

HER2-Positive BC Progression Following Adjuvant Trastuzumab: Clinical Case # 3

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HER2-positive BC progression following adjuvant trastuzumab: a summary of the clinical case (# 3)

Patient	54 year old, postmenopausal, psychiatrist, asymptomatic (skin and small lung metastases)
Primary tumor :	HER-2 (IHC) : 3+; ER : 60%, PR : 40%
Adjuvant therapy :	Adjuvant FEC x 3 → docetaxel x 3 + H → Trastuzumab Adjuvant tamoxifen Radiation to the left breast

Eight months after completion of adjuvant trastuzumab → disease progression

Clinical case # 3: Therapeutic options

- Lapatinib
- Neratinib

HER2 inhibitors single agent

- Trastuzumab + anastrozole
- Lapatinib + Letrozole

HER2 inhibitors + HT

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

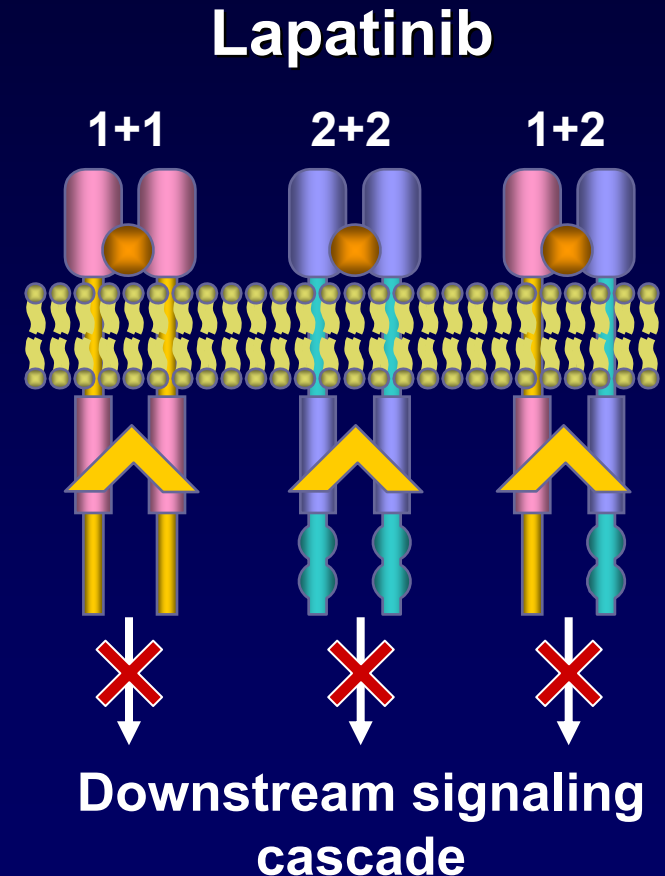
HER2
inhibitors + CT

- Clinical trial of trastuzumab and lapatinib
- Clinical trial of trastuzumab and pertuzumab

Modulators of T
resistance

Lapatinib Mechanism of Action

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



EGF20009 FIRST-LINE LAPATINIB RANDOMIZED PHASE II STUDY

Efficacy by Dose Schedule

Response	N=138	
	500 mg BID (n=69)	1500 mg QD (n=69)
CR	0	0
PR	18 (26%)	15 (22%)
SD	31 (45%)	40 (58%)
PD	16 (23%)	8 (12%)
Unknown	4 (6%)	6 (7%)

Overall RR : 24%; AE = diarrhea, rash, nausea



A Patient With Relapsed Inflammatory Breast Cancer Achieving a Partial Response on Lapatinib Therapy

day 0



2 months



4 months



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

Cohort	N° of pts	Recist	Skin	Combined
A (HER-2 \oplus)	126	15 %	40 %	39 %
B (EGFR \oplus)	12	10 %	8 %	8 %

HER2 \oplus = IHC3 + or FISH +



Lapatinib Monotherapy in Relapsed/Refractory Pretreated Inflammatory BC: Progression-Free Survival

Cohort	N° of pts	Median PFS in weeks	PFS at 12 weeks
A (HER-2 \oplus)	126	15	62 %
B (EGFR \oplus)	12	4	0 %

HER2 \oplus = IHC3 + or FISH +

HKI-272 (Neratinib), An Oral Irreversible Pan erb Receptor Tyrosine Kinase Inhibitor: Phase II Baseline Patient Characteristics

N° of pts	136
Median age	50 (31-83)
ECOG PS % 0-1/2	95/5
Prior CT regimens	
Any setting (%)	87
Metastatic 0/1/≥2 (%)	37/30/33
Prior Trastuzumab (%)	
Adjuvant/Neoadjuvant (%)	23
Metastatic	90

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 pts, 2x: 5%

16% of patients had dose reductions due to diarrhea



TAnDEM study : anastrozole ± trastuzumab

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



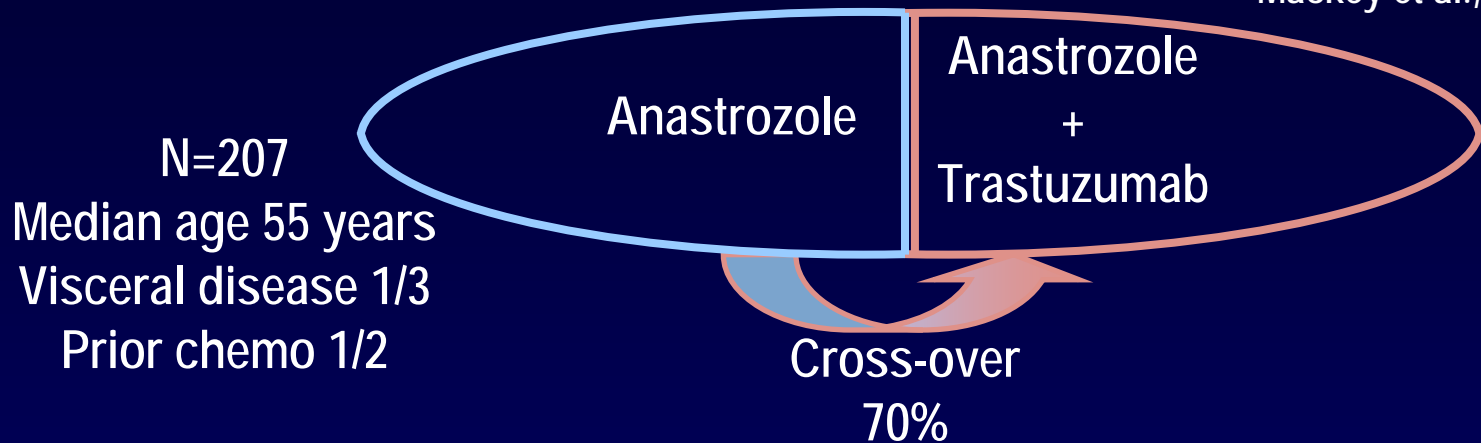
Anastrozole 1 mg daily +
trastuzumab 4 mg/kg loading dose
→ 2 mg/kg qw
until disease progression

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 trial of ANASTROZOLE ± TRASTUZUMAB in advanced HER2+, HR+ breast cancer

Mackey et al., SABC 06, abst. 03



6,8%	Response rate	20,3%
2,4m	Median P.F.S.	4,8m

p 0.0016

23,9m	Median O.S.	28,5m
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32,1m	Median O.S. if no liver mets	41,9m
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p 0.03

Trastuzumab added to anastrozole ↗ RR, PFS (and possibly OS if no liver mets)

Adapted from M. Piccart **IMPORTANCE OF STARTING BIOLOGICAL AGENT SOON**

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

Patient Population

- ER+ and/or PgR+
- Postmenopausal
- HER2+ , HER2-ve / Unknown
- Stage IIIb/IIIc/IV
- No prior treatment for 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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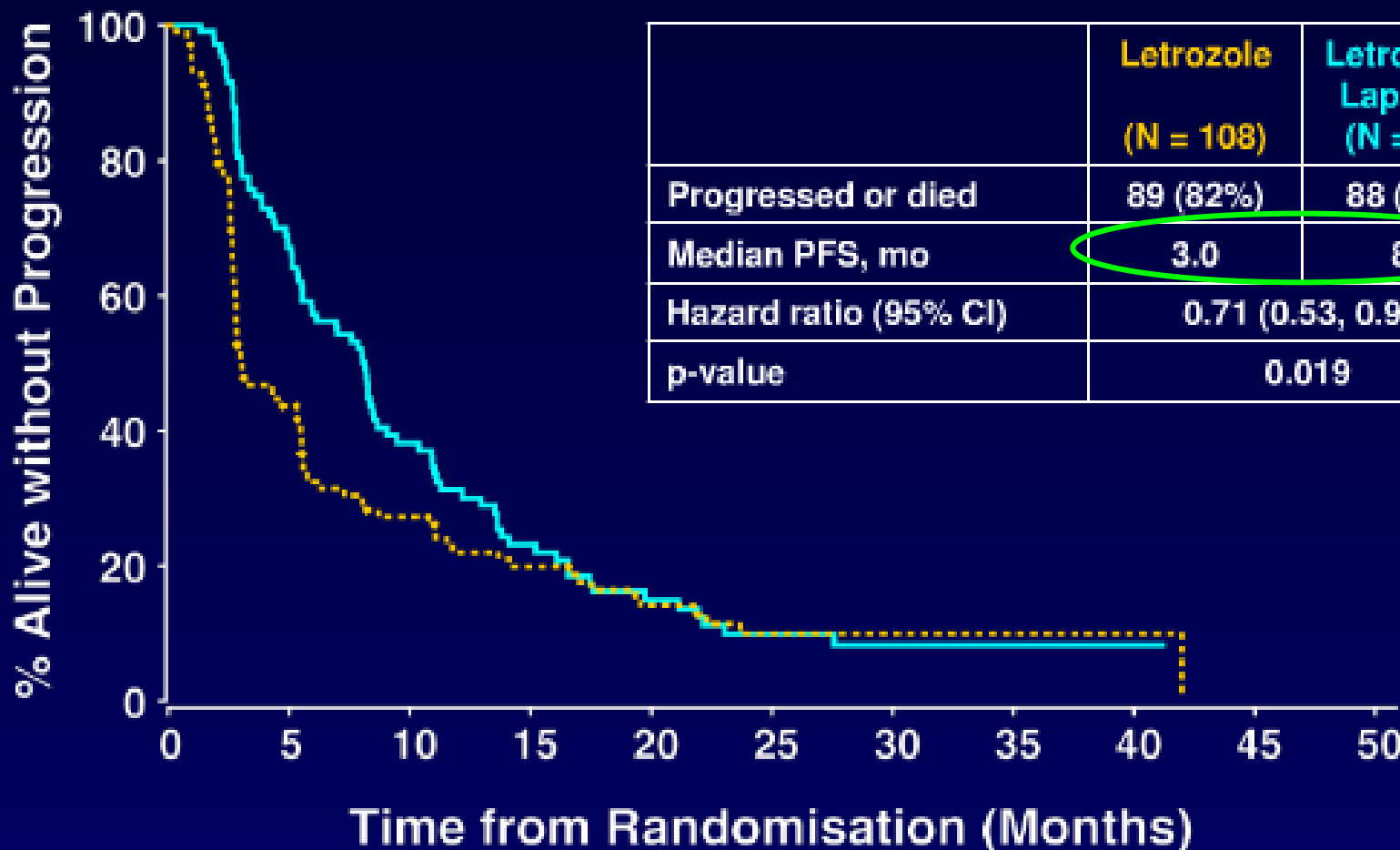
Letrozole 2.5 mg daily +
Placebo

Letrozole 2.5 mg daily +
Lapatinib 1500 mg daily

N=1286 (including n=219 HER2+)

Progression-Free Survival: HER2+ Population

Johnston S, et al. SABCS 2008, Abst # 46

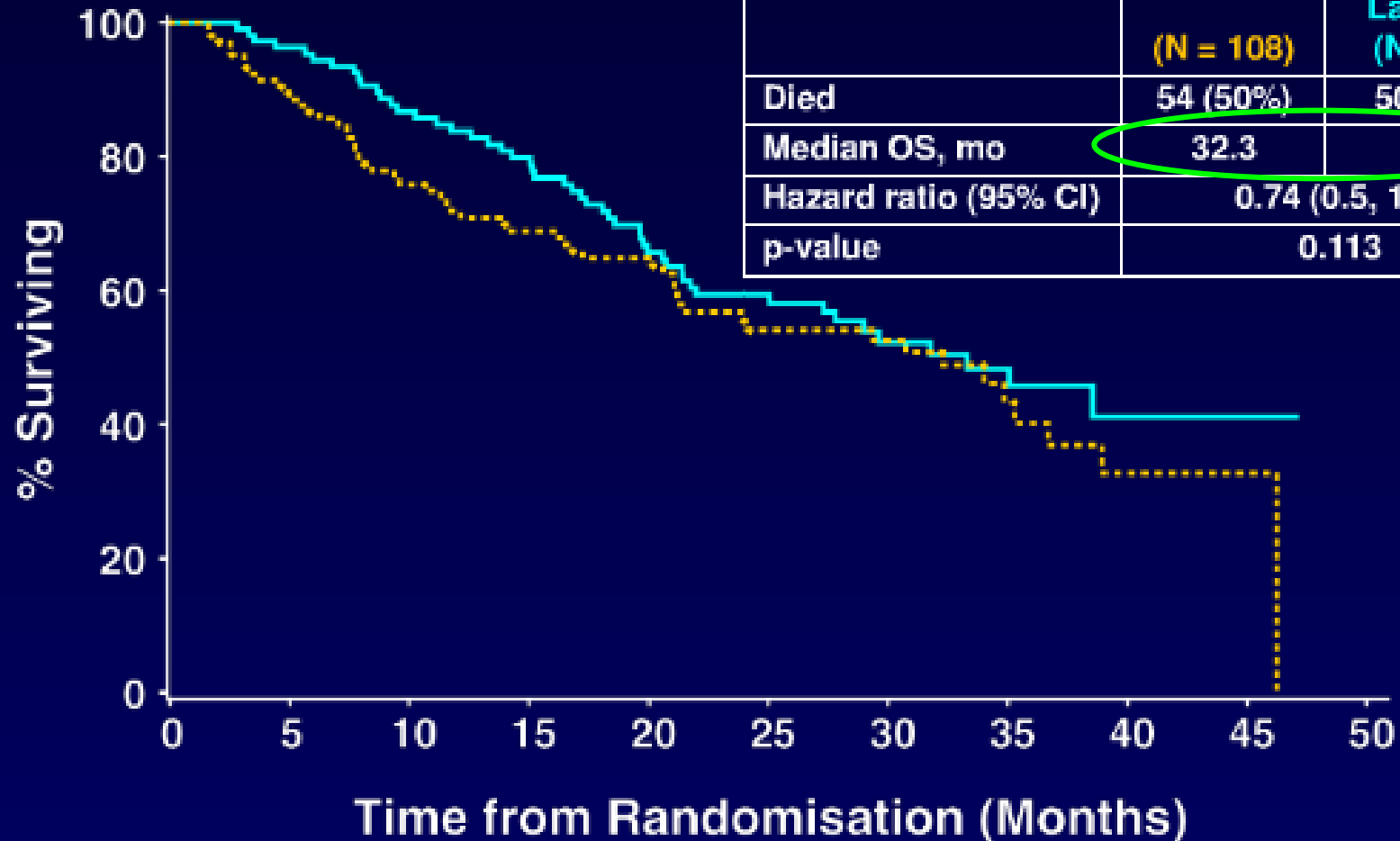


Pts at risk:

	0	5	10	15	20	25	30	35	40	45	50
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

Johnston S, et al. SABCS 2008, Abst # 46



Pts at risk:

	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

Lapatinib (L) + paclitaxel (P) versus paclitaxel as first-line treatment for patients with MBC: A subgroup analysis of HER-2 ⊕ patients

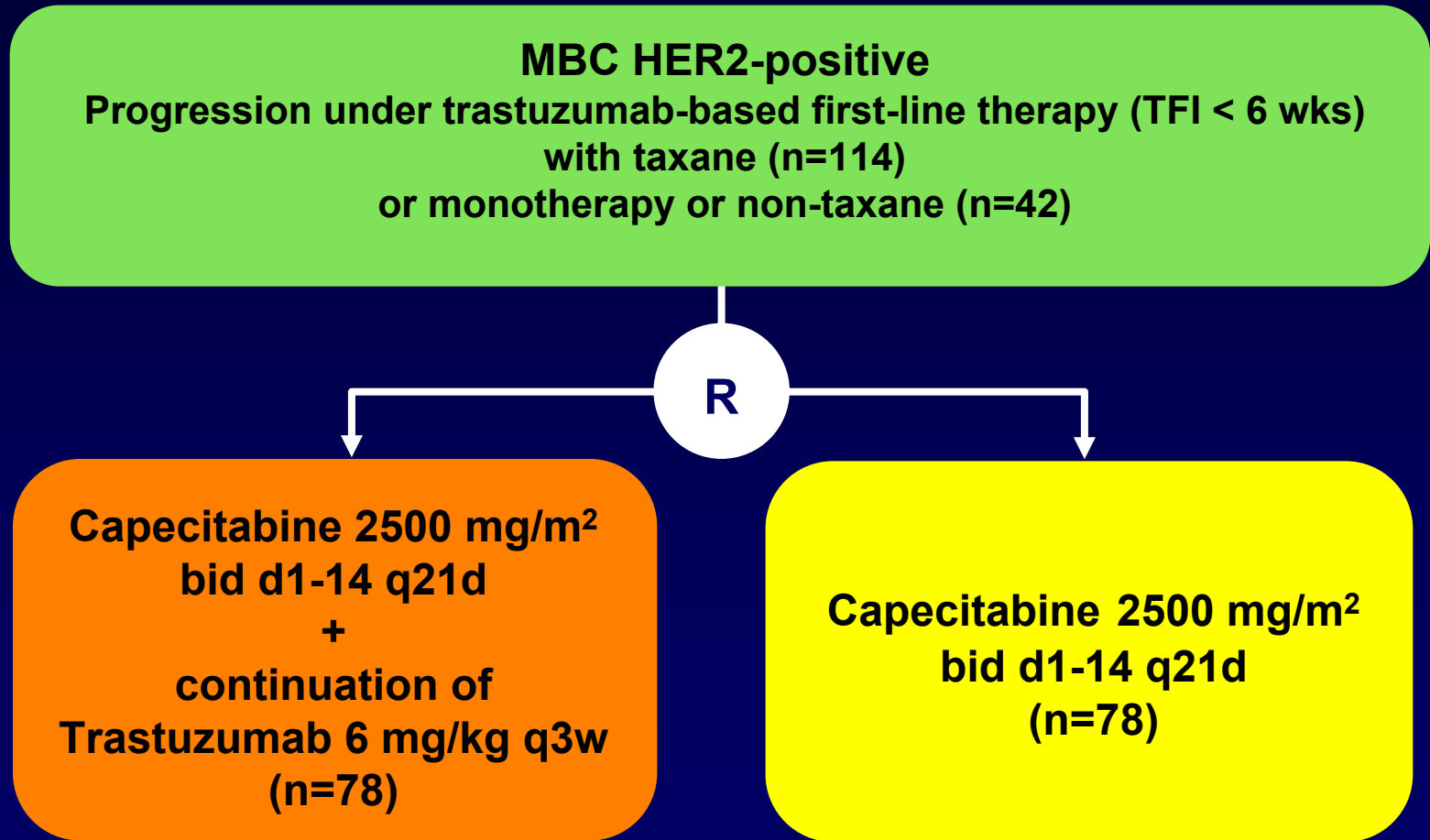
	L + P (n = 52)	P + placebo (n = 39)	P value
Response rate %	60	36	0.027
Median duration of response (mo.)	7.4	5.5	
Median TTP (mo.)	8.1	5.8	0.011
Median OS (mo.)	24	19	0.28

L + P : increase in diarrhea and rash

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

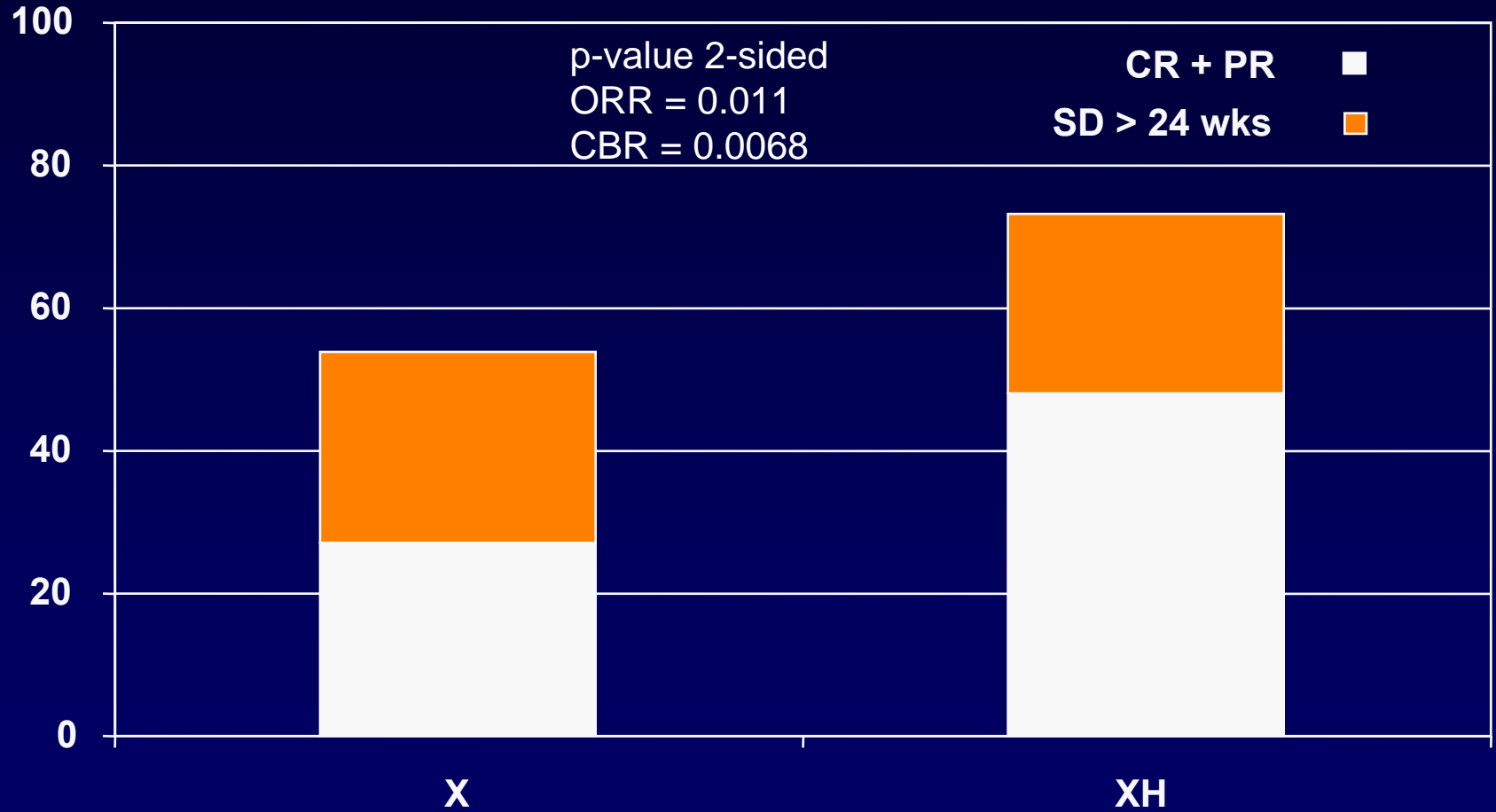
Paclitaxel given q3 weeks

GBG-26: study design



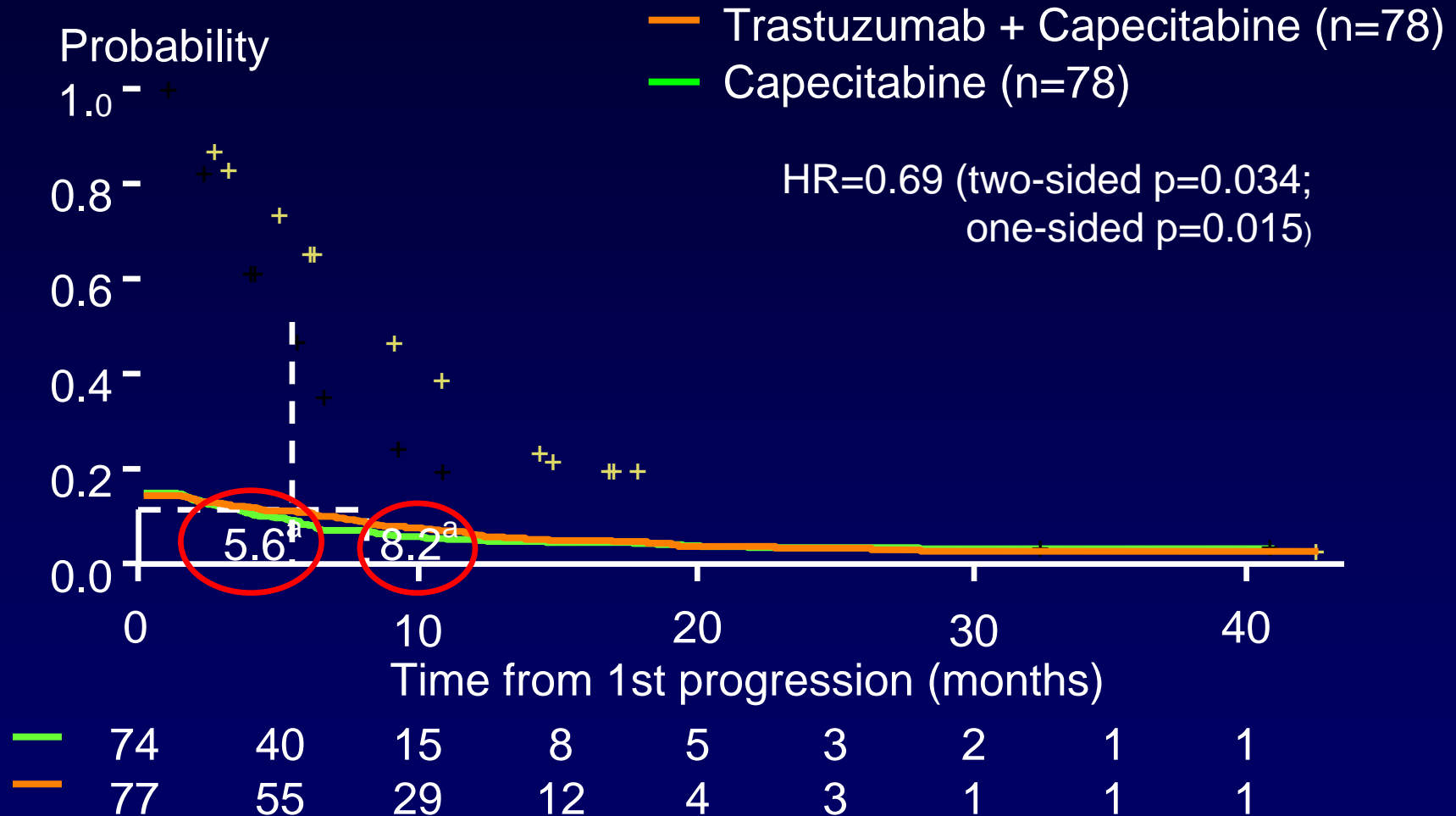
R, randomisation;
TFI, treatment free interval

Trastuzumab beyond progression doubles the response rate (RECIST)



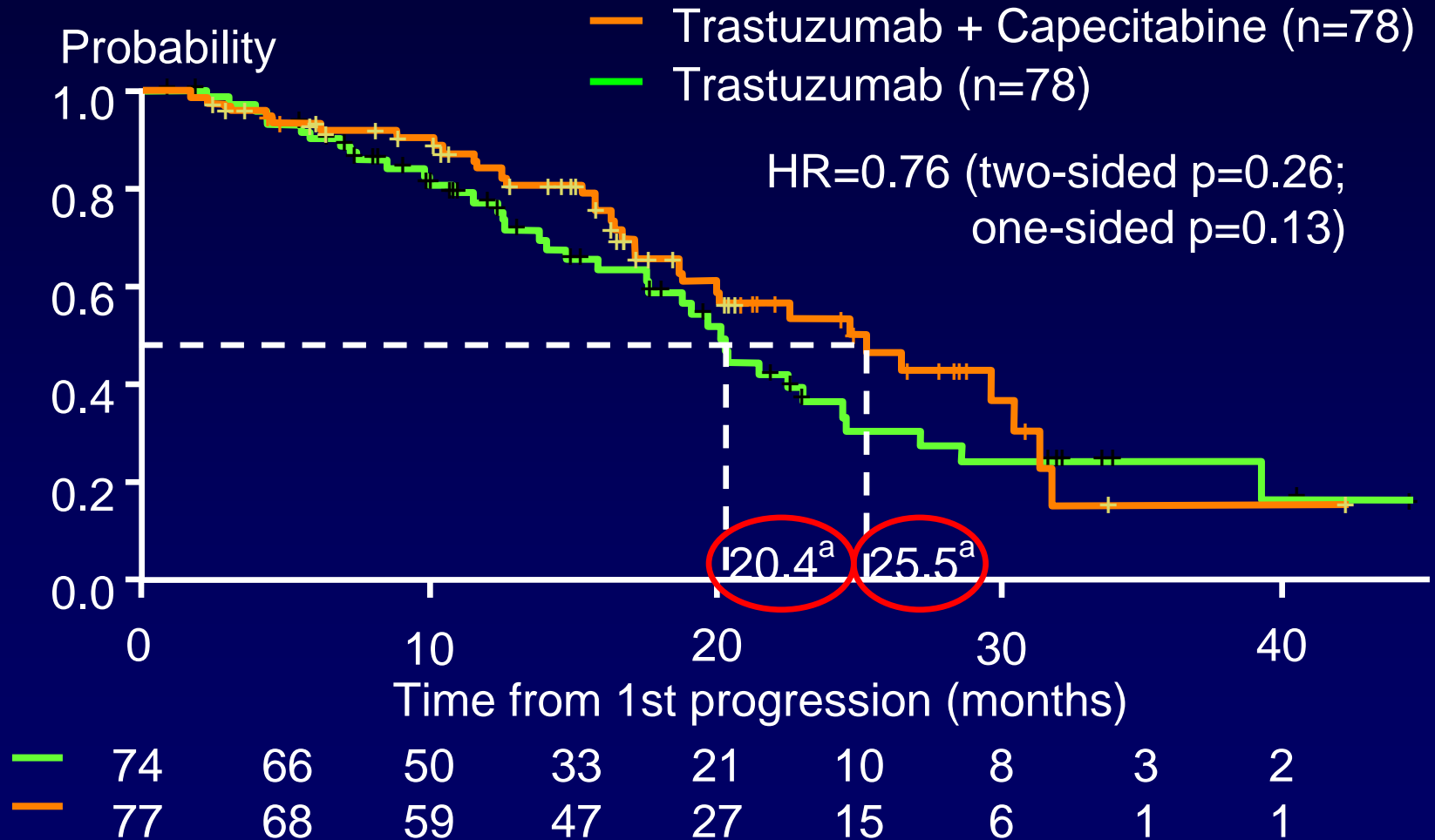
ORR = Overall response rate = CR+PR
CBR = Clinical benefit rate = CR+PR+SD>24wks

Continuation of trastuzumab prolongs time to progression by nearly 3 months



^aMedian TTP in months
TTP, time to progression; HR hazard ratio

Continuation of trastuzumab 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 q 3 wk

Capecitabine 2500 mg/m²/d po days 1-14 q 3 wk

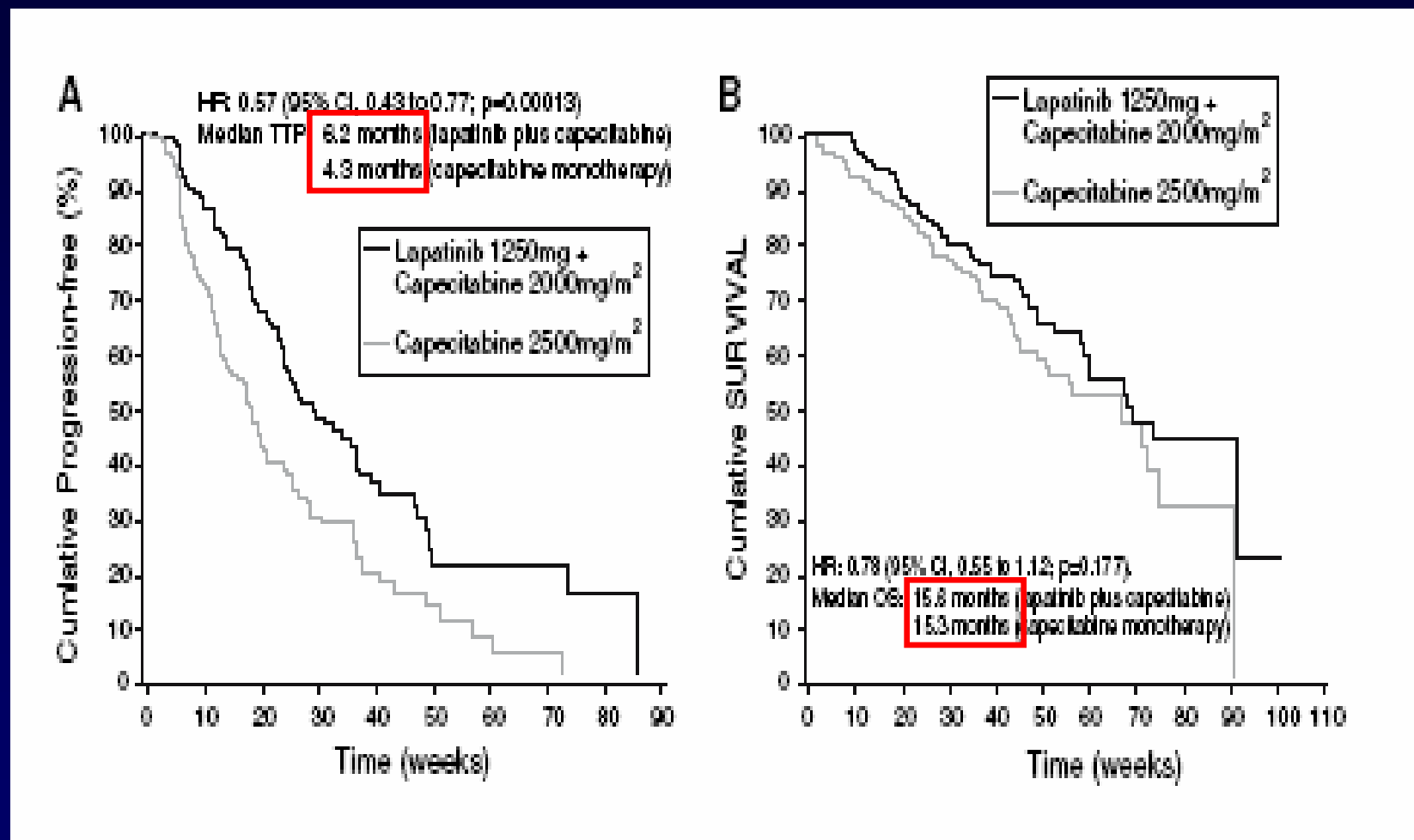
Patients on treatment until progression or unacceptable toxicity, then followed for survival

*Trastuzumab must have been administered for metastatic disease !!

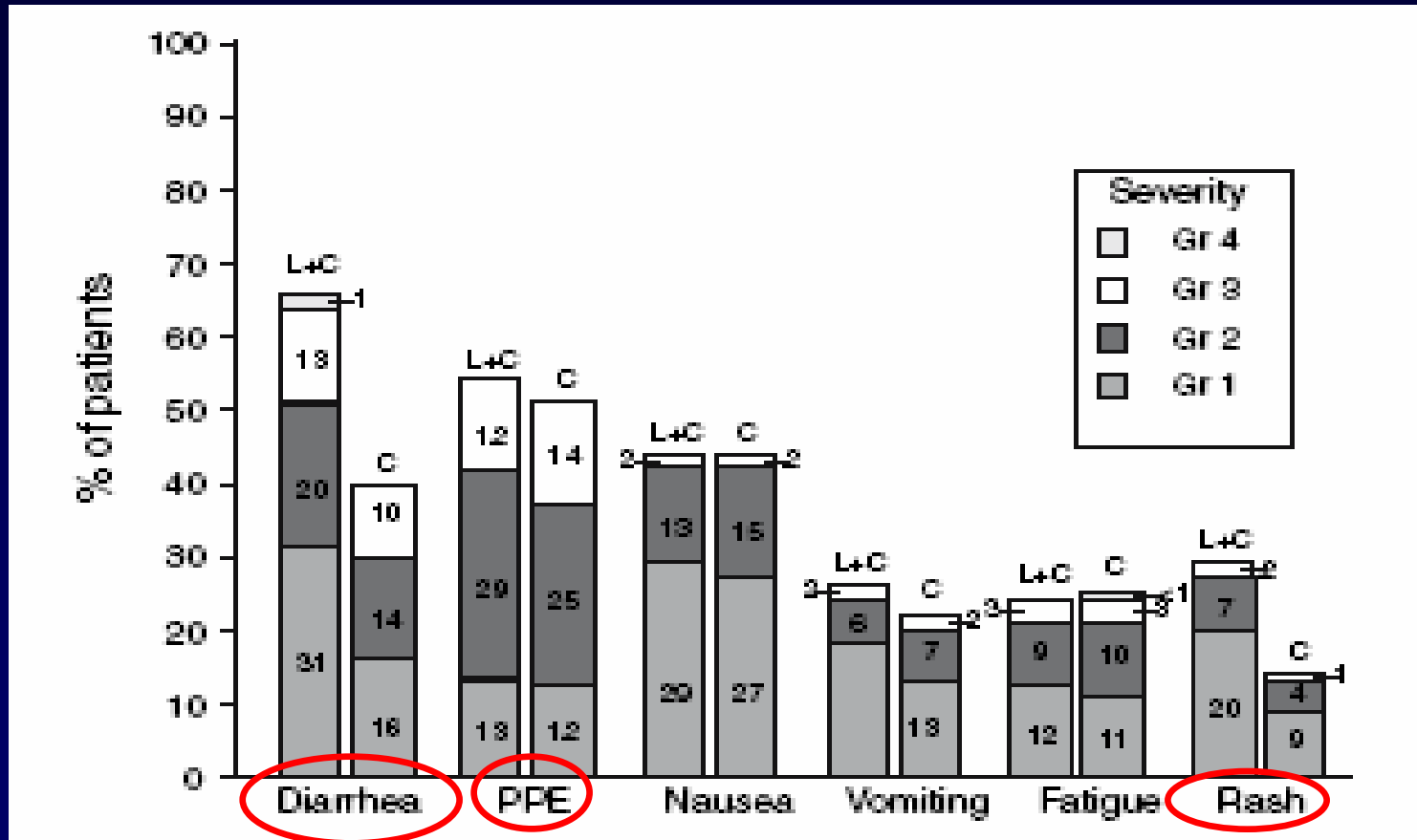
Efficacy Outcomes in the ITT Population as Determined by Independent Review

	Lapatinib + capecitabine (N = 198)	Capecitabine (N = 201)
Progressed or died due to breast cancer, n (%)	82 (41)	102 (51)
Median time to progression, weeks (months)	27.1 (6.2)	18.6 (4.3)
	HR = 0.57 (95% CI 0.43,0.77); P < 0.001	
Died, n (%)	55 (28)	64 (32)
Median overall survival, weeks (months)	67.7 (15.6)	66.6 (15.3)
	HR = 0.78 (0.55,1.12); P = 0.177	
Best response, n (%)		
Complete response (CR)	1 (<1)	0
Partial response (PR)	46 (23)	28 (14)
Stable disease (SD) ^a	75 (38)	59 (29)
Progressive disease (PD)	25 (13)	47 (23)
Not assessable	51 (26) ^b	67 (33) ^c
Response rate (CR + PR) ^d		
Response rate % [95% CI]	23.7 [18.0, 30.3]	13.9 [9.5, 19.5]
Odds ratio	1.9 [1.1, 3.4; P = 0.017]	
Clinical benefit rate (CR + PR + SD ≥ 6 months) % [95% CI]	29.3 [23.1, 36.2]	17.4 [12.4, 23.4]
Odds ratio	2.0 [1.2, 3.3; P = 0.008]	
Median duration of response (months)	7.4	7.0

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



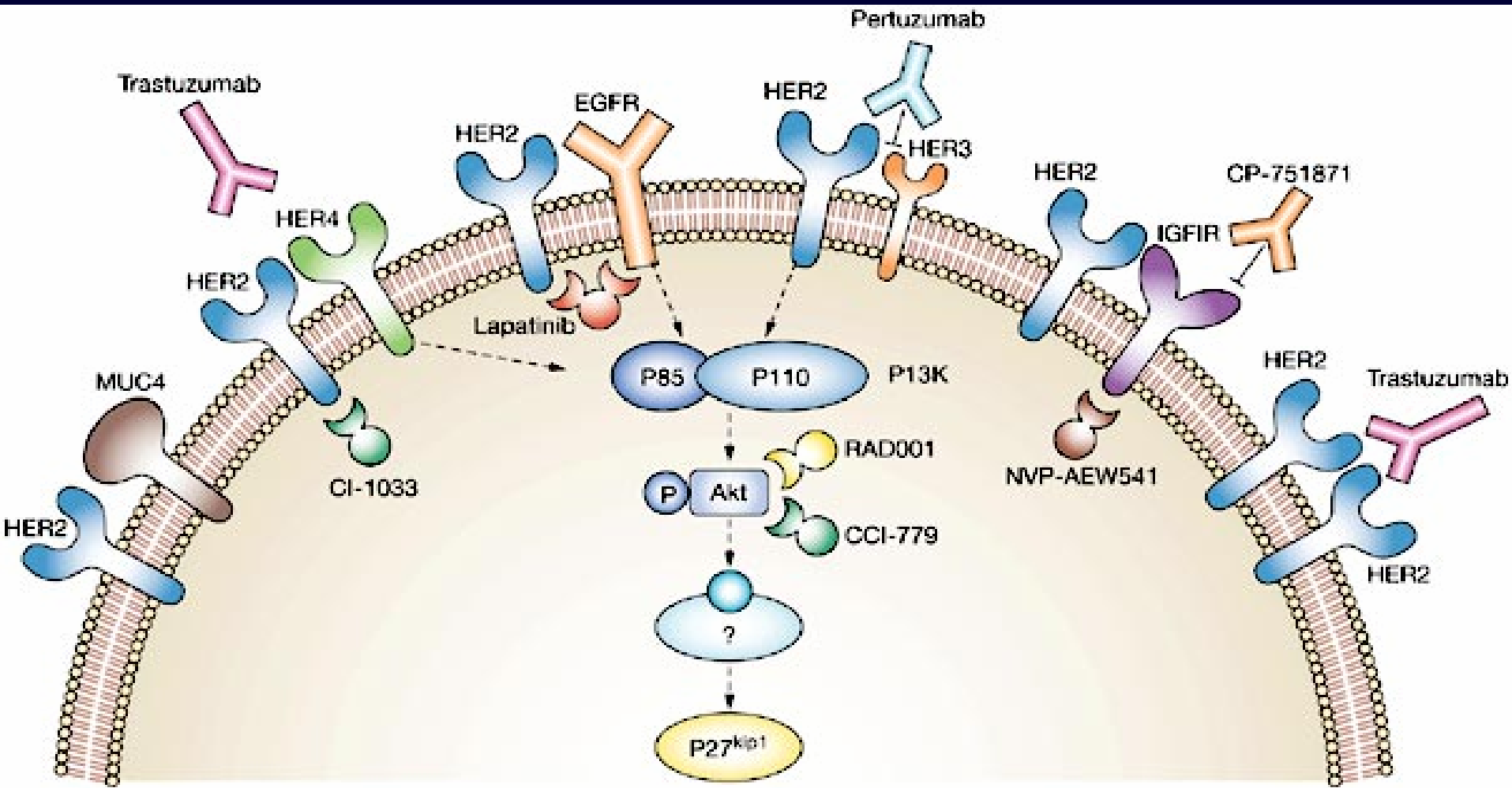
Most Frequent Adverse Events, All Grades



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

	Lapatinib + Capecitabine (n=198)	Capecitabine (n=201)
Pts with symptomatic CNS progression as part of their first progression event	4 (2%)	13 (6,4 %)
	P = 0.045	

Mechanism of HER2 Resistance



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 PD after 4 wk therapy (N=73)

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

Patient and Tumor Characteristics

Study Arms	L	L+T
ITT Population	N=148	N=148
Median Age, Yrs. (range)	51(29-78)	52(26-81)
%ECOG performance status 0/1/2	47/49/4	54/41/5
Median Prior Chemotherapy Regimens	4	5
%Patients \geq 6 Prior Regimens	28	34
Median Prior Trastuzumab Regimens for MBC	3	3
Median Time from Last Trastuzumab, days	25	27
#Patients HER2+	146	147
%ER and PgR Negative	51	51
%Visceral Disease	74	71

Treatment Efficacy

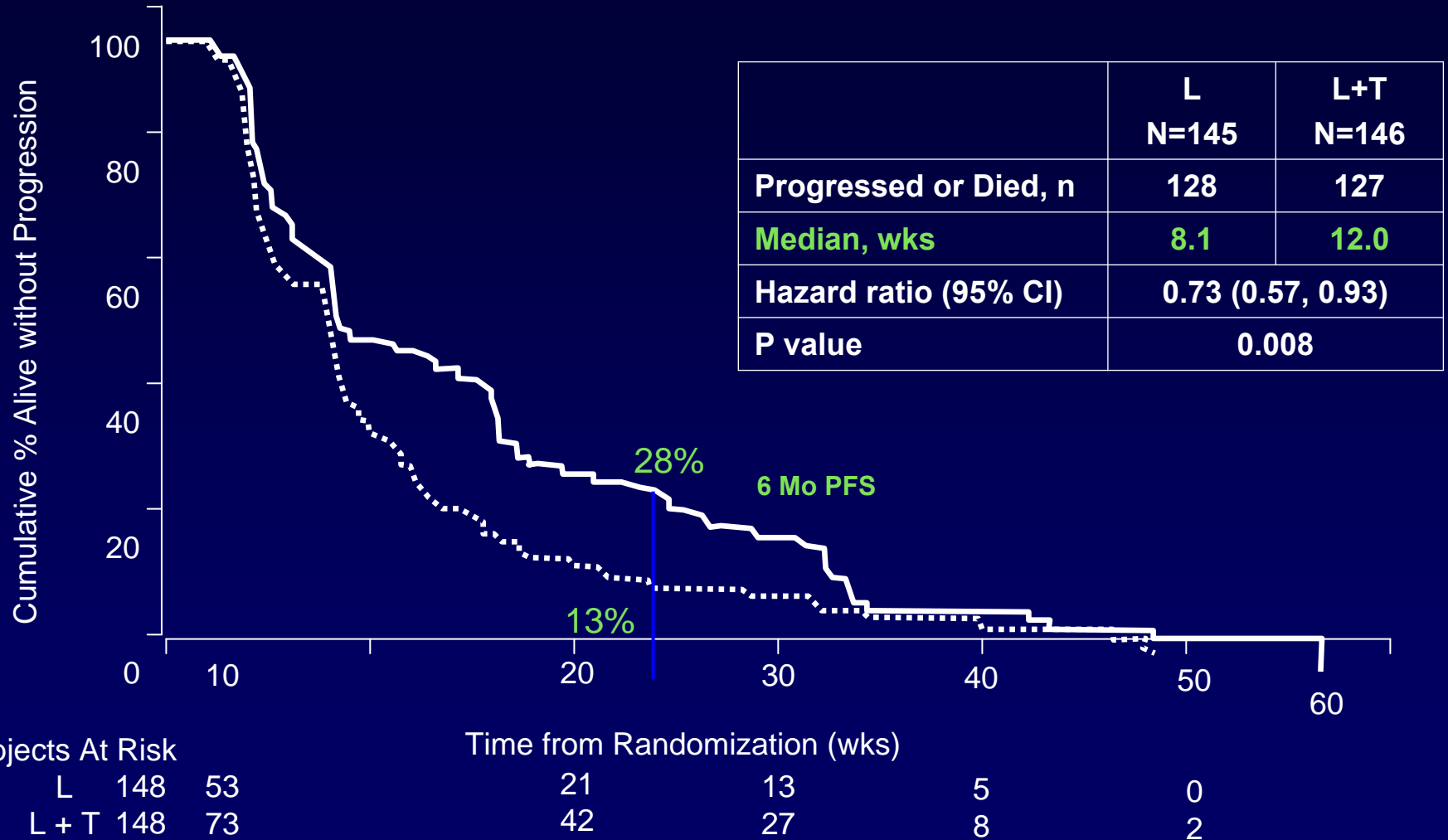
	L N=145	L + T N=146
Response Rate, %* (95% CI)	6.9 (3.4, 12.3)	10.3 (5.9, 16.4)
Odds Ratio (95% CI)	1.5 (0.6, 3.9) P=0.46	
Clinical Benefit Rate, %† (95% CI)	12.4 (7.5, 18.9)	24.7 (17.9, 32.5)
Odds Ratio (95% CI)	2.2 (1.2, 4.5) P=0.01	

*Confirmed CR+PR

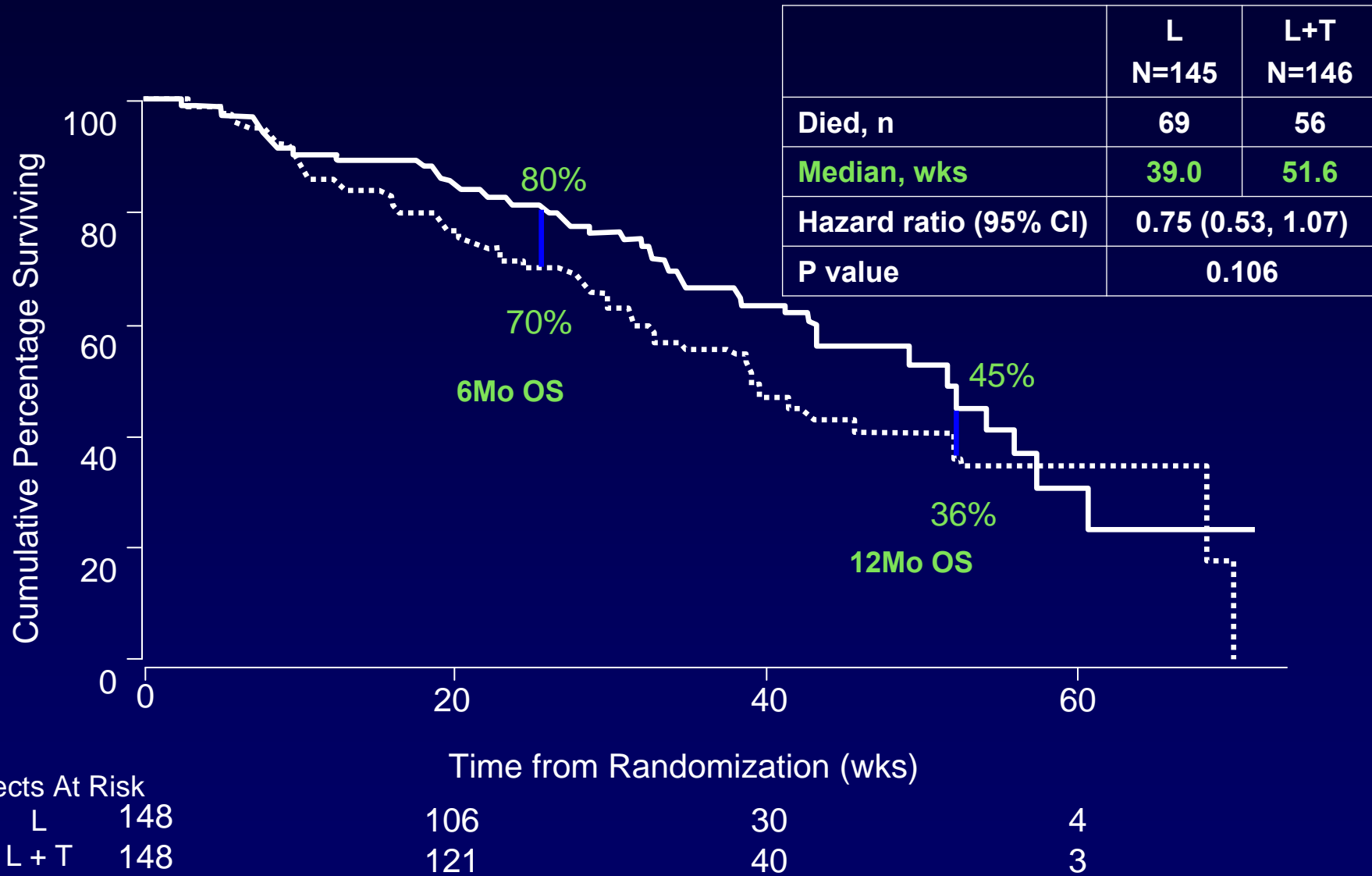
†CR+PR+SD ≥6mo



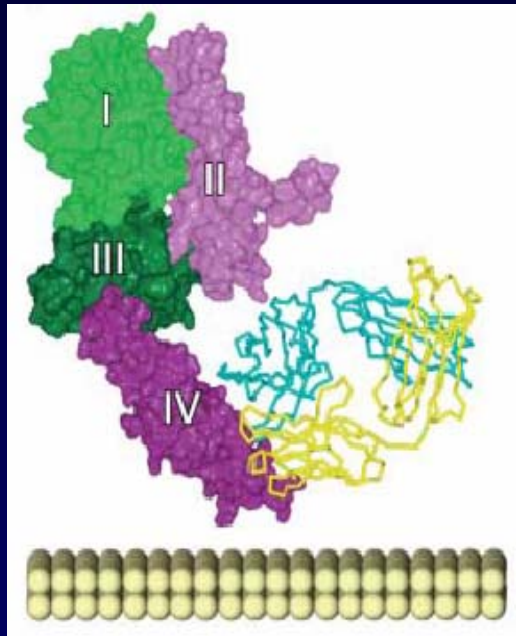
Progression-Free Survival



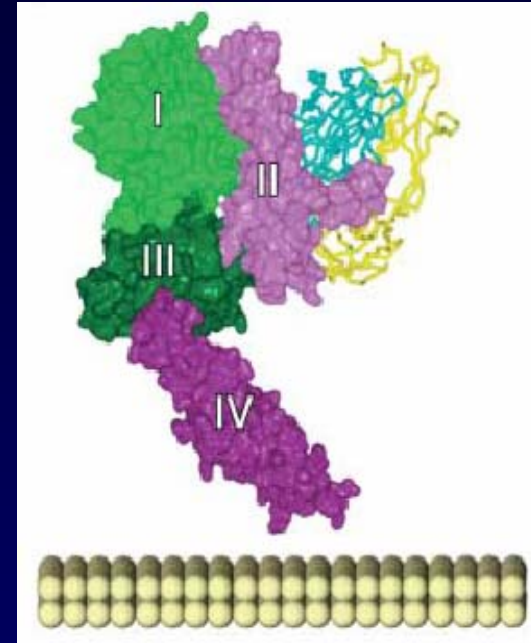
Overall Survival in ITT Population



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 in HER2 \oplus Pts Progressing on Trastuzumab: Main Eligibility Criteria

- **HER2-positive breast cancer (IHC 3+ / FISH+ centrally confirmed) and availability of tumor samples for biomarker assessment**
- **Measurable disease (RECIST)**
- **Up to 3 lines of prior therapies of chemotherapy and / or trastuzumab (including in the adjuvant setting)**
- **Disease progression during trastuzumab as most recent treatment for metastatic disease**
- **Study treatment initiated within 9 weeks of the last dose of trastuzumab**
- **Baseline LVEF $\geq 55\%$ and no decrease of LVEF to $< 50\%$ during prior trastuzumab treatment**

LVEF, left ventricular ejection fraction;
RECIST, Response Evaluation Criteria in Solid Tumors

Trastuzumab + Pertuzumab in HER2 \oplus Pts

Progressing on Trastuzumab: Patient Characteristics

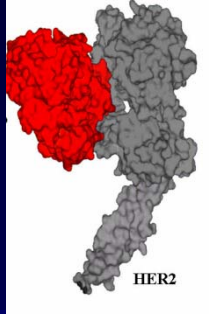
Characteristic	No. patients
No. patients	42
Age (years), median (range)	54 (34-85)
ECOG performance status 0 / 1 (%)	74 / 19
Organ site (target and non-target lesions), n (%)	
Visceral	33 (79)
Lung	18 (43)
Liver	21 (50)
Bone	14 (33)
Lymph nodes	18 (43)
Soft tissue	12 (29)
Other	7 (17)
ER status (%)	
+ve / -ve	45 / 55
Total lesions (target and non-target), median (range)	4 (1-14)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor

Trastuzumab + Pertuzumab: Conclusions

- 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
 - 24% of patients responded (16% PR and 8% CR), and 50% 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

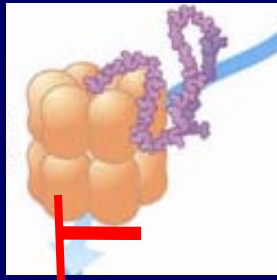
“Other” Anti-HER2 Therapies



- Pertuzumab
 - HER2 dimerization inhibitor

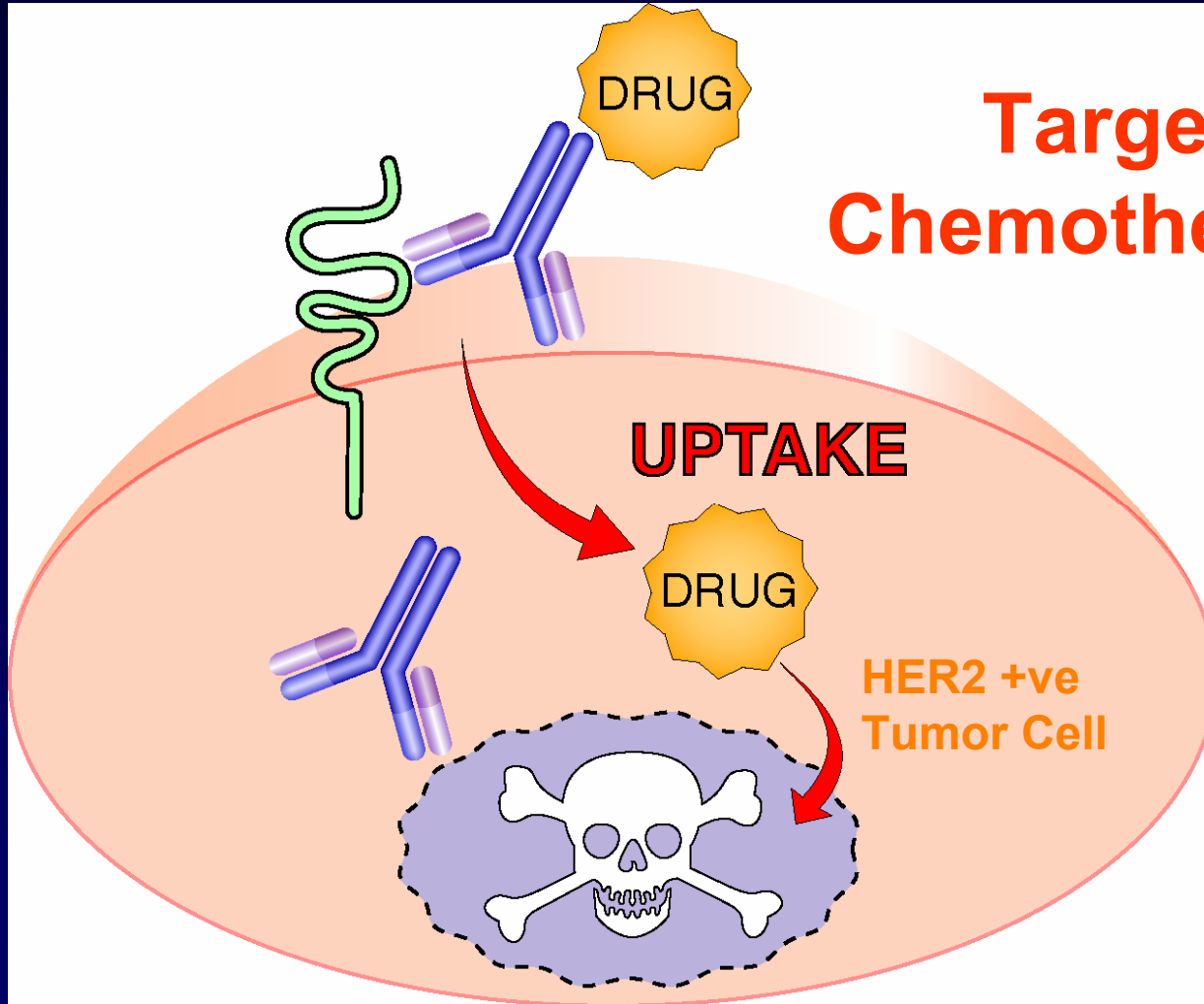


- Trastuzumab-DM1
 - Antibody Drug Conjugate



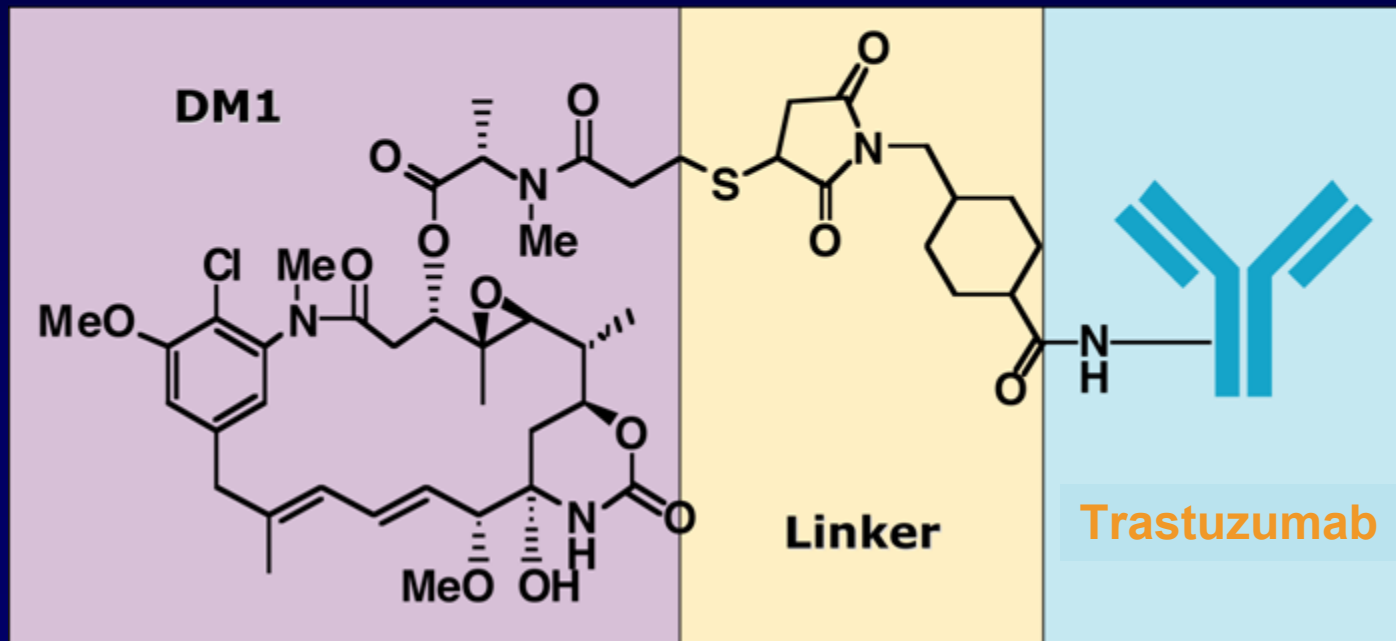
- HSP-90 inhibitors
 - Inhibitors of HSP90 chaperone function

Antibody-Drug-Conjugate Concept



**Targeted
Chemotherapy !!**

Anatomy of Trastuzumab-DM1



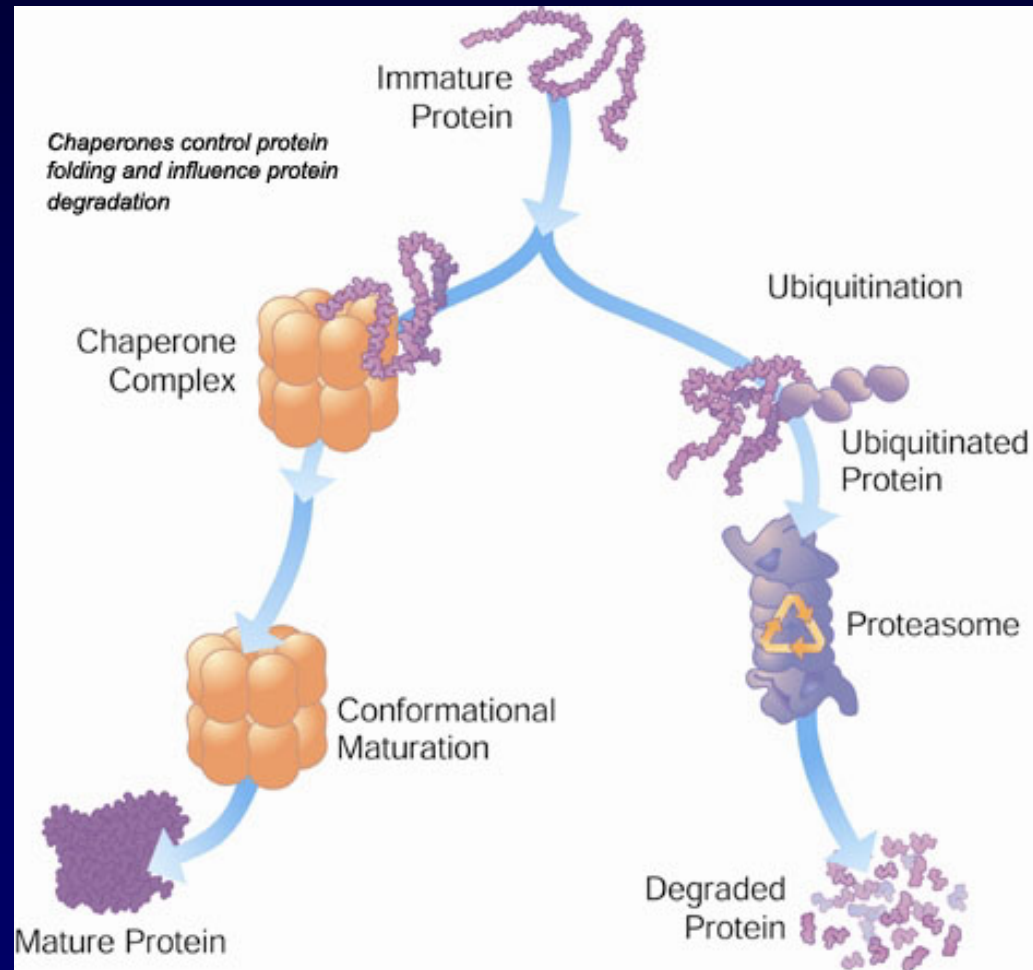
Phase I Trastuzumab-DM1: Summary

- 18 patients with HER2+ MBC previously treated with trastuzumab,
- Grade 4 thrombocytopenia (rapidly reversible) was dose-limiting at 4.8 mg/kg. The MTD of T-DM1 every 3 weeks is 3.6 mg/kg.
- At the MTD, no neuropathy; thrombocytopenia generally Grade 1, non-cumulative, and rapidly reversible . No cardiac toxicity has been observed.
- T-DM1 has demonstrated anti-tumor activity (4 ongoing partial responses) at doses at or below the MTD on a q3-week schedule.
- A phase II trial in HER2-positive metastatic breast cancer has been initiated.



HSP90 as a Therapeutic Target in HER2/neu ⊕ 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 clients include:
 - **HER2**
 - mutant p53
 - ER/PR/AR
 - v-src
 - AKT
 - bcr-abl
 - MET
 - mutant B-RAF
 - Raf kinase



HSP90 Inhibitors in the clinic

1. KOS-953 (17-AAG) + trastuzumab¹:

- Phase I: 17 HER2 (+), trastuzumab refractory MBC (range 1-3 prior rx)
 - 1 confirmed partial response
 - 4 tumor regressions
 - 4 SD (≥ 4 months duration)

2. KOS -1022 + trastuzumab²:

- Phase I activity including 1 patient with a CR in the lung

Clinical Case # 3 : 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

- Clinical trial of trastuzumab and lapatinib
- Clinical trial of trastuzumab and pertuzumab

Modulators of T
resistance

THANK YOU
