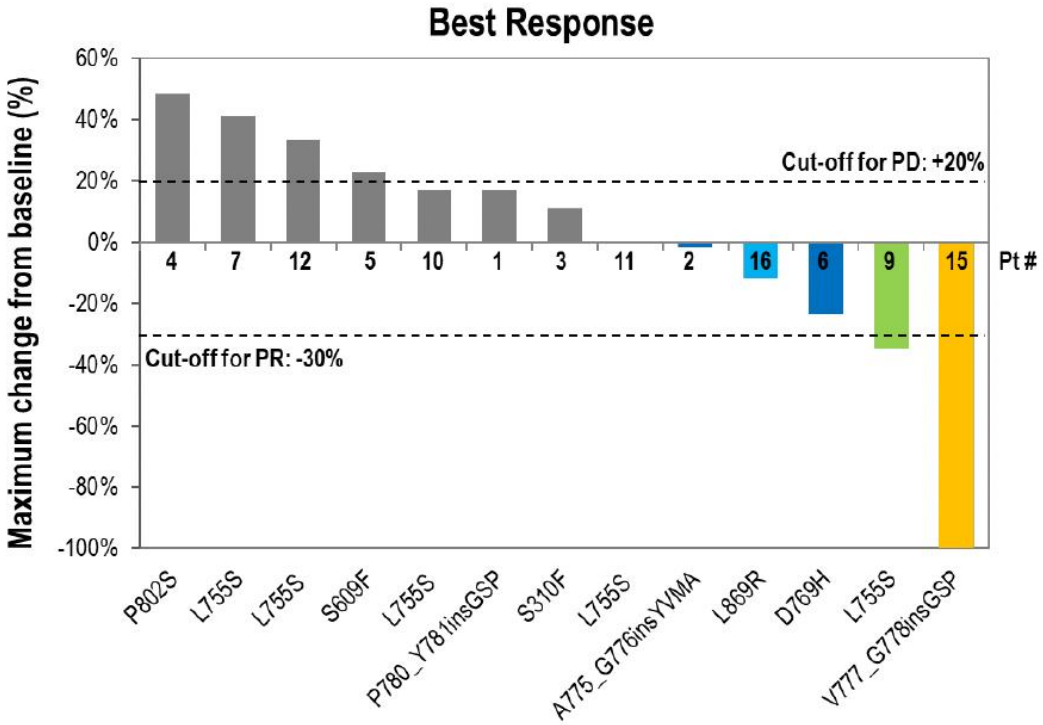
	IC_{50} (nM)	
	Neratinib	Lapatinib
MCF10A - Her2 WT	<2	400 ± 60
G309A	<2	470 ± 50
V777L	<2	1,040 ± 570
D769H	<2	980 ± 950
V842I	<2	650 ± 210
Del755-759	2.1 ± 0.2	660 ± 90
L755S	15 ± 6	> 10,000
BT474 cells	<2	31 ± 2
MCF7 cells	> 3,000	> 10,000

© American Association for Cancer Research

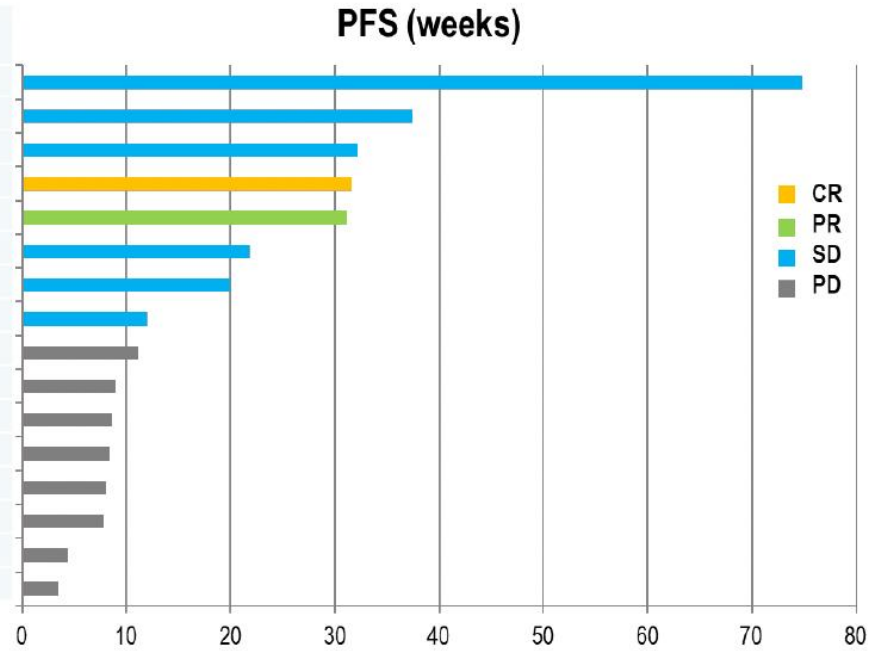
MutHER trial, part 1: Neratinib for HER2 mutated MBC

CBR = 31%

Median PFS = 16 weeks



Prior # regimen for MBC	HER2 Mutation	Pt #
3	P780_Y781insGSP	13
3	L869R	16
2	S310F,V842I	14
3	V777_G778insGSP	15
4	L755S	9
8	L755S	8
4	A775_G776insYVMA	2
6	D769H	6
2	S609F	5
4	P802S	4
3	S310F	3
2	P780_Y781insGSP	1
2	L755S	12
2	L755S	11
2	L755S	7
10	L755S	10



Ma et al., ASCO 2016

© American Association for Cancer Research

A Phase II trial of neratinib (NER) or NER plus fulvestrant (FUL) (N+F) in HER2 mutant, non-amplified (HER2mut) metastatic breast cancer (MBC): Part 2 of MutHER

Cynthia X. Ma[1], Jingqin Luo[2], Rachel Freedman[3], Timothy Pluard[4], Julie Nangia[5], Janice Liu[6], Frances Valdez-Albini[7], Melody Cobleigh[8], Jason Jones[9], Nancy Lin[3], Eric Winer[3], Kelly Marcom[10], Shana Thomas[1], Jill Anderson[1], Brittney Hass[1], Chuck Hensel[11], Richard Bryce[12], Alshad Lalani[12], Lisa Carey[13], Matthew Goetz[14], Feng Gao[2], Gretchen Kimmick[10], Mark Pegram[15], Matthew Ellis[5], Ron Bose[1]

[1]Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; [2]Division of Public Health Science, Department of Surgery, Washington University School of Medicine, St, Louis, MO; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Saint Luke's Cancer Institute, Kansas City, MO; [5]Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX; [6]University of Southern California, Los Angeles, CA; [7]University of Miami, Coral Gables, FL; [8]Rush University Medical Center, Chicago, IL; [9]Avera Cancer Institute, Sioux Falls, SD; [10]Duke Cancer Institute, Durham, NC; [11]Guardant Health Inc, Redwood City, CA; [12]Puma Biotechnology, Los Angeles, CA; [13]University of North Carolina, Chapel Hill, NC; [14]Mayo Clinic, Rochester, MN; [15]Stanford University School of Medicine, Stanford, CA

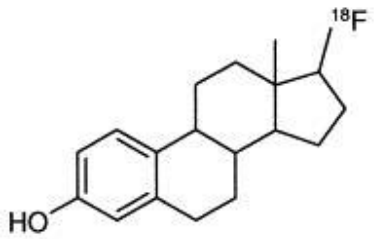
Tumor Characteristics in Relation to CB

AACR American Association for Cancer Research FINDING CURES TOGETHER

Marker	Incidence	CBR		p
		Marker +	Marker -	
Lobular	13 (37.1%)	8/13 (61.5%)	4/22 (18.2%)	0.02
Prior CDK4/6i	22 (63%)	10/22 (45.5%)	2/13 (15.4%)	0.14
Prior mTORi	8 (23%)	4/8 (50%)	8/27 (29.6%)	0.40
TP53 Mut	18 (51.4%)	7/18 (38.9%)	5/17 (29.4%)	0.72
PIK3CA Mut	15 (42.9%)	4/15 (26.7%)	8/20 (40%)	0.49
CDH1 Mut	13 (37.1%)	7/13 (53.8%)	5/22 (22.7%)	0.08
ESR1 Mut	6 (17.1%)	3/6 (30%)	9/29 (31%)	0.39

Imaging
What is new?

ER-targeted PET/CT



18F-Fluoroestradiol (FES)

Adapted from Gary Ulaner

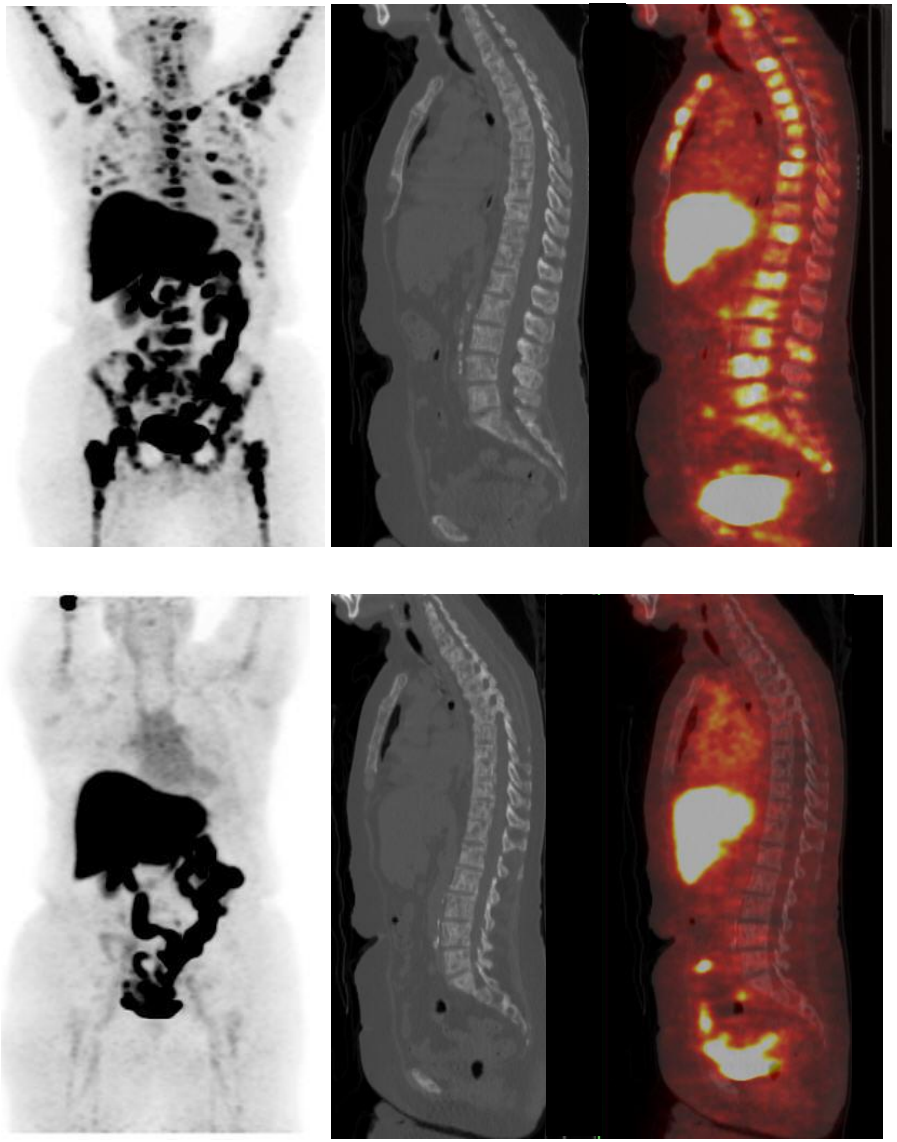
	Disorder	Number of patients	Study aim	Conclusions
Zhao et al, 2013[37]	Uterine tumours	47	Assess relation between tumour ^{18}F-FDG and ^{18}F-FES uptake with ER, GLUT-1, and Ki-67	^{18}F-FES uptake correlated with ERα and PR expression, and ^{18}F-FDG uptake with GLUT-1 and Ki-67
Van Kruchten et al, 2012[28]	Breast cancer	33	Assess clinical value of ^{18}F-FES-PET in patients with unresolved diagnosis after conventional workup	^{18}F-FES-PET aided diagnosis and therapy decision making
Peterson et al, 2011[35]	Breast cancer	239	Assess correlations between ^{18}F-FES uptake and clinical and laboratory data, effects of previous treatments and ^{18}F-FES metabolism	^{18}F-FES uptake correlated positively with BMI and inversely with plasma SHBG levels and binding capacity
Yoshida et al, 2011[40]	Suspected uterine sarcoma	24	Assess usefulness of ^{18}F-FES-PET and ^{18}FDG-PET to differentiate uterine sarcoma from leiomyoma	^{18}F-FDG-to-^{18}F-FES ratios >2·0 differentiated with 90·9% sensitivity and 92·3% specificity
Kurland et al, 2011[41]	Metastatic breast cancer	91	Measure variability in ^{18}F-FES uptake between and within patients	Substantial variation seen between patients (37% had low or absent uptake; roughly 40% had mixed uptake)
Linden et al, 2011[42]	Metastatic breast cancer	30	Measure changes in ^{18}F-FES uptake during treatment with aromatase inhibitors, tamoxifen, or fulvestrant	No effect with aromatase inhibitors, decreases of around 55% with tamoxifen and fulvestrant
Tsujikawa et al, 2009[43]	Endometrial cancer	19	Assess correlation between ^{18}F-FES-PET, ^{18}F-FDG-PET, and ER-status on immunohistochemistry	Correlations for tumour ERα status good
Tsujikawa et al, 2009[44]	Endometrial cancer	31	Assess correlation between ^{18}F-FES-PET, ^{18}F-FDG-PET, and clinicopathological features	^{18}F-FES-to-^{18}F-FDG ratios correlated with tumour aggressiveness
Yoshida et al, 2009[45]	Ovarian cancer	3	Review role of PET in ovarian cancer (plus preliminary results of ^{18}F-FES-PET in three patients)	^{18}F-FES uptake was seen in ER-positive tumours
Dehdashti et al, 2009[46]	Metastatic breast cancer	59	Investigate whether ^{18}F-FES-PET and serial ^{18}F-FDG-PET (plus oestradiol challenge) predicts response to endocrine therapy	Baseline tumour ^{18}F-FES uptake and metabolic flare after oestradiol challenge both predictive of treatment response
Peterson et al, 2008[47]	Primary and metastatic breast cancer	17	Assess correlation between ^{18}F-FES uptake and immunohistochemistry	Good correlation for ERα
Tsujikawa et al, 2008[48]	Endometrial hyperplasia	2	Assess effect of tamoxifen on ^{18}F-FES uptake	Take endocrine therapy into account when using ^{18}F-FES-PET to assess ER status
Tsujikawa et al, 2008[49]	Benign and malignant uterine tumours	38	Assess relation between ^{18}F-FES and ^{18}F-FDG uptake in benign and malignant uterine tumours	^{18}F-FES-to-^{18}F-FDG ratios aided differentiation of diagnosis of uterine tumours
Tsuchida et al, 2007[50]	Healthy volunteers	16	Assess relation between ^{18}F-FES uptake, menstrual cycle, and endogenous oestrogen concentrations	Changes in ^{18}F-FES uptake were consistent with changes in ER concentrations on immunohistochemistry
Yoshida et al, 2007[51]	Endometrial cancer	1	Use ^{18}F-FES-PET to assess response to medoxyprogesterone in endometrial cancer	Focal uptake, confirmed by histology
Kanne et al, 2007[52]	Metastatic breast cancer	1	Investigate use of ^{18}F-FES-PET and ^{18}F-FDG-PET in a patient with gastric linitis plastica from metastasis of ER-positive lobular breast cancer	^{18}F-FES-PET confirmed regional ER binding in metastases
Linden et al, 2006[53]	Metastatic breast cancer	47	Quantify tumour ^{18}F-FES uptake as predictor of response to endocrine therapy	Absence of uptake predicts failure of endocrine therapy
Mortimer et al, 2001[54]	Breast cancer	40	Assess serial ^{18}F-FES-PET and ^{18}F-FDG-PET to predict response to tamoxifen	Increase in ^{18}F-FDG uptake and decrease in ^{18}F-FES uptake after the start of tamoxifen predicted response
Mankoff et al, 2001[55]	Breast cancer	49	Radiation dosimetry of ^{18}F-FES-PET	Radiation dose is similar to commonly used nuclear medicine tests
Tewson et al, 1999[56]	Breast cancer	18	Assess interaction between SHBG and ^{18}F-FES	Around 45% of ^{18}F-FES was bound to SHBG and could affect tracer uptake
Dehdashti et al, 1999[57]	Metastatic breast cancer	11	Asses serial ^{18}F-FES-PET and ^{18}F-FDG-PET to predict response to tamoxifen	Increase in ^{18}F-FDG uptake and decrease in ^{18}F-FES uptake after the start of tamoxifen predicted response
Moresco et al, 1997[58]	Meningioma	6	Assess ER-status of meningiomas by means of ^{18}F-FES-PET	Four of six patients showed focal ^{18}F-FES uptake, and uptake correlated with immunohistochemistry status in five of six patients
Mankoff et al, 1997[59]	Primary or metastatic breast cancer	15	Assess clearance of labelled ^{18}F-FES metabolites	Rapid clearance
Mortimer et al, 1996[60]	Primary or metastatic breast cancer	43	Assess correlation between ^{18}F-FES-PET and ^{18}F-FDG and in-vitro assays for response to therapy	^{18}F-FES-PET had a sensitivity of 76% and specificity of 100% compared with immunohistochemistry
Dehdashti et al, 1995[61]	Primary or metastatic breast cancer	53	Compare ^{18}F-FES-PET with ^{18}F-FDG-PET and immunohistochemistry	^{18}F-FES-PET 88% agreement with immunohistochemistry and provided information not obtained by ^{18}F-FDG-PET
McGuire et al, 1991[62]	Metastatic breast cancer	16	Assess use of ^{18}F-FES-PET in ER-positive metastatic postmenopausal breast cancer	^{18}F-FES-PET sensitivity 93%
Mintun et al, 1989[1]	Primary breast cancer	13	Assess feasibility of ^{18}F-FES-PET to detect primary ER-positive breast-tumour lesions and correlation with in-vitro ER status	Focal uptake seen in all patients with ^{18}F-FES and uptake correlated well with in-vitro assays (r=0·96)

FES PET/CT

- **FES SUV correlates with ER on IHC**
- **FES predicts response to endocrine therapy**

Van Kruchten et al, Lancet Oncology 2013

Complete suppression of FES avidity



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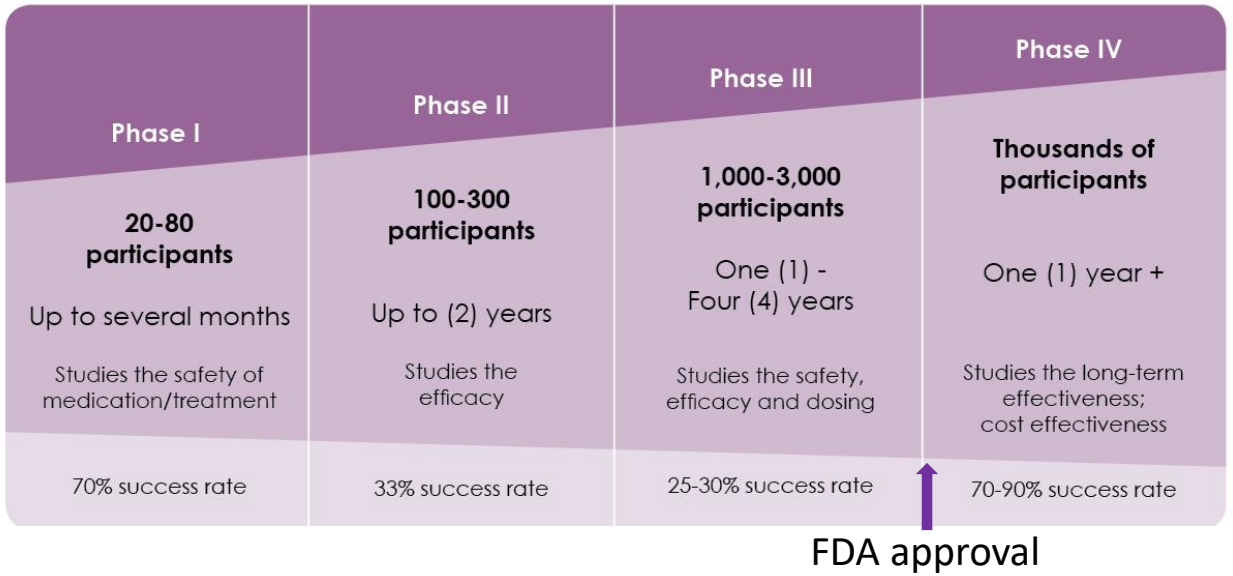
Clinical Trials

What are clinical trial phases?

Clinical trials are conducted in a series of steps (phases) - each phase is designed to answer a separate research question.

- **Phase I:** Testing a new treatment in a small group to evaluate safety, dose, and side effects.
- **Phase II:** Evaluating within a larger group the efficacy and safety of a new treatment
- **Phase III:** A comparison study in a large group to determine if a new treatment works better than standard therapy. These trials typically involve randomization and may have a placebo; the data from a phase 3 trial can be used for FDA drug approval.



Clinical Trials: FAQs

What are the unique aspects related to ILC?

- We are moving away from the requirement of measurable disease to define eligibility criteria

What do expect for novel drugs being developed based on ER status rather than histological subtypes?

- Unless proven otherwise novel hormonal therapies and targeted agents are likely to work equally well for patients diagnosed with ILC or not

Do we need clinical trials specifically for ILC?

- ☑ scientific background must be robust
- ☑ advocate for cohorts representing ILC on specific studies
- ☑ capture information regarding histological subtypes and encourage central path review

Conclusions (and personal bias)

ILC accounts for a unique breast cancer subtype

- We are making real progress!
  - patients are living longer and better
  - promising drugs being developed
  - better longitudinal characterization of the disease to inform tx decisions
  - for patients being tx for advanced disease the clinical evaluation is key, so no reason to be overly concerned about the limitations of current imaging

We will continue to work non-stop to improve outcomes to patients diagnosed with ILC

Acknowledgements

- To my patients who inspire me to continue doing research
- To the EMBRACE team for creating a phenomenal program aimed at improving care and support for patients diagnosed with advanced breast cancer
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Thank you