

Case # 5: HER2-Positive Breast Cancer Progression Following Adjuvant Trastuzumab

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HER2-Positive Breast Cancer (BC) Progression Following Adjuvant Trastuzumab: A Summary of the Clinical Case (# 5)

Patient	51-year-old, postmenopausal for 18 months after chemo, asymptomatic (skin and small asymptomatic lung metastases)
Primary tumor	HER2 (IHC): 3+; ER: 60%, PR: 40%
Adjuvant therapy	Adjuvant docetaxel (Taxotere [®])/carboplatin x 6 + H → trastuzumab (Herceptin [®]) Adjuvant tamoxifen Radiation to the left breast
Six months after completion of adjuvant trastuzumab → disease progression	

Part I: Would You Recommend Biopsy of One of the Skin Lesions to Check Hormone Receptor and HER2 Status?

- Yes
- No

False-Positive PgR Status

Anatomic Pathology / POTENTIAL FALSE POSITIVITY WITH SP2

Potential for False-Positive Staining With a Rabbit Monoclonal Antibody to Progesterone Receptor (SP2)

Findings of the UK National External Quality Assessment Scheme for Immunocytochemistry and FISH Highlight the Need for Correct Validation of Antibodies on Introduction to the Laboratory

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Key Words: Breast hormonal receptors; Progesterone receptor; Rabbit monoclonal antibody; SP2; Quality assurance; Antibody validation

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Breast Intergroup (N9831) Trial¹

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

HERA Trial^{2,3}

- 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

2007 ASCO/CAP Scoring Criteria IHC

- Positive (IHC 3+): >30% tumor cells with intense circumferential membrane staining
- Equivocal (IHC 2+): >10% tumor cells with weak to moderate circumferential membrane staining or $\leq 30\%$ tumor cells with intense circumferential membrane staining



- Negative (IHC 0 or 1+): Absent or partial membrane staining

Criteria For FISH/CISH to Define HER2 Positivity

- Determination of gene amplification by FISH (fluorescence *in situ* hybridization): ratio of HER2 gene copies to chromosome 17 centromeres >2.2

OR

- CISH (chromogenic *in situ* hybridization): >6 HER2 signals/nucleus in $>50\%$ tumor cells

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**

My Reply

- **Would you recommend biopsy of one of the skin lesions to check hormone receptor and HER2 status?**
- **NO because I would have asked for FISH at the start and the M1 pattern is classic**

Part II: Biopsy Was Performed and Confirmed Recurrence of HER2-Positive and Hormone Receptor–Positive Disease. Which of the Following Treatments Would You Recommend Now?

- **Rechallenge with trastuzumab + chemotherapy**
- **Lapatinib (Tyverb[®]) and letrozole**
- **Lapatinib and capecitabine (Xeloda[®])**
- **Trastuzumab (Herceptin[®]) and anastrozole (Arimidex[®])**
- **Lapatinib (Tyverb[®]/Tykerb[®]) and weekly paclitaxel (Taxol[®])**
- **Trastuzumab and lapatinib**
- **Clinical trial of docetaxel + trastuzumab + pertuzumab versus docetaxel + trastuzumab (CLEOPATRA)**
- **Clinical trial of trastuzumab and sunitinib (Sutent[®])**
- **Clinical trial of neratinib versus lapatinib + capecitabine**

Clinical Case #5: Therapeutic Options

- Lapatinib
- Neratinib

HER2 inhibitors single agent

- Trastuzumab + anastrozole
- Lapatinib + letrozole

HER2 inhibitors + HT

- Lapatinib + weekly paclitaxel
- Rechallenge with trastuzumab + chemotherapy
- Lapatinib + capecitabine

HER2
inhibitors + CT

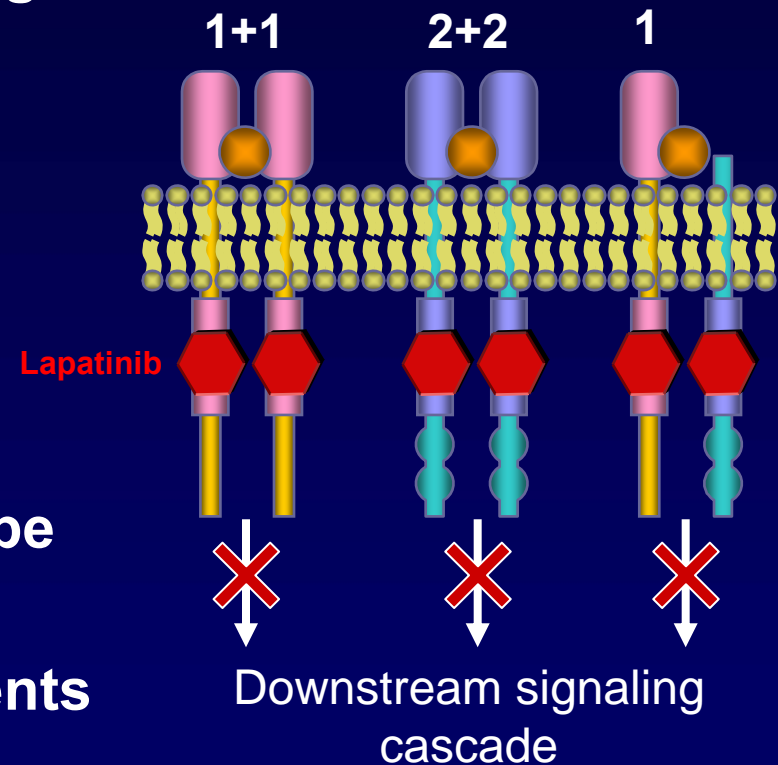
- Trastuzumab and lapatinib
- Trial: trastuzumab and pertuzumab
- Trial: neratinib versus lapatinib + capecitabine
- Trial: trastuzumab and sunitinib

Modulators of T
resistance

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



Lapatinib Monotherapy in Relapsed/Refractory Pretreated Inflammatory BC: Overall Best Response

Cohort	No. of Pts	RECIST	Skin	Combined
A (HER2 \oplus)	126	15%	40%	39%
B (EGFR \oplus)	12	10%	8%	8%

HER2 \oplus = IHC3 + or FISH +

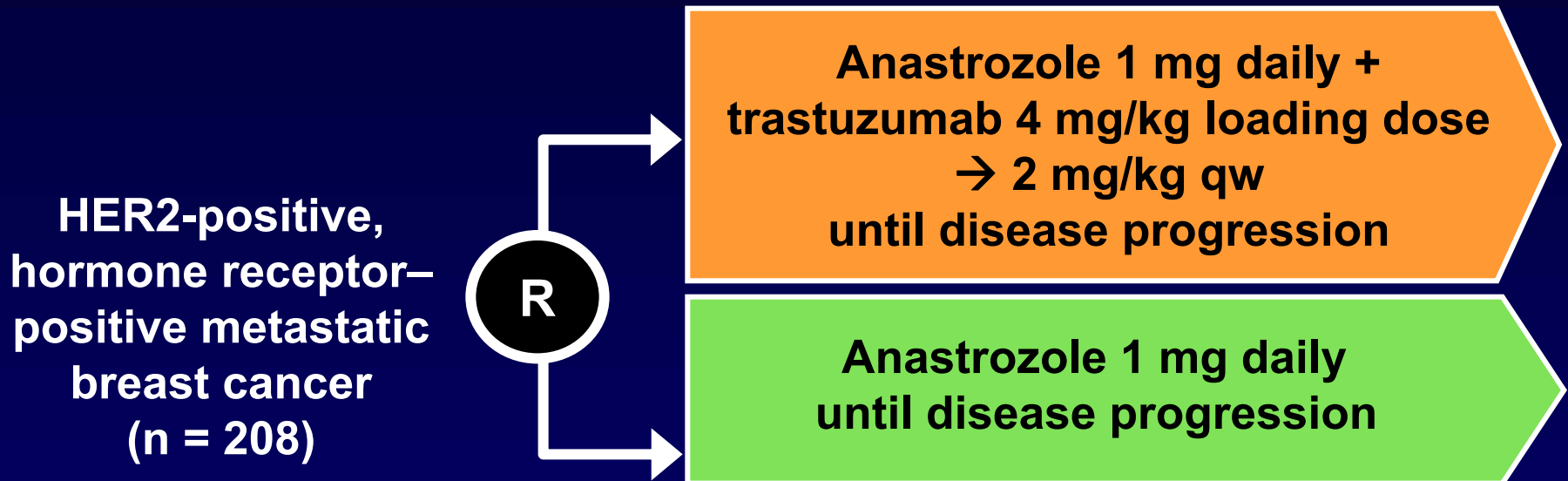
HKI-272 (Neratinib), An Oral Irreversible Pan Erb Receptor Tyrosine Kinase Inhibitor: Tumor Response in Evaluable Population

	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%

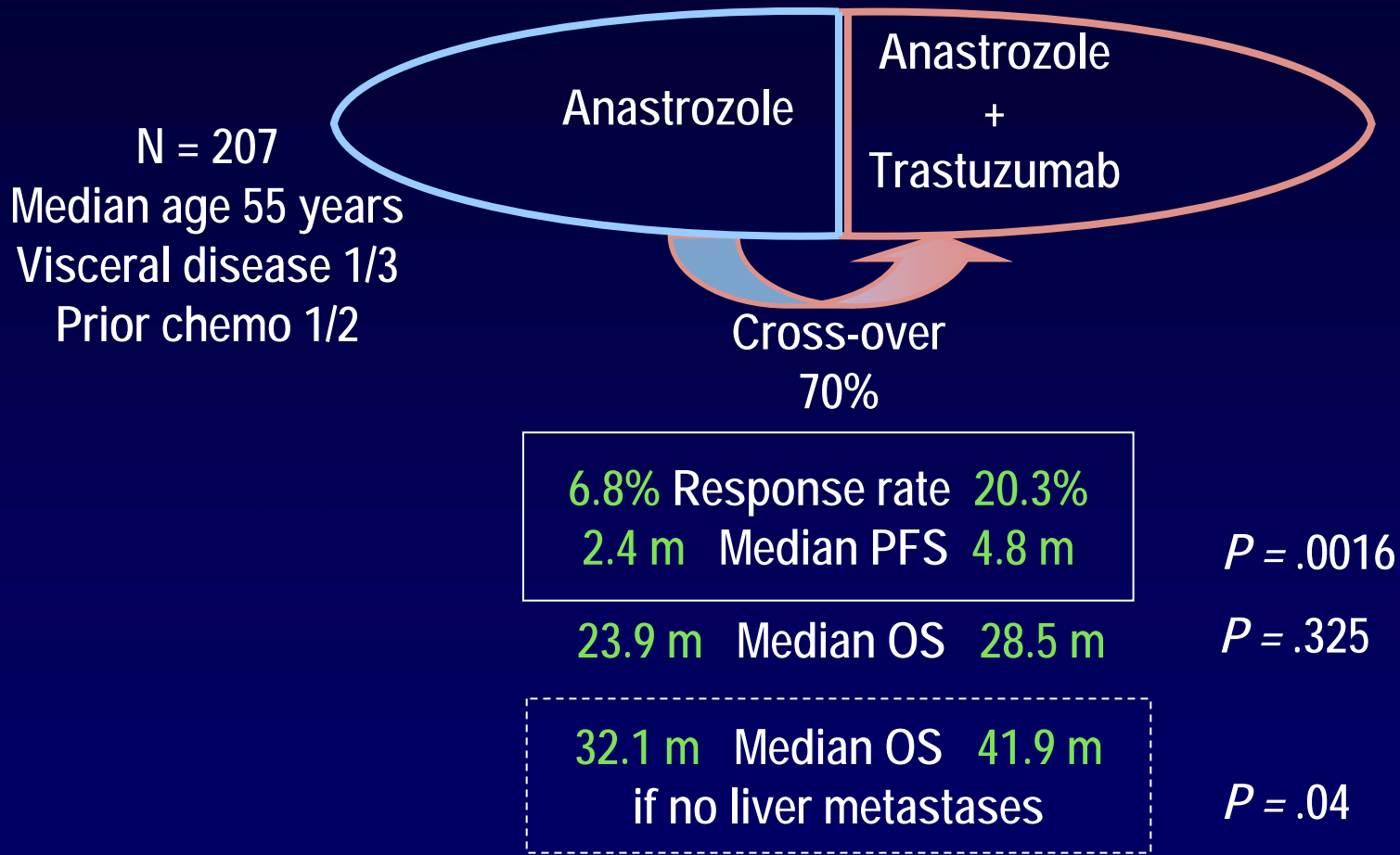
16% of patients had dose reductions due to diarrhea

TAnDEM Study: Anastrozole ± Trastuzumab



- 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 (and possibly OS if no liver metastases)
IMPORTANCE OF STARTING BIOLOGICAL AGENT SOON

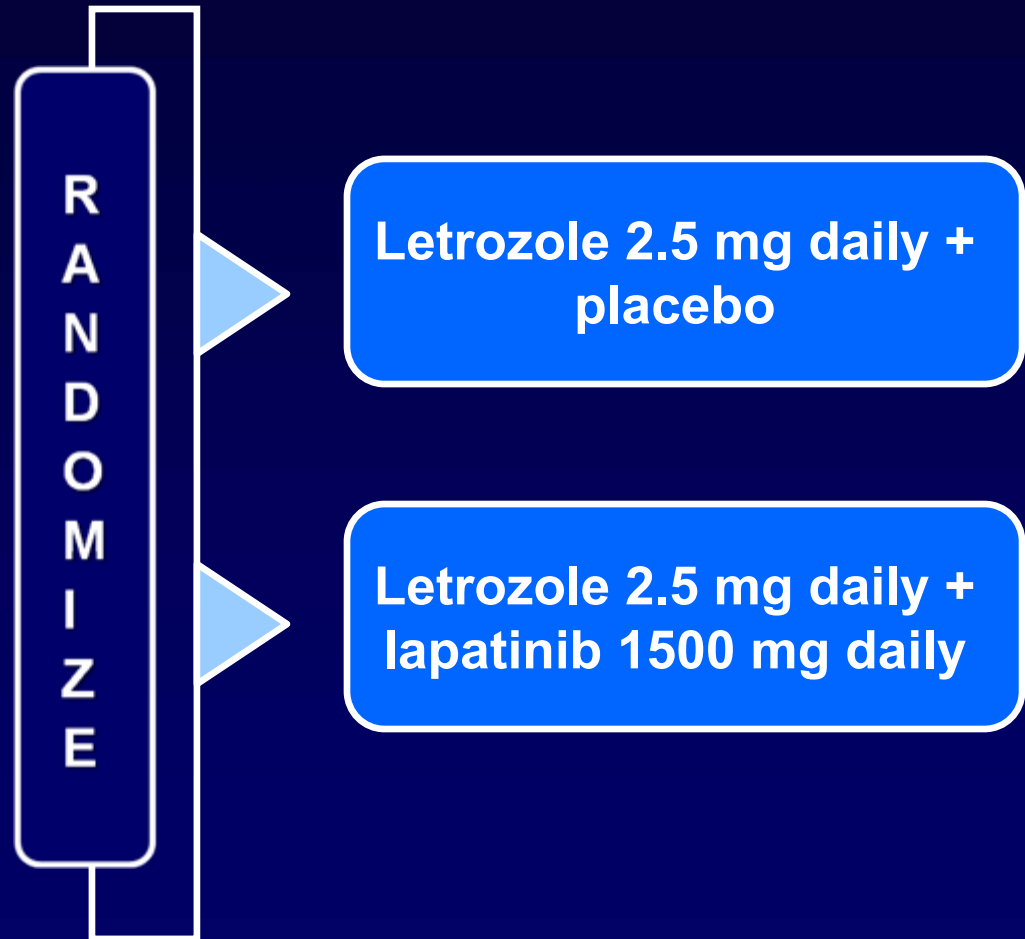
EGF30008: Phase III, Randomized, Double-Blind Controlled Trial: Study Design

Patient Population:

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

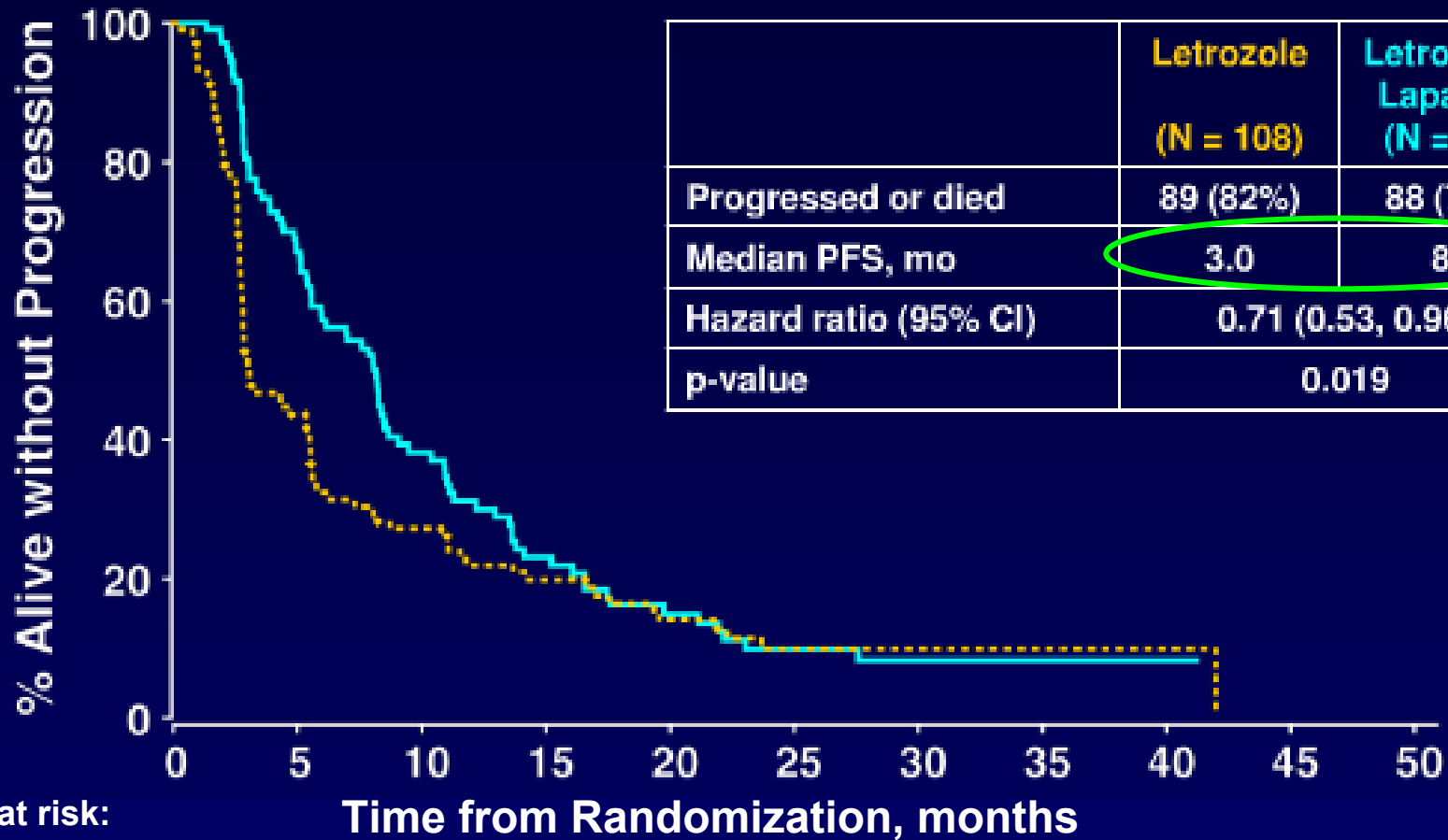
Stratification:

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



N = 1286 (including n = 219 HER2+)

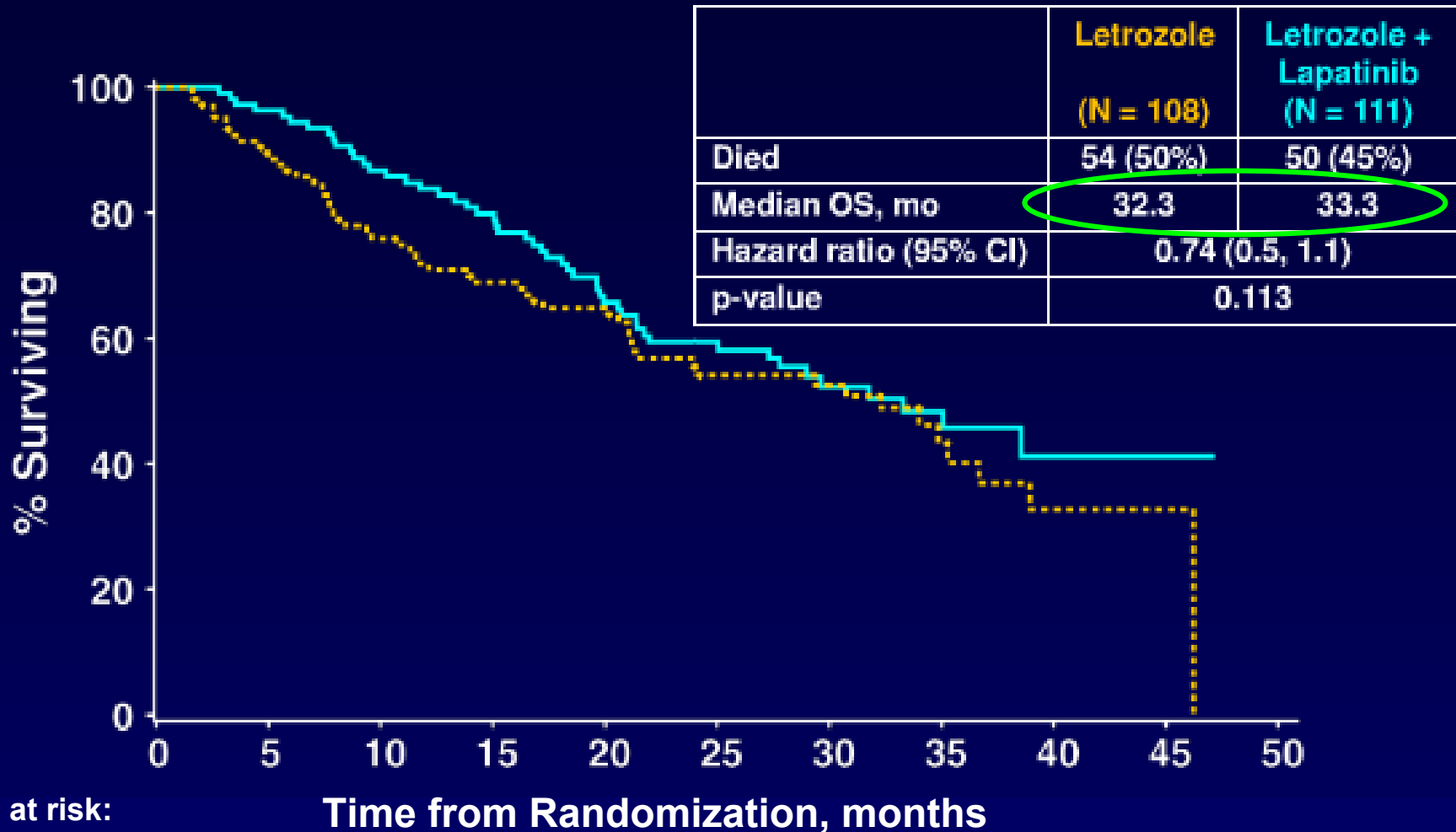
Progression-Free Survival: HER2+ Population



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



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

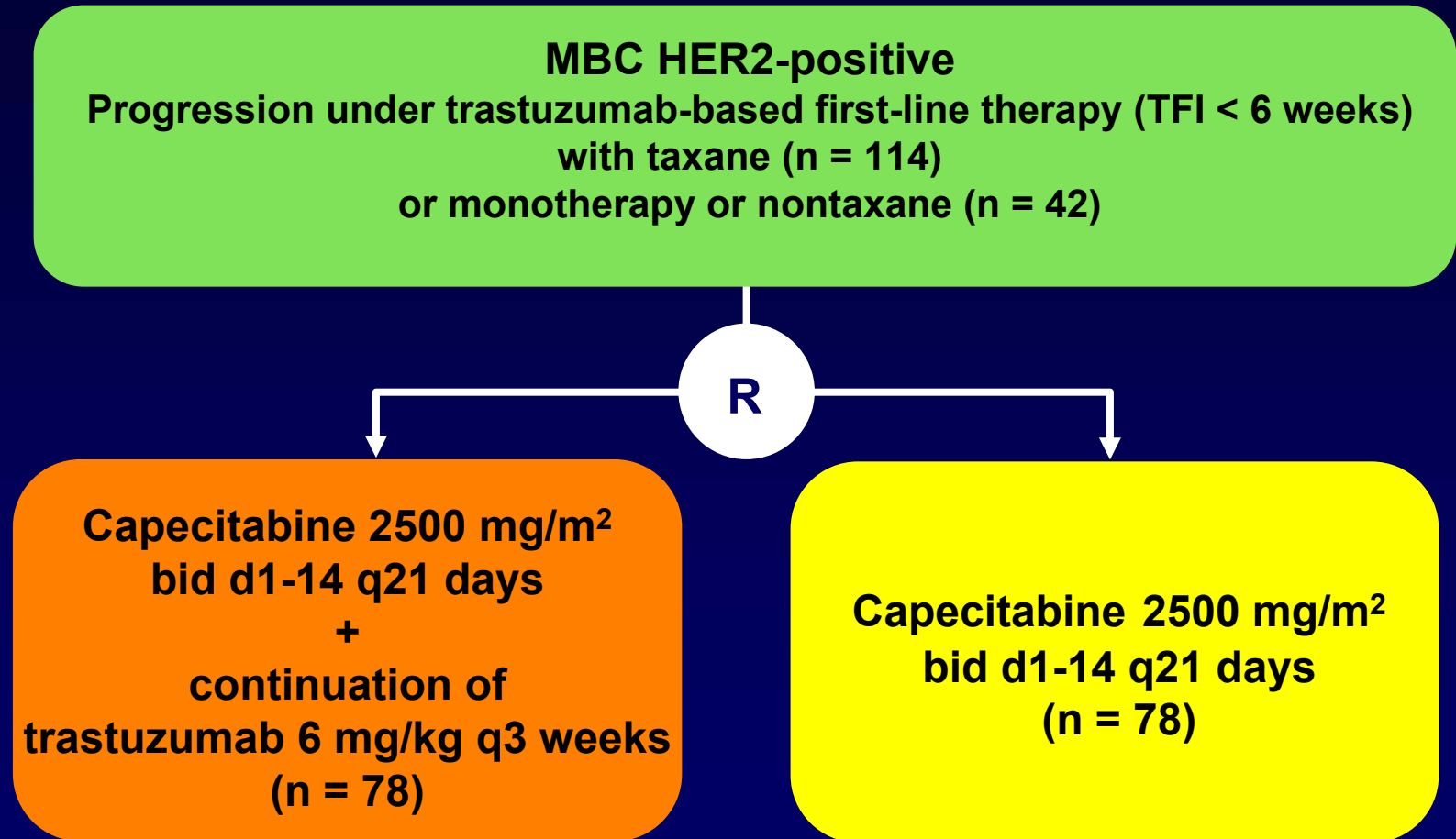
	L + P (n = 52)	P + Placebo (n = 39)	P Value	OR/HR (95% CI)
Response rate, %	63.3	37.8	.023	OR 3.0 (1.1 – 8.5)
Median duration of response, months	7.4	5.6		
Median TTP, months	8.5	5.6	.005	0.53 (0.31 – 0.59)
Median OS, months	24.3	19.2	.365	0.74 (0.4 – 1.4)

L + P: increase in diarrhea and rash

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

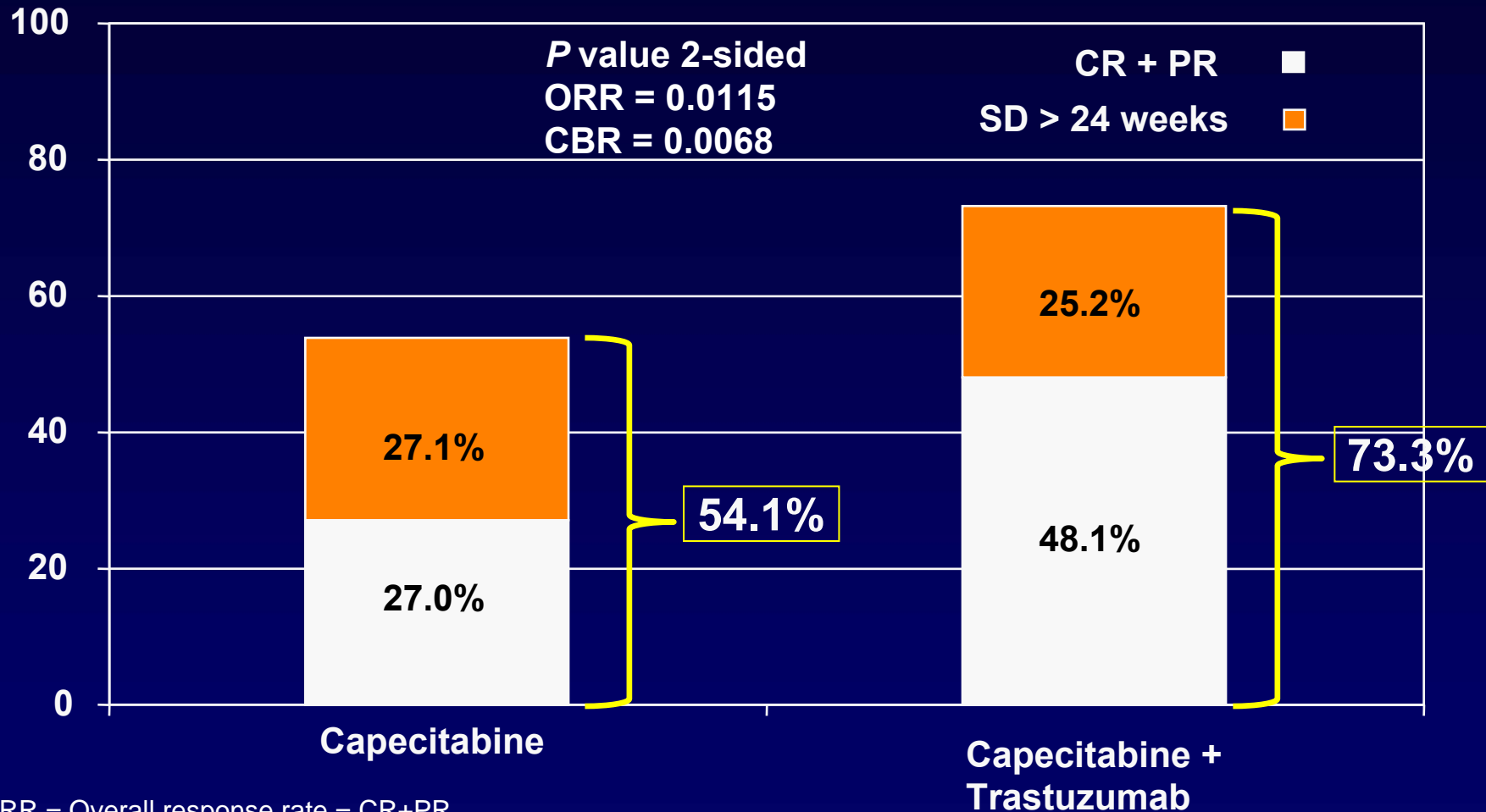
Paclitaxel given q3 weeks

GBG-26: Study Design



R, randomization;
TFI, treatment-free interval

Trastuzumab Beyond Progression Response Rate (RECIST)

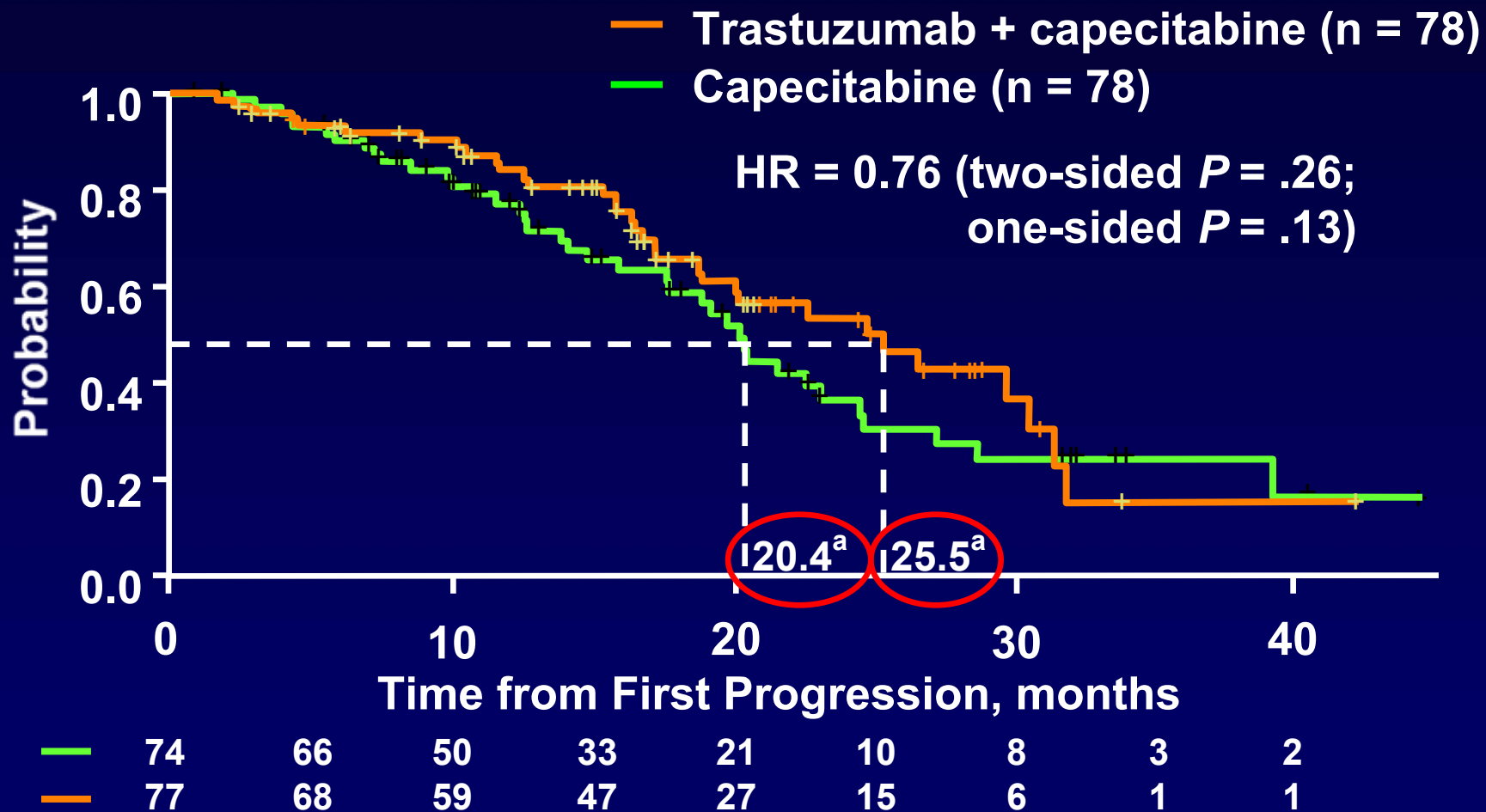


ORR = Overall response rate = CR+PR

CBR = Clinical benefit rate = CR+PR+SD>24 weeks

Von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006.

Continuation of Trastuzumab + Capecitabine Suggests Improvement of Overall Survival



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

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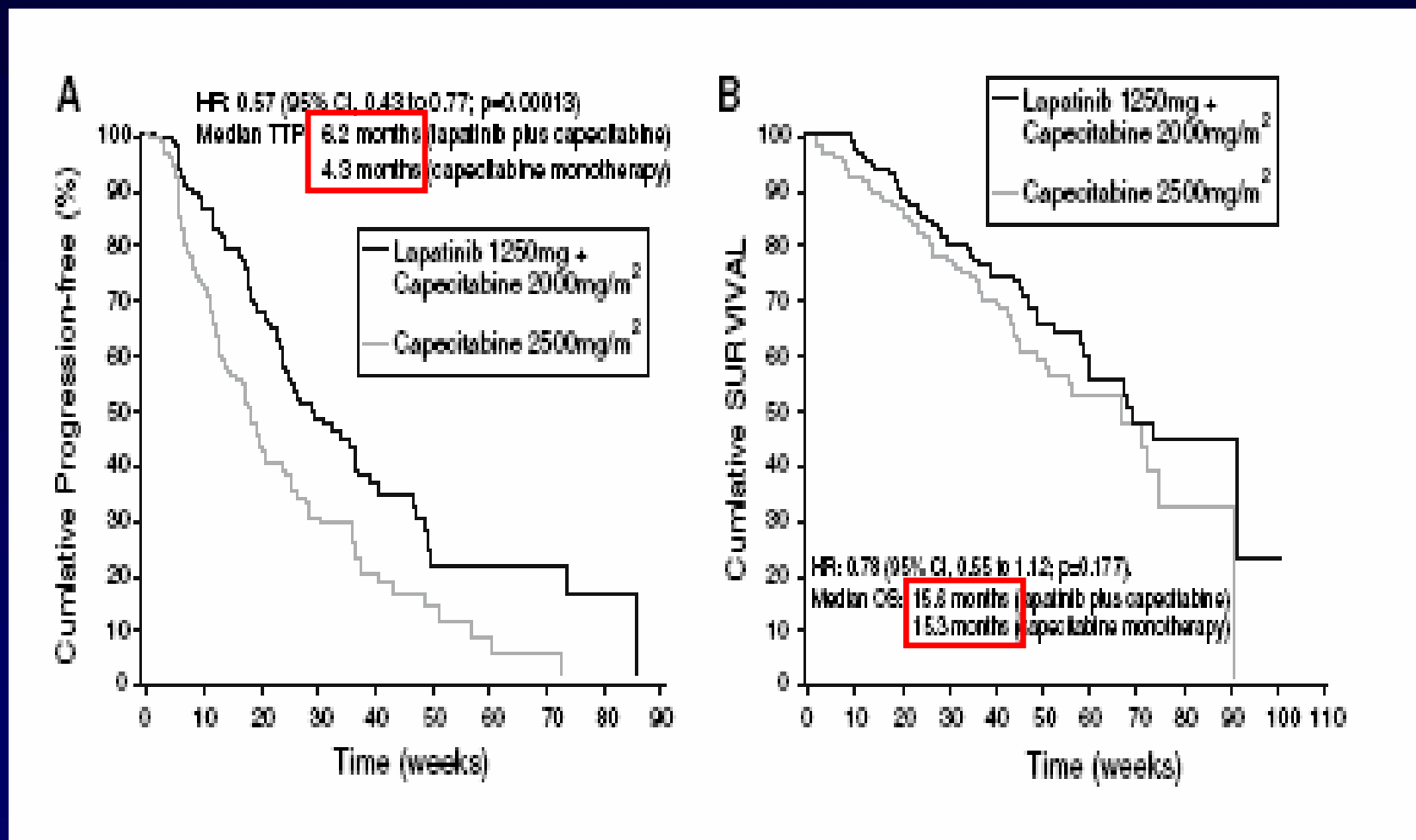
Lapatinib 1250 mg po qd
continuously +
capecitabine 2000 mg/m²/d
po days 1-14 q3 weeks

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!!**

Kaplan-Meier Estimates of Time to Progression (A) and Overall Survival (B) in ITT Population by Independent Review Committee



Capecitabine ± Lapatinib Study in HER2/*neu*+ MBC: Brain Metastases as First Site of Progression

	Lapatinib + Capecitabine (n = 198)	Capecitabine (n = 201)
Patients with symptomatic CNS progression as part of their first progression event	4 (2%)	13 (6.4%)

P = .045

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

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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)

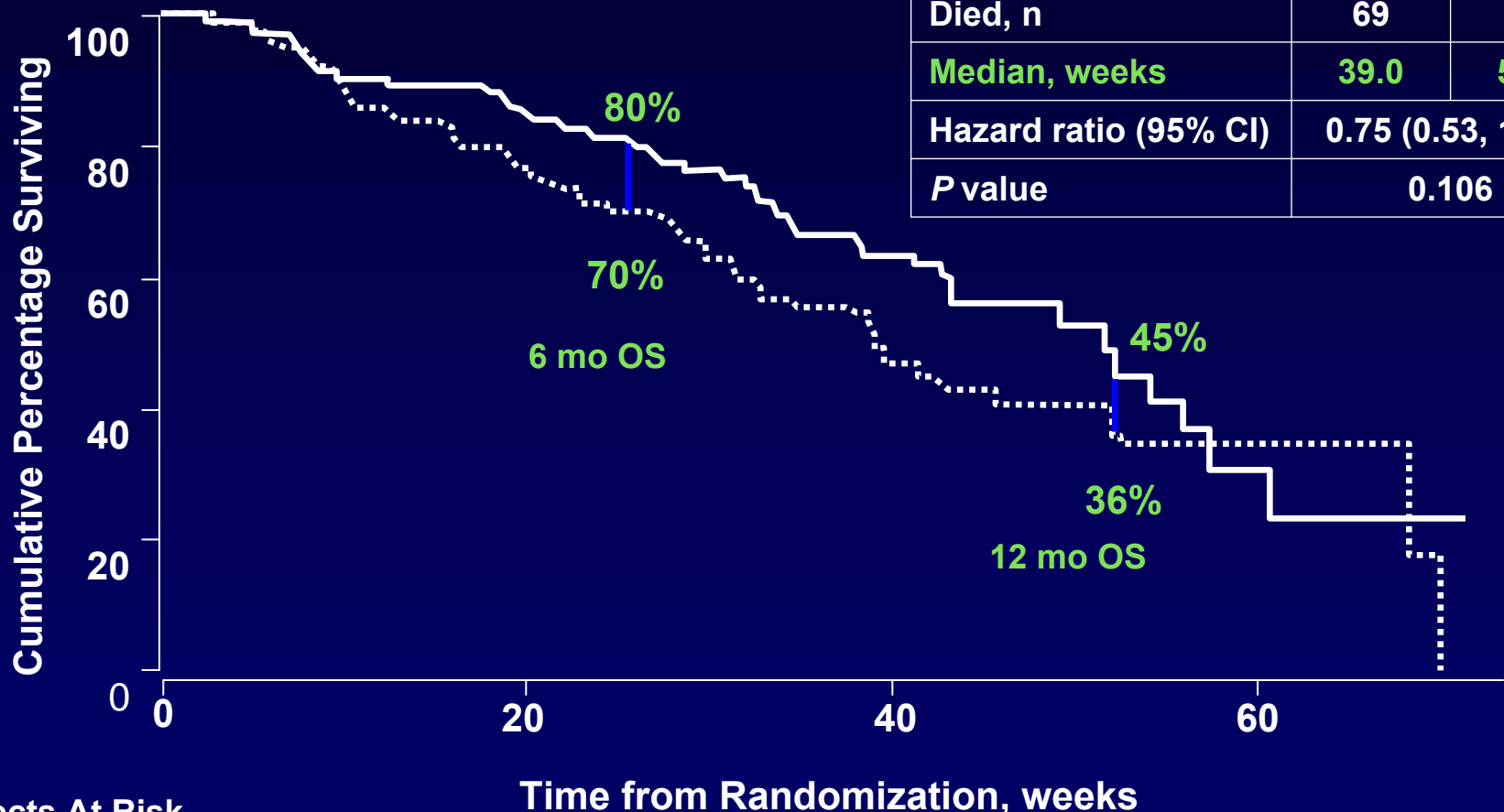
Treatment Efficacy

	L N = 145	L + T N = 146
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

Overall Survival in ITT Population

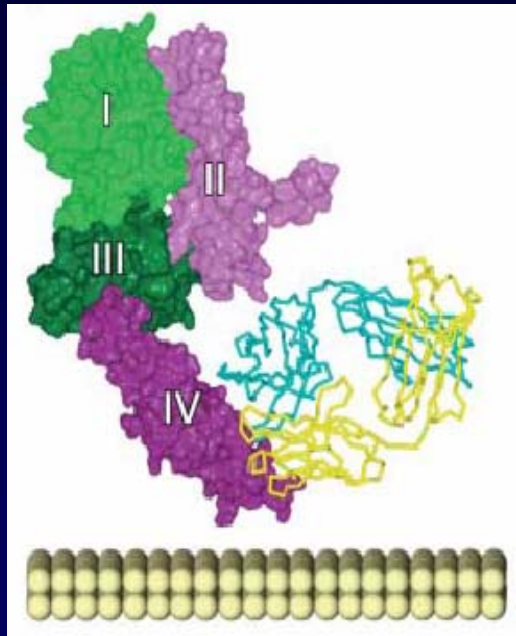
	L N = 145	L+T N = 146
Died, n	69	56
Median, weeks	39.0	51.6
Hazard ratio (95% CI)	0.75 (0.53, 1.07)	
P value	0.106	



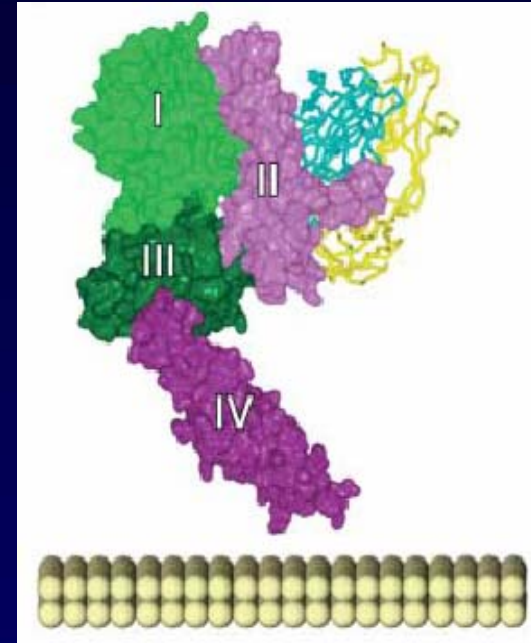
Subjects At Risk		Time from Randomization, weeks			
.....	L	148	106	30	4
—	L + T	148	121	40	3

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

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

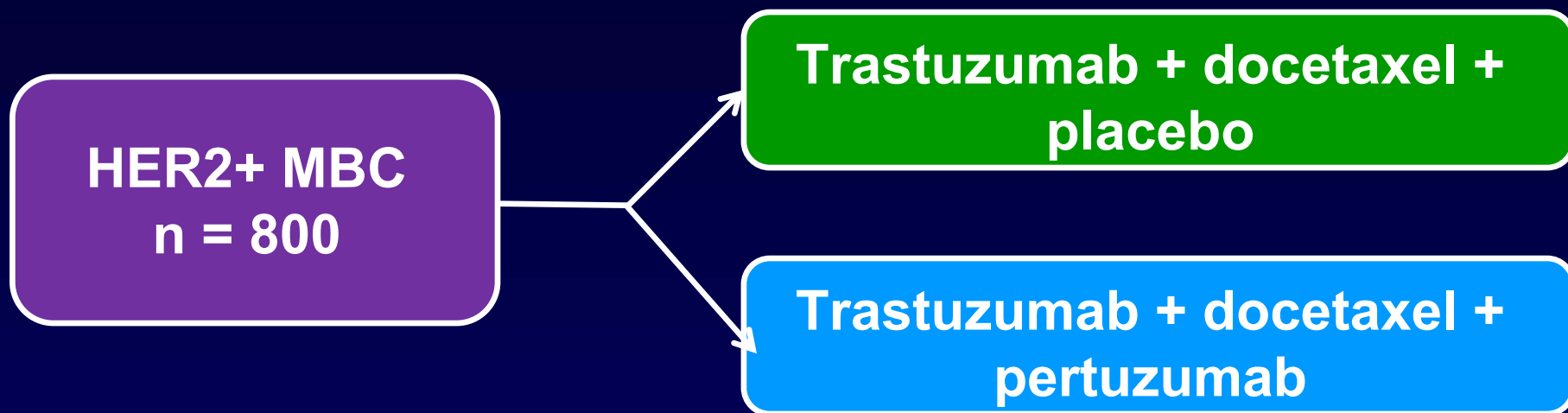
- Activates antibody-dependent cellular cytotoxicity
- Prevents receptor dimerization
- Potent inhibitor of HER-mediated signaling pathways

Trastuzumab + Pertuzumab

Conclusions from Phase II trial

- The combination of trastuzumab and pertuzumab is active in patients with HER2-positive breast cancer with documented progression on trastuzumab as last therapy
- Adverse events were generally grade 1 or 2
- No significant cardiac events have been observed in 66 patients in this study
- Efficacy is highly promising
 - 18.2% of patients responded (15.2% PR and 3% CR), and 39.4% of patients experienced clinical benefit
 - Median PFS is approximately 6 months at present
- A phase III study CLEOPATRA is underway in HER2-positive metastatic breast cancer

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

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Neratinib 240 mg po qd

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

- Primary endpoint: Progression-free survival
- Secondary endpoint: Common Terminology Criteria for Adverse Events [CTCAE] V3

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

Class / Agent	Target / Mechanism	Phase
Monoclonal Antibodies <ul style="list-style-type: none"> • Pertuzumab • Trastuzumab-DM1 • Ertumaxomab 	HER2-dimerization inhibitor HER2/antibody-toxin (trastuzumab-maytansine) conjugate HER2/CD3 trifunctional bispecific antibody	III II II
Signal transduction inhibitors <ul style="list-style-type: none"> • Lapatinib • Neratinib • BIBW 2992 • Gefitinib • Everolimus (RAD001) • Sirolimus (rapamycin) • AP23573 (deforolimus) • Dasatinib 	EGFR and HER-2/TKI EGFR, HER2,3,4/TKI EGFR and HER2/TKI EGFR/TKI mTOR/TKI mTOR/TKI mTOR/TKI Src Inhibitor	III III II II II II II
Heat shock protein inhibitors <ul style="list-style-type: none"> • Tanespimycin 	HSP90 inhibitor	III
Angiogenesis inhibitors <ul style="list-style-type: none"> • Bevacizumab • Pazopanib • Sunitinib 	Anti-VEGF antibody VEGFR, c-kit, PDGFR, TKI VEGFR, c-kit, PDGFR, TKI	III III II
Histone deacetylase inhibitors <ul style="list-style-type: none"> • Panobinostat 	HDAC inhibitor	II
Cyclo-oxygenase inhibitors <ul style="list-style-type: none"> • Apricoxib 	COX-2 inhibitor	II
Immunotherapy <ul style="list-style-type: none"> • HER/<i>neu</i> vaccine 	Recombinant HER2 intracellular domain vaccine	II

Therapeutic Options: My Choice

- Lapatinib
- Neratinib

HER2 inhibitors single agent

- Trastuzumab + anastrozole
- Lapatinib + letrozole

HER2 inhibitors + HT*

- Lapatinib + weekly paclitaxel
- Rechallenge with trastuzumab + chemotherapy
- Lapatinib + capecitabine

HER2
inhibitors + CT

- Trastuzumab and lapatinib
- Clinical trial of trastuzumab and pertuzumab
- Trial: Neratinib versus lapatinib + capecitabine
- Trial: Trastuzumab and sunitinib

Modulators of T
resistance

*Menopause?

THANK YOU
