THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Invasive Lobular Carcinoma
When Non-scary Becomes Scary

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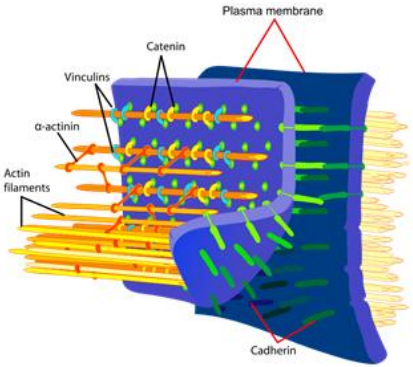
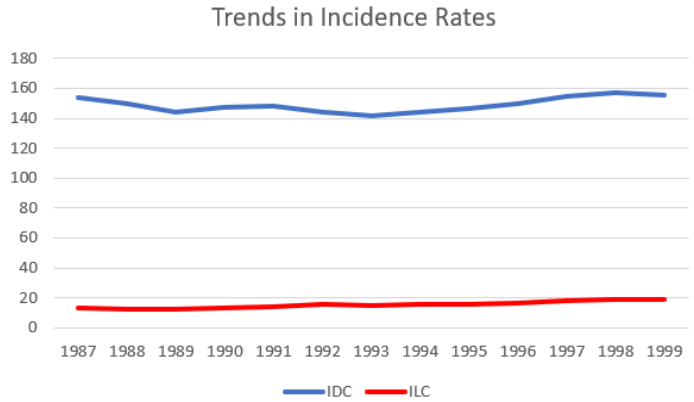
Outline

- Introduce invasive lobular carcinoma (ILC)
- Management of early stage ILC
- Management of advanced stage ILC

What is Invasive Lobular Carcinoma?

- ILC is a type of breast cancer that originate in the Terminal duct lobular units (TDLUs) due to a defective E-cadherin protein after which it has a propensity to migrate toward the lobules of the breast
- 10-15% of all breast cancers
- Incidence rates of ILC are rising faster than IDC





Proportional Change = 1.03

Proportional Change = 2.01

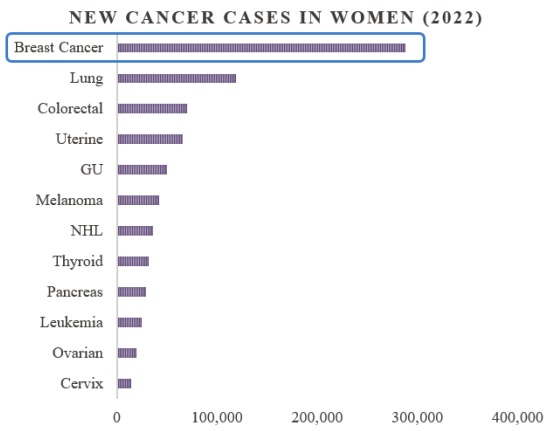
Depiction by Mariana Ruiz Villarreal (MRV@ladyofHats.com)

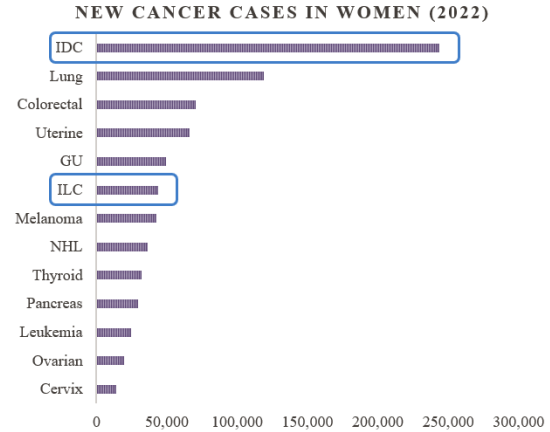
Li CI et al., JAMA, 2003

Epidemiology – Lobular breast cancer is not a “rare” cancer

ILC incidence is ~44,000 cases per year in the US alone

- HR+ ILC has a higher incidence (~41,000) than all TNBC (~29,000) and equal to that of HER2+ (~41,000)
- Double the incidence of all ovarian cancers and cervical cancers combined!
- 6th most common female cancer



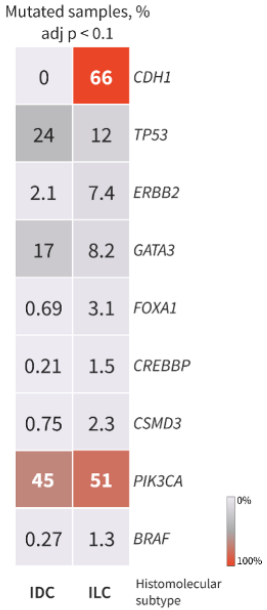


Adapted from the American Cancer Society, Inc.

ILC Diagnosis is Challenging

Characterized microscopically by small cells that insidiously infiltrate the mammary stroma and adipose tissue individually and in a “single file” pattern

- Due to the defective E-cadherin



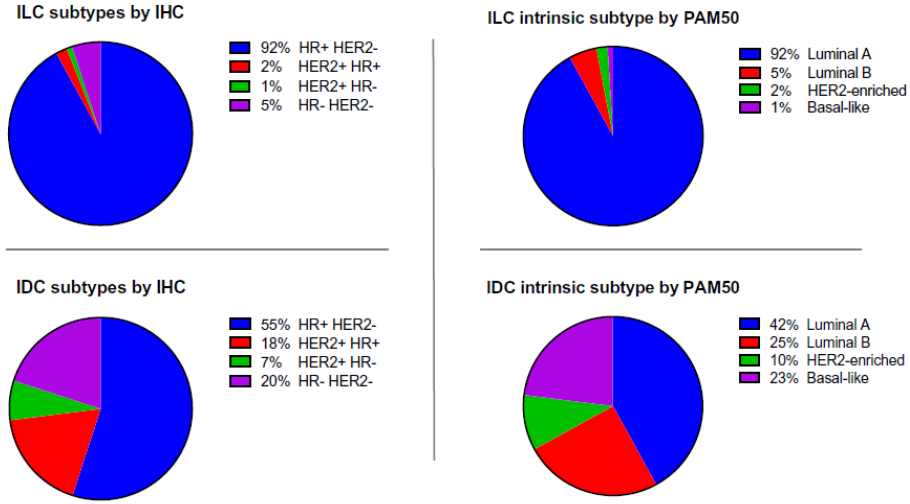
Group	*CDH1*	Expression	
1	Mutated	Low	66% (255)
2	Wild-Type	Low	24% (92)
3	Wild-Type	High	10% (39)

Mouabbi JA ASCO 2023

Introduction: Features of ILC vs IDC – Clinicopathology

	IDC	ILC
Stage at diagnosis[1]		
Stage I	55%	46%
Stage II	35%	33%
Stage III	8%	**17%**
Stage IV	2%	**5%**
Grade[2]		
Grade 1-2	60%	**90%**
Grade 3	40%	10%
Proliferation Activity (Ki67)[3]		
Low (<20%)	35%	**60%**

[1]Oesterreich S et al., *J Natl Cancer Inst* 2022; [2]Pestalozzi BC et al., *J Clin Oncol* 2006; [3]Biglia G et al, *Eur J Surg Oncol*. 2013

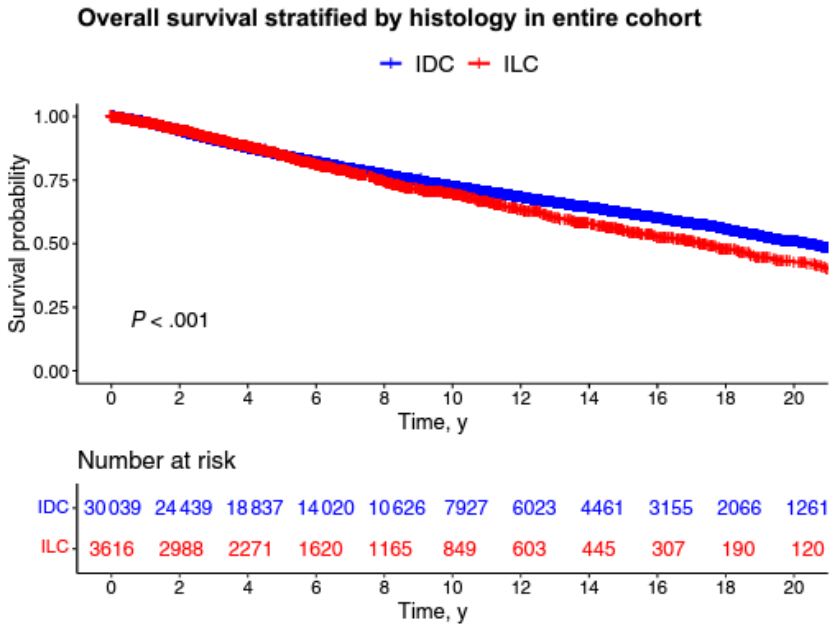


- **90%** of ILC express **AR** (compared to ~50 of IDC)
- Prior studies have shown that most **TN ILC** (5%) are **lumAR** and have high AR expression

Mouabbi JA et al., *Breast Cancer Res* 2022

Introduction: Features of ILC vs IDC – Prognosis

Long-term outcomes of ILC are inferior to that of IDC



- At 10 years, **1 in 3** ILC experienced a recurrence
- At 20 years, **1 in 2** ILC experienced a recurrence

Oesterreich S., Nasrazadani A. et al., *J Natl Cancer Inst* 2022

Features of ILC vs IDC – Distant Mets Sites

Table 2 Metastatic patterns of ILC and their frequency in imaging and at autopsy

Metastatic site	Imaging		Autopsy [30, 33]	
	ILC	IDC	ILC	IDC
Bone	16–34% [5, 10]	10–35% [5, 10]	65%	50%
Bone marrow	0.6–1.0% [5, 32]	0.2–0.4% [5, 32]	NR	NR
Lung	2–9% [5, 10]	7–18% [5, 10]	20%	55%
Liver	4–7% [5, 10]	6–11% [5, 10]	40%	70%
CNS parenchyma	1–2% [5, 10, 31]	2–5% [5, 10, 31]	7%	8%
CNS leptomeninges	16% [30]	0.3% [30]	30%	1.3%
Orbit	1% [35]	0.2% [35]	NR	NR
Pituitary	0.5% [10]	0.1% [10]	NR	NR
GI tract (linitis plastica)	5% [10, 30]	1% [10]	43%	2.6%
Peritoneum and retroperitoneum	18% [31]	1% [31]	93%	8%
Stomach	3% [30]	NR	43%	2.6%
Ovaries	2.2–5.0% [10, 30]	0.7% [10]	36%	2.6%
Uterus/cervix	NR	NR	43%	0%
Soft tissue and skin	32% [10]	27% [10]	NR	NR
Salivary glands	3% [31]	0% [31]	NR	NR
Thyroid	NR	NR	12%	7%

ILC invasive lobular carcinoma, *IDC* invasive ductal carcinoma, *NR* not reported, *CNS* central nervous system, *GI* gastrointestinal.

Mouabbi JA et al., *Breast Cancer Res* 2022

Early Stage ILC

Chemotherapy in early stage ILC

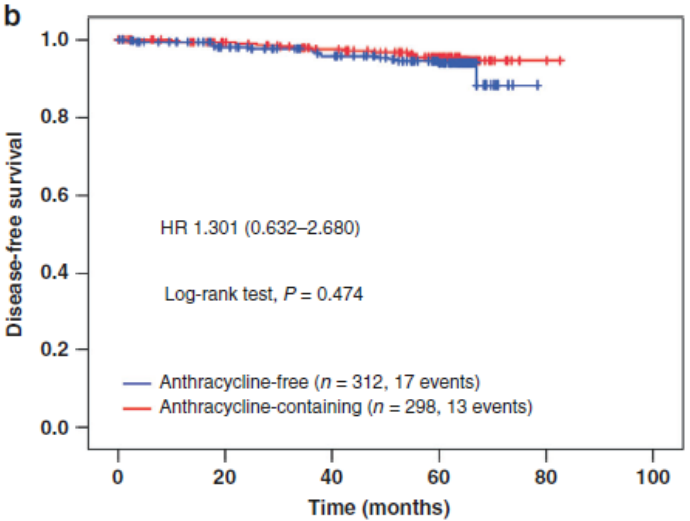
In general, ILC tend to respond poorly to chemotherapy compared to IDC

- Most ILC are LumA (92%): low grade and low proliferation
- Rate of pCR in ILC is <**1%** following anthracycline-based neoadjuvant chemotherapy (vs **20%** in IDC)[1,2]
  - The exception is pleomorphic ILC (5% of all ILCs) which is a more aggressive subtype (higher grade and Ki67) with a reported pCR = 6%

1. Brunello et al., Histopathology. 2012; 2. Mouabbi JA et al., BCRT, 2022

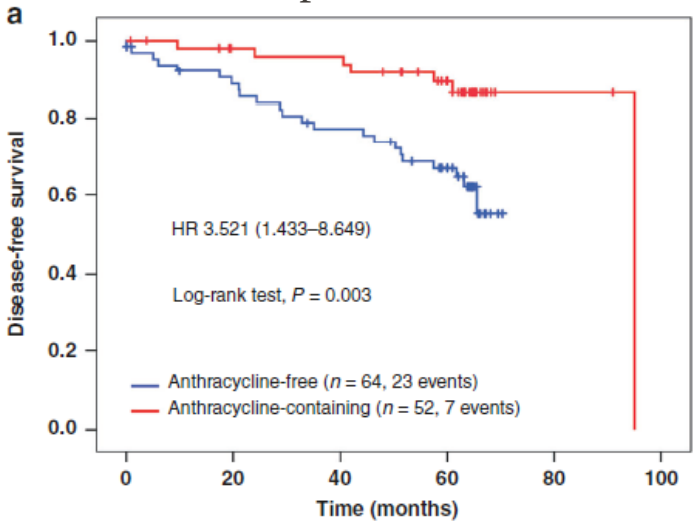
Chemotherapy in early stage ILC

pN0-1



- 9y DFS 90% (similar to what is seen with ET alone in historical data)

pN2-3



- 9y DFS with AC-T 90% vs 58% with TC

De Gregorio A et al., BJC, 2022

Can genomic profiling help predict who can benefit from chemotherapy

	ILC N = 37,685	IDC N = 149,182
Clinical Risk		
Low	57%	65%
High	**43%**	35%
Genomic Risk		
RS≤25	**92%**	83%
RS>25	8%	17%
Discordance		
Clinical High/ RS≤25	**39%**	24%

Abel MK et al., Ann. of Surg., 2022

	ILC N = 1497	IDC N = 5902
Clinical Risk		
Low	48%	57%
High	**52%**	43%
Genomic Risk		
Low	**73%**	58%
High	27%	42%
Discordance		
Clinical High/ Genomic Low	**36%**	18%

Abel MK et al., NPJ, 2021

ILC Prognostic Tool – MDA iLobulaRx

	Overall Survival			Distant Recurrence-free Survival		
Parameter	**Hazard Ratio**	**HR 95% Confidence Limits**	**p-value**	**Hazard Ratio**	**HR 95% Confidence Limits**	**p-value**
Age (year)	1.022	(1.013, 1.031)	<0.001	1.007	(0.999, 1.016)	0.075
Number of lymph nodes	1.068	(1.056, 1.080)	<0.001	1.078	(1.068, 1.089)	<0.001
Pathological tumor size (mm)	1.048	(1.013, 1.085)	0.008	1.061	(1.031, 1.092)	<0.001
ER status						
<10%	-------			-----		
≥10%	0.548	(0.354, 0.849)	0.007	0.620	(0.412, 0.933)	0.022
Grade						
GI	-----			-----		
GII	1.130	(0.862, 1.482)	0.38	1.067	(0.837, 1.361)	0.60
GIII	1.386	(1.017, 1.890)	0.039	1.476	(1.115, 1.953)	0.007
ILC histology						
Non-classical	-----			-----		
Classical	0.632	(0.474, 0.842)	0.002	0.622	(0.480, 0.806)	<0.001
Concomitant LCIS						
Absent	-----			-----		
Present	0.737	(0.608, 0.894)	0.002	0.674	(0.567, 0.801)	<0.001
Adjuvant ET						
None	-----			-----		
Tamoxifen	0.83	(0.640, 1.082)	0.17	0.63	(0.502, 0.823)	<0.001
NSAI	0.61	(0.482, 0.833)	<0.001	0.41	(0.361, 0.495)	<0.001

Table 1. Multivariate Cox proportional hazard model parameter estimates for OS and DRFS

Neoadjuvant Strategy for eILC

- 50% eILC present with Stage II/III and would benefit from neoadjuvant therapy
- 63-71% of ILCs exhibit an activating mutation in the PTEN-PI3K-AKT pathway
  - Most the mutations are present in primary ILC (**Truncal Mutations**)

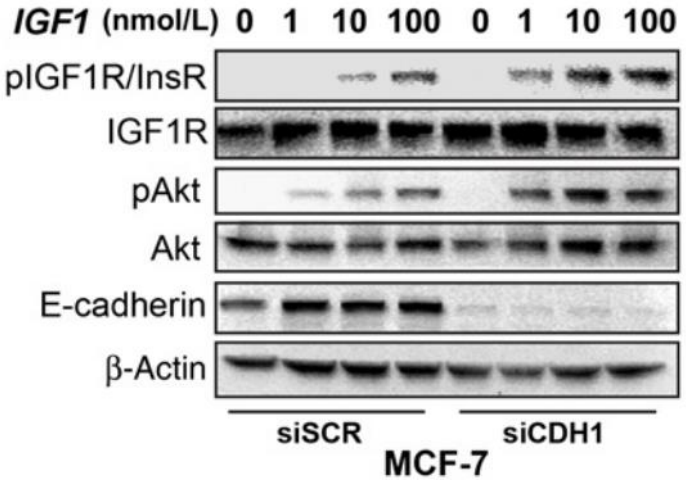
Table 5 Comparison of the prevalence of genetic alterations in patients with primary and metastatic ILC

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

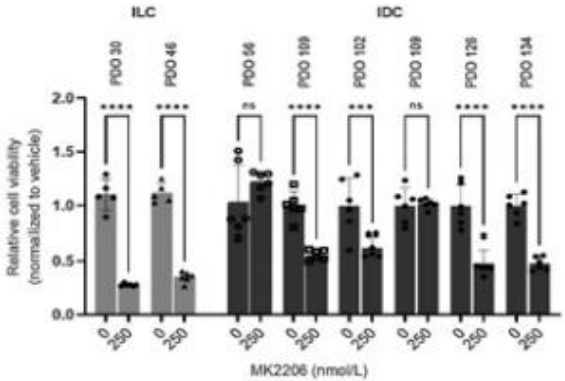
ILC invasive lobular carcinoma, *IDC* invasive ductal carcinoma

Mouabbi JA et al., *Breast Cancer Res Treat.* 2022

Pre-Clinical ILC models show high activation (phosphorylation) of AKT irrespective of an activating mutation



Nagle A … Oesterreich S & Lee A, *Clin Cancer Res.* 2022

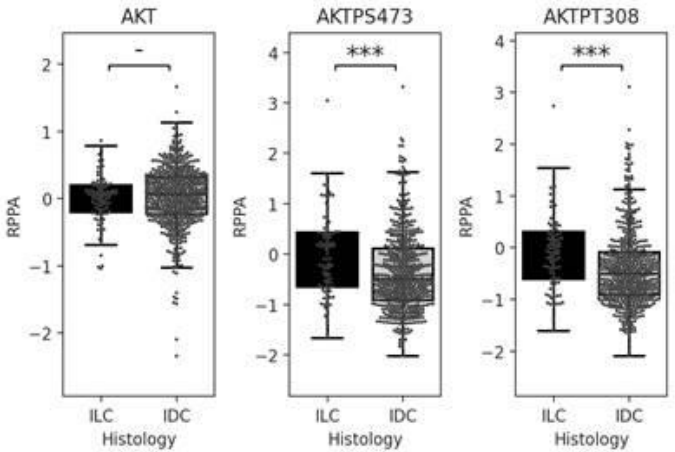


Elangovan A … Oesterreich S & Lee A, *Mol Cancer Res.* 2022

Clinical Evidence that ILC show high activation (phosphorylation) of AKT

Internal analysis: Protein expression of AKT in human ILC (~300 samples) and IDC samples (~1500 samples)

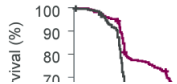
- Similar AKT protein levels in ILC vs IDC
- Significantly higher phosphorylation (activation) of p-AKT S473 and p-AKT T308 in ILC.



Courtesy of BostonGene

CAPItello-291 Trial: Capivasertib (AKTi) + ET in HR+ HER2-ve MBC

CAPItello-291 Trial | Capivasertib 400 mg DIP 4on/3off +



	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)

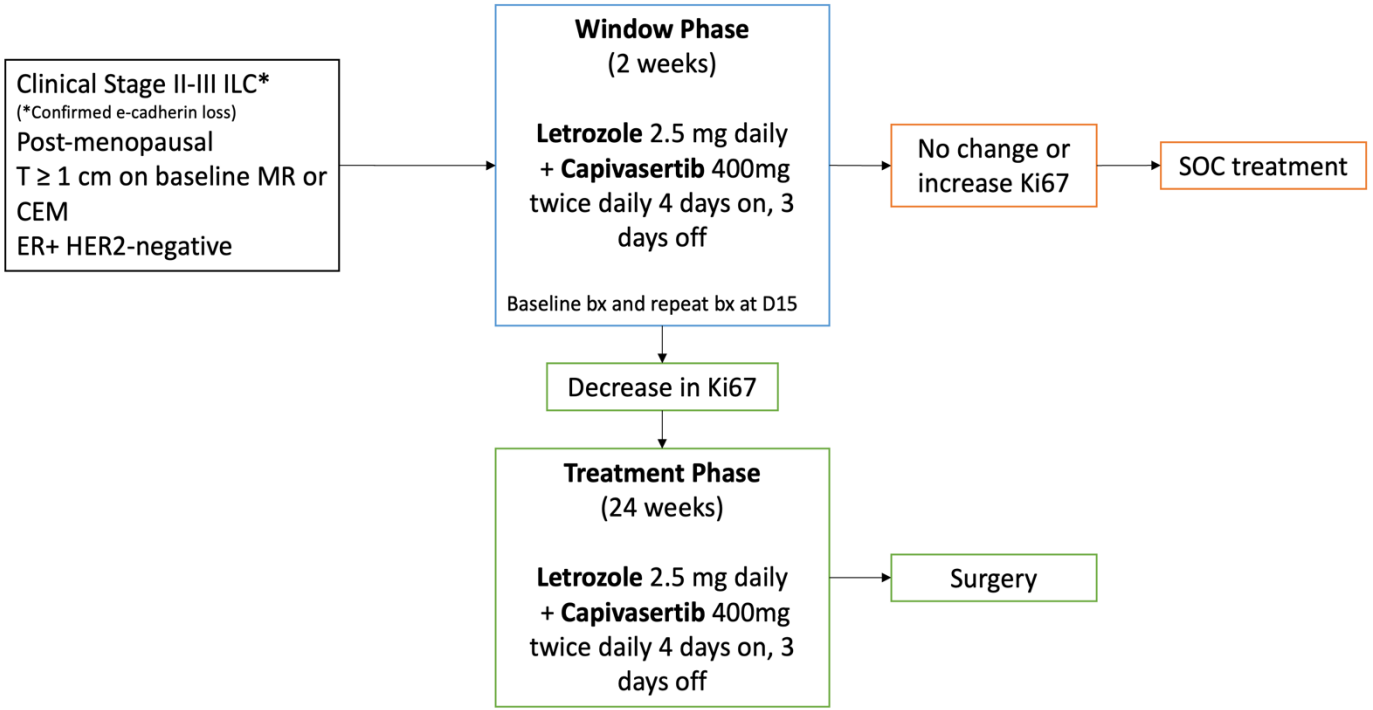
FDA approves capivasertib with fulvestrant for breast cancer

On November 16, 2023, the Food and Drug Administration approved capivasertib (Truqap, AstraZeneca Pharmaceuticals) with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Study arm	**CAPI + FUL**	**PBO + FUL**
ORR in non-altered (OR)	23% vs 12% (2.19)	
ORR in altered (OR)	29% vs 9% (3.93)	

Turner et al., SABCS 2022

NeoAKT trial: Neoadjuvant Study of AKTi + ET in Lobular Breast Cancer



PIs: Jason Mouabbi; Funda Meric-Bernstam

Endocrine Therapy in early stage ILC

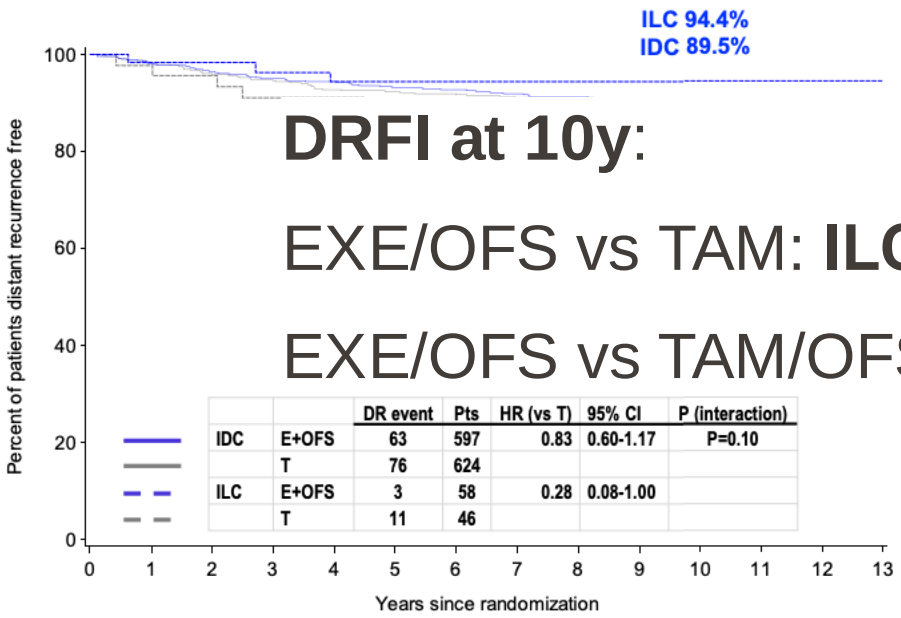
Study	Menopausal Status	Histology	Overall survival benefit with AI versus Tamoxifen
BIG 1–98 [106]	Pre- and Post- menopausal	ILC	Favor AI (HR 0.40, $p = 0.04$)
		IDC	Favor AI (HR 0.73, $p = 0.04$)
ABCSG-8 [107]	Post-menopausal	ILC	Favor AI (HR 0.24, $p = 0.01$)
		IDC	No difference at 3 year (HR 1.08)

HR hazard ratio, *AI* aromatase inhibitor, *ILC* invasive lobular carcinoma; *IDC* invasive ductal carcinoma

Mouabbi JA et al., BCRT 2022

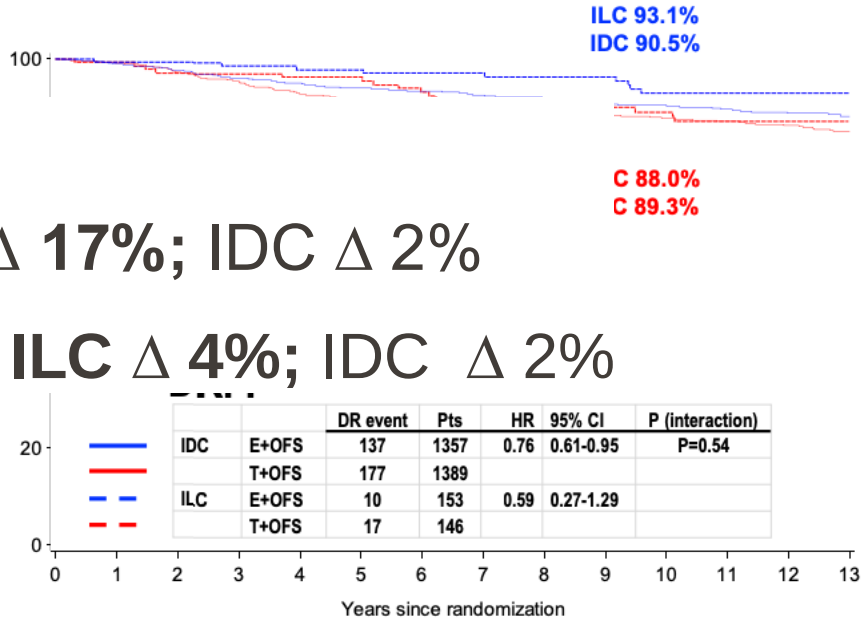
ADJUVANT ENDOCRINE THERAPY FOR PREMENOPAUSAL INVASIVE LOBULAR CARCINOMA

Exemestane + OFS vs. Tamoxifen



		DR event	Pts	HR (vs T)	95% CI	P (interaction)
IDC	E+OFS	63	597	0.83	0.60-1.17	P=0.10
	T	76	624			
ILC	E+OFS	3	58	0.28	0.08-1.00	
	T	11	46			

Exemestane + OFS vs. Tamoxifen + OFS



		DR event	Pts	HR	95% CI	P (interaction)
IDC	E+OFS	137	1357	0.76	0.61-0.95	P=0.54
	T+OFS	177	1389			
ILC	E+OFS	10	153	0.59	0.27-1.29	
	T+OFS	17	146			

DRFI at 10y:

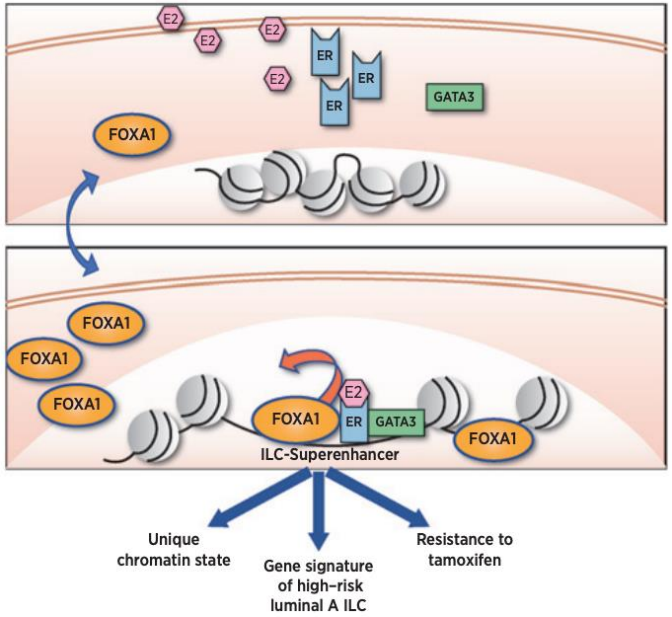
EXE/OFS vs TAM: **ILC Δ 17%;** IDC Δ 2%

EXE/OFS vs TAM/OFS: **ILC Δ 4%;** IDC Δ 2%

Metzger O., ESMO Breast Cancer 2024 Abstract 1090

What is the mechanism of tamoxifen resistance in ILC

Preclinical studies showed that compared to IDC, ILC have a gained FOXA1 (transcription factor) binding which binds to ER and act as an ILC-superenhancer which contributes to tamoxifen resistance



Jeselsohn, Metzger et al. *Cancer Res* 2023

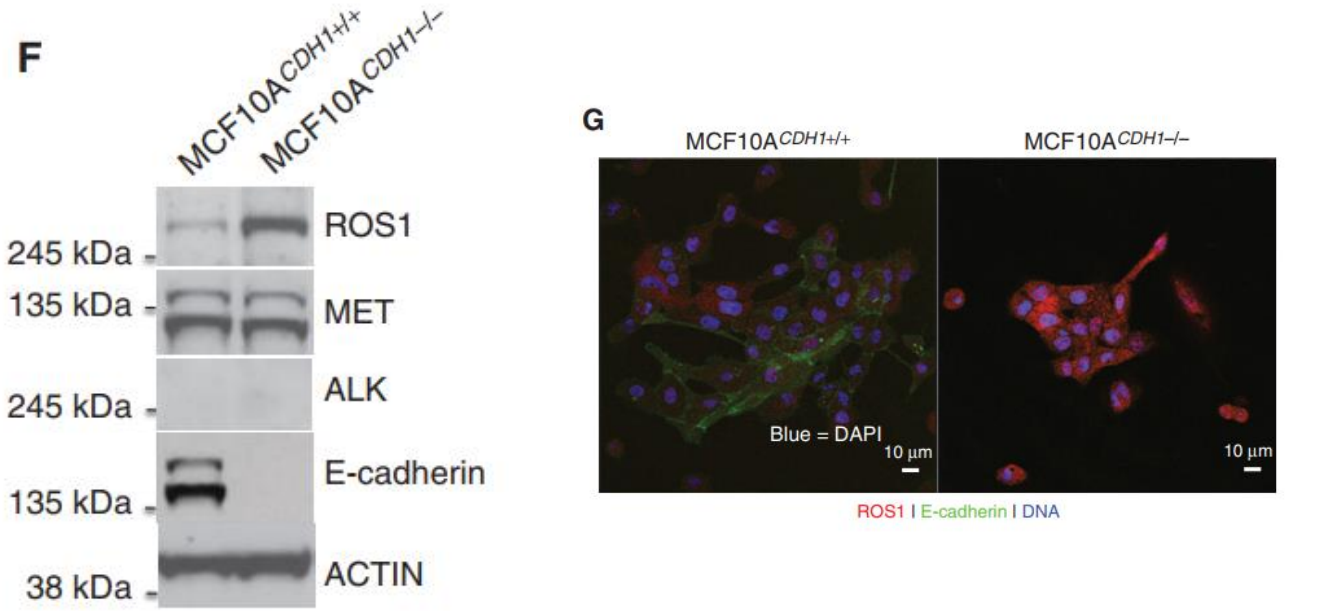
Advanced Stage ILC

Treatment of mILC

- ILC benefit from treatment with Endocrine therapy (ET) + Targeted therapy (CDK4/6is, mTORi & PI3Ki) [1]
- Post ET + CDK4/6is, mPFS to single agent fulvestrant in HR+ HER2- ILC cancer is 2.2 months with a 6-month PFS of 17.7% [2]
- Once endocrine-refractory, ILC have very poor response to subsequent lines of chemotherapy with mPFS 5-8 months [3]

1. Mouabbi JA et al, *NPJ Breast* 2023
2. Mouabbi JA, ESMO Breast Cancer 2024 Abstract 224P
3. Mouabbi JA et al., *Oncologist* 2023

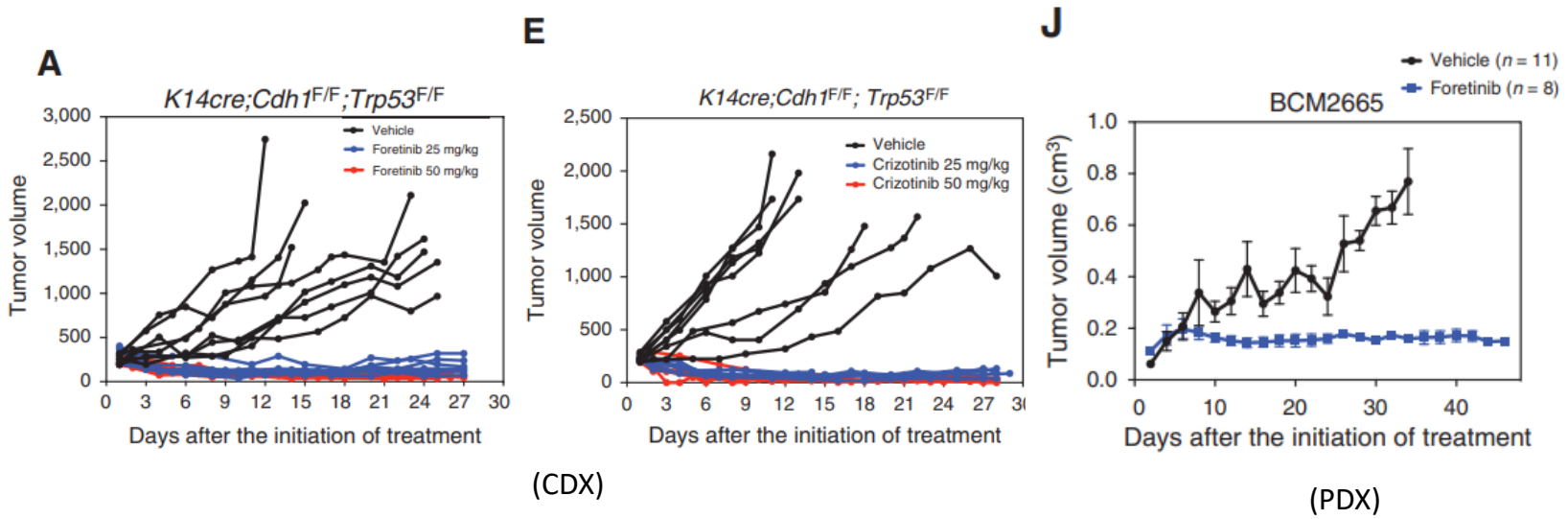
ROS1 inhibition is synthetic lethal with E-cadherin defects in isogenic models



Bajrami I. et al., *Cancer Discov.* 2018

E-cadherin synthetic lethal effects operate in vivo in E-cadherin–defective breast tumors

In Vivo, ROS1 inhibitor produce profound anti-tumor effect in multiple models of E-cadherin-defective breast cancer.



(CDX)

(PDX)

Bajrami I. et al., *Cancer Discov.* 2018

Repotrectinib

Orally administered TKI

Small microcyclic inhibitor of ROS1, NTRK and ALK

Compared to Crizotinib and Entrectinib it has >90-fold greater potency against ROS1

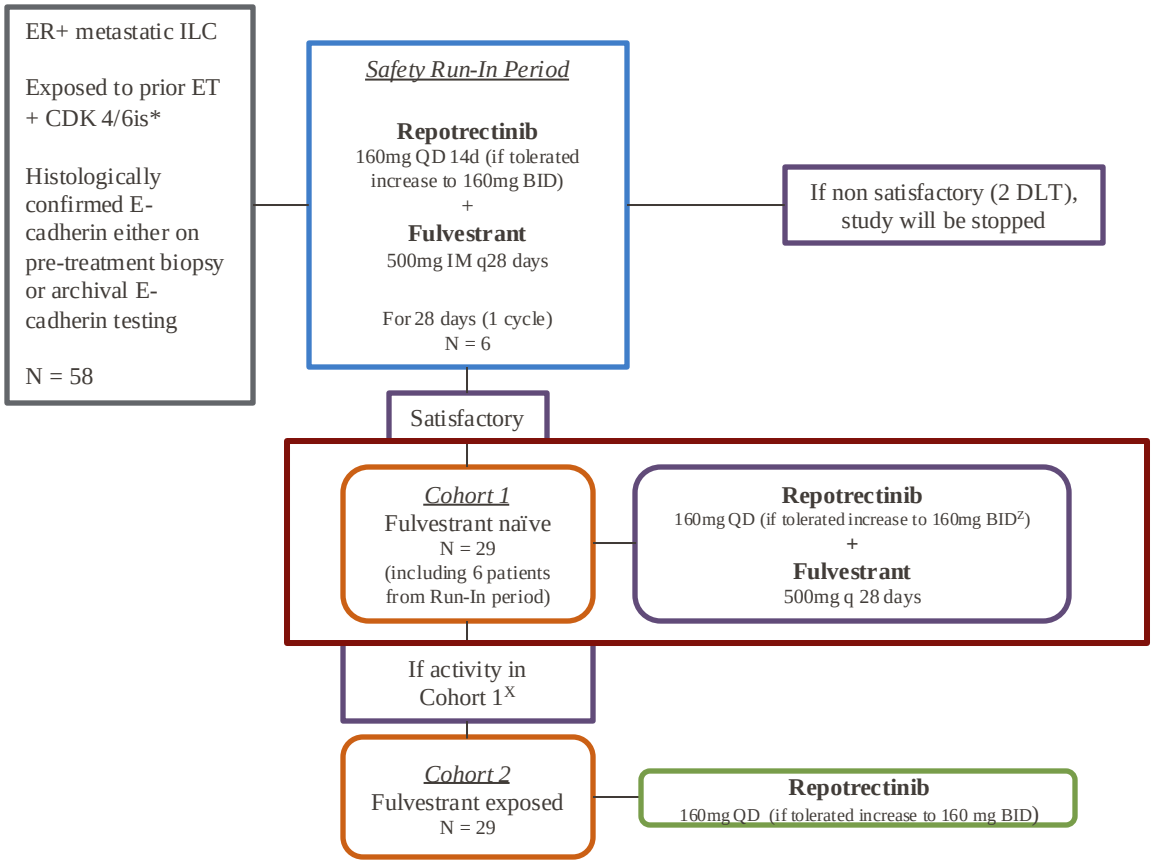
Repotrectinib demonstrates early clinical activity in ROS1+ mNSCLC with high ORR, prolonged mDOR and mPFS

Well tolerated: Most AEs grade ½. Most common AE is grade 1 dizziness (58.4%)

Granted FDA approved for ROS1-positive metastatic NSCLC on November 15 2023

REPLOT Trial: REPotrectinib +/- Fulvestrant in metastatic invasive LObular carcinoma patients who were exposed to endocrine Therapy + CDK4/6is

Co-PIs: Jason Mouabbi and Funda Meric-Bernstam



Activated on 10/9/2024 and open for accrual!

Targeting *HER2* Mutation in mILC

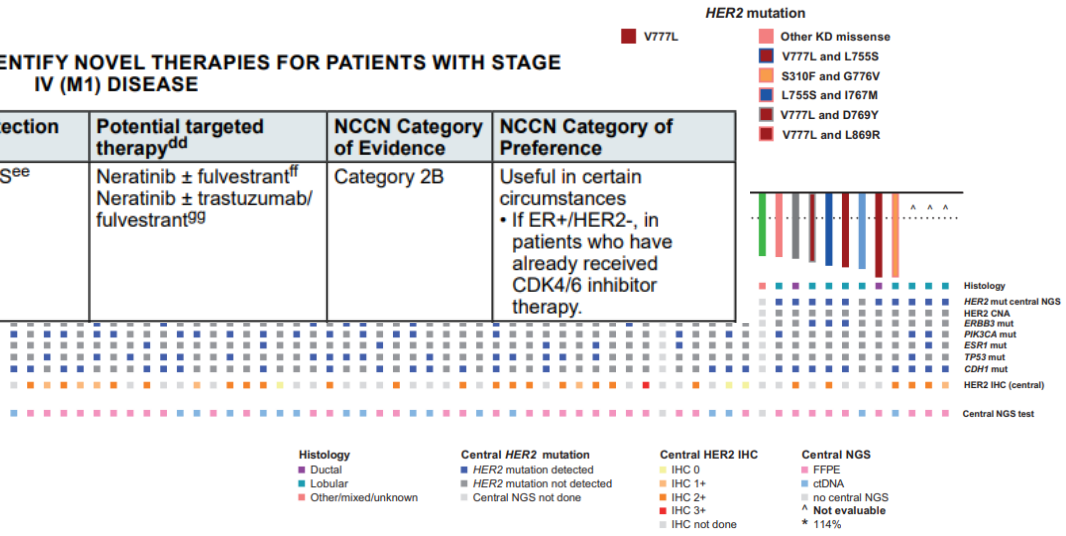
- HER2 mutations are enriched in mILC compared to IDC (15% vs 5%) [1]
- The SUMMIT trial looked at Niratinib efficacy in HER2-mutant breast cancer [2]

- 47% of enrolled
- All got prior CI therapy
- ORR: 41%
- mPFS: 8.3 mon

A

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH STAGE IV (M1) DISEASE

Breast Cancer Subtype	Emerging Biomarkers	Detection	Potential targeted therapy[dd]	NCCN Category of Evidence	NCCN Category of Preference
ER+/HER2- ER-/HER2-	HER2 activating mutations	NGS[ee]	Neratinib ± fulvestrant[ff] Neratinib ± trastuzumab/ fulvestrant[gg]	Category 2B	Useful in certain circumstances • If ER+/HER2-, in patients who have already received CDK4/6 inhibitor therapy.



1. Mouabbi JA et al., *Breast Cancer Res.* 2022
2. Jhaveri et al., *Ann Oncol.* 2023

Immunotherapy in ILC: Unfinished Symphony, The Story Continues...

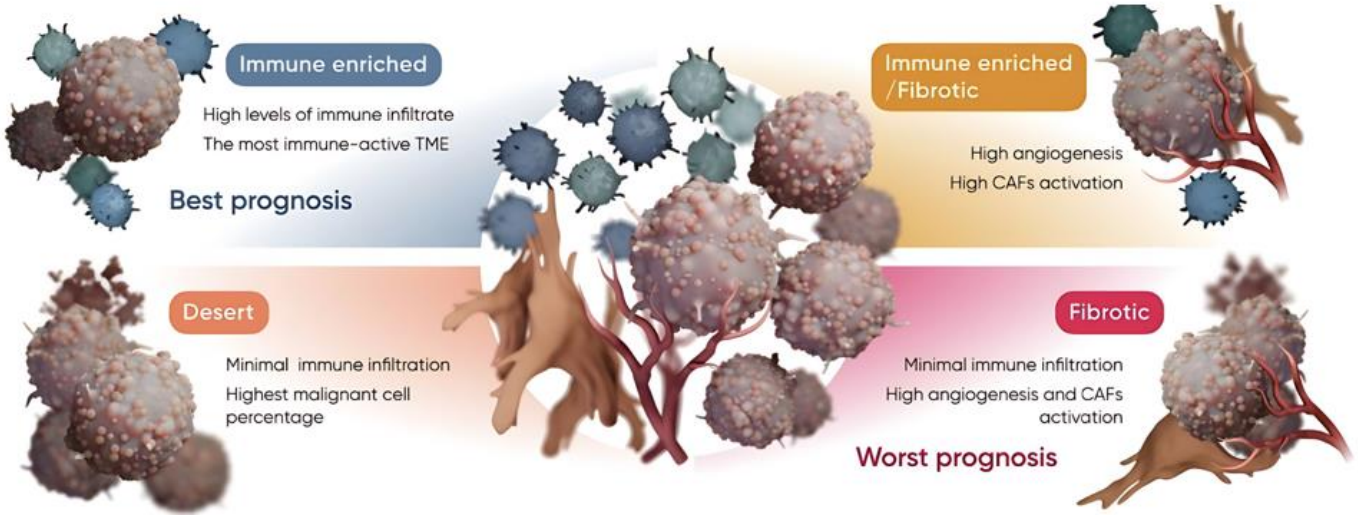
This indicates that certain mILC patients with an immunogenic phenotype may benefit from immunotherapy.

1. Ciriello G et al., *Cell.* 2015; 2. Michaut M. et al., *Sci. Rep.* 2016; 3. Du T et al., *Sci. Rep.* 2018; 4. Mouabbi JA et al. ASCO23; 5. Rugo H. et al., *Clin. Cancer Res*. 2018; 6. Voorwerk L … Kok M., *Nat Cancer*. 2023

Tumor Microenvironment Types (TME)

A component of BostonGene Tumor Portrait™ test

- BostonGene identified 4 distinct Tumor Microenvironment Subtypes by analyzing **29 functional gene expression signatures**
- There are **4 portrait types** associated with disease prognosis
- This model is prognostic in **multiple cancer types**

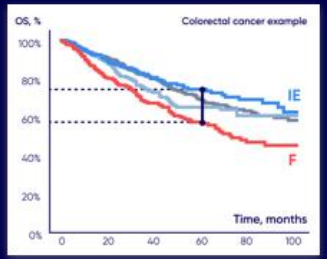


Cancer Cell

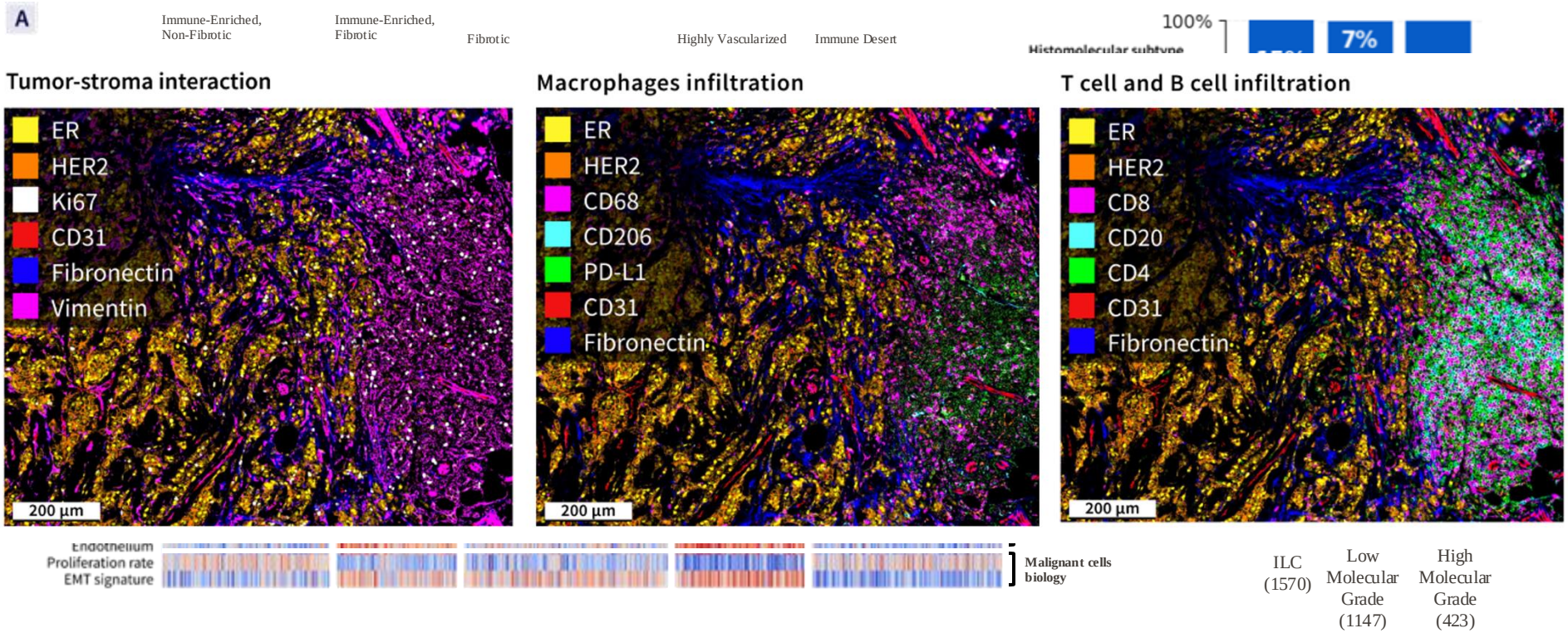
Editors' picks in 2021 — Cutting-edge areas of cancer research and oncology in 2021

The proprietary model was published in Cancer Cell

Bagaev et al., Cancer Cell, 2021

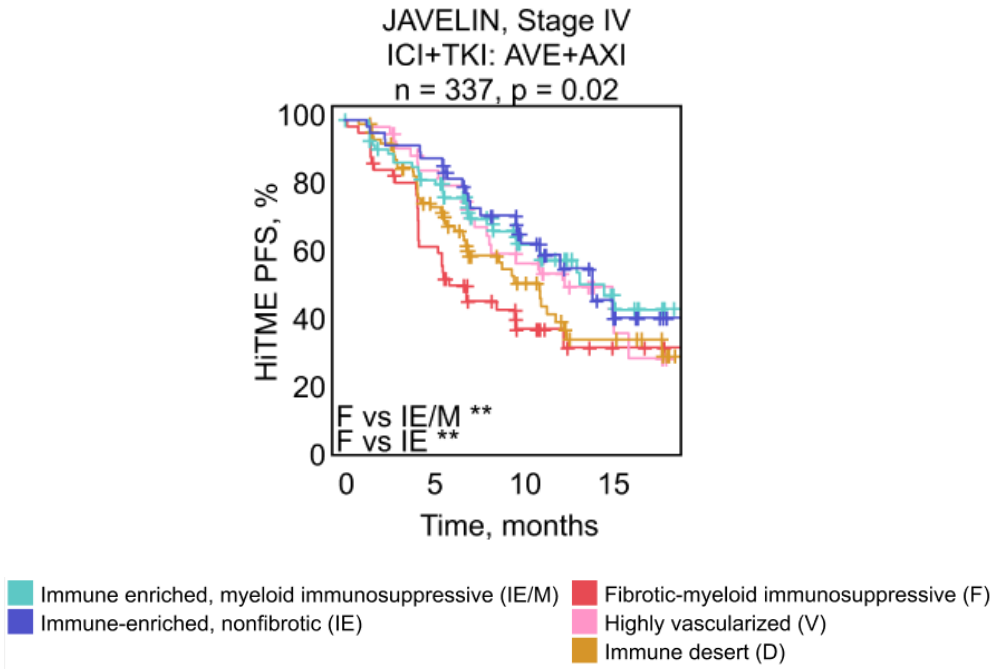


Promising ILC Treatments – Targeting the Tumor Microenvironment



Mouabbi JA et al., ASCO23; Mouabbi JA et al., SABCS23

IO/TKI combo in ccRCC



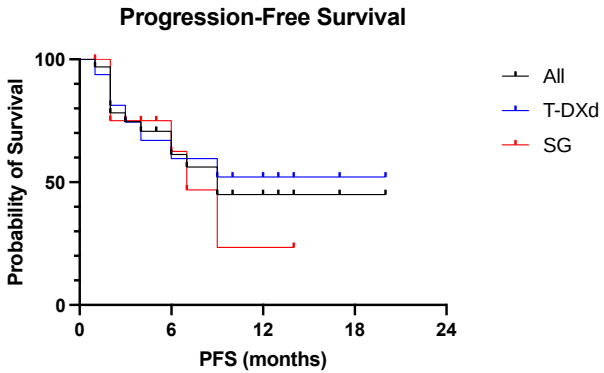
Courtesy of BostonGene

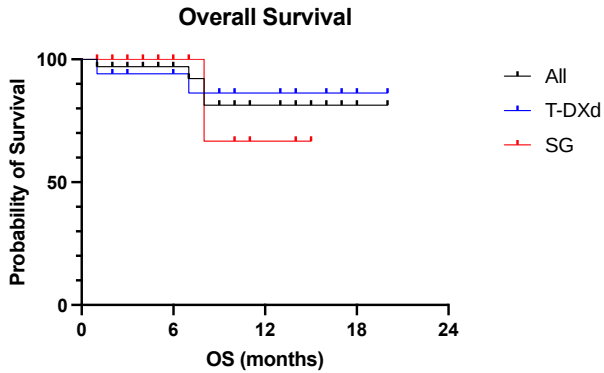
Efficacy of Single-Agent Chemotherapy in Endocrine Therapy-Refractory mILC

	PFS		
	Hazard ratio (95% CI)	*P*-value	Overall *P*-value
Chemotherapeutic agent			
Capecitabine vs taxane	0.63 (0.48-0.82)		*<.001**
Age	0.99 (0.98-1.00)		.161
Race			
Black vs White	2.04 (1.22-3.41)	.006	.074
Hispanic vs White	1.08 (0.69-1.69)	.745	
Asian vs White	1.44 (0.71-2.94)	.310	
Other vs White	0.78 (0.29-2.11)	.627	
Metastatic presentation			
De Novo vs Recurrent	1.08 (0.79-1.49)		.620
Number of metastases			
1 vs 3 or more	0.62 (0.45-0.86)	.004	*.007**
2 vs 3 or more	0.72 (0.54-0.97)	.003	
Location of metastatic site			
Non-Visceral vs Visceral	0.83 (0.64-1.07)		.152
Number of prior endocrine therapies			
1 vs 4	2.59 (1.39-4.82)	.003	*.004**
2 vs 4	2.97 (1.57-5.63)	.001	
3 vs 4	1.96 (1.00-3.86)	.051	
Exposure to prior CDK4/6i			
No vs yes	1.1 (0.79-1.54)		.577
Prior exposure to taxanes in early stage			
No vs yes	1.25 (0.97-1.60)		.087

Mouabbi JA et al., *Oncologist*. 2024

Efficacy of Antibody-Drug Conjugates in Endocrine Therapy-Refractory mILC





	All (n=34)	T-DXd (n=17)	SG (n=17)
mPFS (mo)	9	NR	7
6-month PFS	61%	60%	62%
12-month PFS	45%	52%	23%
mOS (mo)	NR	NR	NR
12-month OS	81%	86%	66%

"If I have seen further, it is by standing on the shoulders of giants." – Sir Isaac Newton

My Giants

- Rachel Layman
- Funda Meric-Bernstam
- Debu Tripathy
- Mo Rimawi
- Kent Osborne
- Gabriel Hortobagyi

Most Important

- To all ILC patients and their family that participated directly or indirectly
- Lobular Breast Cancer Alliance Advocacy
- Donors: Cynthia Jones and Ann Clark

My Clinical Team

- Amber Potter
- Kelsey Wolfe
- Angela Douglas
- Angela Muhammad-Ali

Mentors

- Amy Hassan
- Bora Lim
- Vincente Valero
- Paula Pohlmann
- Aman Buzdar
- Carlos Barcenas
- Suzanne Fuqua
- Rachel Schiff
- Carrie L Dul
- Daniel Lebovic
- Tarik Hadid
- Raymond Hilu
- Matthew Ellis
- Nizar Tannir
- Nagi El Saghir

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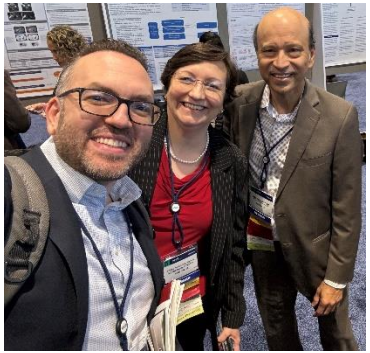

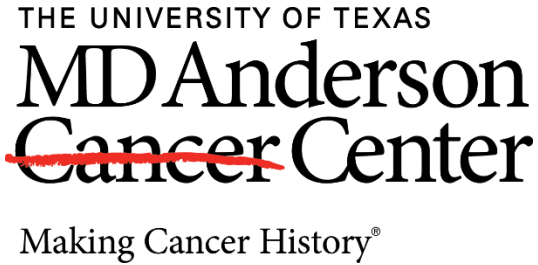
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