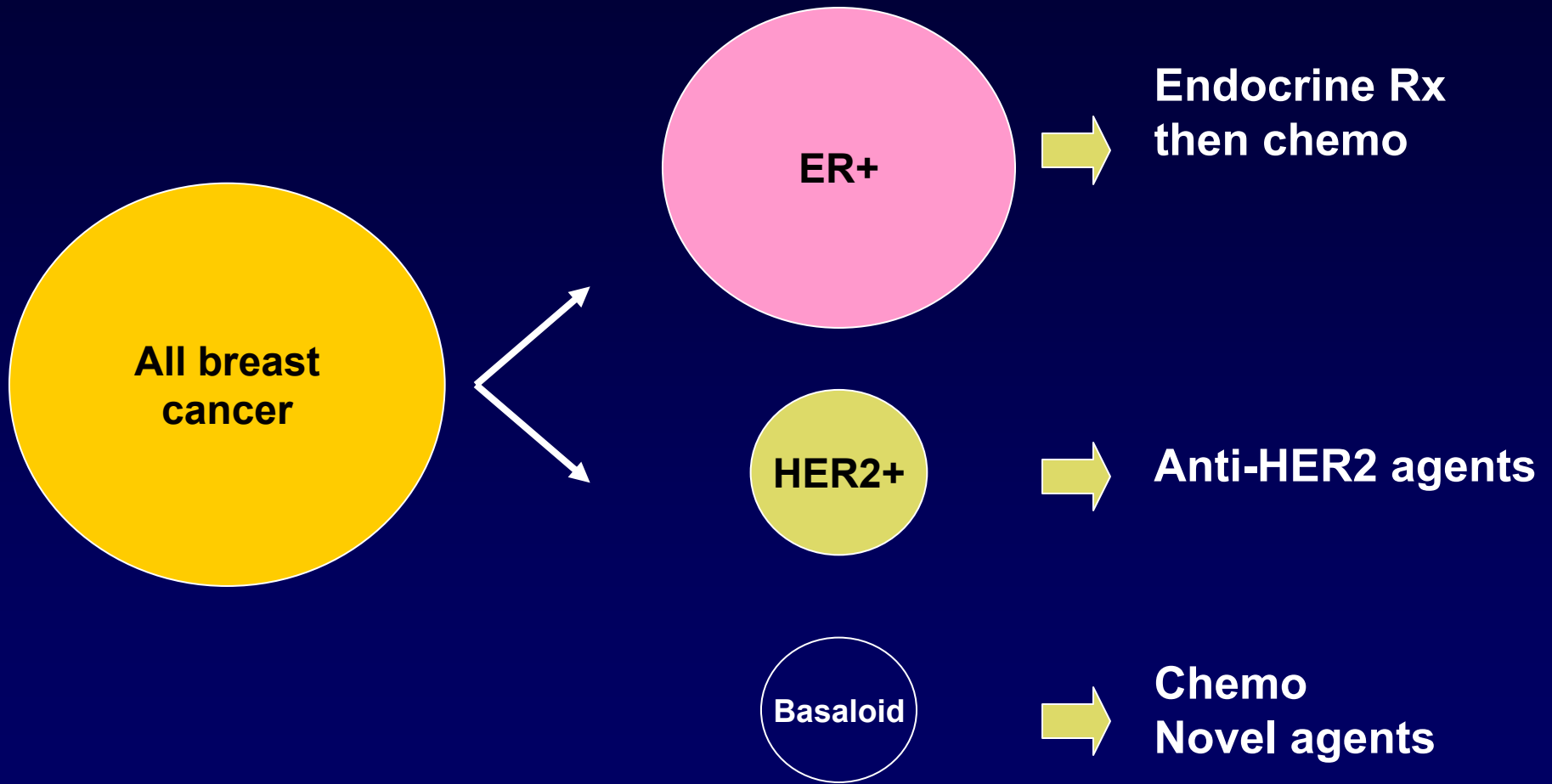


# Case #5—Targeted Therapy for HER2-Overexpressing MBC

**Javier Cortés, MD**  
Department of Oncology  
Vall d'Hebron University Hospital  
Barcelona, Spain

# Breast Cancer Subsets and Treatments



# Breast Intergroup (N9831) Trial<sup>1</sup>

- 1699 patients enrolled (IHC 3+) by local testing
- **355 (20.9%) not confirmed by central testing**

## HERA Trial<sup>2,3</sup>

- 10,890 patients screened at central lab
- **3132 (28.8%) not confirmed HER2 positive**

IHC = immunohistochemistry

# Breast Intergroup (N9831) Trial

- 813 cases enrolled as FISH positive by local testing
- 97 (11.9%) cases were FISH negative at central testing

FISH = fluorescence *in situ* hybridization

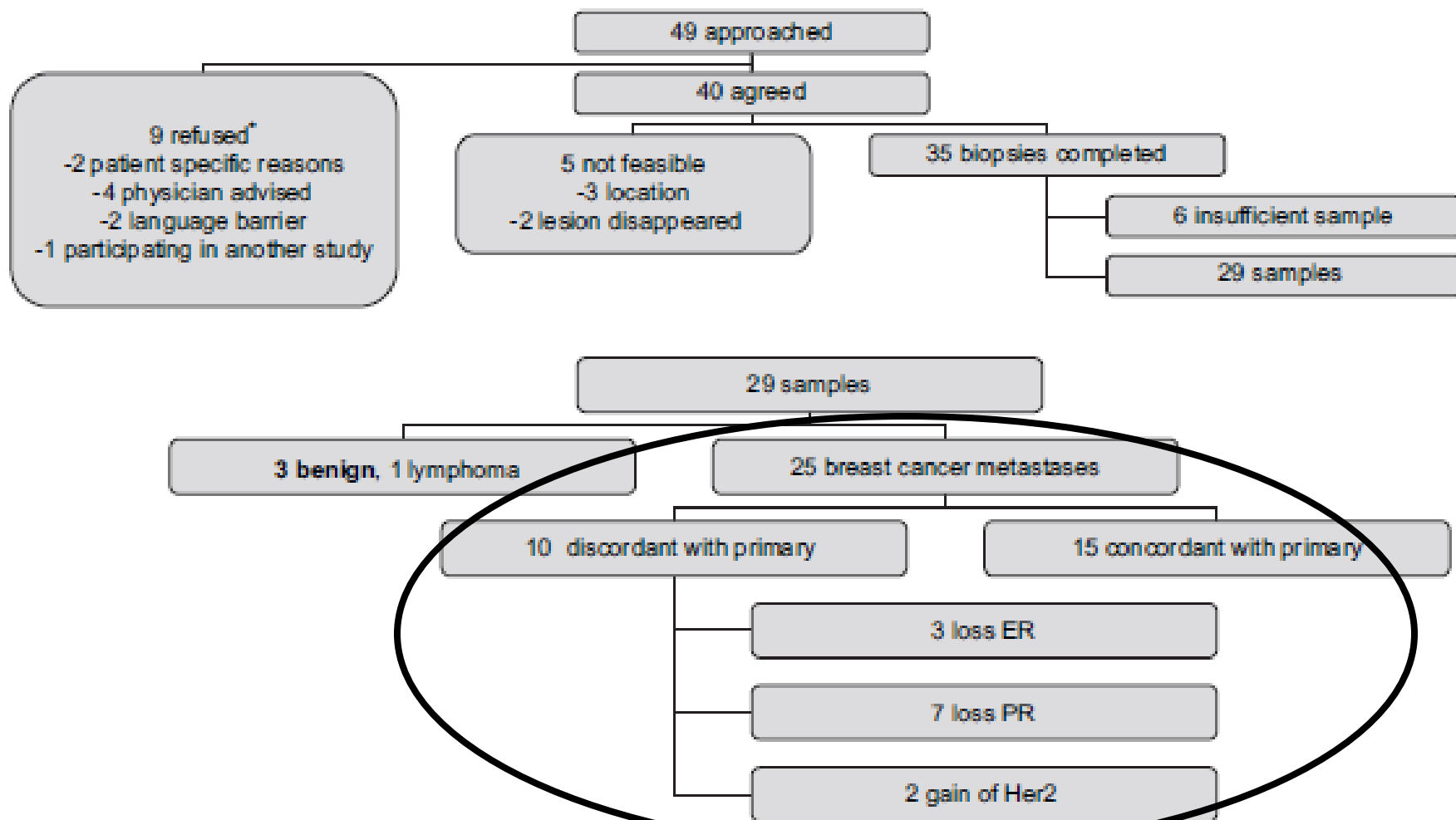
# How to Treat True HR+/HER2+ Breast Tumors?



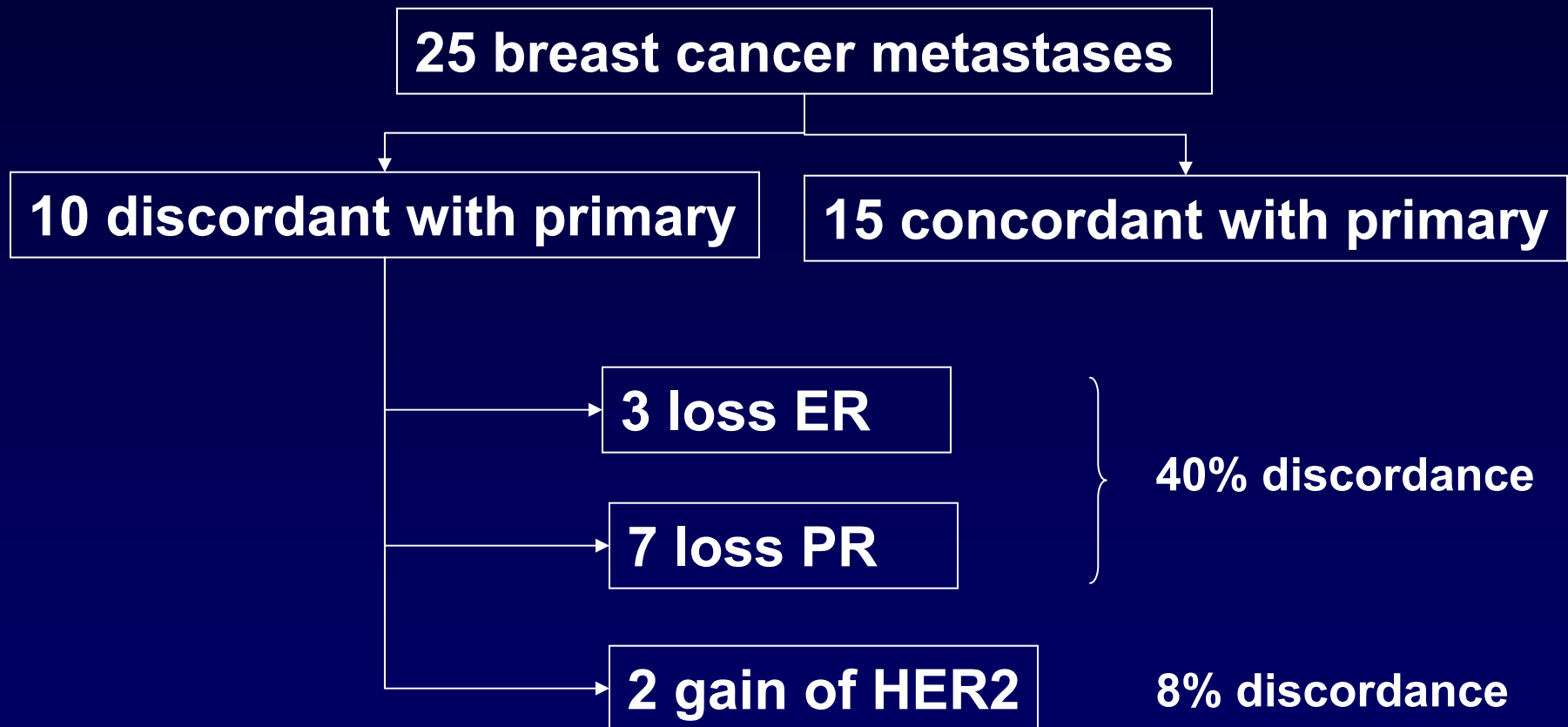
## How to Treat True HR+/HER2+ Breast Tumors **After Recurrence?**

- 6 months after completion of adjuvant trastuzumab

# How to Treat True HR+/HER2+ Breast Tumors After Recurrence?

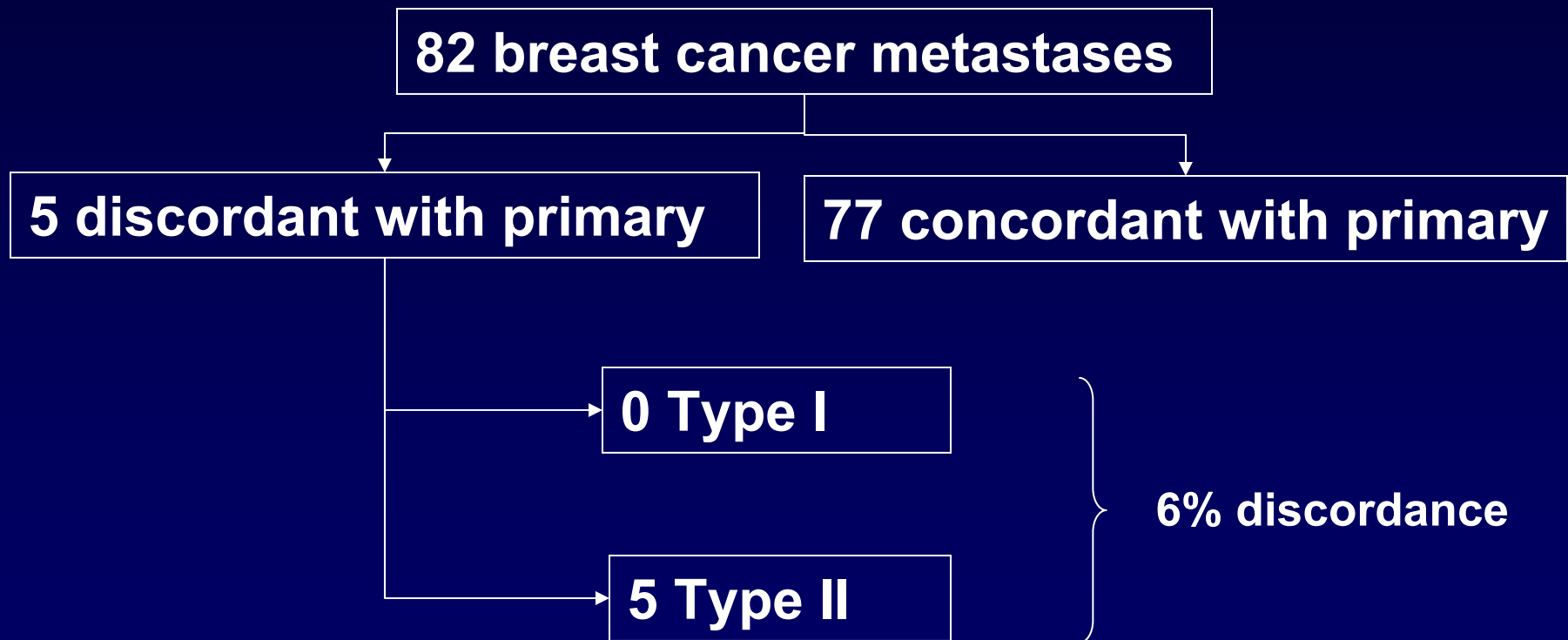


# How to Treat True HR+/HER2+ Breast Tumors After Recurrence? Should We Get a New Biopsy?



# How to Treat True HR+/HER2+ Breast Tumors After Recurrence? Should We Get a New Biopsy?

## *HER2 STATUS*



Type 1: Primary Tumor HER2 neg: Mets HER2 positive

Type 2: Primary Tumor HER2 pos: Mets HER2 negative

# HER2 Status in Primary Carcinomas and Their Metastases

- **86% to 97% of breast carcinomas maintain the same HER2 status during tumor progression**
- **3% to 14% of the cases will either lose or acquire HER2 overexpression or amplification**

**How to Treat True HR+/HER2+ Breast  
Tumors After Recurrence?  
Should We Get a New Biopsy?**

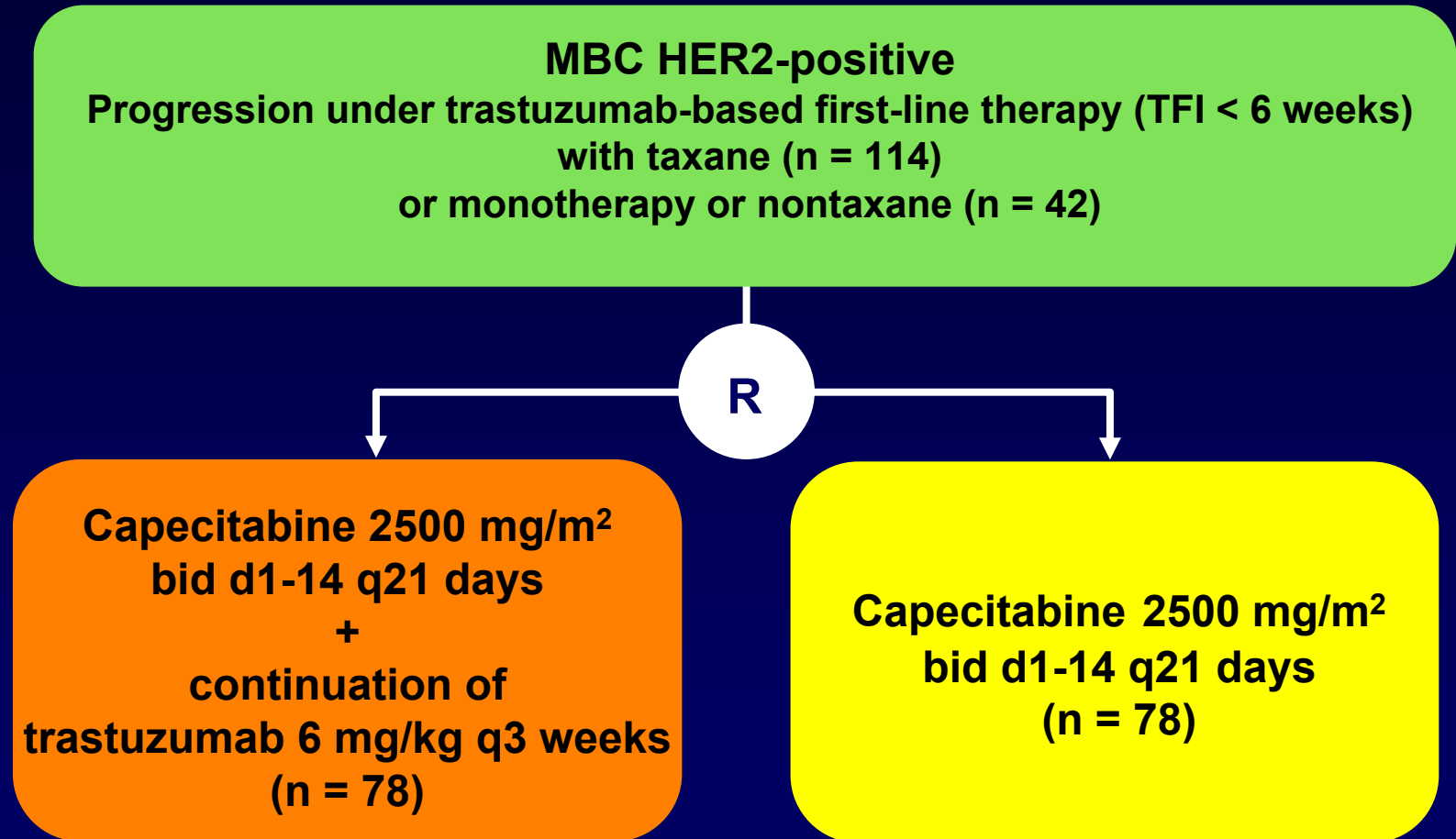
**YES, if possible**

# How to Treat HR+/HER2+ Breast Tumors After Recurrence?

- 6 months after completion of adjuvant trastuzumab

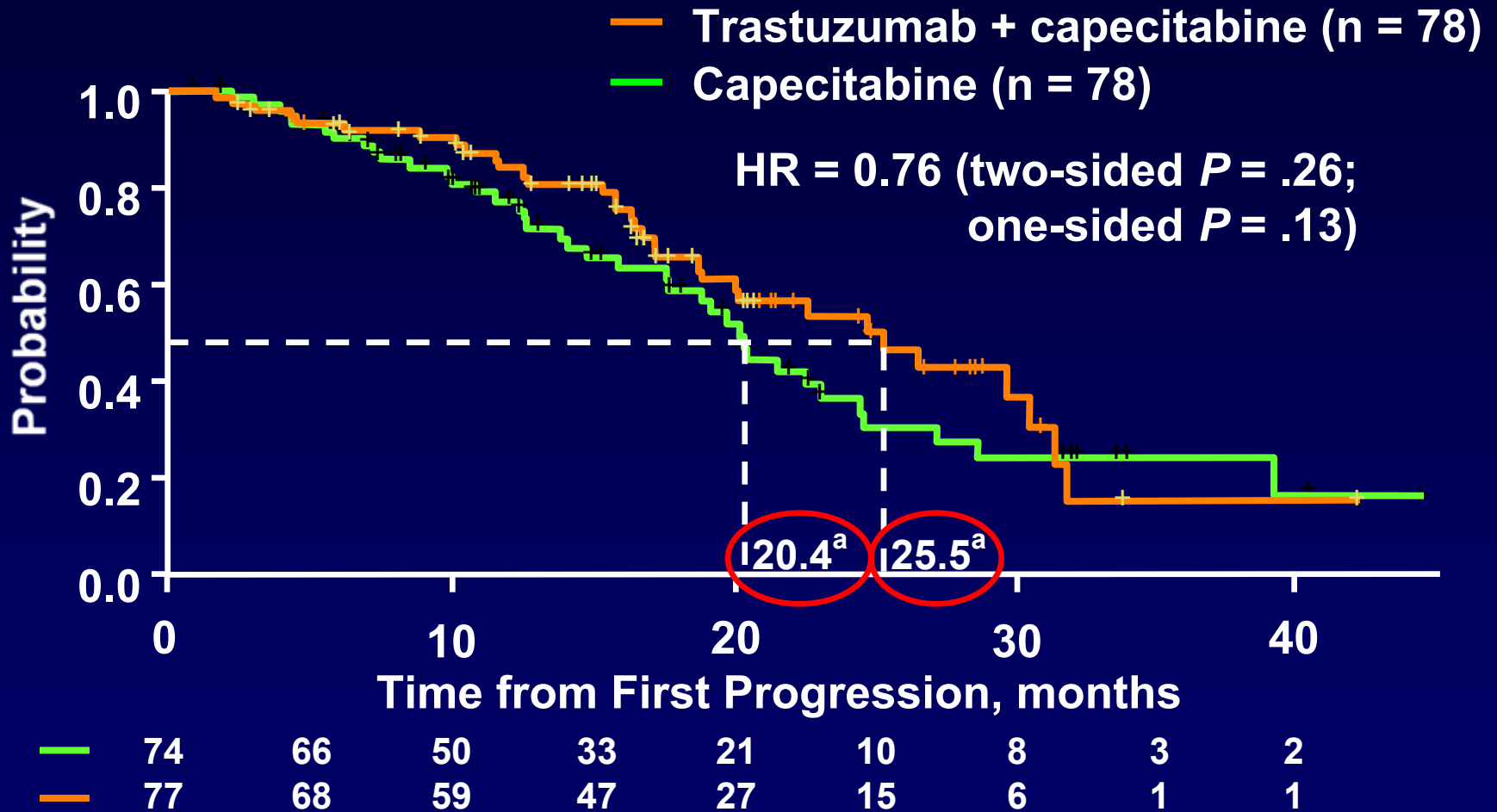
1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine

# GBG-26: Study Design



R, randomization;  
TFI, treatment-free interval

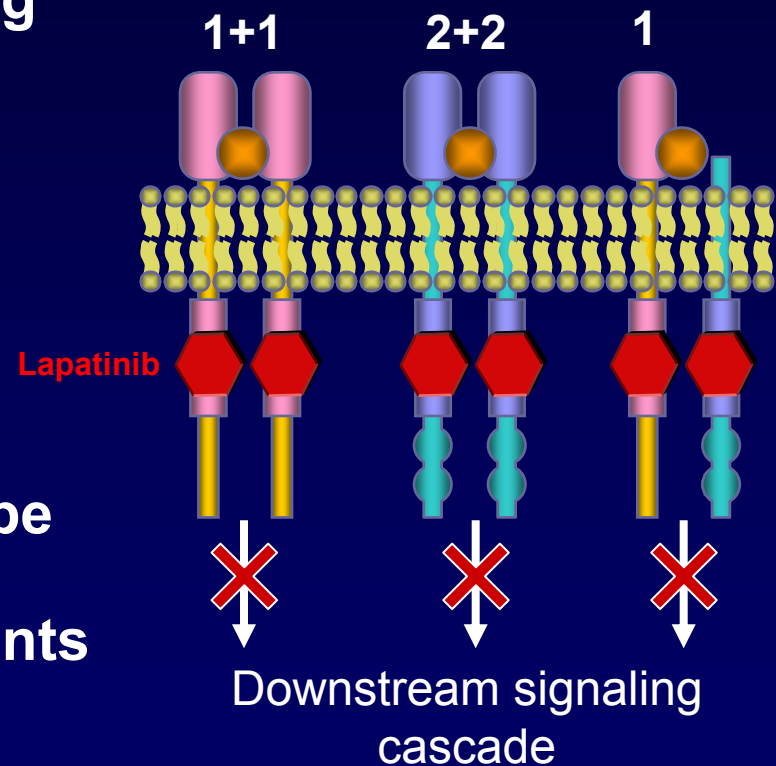
# Continuation of Trastuzumab + Capecitabine Suggests Improvement of Overall Survival



# 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



# 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

# 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/m<sup>2</sup>/d  
po days 1-14 q3 weeks

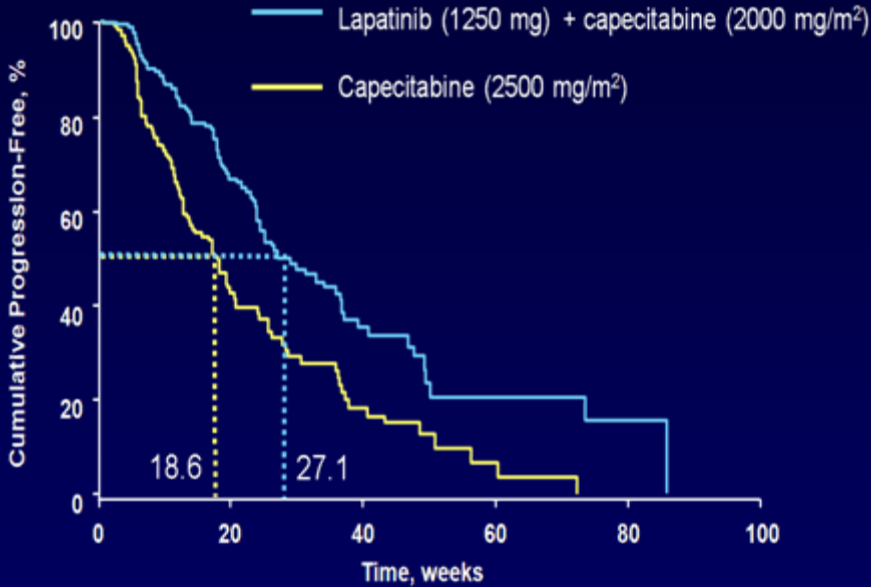
Capecitabine 2500 mg/m<sup>2</sup>/d po  
days 1-14 q 3 weeks

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

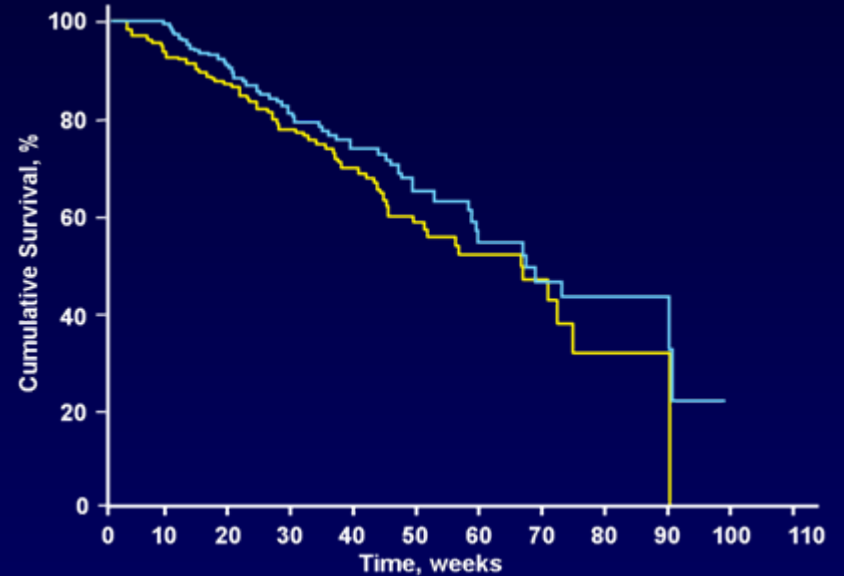
**\*Trastuzumab must have been administered for metastatic disease!!**

# EGF100151

## Median TTP



## Overall Survival



**Hazard ratio 0.57 (95 % CI, 0.43–0.77)**

**Log-rank  $P = .00013$**

	Lapatinib + capecitabine	Capecitabine
No. of pts	198	201
Median OS, mo	15.6	15.3
Hazard ratio (95% CI)	0.78 (0.55, 1.12)	
$P$ value (log-rank, 1-sided)	.177	

# Lapatinib (L) + Paclitaxel (P) Versus Paclitaxel as First-Line Treatment for Patients with MBC: An EGF30001 Subgroup Analysis of HER2+ Patients

	L + P (n = 52)	P + Placebo (n = 39)	P Value	OR/HR (95% CI)
<b>Response rate, %</b>	<b>63.3</b>	<b>37.8</b>	<b>.023</b>	<b>OR 3.0 (1.1 – 8.5)</b>
Median duration of response, months	7.4	5.6		
Median TTP, months	8.5	5.6	.005	0.53 (0.31 – 0.59)
Median OS, months	24.3	19.2	.365	0.74 (0.4 – 1.4)

L + P: increase in diarrhea and rash

→ **SAE-related death: L + P (2.7%) vs P (0.6%) possibly due to a PK interaction**

Paclitaxel given q3 weeks

# Phase III Randomized Open-Label Study of Lapatinib plus Capecitabine vs Trastuzumab + Capecitabine in HER2-Positive Metastatic Breast Cancer

## Inclusion Criteria:

- Stage IV HER2+ breast cancer
- Prior anthracycline and a taxane
- Prior treatment with CT, trastuzumab, HT, RT is permitted
- LVEF  $\geq 50\%$ , normal organ function

## Main Exclusion Criteria:

- History and/or current evidence of CNS metastases
- prior therapy with lapatinib or ErbB2 inhibitor other than trastuzumab

R  
A  
N  
D  
O  
M  
I  
Z  
E

Capecitabine 2500 mg/m<sup>2</sup> bid d1-14 q21 days  
+  
Trastuzumab loading dose 8 mg/kg →  
6 mg/kg q3 weeks

Lapatinib 1250 mg PO qd continuously +  
capecitabine 2000 mg/m<sup>2</sup>/d  
po days 1-14 q3 weeks

- **Primary endpoint:** Incidence of CNS metastases as site of first relapse
- **Secondary endpoints:** Incidence of CNS progression any time, time to first CNS progression, PFS, OS, ORR, CBR, duration of response, toxicity, pharmacogenetics and biomarker analysis

# 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

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

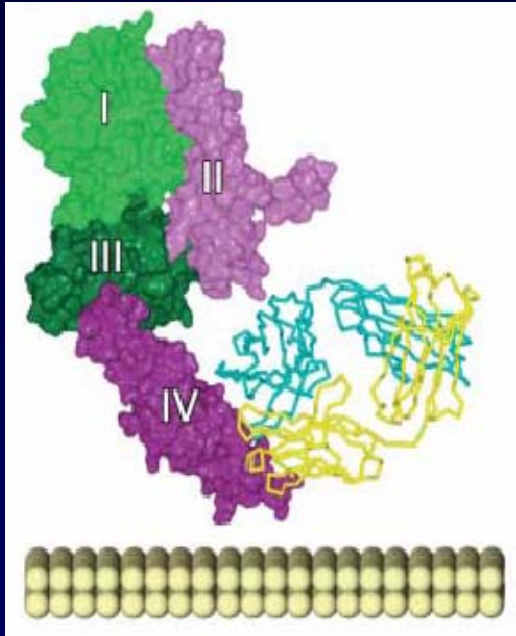
Crossover if PD after 4 wk therapy (N = 73)

# Treatment Efficacy

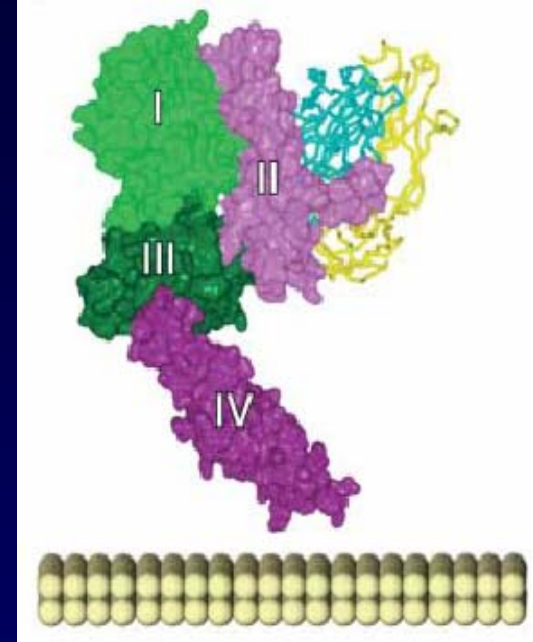
	L N = 145	L + T N = 146
<b>Response rate, %*</b>	<b>6.9</b>	<b>10.3</b>
<b>(95% CI)</b>	<b>(3.4, 12.3)</b>	<b>(5.9, 16.4)</b>
<b>Odds ratio (95% CI)</b>		<b>1.5 (0.6, 3.9)</b> <b>P = .46</b>
<b>Clinical benefit rate, %†</b>	<b>12.4</b>	<b>24.7</b>
<b>(95% CI)</b>	<b>(7.5, 18.9)</b>	<b>(17.9, 32.5)</b>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

\*Confirmed CR+PR †CR+PR+SD ≥6 months

# Trastuzumab and Pertuzumab Bind to Distinct Epitopes on HER2 Extracellular Domain



Trastuzumab



Pertuzumab

- Activates antibody-dependent cellular cytotoxicity
- Enhances HER2 internalization
- Inhibits shedding and, thus, formation of p95
- Inhibits angiogenesis

- Activates antibody-dependent cellular cytotoxicity
- Prevents receptor dimerization
- Potent inhibitor of HER-mediated signaling pathways

# Combination Therapy More Active Than Treatment With Either Agent Alone

Response, n (%)	Cohort 1 and 2 (n = 66)	Cohort 3 (P) (n = 29)	Cohort 3 (H+P) (n = 15)
Complete response (CR)	5 (7.6)	0* (0.0)	0† (0.0)
Partial response (PR)	11 (16.7)	2* (7.4)	3† (27.3)
Objective response rate (ORR)	16 (24.2)	2* (7.4)	3† (27.3)
Stable disease (SD) ≥6 months	17 (25.8)	1* (3.7)	0† (0.0)
Clinical benefit rate (CR + PR + SD ≥6 months)	33 (50.0) <sup>a</sup>	3* (11.1)	3† (27.3)
Progressive disease	33 (50.0)	24* (88.9)	8† (72.7)

P, pertuzumab monotherapy; H+P, trastuzumab / pertuzumab combination therapy

<sup>a</sup>At data cut-off, 21 (31.8%) patients had not yet progressed

\*n=27 as at data cut-off 2 patients had not reached overall best response end point (8 cycles of assessment during this phase). †n=11 as at data cut-off 4 patients had not reached overall best response end point (8 cycles of assessment during this phase)

# Trastuzumab-DM1

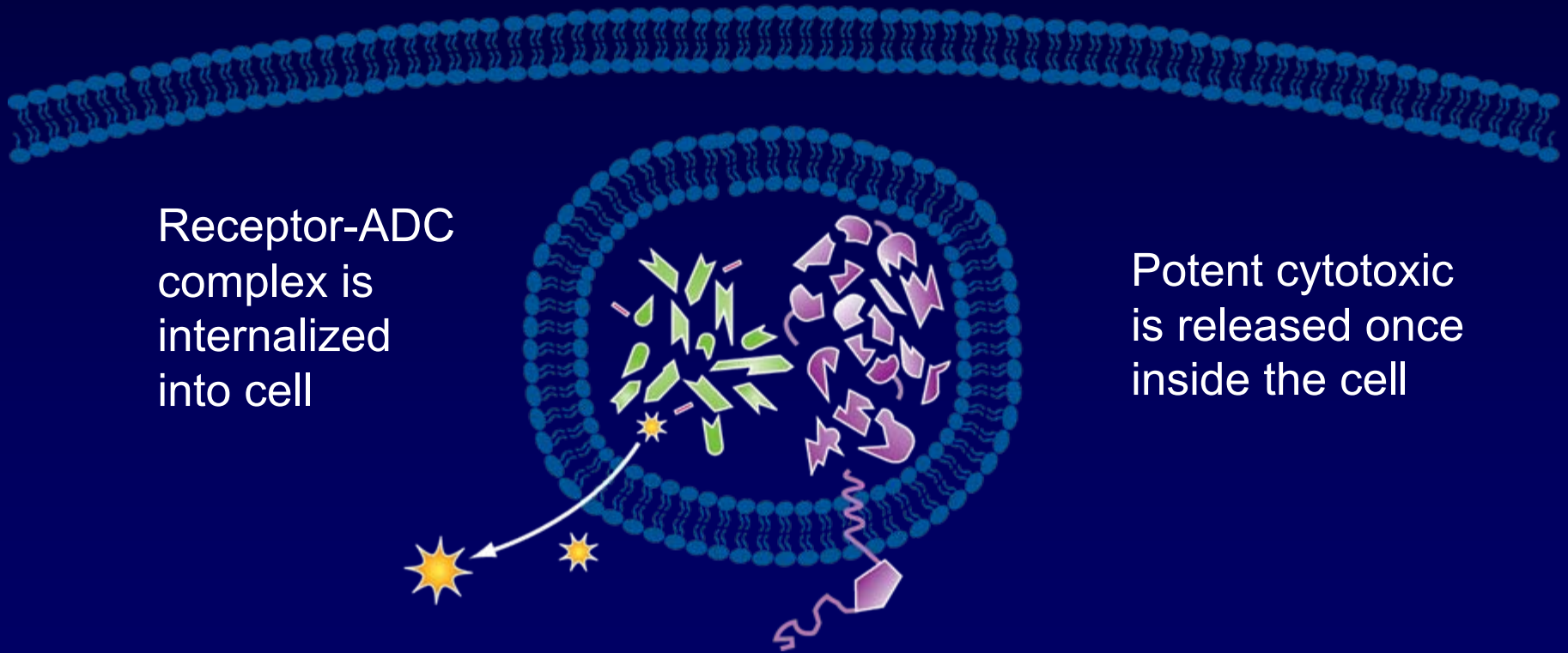
- **Trastuzumab-DM1 (T-DM1) is a novel anti-HER2 antibody drug conjugate in development for treatment of HER2-positive MBC**
- **T-DM1 combines the HER2-inhibiting properties of trastuzumab (Herceptin<sup>®</sup>) with targeted delivery of a highly potent antimicrotubule derivative, DM1**
  - **T-DM1 binds to HER2 with an affinity similar to that of trastuzumab**
  - **It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1**

# HER-Targeted ADCs Selectively Deliver Potent Cytotoxics to HER+ Cells

ADC binds to the HER protein

Receptor-ADC complex is internalized into cell

Potent cytotoxic is released once inside the cell



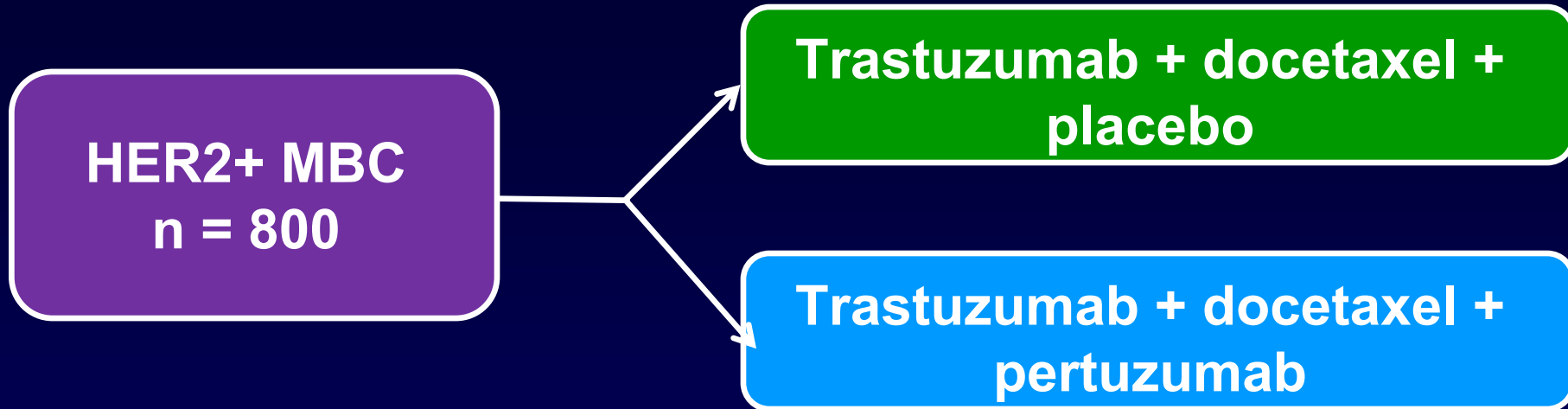
# Anti-Tumor Activity in All Treated Patients (n = 112)

	IRF n (%)	Investigator n (%)
<b>Best Objective Response</b>		
CR	0	3 (2.7)
PR	28 (25.0)	40 (35.7)
SD	54 (48.2)	43 (38.4)
PD	21 (18.8)	22 (19.6)
Unknown	9 (8.0)	4 (3.6)
<b>ORR</b>	<b>28 (25.0)</b>	<b>43 (38.4)</b>
<b>95% CI</b>	<b>17.5–33.6</b>	<b>29.8–47.5</b>
<b>Clinical Benefit*</b>	<b>39 (34.8)</b>	<b>50 (44.6)</b>
<b>95% CI</b>	<b>26.1–43.9</b>	<b>35.5–54.3</b>

CI=confidence interval, CR=complete response, IRF=independent review facility, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease.

\* Includes patients who achieved an objective CR, PR, or SD of ≥6 months.

# CLEOPATRA Study Design



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

## **Enrollment stratified:**

- **Prior treatment for breast cancer**
- **Geographical region of enrollment**

## **Endpoints:**

- **Progression-free and overall survival**
- **Quality of life**
- **Biomarker analysis**

# Nonrandomized Phase II Open-Label Study of Sunitinib + Trastuzumab in Metastatic Breast Cancer

## Inclusion Criteria:

- Unresectable, locally recurrent or metastatic breast cancer
- HER2+ (3+ by IHC or FISH-positive)

## Exclusion Criteria:

- Prior treatment with sunitinib
- Prior treatment with >1 cytotoxic therapy in the advanced setting
- Uncontrolled brain metastases

## Treatment:

Sunitinib 37.5 mg qd

+

Trastuzumab

Qwk – loading dose 4 mg/kg → 2 mg/kg weekly

Or

Q3wk – loading dose 8 mg/kg → 6 mg/kg q3wk

until disease progression or for 18 months

- Primary endpoint: Overall response rate
- Secondary endpoints: Progression-free survival, clinical benefit rate, duration of response, 1-year and overall survival, time to progression, safety
- Prior treatment with trastuzumab or lapatinib in the neoadjuvant or adjuvant metastatic setting permitted
- Hormone therapy in the adjuvant or advanced setting permitted

# Phase III Randomized Open-Label Study of Neratinib vs Lapatinib + Capecitabine in HER2-Positive Locally Advanced Metastatic Breast Cancer

## Inclusion Criteria:

- Stage IIIB, IIIC, or IV HER2+ breast cancer
- Prior treatment with trastuzumab, and anthracycline, and a taxane
- Adequate renal and cardiac function

## Exclusion Criteria:

- >2 trastuzumab regimens or prior treatment with capecitabine or lapatinib
- Bone or skin as only site of disease
- Active CNS metastases
- GI disorder with diarrhea

R  
A  
N  
D  
O  
M  
I  
Z  
E

Neratinib 240 mg PO qd

Lapatinib 1250 mg PO qd continuously +  
capecitabine 2000 mg/m<sup>2</sup>/d  
PO days 1-14 q3 weeks

- Primary endpoint: Progression-free survival
- Secondary endpoint: Safety, quality of life

# How to Treat True HR+/HER2+ Breast Tumors After Recurrence?

# Benefit of Adding Trastuzumab to Standard Chemotherapy for HER2+ Metastatic Breast Cancer: FIRST-LINE

Outcome	Trastuzumab + Chemotherapy (n = 92)	Chemotherapy Alone (n = 94)	P Value
ORR, %	50.0	32.0	<.001
Median DR, m	9.1	6.1	<.001
Median TTP, m	7.4	4.6	<.001
Median OS, m	25.1	20.3	.046

Outcome	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)	P Value
ORR, %	61.0	34.0	.0002
Median DR, m	11.7	5.7	.009
Median TTP, m	11.7	6.1	.0001
Median OS, m	31.2	22.7	.0325

# TAnDEM Study: Anastrozole ± Trastuzumab

HER2-positive,  
hormone receptor-  
positive metastatic  
breast cancer  
(n = 208)

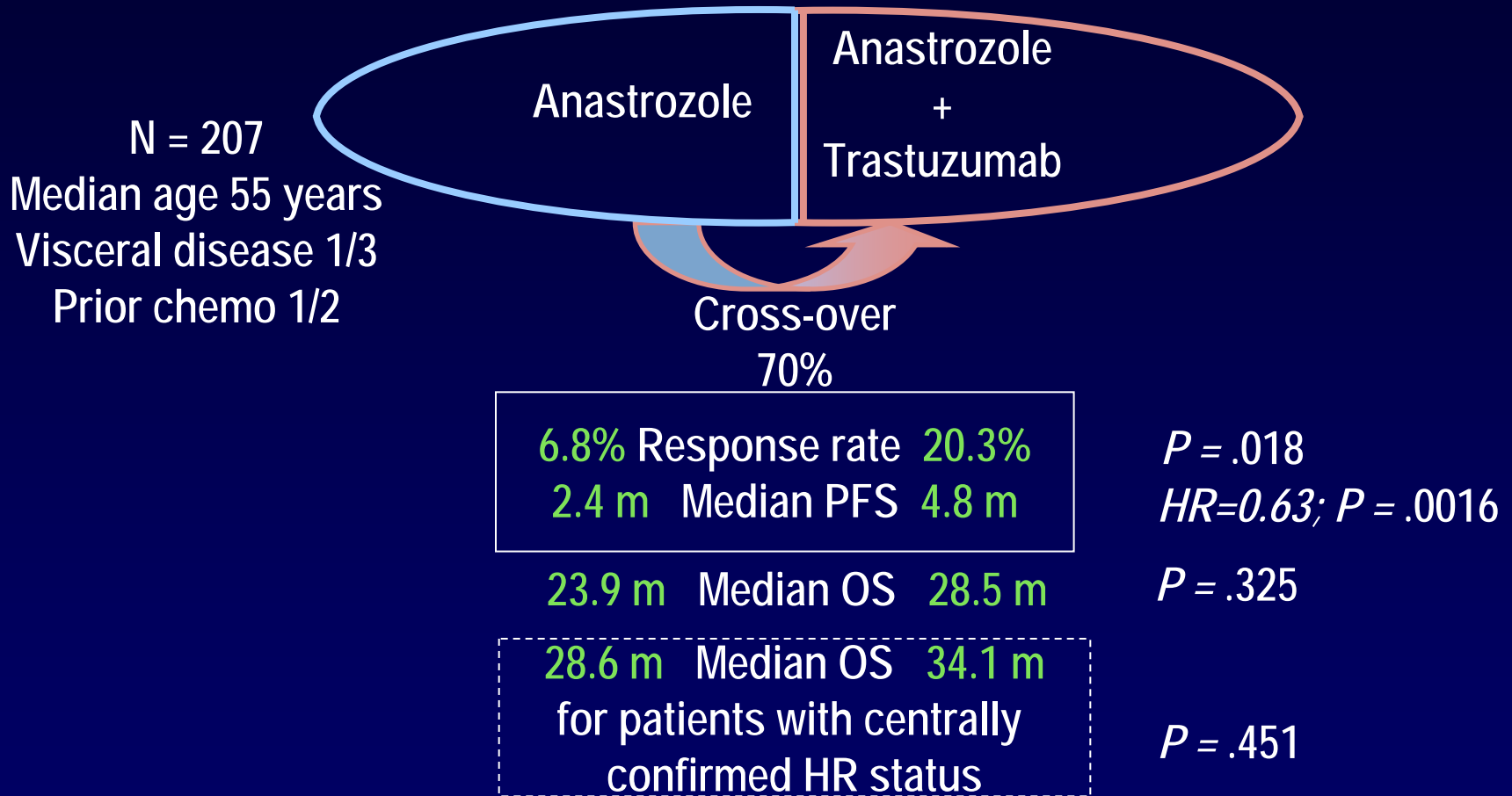
R

Anastrozole 1 mg daily +  
trastuzumab 4 mg/kg loading dose  
→ 2 mg/kg qw  
until disease progression

Anastrozole 1 mg daily  
until disease progression

- Crossover to receive trastuzumab was actively offered to all patients who progressed on anastrozole alone

# TAnDEM Study: Randomized, Open-Label Trial of Anastrozole ± Trastuzumab in Advanced HER2+, HR+ Breast Cancer



Trastuzumab added to anastrozole ↗ RR, PFS, TTP and CBR

# EGF30008: Phase III, Randomized, Double-Blind Controlled Trial: Study Design

## Patient Population:

- ER+ and/or PgR+
- Postmenopausal
- HER2+, HER-ve/Unknown
- Stage IIIb/IIIc/IV
- No prior treatment for metastatic breast cancer (MBC)

## Stratification:

- Disease sites
  - Bone only/visceral or soft tissue
  - Interval since adjuvant tamoxifen therapy
    - <6 mo / ≥6 mo or none

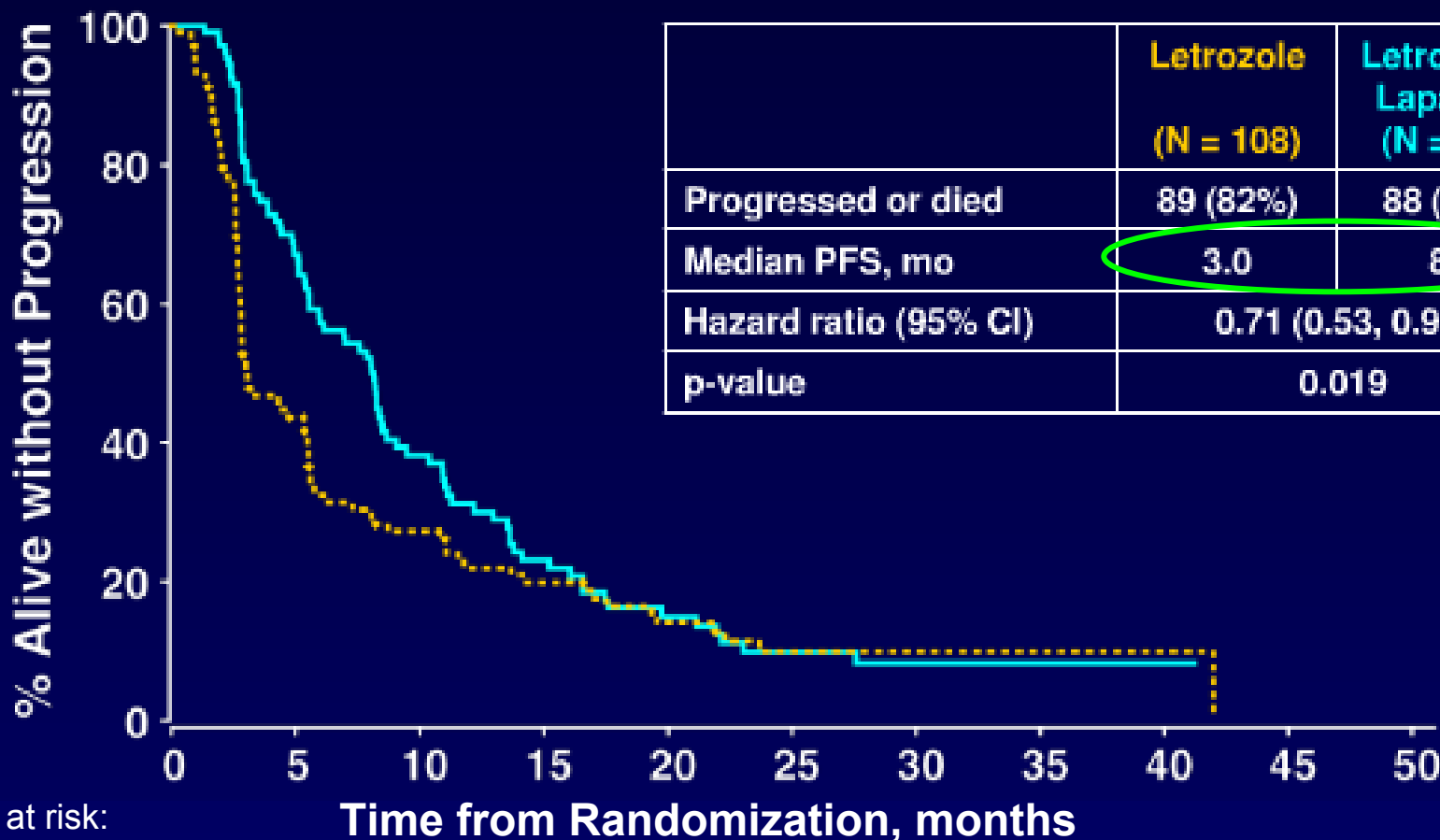


Letrozole 2.5 mg daily +  
placebo

Letrozole 2.5 mg daily +  
lapatinib 1500 mg daily

N = 1286 (including n = 219 HER2+)

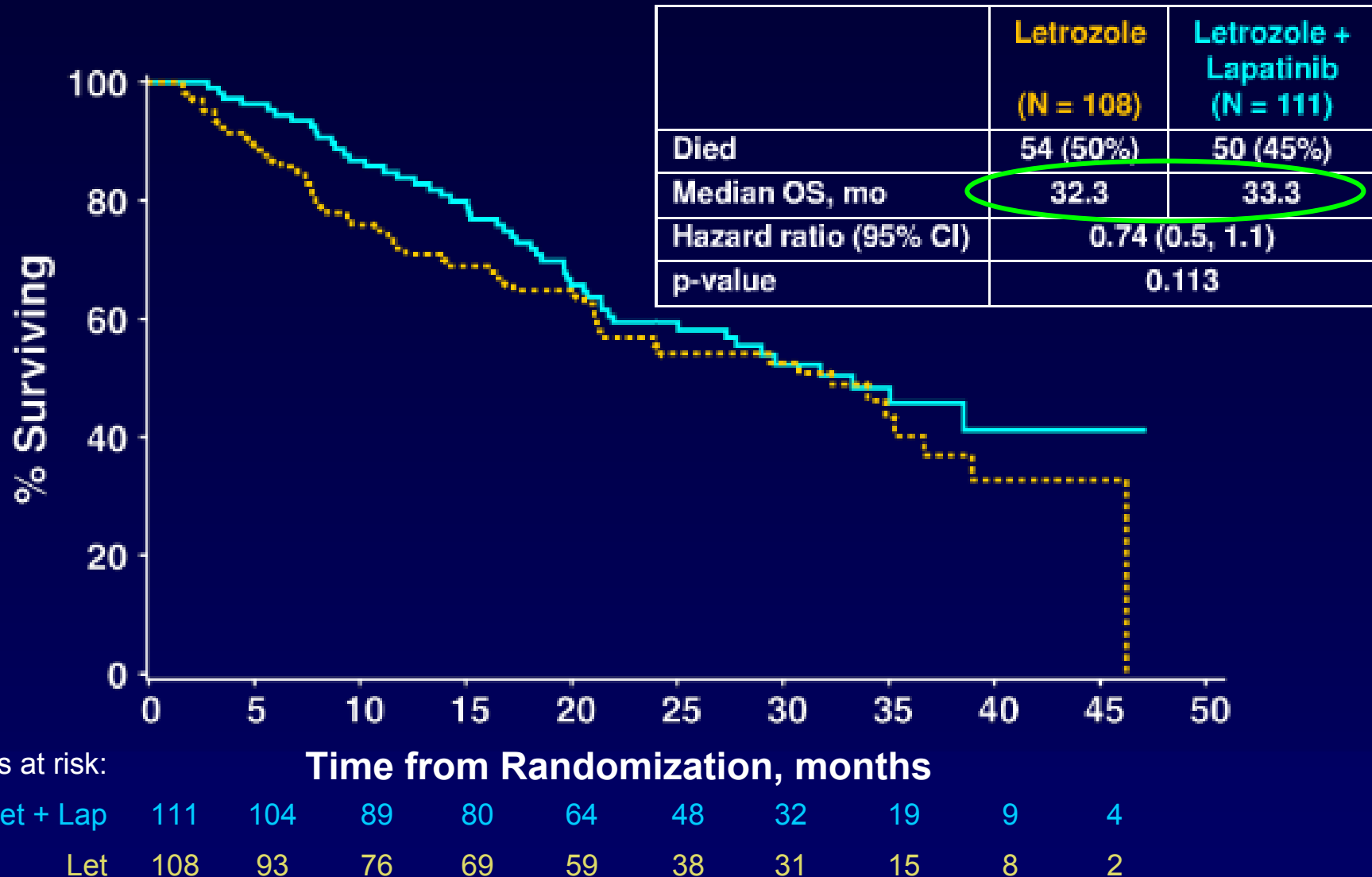
# Progression-Free Survival: HER2+ Population



Pts at risk:

	0	5	10	15	20	25	30	35	40
Let + Lap	111	69	33	20	12	8	4	1	1
Let	108	43	26	18	12	7	5	2	2

# Overall Survival: HER2+ Population



# Novel Anti-HER2 Strategies in Phase II and III Clinical Trials

Class / Agent	Target / Mechanism	Phase
<b>Monoclonal Antibodies</b>		
• Pertuzumab	HER2-dimerization inhibitor	III
• Trastuzumab-DM1	HER2/antibody-toxin (trastuzumab-maytansine) conjugate	III
• Ertumaxomab	HER2/CD3 trifunctional bispecific antibody	II
<b>Signal transduction inhibitors</b>		
• 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
<b>Heat shock protein inhibitors</b>		
• Tanespimycin	HSP90 inhibitor	III
<b>Angiogenesis inhibitors</b>		
• Bevacizumab	Anti-VEGF antibody	III
• Pazopanib	VEGFR, c-kit, PDGFR, TKI	III
• Sunitinib	VEGFR, c-kit, PDGFR, TKI	II
<b>Histone deacetylase inhibitors</b>		
• Panobinostat	HDAC inhibitor	II
<b>Cyclo-oxygenase inhibitors</b>		
• Apricoxib	COX-2 inhibitor	II
<b>Immunotherapy</b>		
• HER/neu vaccine	Recombinant HER2 intracellular domain vaccine	II

# How to Treat HR+/HER2+ Breast Tumors After Recurrence?

- **Combined chemotherapy and anti-HER2 therapy will remain as the therapy of choice at this time**
- **However:**
  - **The combination of anti-HER2 and hormonal therapy is a valid option in individualized clinical settings.**

# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy ✓
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine

# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole **X**
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole **X**
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine


# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>) ✓✓
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel ✓
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine

# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib ✓
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine

# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA) 
8. Clinical trial of neratinib versus lapatinib + capecitabine

# How Would I Treat This Patient?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib (Tyverb<sup>®</sup>) and letrozole
3. Lapatinib and capecitabine (Xeloda<sup>®</sup>)
4. Trastuzumab and anastrozole
5. Lapatinib and weekly paclitaxel
6. Trastuzumab and lapatinib
7. Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)
8. Clinical trial of neratinib versus lapatinib + capecitabine



# How Would I Treat This Patient?

- 1. Clinical trial of neratinib versus lapatinib + capecitabine**
- 2. Lapatinib and capecitabine (Xeloda®)**