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

Targeting EGFR in Inflammatory Breast Cancer

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Enhanced Drug-Development Guide & Evaluation (EDGE) Preclinical Solutions

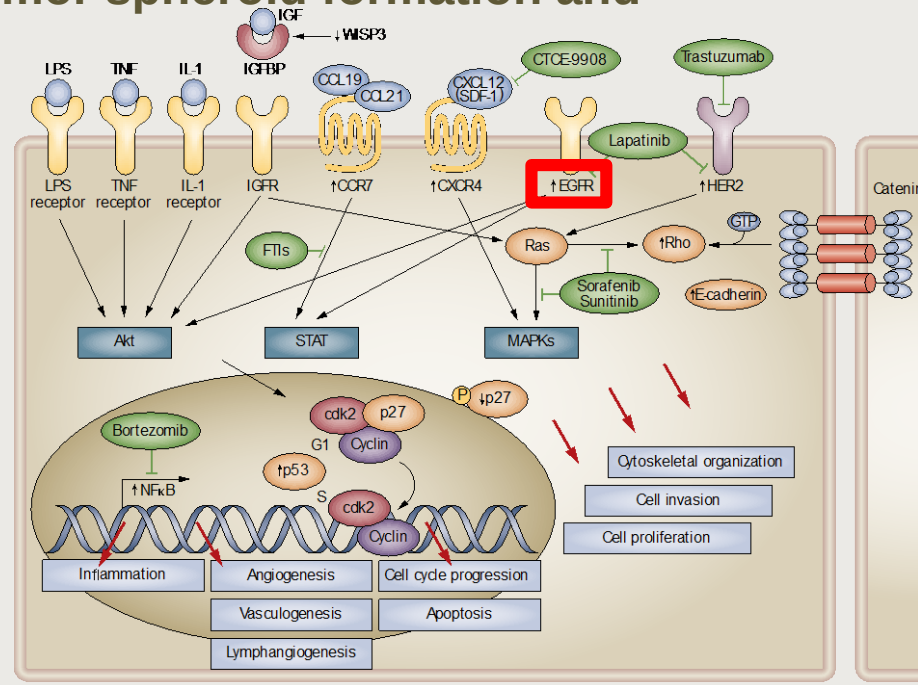
Department of Breast Medical Oncology

Teamoncology

Naoto Ueno

Why EGFR as a target in IBC?

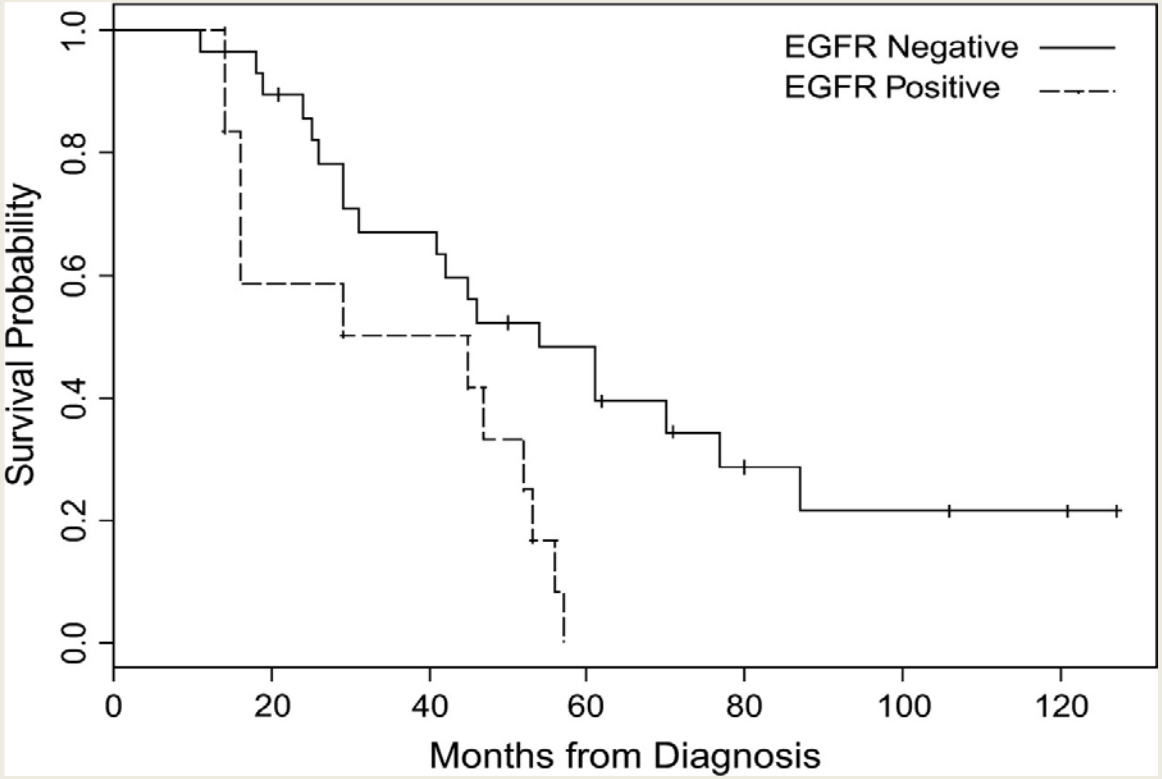
- **Hyperactivation of interferon-α & hypoactivation of EGFR and TGF-β were markedly associated with pCR in IBC**
- **In a preclinical IBC model, treatment with an EGFR inhibitor reversed the mesenchymal phenotype of IBC cells to an epithelial phenotype and inhibited tumor growth and metastatic progression.**
- **In a HR+ IBC preclinical model, bisphenol A activated EGFR and elicited ERK signaling, leading to tumor spheroid formation and resistance to EGFR inhibition.**



Bertucc F et al. Ann Oncol 2014;25358-365
Sauer et al. Carcinogenesis 38, 2017;252
Zhang D et al. Clin Cancer Res 2009;15;6639

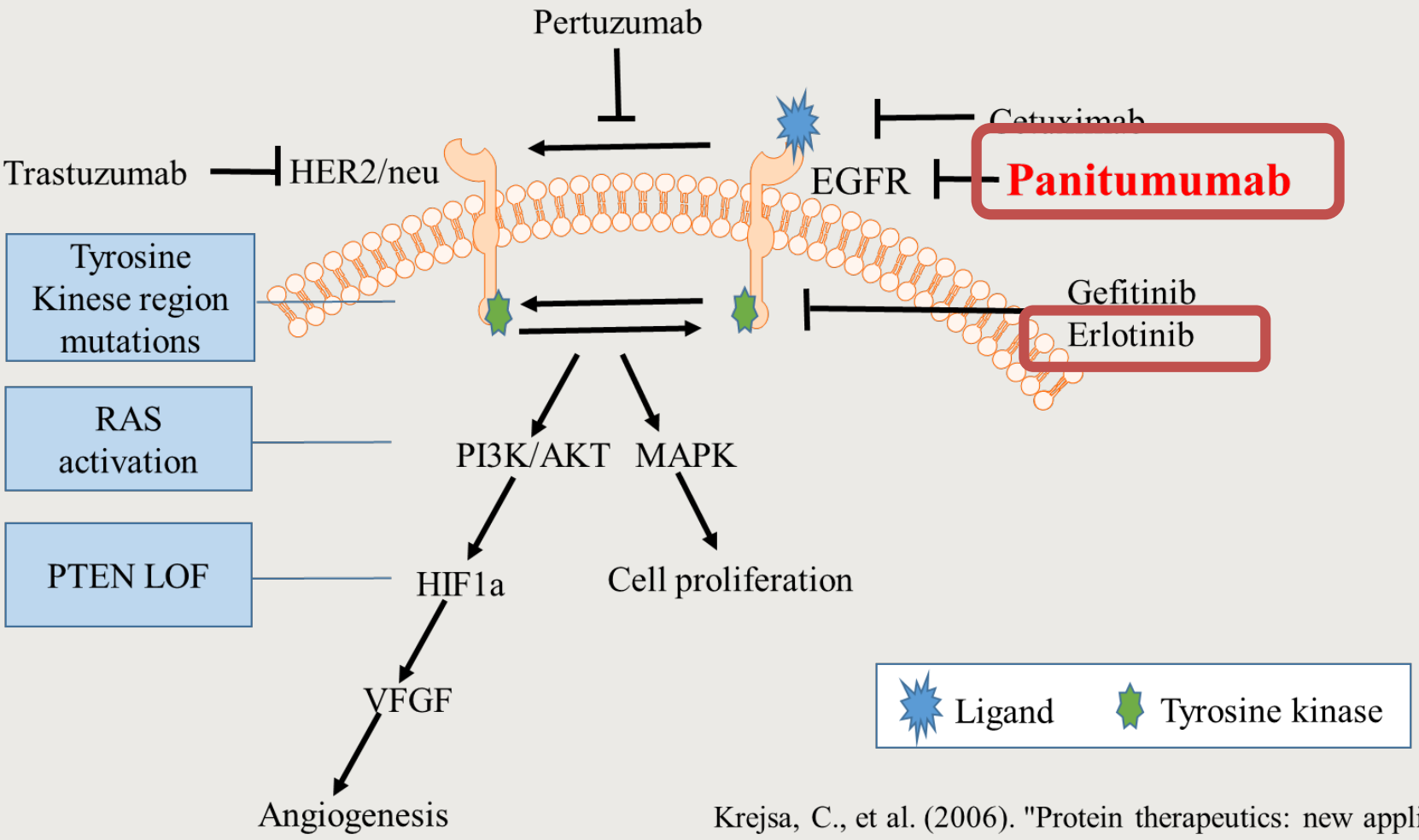
EGFR as a therapeutic target in IBC

- **EGFR overexpression was detected in 30% of IBC.**
- **Expression of EGFR is associated with poor outcome and high risk of recurrence.**



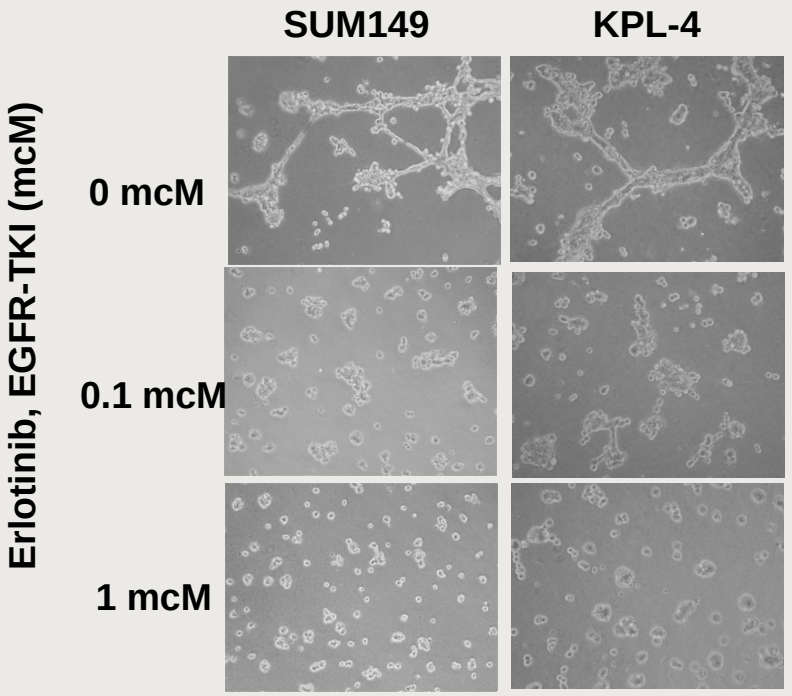
Cabioglu N, et al. Ann Oncol 2007;18:1021

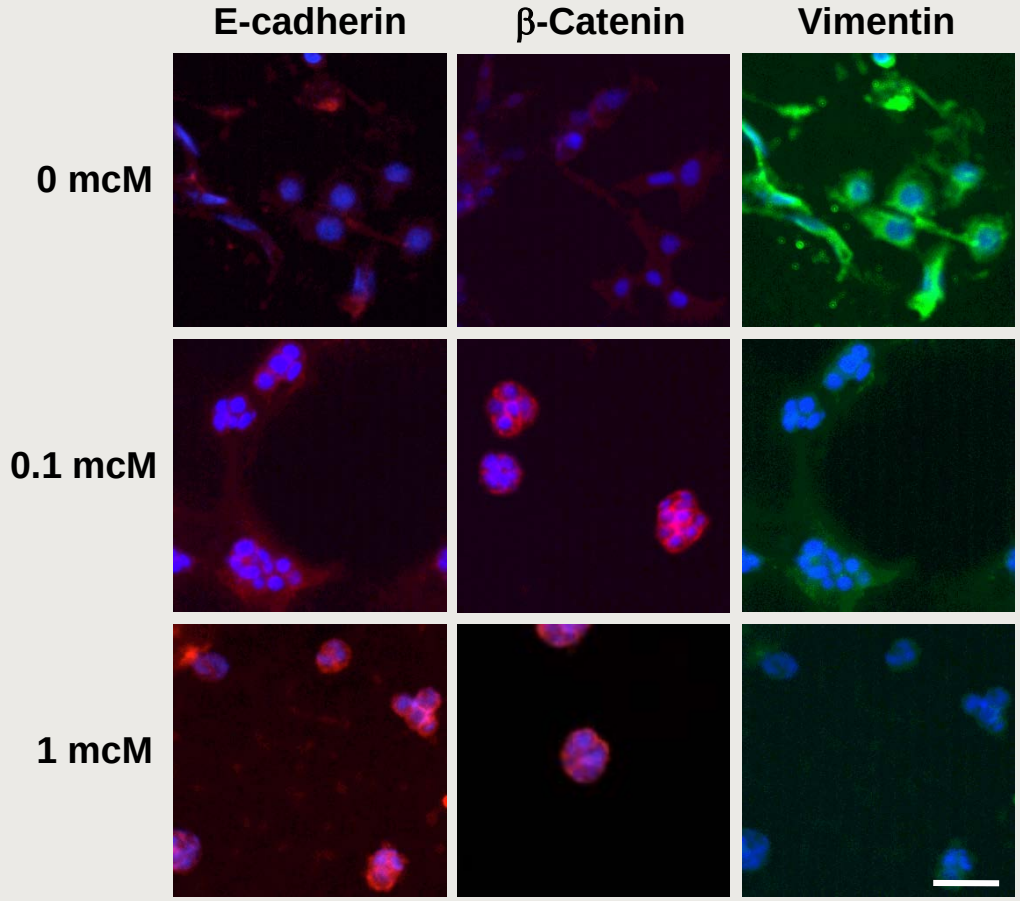
EGFR targeting therapy



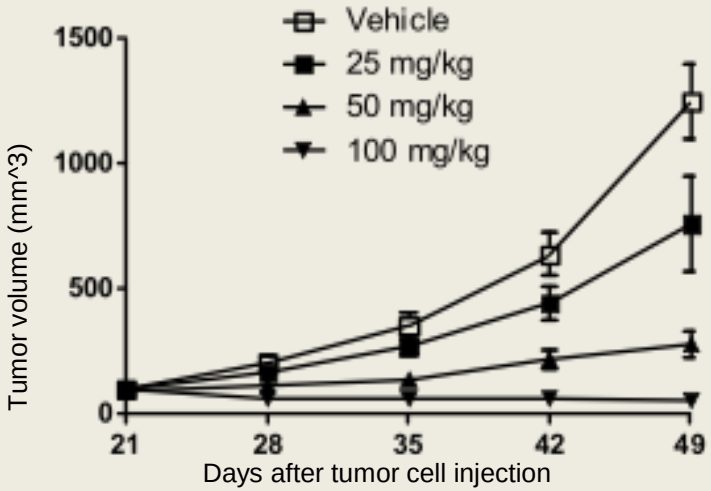
Krejsa, C., et al. (2006). "Protein therapeutics: new applications for pharmacogenetics." Nat Rev Drug Discov **5**(6): 507-521.

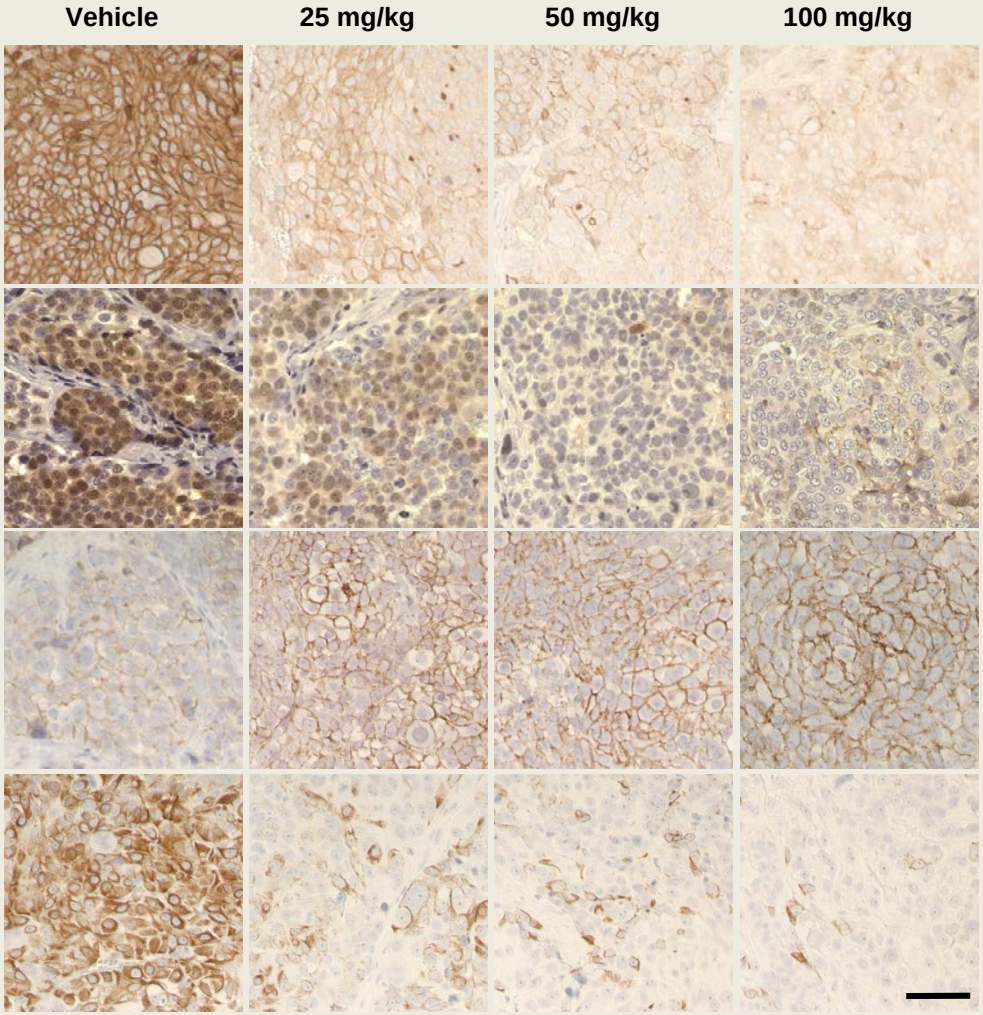
EGFR-targeted therapy reversed EMT

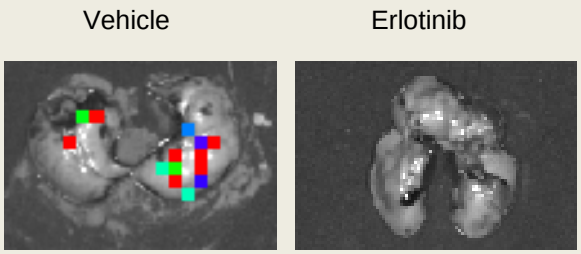


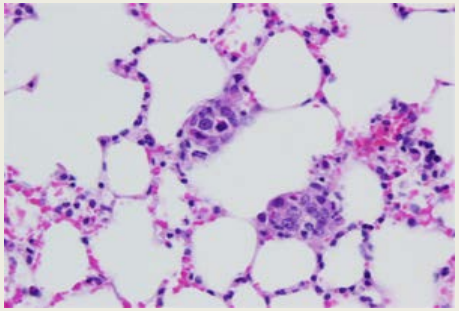


Zhang D et al. Clin Cancer Res 2009;15;6639





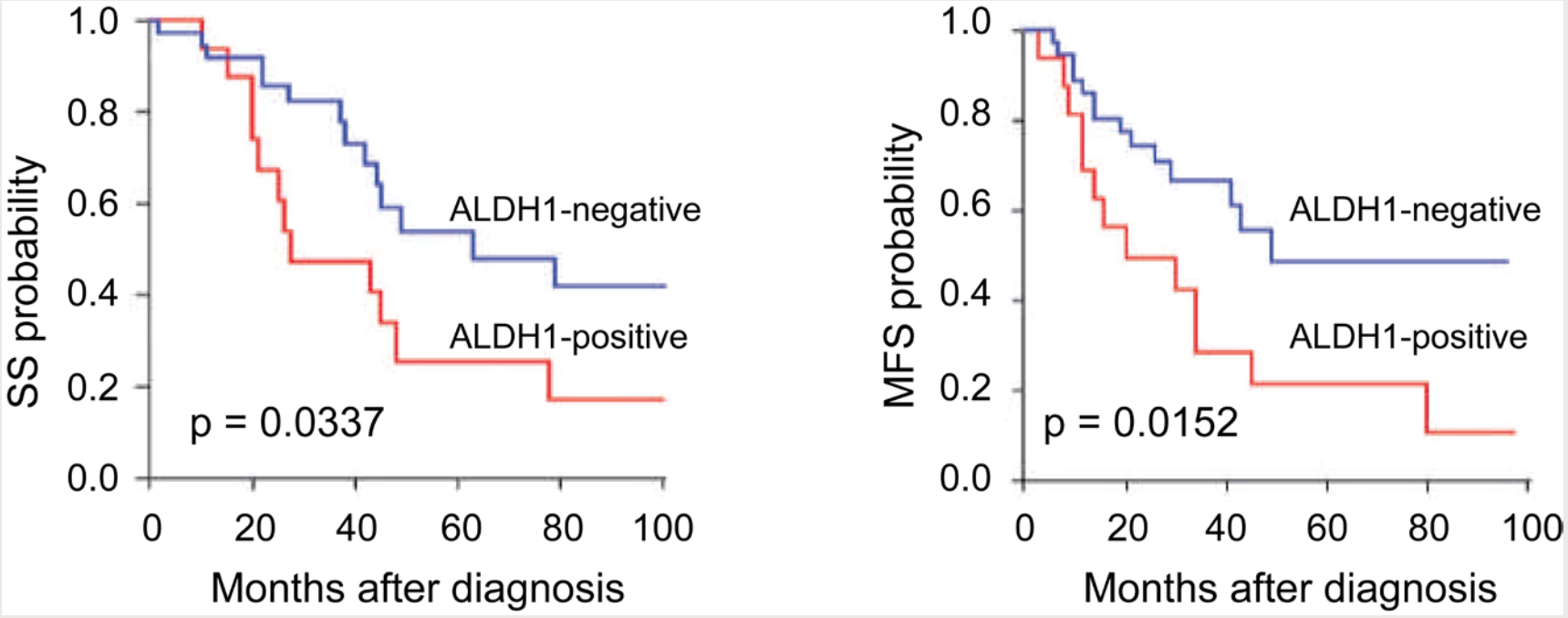




Group	No. of Mice	Incidence of lung metastasis
control (vehicle)	3 of 7	(43%)
25 mg/kg erlotinib	0 of 7	(0%)
50 mg/kg erlotinib	0 of 7	(0%)
100 mg/kg erlotinib	0 of 7	(0%)

Zhang D et al. Clin Cancer Res 2009;15;6639

Cancer stem cells mediate metastasis and poor clinical outcome in IBC

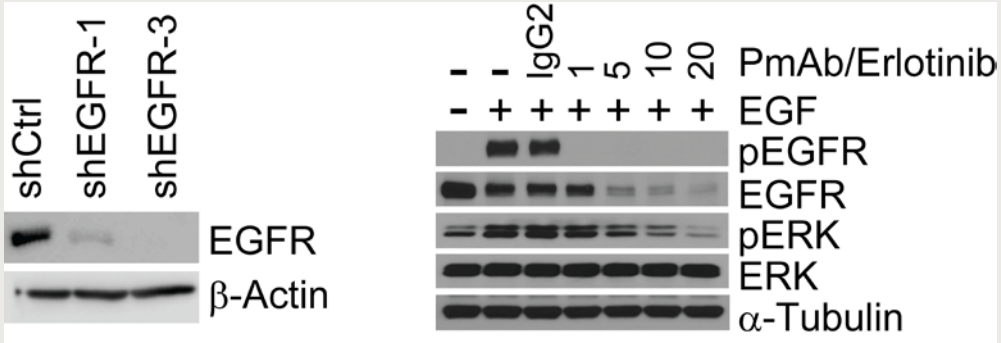


Development of novel therapies targeting IBC CSCs will improve outcomes of patients with this disease.

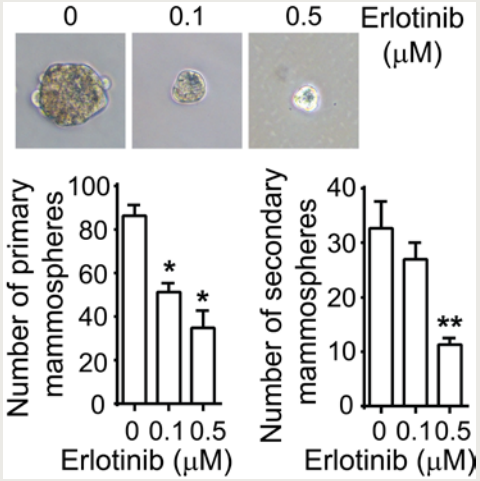
Charafe-Jauffret E, et. al., Clin Cancer Res. 2009; 16(1):45-55

Inactivation of EGFR signaling reduces the IBC CSC markers

Inactivation of EGFR signaling

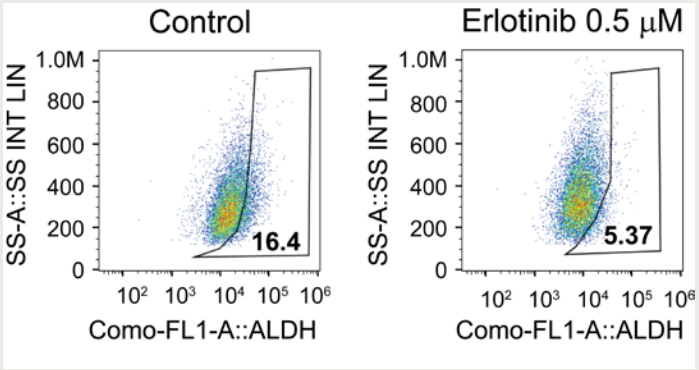


Mammosphere formation

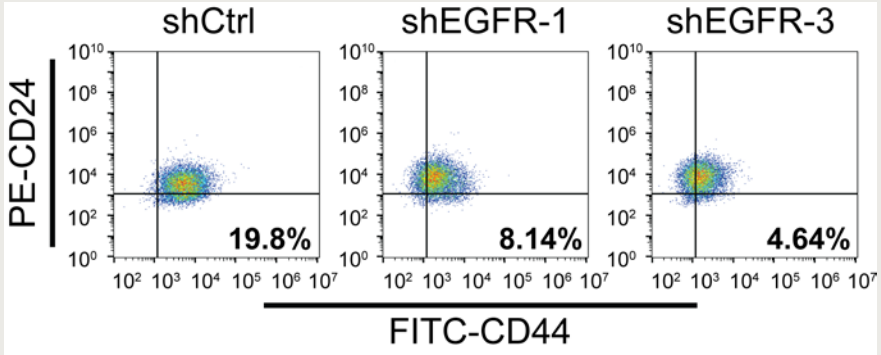


SUM149

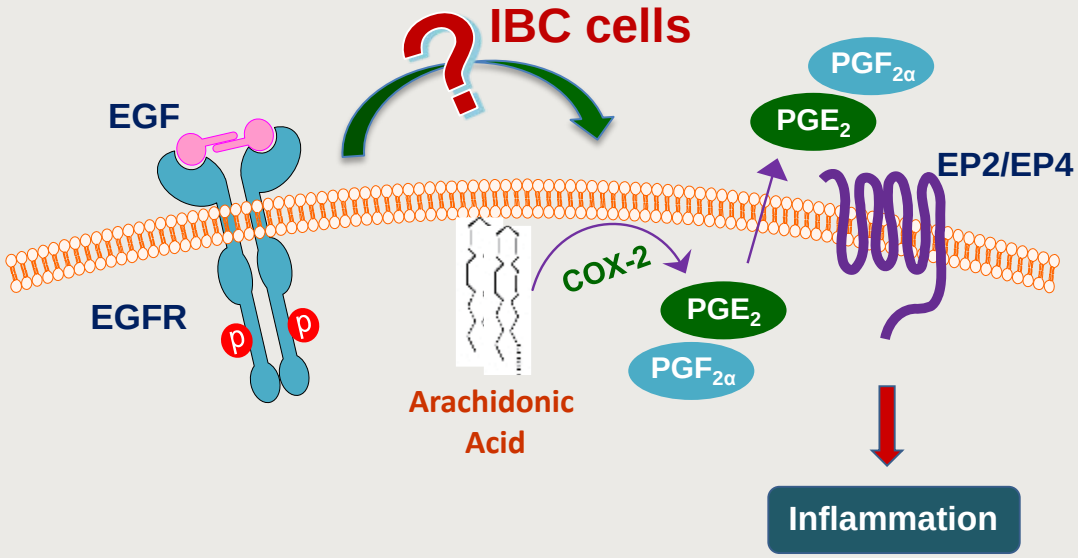
ALDH activity

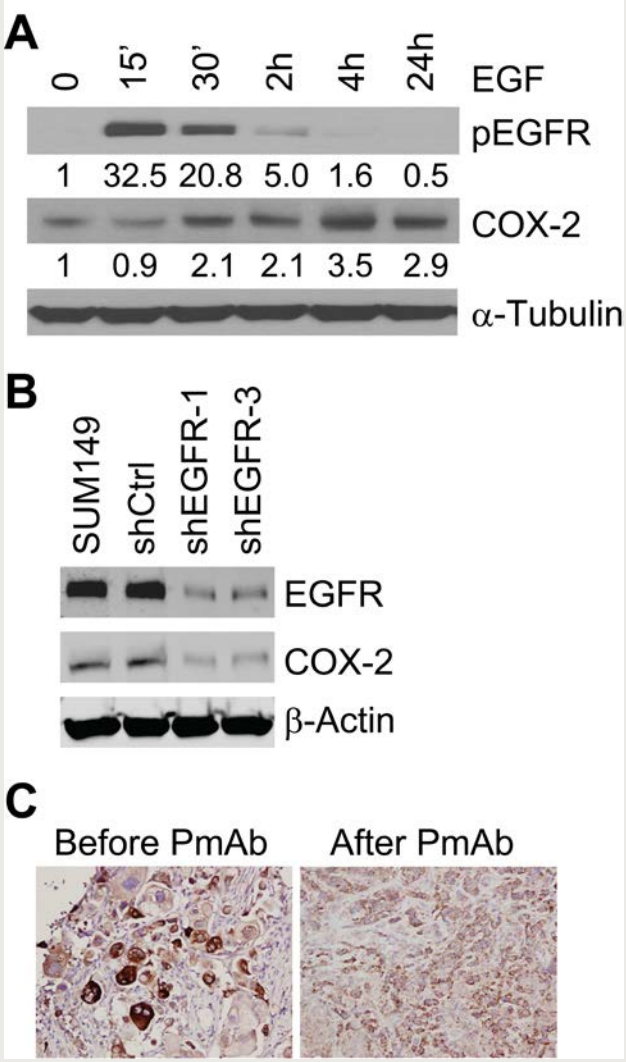


CD44+/CD24- subpopulation



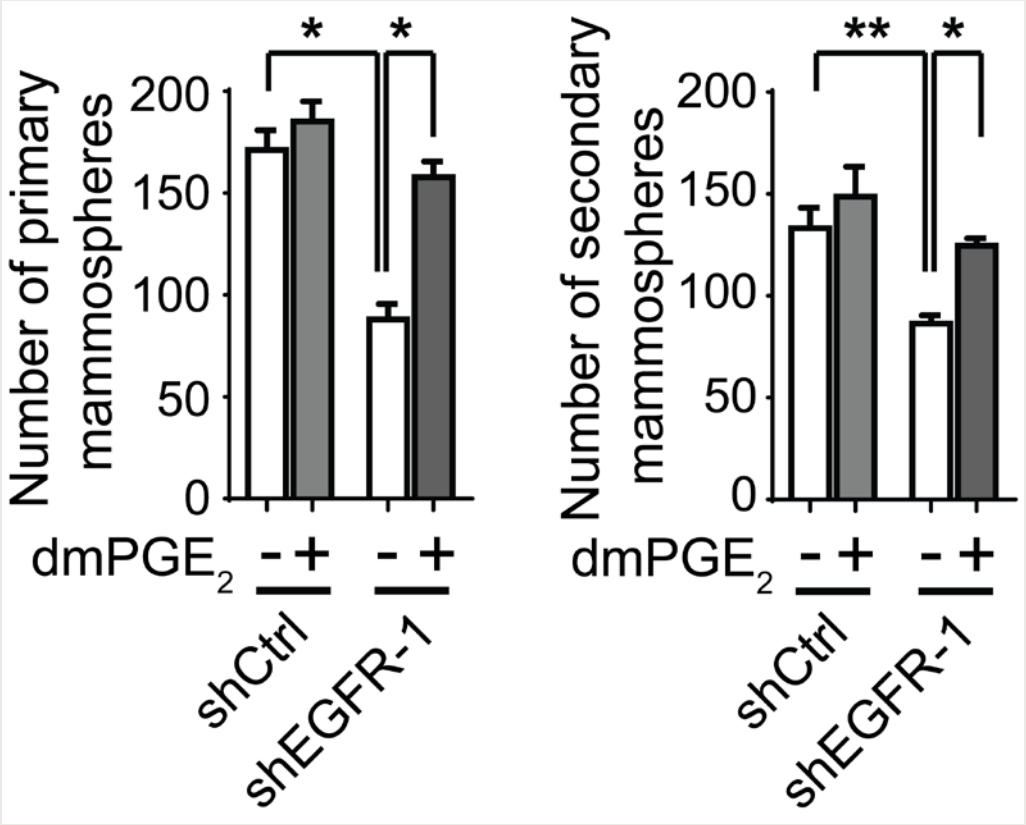
The COX-2 inflammatory pathway is functionally linked to EGFR signaling in IBC





Wang X, et al. Oncotarget. 2017 15;8:67904. PMCID: PMC5620223

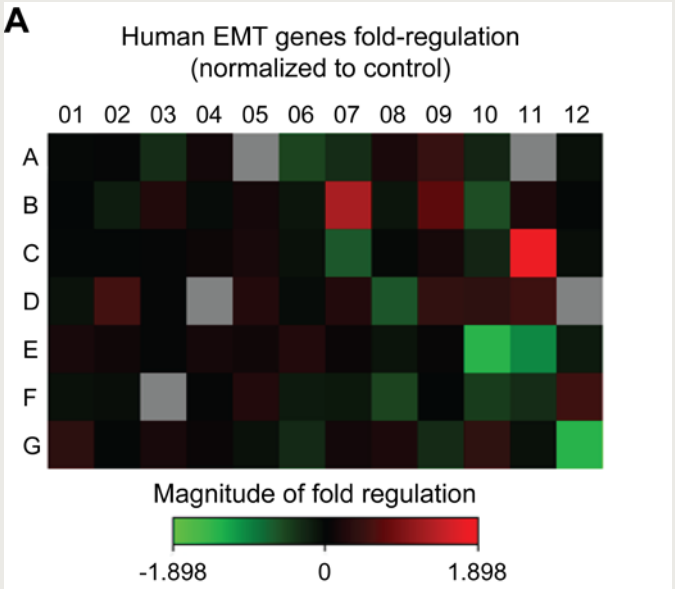
COX-2 mediates the EGFR-regulated CSC phenotype in IBC cells



Wang X, et al. Oncotarget. 2017 15;8:67904. PMCID: PMC5620223

Nodal is a potential downstream molecule that mediates EGFR/COX-2-regulated IBC CSC

A

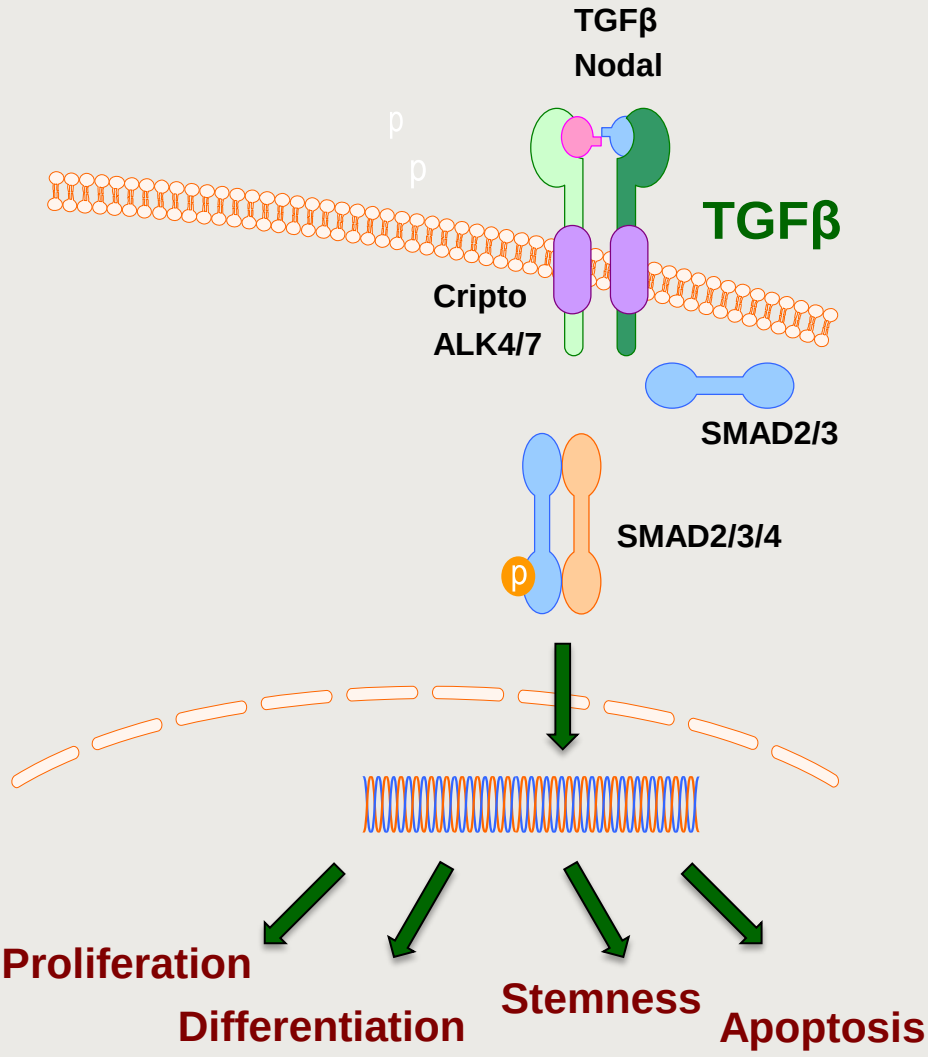


B

Human EMT PCR Array

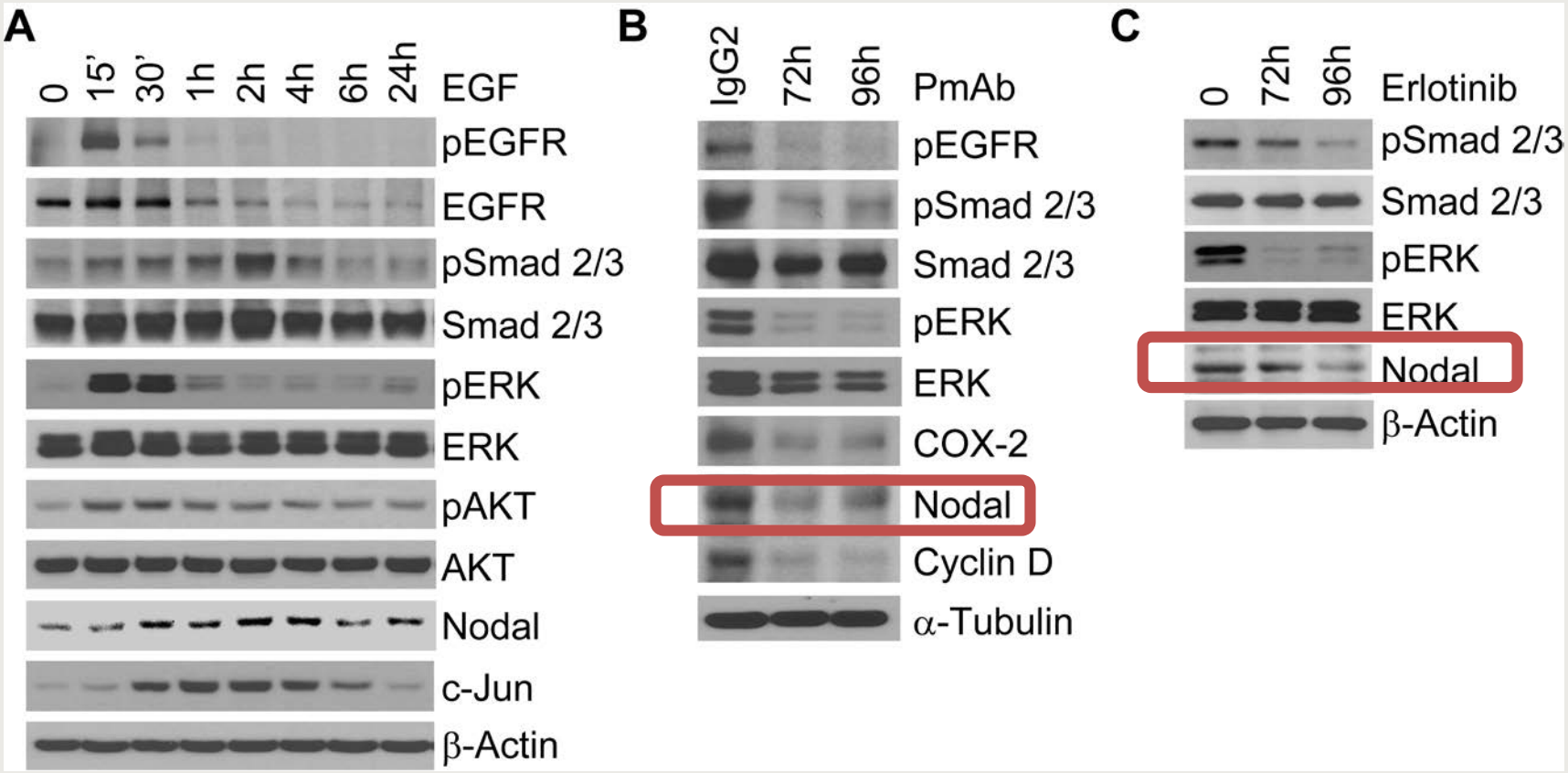
Top 5 genes down-regulated by celecoxib in SUM149

Position	Gene of interest	Fold-regulation	*P*-value
E10	SNAI1	-2.39	0.001
G12	ZEB2	-2.37	0.041
E11	SNAI2	-2.01	0.001
D8	NODAL	-1.63	0.030
C7	ITGA5	-1.63	0.002



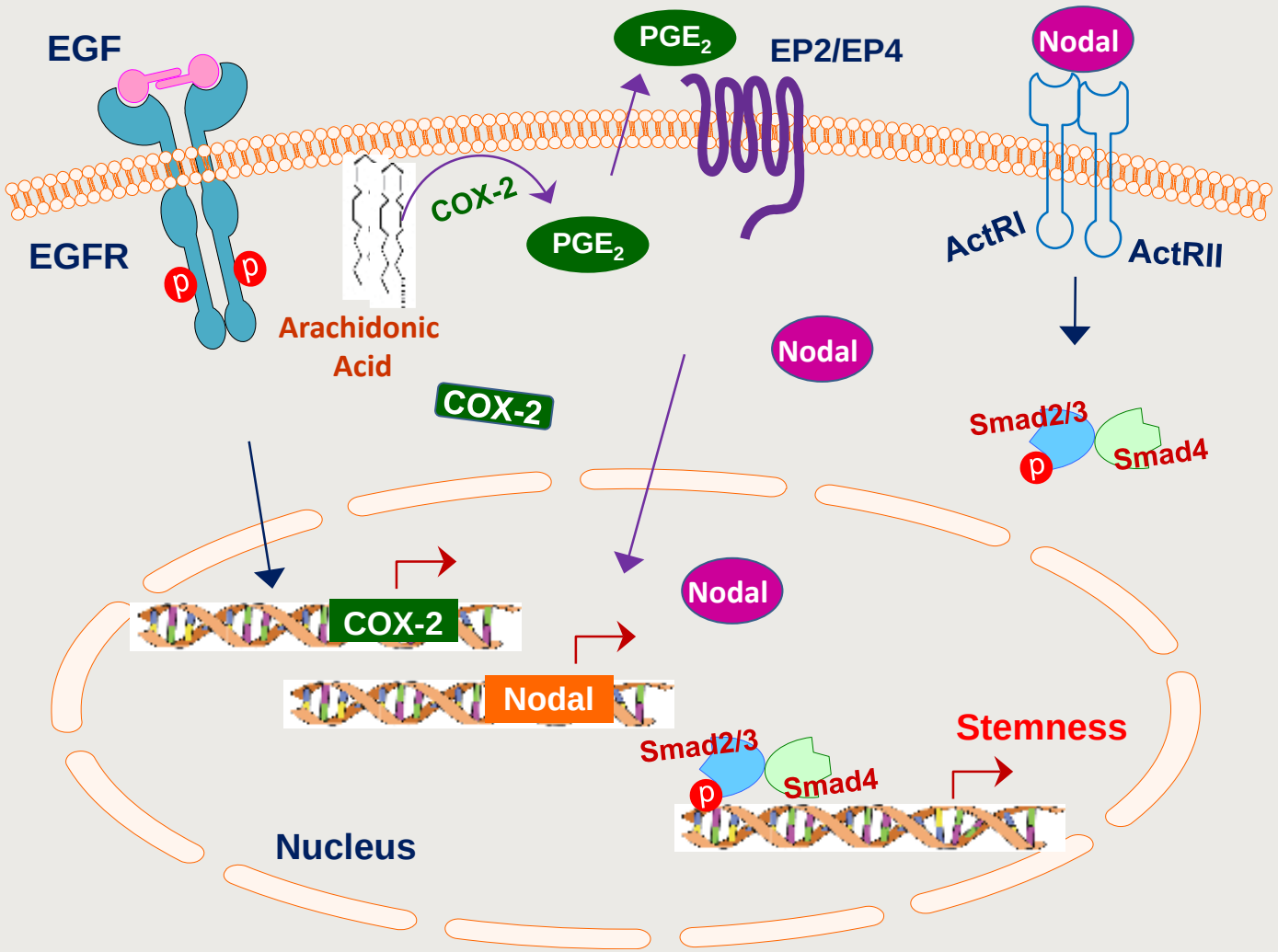
Wang X, et al. Oncotarget. 2017 15;8:67904. PMCID: PMC5620223

EGFR regulates Nodal signaling in IBC



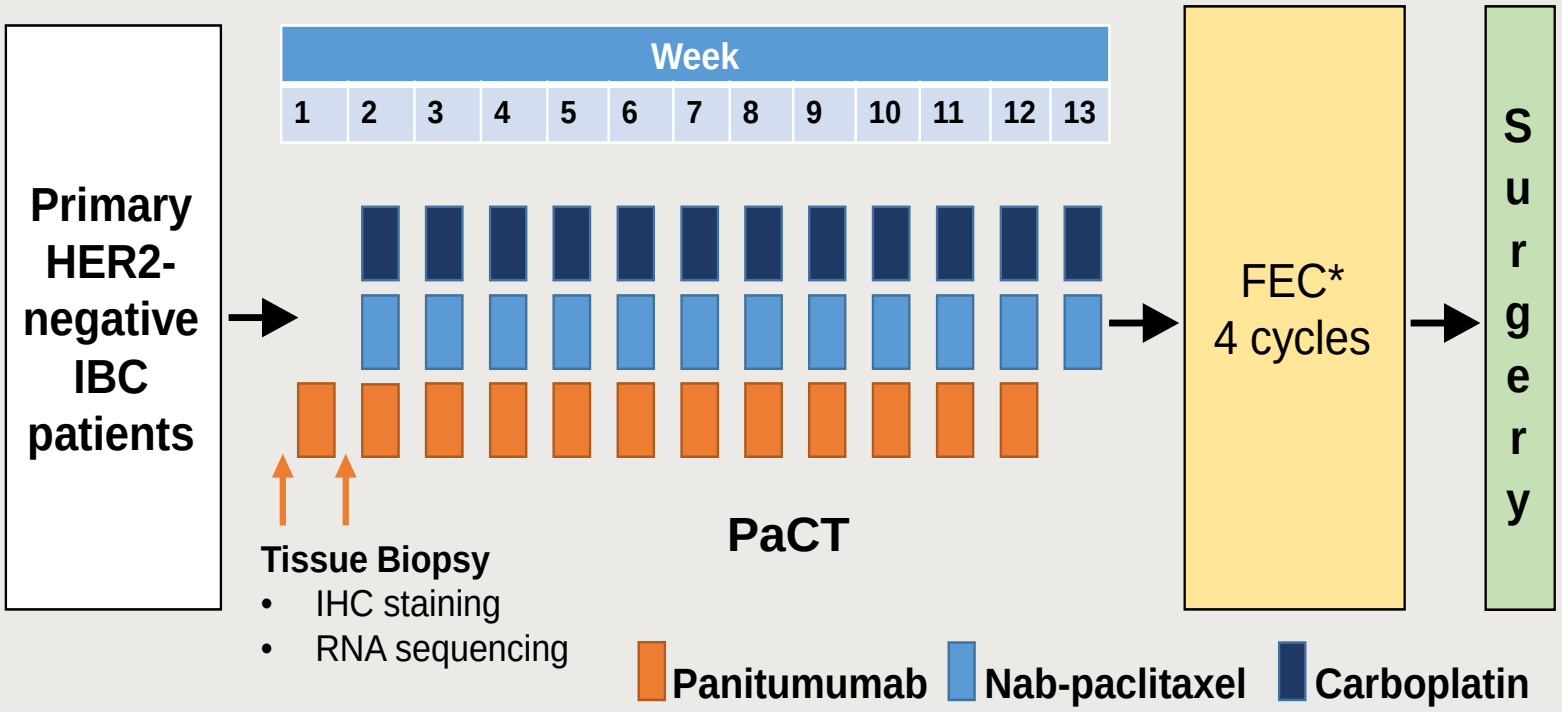
Wang X, et al. Oncotarget. 2017 15;8:67904. PMCID: PMC5620223

Model



Wang X, et al. Oncotarget. 2017 15;8:67904. PMCID: PMC5620223

Phase II Study of Neoadjuvant Panitumumab + Chemotherapy with low HER2 IBC



Primary Objective: pCR
Secondary Objective: EGFR Expression
Explorratoory Objective: Monitoring Dynamic Change of Genomic under Panitumaub monotherapy

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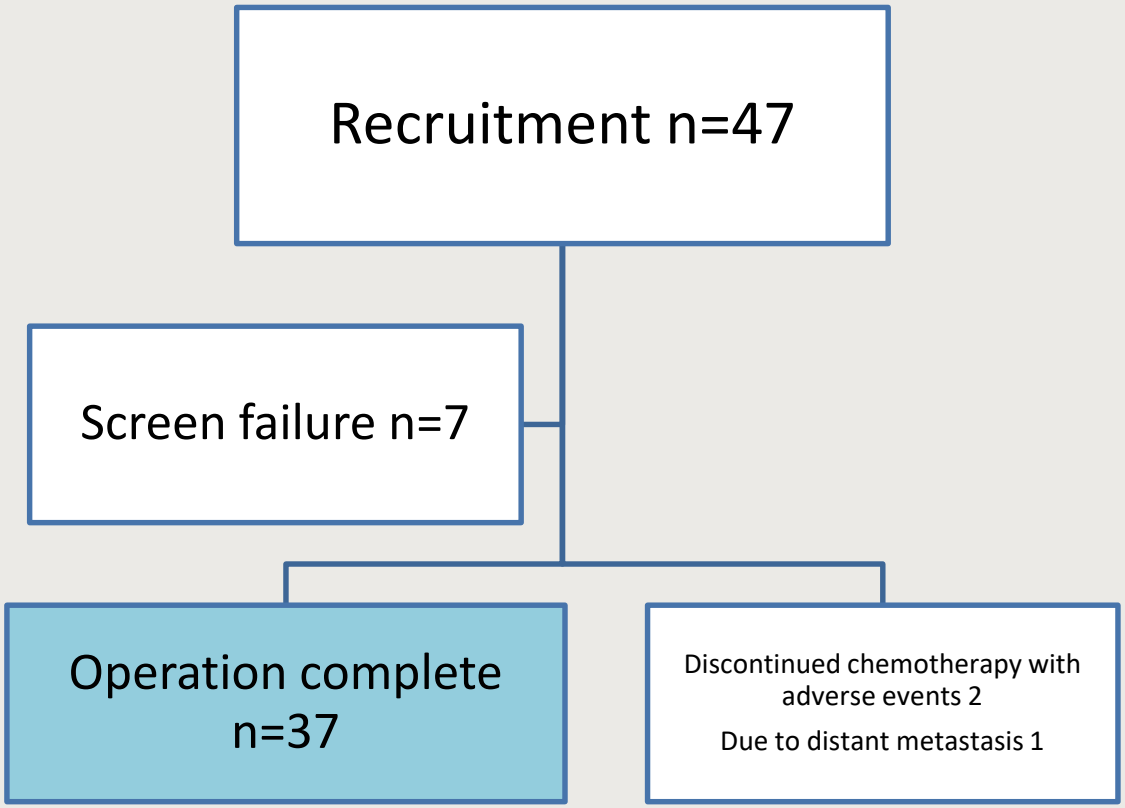
Outcome



Matsuda N, et al. ASCO 2016
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Table 2. Hematological and nonhematological toxicities[a] by CTCAE in PNC regimen occurring in ≥10% of patients								
Toxicity	Weekly (n=17), number (%)				3 weeks on 1 week off (n=23), number (%)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematological								
Neutropenia	0	3 (18)	3 (18)	7 (41)	0	10 (25)	7 (17.5)	5 (12.5)
Leucopenia	0	12 (71)	3 (18)	0	9 (22.5)	11 (27.5)	5 (12.5)	5 (12.5)
Anemia	0	5 (29)	3 (18)	0	1 (2.5)	9 (22.5)	10 (25)	2 (5)
Thrombocytopenia	0	0	4 (24)	0	0	1 (2.5)	3 (7.5)	2 (5)
Hypomagnesemia	0	0	1 (6)	0	0	1 (2.5)	1 (2.5)	0
Nonhematological								
Skin rash	5 (29)	7 (41)	2 (12)	0	7 (30)	11 (48)	4(17)	0
Skin peeling	3 (18)	1 (6)	0	0	5 (22)	1 (4)	0	0
Hand-foot reaction	3 (18)	2 (12)	0	0	2 (9)	2 (9)	0	0
Stomatitis	4 (24)	5 (29)	1 (6)	0	7 (30)	4 (17)	0	0
Alopecia	2 (12)	12 (71)	0	0	0	23 (100)	0	0
Nausea	7 (41)	3 (18)	0	0	8 (35)	12 (52)	1 (4)	0
Vomiting	3 (18)	3 (18)	0	0	8 (35)	3 (13)	1 (4)	0
Constipation	6 (35)	3 (18)	1 (6)	0	9 (39)	5 (22)	0	0
Fatigue	2 (12)	9 (53)	2 (12)	0	6 (26)	15 (65)	1 (4)	0
Diarrhea	9 (53)	2 (12)	0	0	5 (22)	4 (17)	2 (8)	0
Myalgia	6 (35)	2 (12)	0	0	8 (35)	5 (22)	0	0
Mucositis	3 (18)	1 (6)	0	0	6 (26)	3 (13)	0	0
Infection	0	2 (12)	1 (6)	0	0	7 (30)	0	0
Paresthesia	2 (12)	3 (18)	0	0	7 (30)	4 (17)	0	0

CTCAE, Common Terminology Criteria for Adverse Events.

[A] Adverse events possibly, probably, or definitely related to treatment with PNC regimen (panitumumab, nab-paclitaxel, and carboplatin) or FEC regimen (5-fluorouracil, epirubicin, and cyclophosphamide).

Treatment Response to PaCT/FEC

	Response	N=37 (%)	Non-pCR (n=26)		pCR (n=11)	
			TNBC	HR+	TNBC	HR+
Pathological response	**RCB-0 (pCR)**	11 (30)	-	-	8	3
	RCB-I	3 (8)	3	-	-	-
	RCB-II	10 (27)	3	7	-	-
	RCB-III	13 (35)	3	10	-	-

	TNBC (n=17)	ER+/HER2- (n=20)	ER+/HER2+	ER-/HER2+	Total
pCR rate	47% (8/17)	15% (3/20)	Not Eligible	Not Eligible	30% (11/37)
pCR/RCB-I rate	65% (11/17)	15% (3/20)	Not Eligible	Not Eligible	38% (14/37)

Matsuda N, et al. ASCO 2016
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Comparison to Historical Data

		TNBC	ER+/HER2-	ER+/HER2+	ER-/HER2+	Total
Non-IBC	Historic pCR	30-40%	7-16%	35%	40-60%	
IBC	pCR with standard chemo	12%	7%	30%	15%	
	pCR with PaCT	44% (60%)	17%	Not Eligible	Not Eligible	36%

Matsuda N, et al. ASCO 2016
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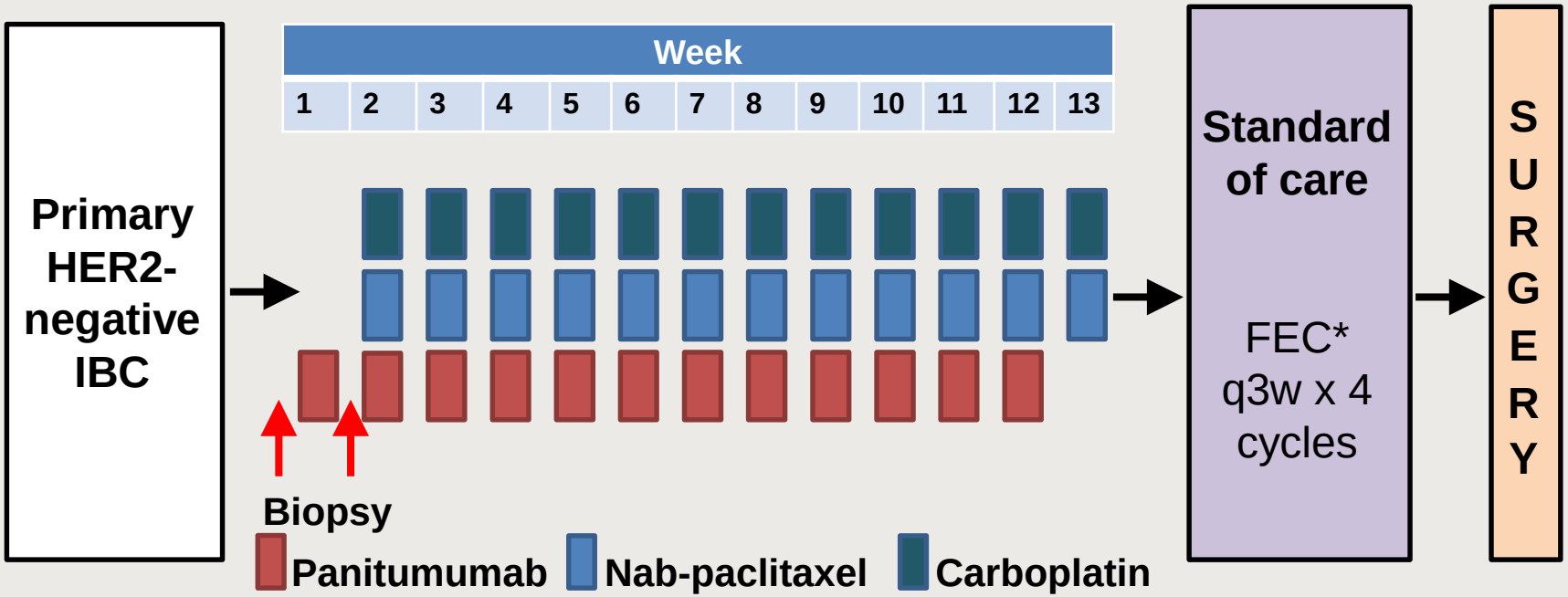
Masuda H, Brewer TM, et al. PubMed PMID: 24351399; PMCID: 3905780.

Biomarker Study



*FEC: Fluorouracil (500 mg/m^2), Epirubicin (100 mg/m^2), Cyclophosphamide (500 mg/m^2), every 3 weeks

EGFR, pEGFR, pAKT,
pMAPK, p27, EMT markers
RNA-seq
Multiplex imaging

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Expression of Candidate Proteins at Baseline and Week 2 and Change in Expression of Candidate Proteins between Baseline and Week 2 by Patient pCR Status [a]

	No pCR (N=26)		pCR (N=11)		
Variable	N	Median (range)	N	Median (range)	P Value
EGFR					
Baseline	18	0 (0-300)	5	120 (0-300)	.14
Week 2	3	285 (20-300)	4	105 (10-285)	.48
Change	3	0 (0-265)	2	7.5 (-15-30)	.77
pEGFR					
Baseline	**7**	**60 (20-300)**	**4**	**160 (160-300)**	**.05**
Week 2	**6**	**225 (30-300)**	**4**	**110 (0-240)**	**.28**
Change	**6**	**185 (-30-280)**	**4**	**-50 (-300-80)**	**.09**
E-cadherin					
Baseline	12	170 (0-300)	7	5 (0-300)	.49
Week 2	6	300 (300-300)	4	300 (180-300)	.31
Change	6	90 (0-300)	4	89.5 (0-300)	1.00
Vimentin					
Baseline	9	0 (0-210)	7	30 (0-60)	.31
Week 2	5	15 (0-270)	4	40 (5-270)	.38
Change	4	9.5 (0-110)	4	25 (-25-210)	.66
COX-2					
Baseline	**12**	**115 (0-300)**	**7**	**240 (150-300)**	**.05**
Week 2	**6**	**200 (80-300)**	**4**	**160 (80-300)**	**.66**
Change	**6**	**15 (-140-240)**	**4**	**-85 (-160-140)**	**.59**
Nodal					
Baseline	11	240 (70-300)	7	285 (80-300)	.58
Week 2	6	250 (0-300)	4	180 (160-300)	.91
Change	5	0 (-100-120)	4	0 (-100-80)	1.00

[A] Gene expression in patient samples was measured by immunohistochemical staining before (baseline) and after (week 2) the first dose of PmAb.

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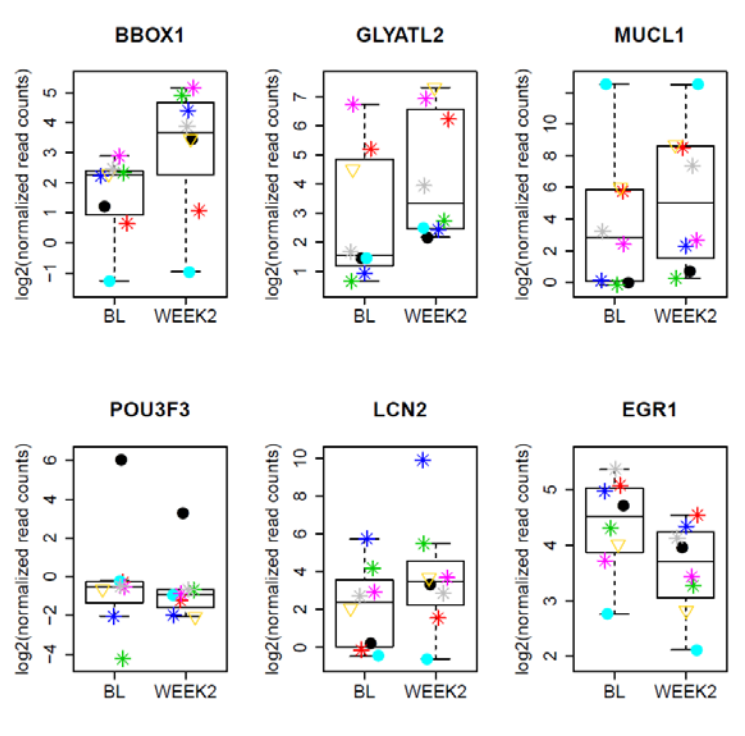
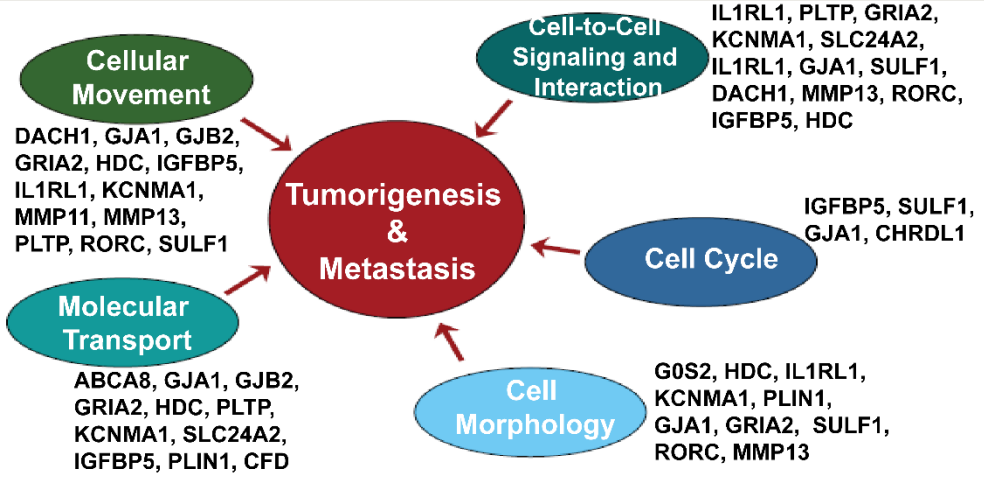
Genes differentially expressed after PmAb treatment by RNA-Seq analysis

Candidates of PmAb-regulated genes in IBC patients with TN-IBC

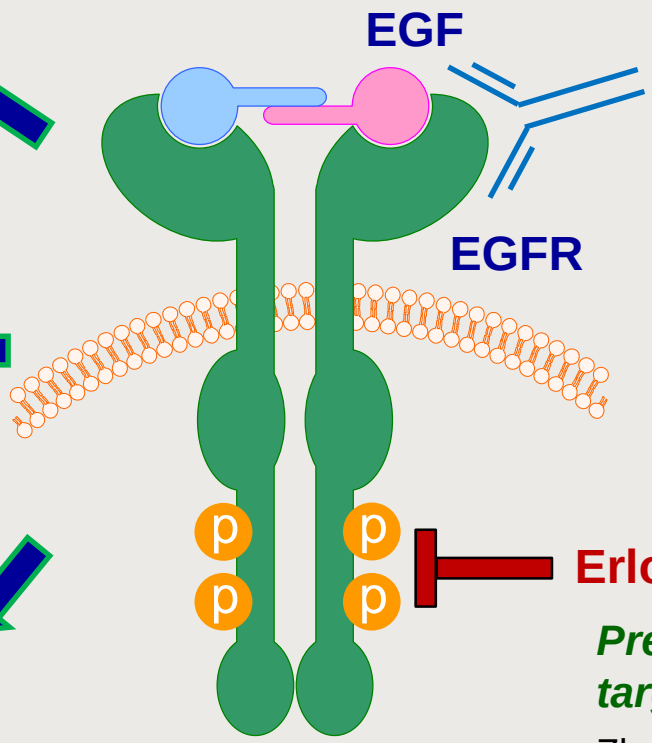


Molecular and cellular function of PmAb-regulated genes in IBC patients with HR+/HER2- subtype



Genes whose change in expression after PmAb treatment predicting pCR status have not been identified yet.

Conclusions and Future Directions



Inflammation and cancer stem cells

Predictive biomarker

Tumor microenvironment

Panitumumab clinical trials

Single-arm trial in patients with HER2-negative IBC

Randomized trial in patients with TN-IBC

Erlotinib

Preclinical study of targeting EGFR in IBC

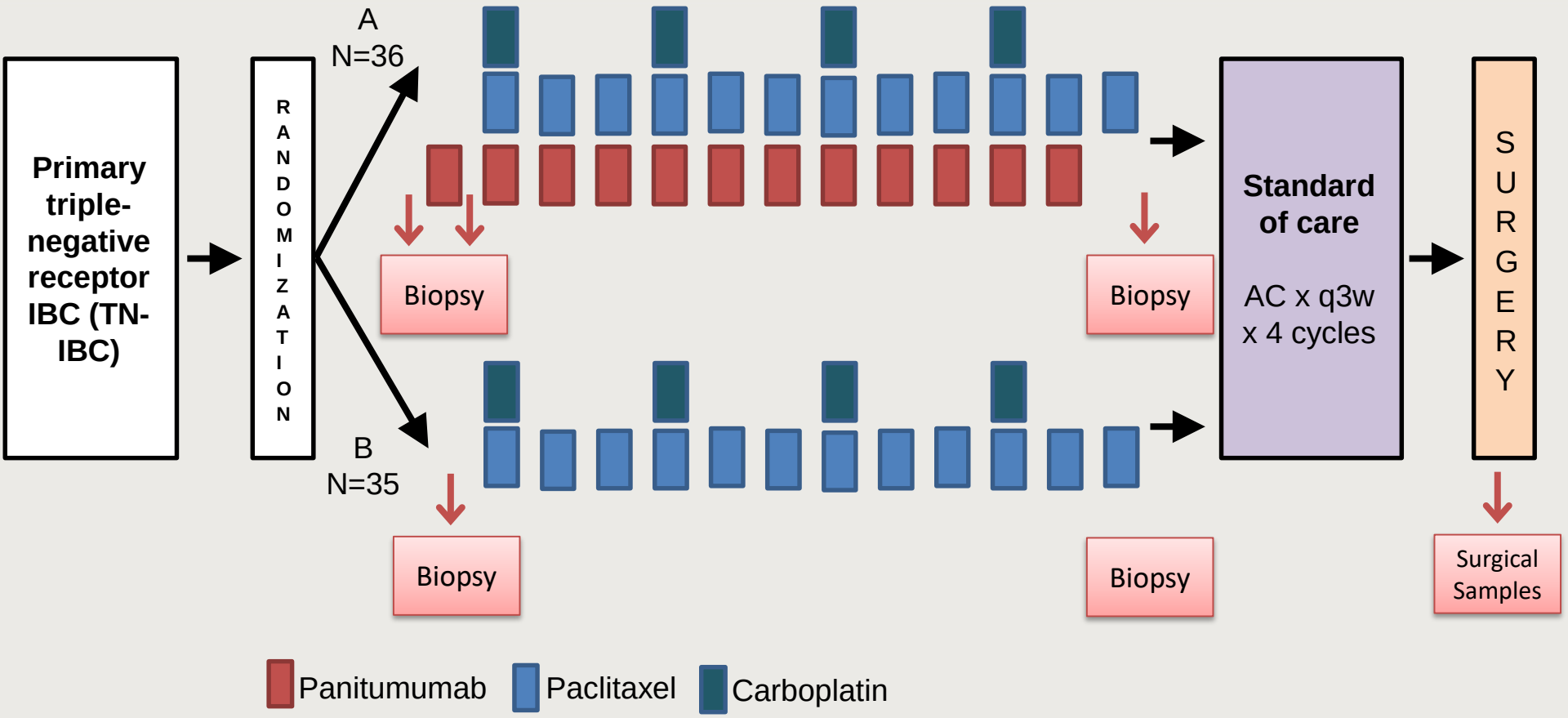
Zhang D, et. al., *Clin Cancer Res* 2009; 15: 6639-48.

Enhance the therapeutic efficacy of EGFR-targeted therapy in IBC

COX2/Nodal/CSC, microenvironment changes, chemokine, cytokine N=36, 72 samples

Arginine methylation, N=72, 72 samples

RNA seq Baseline, N=72, Post PmAb N=36, Residual = 60



Randomized Phase II study of panitumumab and neoadjuvant chemotherapy (PmAb/NAC) in patients with triple negative receptor (TN)-IBC.

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- State of Texas funding for research of rare and aggressive breast cancers
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Celgene

AMGEN

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We are all part of the cure

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Paul H Levine
Melanie Royce

Other Collaborators

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Kazuo Shirakawa

and many, many others

Patients with IBC who participated in the Study

Any Questions?

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