

HER2/NEU and breast cancer.

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HER-2/*neu* Amplification and Overexpression in Breast Cancer

- Amplification and overexpression: key to
 - prognosis
 - predictive response
 - therapy type and response

HER2-neu Oncogene Expression

- HER2-neu (human epidermal growth factor receptor 2)
 - expression levels altered by gain in copy number or mutations that result in increased levels of expression
 - overexpression associated with
 - poor prognosis
 - predicted therapy response

Laboratory evaluation of HER-2/neu status:

- Protein overexpression
 - Immunohistochemistry (IHC)
 - ELISA (serum)
- Gene amplification
 - FISH, PCR
- mRNA levels
 - RT-PCR

IHC: HER-2/*neu* oncoprotein detection

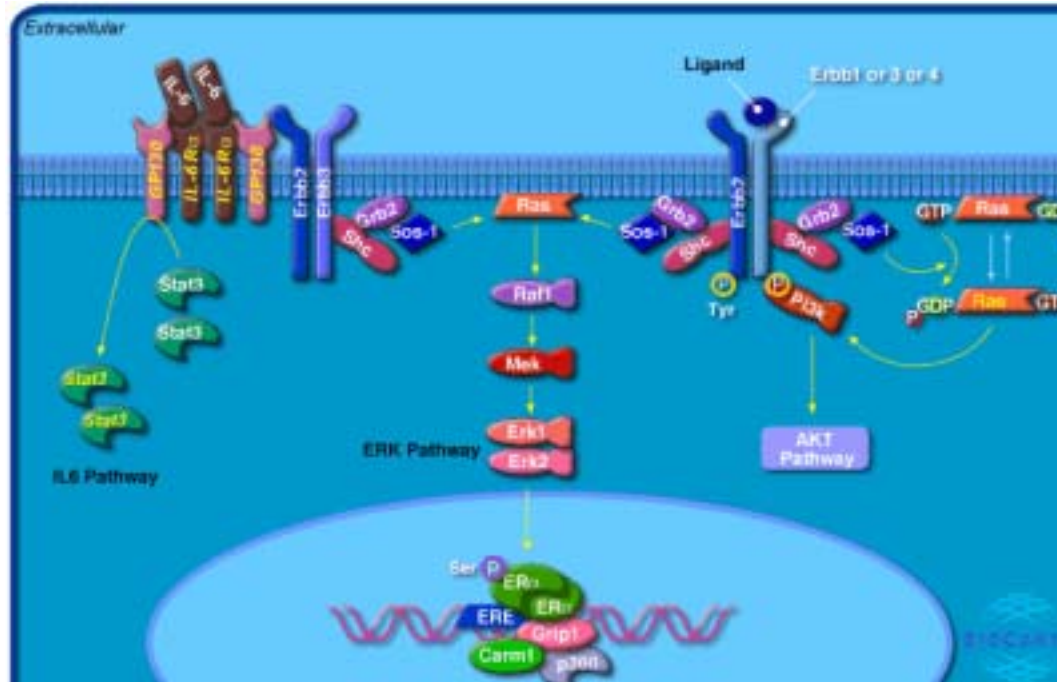
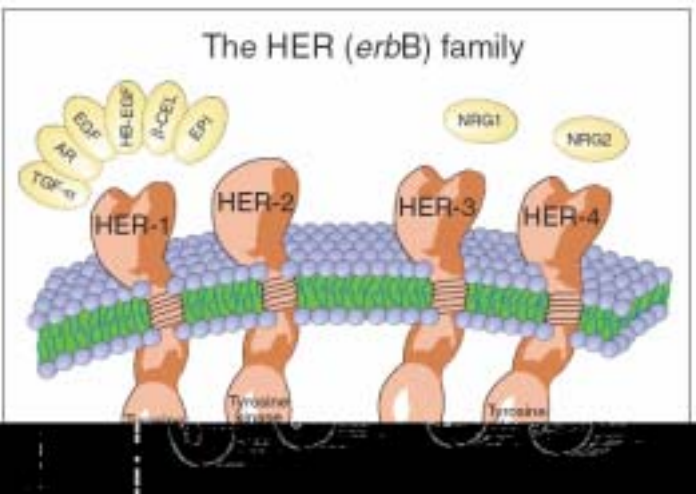
- Monoclonal antibodies: CB11, Tab 250
 - 77-91% concordance with FISH
 - equivocal IHC result: weak to moderate intensity partial cell membrane staining around a minority of tumour cells
 - retest with FISH

HER2/neu Positivity:

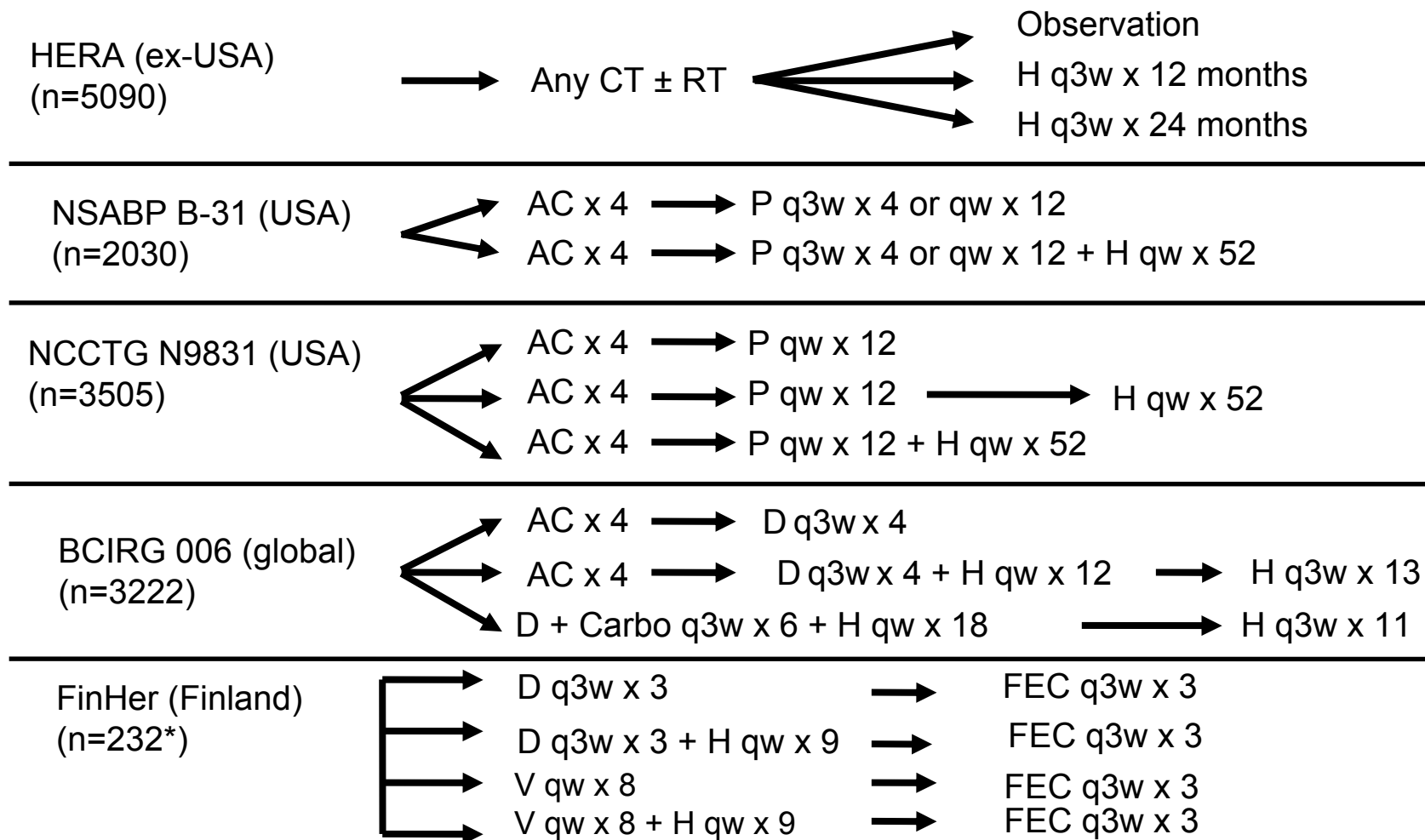
- IHC3+ or FISH+ patients eligible for Herceptin therapy
- Therapy approved for metastatic disease
 - 1° and metastatic HER2/neu status highly concordant
 - predictor of therapy response
 - chemotherapy
 - hormone therapy

What is the HER-2/*neu* gene?

- Human epithelial growth factor receptor 2 (HER-2) – *c-erb B2*
- Plays a key role in the regulation of cell growth and cell-cell communication
- Ligand will bind → receptor will form homo/hetero dimer with other HERr → initiate signal cascade “**transduction cascade**”
- No known ligand for HER-2
- Is the preferred dimerization partner of other HERr

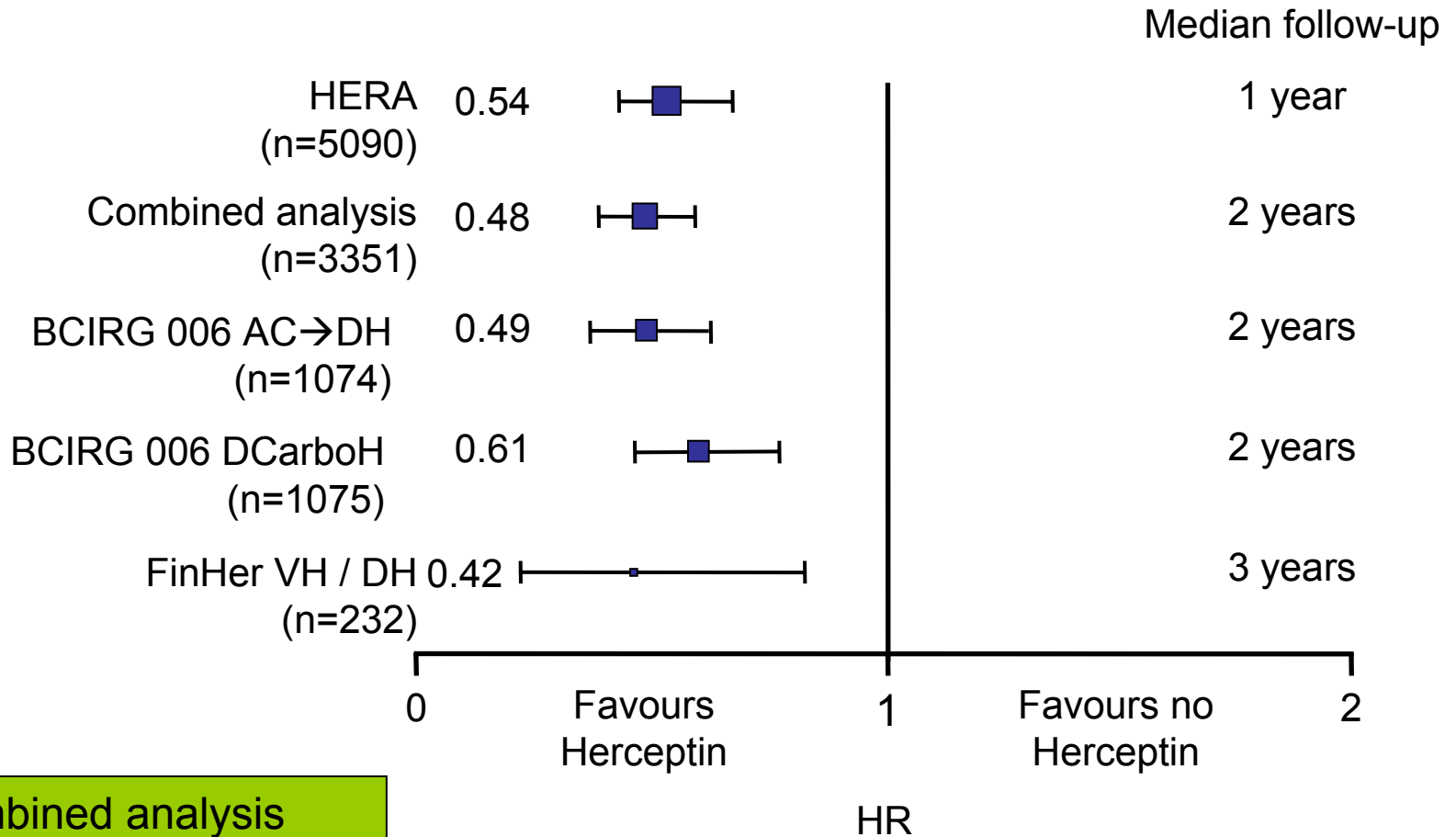


Herceptin in early breast cancer



H, Herceptin; A, doxorubicin; C, cyclophosphamide; D, docetaxel; P, paclitaxel; Carbo, carboplatin; E, epirubicin; F, 5-fluorouracil; M, methotrexate

Herceptin 4 yrs DFS



In combined analysis
Ook overlevingsvoordeel:
87% → 91%
HR 0.67 p < 0.02

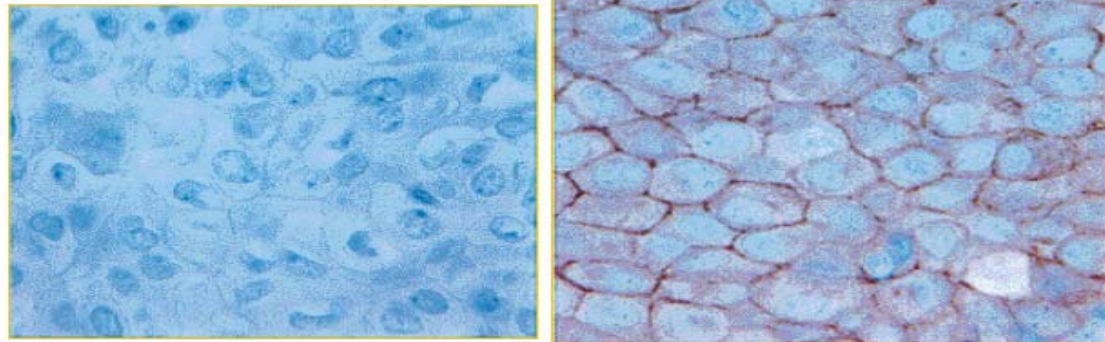
Piccart-Gebhart et al 2005;
Romond et al 2005;
Slamon et al 2005; Joensuu et al 2006

HER-2/*neu* and breast cancer

- Between 20% - 30% of invasive breast cancers overexpress HER-2
- Overexpression due to gene amplification in tumors
 - Associated with adverse prognosis for patients
 - Predictor of benefit for some drug therapy
- Two diagnostic methods to measure HER-2 status

- FISH

- IHC staining



Immunohistochemical staining

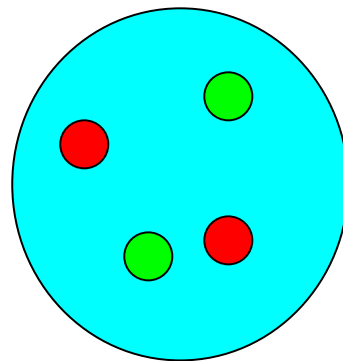
- Ventana PATHWAY™ HER-2: automated slide staining system

Staining Pattern	Number of receptors	Score
No membrane staining (normal tissue)	~20000	0
Faint, partial membrane staining, <10% of cells weak complete staining	~100000	1+
Light/moderate complete membrane staining in >10% of cells	~500000	2+
Intense complete stain of membrane in >10%	~2300000	3+

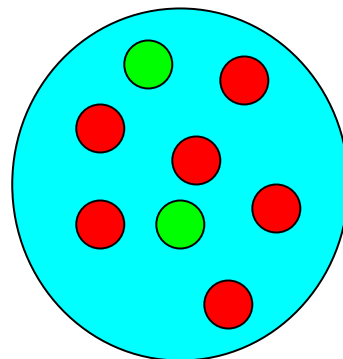
CEP 17 q11.1 — q11.2 HER-2



17



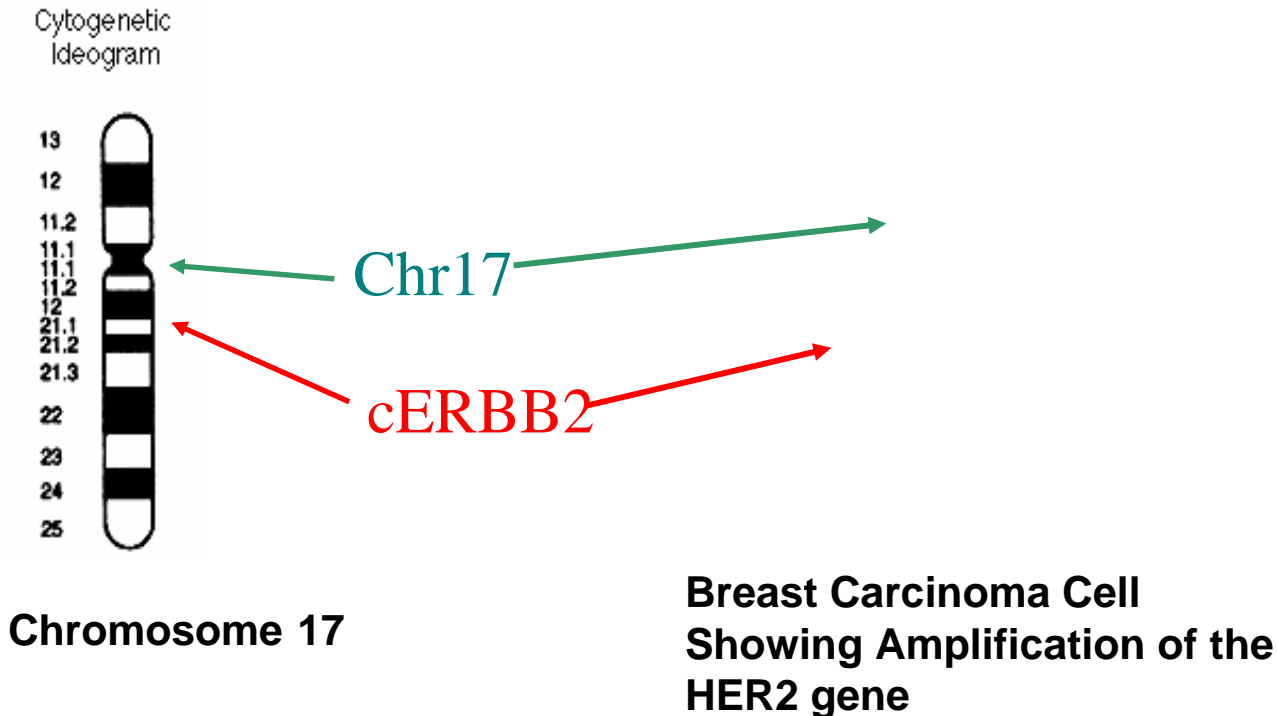
normal



amplified

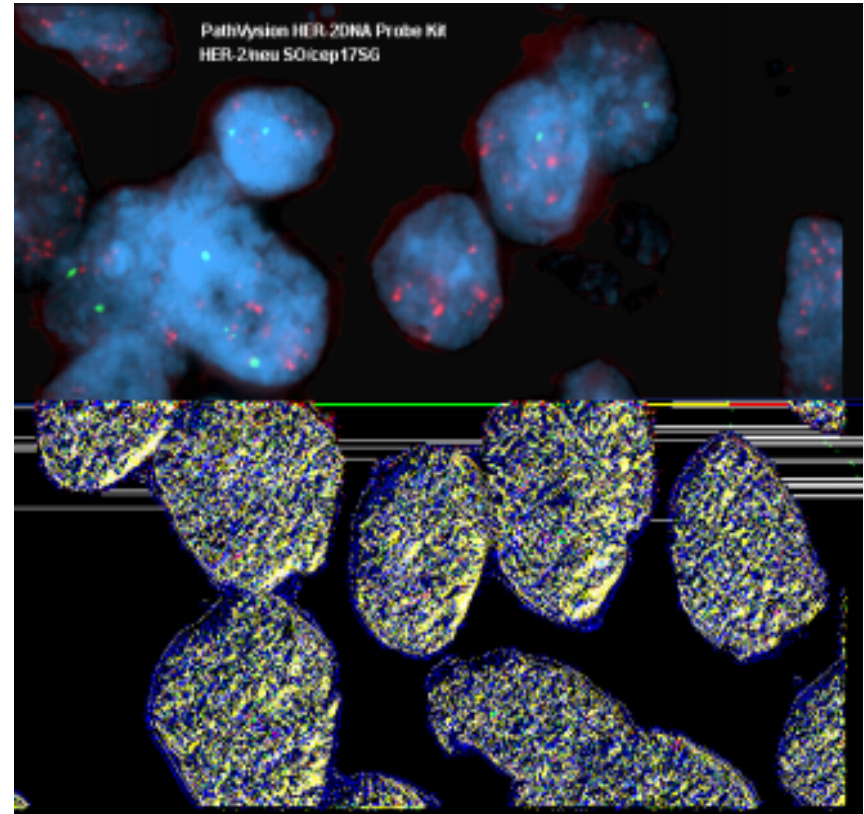
Fluorescent *In Situ* Hybridization - FISH

- Abbott-Vysis PathVysion™ HER-2 DNA Probe Kit
- Gene amplification status is based on ratio of red to green signal:
 - Ratio of 2.0 is the criterion for gene amplification
 - >10 gene copies = high-level
 - Subpopulations exhibiting low amplification = low-level
 - Significant heterogeneity but ratio <2 = mosaic



HER2/neu Gene Amplification

- Paraffin-embedded, formalin fixed tissue sections
 - tissue specific pretreatment
 - ratio analysis of HER2/neu:CEP 17 probes
 - ratio ≥ 2 amplification



Closing though

1. Receptor activity as a potential predictive marker
 - Phosphorylation must occur for signal transduction
 - Monoclonal Ab exists for phosphorylated HER-2
- One study: Thor et al. (2000)
 - Phosphorylation state matters!