

HER2-Amplified Breast Cancer: Refining Our Approach to Achieve Improved Clinical Outcomes

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“Standard” of Care In HER2-Amplified Metastatic Breast Cancer (MBC)

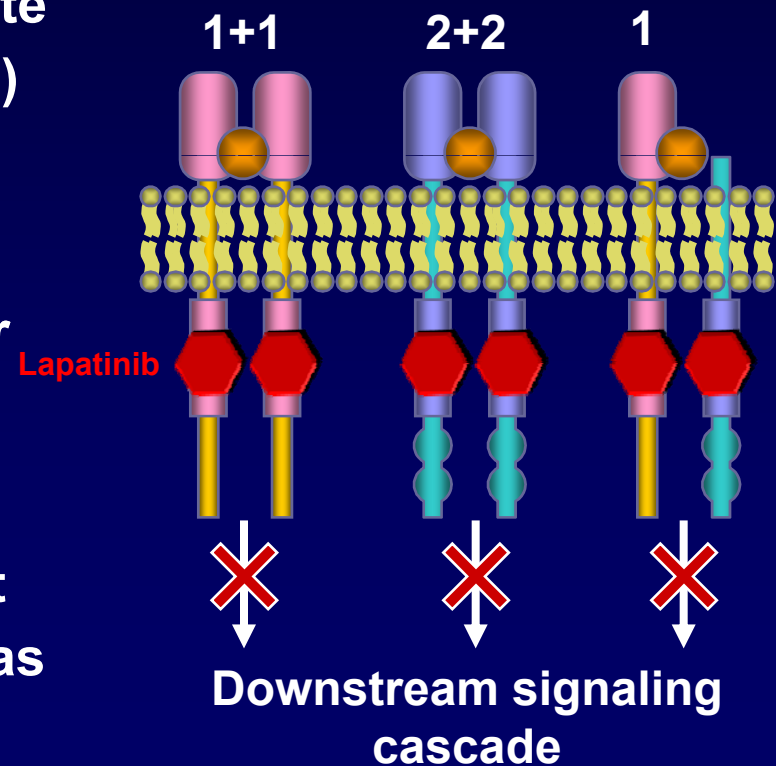
- **First-line registration**
 - Paclitaxel Trastuzumab
 - Docetaxel Trastuzumab
- **After taxanes trastuzumab progression**
 - Capecitabine Lapatinib
 - Capecitabine Trastuzumab
- **Endocrine treatment combinations**
 - Anastrozole Trastuzumab
 - Letrozole Lapatinib

Anti-HER2 Treatments After First-Line Trastuzumab

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

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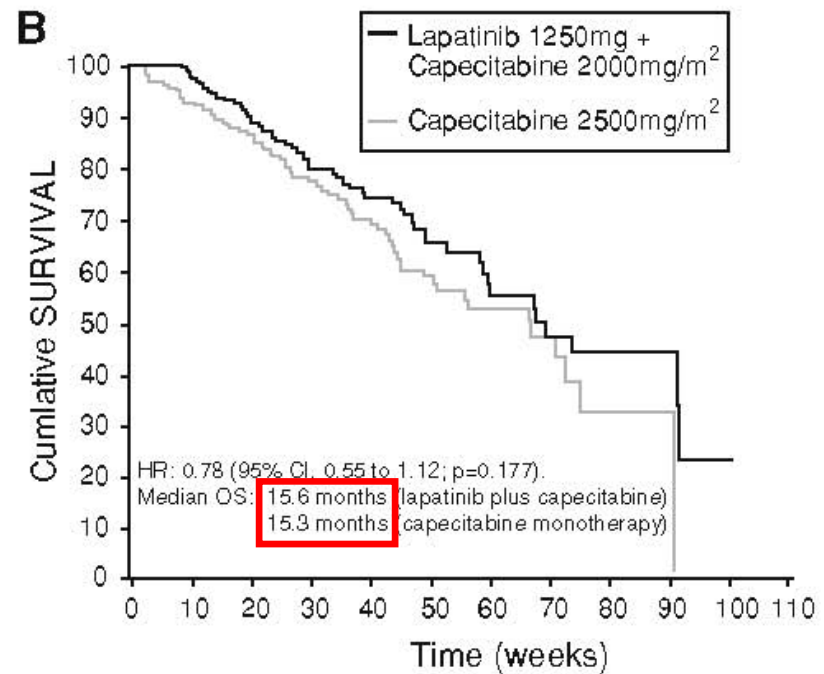
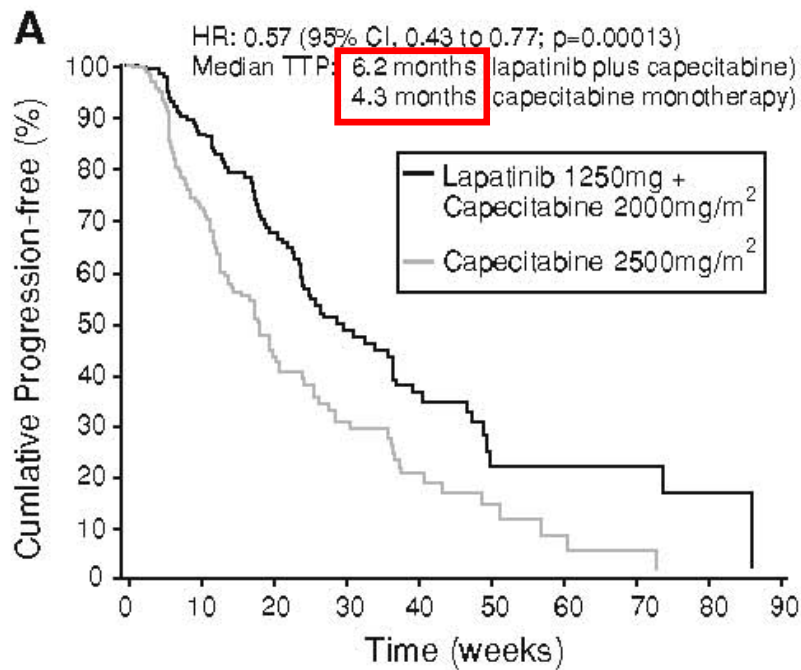
Lapatinib 1250 mg PO qd
continuously +
capecitabine 2000 mg/m²/d
PO days 1-14 q3 weeks

Capecitabine 2500 mg/m²/d PO
days 1-14 q3 weeks

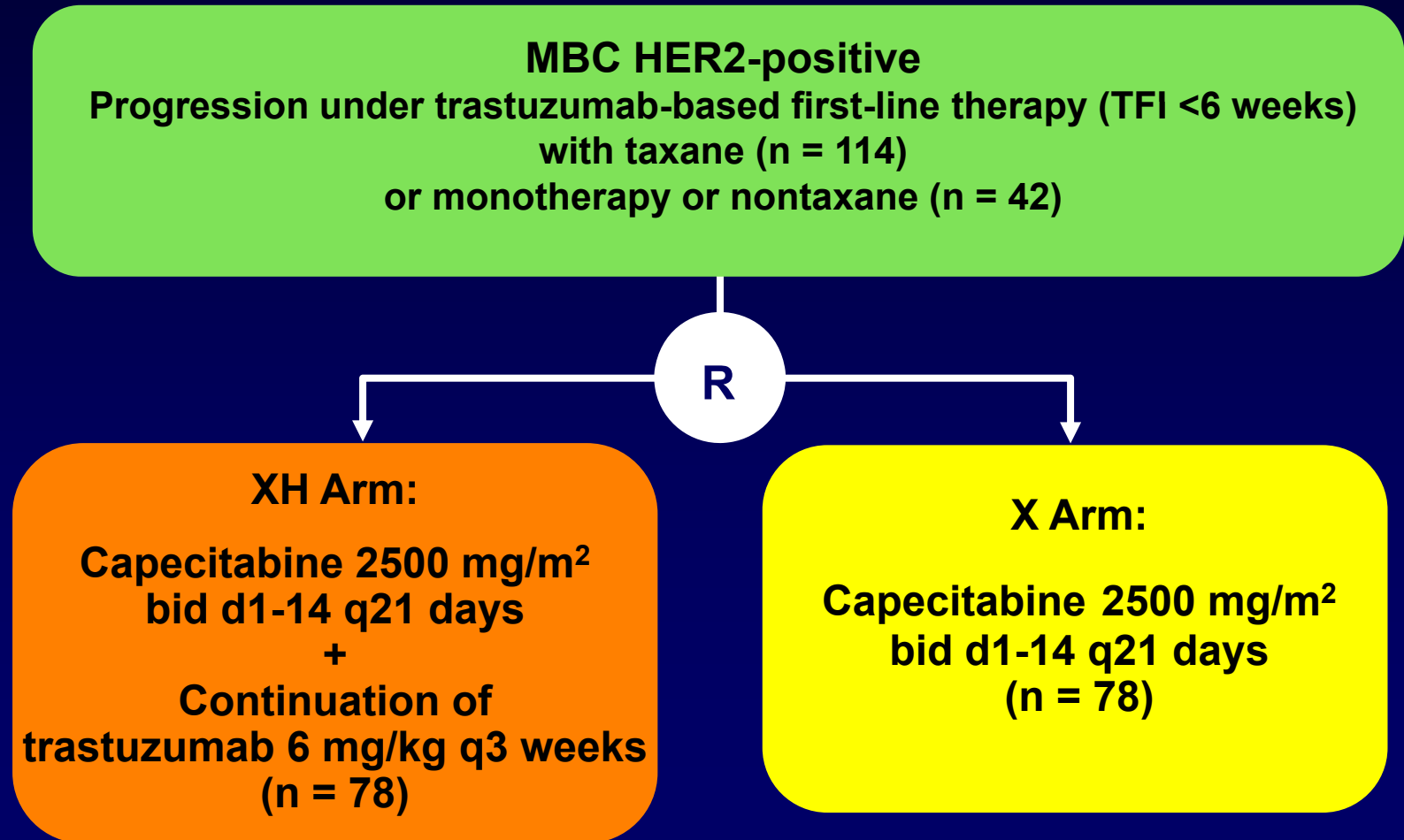
Patients on treatment until
progression or unacceptable
toxicity, then followed for survival

*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

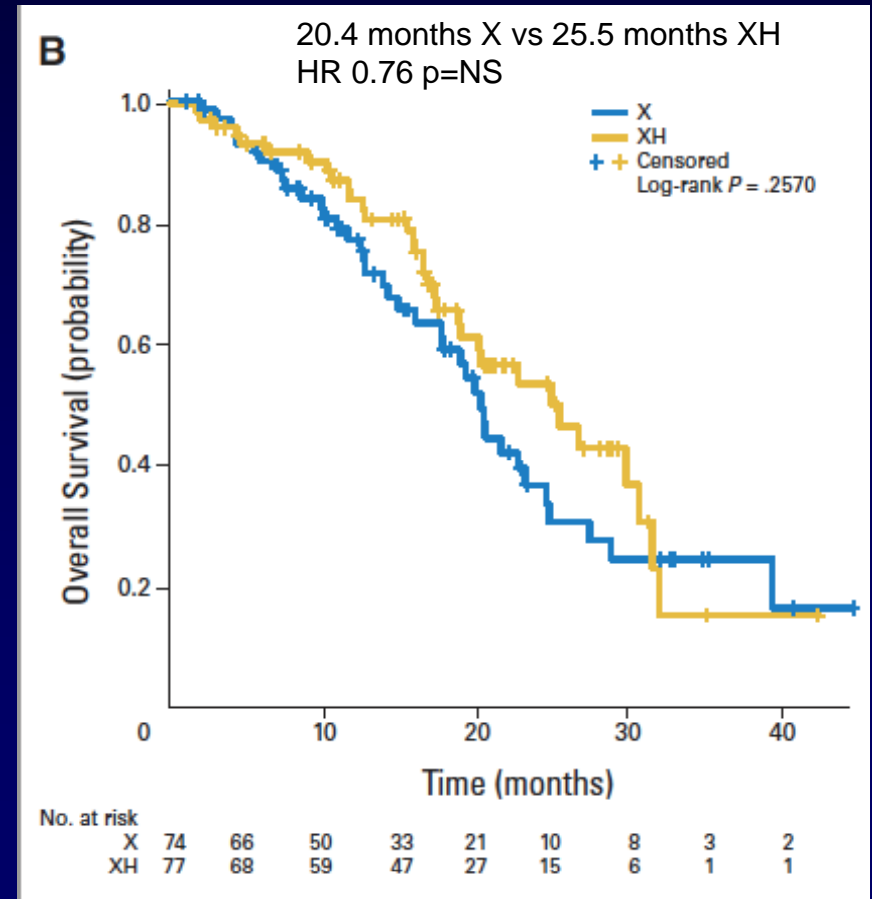
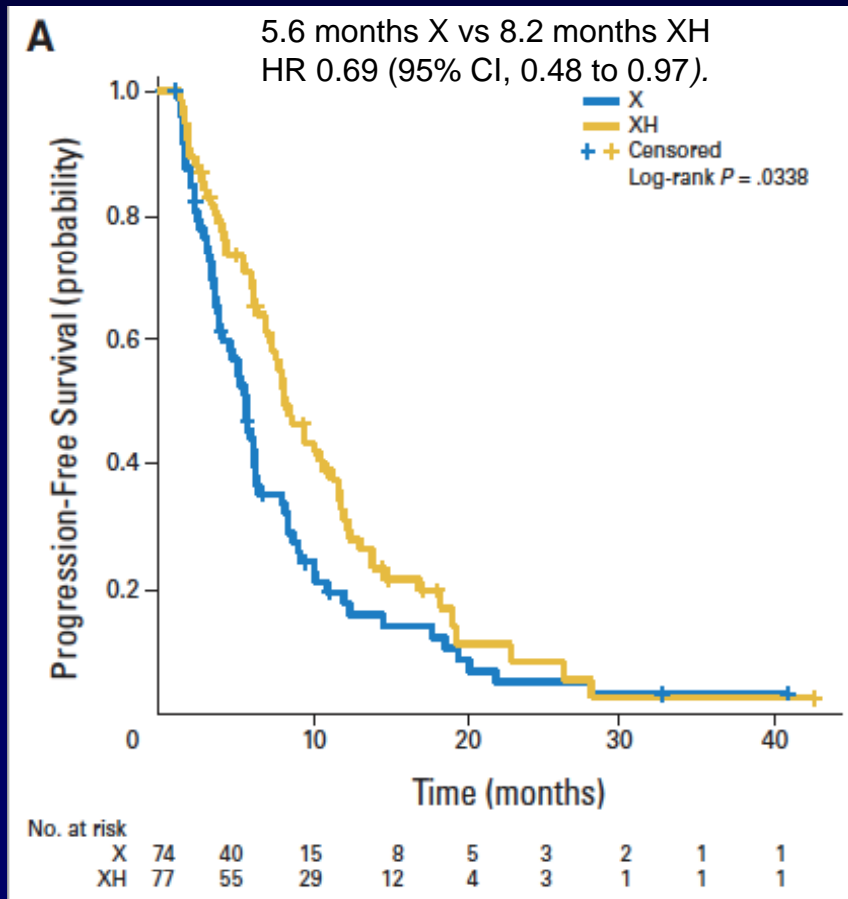


GBG-26: Study Design



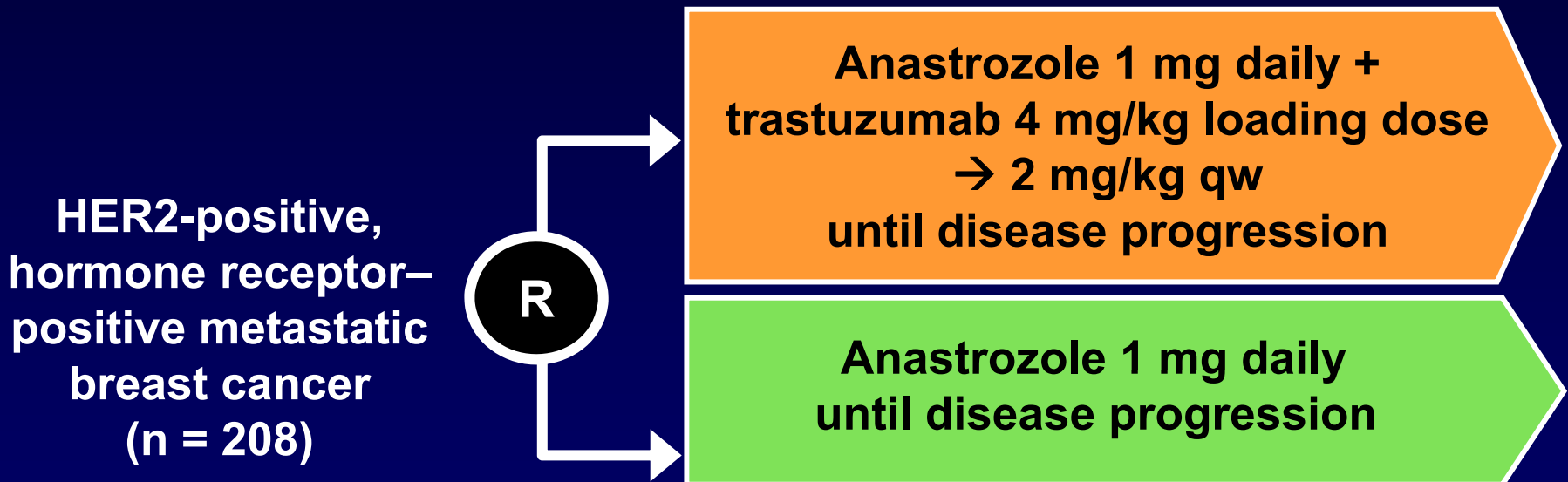
R, randomization;
TFI, treatment-free interval

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



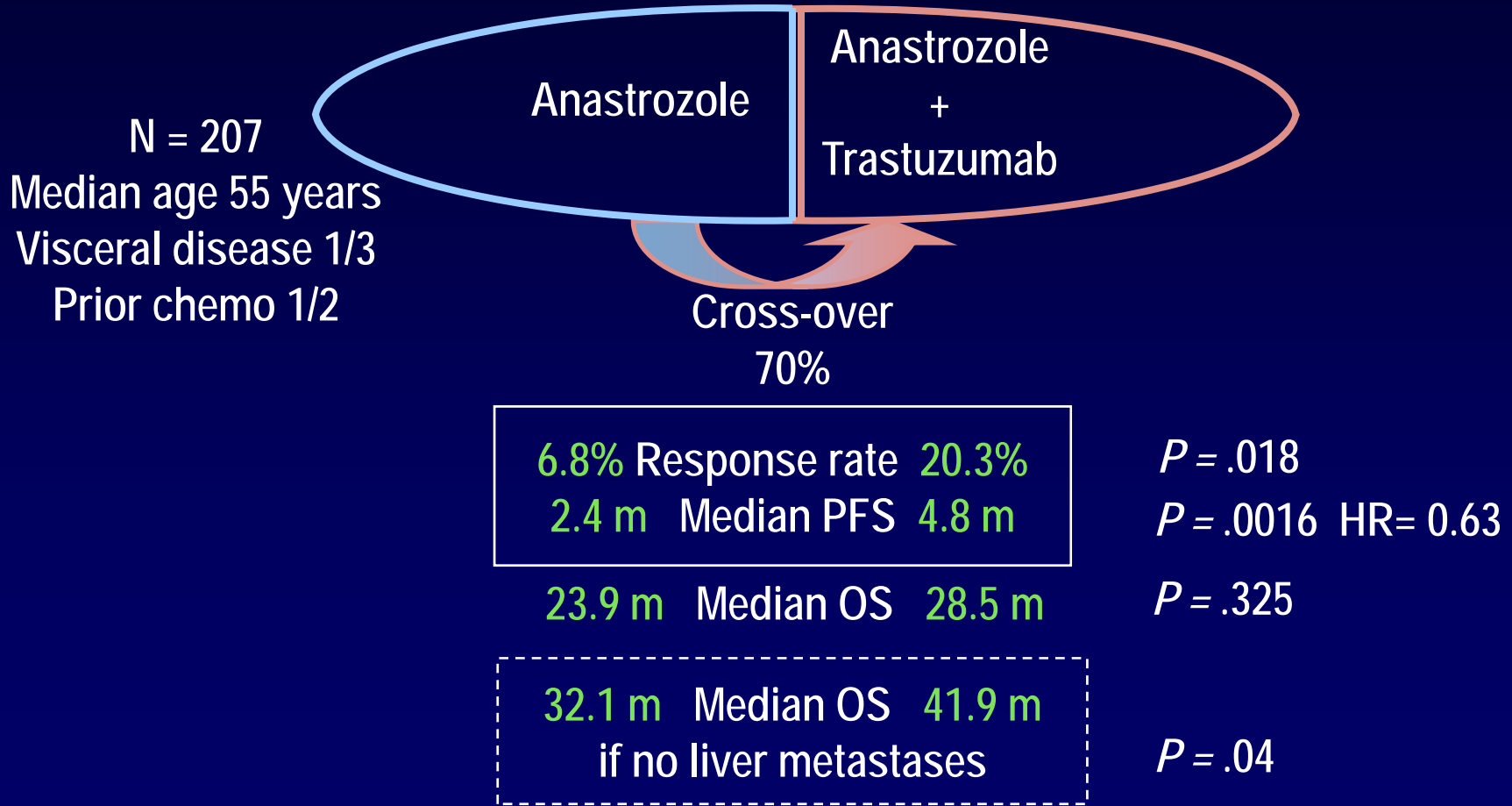
Anti-HER2 Treatments Combined with Endocrine Treatments

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 BIOLOGIC 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

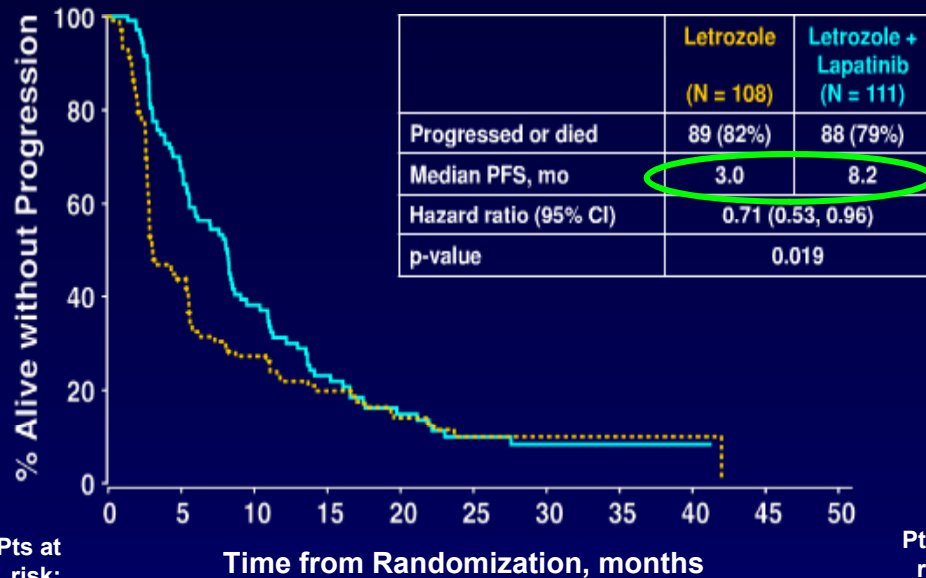
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Letrozole 2.5 mg daily +
placebo

Letrozole 2.5 mg daily +
lapatinib 1500 mg daily

N = 1286 (including n = 219 HER2+)

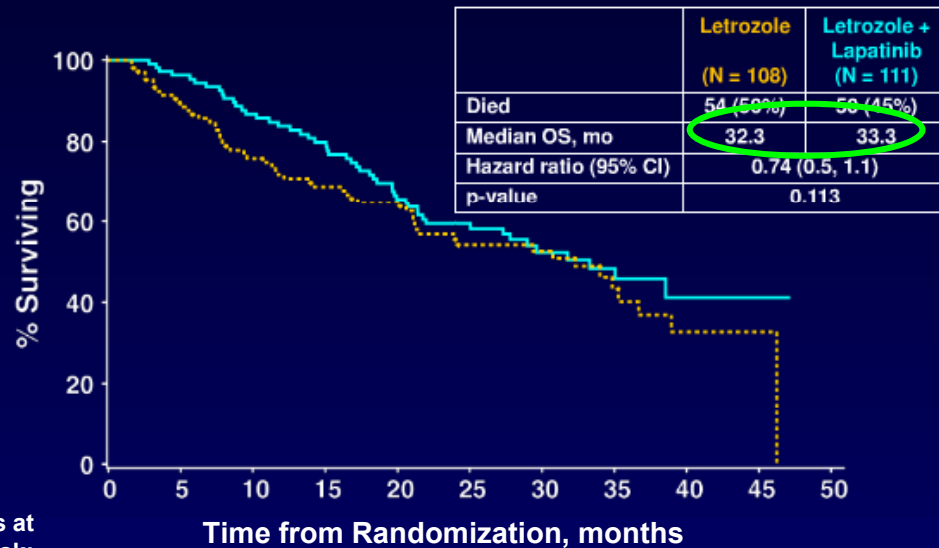
Progression-Free Survival and Overall Survival: HER2+ Population



Pts at risk:

Time from Randomization, months

	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

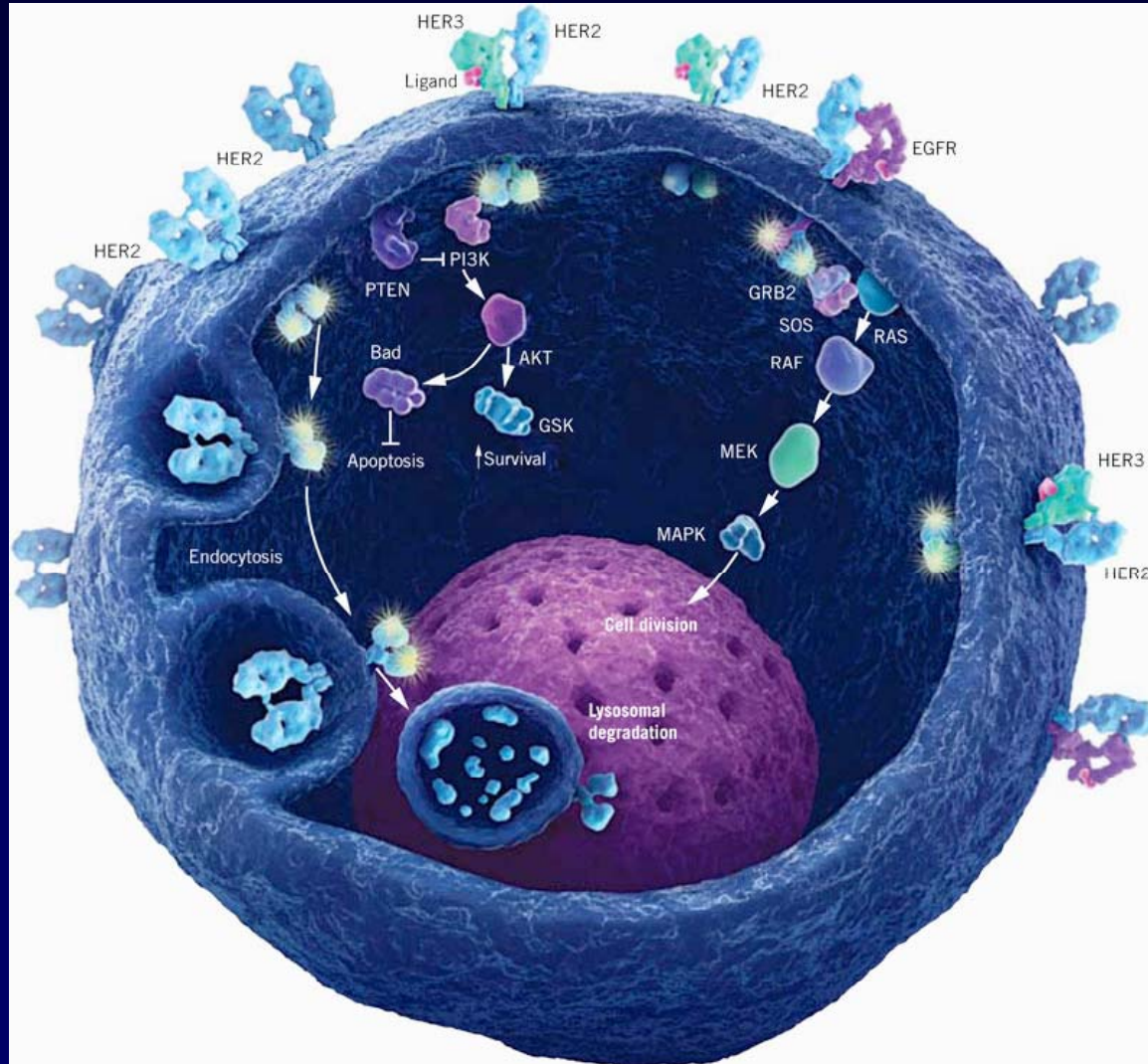


Pts at risk:








Time from Randomization, months

	0	5	10	15	20	25	30	35	40	45
Let + Lap	111	104	89	80	64	48	32	19	9	4
Let	108	93	76	69	59	38	31	15	8	2

HER2 Signaling Pathways



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  III  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/neu vaccine 	Recombinant HER2 intracellular domain vaccine	II

Approaches to “Optimize” anti-HER2 Targeting

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

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

HER2+ = 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

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

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



Crossover if progressive disease after 4 week 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

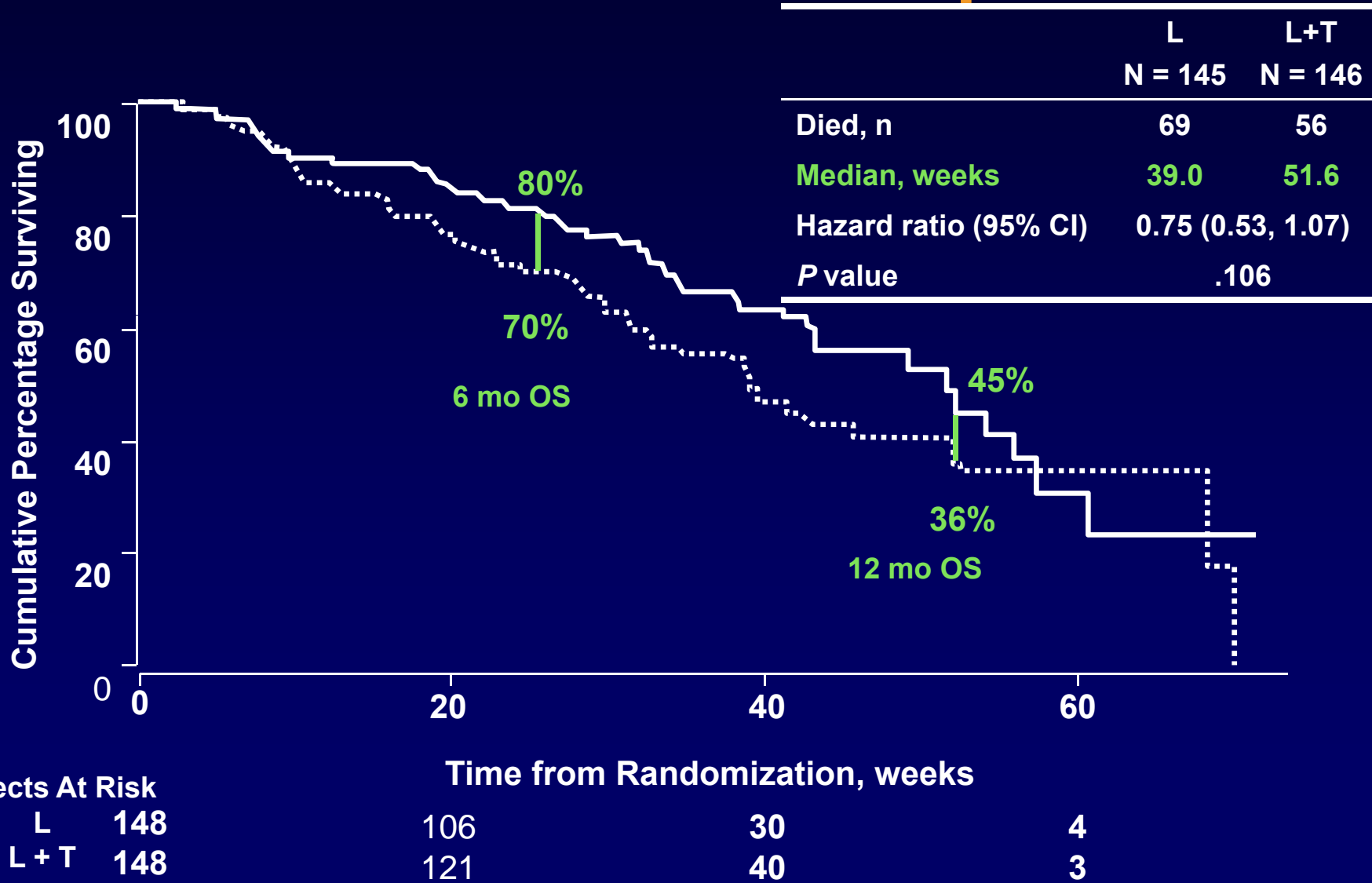
*Confirmed CR+PR †CR+PR+SD ≥6 months

Treatment Efficacy

	L N = 145	L + T N = 146
Response rate, %* (95% CI)	6.9 (3.4, 12.3)	10.3 (5.9, 16.4)
Odds ratio (95% CI)		1.5 (0.6, 3.9) P = .46
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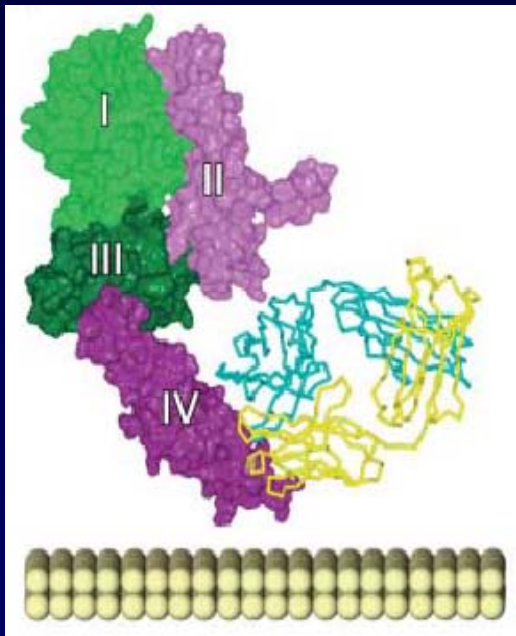
*Confirmed CR+PR †CR+PR+SD ≥6 months

Overall Survival in ITT Population

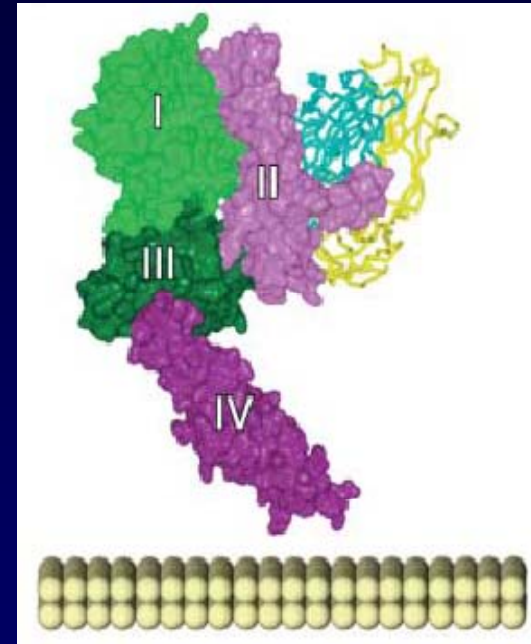


O'Shaughnessy J, et al. *J Clin Oncol*. 2008;26 (May 20 Suppl): Abstract 1015.

Trastuzumab and Pertuzumab Bind to Distinct Epitopes on HER2 Extracellular Domain



Trastuzumab



Pertuzumab

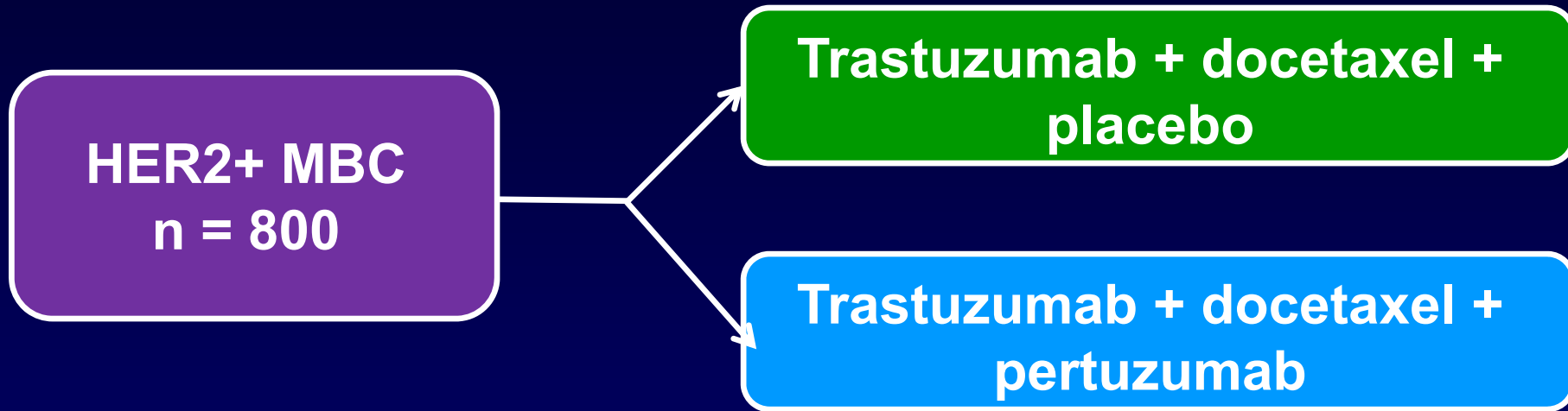
- Activates antibody-dependent cellular cytotoxicity
- Enhances HER2 internalization
- Inhibits shedding and, thus, formation of p95
- Inhibits angiogenesis

- 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**

Trastuzumab-DM1 *Molecular Structure*



- Trastuzumab-DM1 (T-DM1) contains the humanized anti-HER2 MoAb trastuzumab (T) to which a highly potent antimicrotubule drug (DM1), derived from maytansine, has been chemically linked
- The MCC linker employed in T-DM1 provides a stable bond between T and DM1 that is designed to prolong exposure and reduce the toxicity of T-DM1 while maintaining activity

T-DM1, Phase II Results

N = 112, all pretreated with anti-HER2 treatment and >50% had received trastuzumab and lapatinib

	Independent Committee Evaluation n = 112	Investigators Evaluation n = 112
Complete responses	0 (0%)	3 (2.7%)
Partial responses	28 (25%)	40 (35.7%)
Stable disease	54 (48.2%)	43 (38.4%)
Progression	21 (18.8%)	22 (19.6%)
ORR	28 (25%)	43 (38.4%)
95% CI	(17.5 – 33.6)	(29.8 – 47.5)
Clinical benefit	39 (34.8%)	50 (44.6%)
95% CI	(26.1 – 43.9)	(35.5 – 54.3)

Phase III Randomized Study of Trastuzumab-DM1 vs Lapatinib + Capecitabine in HER2-Positive Locally Advanced Metastatic Breast Cancer

Inclusion Criteria:

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- Prior treatment with trastuzumab, and anthracycline, and a taxane
- Adequate renal and cardiac function

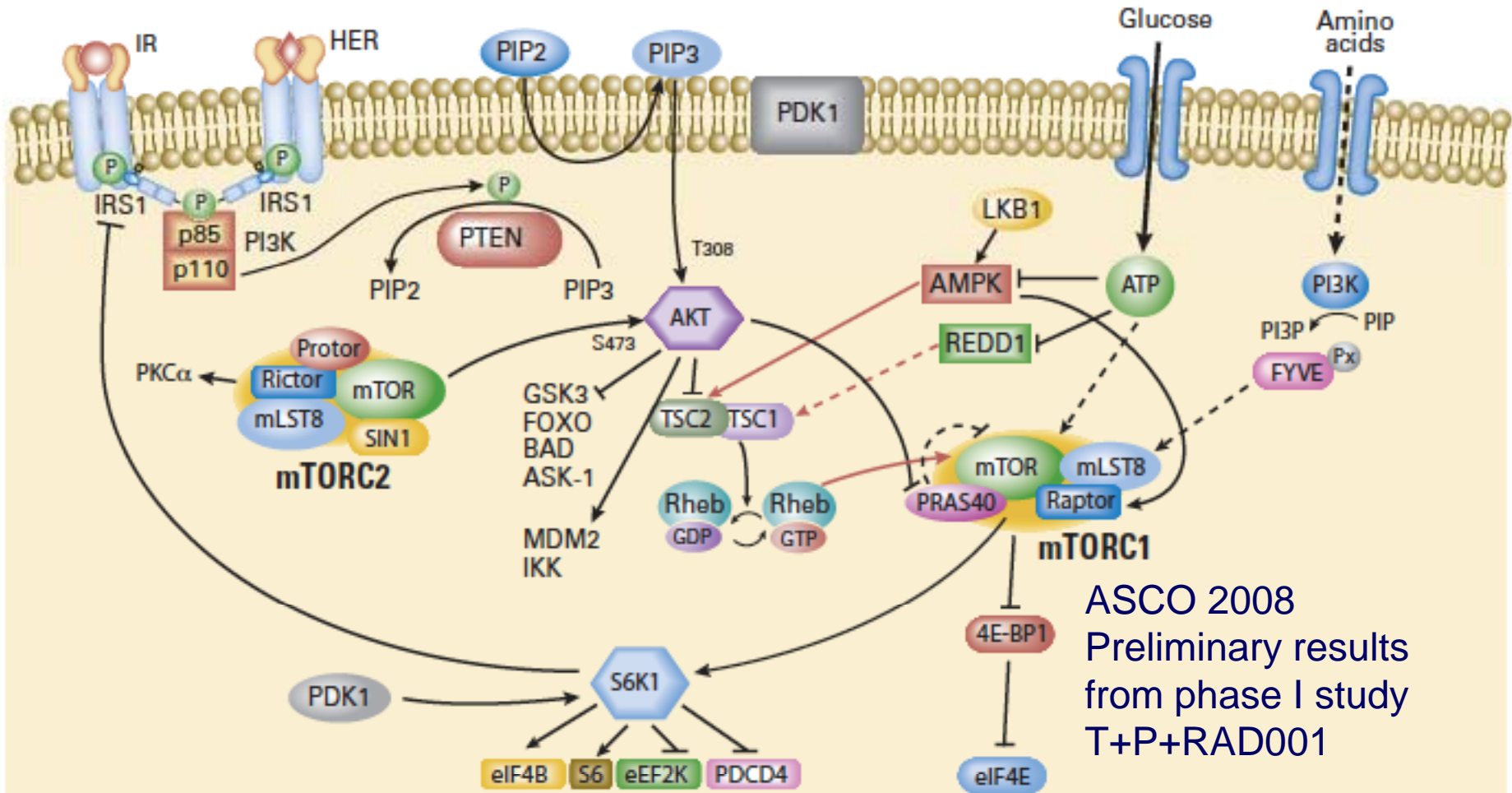
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T-DM1 3.6 mg/kg/3weeks

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

**Approaches to
“Circumvent” the Resistance
of Anti-HER2 Treatments**



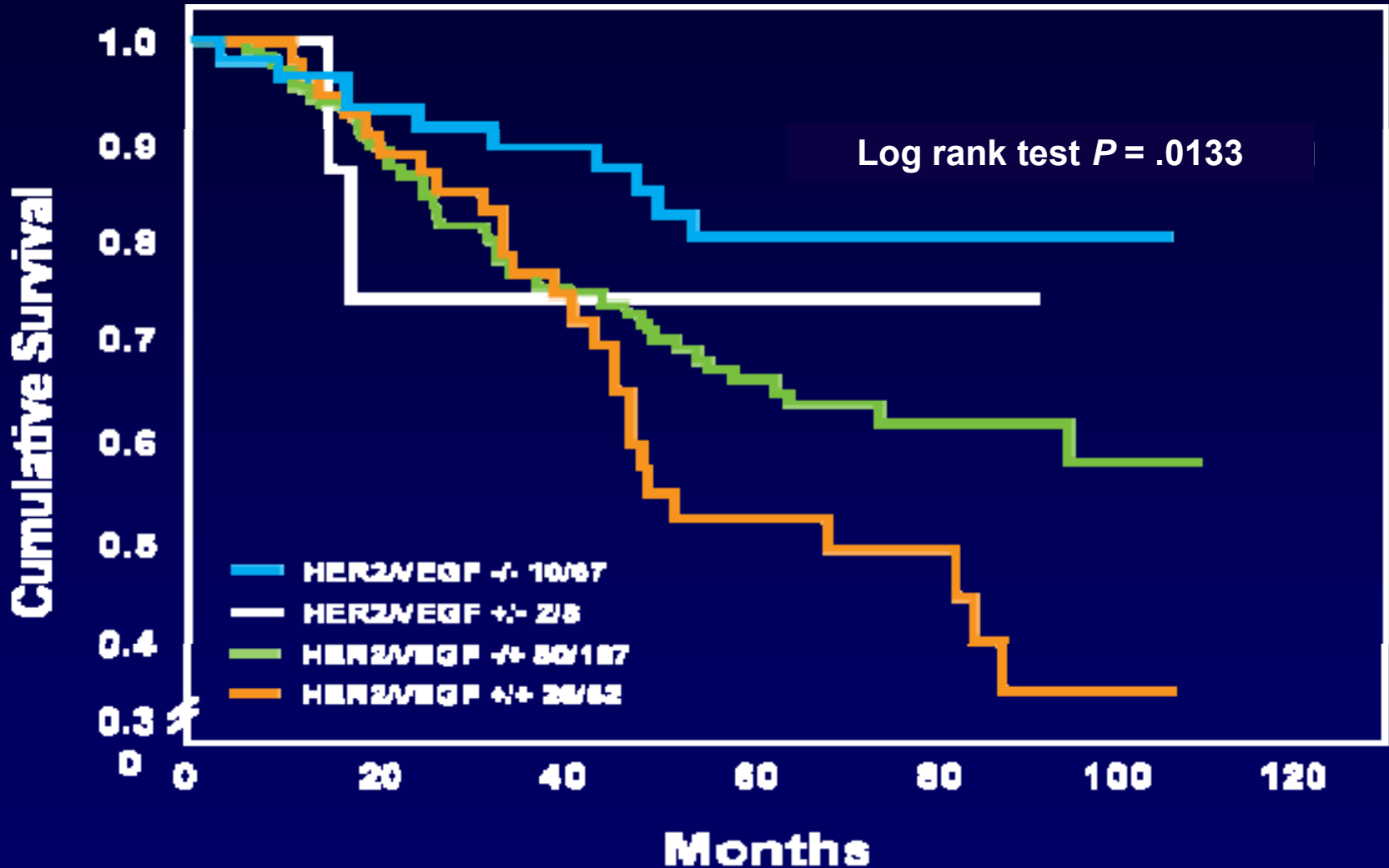
↑ Translation, ↑ Cell growth, ↑ Ribosome biogenesis, ↑ Metabolism, ↑ Proliferation, ↓ Autophagy

Fig 1. The mammalian target of rapamycin (mTOR) signaling network. Arrows represent activation, bars represent inhibition. mTOR signaling regulates multiple critical cellular processes by integrating energy and nutrient status and PI3K/Akt signaling induced by growth factors and insulin.

Meric-Bernstam F, et al. *J Clin Oncol.* 2009;27(13):2278-2287.
 André F, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract 1003.

Approaches to Combine Anti-HER2 and Antiangiogenic Treatments

Angiogenesis and HER2 Amplification



Phase II Trastuzumab + Bevacizumab in First-Line MBC

Previously untreated
HER2-positive
locally recurrent or
MBC
(n = 37)

Trastuzumab +
Bevacizumab
until PD

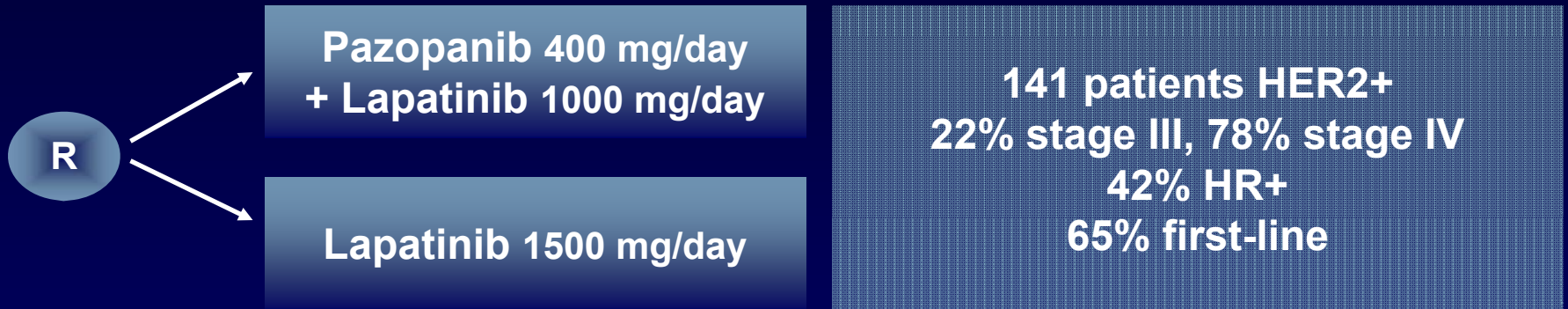
- ORR: 54.1%
 - 1 CR, 19 PR, 11 SD, 6 PD
- 1 grade 4 left ventricular dysfunction
 - (12 grade 1/2, 0 grade 3)^a
- Grade 3 dyspnea, hypertension, and proteinuria reported (9 events)
- Phase III (AVEREL study) ongoing

Trastuzumab: 4 mg/kg loading dose, 2 mg/kg qw
Bevacizumab: 10 mg/kg day 7 then q2w

^aNCI-CTC v2.0

Pegram M, et al. *Breast Cancer Res Treat.* 2004;88: Abstract 3039. Pegram M, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 301.

Pazopanib (P) + Lapatinib (L) vs Lapatinib



	P	P+L	P Value
PFS 12 weeks	63.2%	84.1%	.0091
RO	36%	44%	

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

Conclusions: Refining Our Approach to Achieve Improved Clinical Outcomes

- **Optimizing HER2 combinations**
 - Chemotherapy
 - Endocrine treatments
- **Optimizing HER2 targeting:**
 - MAB vs NIB
 - MAB + NIB
- **Circumvent anti-HER2 treatments resistance**
- **Combining anti-HER2 and antiangiogenic treatments**