

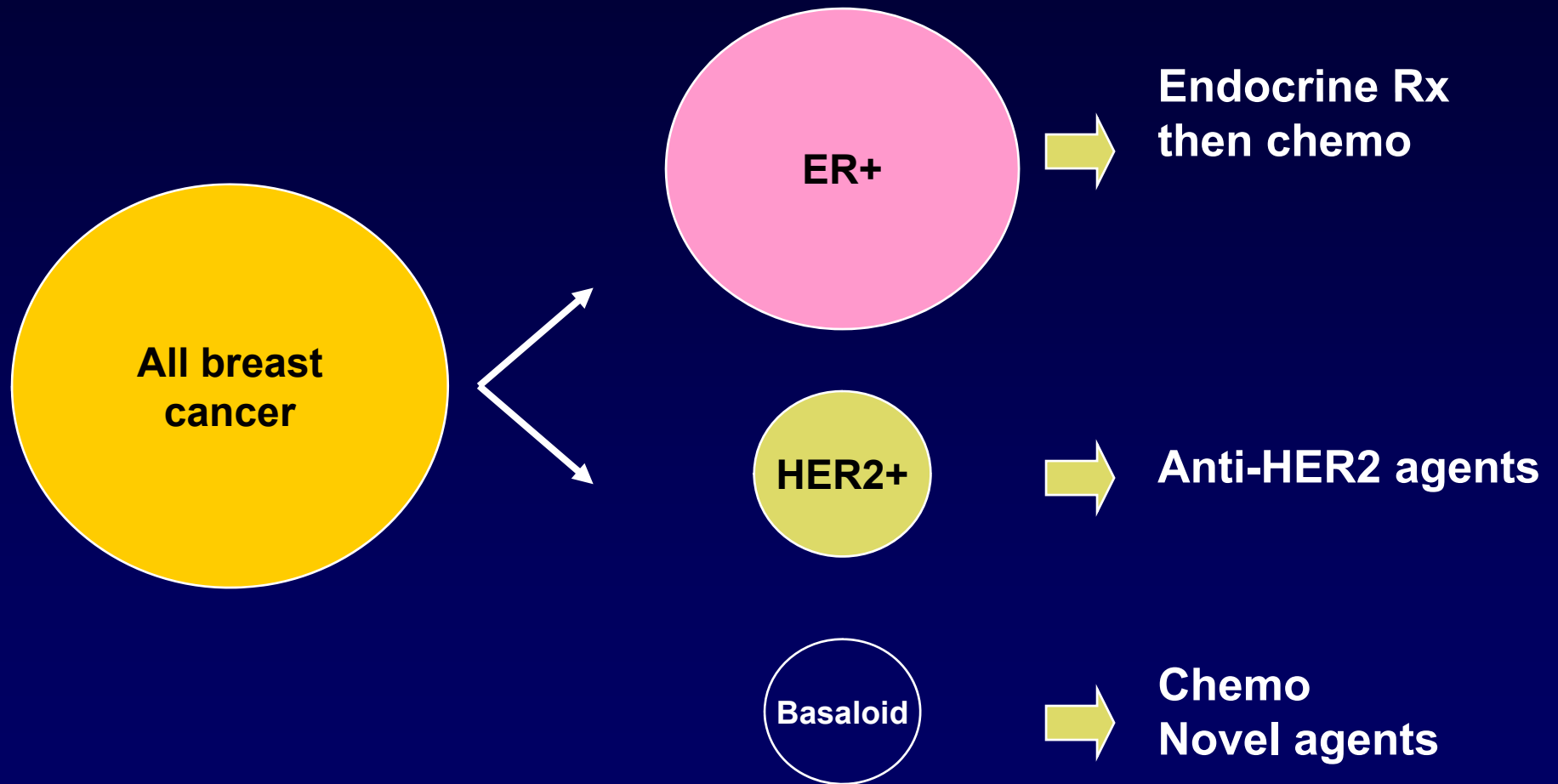
What Surgeons Need to Know About Targeted Therapy in Breast Cancer

Helen Gogas, MD
1st Department of Medicine
University of Athens
Athens, Greece

Rationale for Targeted Therapies

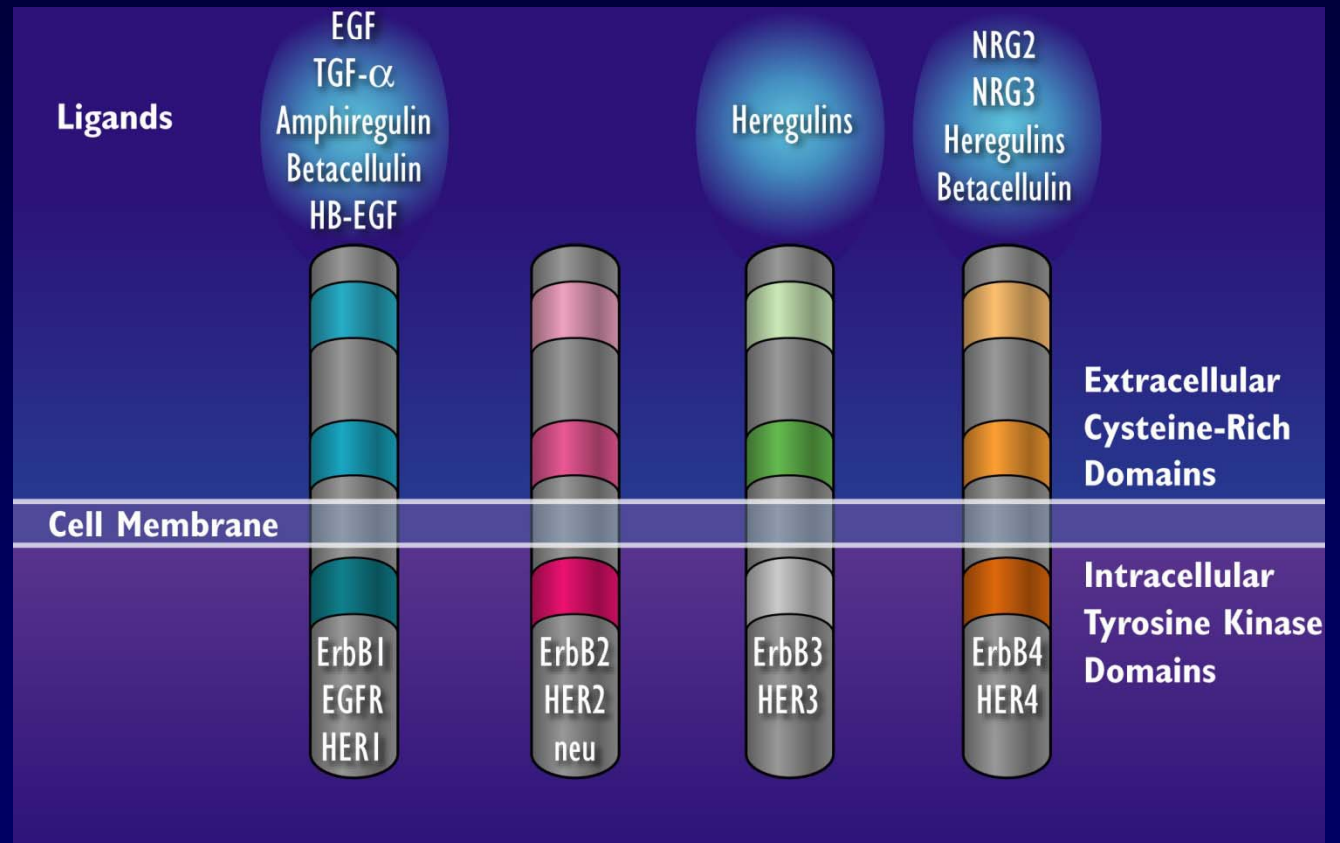
- **Randomized clinical trials have clearly demonstrated the efficacy of systemic adjuvant chemotherapy or hormone therapy in women with breast cancer**
- **The survival improvement is modest mainly due to the unselective inclusion of patients within a broad category of risk**
- **Identification of biologic markers that might have the ability to predict therapeutic response is crucial**
- **Axillary lymph node status, tumor size, and tumor grade are of prognostic value in patients with operable breast cancer**
- **Only the expression of hormone receptors and HER2 status are a clinically useful markers that predict response to treatment**

Breast Cancer Subsets and Treatments



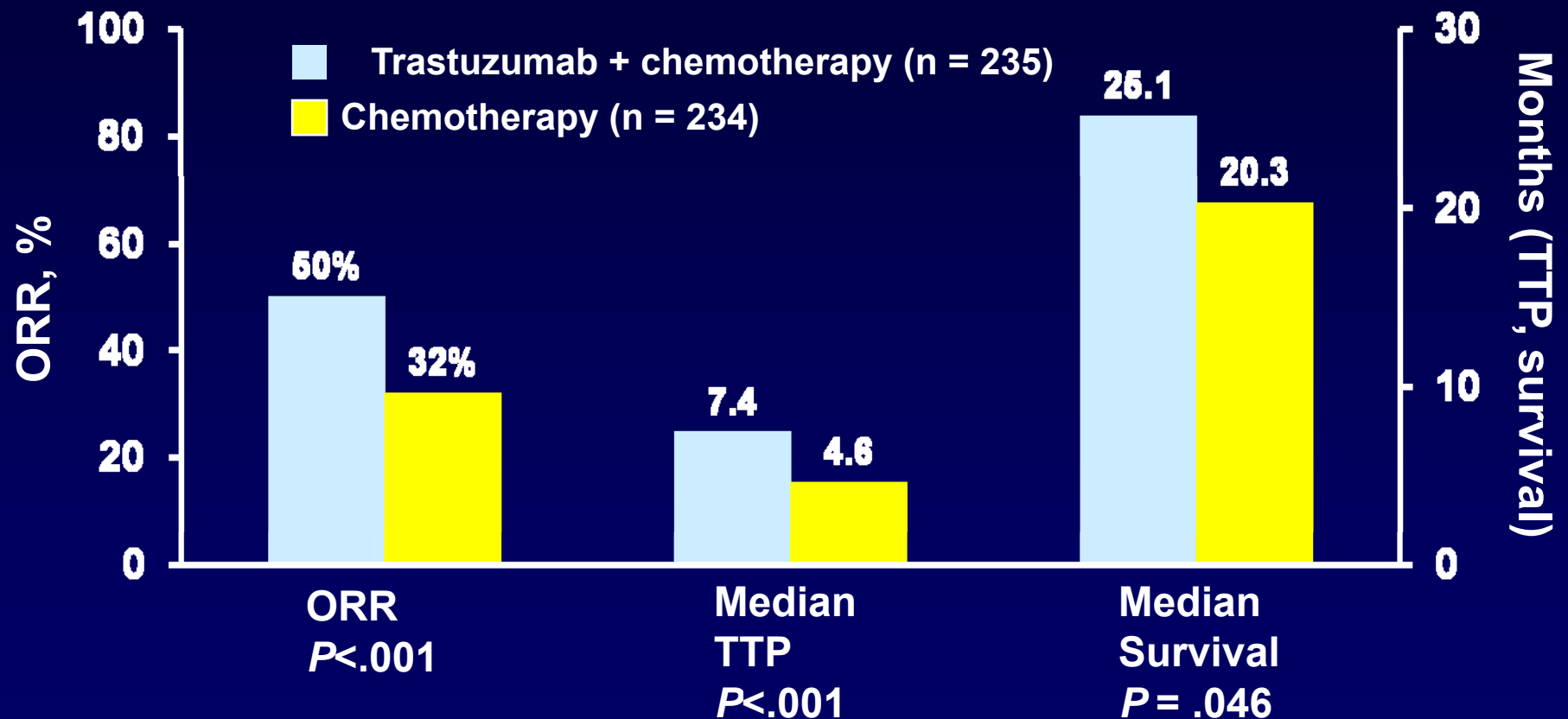
Trastuzumab Targets the Human Epidermal Growth Factor Receptor 2 (HER2)

- The HER2 gene is localized to chromosome 17q
- HER2 is a tyrosine kinase transmembrane growth factor receptor



Fernandes AM, et al. *Cancer Lett.* 1999;142(1):55-63.
Moghal N, et al. *Curr Opin Cell Biol.* 1999;11(2):190-196.
Yarden Y, et al. *Nat Rev Mol Cell Biol.* 2001;2(2):127-137.

Chemotherapy +/- Trastuzumab in Metastatic Breast Cancer

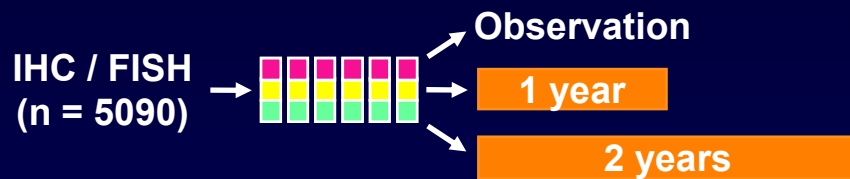


65% of Chemo-alone group crossed over to trastuzumab at progression

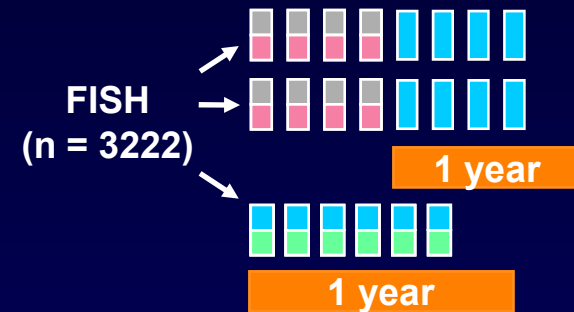
Trastuzumab received US Food and Drug Administration (FDA) approval in 1998 for use in metastatic breast cancer that overexpresses HER2

Adjuvant Trastuzumab Has an Extensive Evidence Base with >13,000 Patients Treated in 4 Major Trials

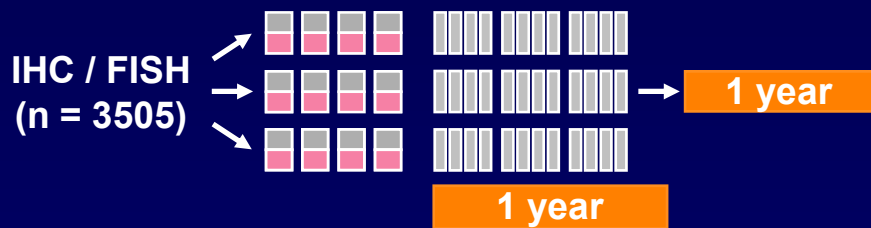
HERA¹ (ex-USA)



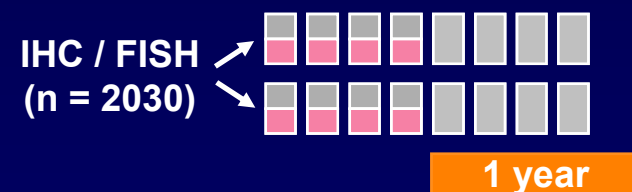
BCIRG 006³ (global)



NCCTG N9831² (USA)



NSABP B-31² (USA)



CTx, chemotherapy; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry

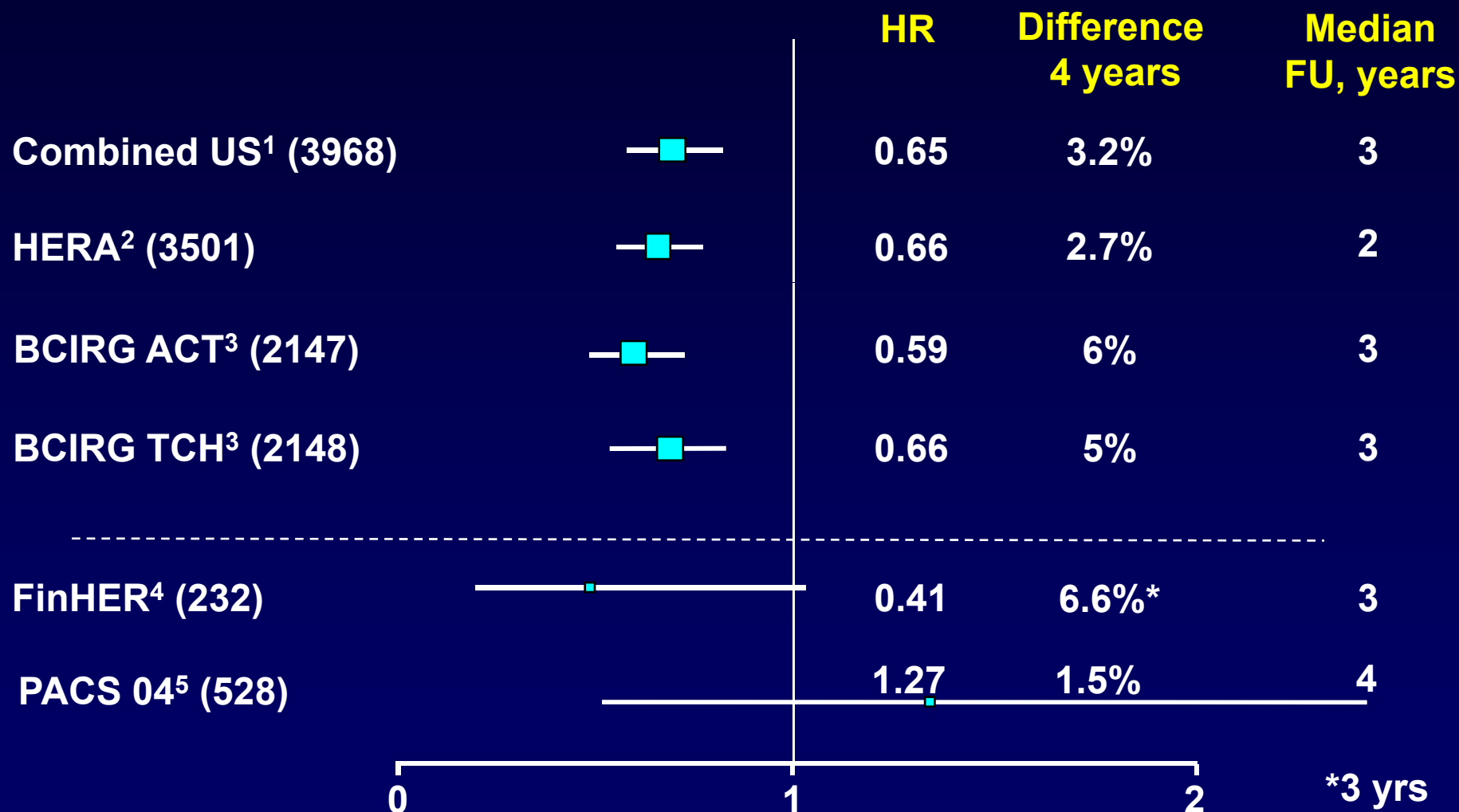
1. Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353(16):1659-1672. 2. Romond EH, et al. 2005;353(16):1673-1684. 3. Slamon D, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 52.

Patient and Tumor Characteristics, %

	B-31	N9831	BCIRG 006	HERA
Age <50 years	51	51	52	51
ER (HR) positive	52	52	54	50
Tumor <2 cm	39	39	40	40
N+ 0	0	12	29	32
1-3	57	49	39	29
≥ 4	33	39	33	28

1. Piccart-Gebhart MJ, et al. *N Engl J Med.* 2005;353(16):1659-1672. 2. Romond EH, et al. 2005;353(16):1673-1684. 3. Slamon D, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 52.

Adjuvant Trastuzumab Trials: Overall Survival



1. Perez EA, et al. *J Clin Oncol.* 2007;25(18S): Abstract 512. 2. Smith I, et al. *Lancet.* 2007;369(9555):29-36. 3. Slamon D, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 52. 4. Joensuu H, et al. *N Engl J Med.* 2006;354(8):809-820. 5. Spielmann M, et al. *Breast Cancer Res Treat.* 2007;106(Suppl 1): Abstract 72.

Trastuzumab received FDA approval for node-positive breast cancer and high-risk node-negative breast cancer in the **adjuvant** setting in 2006

- Trastuzumab-1-year given either concomitantly or sequentially with chemotherapy is standard of care for most HER2-positive early stage breast cancers
- Is trastuzumab necessary for **tumors <1 cm?**

Unanswered Questions in Early-Stage HER2-Positive Breast Cancer

- **Ideal Approach: Concurrent vs Sequential—**which is superior (NCCTG)?
- **Is there still a need for anthracyclines?**
- **Trastuzumab in small, node-negative tumors?**
- **Optimal duration of trastuzumab—(< or > 1 year?)**
(Hellenic, French (PHARE) trial, Finnish (SOLD) trial, HERA)
- **Role of TKIs vs trastuzumab** (ALTTO Trial)?
- **The addition of bevacizumab** (BETH)?
- **Improved predictors of toxicity (cardiac biomarkers, cardiac MRI) and prevention of toxicity?**
- **Long-term toxicity?**

**Anti-HER2 Therapy
Beyond Progression
on Trastuzumab**

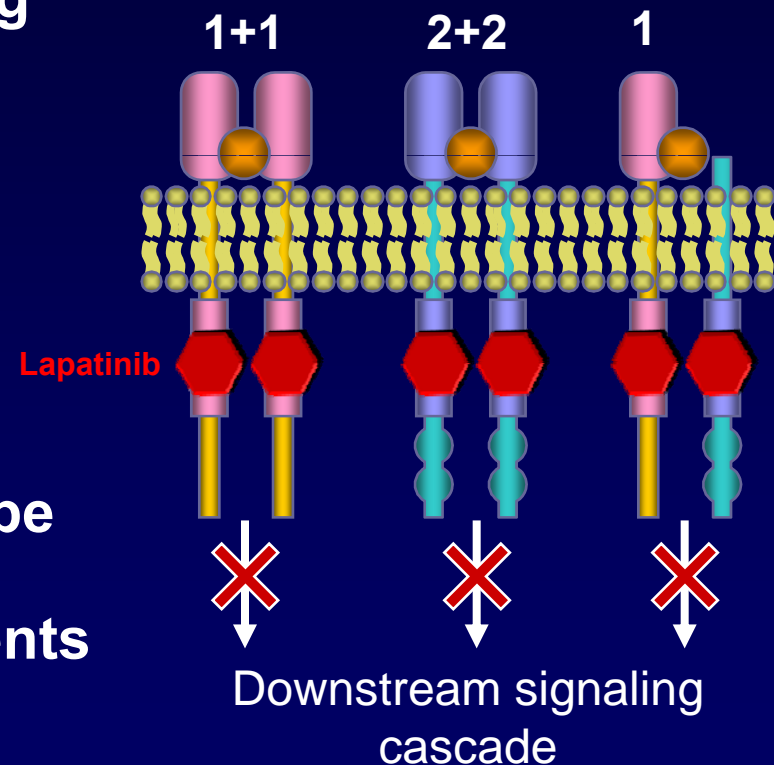
Accomplishments in HER2+ Metastatic Breast Cancer (MBC)

- Outcome of HER2-positive patients receiving trastuzumab is similar to HER2-normal patients
- Trastuzumab in combination with chemotherapy is now the standard of care
- Promising results also seen with aromatase inhibitors (AIs) and anti-HER2
 - TANDEM trial (Anastrozole vs anastrozole +trastuzumab)
Kaufman B, et al. *J Clin Oncol*. 2009 Sept 28. [Epub ahead of print].
 - EGF30008 trial (Letrozole vs letrozole + lapatinib)
Johnston S, et al. *J Clin Oncol*. 2009 Sep 28. [Epub ahead of print]
- Relapse on/after trastuzumab
 - May be re-challenged with chemo and trastuzumab (if not clearly trastuzumab resistant) or treated with capecitabine and lapatinib

Lapatinib: An Oral, Intracellular, Small Molecule Tyrosine Kinase Inhibitor

Mechanism of Action

- Binds to intracellular ATP binding site of EGFR (ErbB-1) and HER2 (ErbB-2) preventing phosphorylation and activation
- Active for truncated Erb-B2 receptor (p95ErbB-2)
- Dual blockade of signaling may be more effective than the single-target inhibition provided by agents such as trastuzumab



Capecitabine + Lapatinib Versus Capecitabine in LABC or MBC: Study EGF 100151

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Stratification:

- Disease sites
- Stage of disease

R
A
N
D
O
M
I
Z
E

Lapatinib 1250 mg PO qd
continuously +
capecitabine 2000 mg/m²/d
PO days 1-14 q3 weeks

Capecitabine 2500 mg/m²/d PO
days 1-14 q 3 weeks

Patients on treatment until
progression or unacceptable
toxicity, then followed for survival

***Trastuzumab must have been administered for metastatic disease!!**

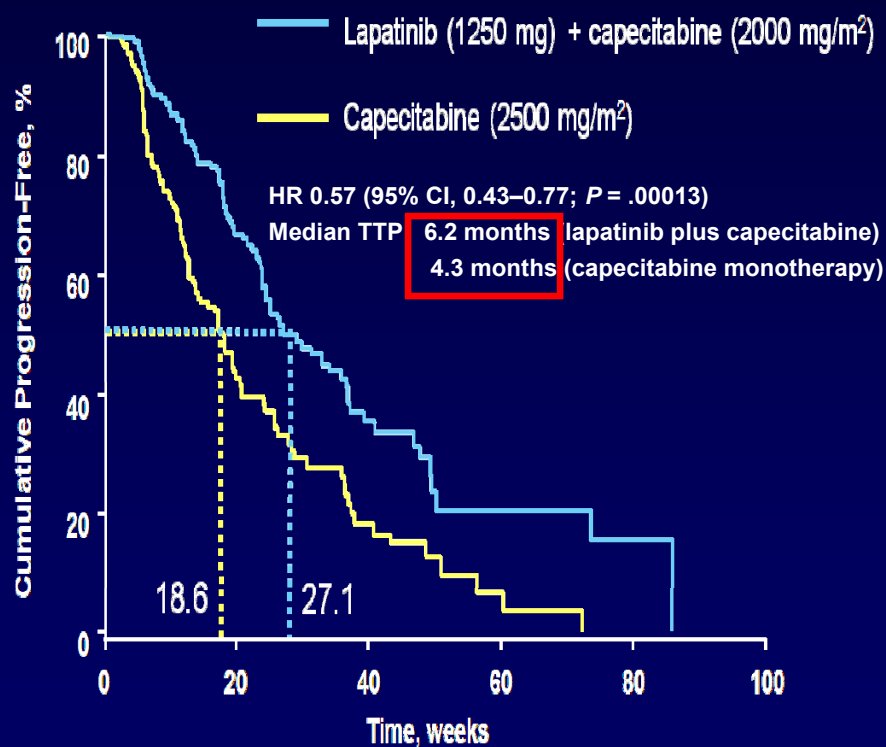
Geyer C, et al. *N Engl J Med.* 2006;355(26):2733-2743.

Cameron D, et al. *Breast Cancer Res Treat.* 2008;112(3):533-543.

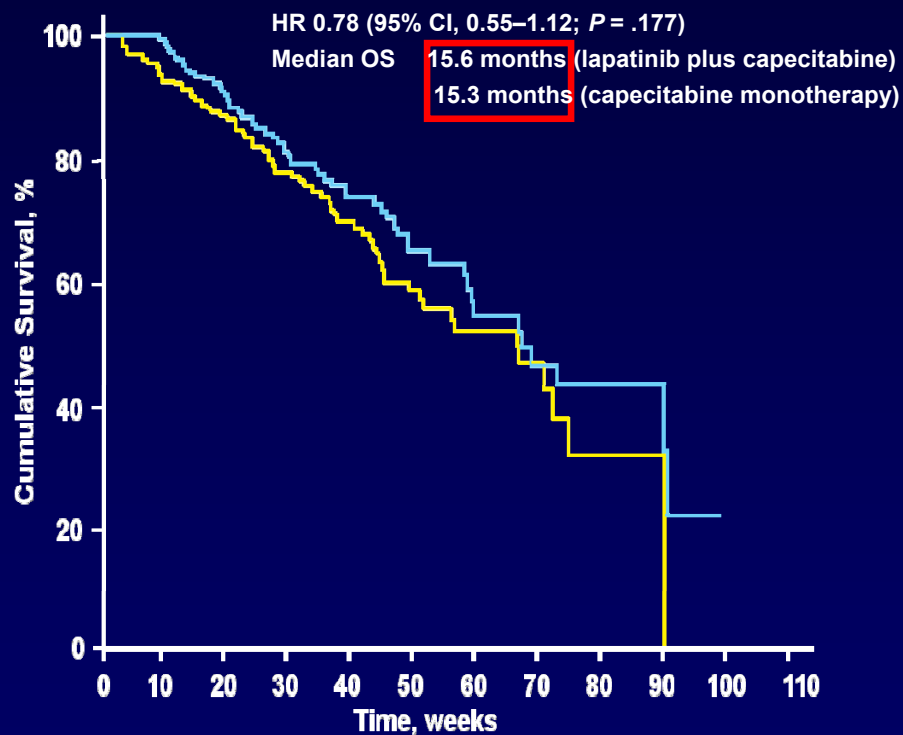
LABC = locally advanced breast cancer

Study EGF100151: Kaplan-Meier Estimates of Time to Progression and Overall Survival in ITT Population by Independent Review Committee

Median TTP



Overall Survival



EGF 104900: Phase III Study to Test if Total HER2+ Blockade Improves Clinical Outcome

Key Inclusion

- HER2+(FISH+/ IHC3+) MBC
- Progression on
 - Anthracycline
 - Taxane
 - Trastuzumab
- Progression on most recent trastuzumab regimen

- Stratification factors
 - Visceral disease
 - Hormone receptor

R
A
N
D
O
M
I
Z
A
T
I
O
N

Lapatinib 1500 mg/day PO
N = 148



Crossover if PD after 4 wk therapy (N = 73)

Lapatinib 1000 mg/day PO
Trastuzumab 4→2 mg/kg IV qw
N = 148

Treatment Efficacy

	L N = 145	L + T N = 146
Response rate, %*	6.9	10.3
(95% CI)	(3.4, 12.3)	(5.9, 16.4)
Odds ratio (95% CI)		1.5 (0.6, 3.9) P = .46
Clinical benefit rate, %†	12.4	24.7
(95% CI)	(7.5, 18.9)	(17.9, 32.5)
Odds ratio (95% CI)		2.2 (1.2, 4.5) P = .01
Progression-free survival (median), weeks	8.1	12.0
Odds ratio (95% CI)		0.73 (0.57, 0.93) P = .008

*Confirmed CR+PR †CR+PR+SD ≥6 months

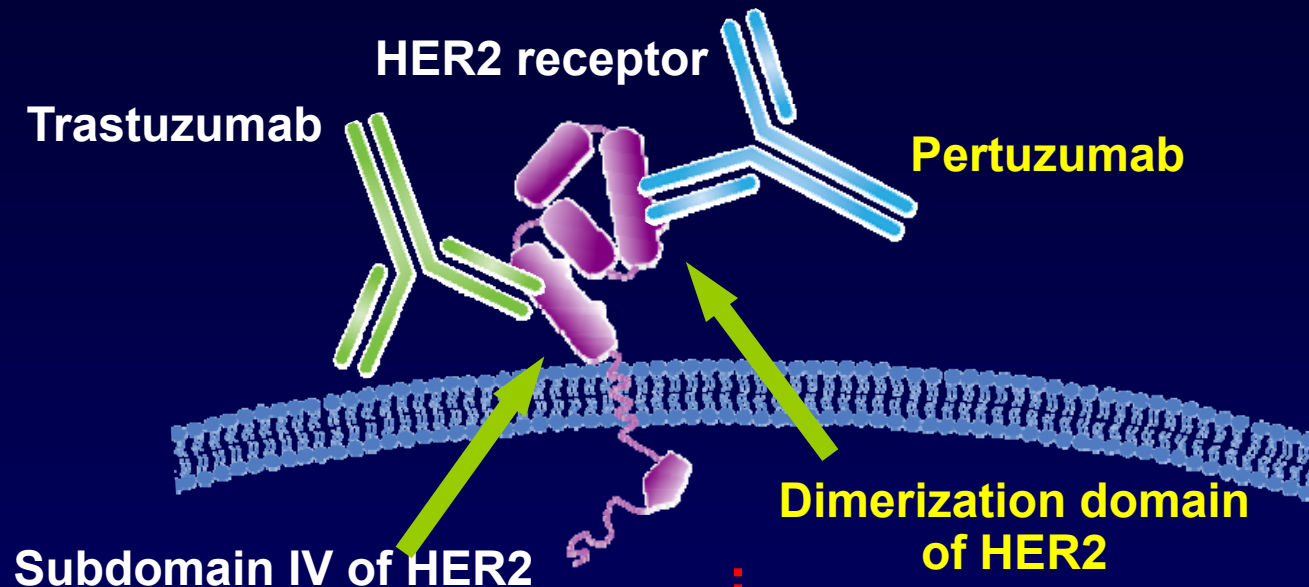
O'Shaughnessy J, et al. *J Clin Oncol*. 2008;26 (May 20 Suppl): Abstract 1015.

HKI-272 (Neratinib), An Oral Irreversible Pan Erb Receptor Tyrosine Kinase Inhibitor: Tumor Response in Evaluable Population

	Prior Trastuzumab (n = 61)	No Prior Trastuzumab (n = 66)
Objective response rate, %	26	56
PR, %	26	56

Daily oral dose: 240 mg; dose reduction -1x: 24% of patients, 2x: 5%
16% of patients had dose reductions due to diarrhea

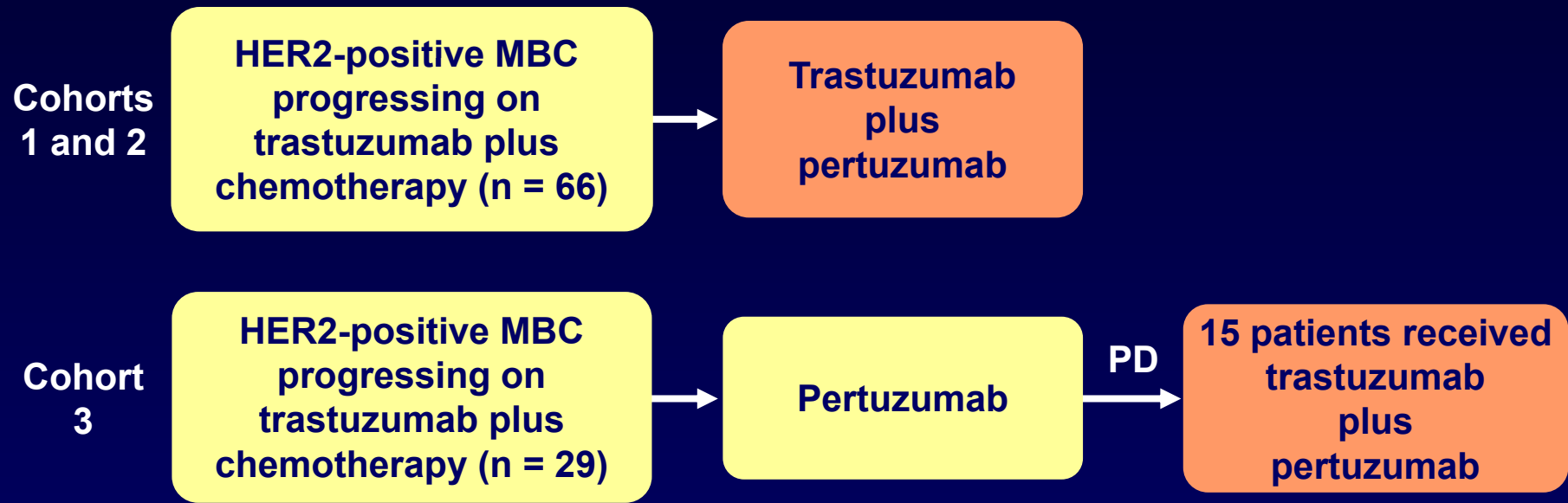
Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



- Trastuzumab continually suppresses HER2 activity
- Flags cells for destruction by the immune system
- Does not inhibit HER2 dimerization

- Pertuzumab inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways
- Flags cells for destruction by the immune system

A Phase II Trial of Trastuzumab Plus Pertuzumab in Patients with HER2-Positive MBC Progressing During Trastuzumab Therapy



Primary objectives

- Safety
 - Evaluate safety of combined antibody treatment
- Efficacy
 - Response rate plus stabilisation of disease = clinical benefit rate

Gelmon KA, et al. *J Clin Oncol*. 2008;26(May 20 suppl): Abstract 1026.

Cortés J, et al. *J Clin Oncol*. 2009;27(15S): Abstract 1022.

Pertuzumab/Trastuzumab Combination Therapy More Active than Treatment with Either Agent Alone

Response, n (%)	Cohort 1 and 2 (n = 66)	Cohort 3 (P) (n = 27)	Cohort 3 (T+P) (n = 11)
CR	5 (7.6)	0 (0.0)	0 (0.0)
PR	11 (16.7)	2 (7.4)	3 (27.3)
ORR	16 (24.2)	2 (7.4)	3 (27.3)
SD ≥6 months	17 (25.8)	1 (3.7)	0 (0.0)
Clinical benefit rate (CR + PR + SD ≥6 months)	33 (50.0)	3 (11.1)	3 (27.3)
Progressive disease	33 (50.0)	24 (88.9)	8 (72.7)

T-DM1: First-in-Class Antibody-Drug Conjugate (ADC)



Target expression: HER2

Monoclonal antibody: Trastuzumab



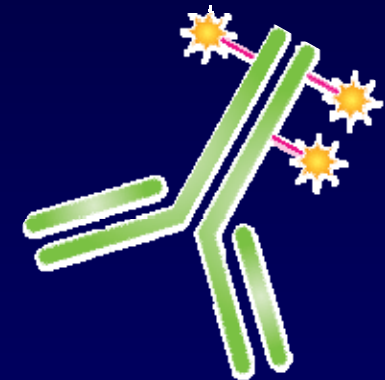
Cytotoxic agent: DM1

**Highly potent chemotherapy
(maytansine derivative)**



Linker

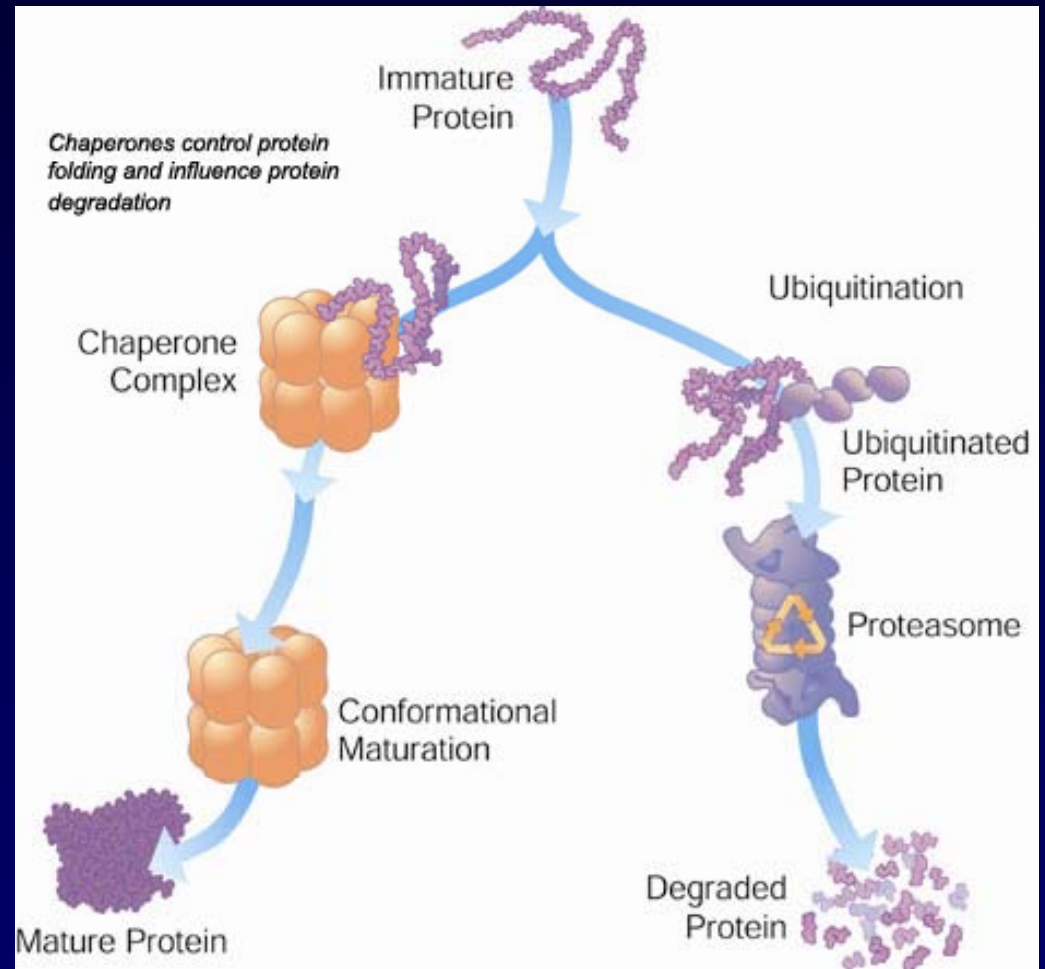
**Systemically stable
Breaks down in target cancer cell**



T-DM1

HSP90 as a Therapeutic Target in HER2/*neu* Positive Metastatic Breast Cancer

- HSP90 = Chaperone protein
- Required for the maturation and stabilization of client proteins
- Inhibition of HSP90 chaperone function induces proteasomal degradation of these clients
- Key targets include:
 - HER2
 - Mutant p53
 - ER/PR/AR
 - v-src
 - AKT
 - bcr-abl
 - MET
 - Mutant B-RAF
 - Raf kinase

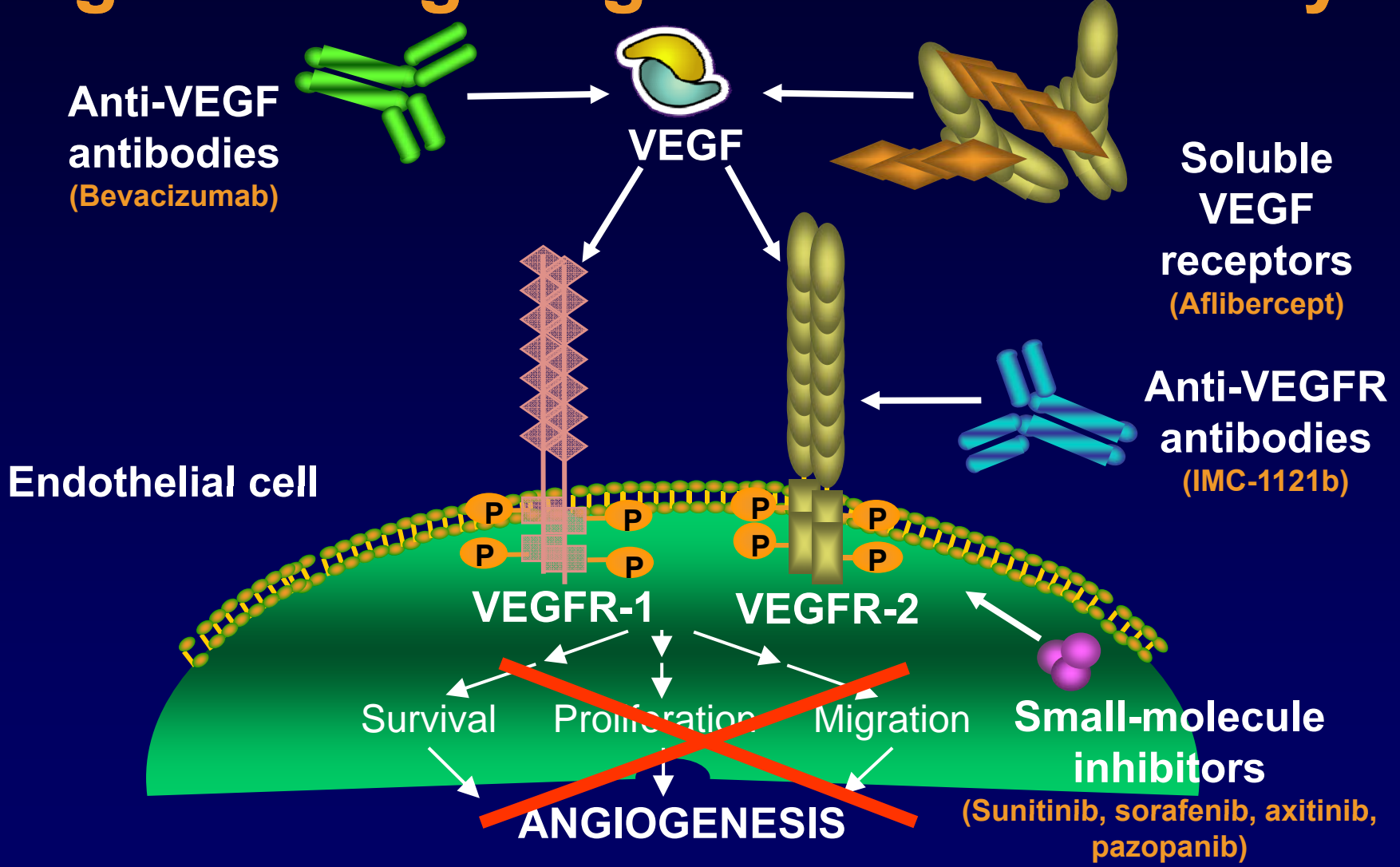


Novel Anti-HER2 Strategies—A Few More....

Class / Agent	Target / Mechanism	Phase
Monoclonal Antibodies		
• Pertuzumab	HER2-dimerization inhibitor	III
• Trastuzumab-DM1	HER2/antibody-toxin (trastuzumab-maytansine) conjugate	III
• Ertumaxomab	HER2/CD3 trifunctional bispecific antibody	II
Signal transduction inhibitors		
• Lapatinib	EGFR and HER-2/TKI	III
• Neratinib	EGFR, HER2,3,4/TKI	III
• BIBW 2992	EGFR and HER2/TKI	II
• Gefitinib	EGFR/TKI	II
• Everolimus (RAD001)	mTOR/TKI	II
• Sirolimus (rapamycin)	mTOR/TKI	II
• AP23573 (deforolimus)	mTOR/TKI	II
• Dasatinib	Src Inhibitor	II
Heat shock protein inhibitors		
• Tanespimycin	HSP90 inhibitor	III
Angiogenesis inhibitors		
• Bevacizumab	Anti-VEGF antibody	III
• Pazopanib	VEGFR, c-kit, PDGFR, TKI	III
• Sunitinib	VEGFR, c-kit, PDGFR, TKI	II
Histone deacetylase inhibitors		
• Panobinostat	HDAC inhibitor	II
Cyclo-oxygenase inhibitors		
• Apricoxib	COX-2 inhibitor	II
Immunotherapy		
• HER/ <i>neu</i> vaccine	Recombinant HER2 intracellular domain vaccine	II

Adapted from Bedard PL ,et al. *J Mammary Gland Biol Neoplasia*. 2009;14(1):55-66.

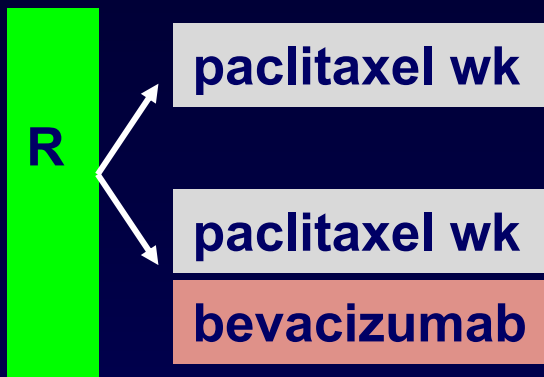
Agents Targeting the VEGF Pathway



Modified from: Ferrara N. *Oncologist*. 2004;9(suppl 1):2-10.

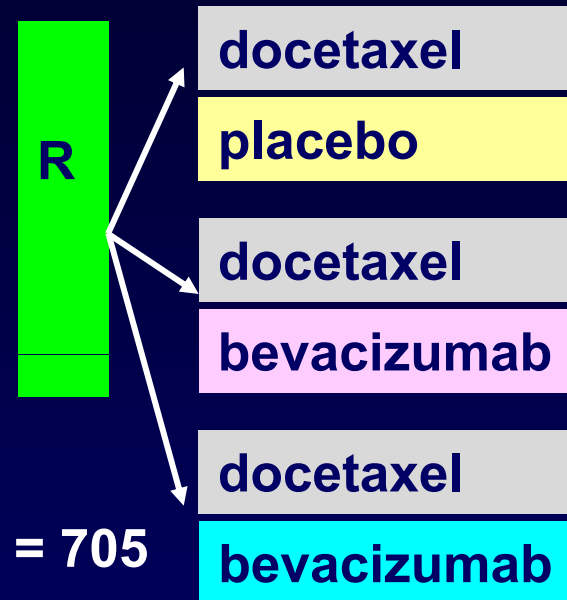
Bevacizumab for First-Line MBC

E2100¹



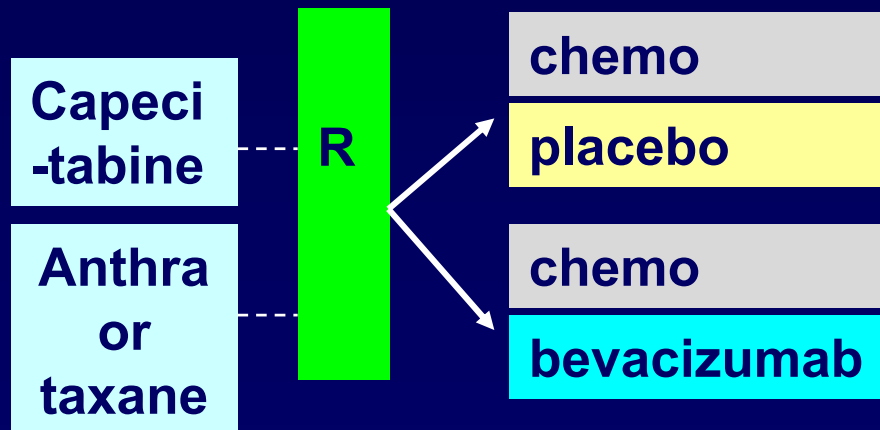
N = 722

AVADO²



N = 705

RIBBON-1³



N = 1237

- Bevacizumab 10 mg/kg q2w
- Bevacizumab 7.5 mg/kg q3w
- Bevacizumab 15 mg/kg q3w

1. Miller K, et al. *N Engl J Med.* 2007;357(26):2666-2676. 2. Miles D, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract 1011. 3. Robert NJ, et al. *J Clin Oncol.* 2009;27(15): Abstract 1005.

Bevacizumab for First-Line MBC

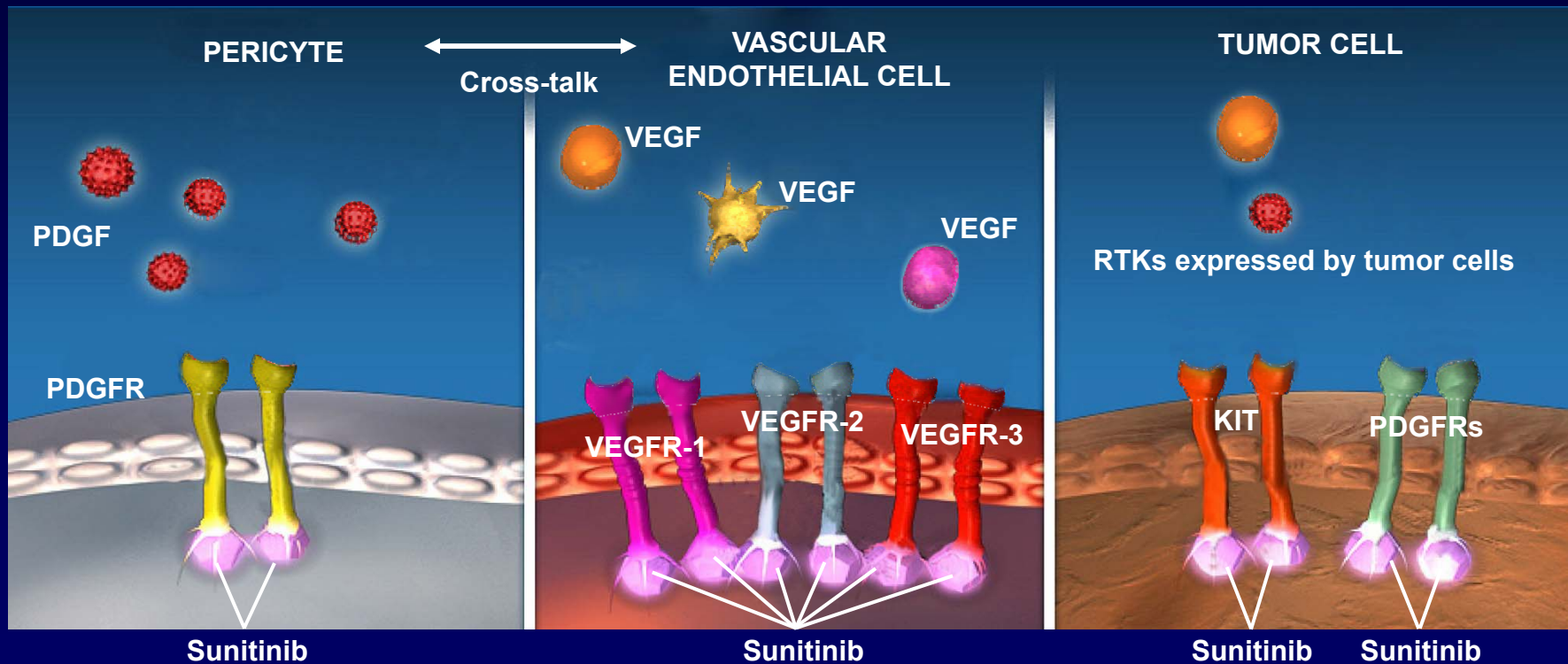
Summary of 3 randomized trials

- **Improvement in response rates: All trials (magnitude: 6% to 16 %)**
- **Improvement in progression-free survival: All trials (magnitude: 0.8 months to 5.6 months)**
- **No significant improvement in survival: All trials**

VEGF-TKIs (eg, Sunitinib):

Antiangiogenic Effects

Antitumor Effects



Mendel DB, et al. *Clin Cancer Res.* 2003;9(1):327-337. Hicklin DJ, et al.s. *J Clin Oncol.* 2005;23(5):1011-1027. Erber R, et al. *FASEB J.* 2004;18(2):338-340.

Rationale for Use of Sunitinib in MBC

- Bevacizumab is a highly selective VEGF-antagonist
- Angiogenesis is driven by multiple stimulating factors
- Sunitinib is a multitargeting kinase inhibitor (VEGFR; KIT; PDGFR; colony-stimulating factor-1 receptor)
- Preclinical and phase I data demonstrate synergistic effects between sunitinib and cytotoxic agents*
- Sunitinib is active in A/T pretreated MBC, as shown in a recently published phase II trial (N = 64, ORR 11%, CBR 16%, TTP 10 weeks)

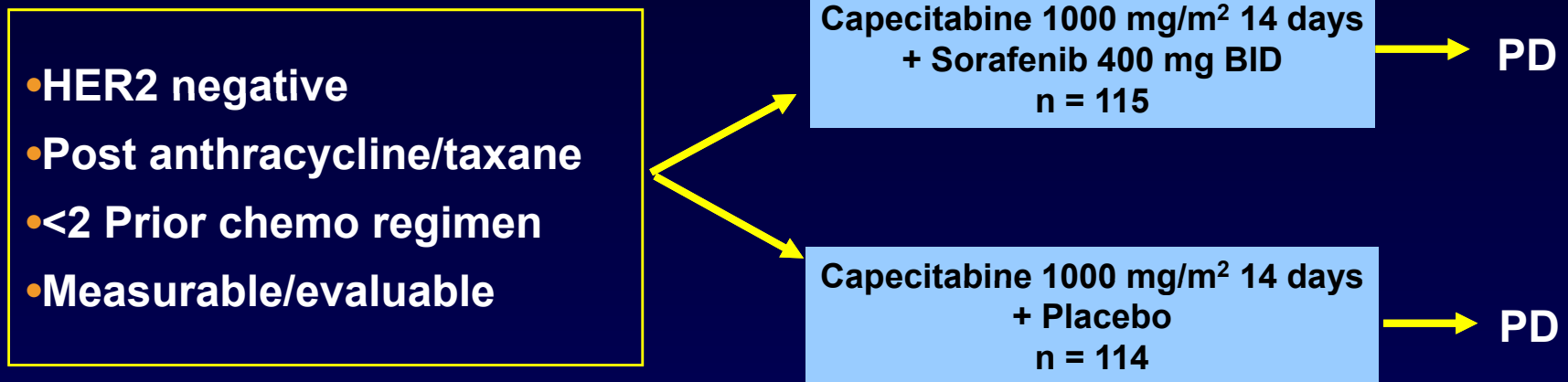
Burstein HJ, et al. *J Clin Oncol*. 2008;26(11):1810-1816.

* Abrams TJ, et al. *Mol Cancer Ther*. 2003;2(5):471-478.

Completed Sunitinib Trials

- **SUN 1064: Sunitinib Malate + Docetaxel vs Docetaxel in First-Line Advanced Breast Cancer**
- **SUN 1099: Sunitinib + Capecitabine vs Capecitabine in Second-Line Advanced Breast Cancer**
- **SUN 1077: Sunitinib Malate vs Standard-of-Care in Triple-Negative Advanced Breast Cancer**

SOLTI-0701: Capecitabine ± Sorafenib



	CAP+SOR	CAP+PL	HR (95% CI)	P Value
PFS	6.4 months	4.1 months	0.576 (0.410 – 0.809)	.0006
ORR	38%	31%		

- Grade 3/4 toxicities included (CAP+SOR vs CAP+PL): Hand-foot skin reaction (45% vs 13%), diarrhea (5% vs 5%), and neutropenia (5% vs 3%)

Important to Know

Essential Role of Supportive Care in Patients Treated with Targeted Therapy

Guidelines based management (prophylaxis, early, intervention) of class specific side effects is mandatory:

- Diarrhea
 - Mucositis
 - Fatigue
 - Hand Food Syndrome
 - Cardiotoxicity
 - Hypertension
 - Risk of bleeding
-
- The diagram uses yellow brackets to group side effects to specific drug classes. The top two side effects (Diarrhea and Mucositis) are grouped together and linked to Lapatinib and Neratinib. The next two (Fatigue and Hand Food Syndrome) are grouped together and linked to Sunitinib and Sorafenib. The bottom three (Cardiotoxicity, Hypertension, and Risk of bleeding) are grouped together and linked to Trastuzumab, Sunitinib, and Sorafenib.
- | |
|-----------------------------------|
| Lapatinib, Neratinib |
| Sunitinib, Sorafenib |
| Trastuzumab, ? Sunitinib |
| Bevacizumab, Sunitinib, Sorafenib |

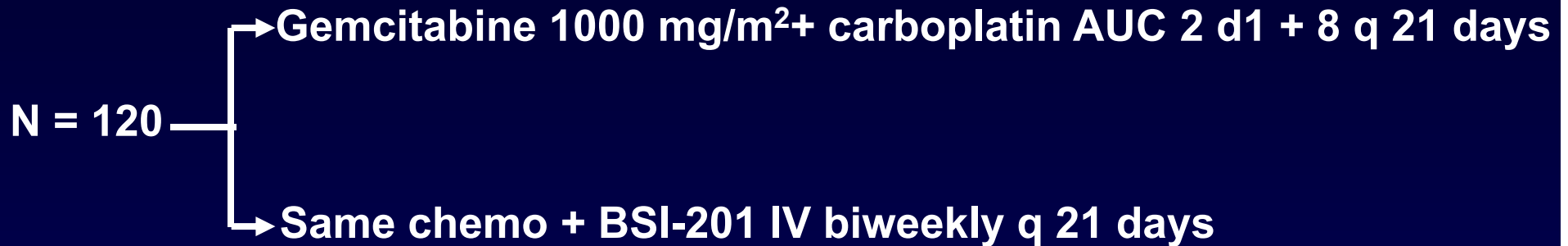
*Not all agents in clinical trials included

Poly (ADP-ribose) Polymerase-1 (PARP 1) as a Treatment Target in Triple-Negative Breast Cancer

- **Nuclear enzyme involved in DNA base excision repair**
- **Upregulated in majority of triple-negative breast cancers**
- **Key role in BRCA1-deficient cell lines***

*Farmer H, et al. *Nature*. 2005;434(7035):917-921.

A Phase II Randomized Trial Testing a PARP 1 Inhibitor BSI-201 in Patients with Triple-Negative Metastatic Breast Cancer



	Chemo	Chemo + PARP Inhibitor	HR (95% CI)	P Value
% Clinical benefit rate	21	62	-	.0002
Median PFS, months	3.3	6.9	.034 (0.20-0.58)	.0001
Median OS, months	5.7	9.2	0.34 (0.18-0.64)	.0005

No increase in toxicity in the PARP inhibitor arm

A Phase II Trial Testing Olaparib (a PARP 1 Inhibitor) in BRCA-Deficient Advanced (Heavily Pretreated) Breast Cancer

Cohort 1 : N = 27 Olaparib 400 mg PO bid

Cohort 2 : N = 27 Olaparib 100 mg PO bid

	Cohort 1 400 mg	Cohort 2 100 mg
% Overall response rate	41	22
% Complete/partial response rate	4/37	0/22

Main G3 side-effects : fatigue (6 patients), nausea (5 patients), vomiting (3

Future Is Bright!

Thank You