IBZ
Interdisziplinäres
Brustzentrum München

Molekulare Grundlagen der Anti-HER2 Resistenz und Möglichkeiten der Überwindung

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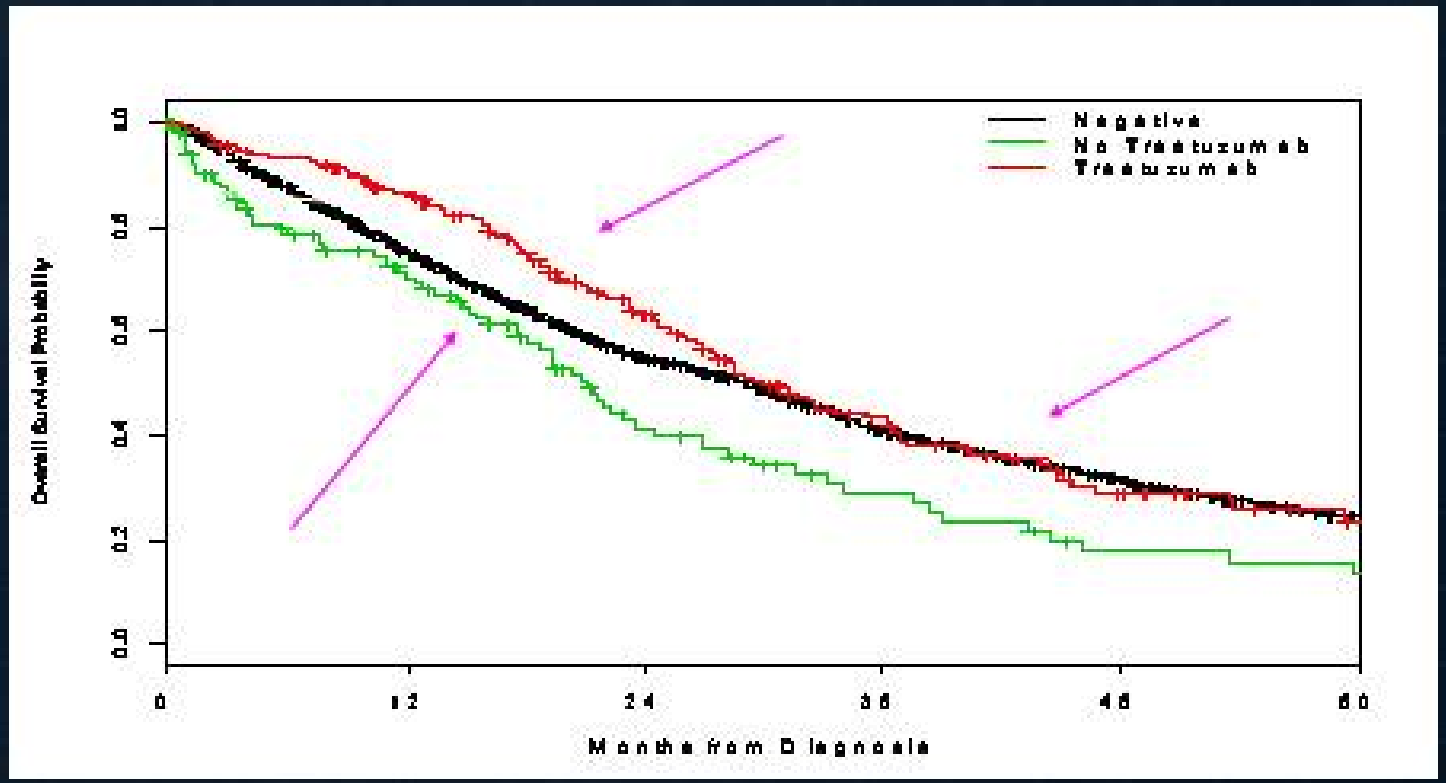
Frauenklinik und Poliklinik der
Technischen Universität München
Klinikum rechts der Isar
Direktorin: Prof. Dr. M. Kiechle

Patient Selection Process

Overall Survival by Trastuzumab Treatment Groups

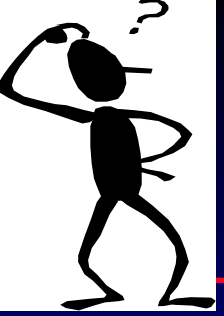


ASCO Annual Meeting

ASCO Annual '08 Meeting

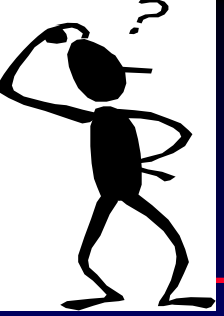
2008 ASCO Merit Award Recipient

Dawood et al, ASCO 2008



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

S. Paik, personal communication 2001

VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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**

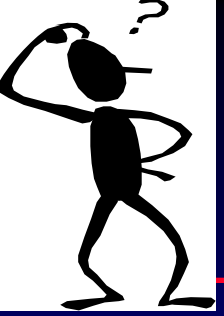
Table 3. Sources of HER2 Testing Variation

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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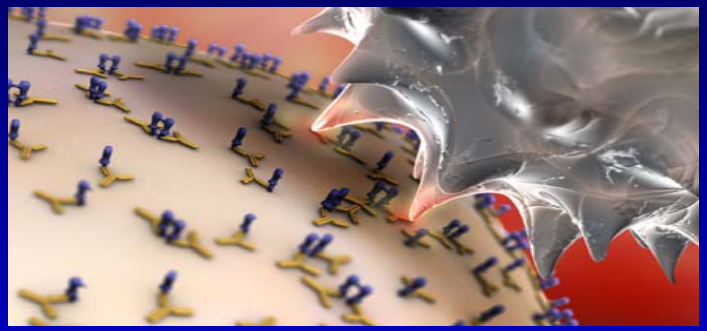
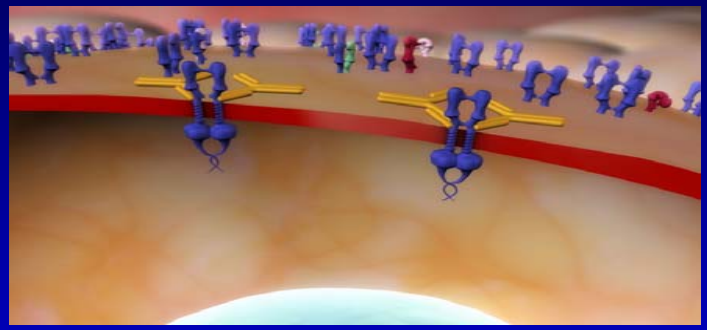
- …

Trastuzumab wirkt beim frühen und fortgeschrittenen Mammakarzinom



Aktivierung der Antikörper-vermittelten Zytotoxizität (ADCC)



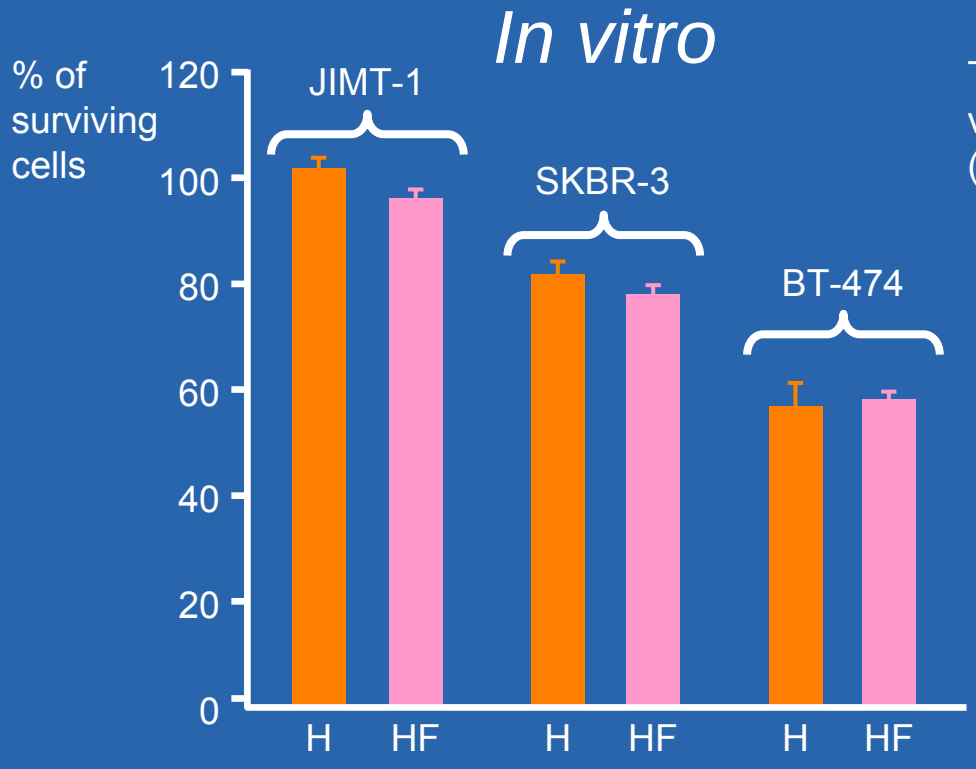
Inhibition der HER2 vermittelten Signaltransduktion

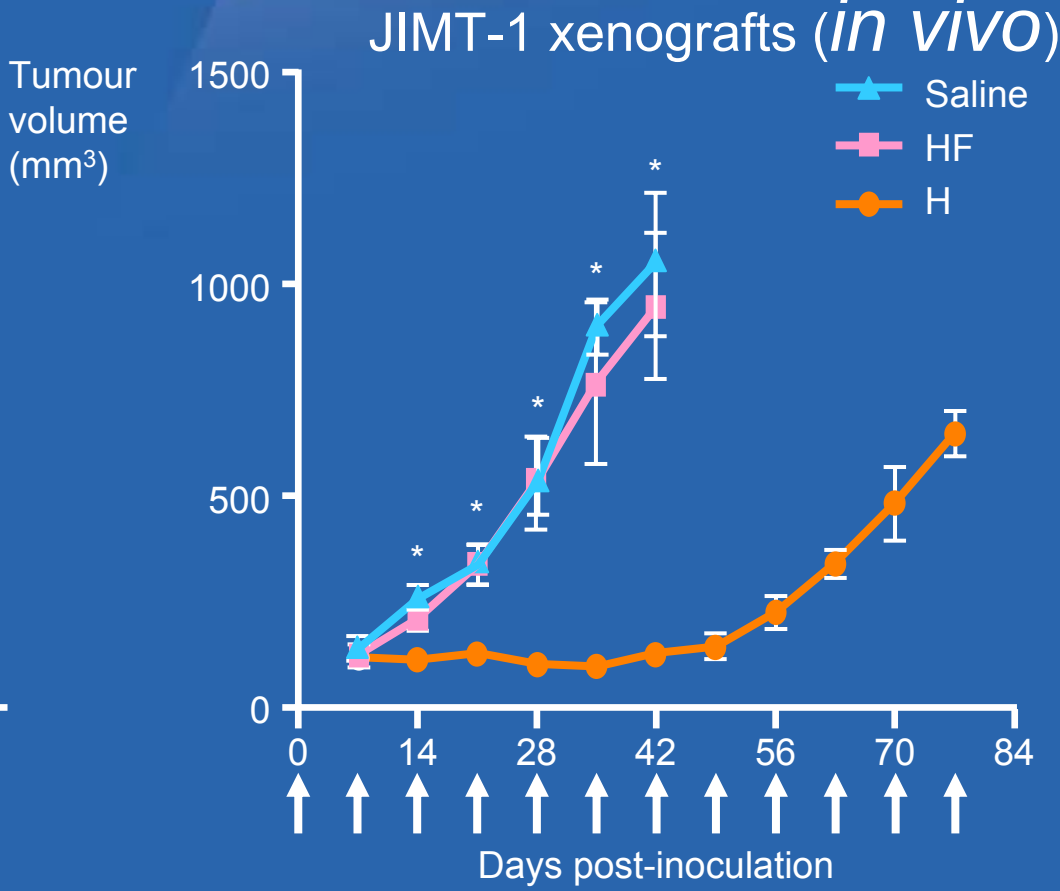
<u>Zusätzliche Mechanismen</u>

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

ADCC, antibody-dependent cellular cytotoxicity

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')$_2$

Barok et al 2007

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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 Zerbini, Roberta Camisa, Gianpaolo Bisagni, Tonia Maria Neri, and Andrea Ardizzoni

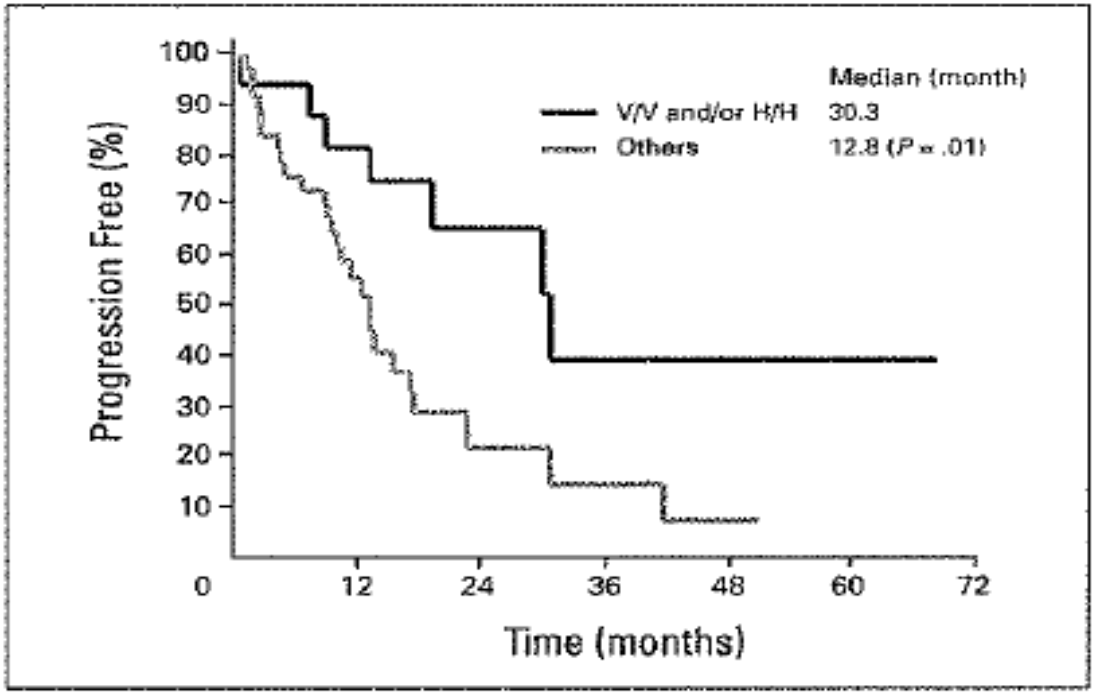
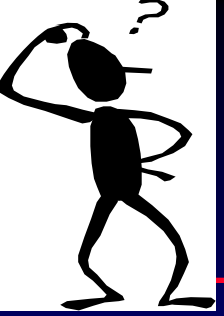


Fig 2. Progression-free survival (PFS) by immunoglobulin G (IgG) fragment C receptor IIIa (FcγRIIIa) 158 valine (V)/phenylalanine (F) and FcγRIIa 131 histidine (H)/arginine (R) polymorphisms. PFS curves were plotted by FcγRIIIa 158 V/F and FcγRIIa 131 H/R genotype. Others represent patients without either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

Musolino et al, JCO 2008



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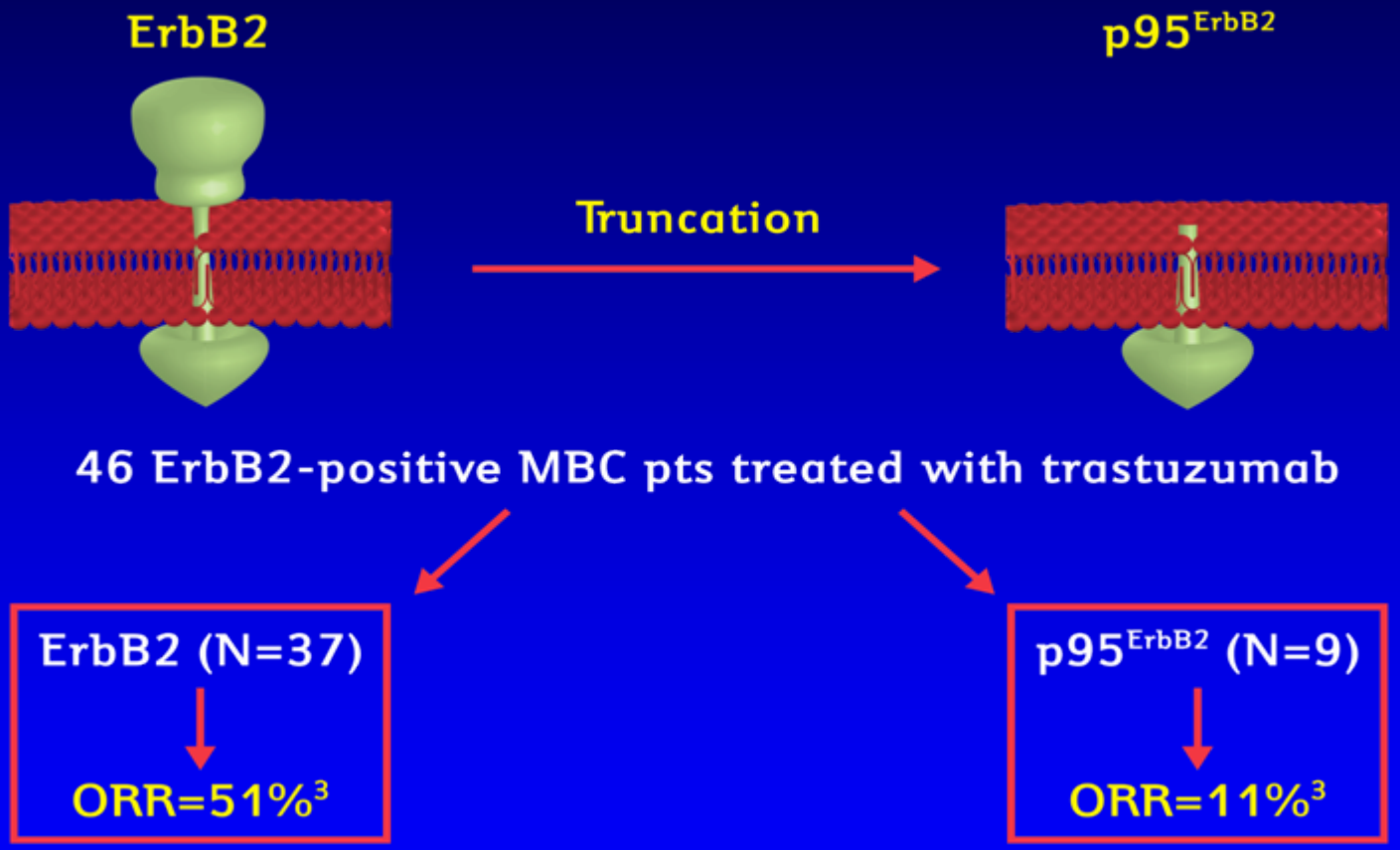
- . . .

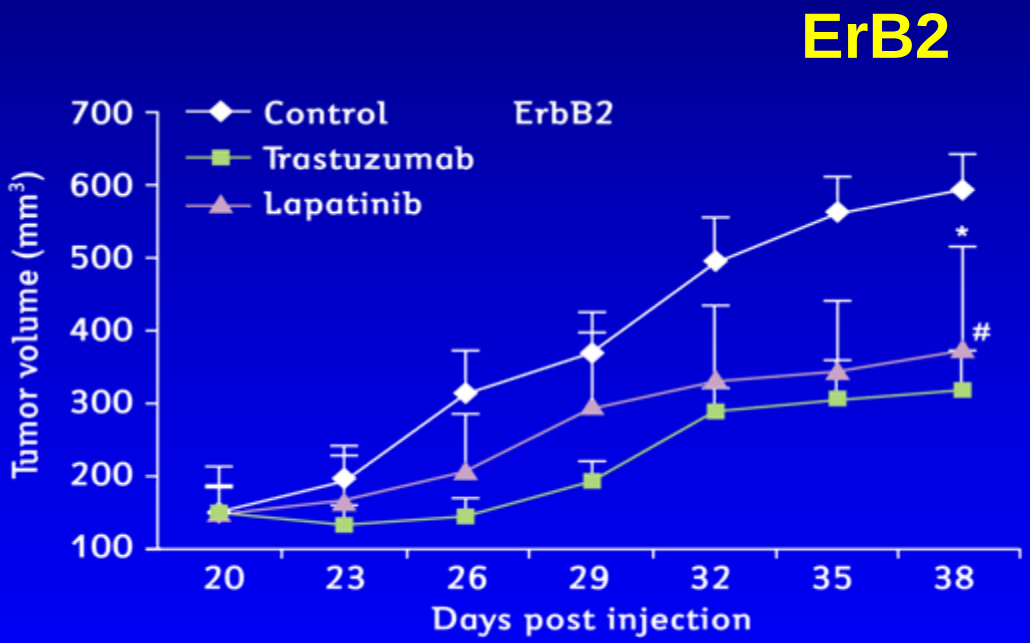
Benefit von Trastuzumab verringert bei Tumoren mit $p95^{ErbB2}$ Expression (ohne extrazelluläre Domaine)

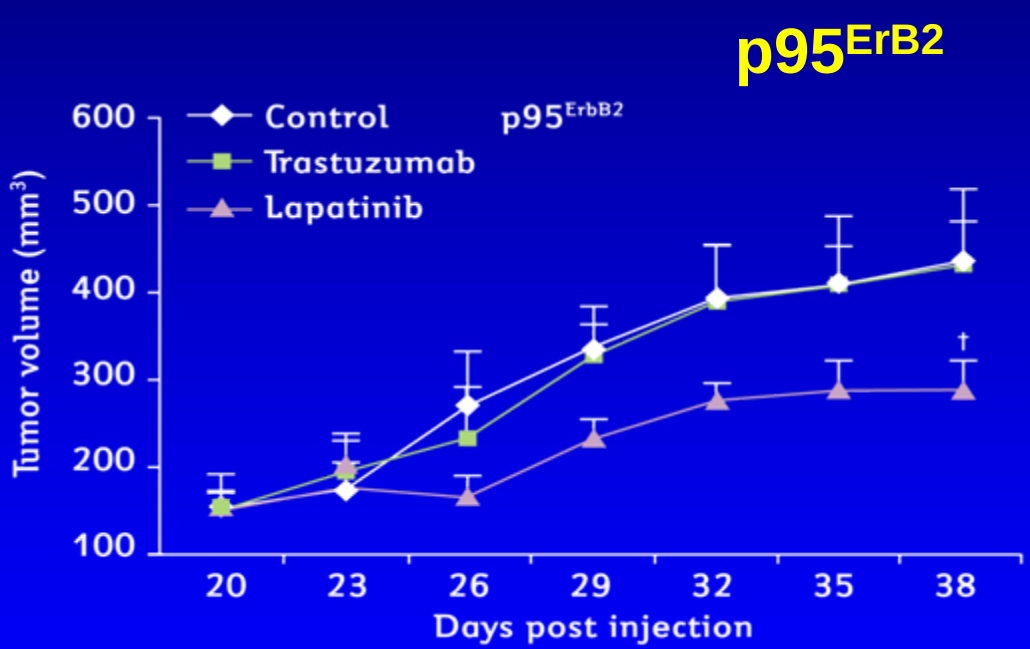


MBC = metastatic breast cancer; pts = patients; ORR = overall response rate

1. Saez et al. *Clin Cancer Res* 2006;**12**:424-31; 2. Xia et al. *Oncogene* 2004;**23**:646-53; 3. Scaltriti et al. *J Natl Cancer Inst* 2007;**99**:628-38.

Lapatinib, nicht aber Trastuzumab ist bei Tumoren mit $p95^{ErbB2}$ Expression wirksam





Scaltriti et al. *J Natl Cancer Inst* 2007;**99**:628-38

PTEN als Prädiktor für **Trastuzumab-Resistenz**

PTEN: Tumorsuppressorgen

Geringe PTEN-Expression assoziiert mit höherer Invasivität und schlechterer Prognose

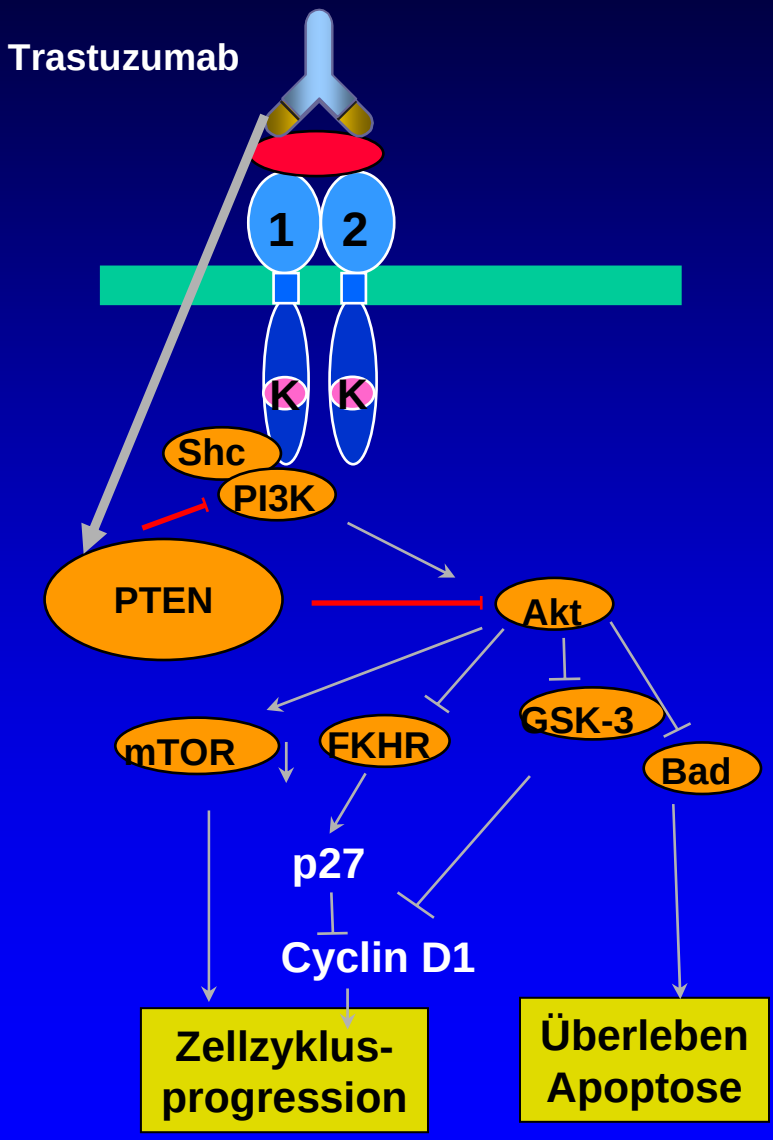
Trastuzumab aktiviert PTEN (Tumorsuppressorgen)

- → Inhibition von Akt
- → Inhibition der Zellproliferation

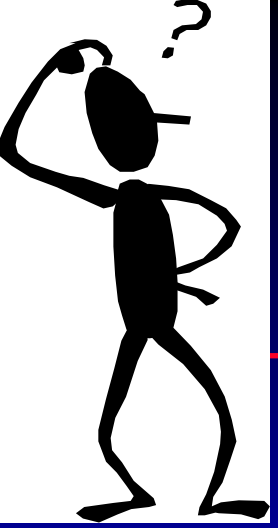
Bei Fehlen oder Mutation von PTEN:

- → 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



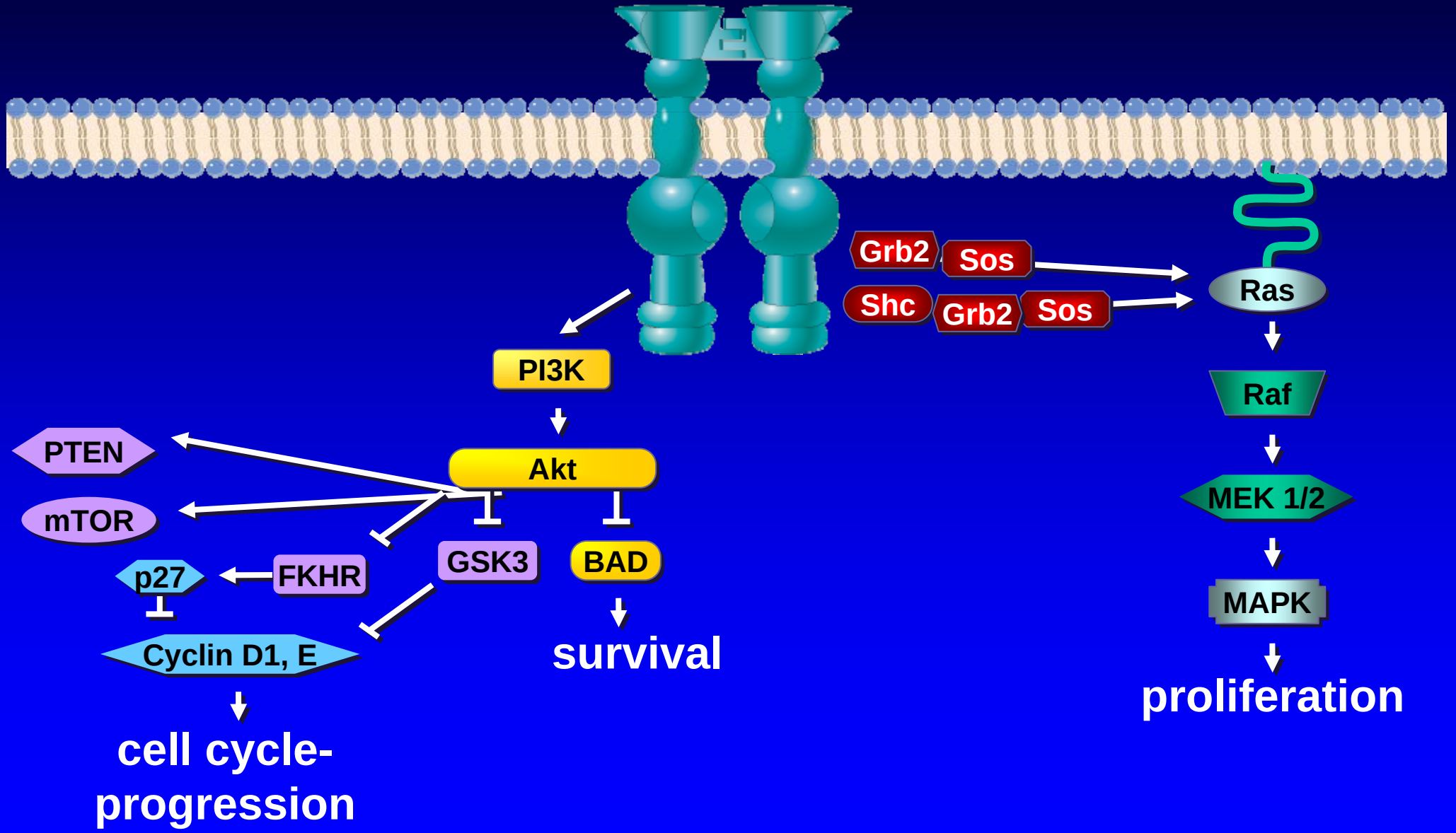
Fujita et al., British Journal of Cancer (2006) 94; Nagata et al., Cancer Cell (2004) 6



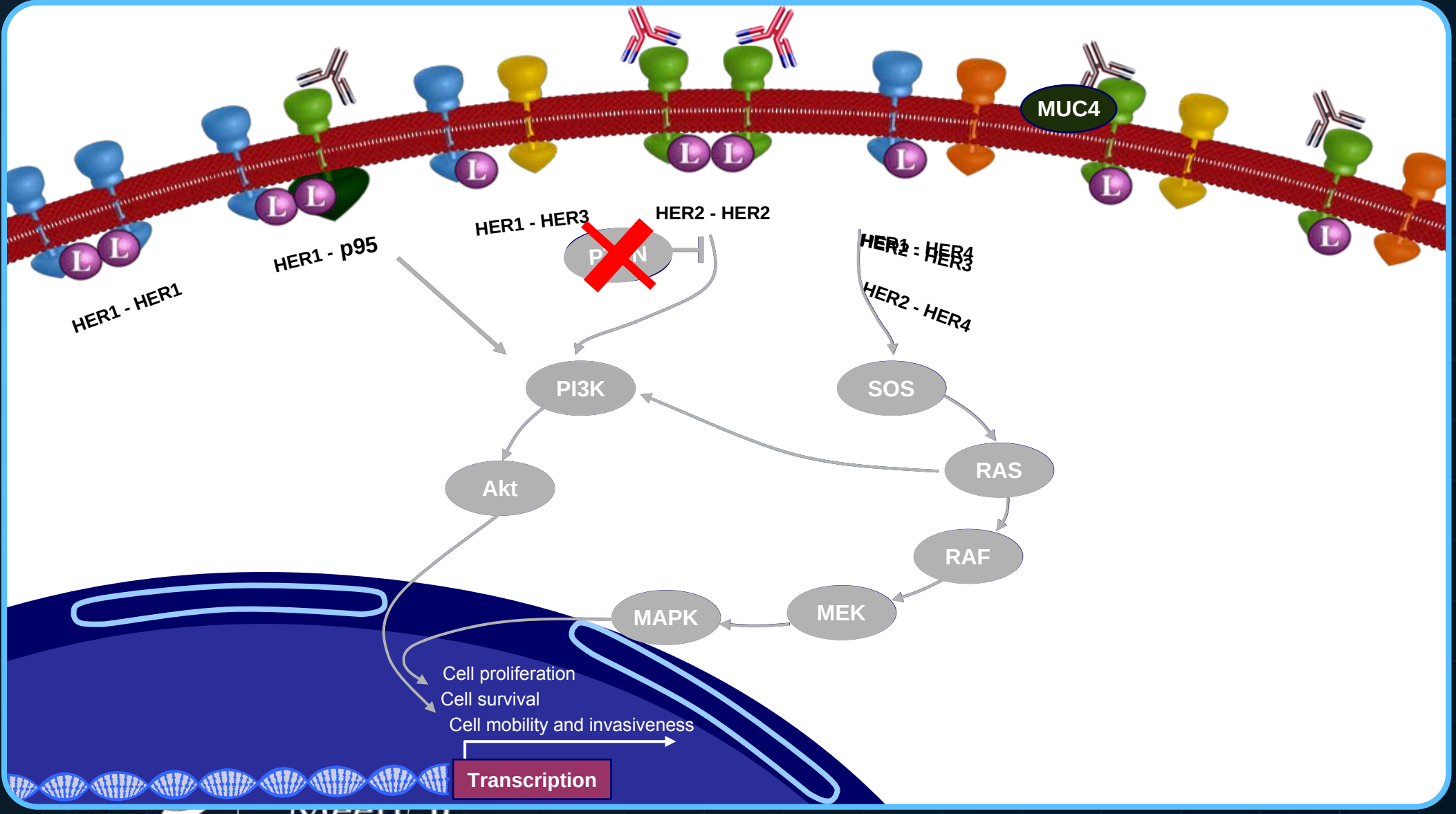
Anti-HER2 Resistenz:
Therapeutische Ansatzpunkte

- 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

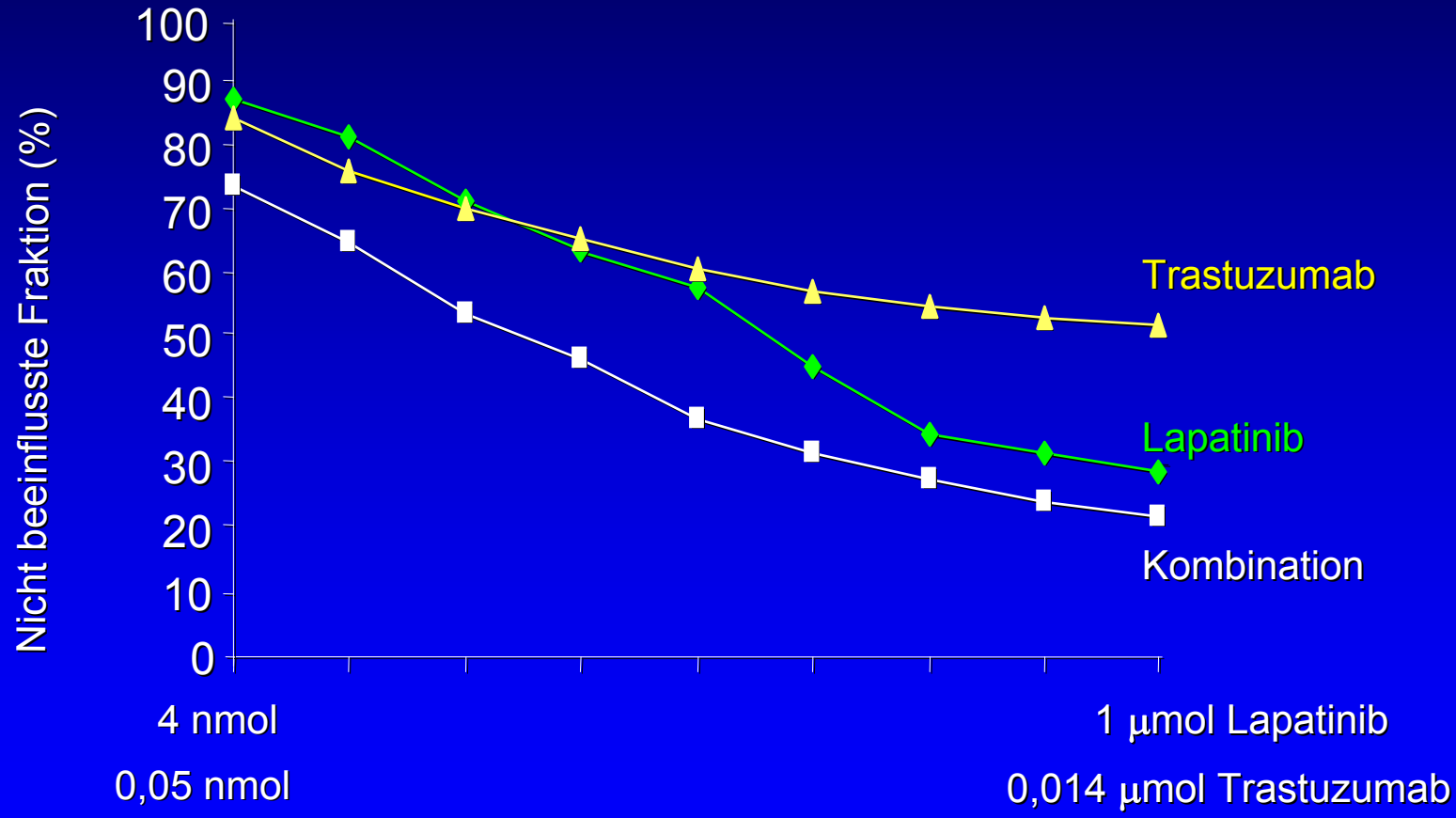


Total Blockade of HER2 May Provide Greater Anti-tumor Activity and Overcome Resistance



J. O'Shaughnessy et al, ASCO 2008

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

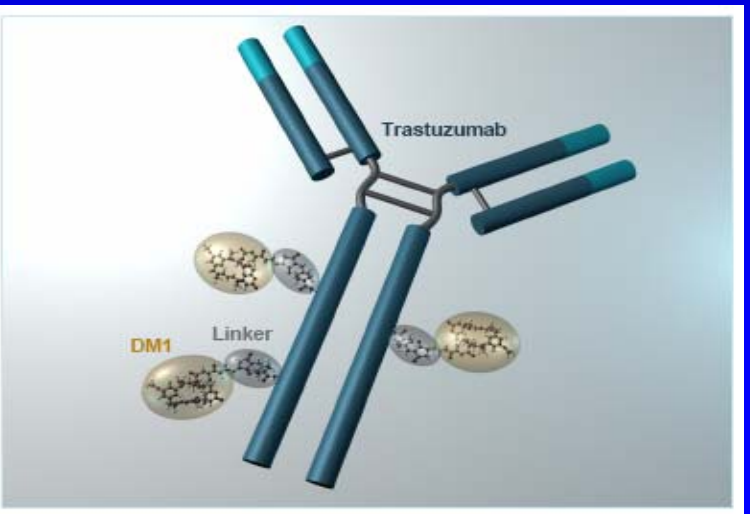


*Die klinische Bedeutung dieses in-vitro-Experiments ist nicht bekannt

Konecny et al. *Proc AACR* 2002; 42 (abstract 4974).

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



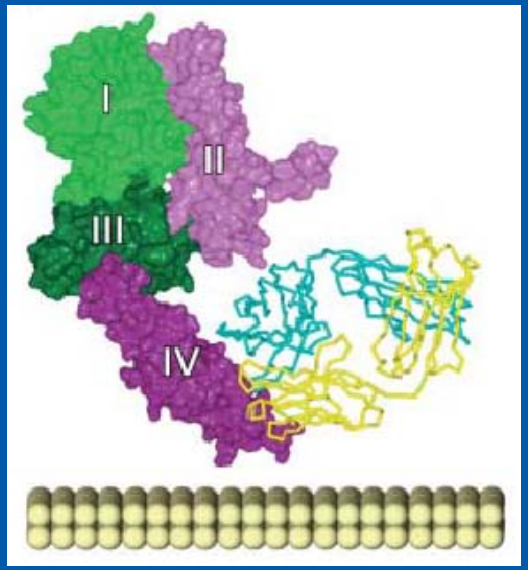
nach Ian E. Krop et al. SABCS 2007, abs 310

Conclusions

- In these 24 patients with HER2+ MBC previously treated with Trastuzumab, Grade ≥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.

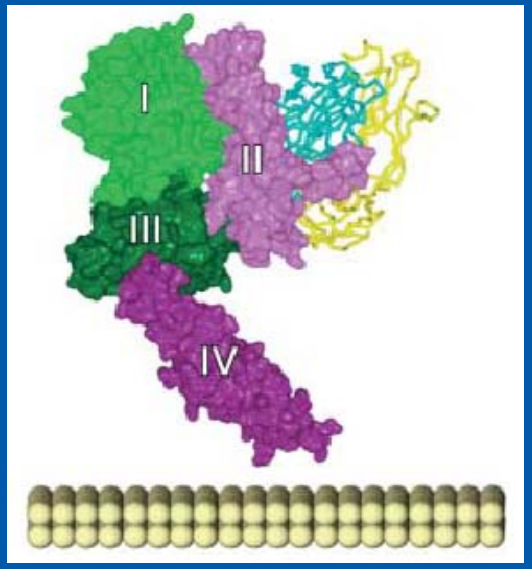
nach Ian E. Krop et al. SABCS 2007, abs 310

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

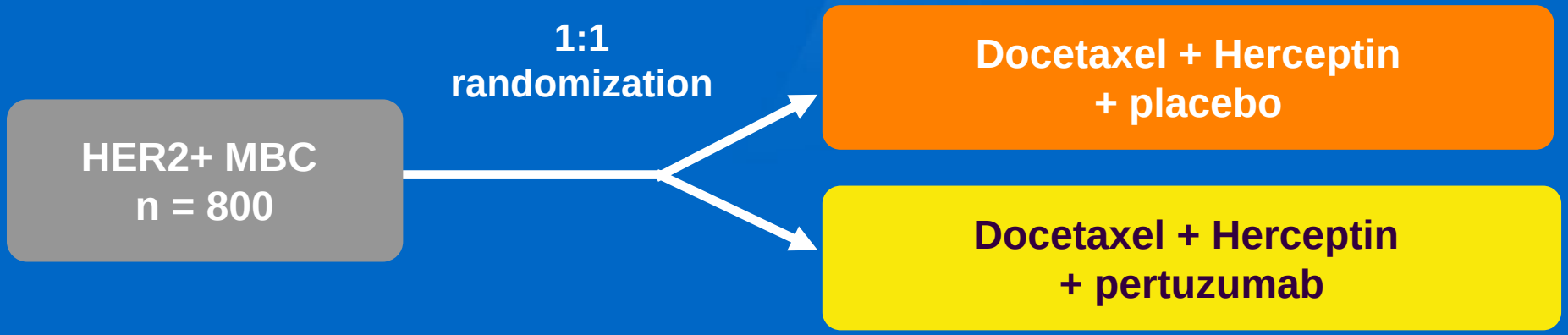


Pertuzumab

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

Hubbard 2005

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**

Data on file

ALTTO: Pre-defined subgroup analyses

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

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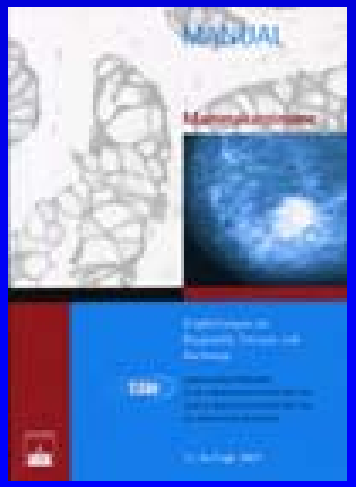

Tumorzentrum München:

- ✓ Patientinnenratgeber Mammakarzinom
- ✓ Manual Mammakarzinom für Ärzte

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