Mechanisms of resistance to Her2 inhibitors

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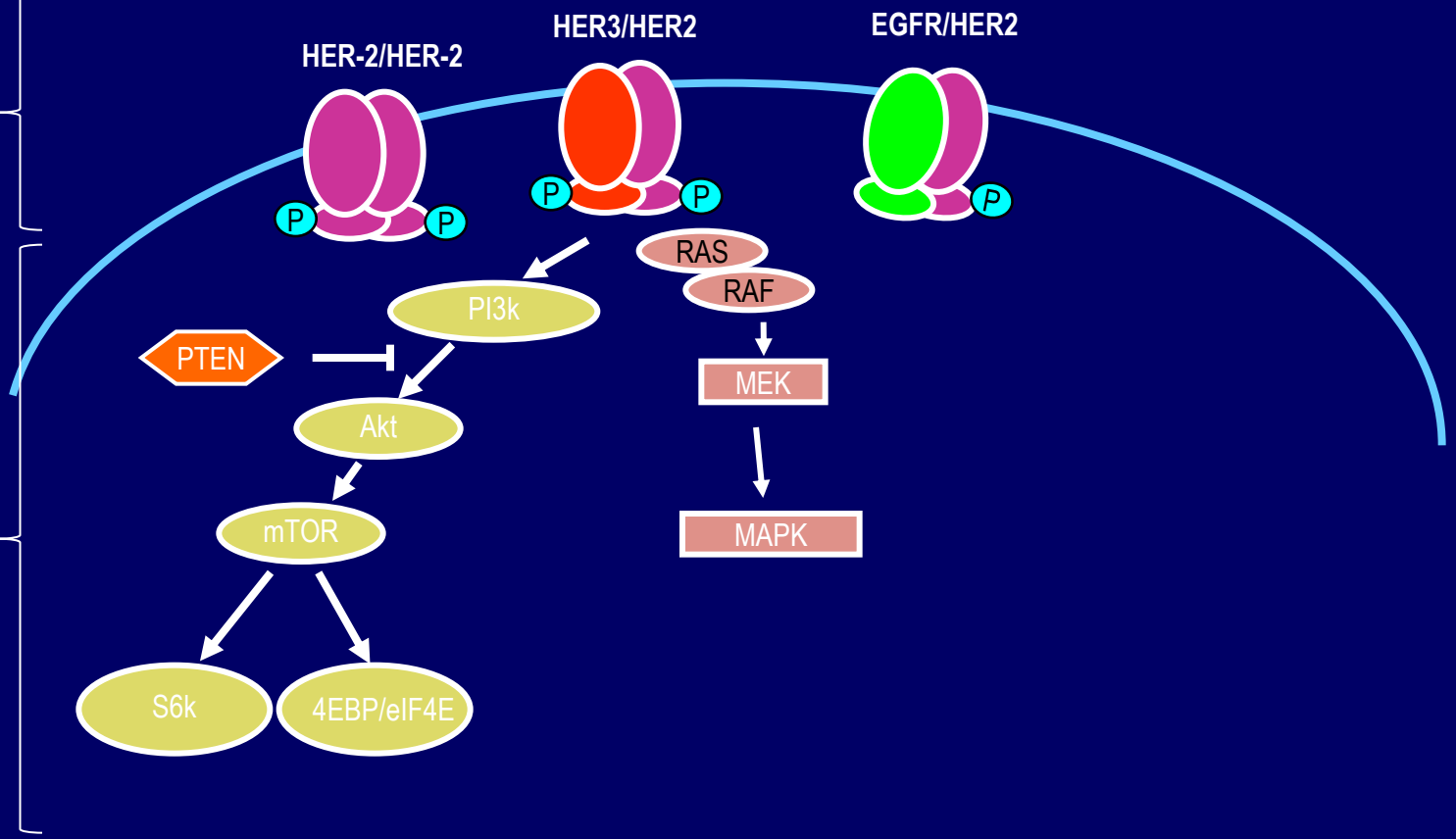
Outline

- **ERBB2: a driver of oncogenesis**
- **Is Her2 status predictive for the sensitivity to Her2 inhibitor ?**
- **Dual Her2 inhibitor to optimally block Her2**
- **PI3K/mTOR activation as mechanism of resistance to optimal Her2 blockade**
- **Combining immunotherapeutics and anti-Her2**

Her2 signaling

Tyrosine kinase:
Truncated Her2
Activation IGF1R/Her3

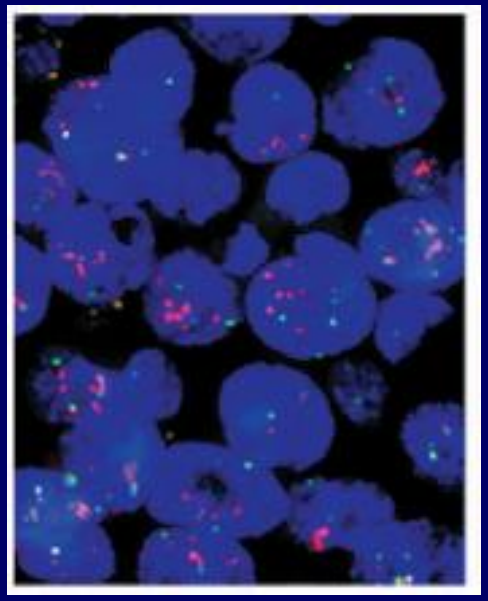
Downstream signalling



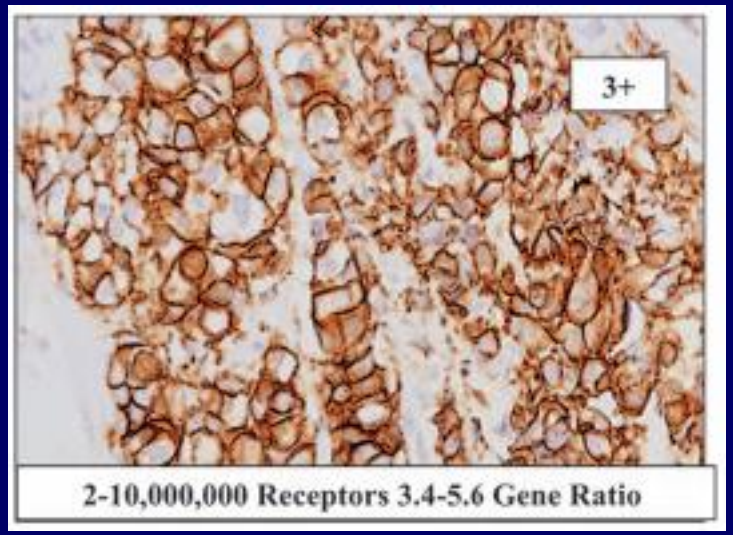
ERBB2-amplified breast cancers

10-15% breast cancer

Amplification

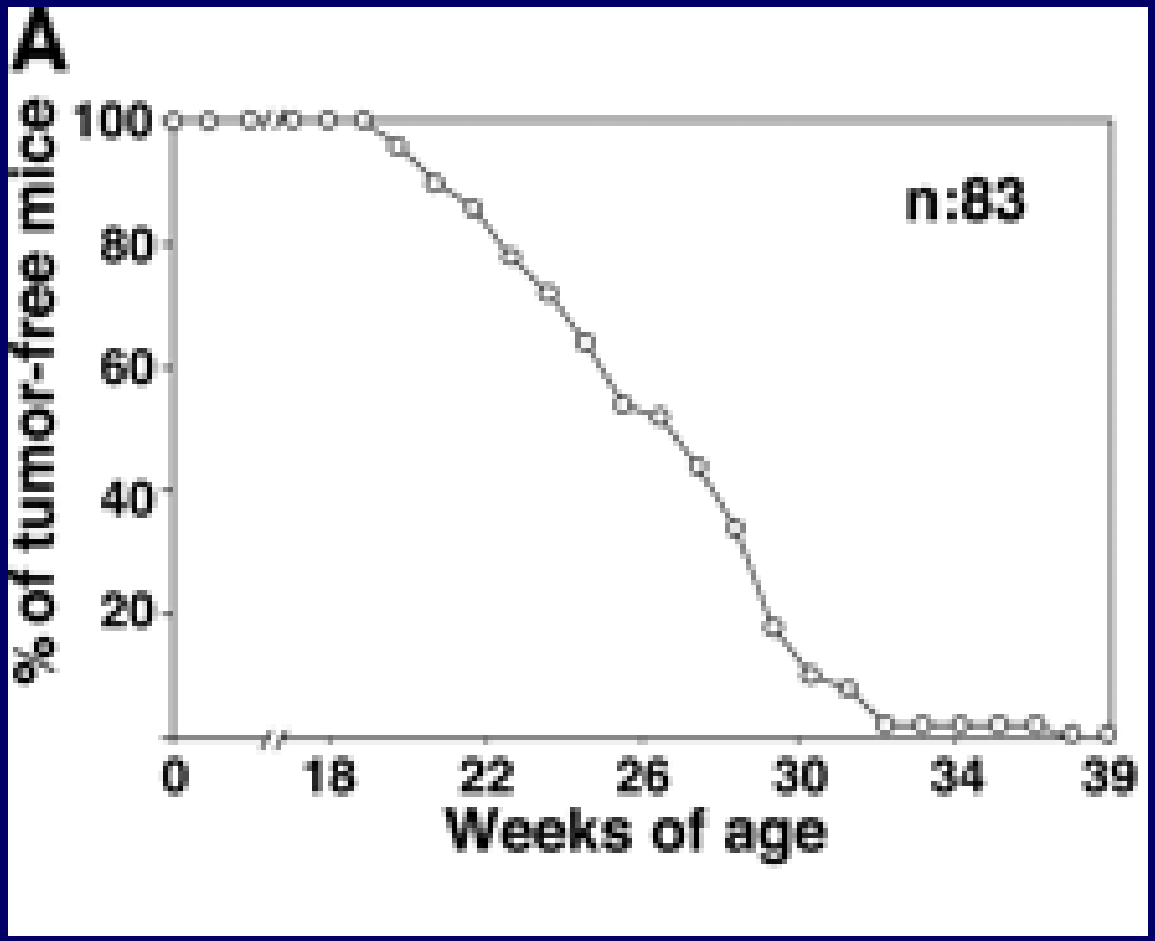


Expression



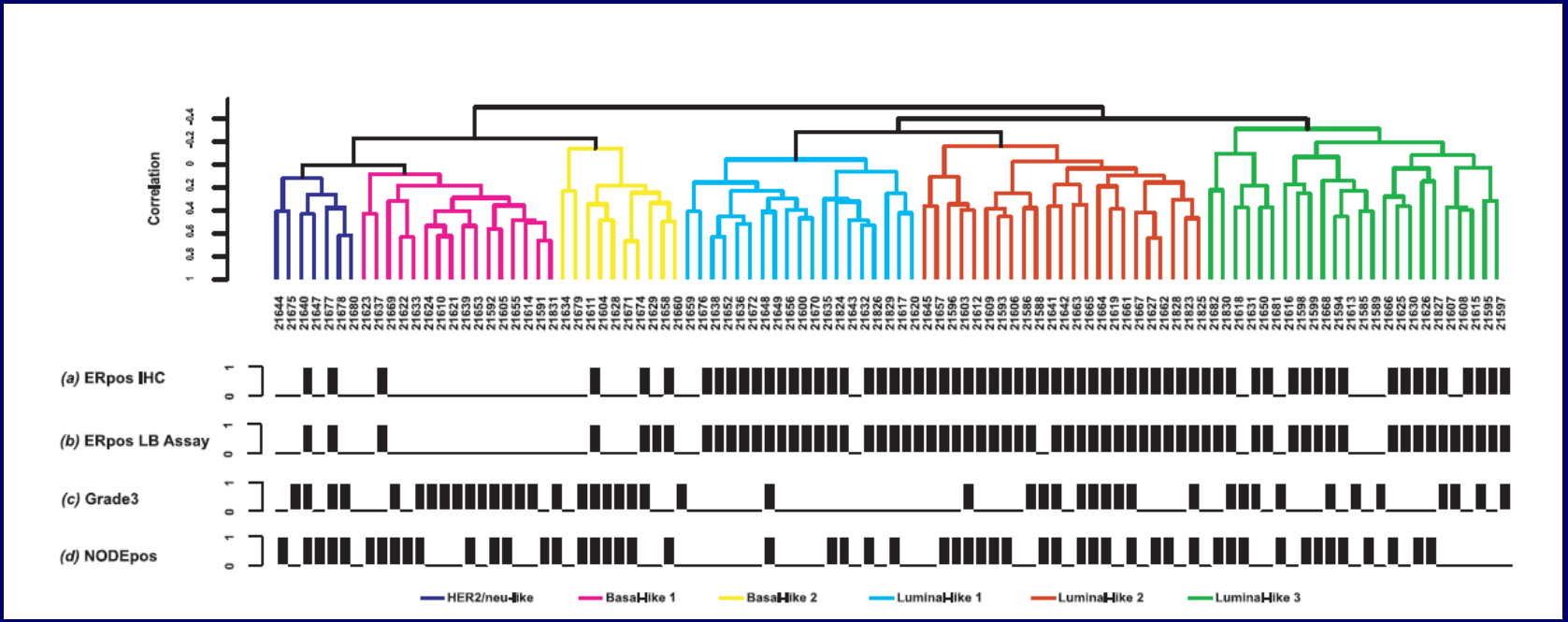
Her2: discovered by Padhy/weinberg (Cell,1982)

ERBB2-transgenic mice develop cancers



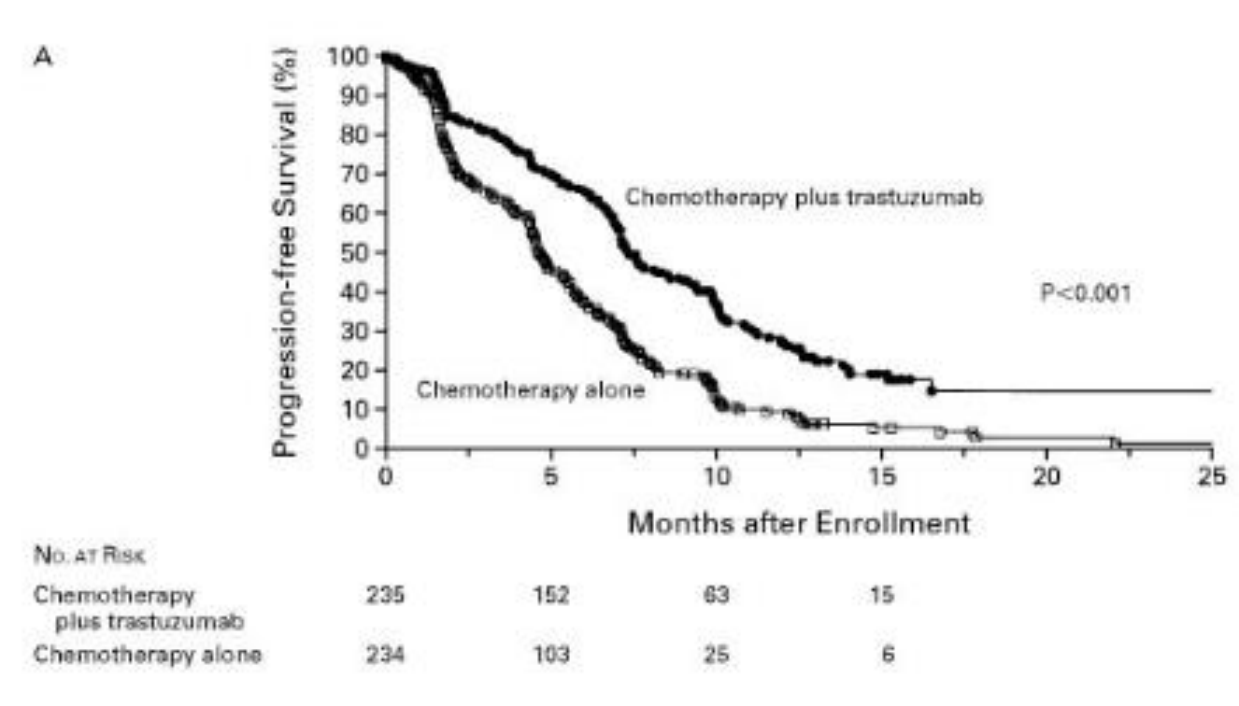
Takeushi, Cancer Res, 2004

ERBB2 subtype



Her2+/ER- is a different subtype than Her2+/ER+

Trastuzumab: Anti-Her2 antibody



High efficacy in patients with Her2-overexpressing breast cancer but…
Treatment resistance occurs in most patients with Her2+++ metastatic breast cancer and half of the patients at risk of relapse:
How to predict, avoid or to delay resistance ?

Slamon, New England J Medicine, 2001

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Does ERBB2 expression / amplification predict trastuzumab ?
Metastatic setting

Table 2. Tumor Response in Assessable Patients

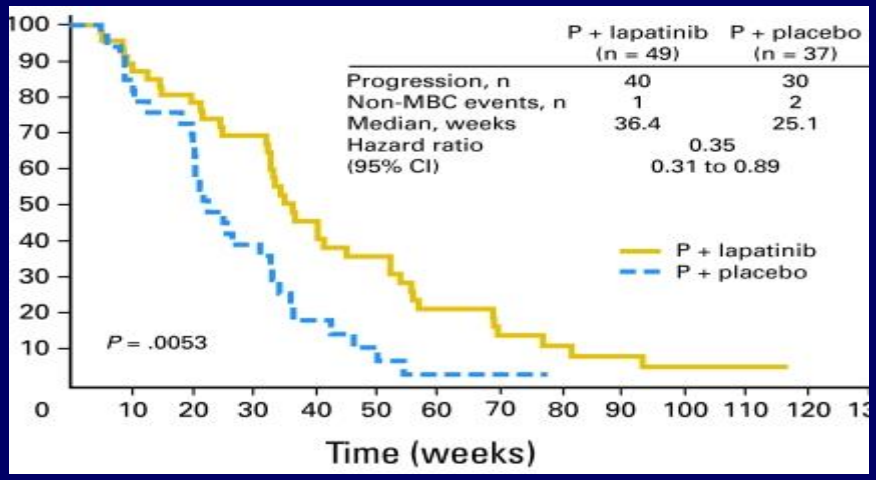
Subset	Objective Response		Clinical Benefit*	
	No.	%	No.	%
All assessable patients, n = 111 (95% CI)	29	26 (18.0-34.3)	42	38
Trastuzumab				
2 mg/kg weekly, n = 58 (95% CI)	14	24 (13.1-35.2)	20	34
4 mg/kg weekly, n = 53 (95% CI)	15	28 (16.2-40.4)	22	42
Estrogen receptor				
Positive, n = 52	12	23	19	36
Negative, n = 54	16	30	21	39
Progesterone receptor				
Positive, n = 46	10	22	16	35
Negative, n = 57	18	32	24	42
Lung or liver metastases, n = 74	16	22	24	32
Disease-free interval				
≤ 12 months, n = 30	6	20	9	30
> 12 months, n = 81	23	28	33	41
Previous adjuvant doxorubicin, n = 57	18	32	23	41
Previous transplant, n = 14	5	36	6	43
HER2				
3+, n = 84	29	35	40	48
2+, n = 27	0	0	2	7
FISH				
Positive, n = 79	27	34	38	48
Negative, n = 29	2	7	3	10

*Clinical benefit = complete, partial, or minor response or stable disease > 6 months.

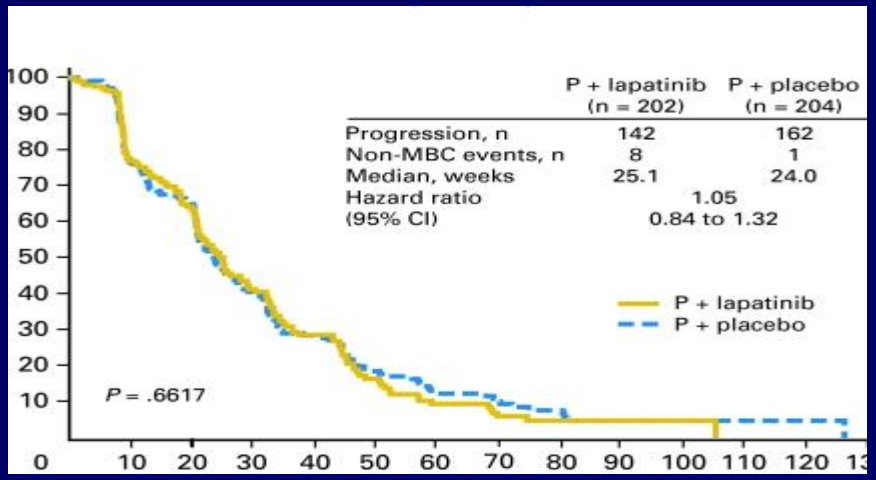
Vogel, JCO, 2002

Does ERBB2 expression / amplification predict lapatinib ? Metastatic setting

Amplification ERBB2 (15%)



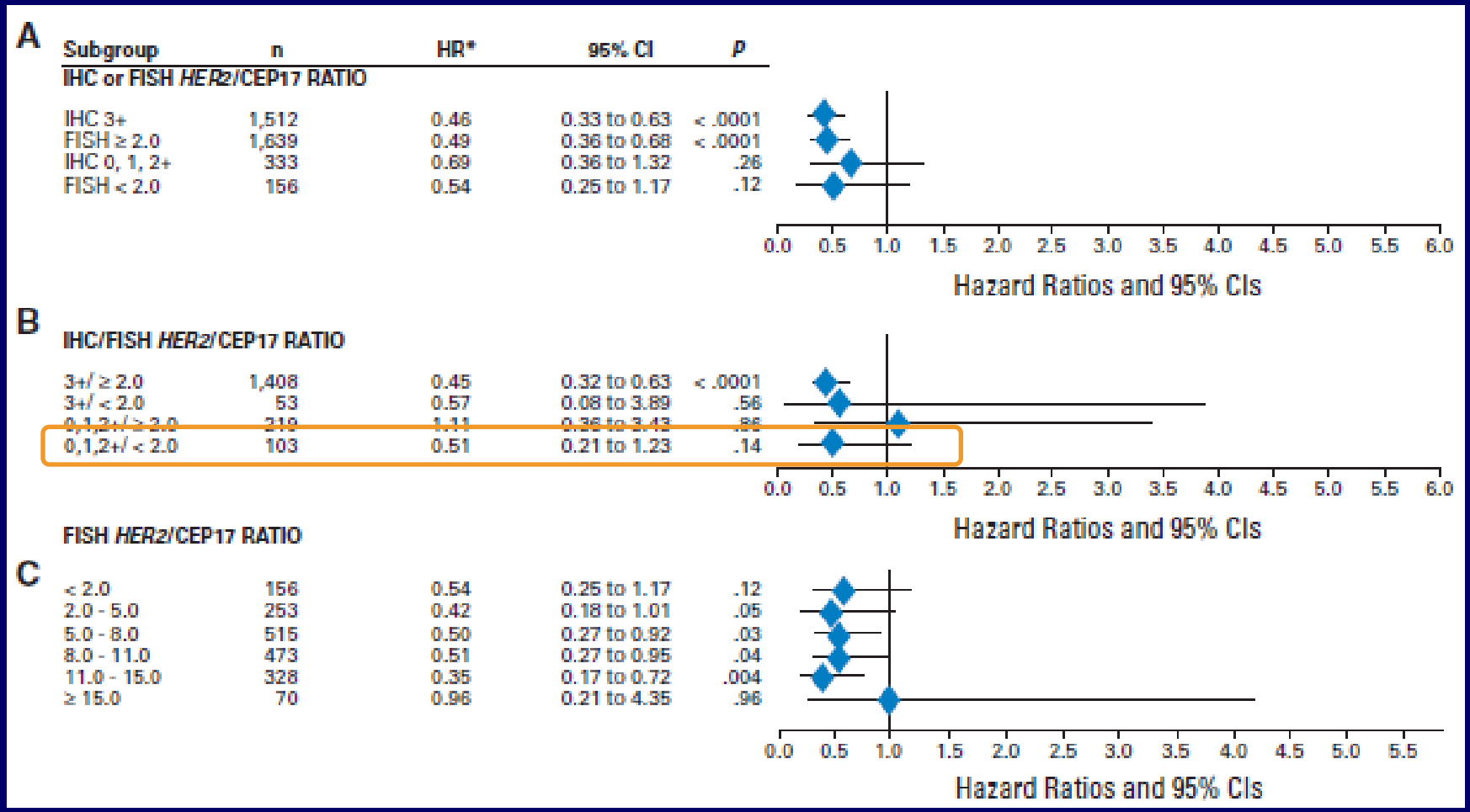
ERBB2 normal (85%)



Di Leo, J Clin Oncol

Does ERBB2 expression / amplification predict trastuzumab ? Adjuvant setting

Patients included to be Her2+++
Her2 status re-assessed in a retrospective analysis



Perez, J Clin Oncol

Does ERBB2 expression / amplification predict trastuzumab ? Adjuvant setting

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Table 1. Relative Risks of Disease Progression and Death among Patients in the ACTH Group as Compared with the ACT Group.*

End Point and Central HER2 Assay†	ACT	ACTH	Relative Risk (95% CI)	P Value	P Value for the Interaction
	no. of events/total no. of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37–0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14–0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43–0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01–0.64)	0.017	

Paik, NEJM

Take home message

- In the metastatic setting, data from phase II and phase III suggest that Her2 expression is predictive for the efficacy of trastuzumab and lapatinib respectively

- In the adjuvant setting, two retrospective analyses from randomized trials report that patients with Her2-normal BC could benefit from trastuzumab
  - NSABP trial is currently validating (or not) this hypothesis

- Message: NEED to validate lack of activity in target-negative cohorts before moving full development +++

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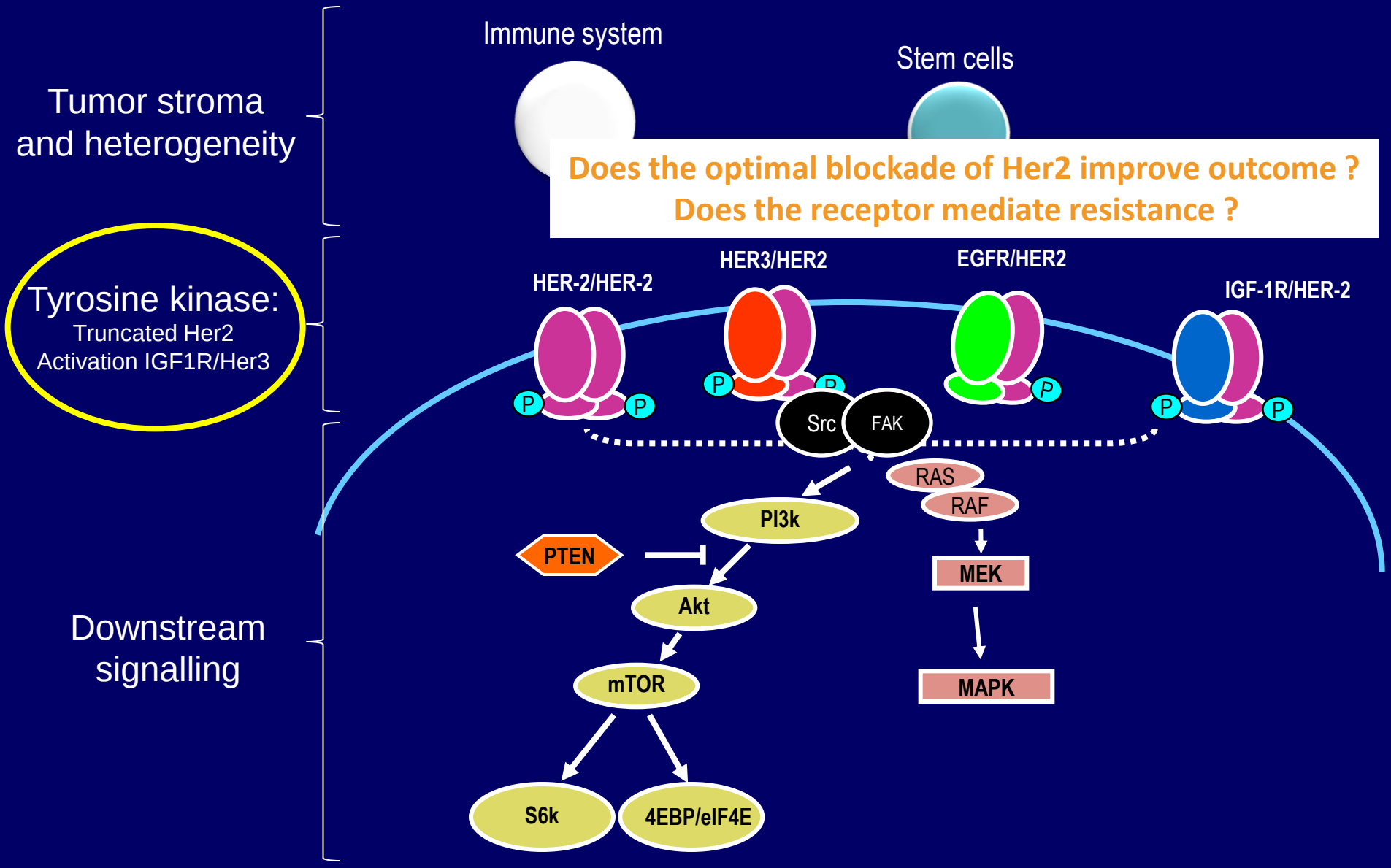
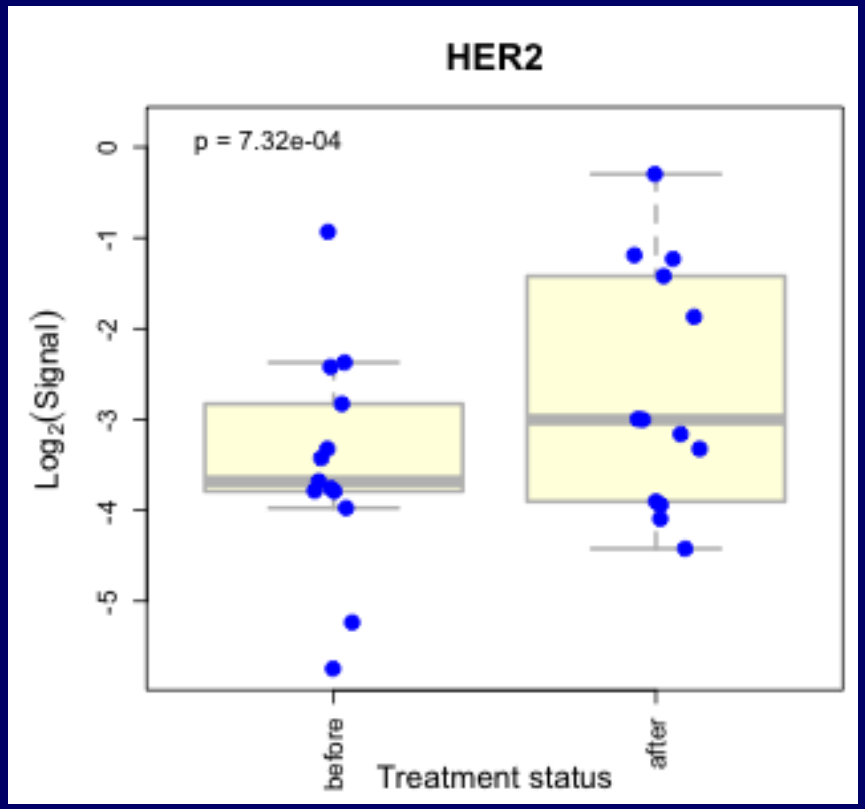
Her2 signaling, trastuzumab activity: Key players



Dual blockade on Her2 improves efficacy endpoints

Drug	Characteristics	Efficacy
Lapatinib	Tyrosine kinase inhibitor	Dual inhibition improves outcome in metastatic setting (Blackwell, JCO) Dual inhibition increase pCR rates in neoadjuvant setting (Baselga, Lancet) Non-significant improvement of DFS in the adjuvant setting (Piccart, JCO)
pertuzumab	Anti Her2 antibody	Dual inhibition combined with docetaxel improves outcome in first line setting (Swain, NEJM) Dual inhibition increases pCR rates in the neoadjuvant setting (Gianni, Lancet Oncol)
two fold increase in trastuzumab doses ?????		*??????????*

Short term adaptation to trastuzumab single agent



Trastuzumab exposure increases Her2 expression

Long term adaptation to trastuzumab (2ry resistance)

ERBB2 mutations

Prior trastuzumab	Mutation	Description	Number of mutant reads	Number of reference reads	Allelic Fraction	Present in Primary Tumor?	Receptor Status of Metastatic Biopsy
No	p.L374V	Novel mutation	26	1769	1%	Not Available	HER2+ / ER- (Primary was HER2+ / ER+)
No	p.L403V	Novel mutation	8	207	4%	Not Available	HER2+ / ER- (Primary was HER2- / ER+)
Yes	**p.D742N**	**Novel kinase domain mutation**	20	336	6%	No	HER2+ / ER+
Yes	**p.L755S**	**Known activating kinase domain mutation**	79	127	38%	Yes (23%)	HER2+ / ER+
Yes	**p.L755S**	**Known activating kinase domain mutation**	173	227	44%	Yes (25%)	HER2+ / ER-
Yes	**p.L755S**	**Known activating kinase domain mutation**	50	102	33%	Yes (25%)	HER2+ / ER+
Yes	p.D1013H	Novel mutation	46	3465	1%	Not Available	HER2+ / ER+
	p.S1051C	Novel mutation	43	2482	2%		
No	p.L1109V	Novel mutation	122	4346	3%	Yes (4%)	HER2+ / ER+

As opposed to other models (EGFR, ALK, Braf), there are no evidence for Cancer evolution after resistance to trastuzumab
What about after dual blockade ?

Wagle, SABCS, 2014

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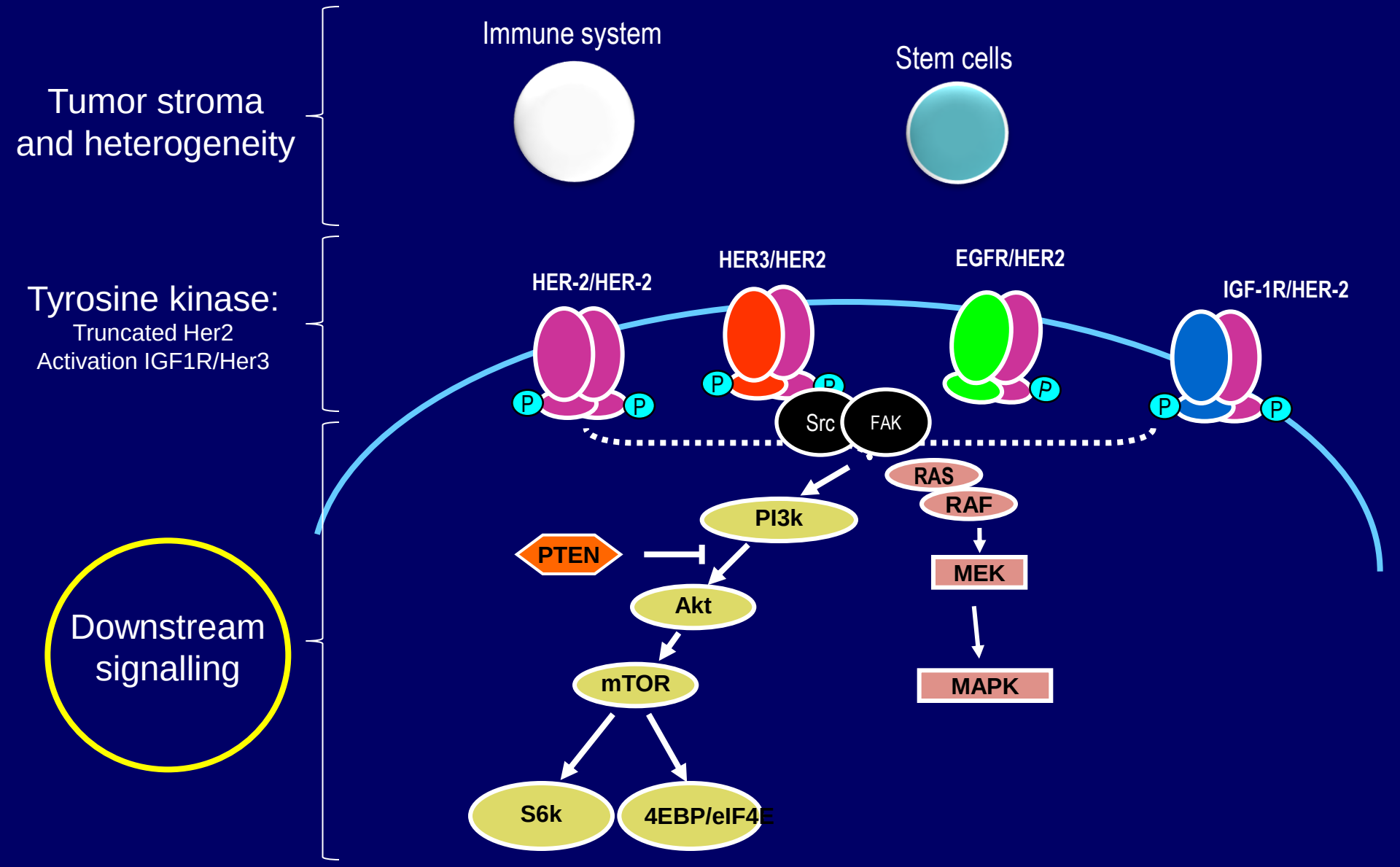
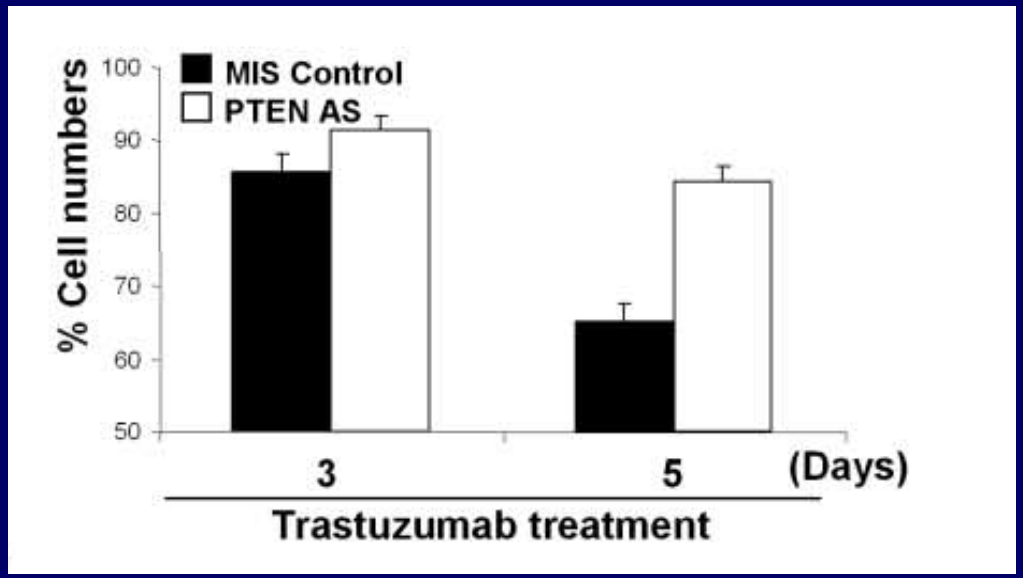
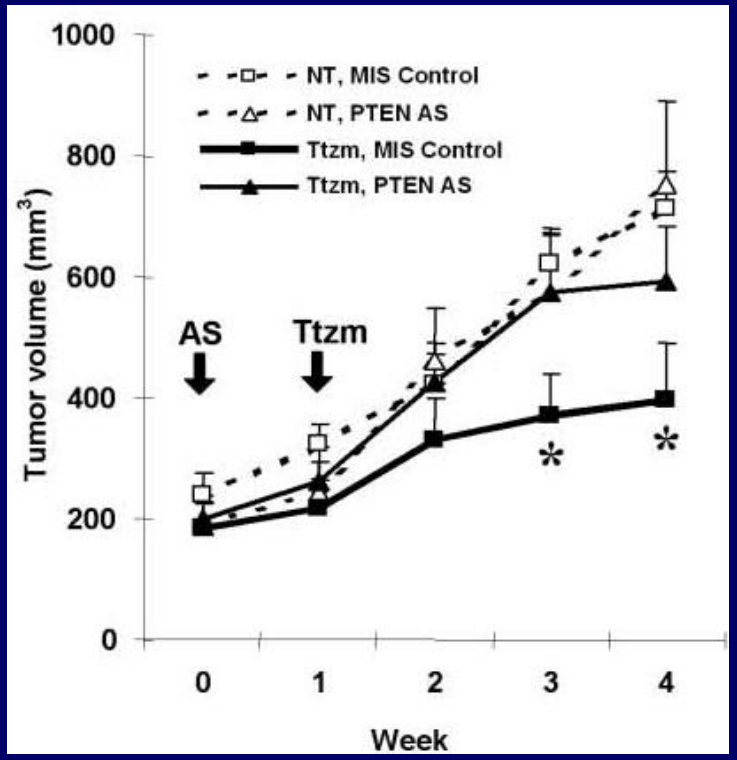


Does mTOR activation mediate resistance to trastuzumab ?

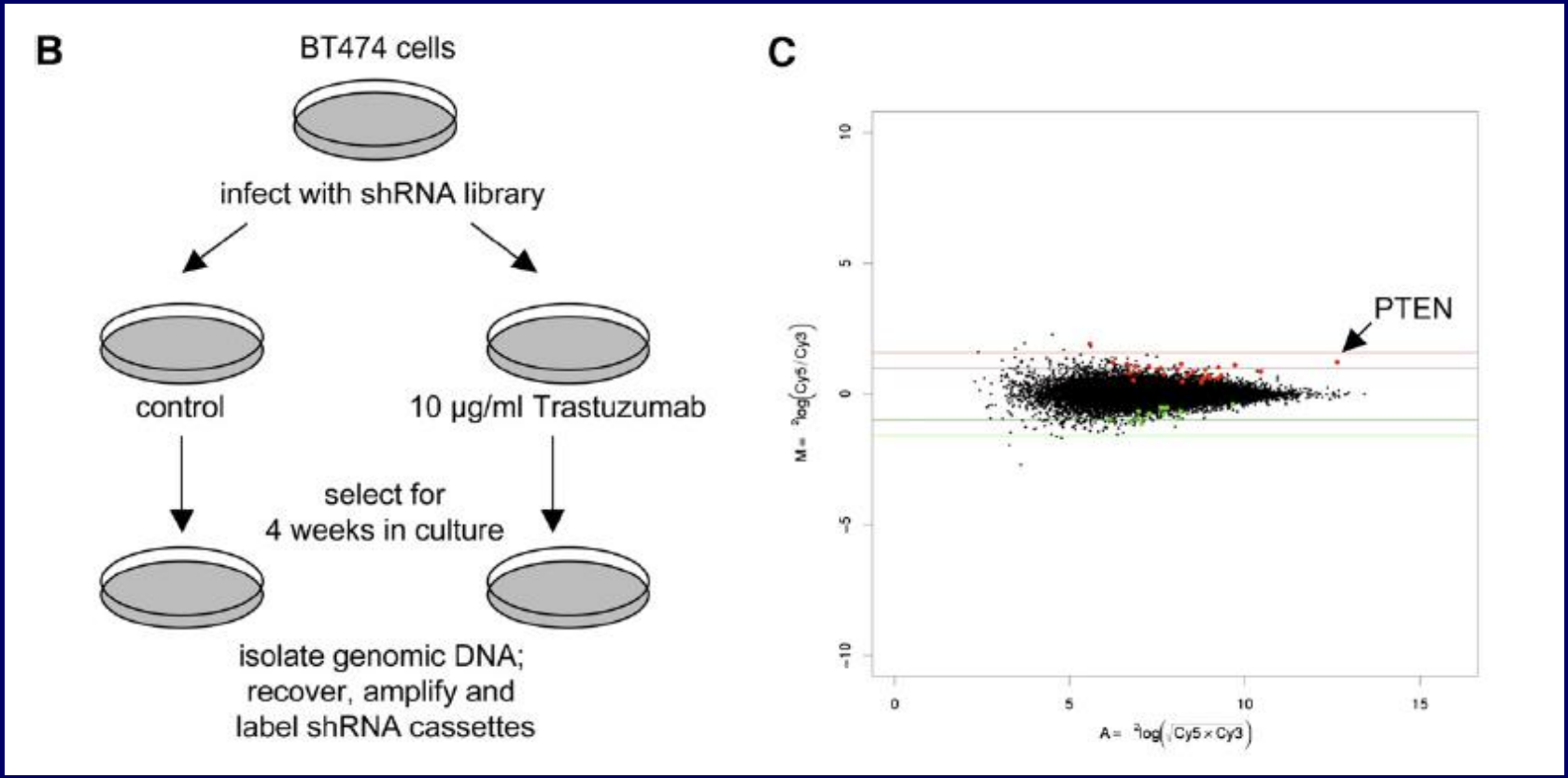




PTEN loss (leading to mTOR activation) mediates resistance to trastuzumab in vitro and in vivo

Nagata, Cancer Cell, 2004

Is it a predominant pathway ?



shRNA screening suggests that mTOR pathway is the dominant mechanism of resistance

Berns, Cancer Cell, 2007

Rationale for PI3Ki in HER2+ MBC

Frequency of mutations in PIK3CA

n = 547[1]	Mutation	
	PIK3CA	PTEN
All breast tumors	117/547 (21.4%)	2/88 (2.3%)
HER2+	17/75 (22.7%)	0/10 (0%)

n = 1502[2]	Alterations	
	PIK3CA Mutation	PTEN Loss
All breast tumors	356/1502 (23.7%)	435/1502 (29%)
HER2+	113/568 (19.9%)	114/568 (20%)

1. Stemke-Hale K, et al. *Cancer Res.* 2008;68(15):6084-6091. 2. Gardner H. Oncology Translational Laboratories, Novartis.

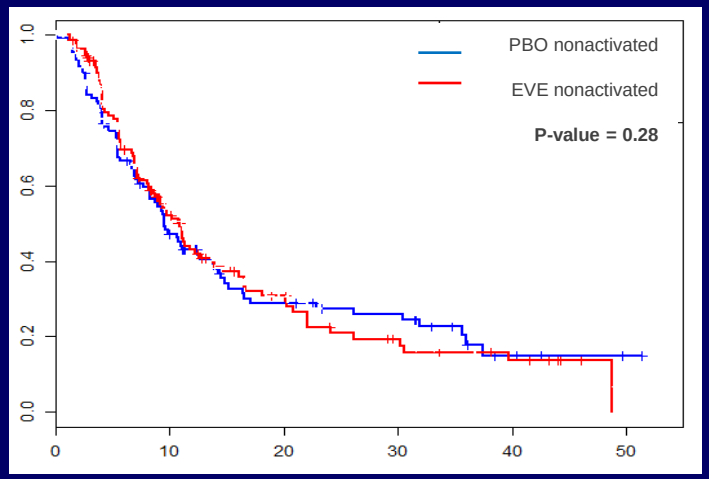
Does PIK3CA mutation / PTEN loss predict resistance to Her2 inhibitors ?

Drug	Setting	Results	Evidence supporting the data	References
Trastuzumab	Adjuvant	PTEN: not predictive PIK3CA mutation: not predictive	Retrospective analysis of single randomized trial	Perez, JCO Loi, JNCI
Trastuzumab / lapatinib	Neoadjuvant	PIK3CA mutations: predictive	Metaanalysis of clinical trials	Loibl, ASCO, 2015
Trastuzumab / pertuzumab	Metastatic first line	PIK3CA mutations: Poor outcome, not predictive	Retrospective analysis of single randomized trial	Baselga, JCO

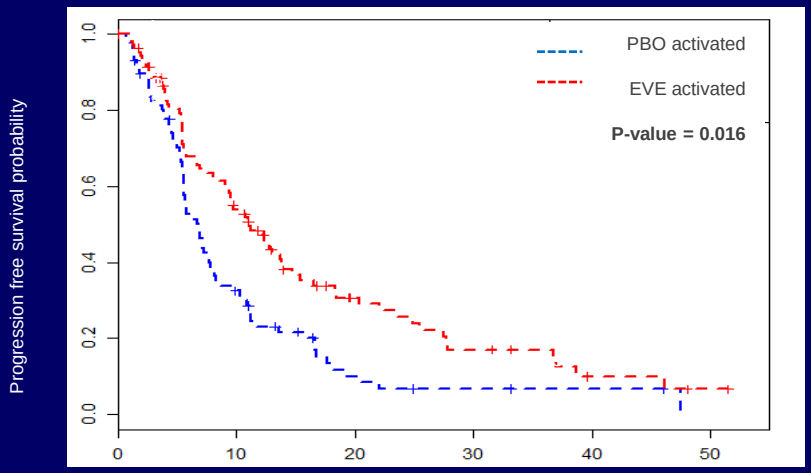
How to reverse resistance to trastuzumab in PIK3CA mutant BC ?

Everolimus efficacy (BOLERO1&3)

PIK3CA WT and PTEN normal



PIK3CA mut and/or PTEN loss



Interaction test, p=0.01

Slamon, ASCO, 2015

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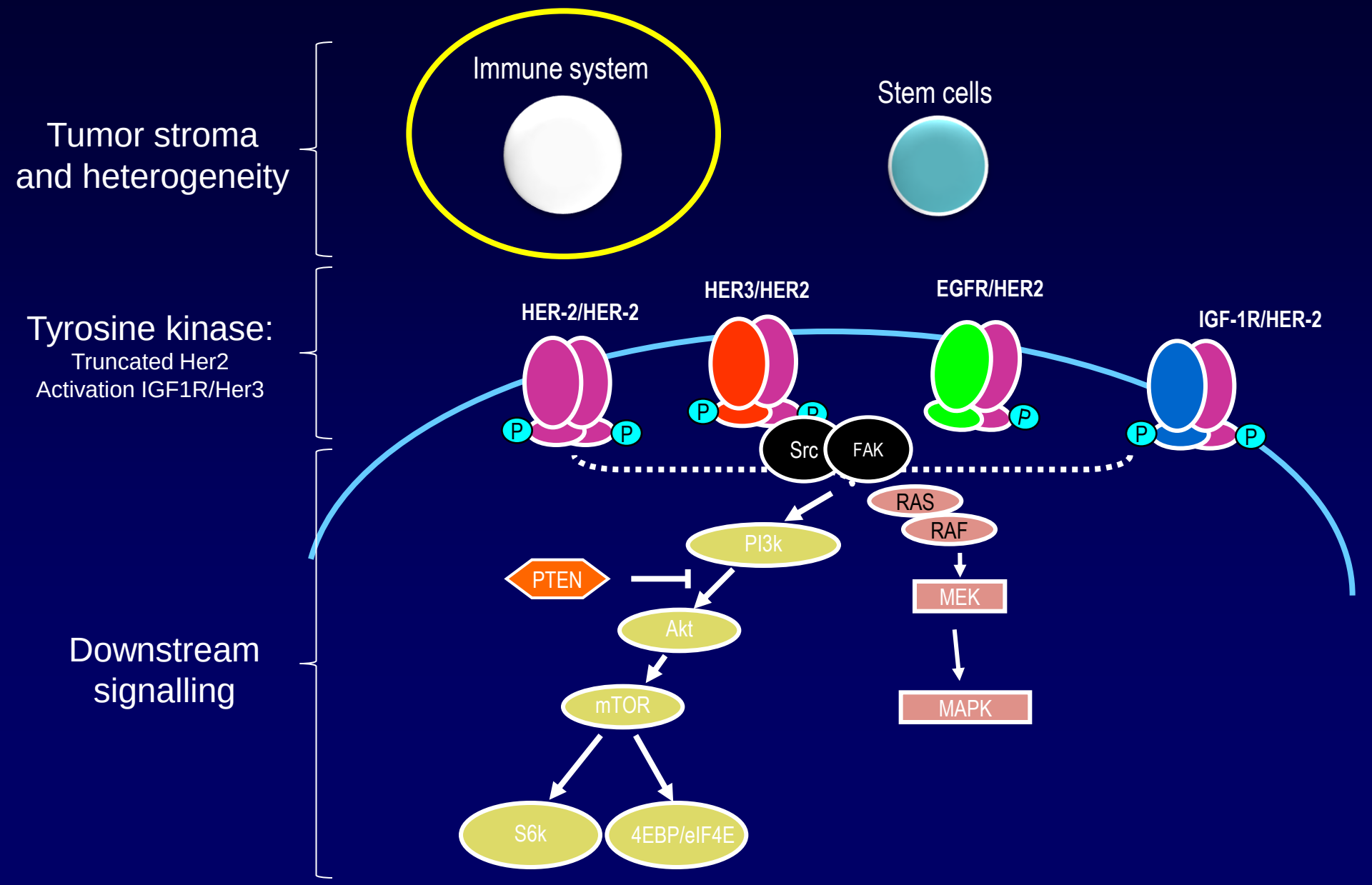
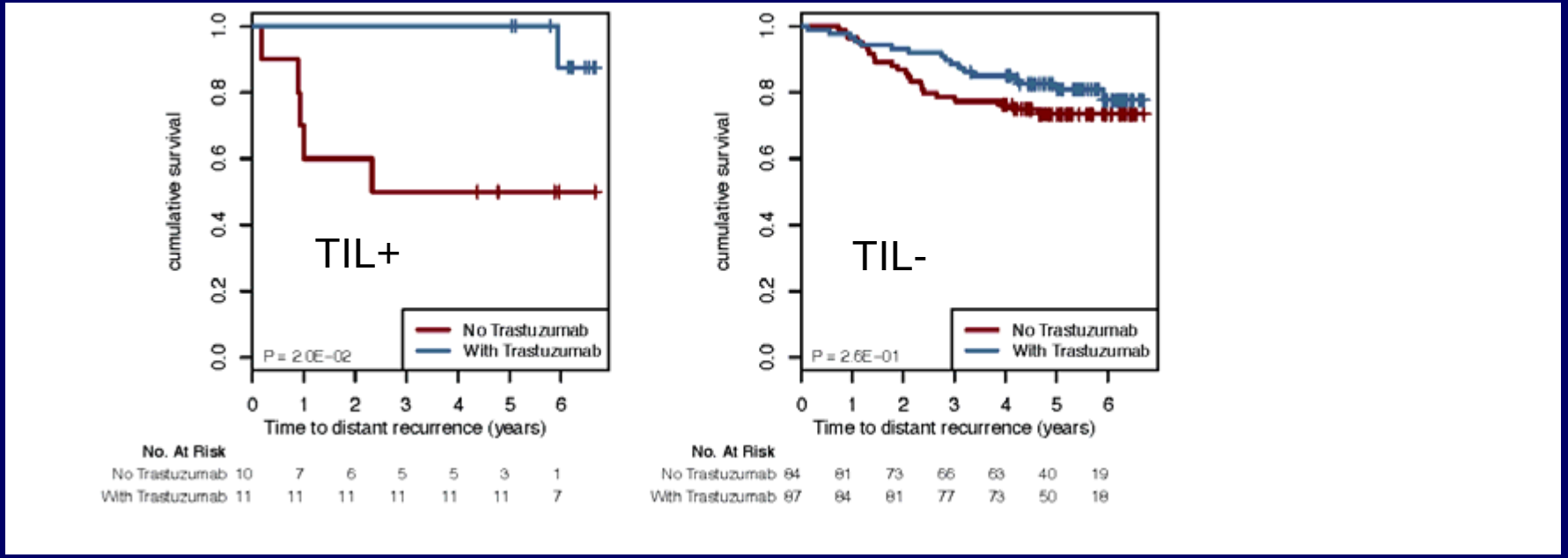
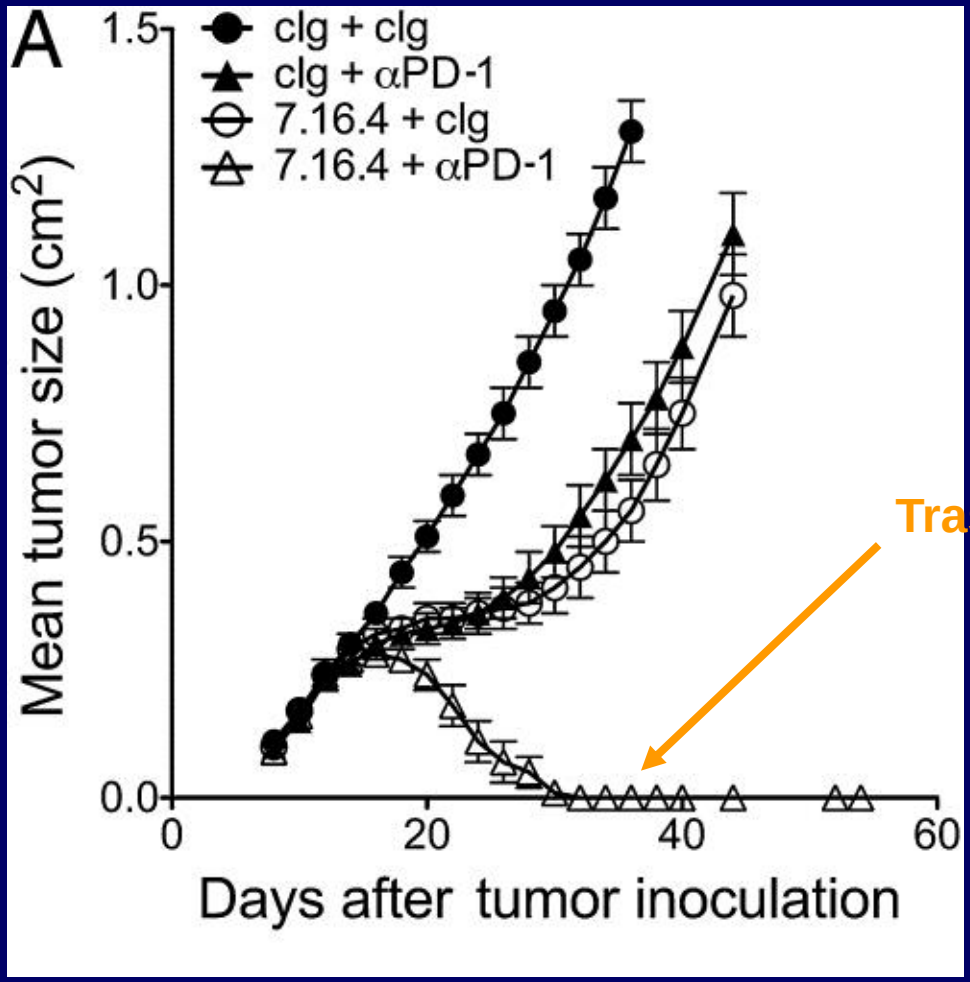


Lymphocytic infiltration assessed by HES and resistance to trastuzumab



Loi S, Annals of Oncol, 2014

Activating immune system to reverse resistance to trastuzumab



Trastuzumab + anti-PD-1

Stagg J, et al. *Proc Natl Acad Sci U S A*. 2011;108(17):7142-7147.

Conclusion

- **No validated biomarker of resistance**

- **Four strategies to overcome resistance:**
  - **Optimal targeting of the receptor (dual blockade)**
  - **PI3K/mTOR inhibition in patients with PIK3CA mutations**
  - **Immune checkpoints modulators**
  - **ER blockade**