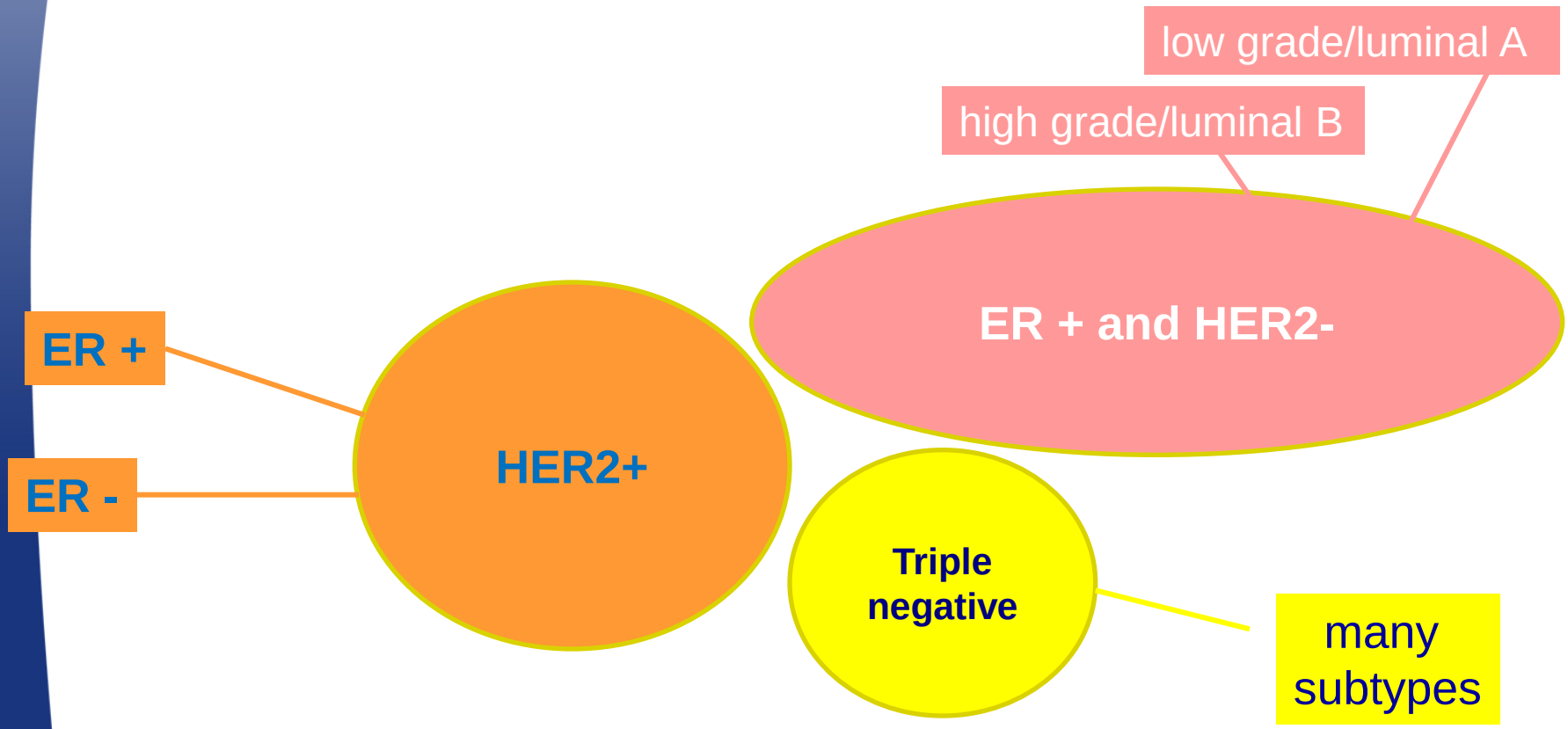
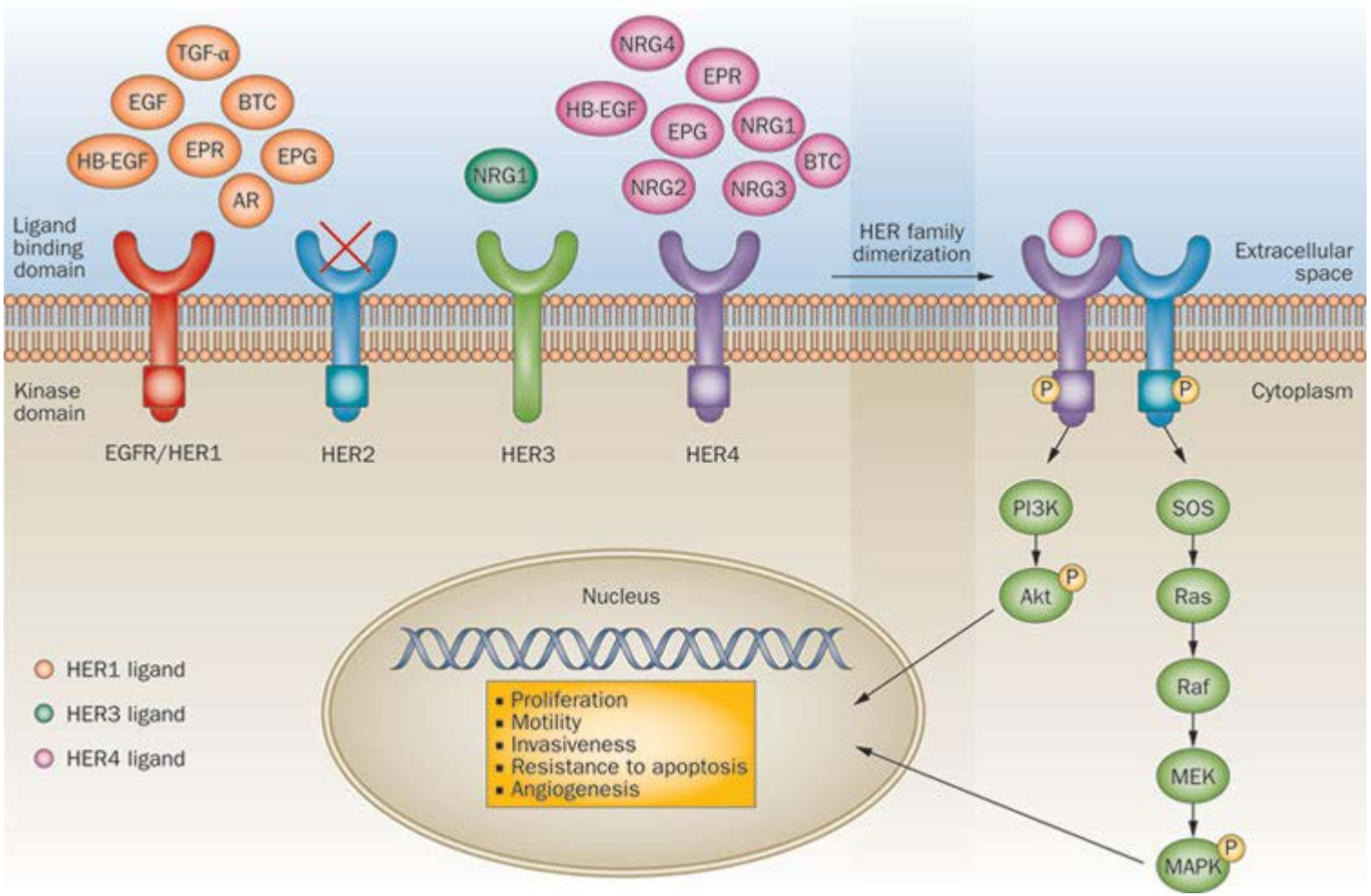
HER2+ carcinoma of the breast

Inge Konings, MD, PhD
Personalized Therapy
November 2017

It’s all about subtypes…



Her2 signaling



Her2+ breast cancer

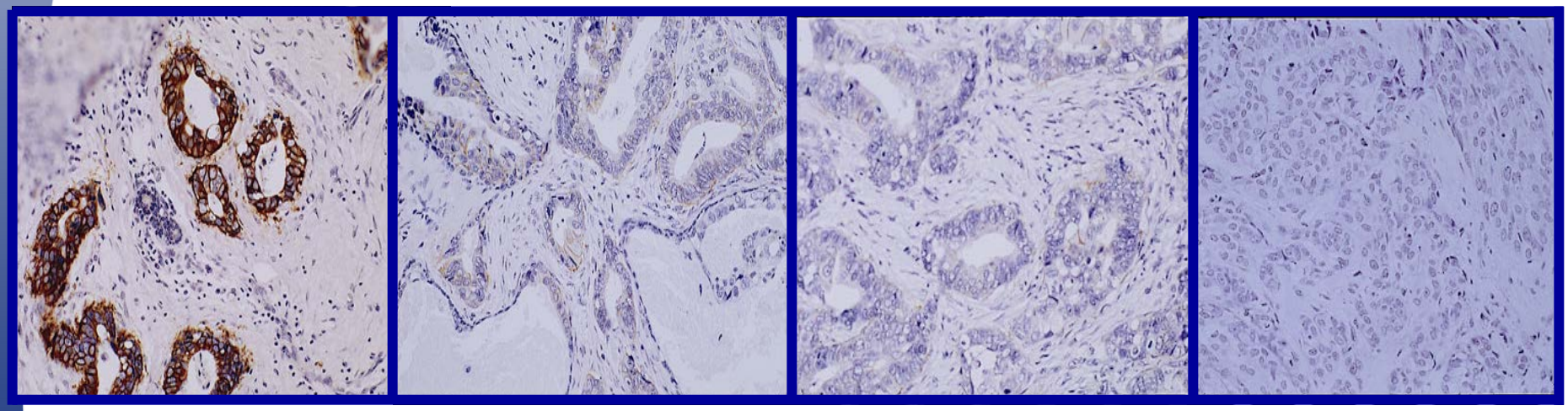
- 15-25% overexpression of Her2
  – worse prognosis
  – ↑ recurrence

- 1998 registration Her2-targeted antibody **trastuzumab** (Herceptin®) in combination with paclitaxel for metastatic breast cancer

Slamon 2001

VUmc VU University Medical Center Amsterdam

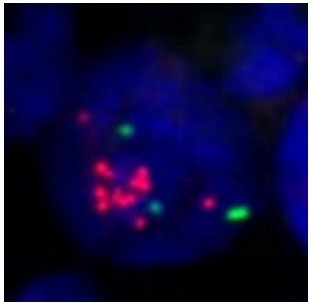
Her2 status



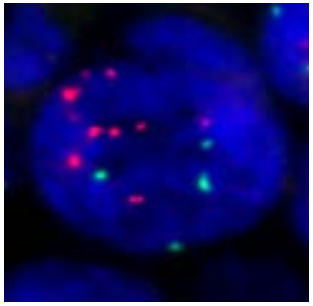
3+ 2+ 1+ Negative/0

IHC

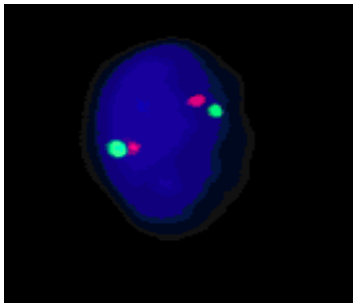
FISH



High amplification



Low amplification



Normal

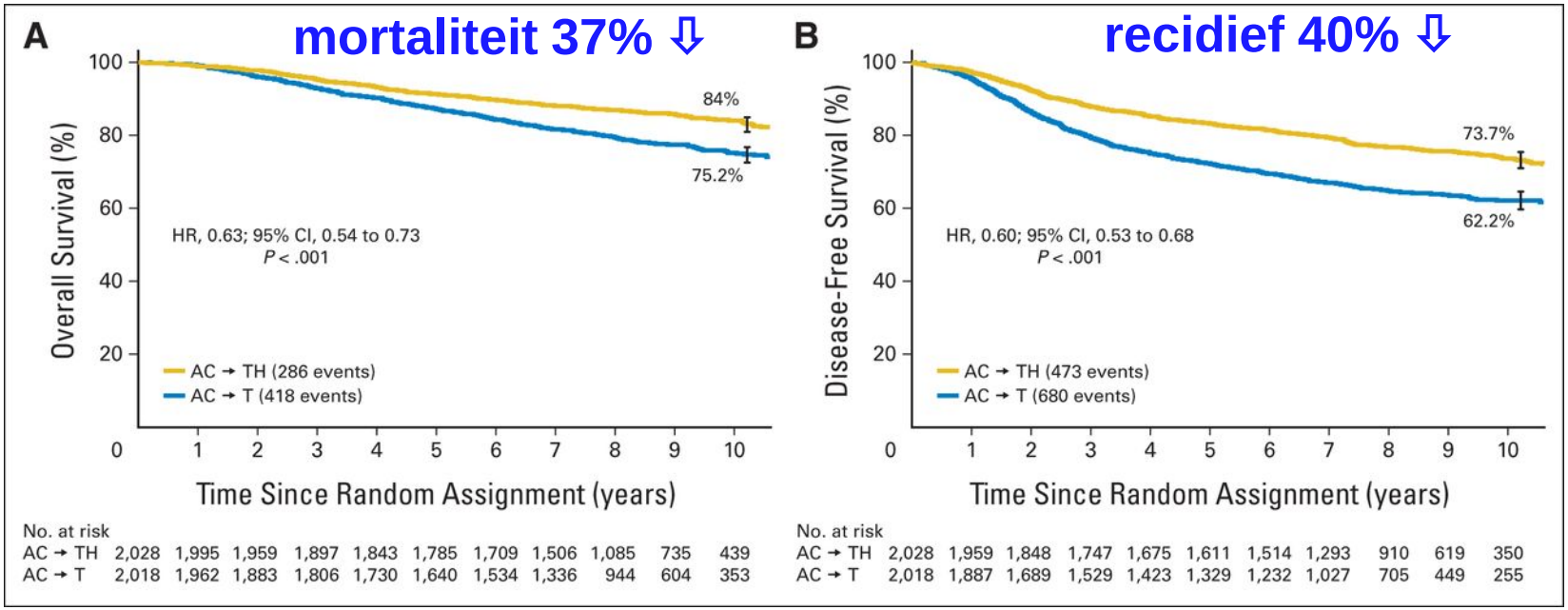
(Neo)Adjuvant treatment

- >14.000 patients in phase III studies

  HERA; NSABP B31/NCCTG N9831; Slamon; FinHer; PHARE

- Chemotherapy +/- trastuzumab (9 wk - 24 mnths)

(A) Overall survival and (B) disease-free survival from combined data analysis NCCTG N9831 and NSABP B-31



NCCTG N9831	NSABP B-31
HER2+ (IHC 3+ or FISH+)	HER2+ (IHC 3+ or FISH+)
Node+ or high-risk node-	Node+
Normal LVEF	Normal LVEF

Edith A. Perez et al. JCO 2014;32:3744-3752

Toxicity?

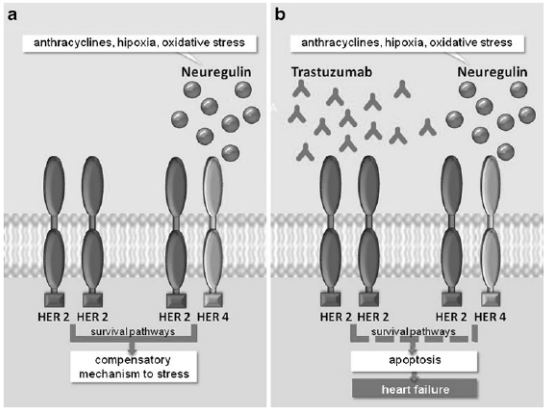
Cardiotoxicity trastuzumab

Table 1 Trastuzumab-related cardiac toxicity in adjuvant RCT

	Criteria to discontinue trastuzumab	Cardiac monitoring	CHF	Asymptomatic decline of LVEF
Concurrent trastuzumab and chemotherapy				
NSABP B31	Symptomatic cardiac dysfunction	Baseline	4.1%	14%
NCCTG N9831	Absolute LVEF drop of 16% or Decline of 10–15% resulting in a final LVEF<LLN	After AC 6,9,18 months after randomization	3.5%	10.8%
Sequential trastuzumab after chemotherapy				
HERA	Symptomatic cardiac dysfunction Absolute LVEF value of 45% or LVEF<50% with a decrease of 10% from baseline	Baseline 3, 6,9,18,24, 30,36, 60 months after randomization	1.8%	6.9%
Trastuzumab with and without anthracyclines				
BICIRG 006	Symptomatic cardiac dysfunction Decline of more than 15% from pretreatment levels	Not reported	1.6% with anthra 0.4% without anthra	17.3% with anthra 8% without anthra
Trastuzumab before treatment with anthracyclines				
FinHER	Not reported	Baseline After FEC 12,36 months after chemotherapy	0%	3.5%

Di Cosimo Targ Oncol 2011

Cardiotoxicity trastuzumab



- Impaired cardiomyocyte function by blocking NRG-1 mediated activation

- Downregulation of antiapoptotic protein BCL-XL + upregulation of pro-apoptotic protein BCL-XS → deferred mitochondrial function

- Upregulation of angiotensin II

→Inhibition of NRG-1

→ more oxidative stress

→ cytotoxic vicous circle

Pondé, ESMO Open 2016

(Neo)Adjuvant treatment

Standaard: AC-TH

A = doxorubicine + **C** = cyclofosfamide

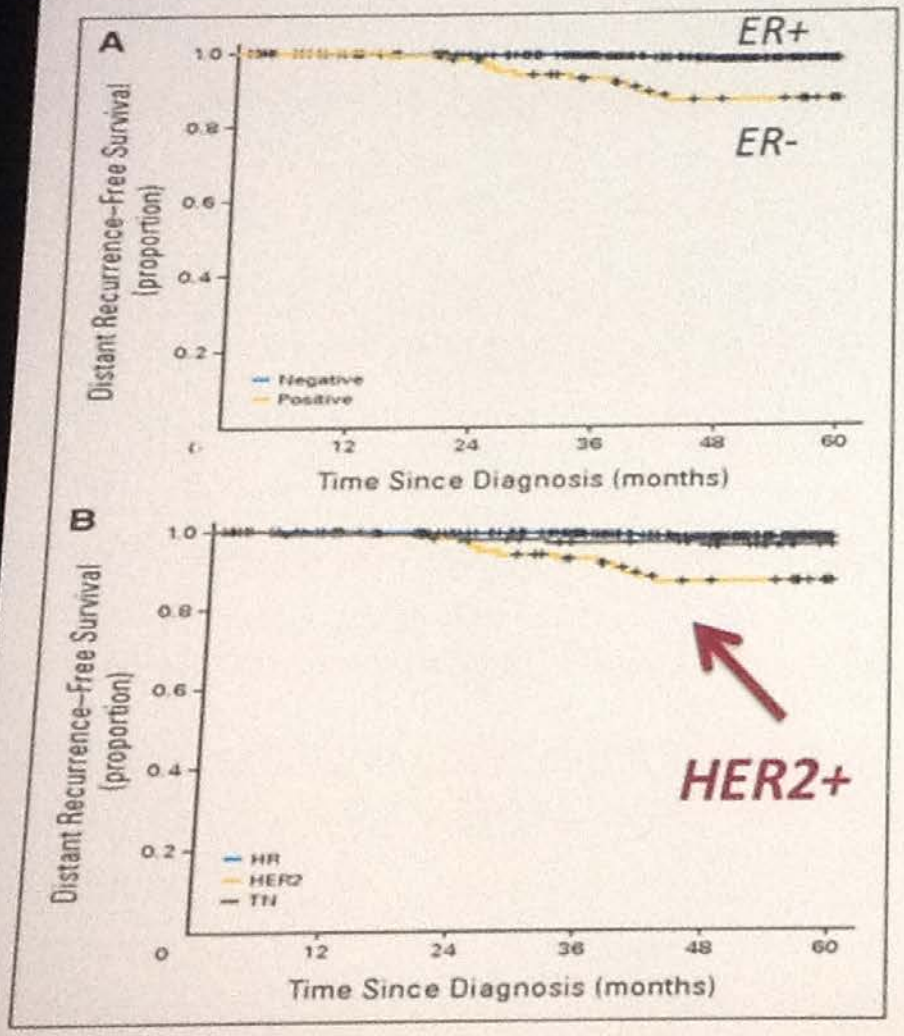
Followed by **T**= paclitaxel + **H** = Herceptin® (12 months)

Dutch guidelines adjuvant treatment:

when N+ or “unfortunate” N0, <70 j

- *T 1.1-2cm AND grade 2*
- *<35j, T>1cm or > grade 1*
- *T>2cm*
- *Her2*

Distant Disease Free Survival in Patients With HER2+ Disease



HER2 status	n	5 yr RFS	5 yr Distant RFS
HER2+	98	77.1%	84.4%
HER2-	867	93.7%	97.2%

Low risk, T1a-b, N0
10% Her2 +
No adjuvant chemoTx
55% adjuvant HT

Gonzalez-Angulo et al,, JCO 2009

Standard: AC-TH

also for small tumors ?
(5 j DFS 84.4%)

Toxicity antracyclines

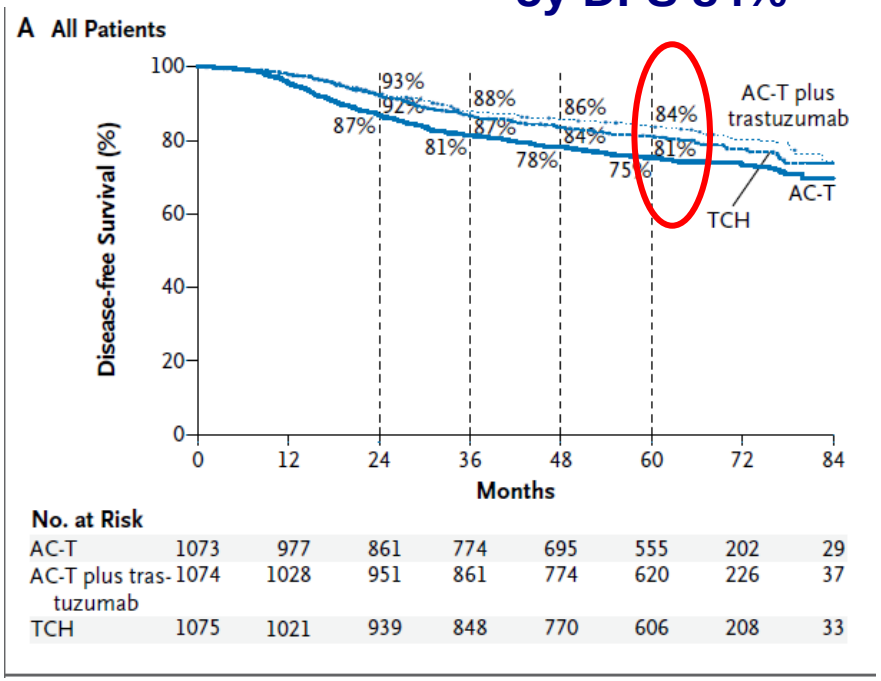
- Pancytopenia
- AML/MDS
- Cardiotoxicity

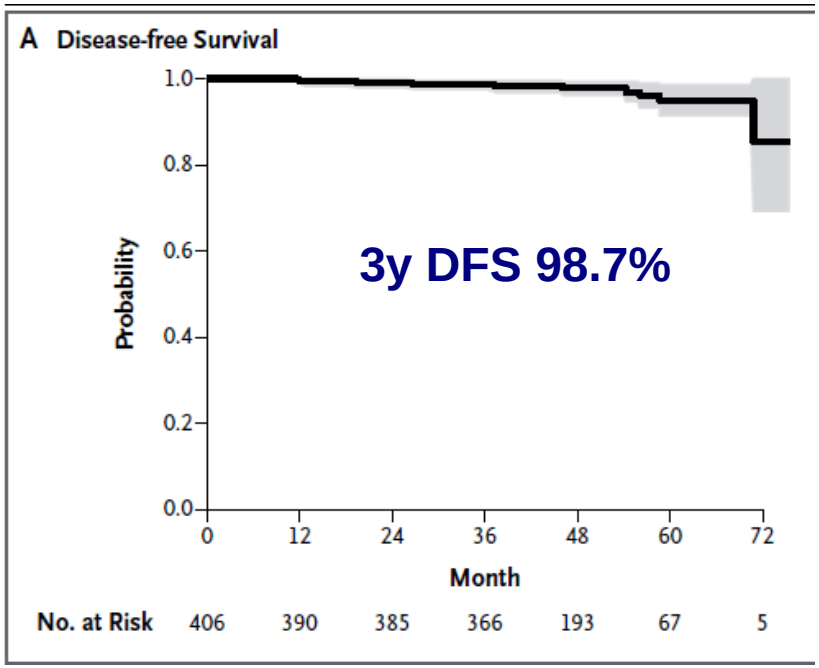
Adjustment:

carboplatin + paclitaxel
when antracyclines are
contraindicated

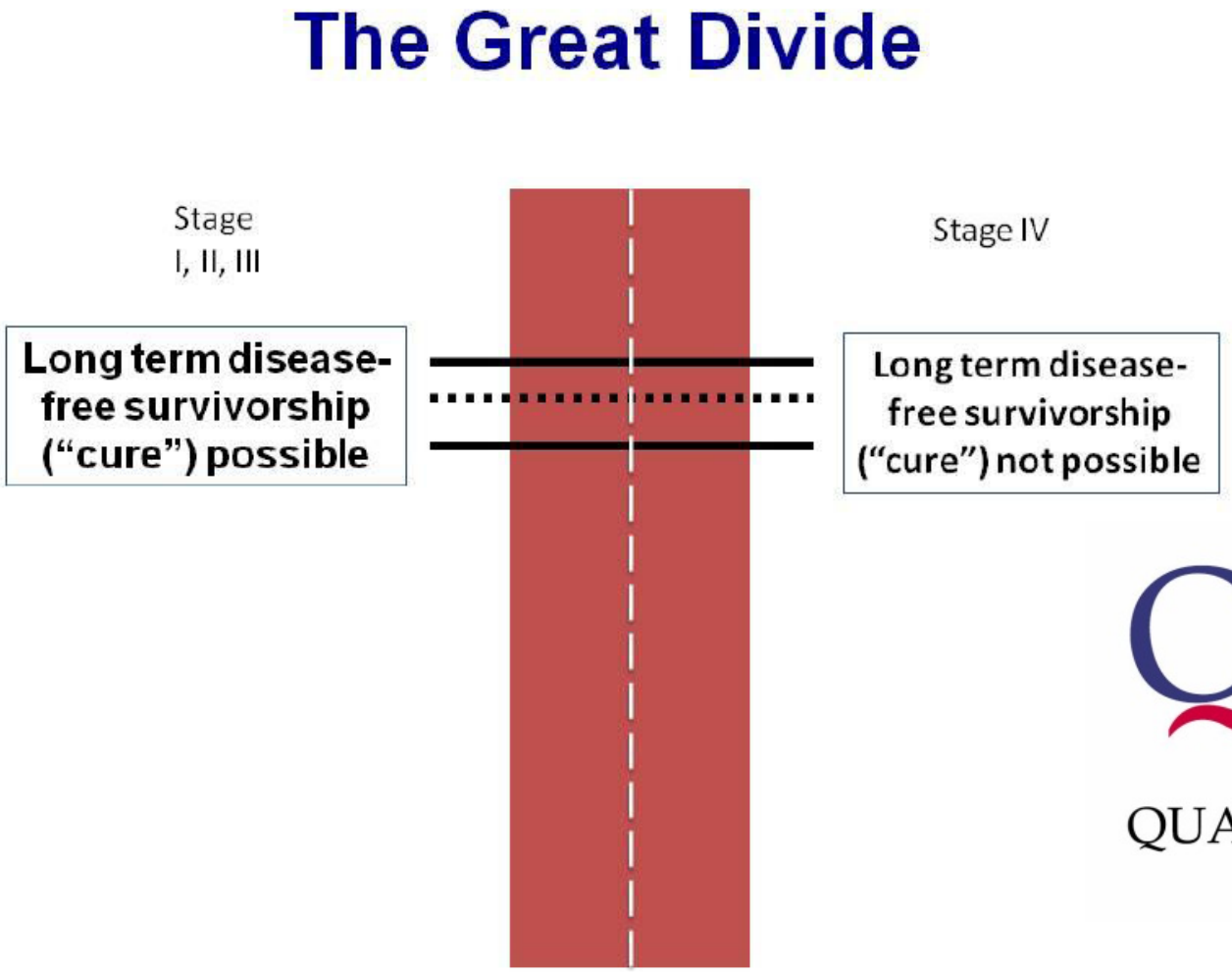
only paclitaxel + trastuzumab
For small tumors
(stage II, < 3cm, N0)

5y DFS 84%





Metastatic breast cancer



QOL

QUALITY of LIFE
MEASURES

Metastatic breast cancer

- No cure
- Symptomatic treatment, improvement of Quality of Life
- Improve overall survival

Metastatic breast cancer

- treatment
  → search for balance between pros and cons

- Median survival ~ 2 jaar
  → wide spread
  → dependent on tumor load

- Local vs. systemic treatment

Therapeutic options for MBC

- Hormonal therapy → when ER+

- Chemotherapy (± bevacizumab) → when HER2-
- Chemotherapy ± HER-gerichte therapie → when HER2+

- Radiotherapy (bone, brain)
- (Neuro-)surgery
- Supportive measures
  - Bisfosfonates / denosumab
  - Palliative care

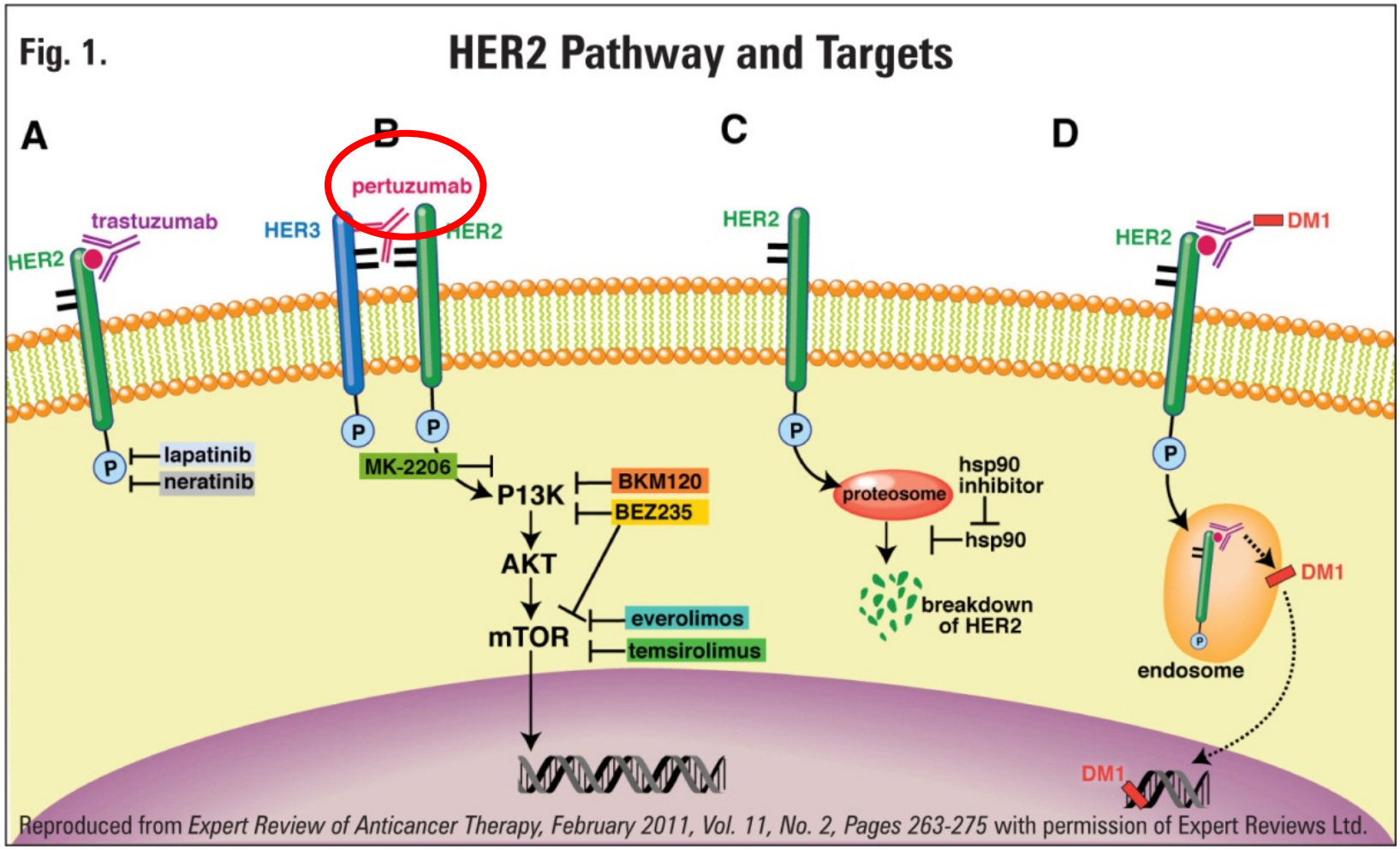
Chemotherapy or hormonal therapy ?

- Receptorstatus
- Metastases:
  - Quickly progressive?
  - Visceral load?
  - No response on hormonal therapy
- Age / Comorbiditeit

Her2+ MBC

	RR	Response duur	TTP
Trastuzumab 1e lijn *Vogel 2002*	35%	12 mnd	3-4 mnd
Trastuzumab > 2e lijn *Cobleigh 1999, Estrevez 2003*	10-20%	9 mnd	
Trastuzumab + anastrozol *Kaufman 2009*	20%		4-6 mnd
Trastuzumab + taxol *Slamon 2001*	40-60%		7-10 mnd

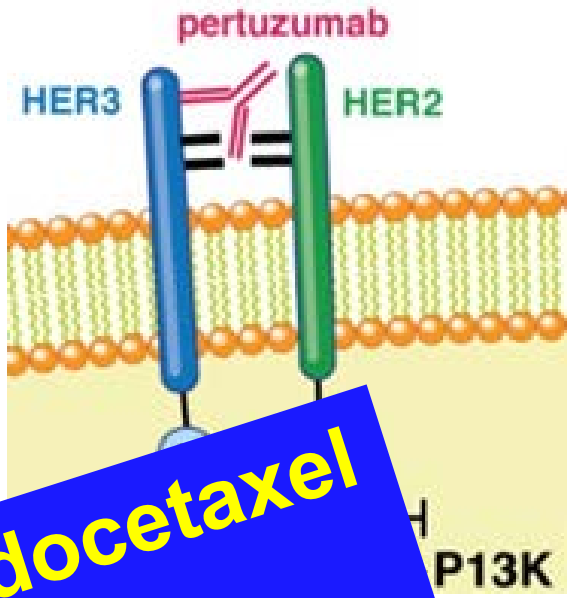
Treatment HER2+ MBC

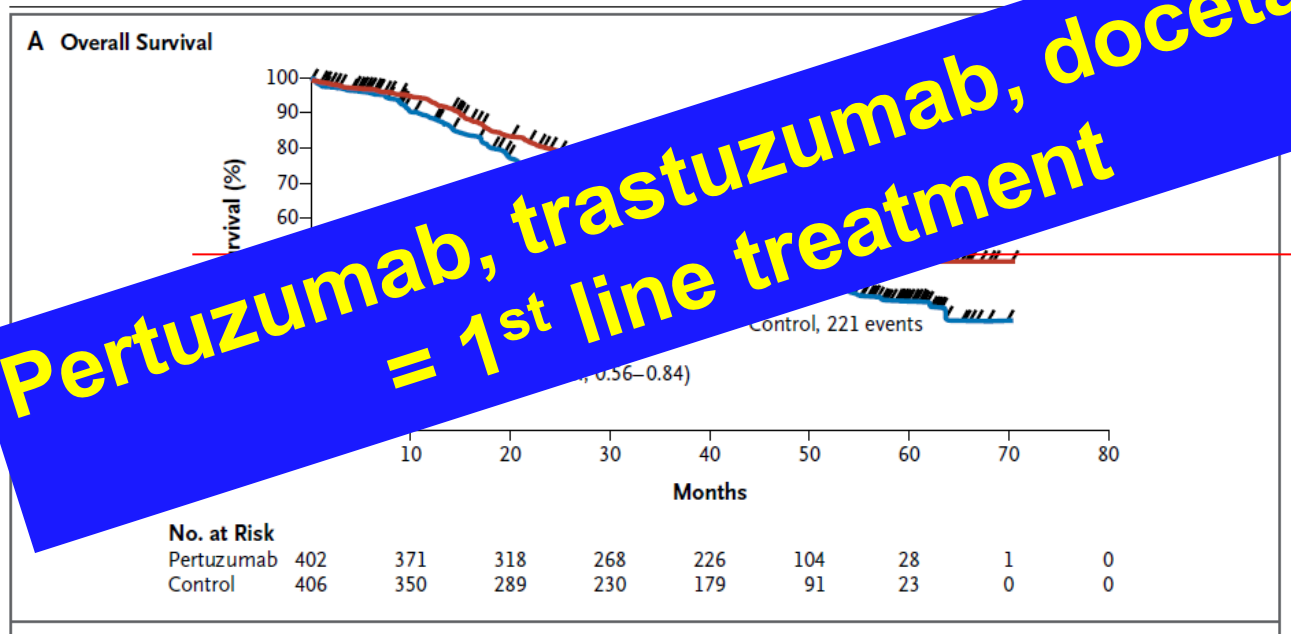


Pertuzumab (Perjetta®)

CLEOPATRA study

mOS 40.8 mnd vs 56.5 mnd

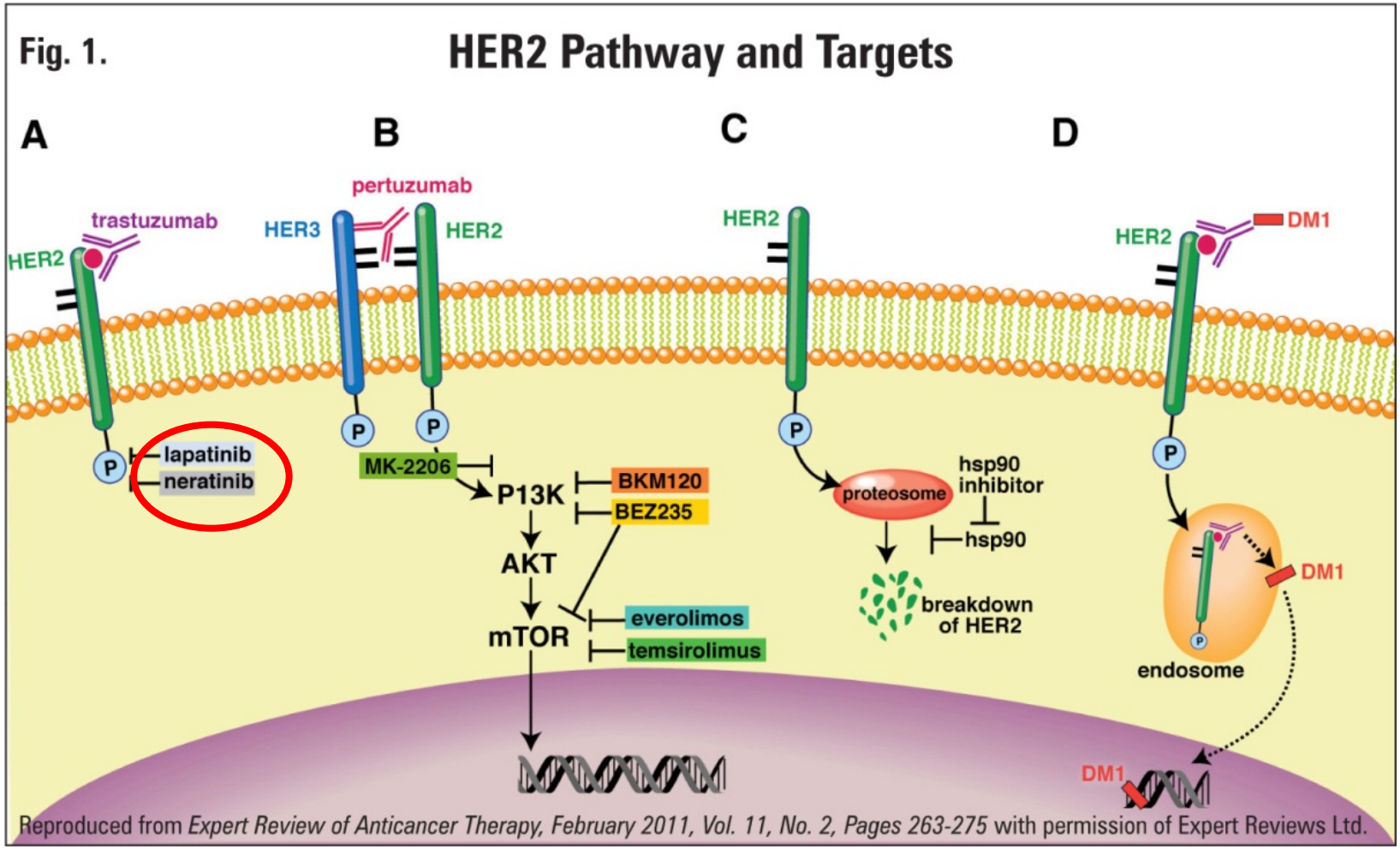




Pertuzumab, trastuzumab, docetaxel = 1st line treatment

Swain, NEJM 2015

Treatment HER2+ MBC



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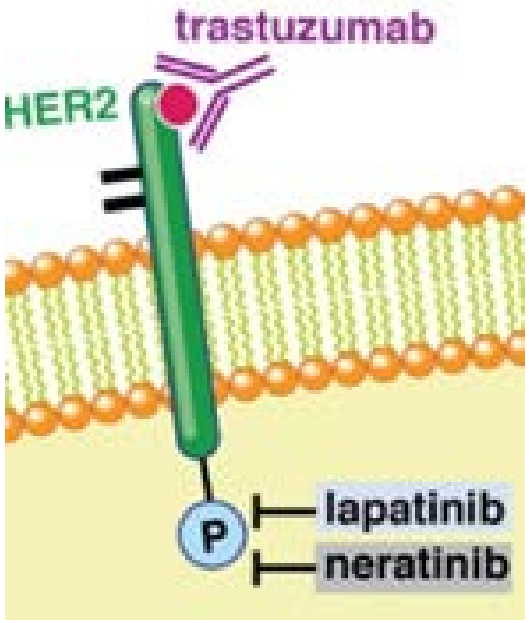
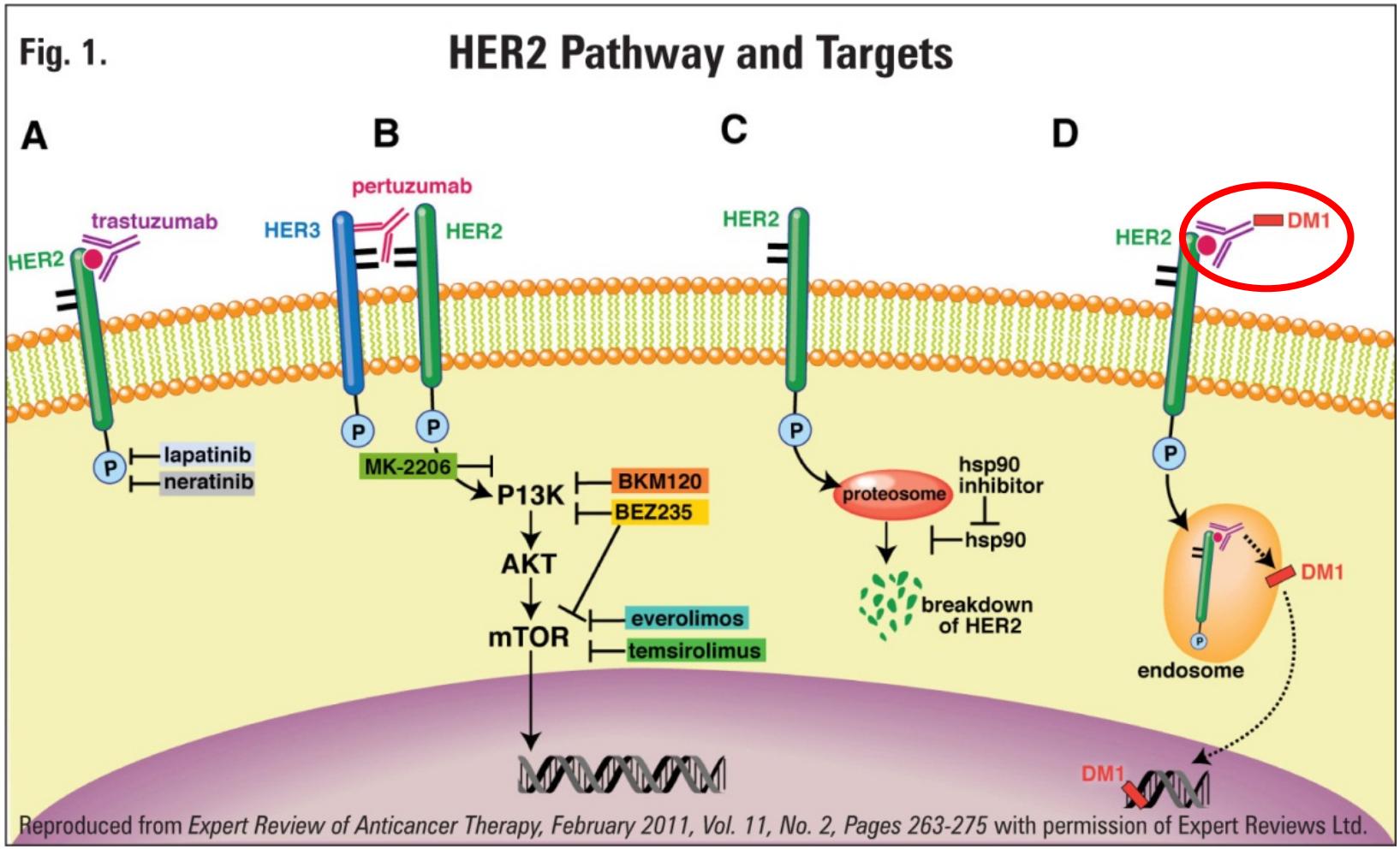
Lapatinib (Tykerb®)



- Tyrosine kinase inhibitor EGFR/Her2
- 1st line combined with letrozol
  PFS 8.3 mnd vs 3.0 mnd
  Johnston 2009
- 2e line combined with capecitabine
  PFS 8.4 mnd vs 4.4mnd
  Geyer 2007
- *BUT:* Diarrhea, rash, mucositis

Treatment HER2+ MBC



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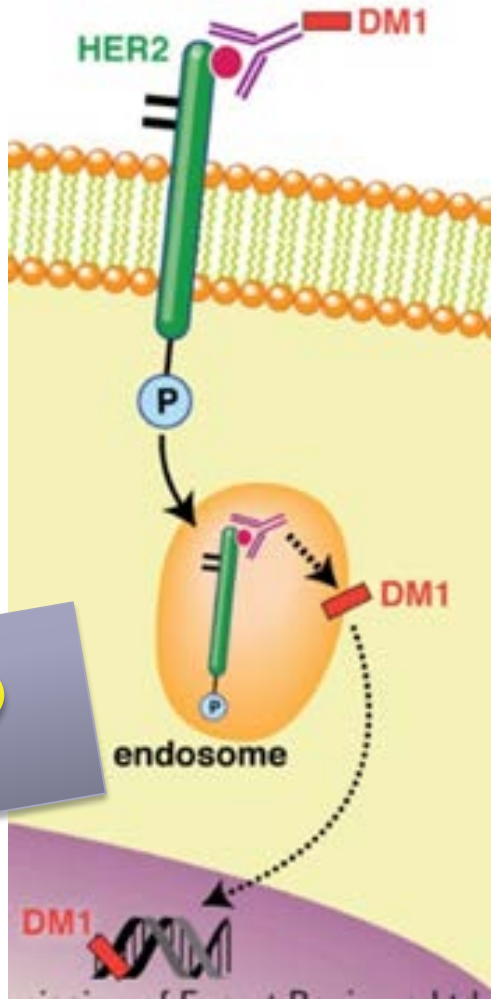
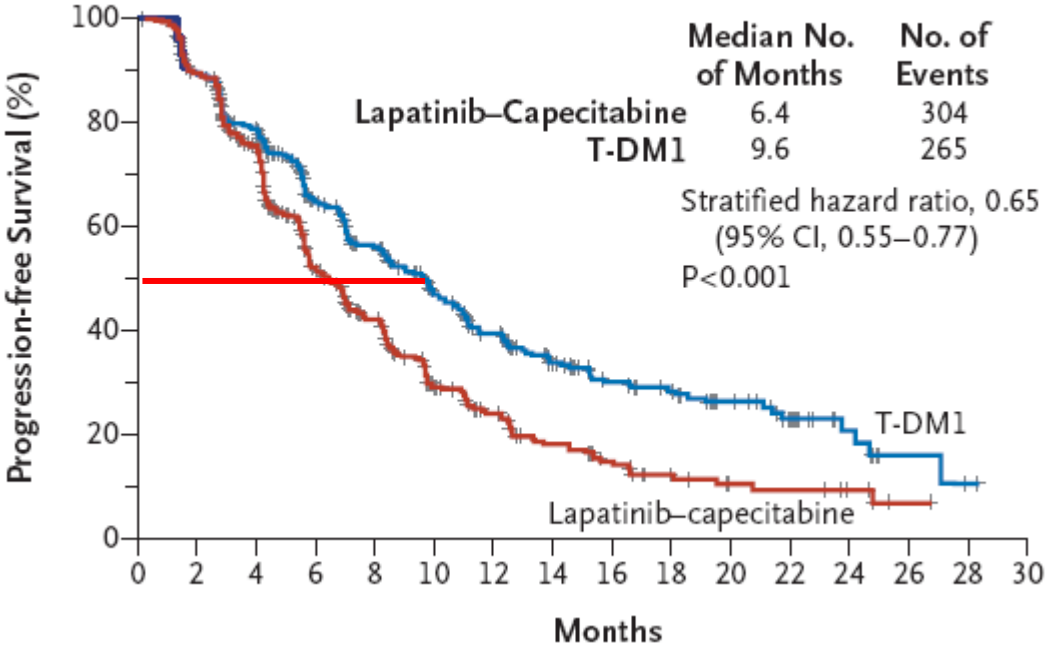
T-DM1 (Kadcyla®)

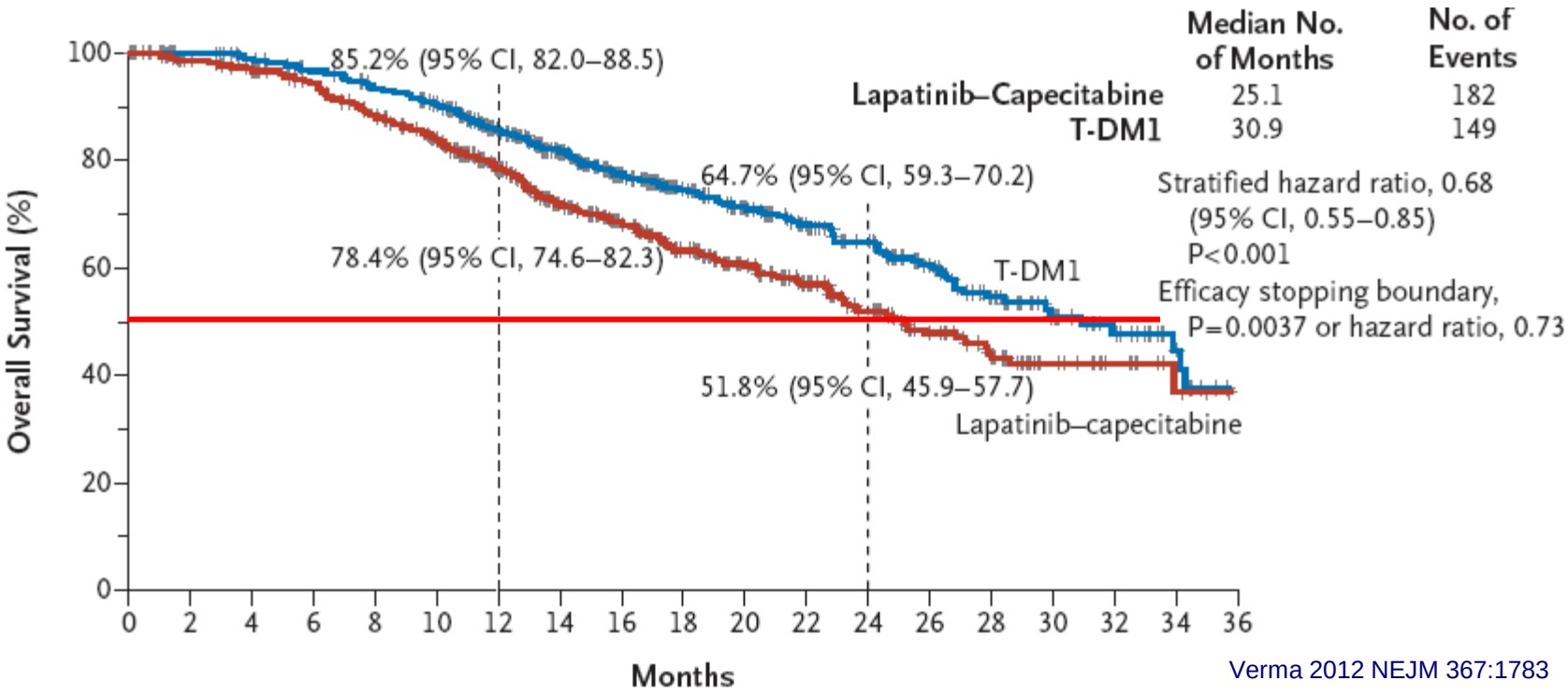
= Trastuzumab - maytansine
inhibits microtubuli formation



VUmc VU University Medical Center Amsterdam

EMILIA studie
T-DM1; 2nd line



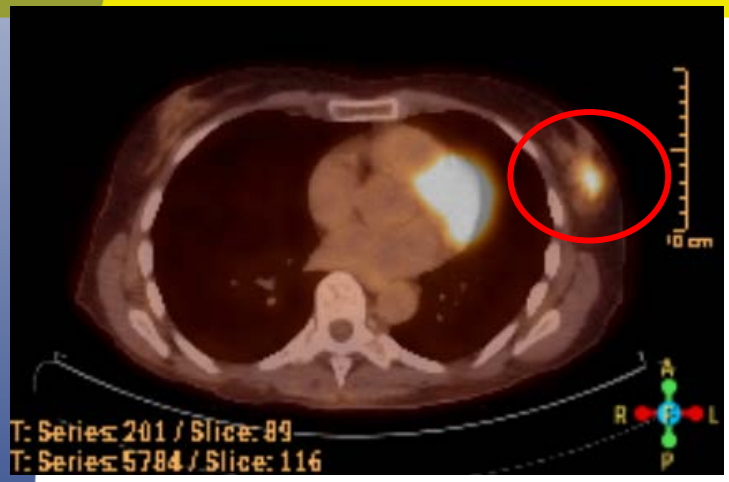


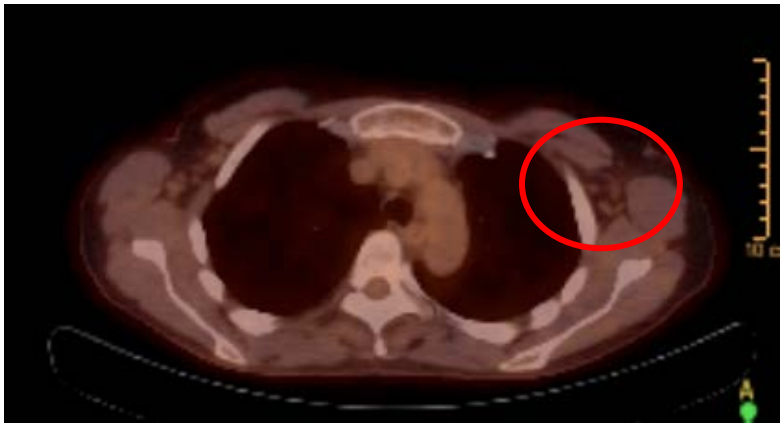
Verma 2012 NEJM 367:1783

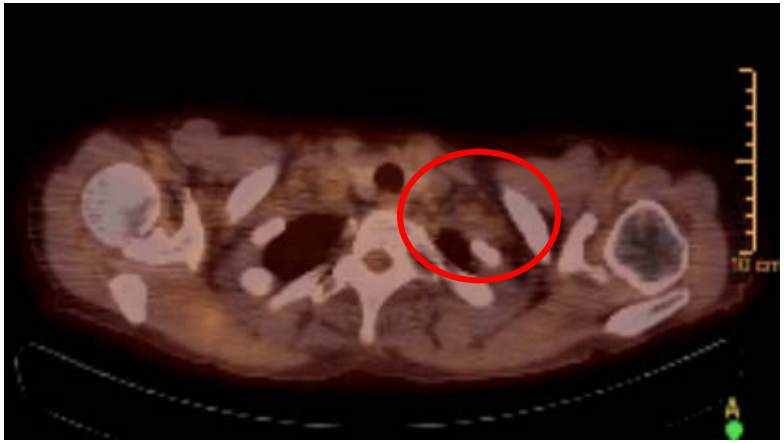
before

after

VU University Medical Center







Brain metastasis in HER2+ BC

- HER2+ MBC have improved overall survival
- Moderate penetration of current treatments to the brain
- No preferred treatment

  (HER2-targeted or ‘classic” chemo)