

# Molekulare Grundlagen der Anti-HER2 Resistenz und Möglichkeiten der Überwindung



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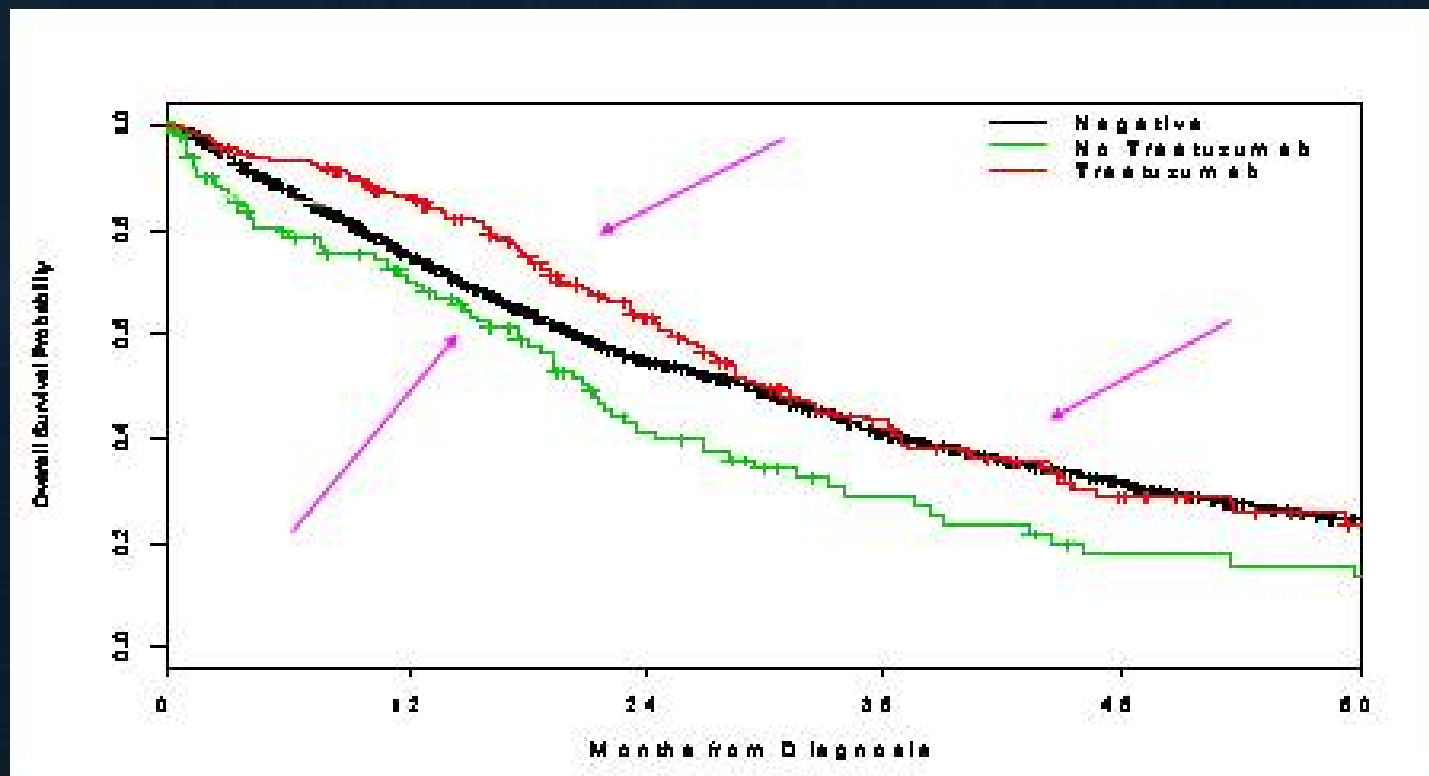


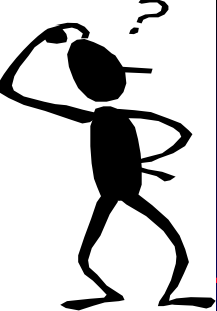
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Technischen Universität München  
Klinikum rechts der Isar  
Direktorin: Prof. Dr. M. Kiechle



# Patient Selection Process

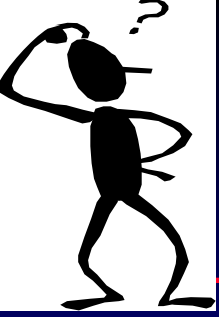
## Overall Survival by Trastuzumab Treatment Groups





# Versagen von Anti-HER2 Therapie

- Zielstruktur vorhanden ?
  - Methodik (IHC, FISH, CISH, SISH)
  - klonale Selektion (Primärtumor vs. Metastase)
- Umgebung der Zielstruktur (Immunfunktion)
- Zielstruktur aktiv, Angriffspunkte zugänglich ?
  - HER2 Rezeptor (p95-HER2, p-HER2, MUC4)
  - weitere Zielstrukturen in HER Familie (HER1, HER3)
- Umgehung der Zielstruktur (Redundante Signalwege)
- ...



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# NSABP-B-31 central evaluation (n=104)

Test for study inclusion *	Laboratory	Central Herceptest	Central PathVysion FISH - Test	Negative with both methods
		0-2+	Non amplified	
Herceptest 3+ (n=80)	NO Reference Laboratory	10/52	12/52	10/52 (19%)
	Reference laboratory	1/28	1/28	1/28 (4%)
Other IHC Tests (n=24)	NO Reference laboratory	11/23	9/23	8/23 (35%)
	Reference laboratory	0/1	0/1	0/1 (0%)

• Cases included on the basis of local FISH results, are not part of this analysis

## American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

*Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, K. Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijve and Daniel F. Hayes*

- ✓ Gewebeprobe
- ✓ Testsystem
- ✓ Interpretation
- ✓ Bericht

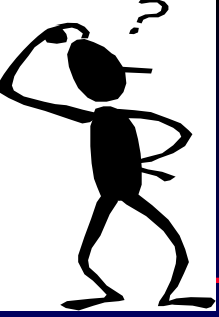
**Table 3.** Sources of HER2 Testing Variation

Preanalytic
Time to fixation
Method of tissue processing
Time of fixation
Type of fixation
Analytic
Assay validation
Equipment calibration
Use of standardized laboratory procedures
Training and competency assessment of staff
Type of antigen retrieval
Test reagents
Use of standardized control materials
Use of automated laboratory methods
Postanalytic
Interpretation criteria
Use of image analysis
Reporting elements
Quality assurance procedures
Laboratory accreditation
Proficiency testing
Pathologist competency assessment

Abbreviation: HER2, human epidermal growth factor receptor 2.

# HER2 Status in Primärtumor und Metastase

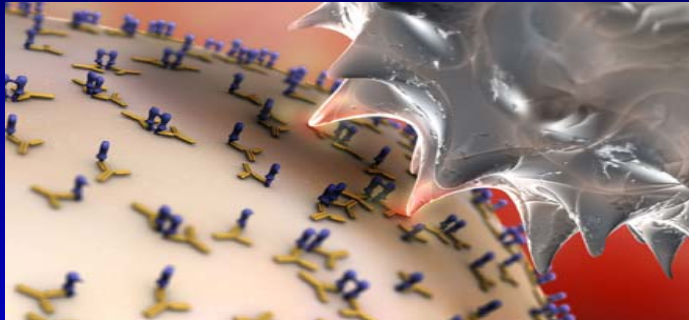
Author	n	Konkordanz	Bemerkungen
Cardoso (2001)	370	98 %	
Gancberg (2002)	107	93 %	
Meng (2004)	31	97 %	CTCs: 37.5% Diskordanz
Carlsson (2004)	47	85 %	
Tapia (2007)	105	93%	
Fehm (2007)	77 %	72 %	Serum and CTCs



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# Trastuzumab wirkt beim frühen und fortgeschrittenen Mammakarzinom



Aktivierung der  
Antikörper-vermittelten  
Zytotoxizität (ADCC)

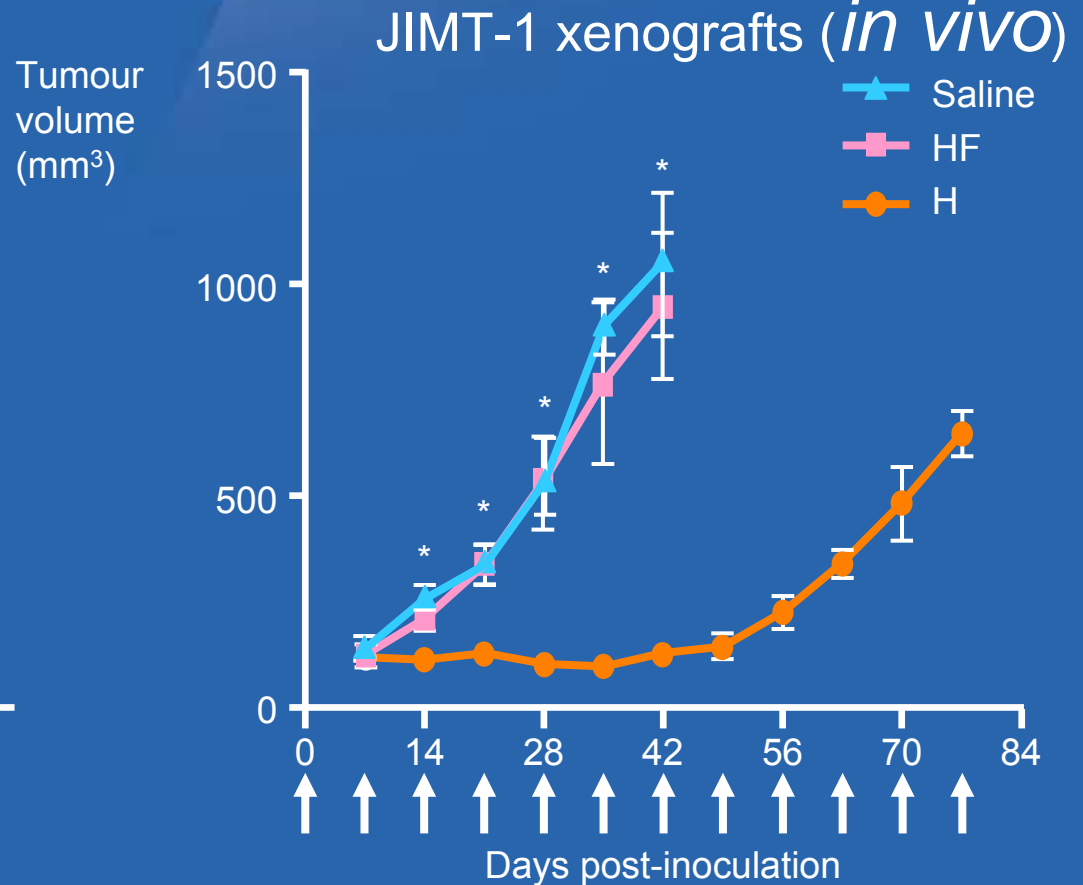
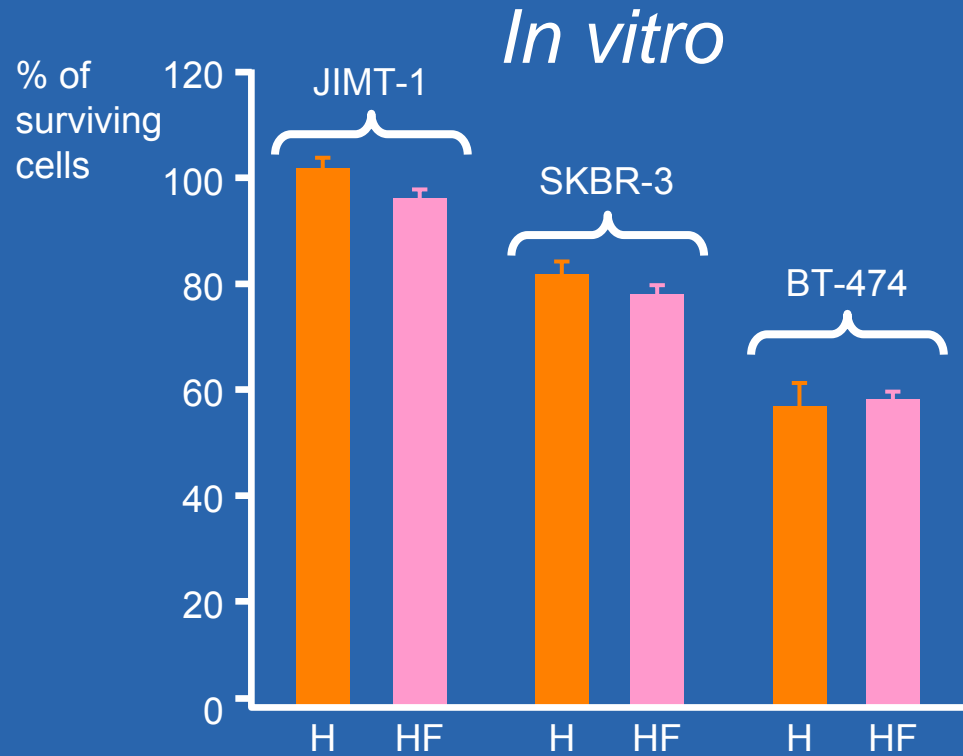


Inhibition der HER2  
vermittelten Signaltransduktion

## Zusätzliche Mechanismen

- Verhinderung der p95 HER2 Bildung
- Hemmung der HER2-regulierten Angiogenese

# Herceptin *in vivo* vs *in vitro* activity JIMT-1 tumours



● ADCC is a major MoA only apparent in the *in vivo* model

\*p<0.05; HF, Herceptin-F(ab')<sub>2</sub>

## Immunoglobulin G Fragment C Receptor Polymorphisms and Clinical Efficacy of Trastuzumab-Based Therapy in Patients With HER-2/*neu*-Positive Metastatic Breast Cancer

Antonino Musolino, Nadia Naldi, Beatrice Bortesi, Debora Pezzuolo, Marzia Capelletti, Gabriele Missale, Diletta Laccabue, Alessandro Zerlini, Roberto Comin, Giuseppe Biasoni, Tiziana Motta, and Andrea Ardizzoni

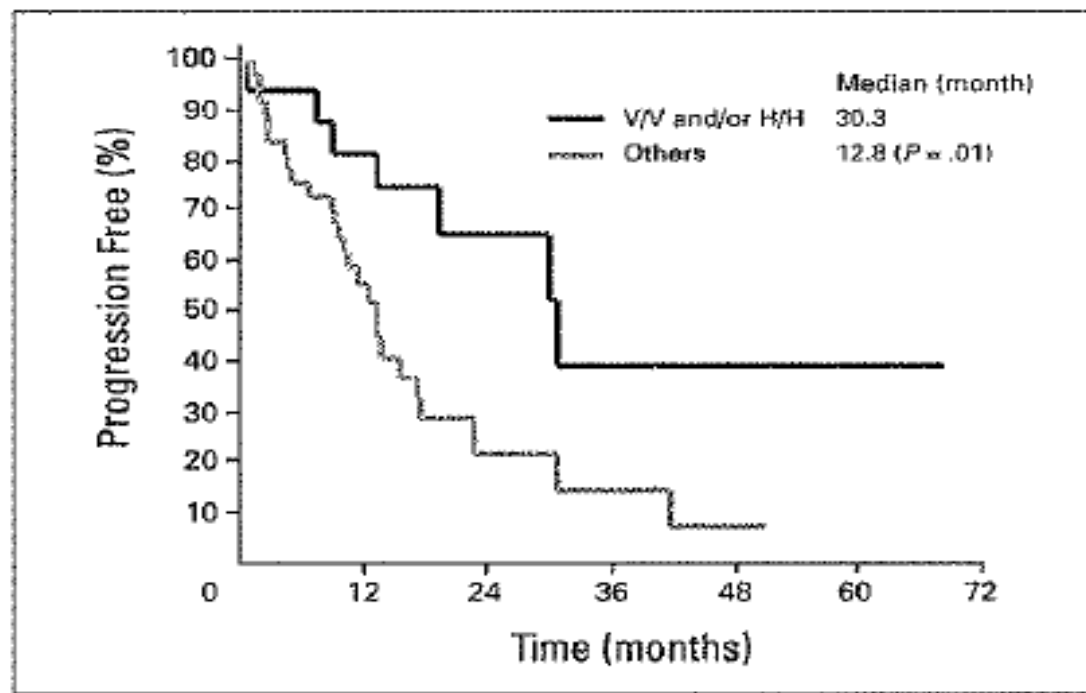
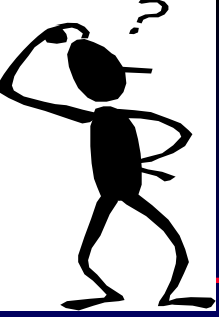


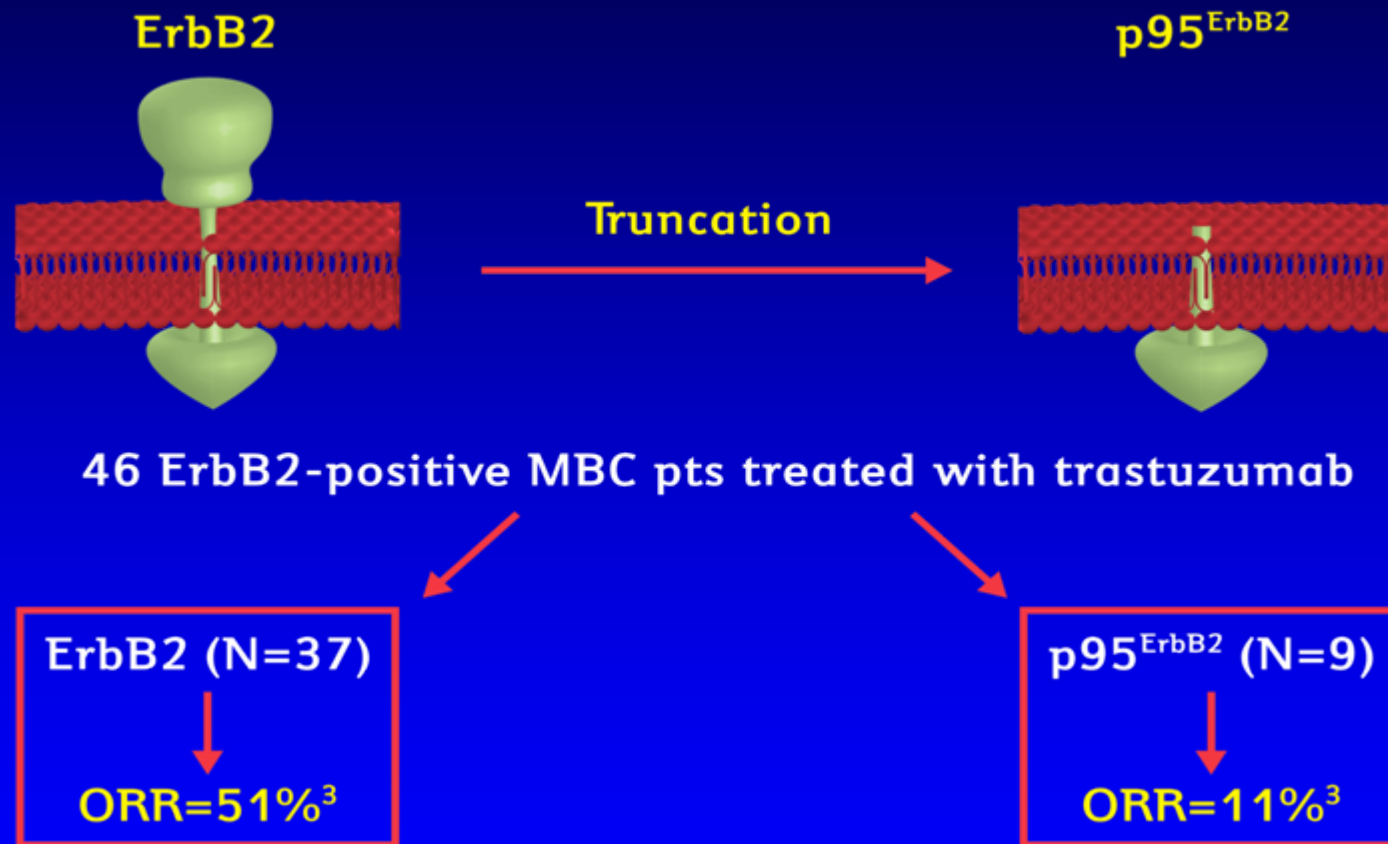
Fig 2. Progression-free survival (PFS) by immunoglobulin G (IgG) fragment C receptor 3 (FcγRIIIa) 158 valine (V)/phenylalanine (F) and FcγRIIIa 131 histidine (H)/arginine (R) polymorphisms. PFS curves were plotted by FcγRIIIa 158 V/F and FcγRIIIa 131 H/R genotype. Others represent patients without either FcγRIIIa 158 V/V or FcγRIIIa 131 H/H genotype.



# Versagen von Anti-HER2 Therapie

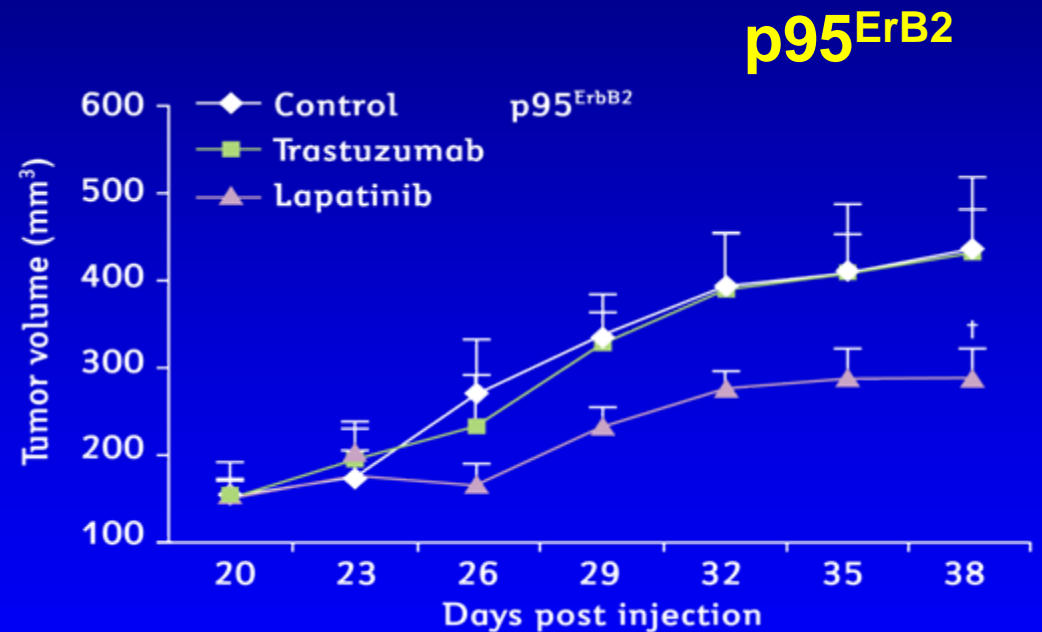
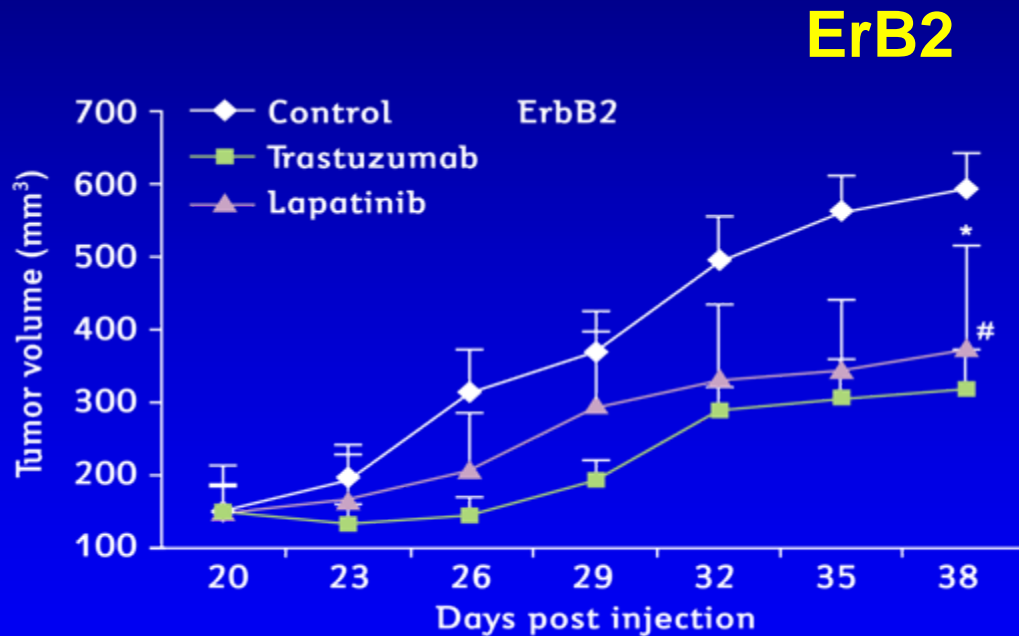
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# Benefit von Trastuzumab verringert bei Tumoren mit p95<sup>ErbB2</sup> Expression (ohne extrazelluläre Domäne)



MBC = metastatic breast cancer; pts = patients; ORR = overall response rate

# Lapatinib, nicht aber Trastuzumab ist bei Tumoren mit p95<sup>ErB2</sup> Expression wirksam



# PTEN als Prädiktor für Trastuzumab-Resistenz

## PTEN: Tumorsuppressorgen

Geringe PTEN-Expression assoziiert mit höherer Invasivität und schlechterer Prognose

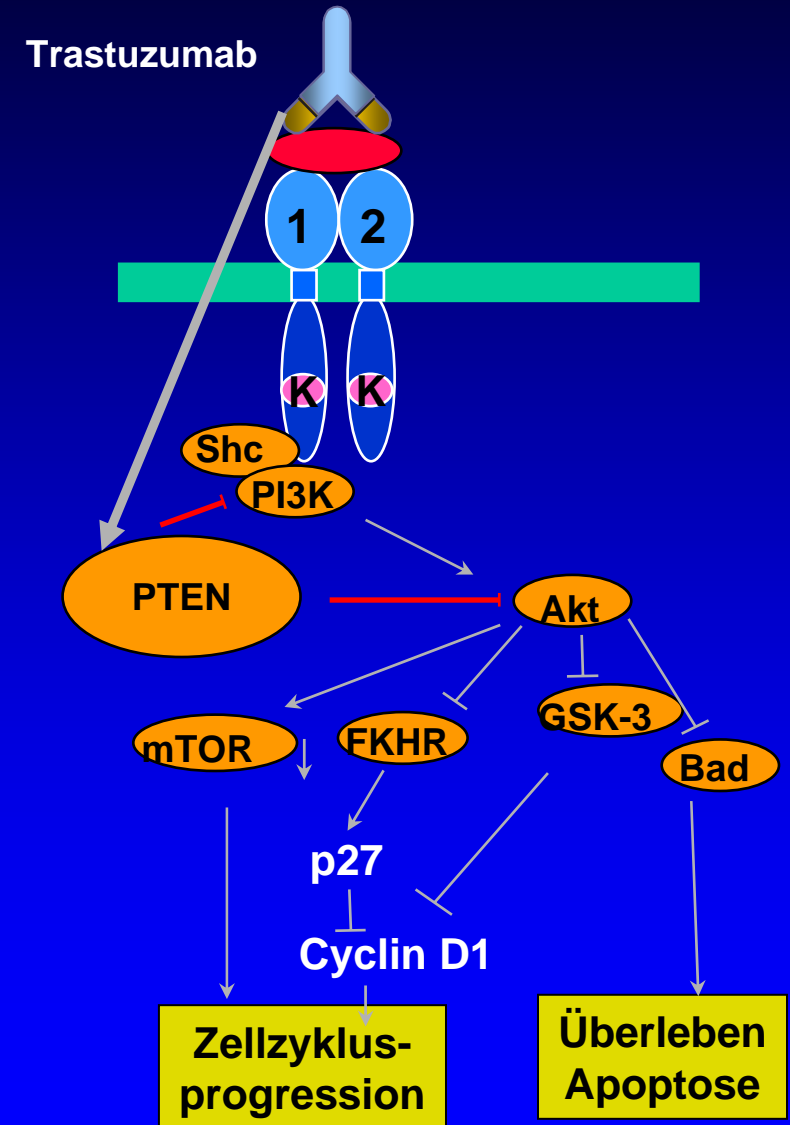
Trastuzumab aktiviert PTEN (Tumorsuppressorgen)

- Inhibition von Akt
- Inhibition der Zellproliferation

Bei Fehlen oder Mutation von PTEN:

- Blockade der Trastuzumab-vermittelten Inhibition der Zellproliferation
- Resistenz auf Trastuzumab-Therapie

**PTEN- Defizienz = prädiktiver Marker für Trastuzumab-Resistenz in vitro, in vivo und in der Klinik**



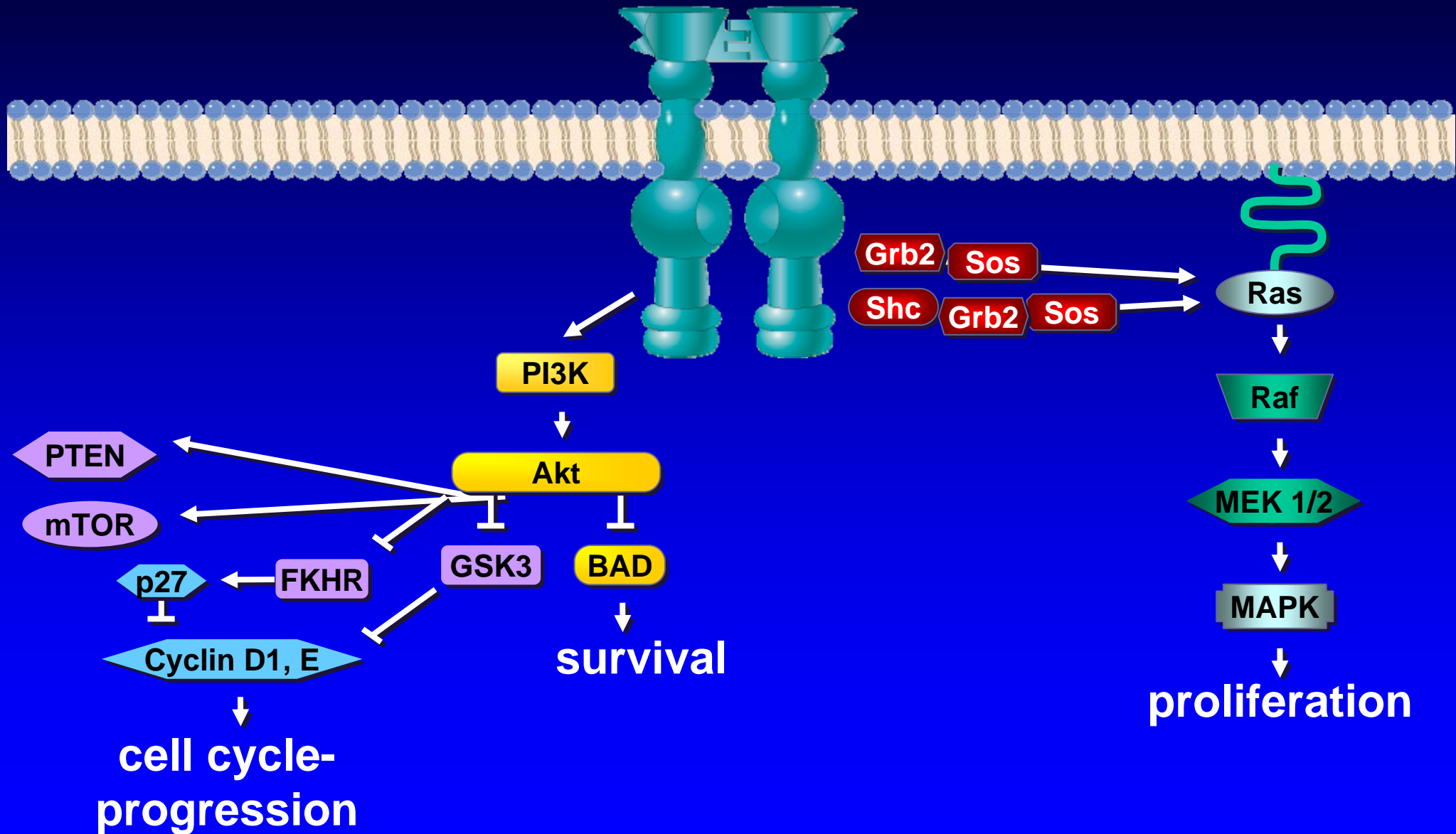


# Anti-HER2 Resistenz: Therapeutische Ansatzpunkte

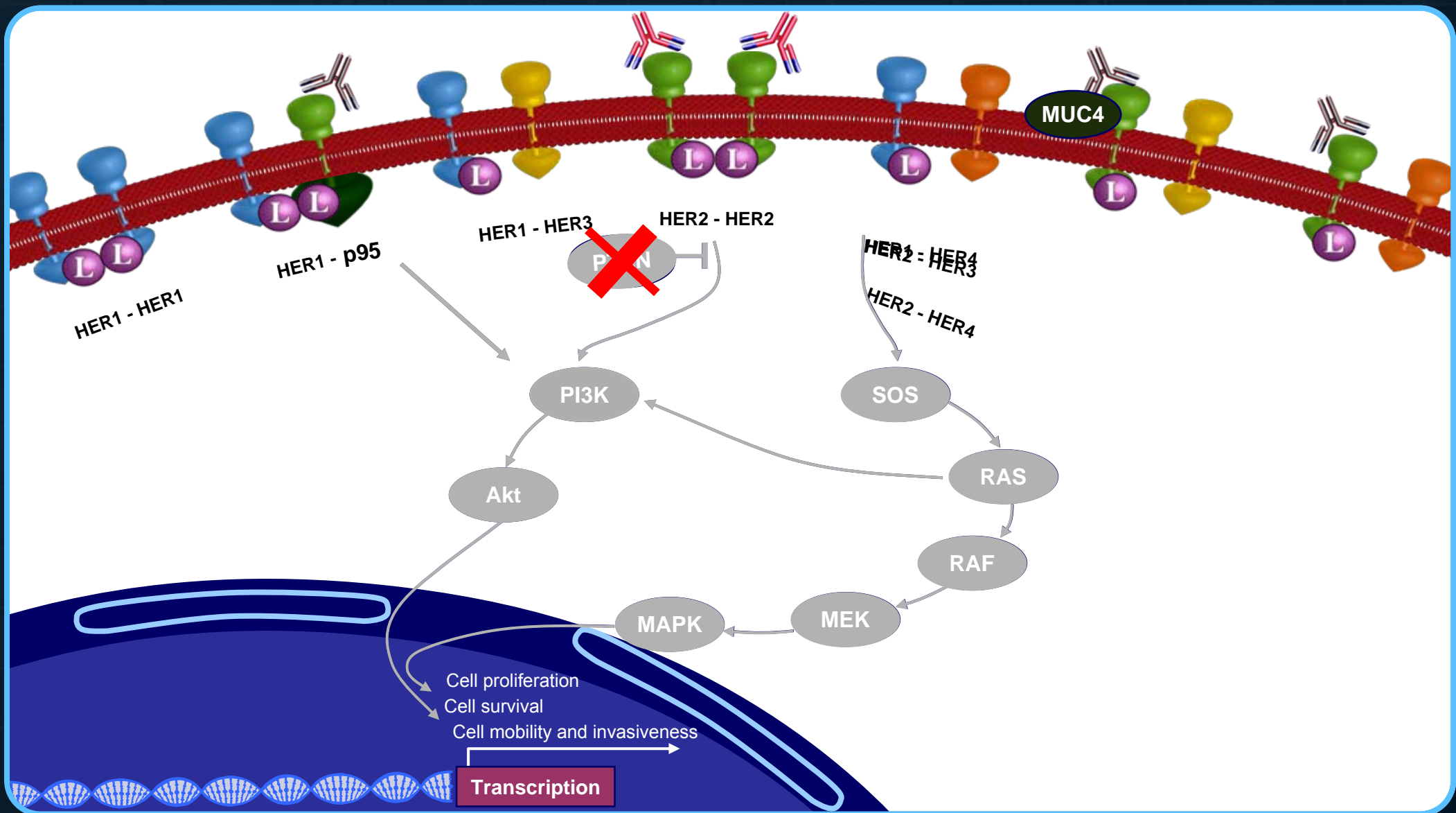
- **Optimale Patientenselektion**
  - Methodik (ASCO-CAP Guidelines)
  - Testung an Metastase
  - prädiktive Marker (c-Myc, PTEN, p-95 HER2, ...)
- **Alternative Therapeutika**
  - Trastuzumab, Trastuzumab-DM1, Lapatinib, Pertuzumab, ...
- **Multi-targeting** (Kombinationen, verschiedene Signalwege)
- ...



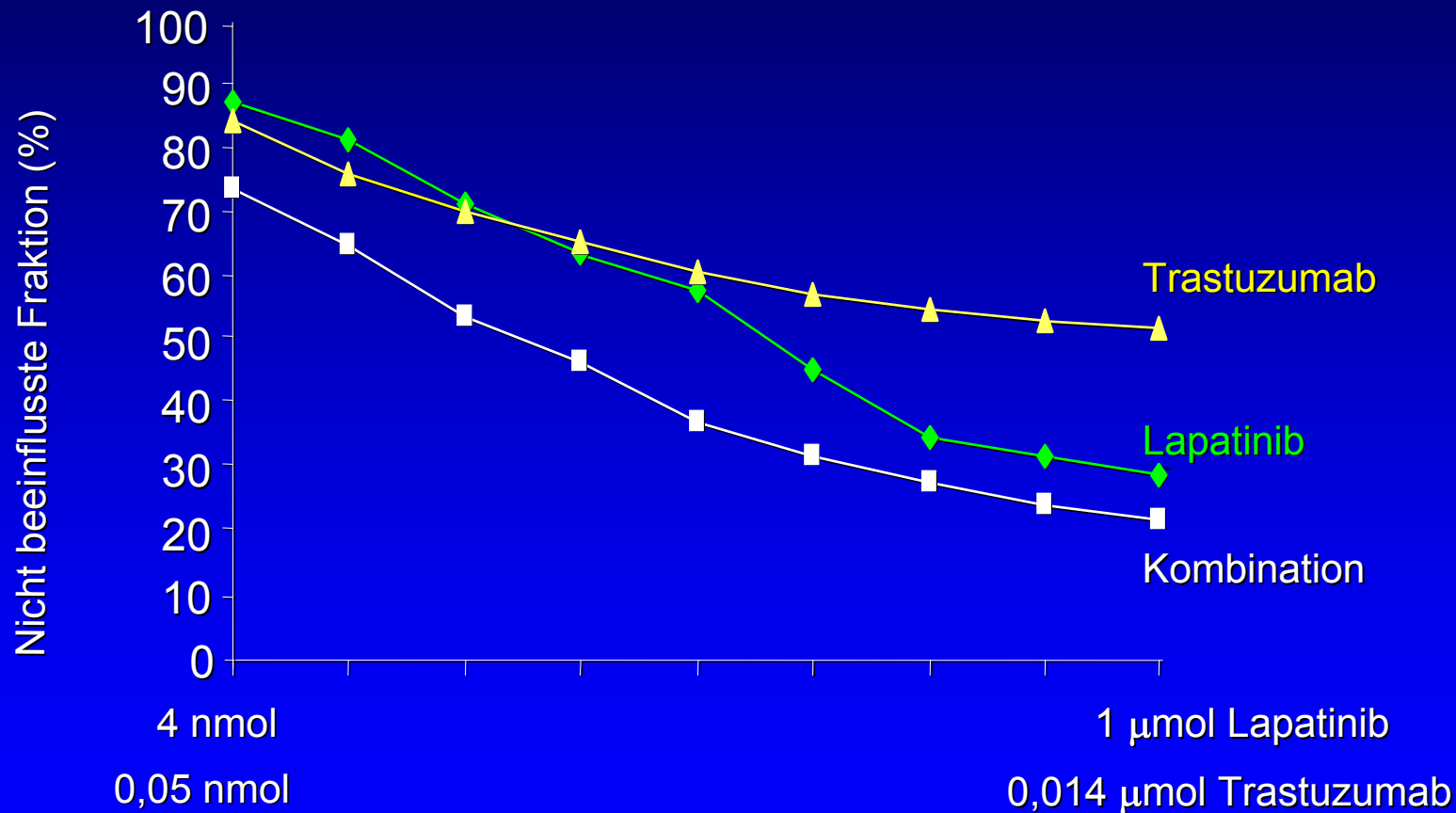
# ErbB - signal transduction pathways



# Total Blockade of HER2 May Provide Greater Anti-tumor Activity and Overcome Resistance



# Lapatinib + Trastuzumab *in vitro* bei ErbB2-überexprimierenden MDA-MB-361 Brustkrebszellen\*

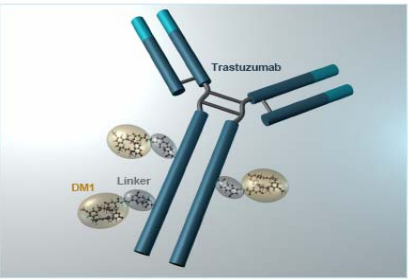


\*Die klinische Bedeutung dieses in-vitro-Experiments ist nicht bekannt

# Trastuzumab-DM1

- Antibody-drug conjugate
- Binds to HER2 with affinity similar to trastuzumab
- Provides intracellular delivery of mertansine
  - Derivative of maytansine, a natural-product microtubule polymerization inhibitor
  - 20-100 more potent than vincristine

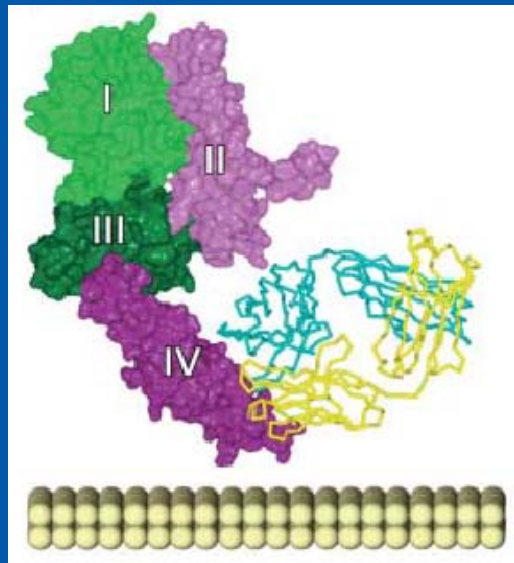




# Conclusions

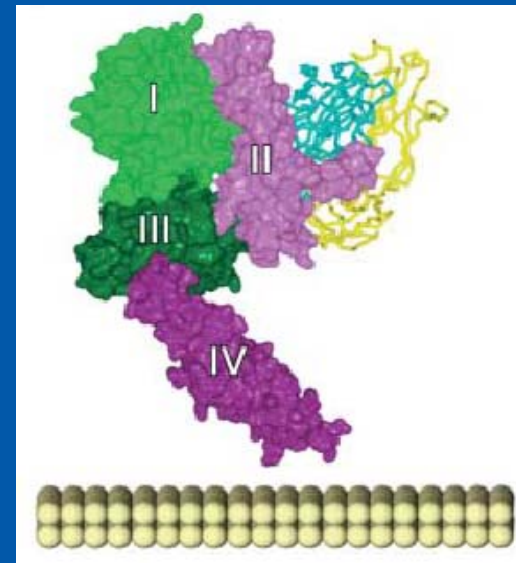
- In these **24 patients with HER2+ MBC** previously treated with Trastuzumab, Grade  $\geq 2$  AEs have been infrequent and manageable.
- No cardiac-specific toxicity has been observed.
- **Rapidly reversible Grade 4 thrombocytopenia** was dose-limiting at 4.8 mg/kg; the MTD of T-DM1 every 3 weeks is 3.6 mg/kg.
- T-DM1 has demonstrated anti-tumor activity (**6 partial responses**) at doses at or below the MTD.
- A phase II trial of T-DM1 in HER2-positive MBC is underway. Dose-escalation of a weekly schedule of TDM-1 is ongoing until an MTD is determined.

# Herceptin and pertuzumab bind to distinct epitopes on HER2 extracellular domain



Herceptin

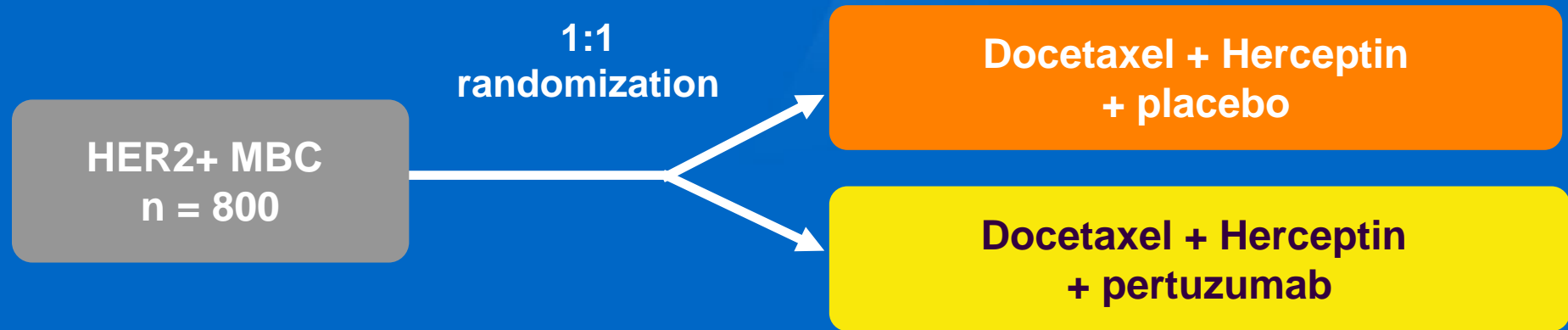
- Activates antibody-dependent cellular cytotoxicity
- Inhibits HER2-mediated signalling
- Inhibits shedding and, thus, formation of new p95
- Inhibits HER2-related angiogenesis



Pertuzumab

- Activates antibody-dependent cellular cytotoxicity
- Prevents receptor dimerisation
- Potent inhibitor of HER2/HER2- and HER2/HER3-mediated signalling pathways

# CLEOPATRA: Phase III study of Herceptin + pertuzumab in HER2+ MBC



An international Phase III randomized, double-blind, placebo-controlled study  
(approximately 250 sites worldwide)

## Endpoints:

- Progression-free survival
- Overall survival
- Biomarker analysis

# ALTT0: Pre-defined subgroup analyses

Molecular marker	Distribution	Hypotheses
<b>c-Myc</b>	c-Myc co-amplified 30%  c-Myc not co-amplified 70%	<b><i>“Exquisitely sensitive to trastuzumab”</i></b>  Group where L benefits more likely (80% power for any pair-wise comparison to detect <b>DFS 0.754</b> )
<b>PTEN</b>	Loss / reduced expression in 40%	<b><i>“Resistant to trastuzumab”</i></b>  Group where L benefits more likely (80% power for any pair-wise comparison to detect <b>DFS 0.72</b> )
<b>p95HER2</b>	Seen in 10%	<b><i>“Resistant to trastuzumab”</i></b>  Group where L benefits more likely (80% power for any pair-wise comparison to detect <b>DFS 0.638</b> )

# Evidenzbasierte Brustkrebs-Therapie



[www.karger.com/brc](http://www.karger.com/brc)

Leitlinien für Diagnostik und Therapie, jährlich aktualisiert



AGO (DKG, DGGG)  
[www.ago-online.org](http://www.ago-online.org)



Tumorzentrum München:

- ✓ Patientinnenratgeber Mammakarzinom
- ✓ Manual Mammakarzinom für Ärzte

<http://www.med.uni-muenchen.de/TZMuenchen/manuale.htm>