



GOOD SCIENCE  
BETTER MEDICINE  
BEST PRACTICE

# Characterization of HER-2/neu breast cancer



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# Outline

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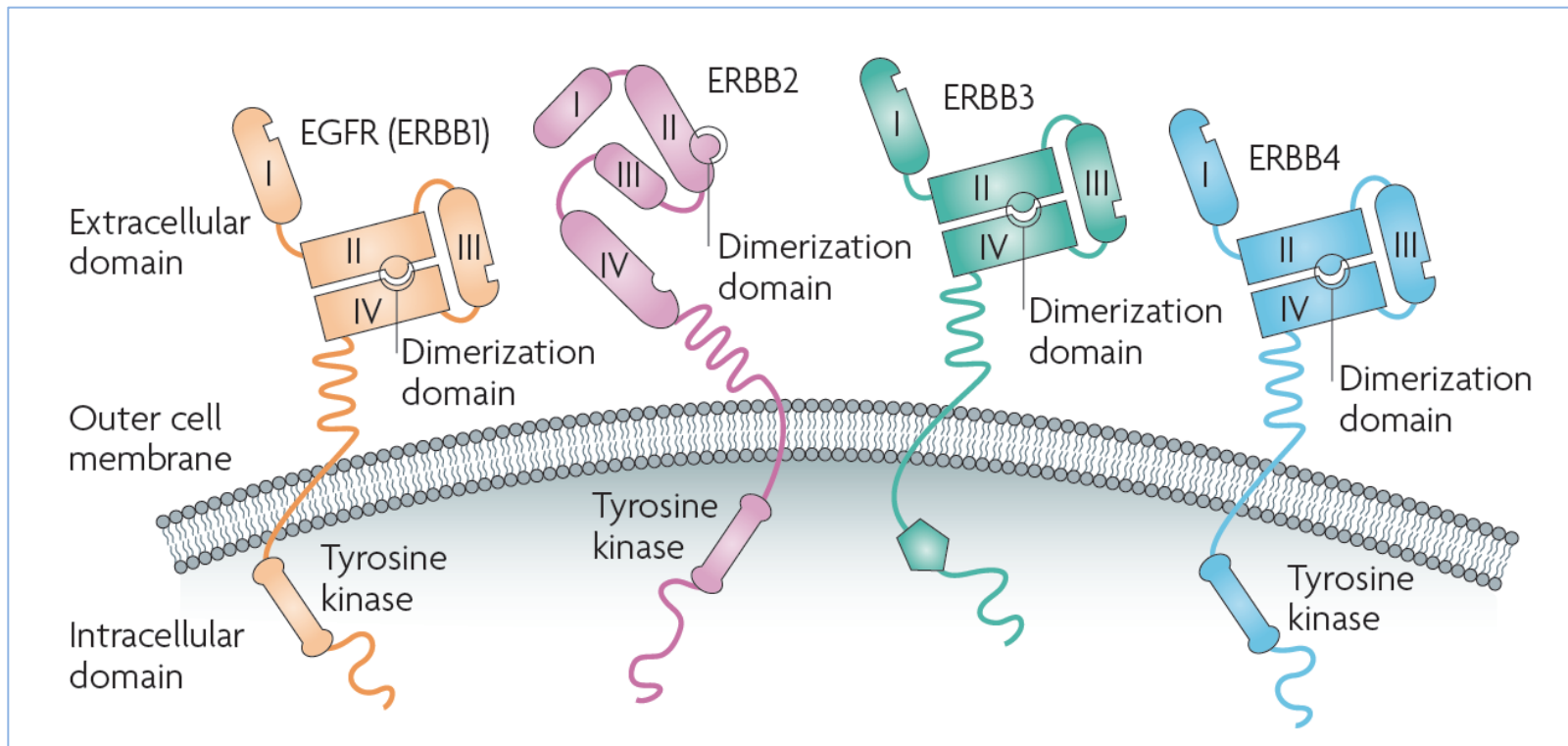
- Description of HER2 as a therapeutic target
- Anatomopathological features
- Genomic landscape: subclassification of HER2
- Identification of *ErBB2*-driven tumors
- Ongoing projects
- Summary

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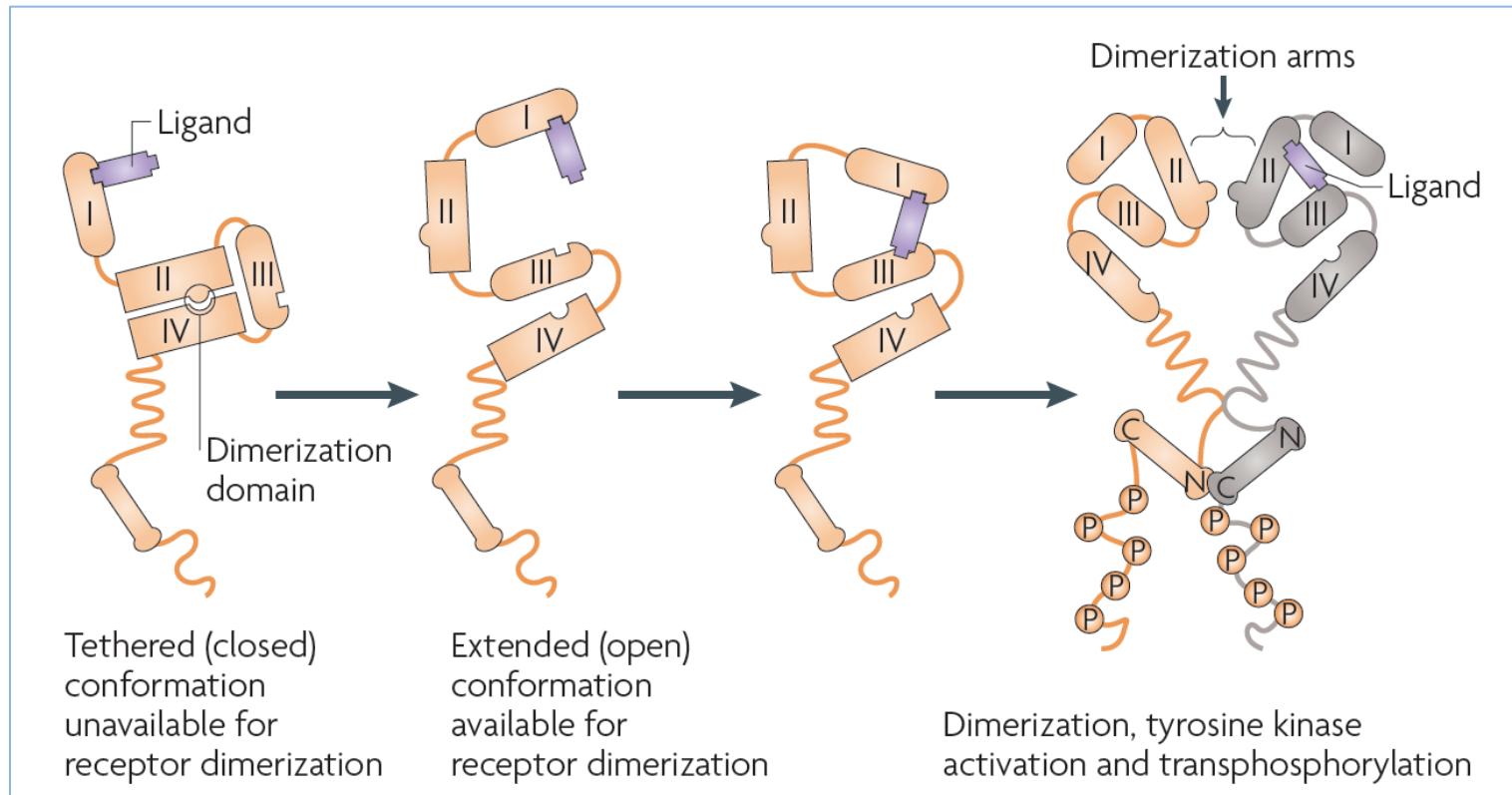
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# EGF Receptor family



*Baselga and Swain, Nat Rev Cancer 2009; 9:463*

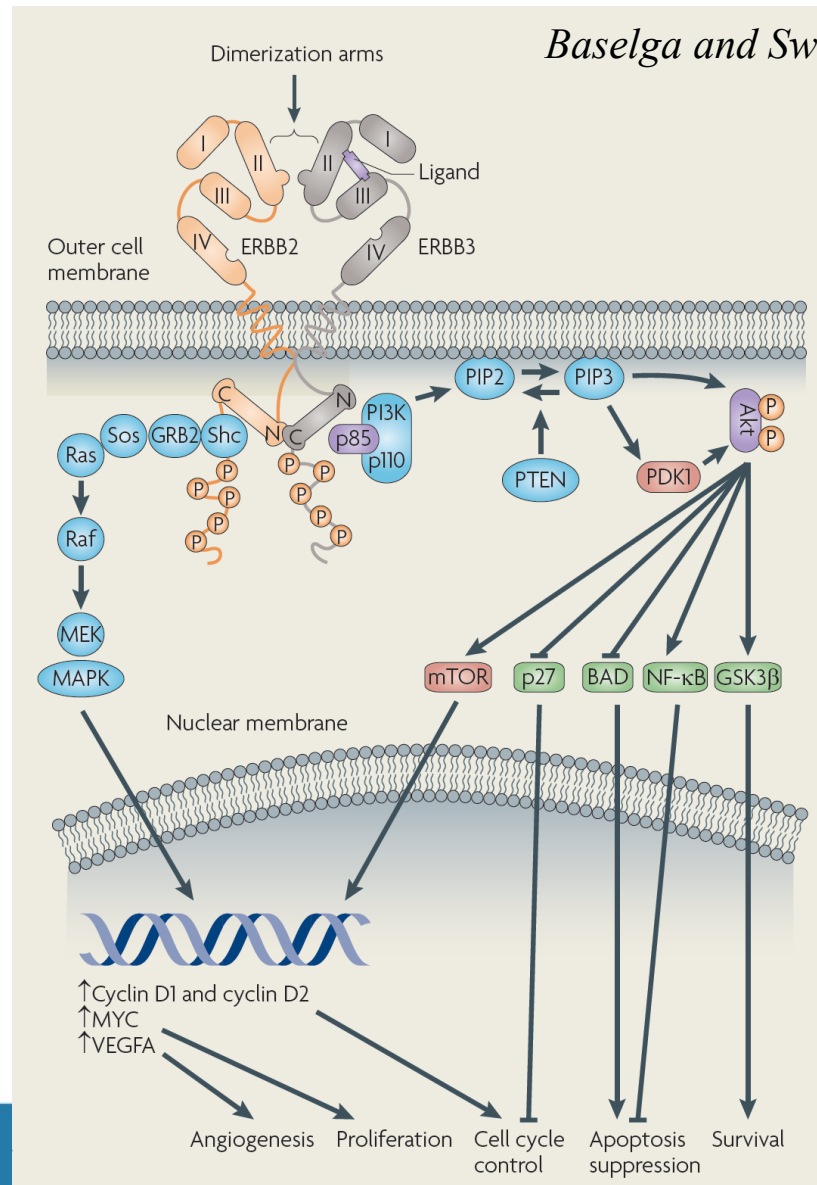
# Receptor dimerisation



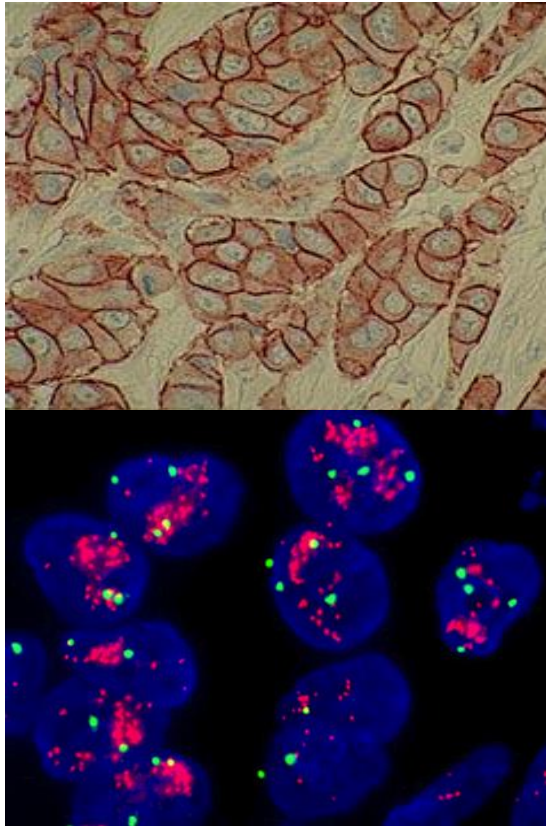
*Baselga and Swain, Nat Rev Cancer 2009; 9:463*

# HER2 signalling pathway

*Baselga and Swain, Nat Rev Cancer 2009; 9:463*



# HER2-positive breast cancer



Overexpressed/amplified in  
around 15-20% breast cancer

## Shortened Median Survival\*

HER2 positive	3 years
HER2 normal	6-7 years

\* Combined metastatic and adjuvant patients

Slamon et al. *Science*. 1987;235:177

Pauletti et al. *J Clin Oncol*. 2000;18:3651

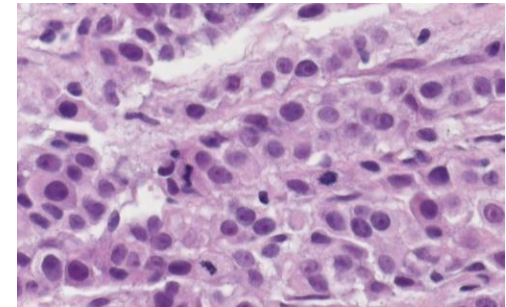
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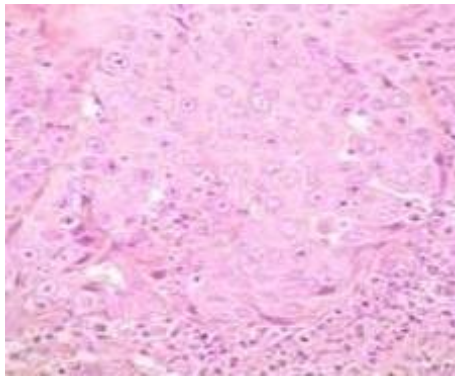
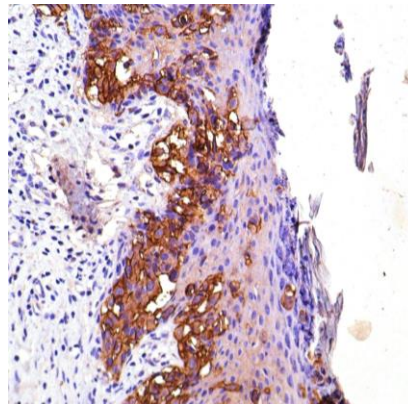
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# Anatomopathological features

- ILC lower HER2-positive rate (<10%) restricted to pleomorphic subtype



- Paget's disease



- Medullary carcinomas are typically HER2-negative

# Anatomopathological features

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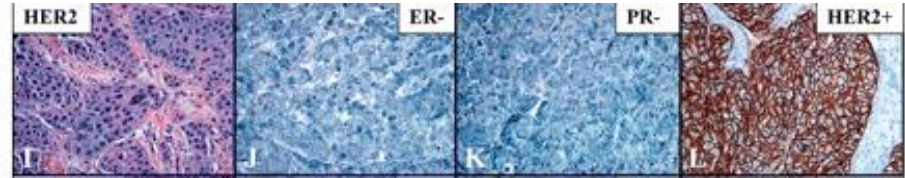
- high tumor grade,
- DNA aneuploidy,
- high cell proliferation rate,
- cell motility,
- tumor invasiveness,
- reduced apoptosis,
- progressive regional and distant metastases at presentation

*Schechter, Nature 1984; 312:513*

*Moasser, Oncogene 2007; 26:6469*

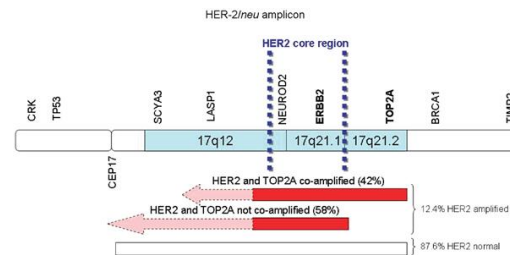
# Molecular alterations

- Lower ER and/or PR expression



*Sandhu et al, LabMed 2010; 41:364*

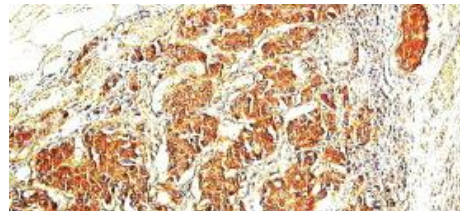
- Co-amplification *TOP2A*



- High frequency of *PIK3CA* and *TP53* mutations

*The cancer Genome Atlas Network, Nature 2012; 490:61*

- Higher levels of VEGF



*Hoar et al, Eur J Cancer 2003; 39:1698*

*Konecny et al, Clin Cancer Res 2004; 10:1706*

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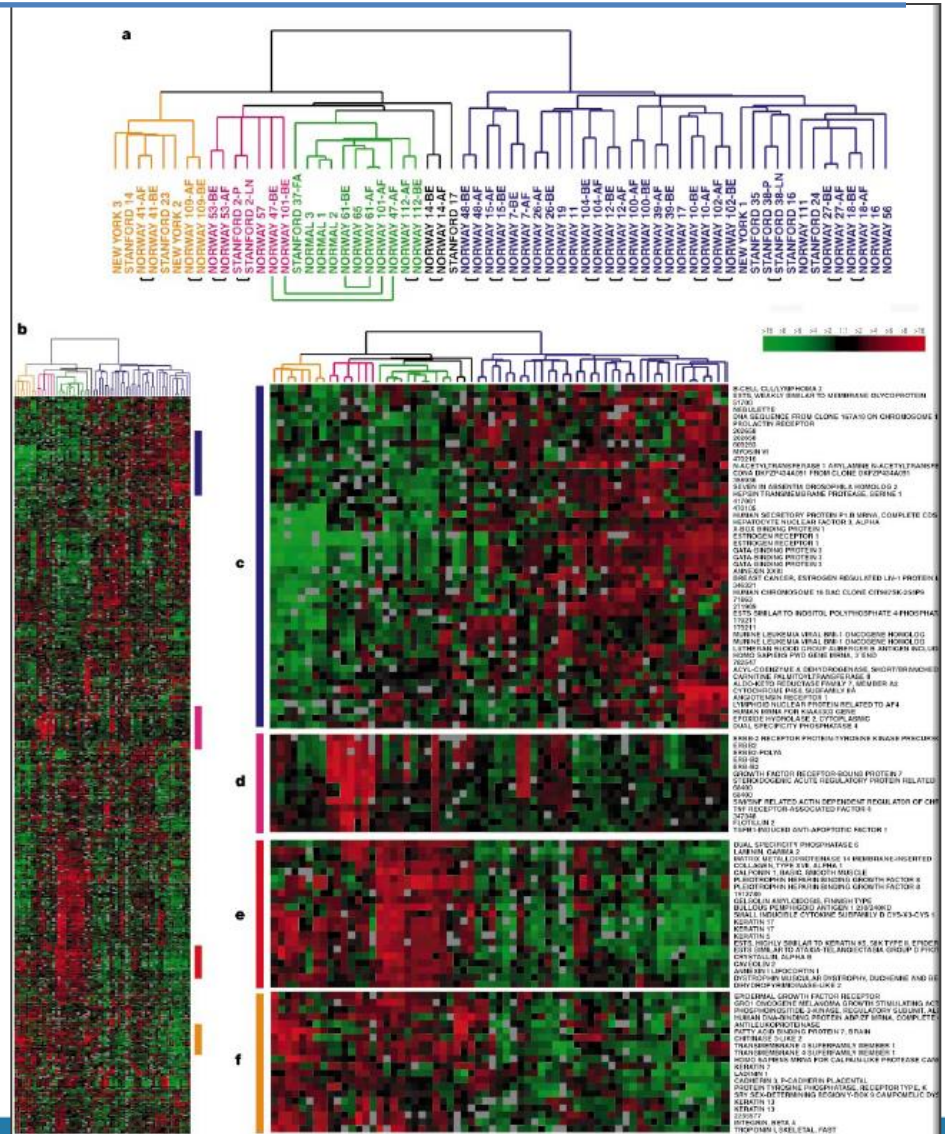
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# Molecular portraits of breast cancer

- Luminal A
- Luminal B
- Basal-like
- HER2
- Normal-like

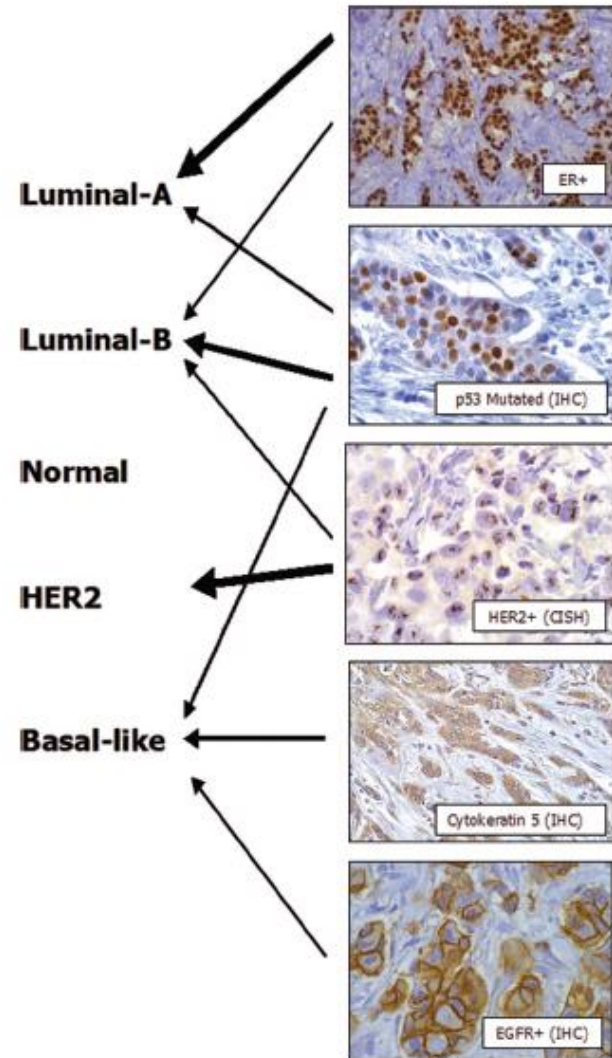
Perou et al *Nature* 2000

Sorlie et al *Proc Natl Acad Sci USA* 2001



# Molecular portraits of breast cancer

- Positive Her2-status does not constitute a unique molecular category and is identified in both the HER2 and luminal tumor classes



# Does ER status define two distinct subtypes?

Meta-analysis 11 datasets of BC samples with GE and outcome data; 2 aCGH and 74 HER2+ neoadjuvantly trastuzumab-treated patients:

- Significant molecular differences in HER2+BC according to ER status
- *ESR1* significantly inversely correlated with *ERBB2*, *EGFR* and gene sets of *RAS*, *RAF*, *MAPK* and *MEK* pathway activation
- *ESR1* positively correlated with *ERBB3* and *AKT1*
- A gene set of PI3K/AKT pathway activation predict pCR in trastuzumab-CT patients in ER+/HER2+ but not ER-/HER2+

*Loi et al, JCO 2010; 28: 15s (Suppl; abstract 522)*

# Does ER status define two distinct subtypes?

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elzbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

*Lancet Oncol* 2012; 13: 25-32

Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
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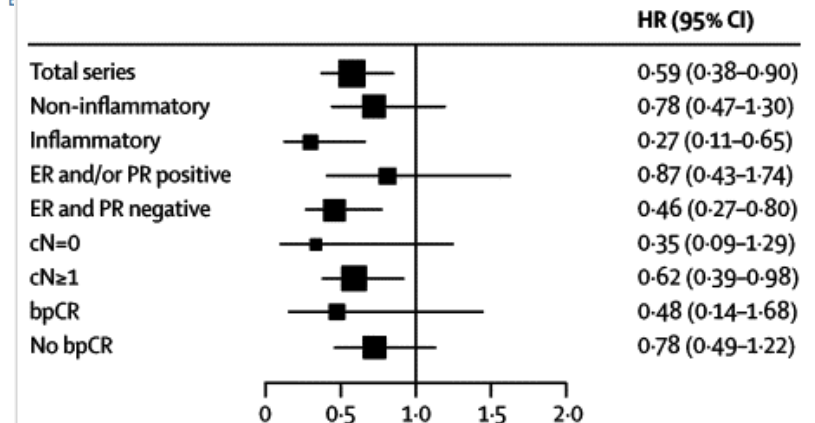
A panel of biomarkers HER1, HER2, HER3, IGF1R, PTEN, pAKT, amphiregulin, betacellulin, TGF $\alpha$  and *PIK3CA* mutation status

THE LANCET

Volume 375, Issue 9712, 30 January–5 February 2010, Pages 377–384

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

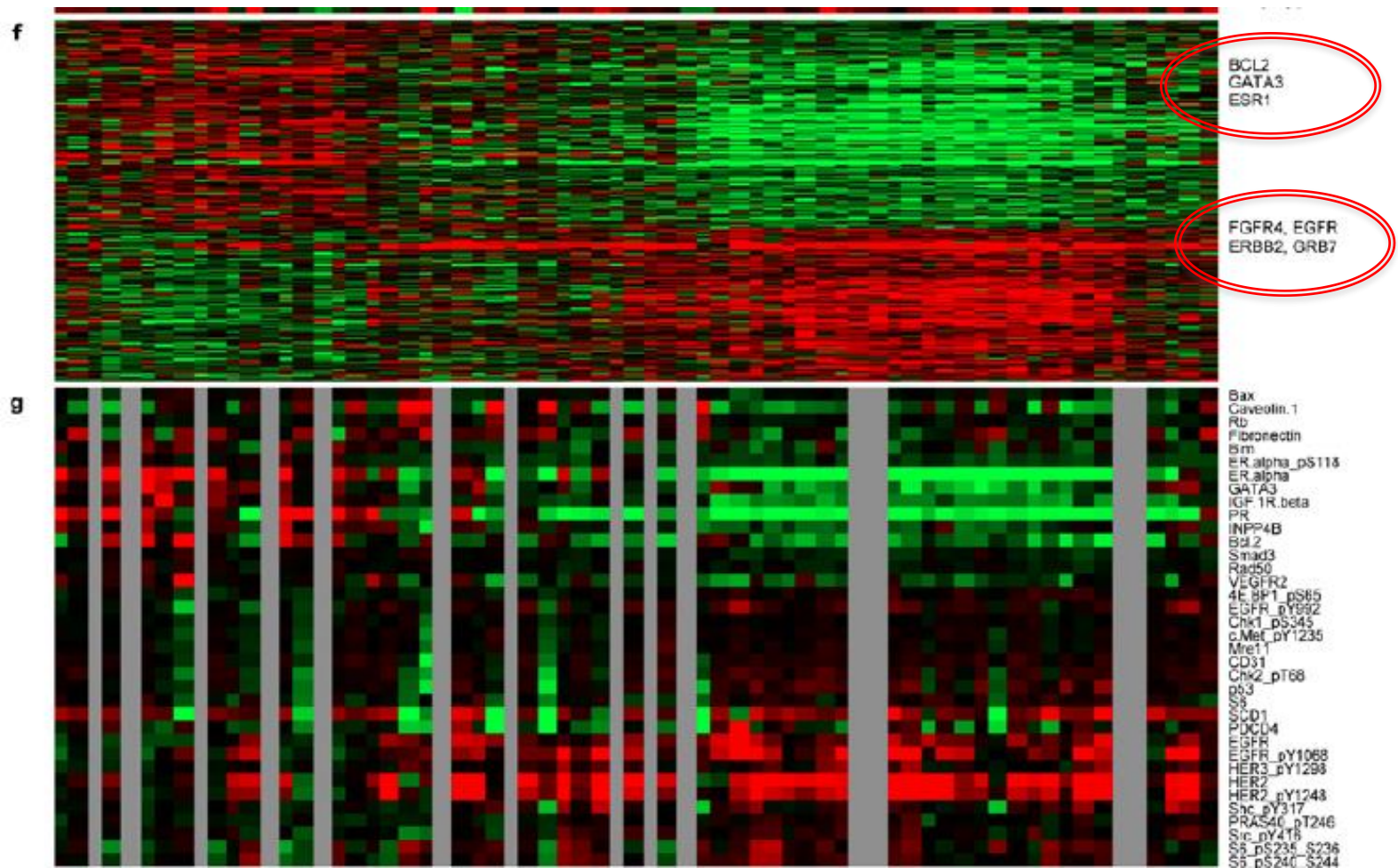
Dr Luca Gianni, MD<sup>a</sup>, Wolfgang Eiermann, MD<sup>b</sup>, Vladimir Semiglazov, MD<sup>c</sup>, Alexey Manikhas, MD<sup>d</sup>, Ana Lluch, MD<sup>e</sup>, Sergey Tjulandin, MD<sup>f</sup>, Milvia Zambetti, MD<sup>g</sup>, Federico Vazquez, MD<sup>g</sup>, Mikhail Byakhov, MD<sup>h</sup>, Mikhail Lichinitser, MD<sup>i</sup>, Miguel Angel Climent, MD<sup>j</sup>, Eva Ciruelos, MD<sup>j</sup>, Belén Ojeda, MD<sup>k</sup>, Mauro Mansutti, MD<sup>l</sup>, Alla Bozhok, MD<sup>c</sup>, Roberta Baronio, MSc<sup>m</sup>, Andrea Feyereislova, MD<sup>n</sup>, Claire



ER-positive and ER-negative/HER2-positive breast cancer are driven by distinct biologic mechanisms



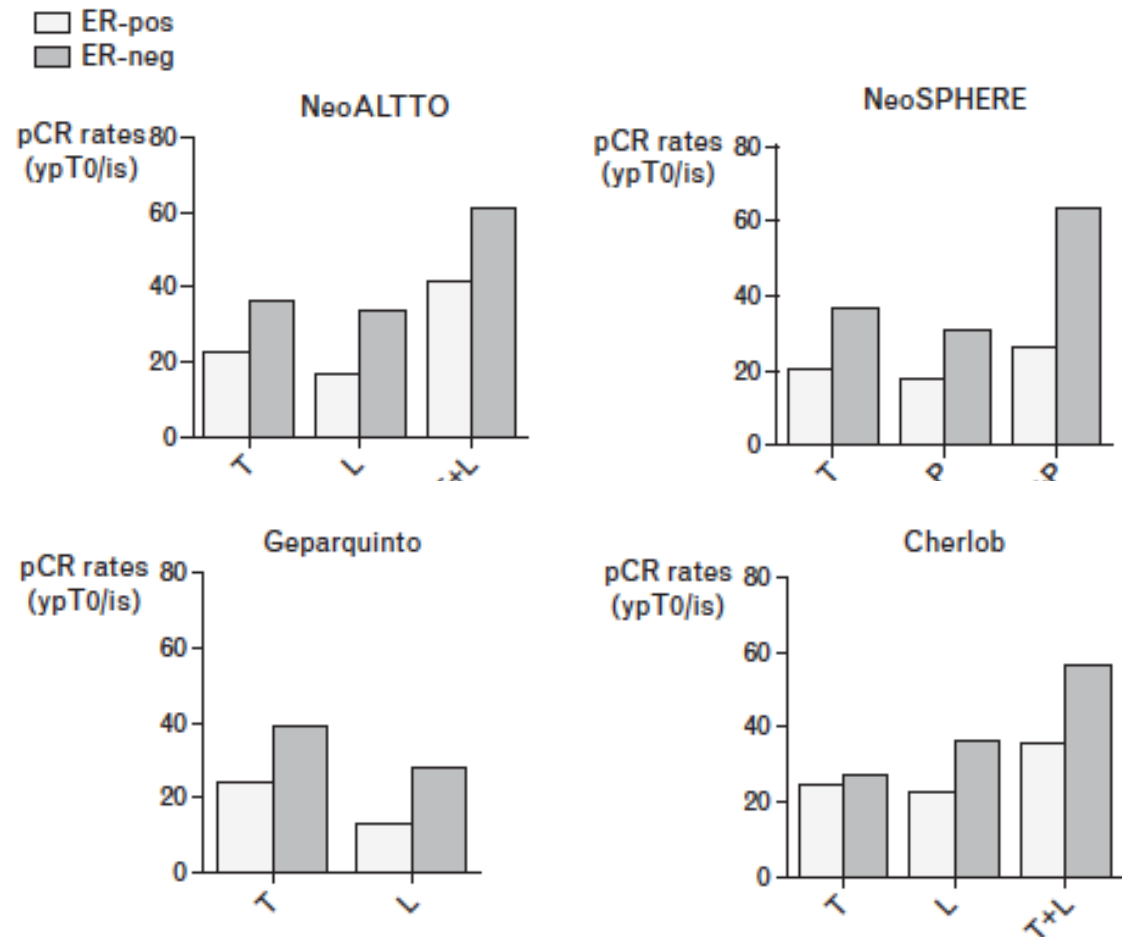
# Does ER status define two distinct subtypes?



*The cancer Genome Atlas Network, Nature 2012; 490:61*

# Does ER status define two distinct subtypes?

Lower rates of pCR with neoadjuvant CT+ anti-HER2 in ER+/HER2+

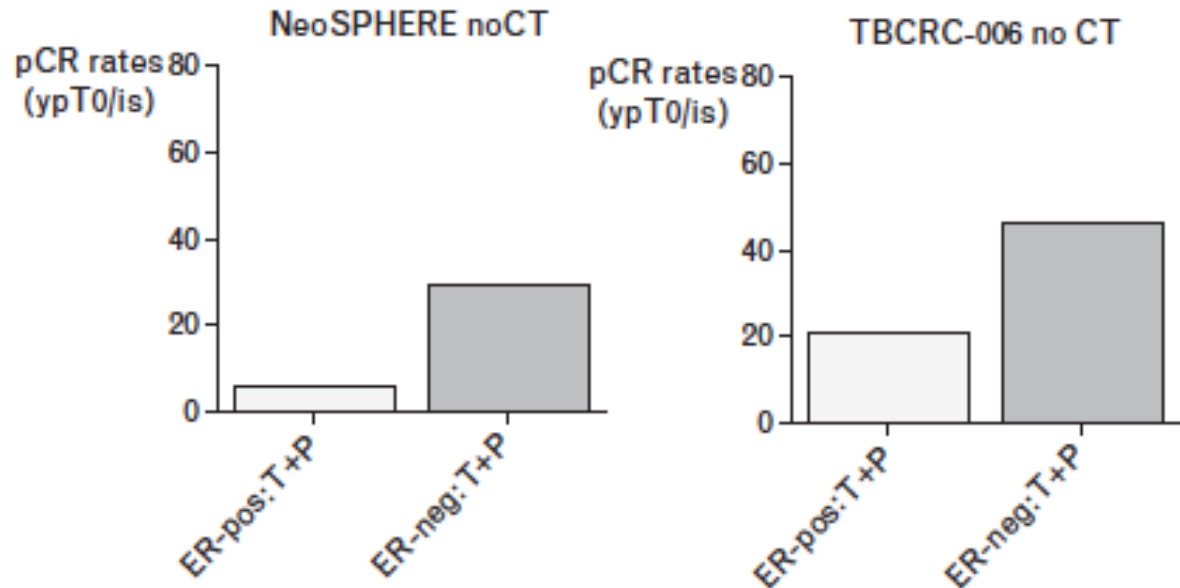


Loi et al. *Current Opinion Oncol* 2011; 23

# Does ER status define two distinct subtypes?

Lower  
sensitivity to  
anti-HER2 in  
ER+/HER2+

(b)



*Loi et al. Current Opinion Oncol 2011; 23*

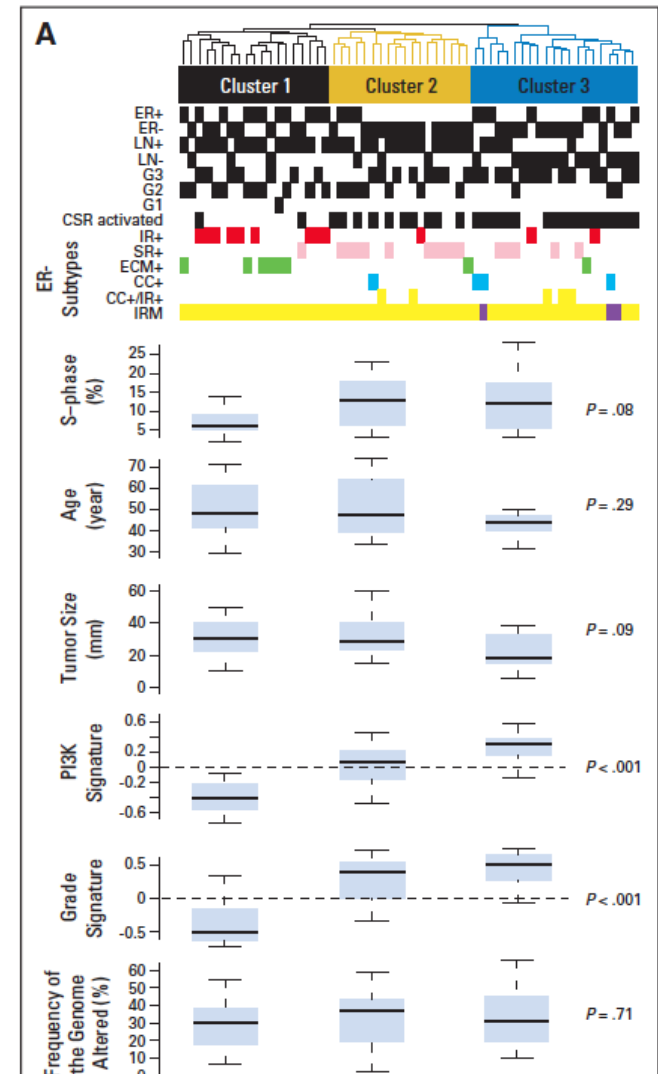
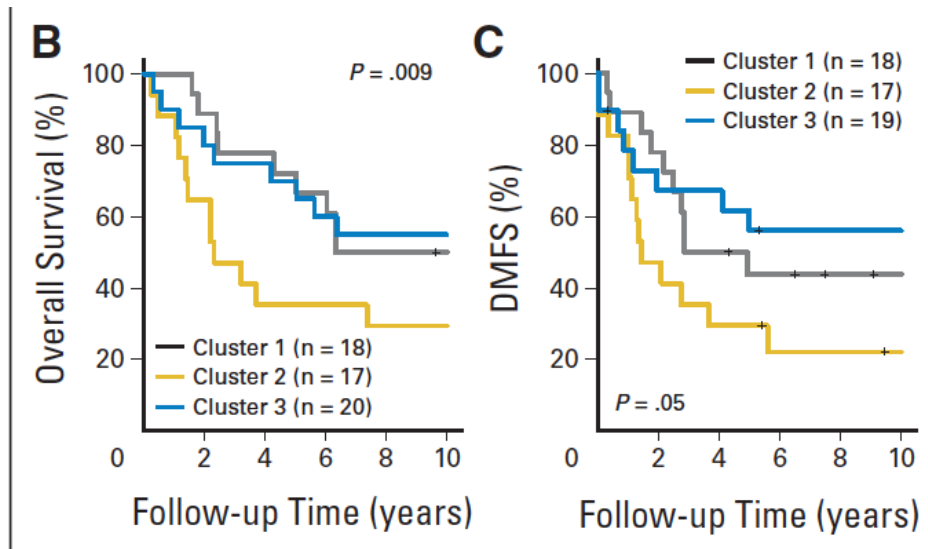
# HER-2 Signatures

VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

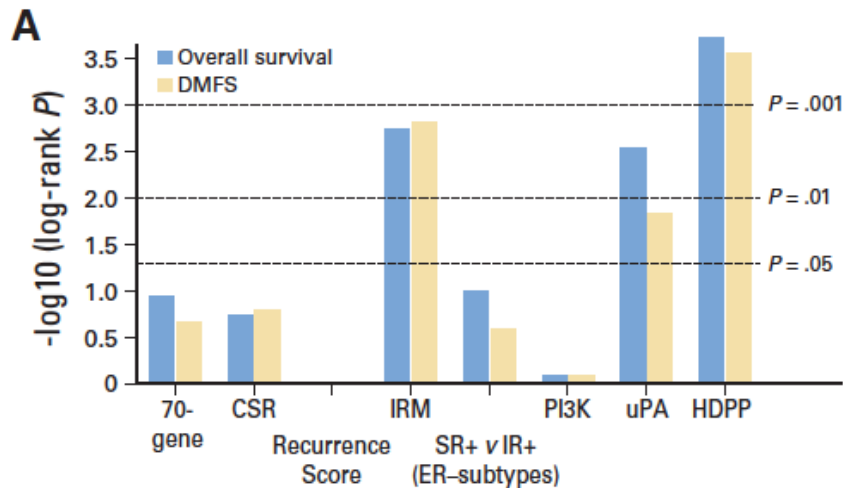
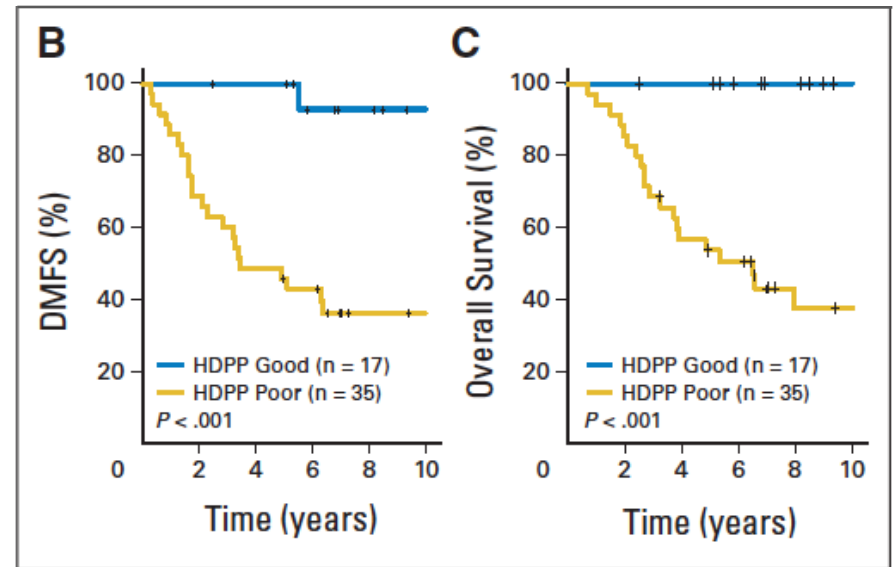
## Identification of Subtypes in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer Reveals a Gene Signature Prognostic of Outcome

Johan Staaf, Markus Ringnér, Johan Vallon-Christersson, Göran Jönsson, Pär-Ola Bendahl, Karolina Holm, Adalgeir Arason, Haukur Gunnarsson, Cecilia Hegardt, Bjarni A. Agnarsson, Lena Luts, Dorthe Grabau, Mårten Fernö, Per-Olof Malmström, Oskar Th. Johannsson, Niklas Loman, Rosa B. Barkardottir, and Åke Borg



# HER-2 Signatures

creation of the  
HER2-derived  
prognostic  
predictor (HDPP)

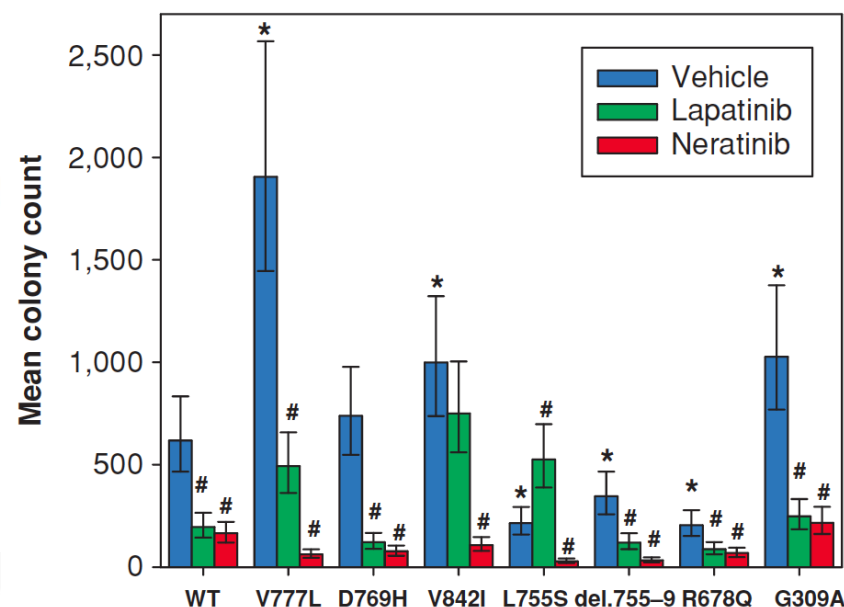
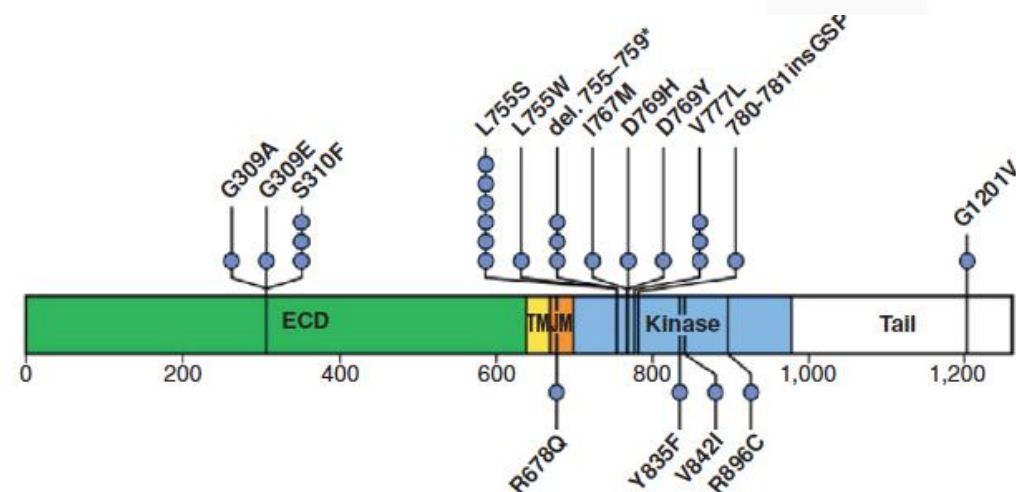


comparison with  
different  
prognostic  
predictors

Staaf et al, *J Clin Oncol* 2010; 28:1813

# Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer

Ron Bose<sup>1,2</sup>, Shyam M. Kavuri<sup>1</sup>, Adam C. Searleman<sup>1</sup>, Wei Shen<sup>1</sup>, Dong Shen<sup>3</sup>, Daniel C. Koboldt<sup>3</sup>, John Monsey<sup>1</sup>, Nicholas Goel<sup>1</sup>, Adam B. Aronson<sup>1</sup>, Shunqiang Li<sup>1,2</sup>, Cynthia X. Ma<sup>1,2</sup>, Li Ding<sup>1,2,3,4</sup>, Elaine R. Mardis<sup>2,3,4</sup>, and Matthew J. Ellis<sup>1,2</sup>



Bose et al, Cancer Discovery 2013; 3:224

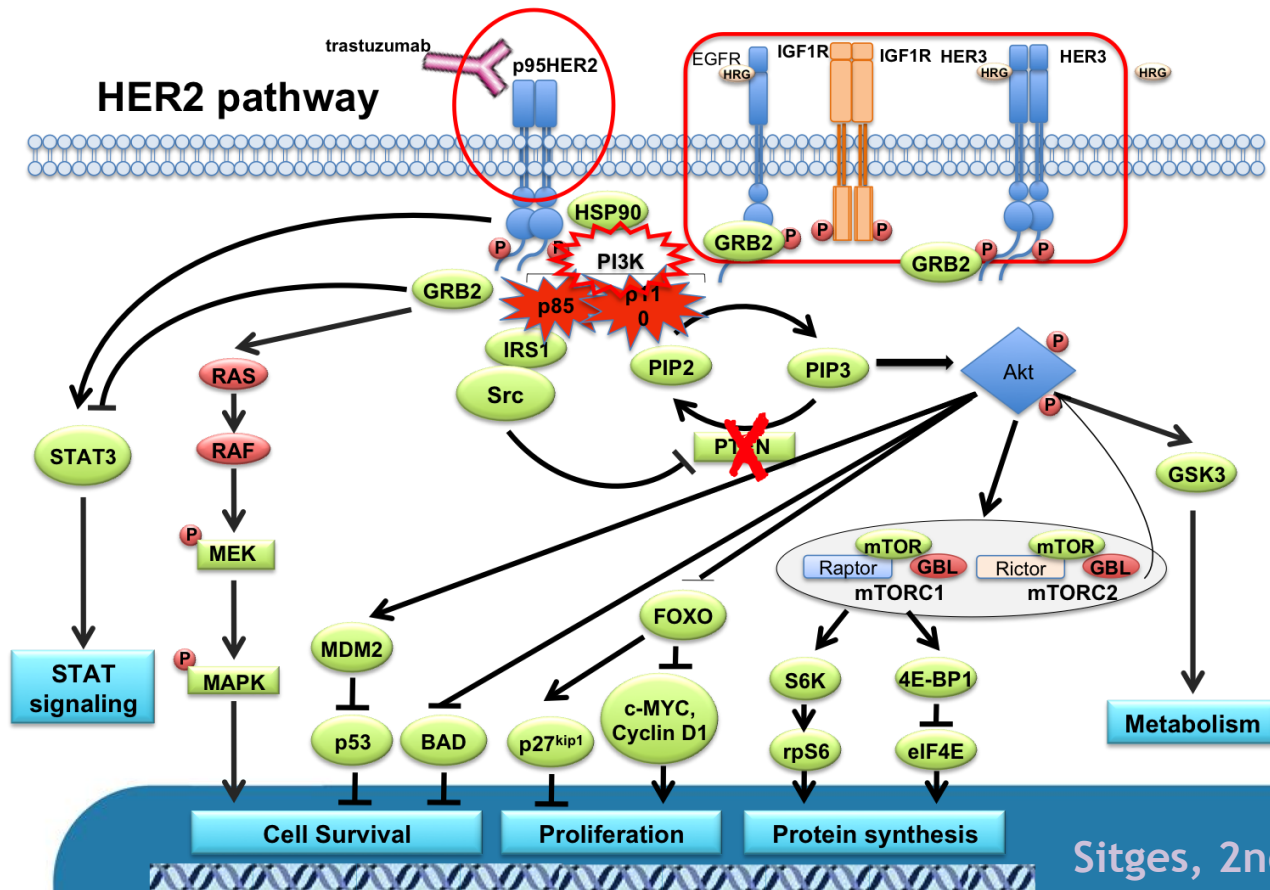
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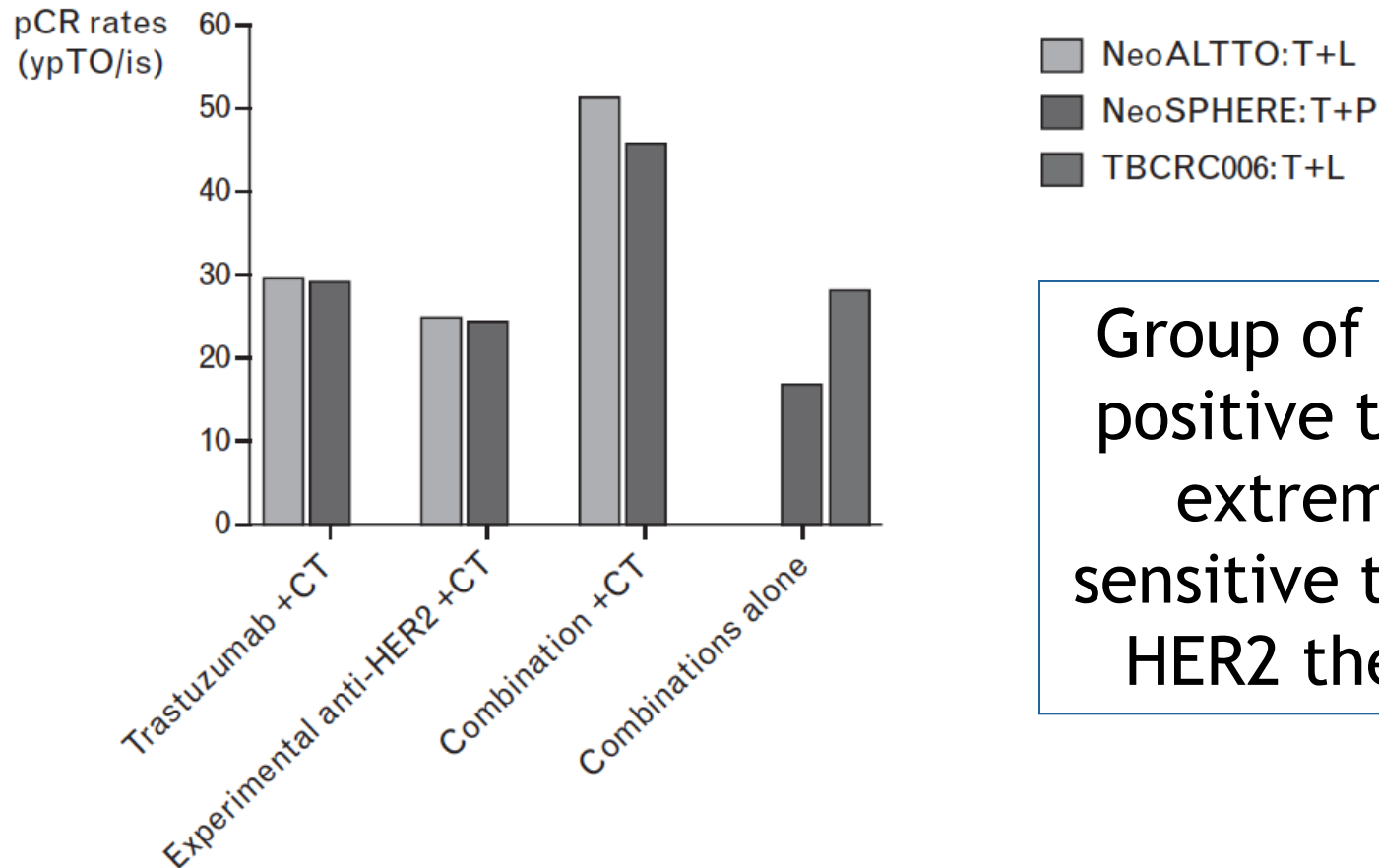
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## Highly dependent HER2 tumors

- ~40% of primary resistance to combination trastuzumab + chemotherapy in patients with metastatic HER2-positive breast cancer and in responders TTP ~ 12mo



# Highly dependent HER2 tumors



Group of HER2-positive tumors extremely sensitive to anti-HER2 therapy

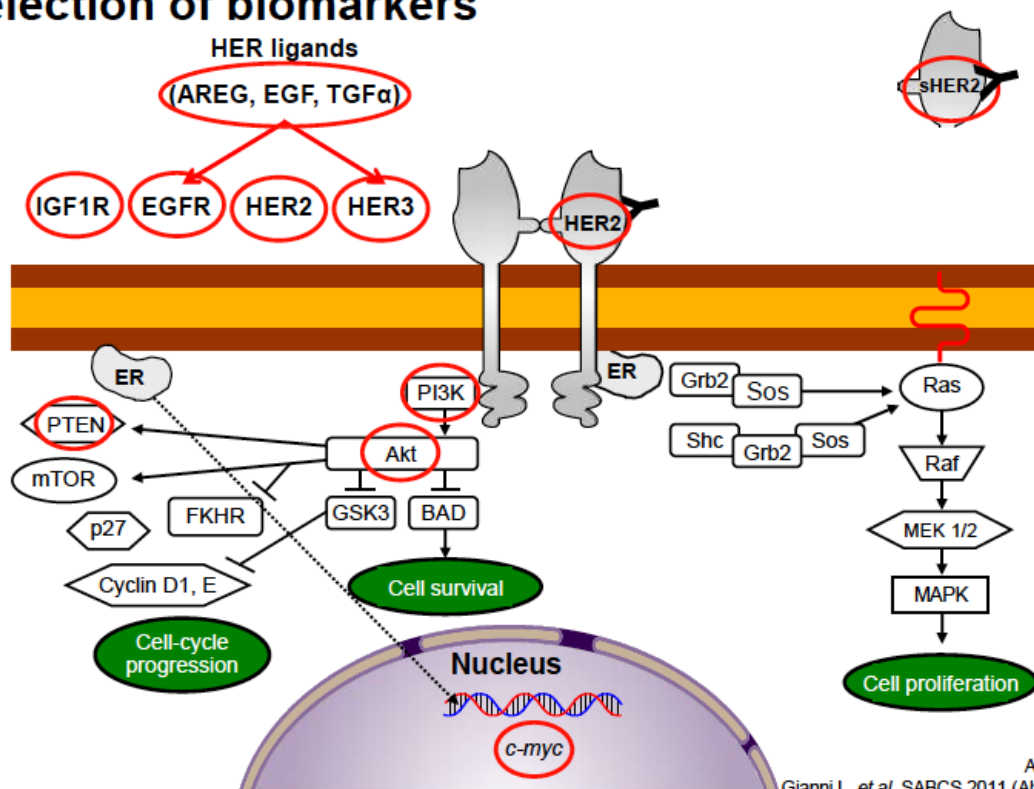
*Loi et al. Current Opinion Oncol 2011; 23*

# Biomarkers sensitivity

## Biomarker analyses in CLEOPATRA: A Phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC)

J Baselga,<sup>1</sup> J Cortés,<sup>2</sup> S-A Im,<sup>3</sup> E Clark,<sup>4</sup>  
A Kiermaier,<sup>5</sup> G Ross,<sup>4</sup> and S M Swain<sup>6</sup>

### Selection of biomarkers



HER2 was the only marker for selecting HER2-targeted therapy

*PIK3CA* mutations not associated with resistance but poorer prognostic factors

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# ICGC HER2-Positive tumors



International  
Cancer Genome  
Consortium

<https://icgc.org>

Vol 464 | 15 April 2010 | doi:10.1038/nature08987

nature

## PERSPECTIVES

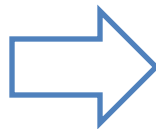
### International network of cancer genome projects

The International Cancer Genome Consortium\*

The International Cancer Genome Consortium (ICGC) was launched to coordinate large-scale cancer genome studies in tumours from 50 different cancer types and/or subtypes that are of clinical and societal importance across the globe. Systematic studies of more than 25,000 cancer genomes at the genomic, epigenomic and transcriptomic levels will reveal the repertoire of oncogenic mutations, uncover traces of the mutagenic influences, define clinically relevant subtypes for prognosis and therapeutic management, and enable the development of new cancer therapies.

**ICGC Goal:** « To obtain a **comprehensive** description of **genomic, transcriptomic and epigenomic changes** in **50 different tumor types and/or subtypes** which are of clinical and societal importance across the globe »

53 projects  
to date



Breast cancer subtype defined  
by an amplification of the  
HER2 gene

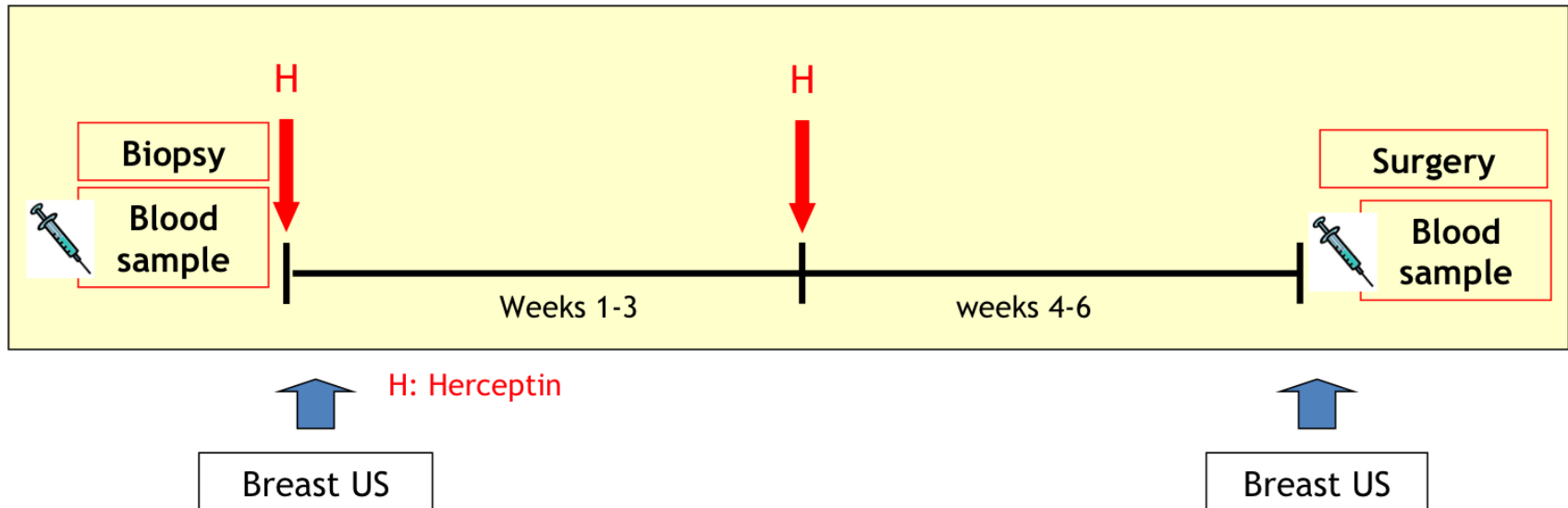
# Biomarkers high sensitivity



<http://www.responsify-fp7.eu>



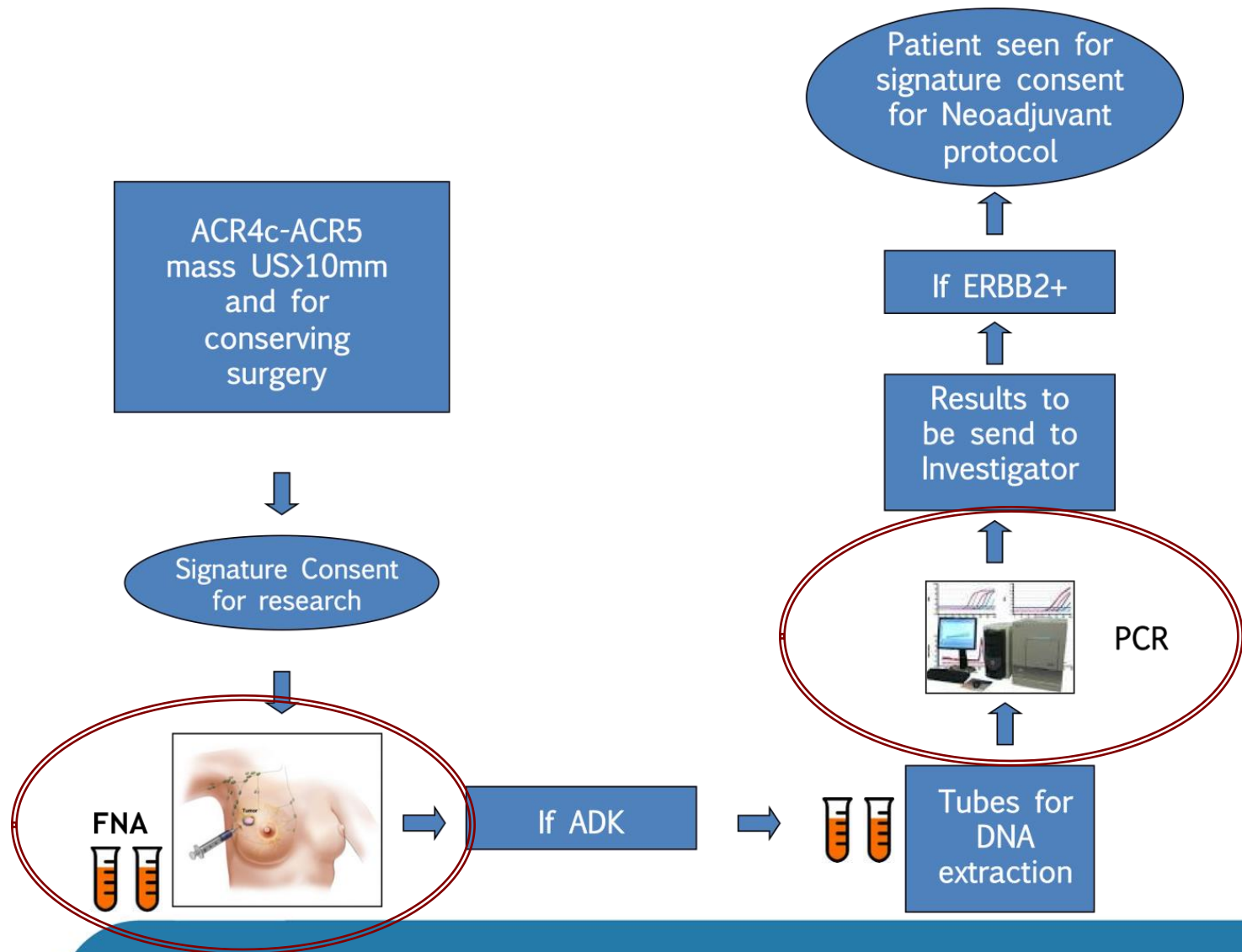
## Protocol HERBIN (Herceptin Biomarker INvestigation)



Pre-operative setting ( $\neq$  neoadjuvant)

\* 2 frozen biopsies + 1 paraffine

# Biomarkers high sensitivity



# Summary

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- *ErbB2* amplification is common in BC and associated to anatomopathological and clinical features of worse prognosis
- Certain molecular alterations associated to *ErbB2* amplification
- Heterogeneous group of tumors at least divided by the presence of HR
- Need to know better differential characteristics and identify those tumors highly dependent to *ErB2* signalling