STELLENWERT DER erbB TYROSINKINASE-INHIBITOREN BEIM MAMMAKARZINOM

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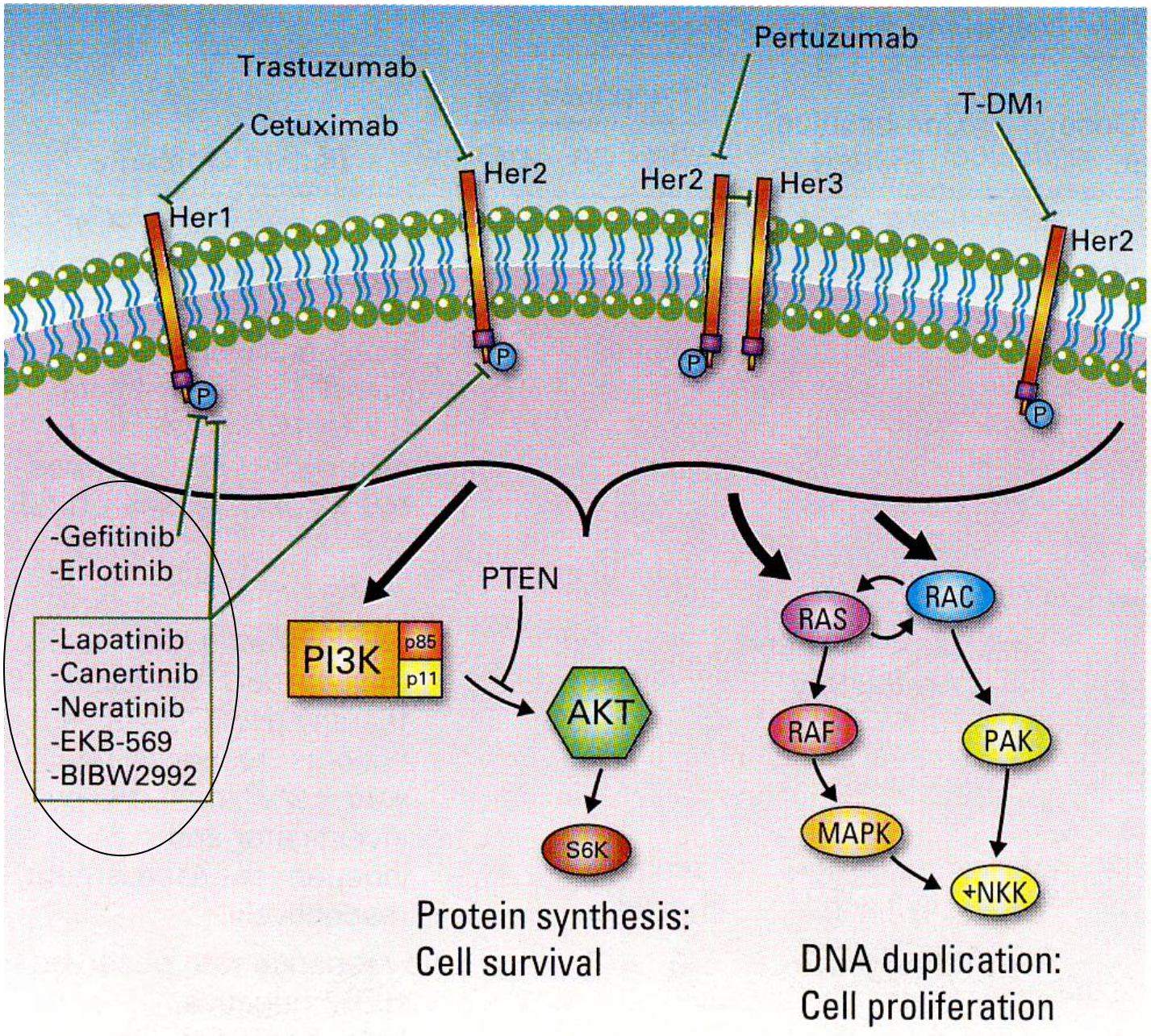

Trastuzumab
Cetuximab
Pertuzumab
T-DM1
Her1
Her2
Her2
Her3
Her2
P
P
P
P
-Gefitinib
-Erlotinib
-Lapatinib
-Canertinib
-Neratinib
-EKB-569
-BIBW2992
PI3K
p85
p11
PTEN
AKT
S6K
RAS
RAC
RAF
PAK
MAPK
+NKK
Protein synthesis:
Cell survival
DNA duplication:
Cell proliferation

ERLOTINIB
Monotherapie 150 mg/d

EGFR-Inhibitor **Phase II** **Bei Progression:**	
Nach Anthra, Taxan, Capecit. (n=47) **Nach 1 palliat. Chemother.** (n=22)	PR: 3% PR: 3%
	Diarrhö Hauttox. Asthenie Übelkeit

Dickler, Breast Ca Res Treat 115 (2008) 115

ERLOTINIB 150 mg + LETROZOL

EGFR-Inhibitor **Phase II** **Hormonsensitiv, Postmenopause** **1. oder 2. Linie Endokrine Therapie**	
N= 22 **Klinischer Nutzen** **CR** **PR**	 11/20 Pat. 1/20 4/20
	Mediane TTP 13 Mon

Mayer, Breast Ca Res Treat 100 (Suppl 1) Abstr 4052

GEFITINIB
Monotherapie 500 mg/d

EGFR-Inhibitor	**Klinischer Nutzen**
TAM / AI-Resistenz (n=40)	0%
HR-neg (n=25)[1]	8%
Tamoxifen-Resistenz (n= 54)[2]	54%
Phase II (n=31)[3]	0%

1 Green, Ann Oncol 20 (2009) 1813
2 Gutteridge, Int J Cancer 126 (2010) 1806
3 Baselga, JCO 23 (2005) 5323

GEFITINIB
Phase II randomisiert HR-pos.

EGFR-TKI Vortherapie Tamoxifen N=93	**G + Anastrazol**	**G + Placebo**
PFS	14,7 Mon	8,4 Mon
Clinical Benefit Rate	49%	34%
CR + PR	12%	2%

Cristofanilli, Clin Cancer Res 16 (2010) 1904

GEFITINIB 250 mg/d
Phase II randomisiert HR-pos.

EGFR-TKI **Keine** pall. antihorm. Ther., Kein AI adj, kein Fulvestrant N=142	**G +** **Anastrazol**	**G +** **Fulvestrant**
Clinical Benefit Rate	42%	38%
CR	3%	4%
PR	21%	17%
PFS	5,7 Mon	5,2 Mon
Gesamtüberleben	30 Mon	24 Mon
		Diarrhö ^ Neutrop ^

Carlson, JCO 27 (2009) Abstr. 1013

GEFITINIB 250 mg/d
Phase II NEOADJ. randomisiert HR-pos.

EGFR-TKI N=260	**G +** **Anastrazol**	**Anastrazol**
Ki 67 nach 16 Wo	-77%	-84% (n.s.)
CR+PR	48%	61% (n.s.)
	Diarrhö, **Hautreaktionen,** **Alopezie,** **Trockene Haut** **Übelkeit**	

Smith, JCO 25 (2007) 3816

EGF100151: Pivotal Study design

ErbB2+ LABC or MBC with prior exposure to an anthracycline, a taxane and trastuzumab*

N= 588 patients planned

RANDOMIZE

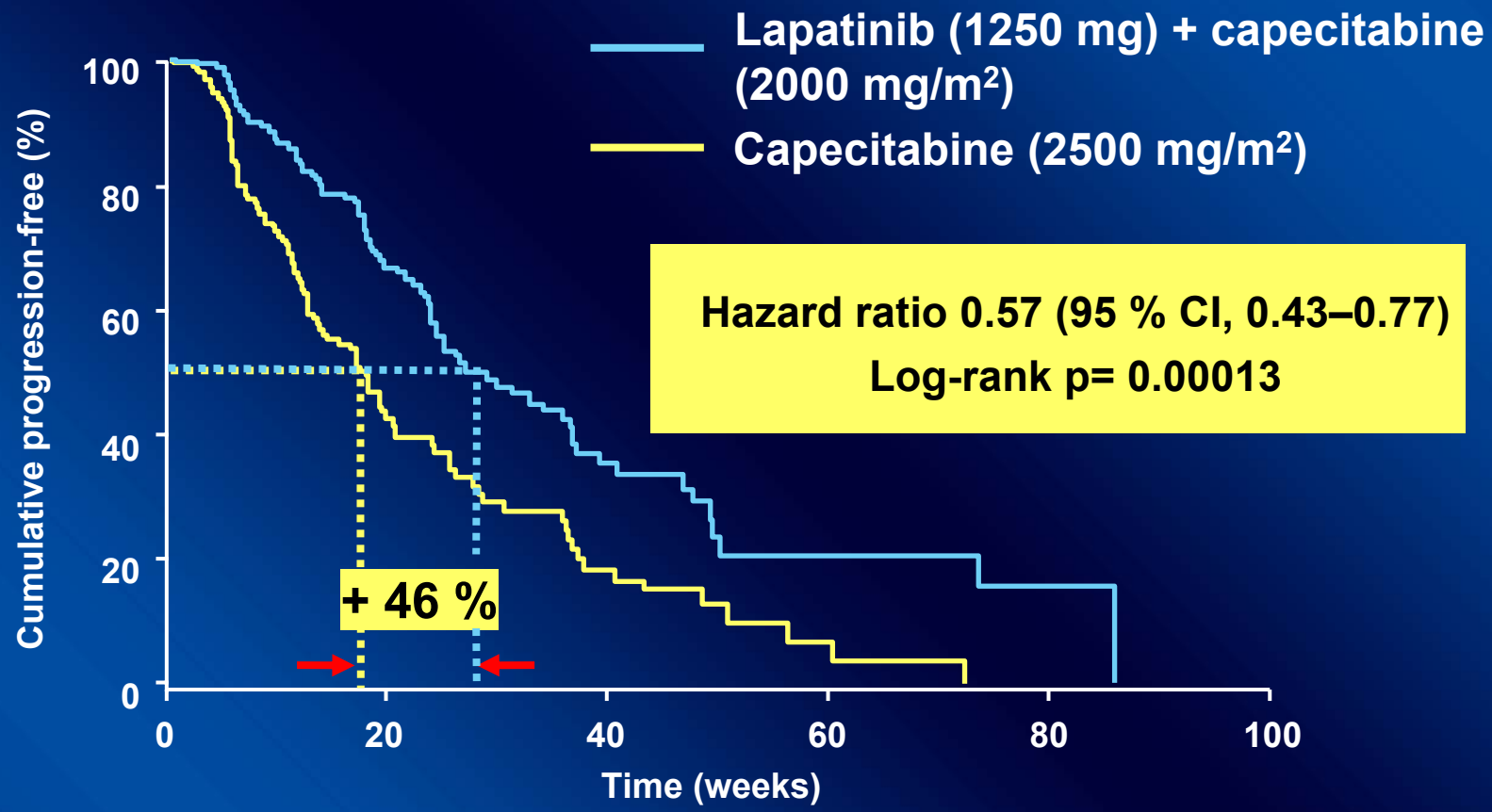
Lapatinib 1250 mg/d po + Capecitabine 2000 mg/m^2/d po days 1–14 q3 wk

Capecitabine 2500 mg/m^2/d po days 1–14 q3 wk

*Trastuzumab must have been administered for metastatic disease

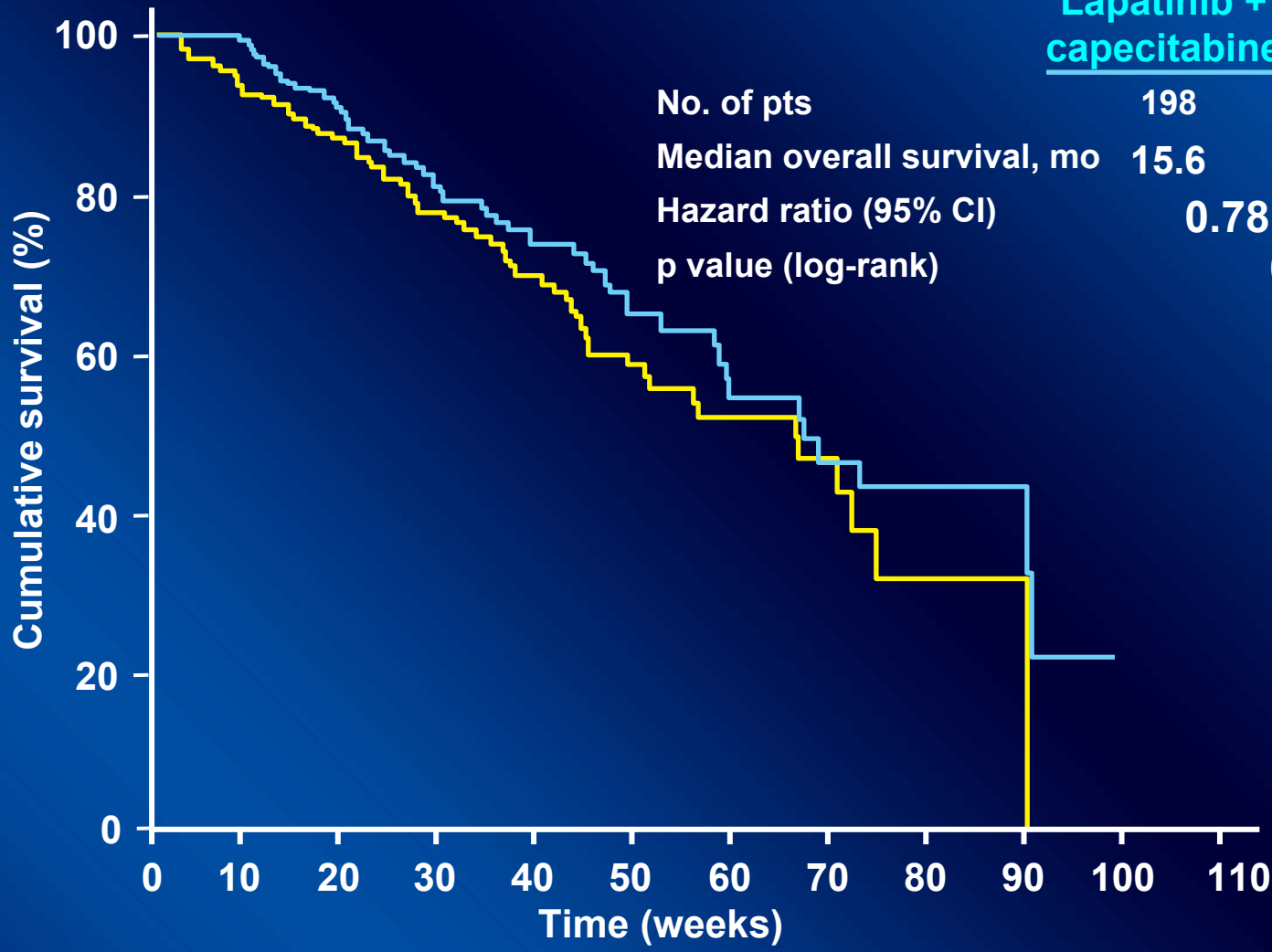
Geyer *et al. N Engl J Med* 2006; 355: 2733–43

Median TTP: 27.1 vs 18.6 weeks



Cameron *et al. Breast Cancer Res Treat* 2008; 112: 533–543

Overall survival



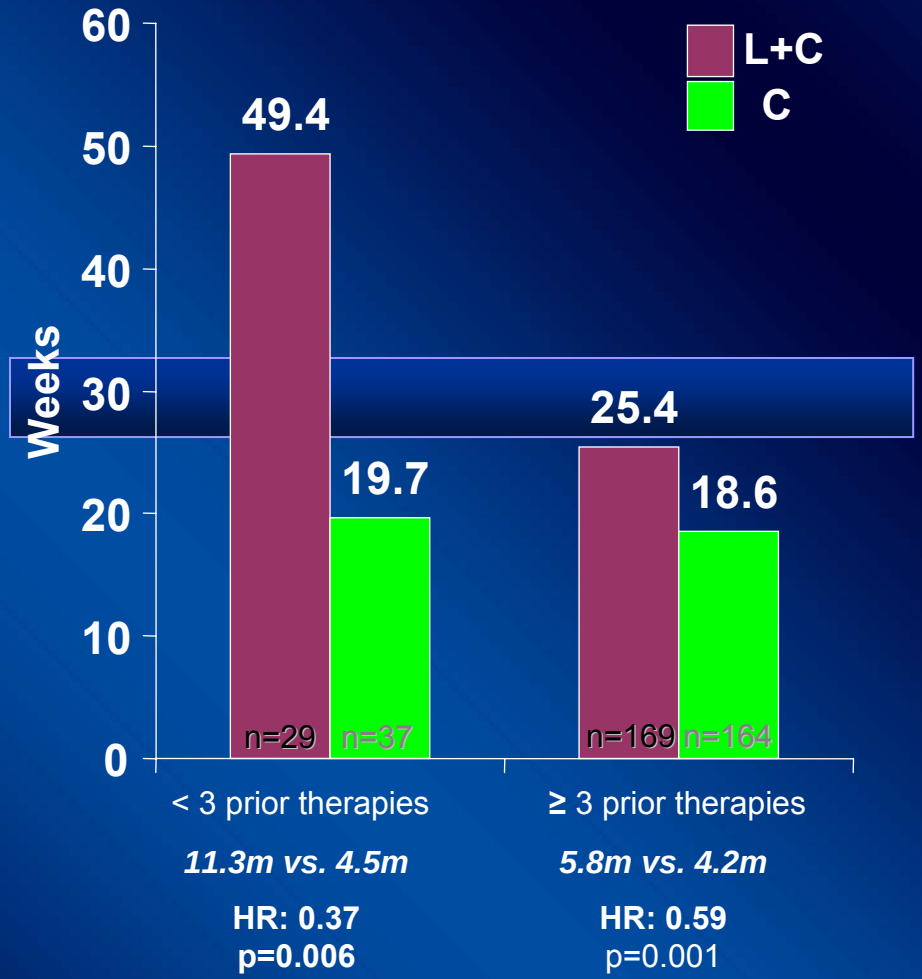
	Lapatinib + capecitabine	Capecitabine
No. of pts	198	201
Median overall survival, mo	15.6	15.3
Hazard ratio (95% CI)	0.78 (0.55, 1.12)	
p value (log-rank)	0.177	

Cameron *et al. Breast Cancer Res Treat* 2008; 112: 533–543

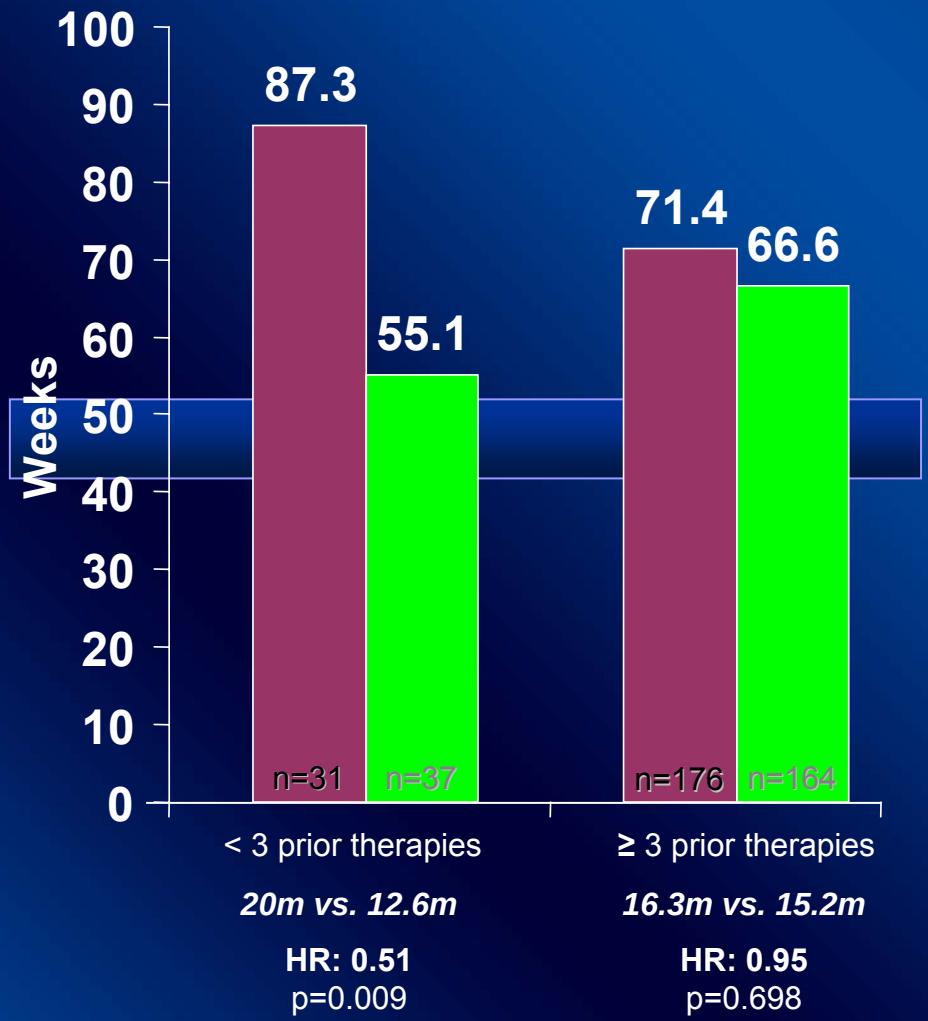
<3 vs ≥3 or more prior lines of therapies

Crown et al.

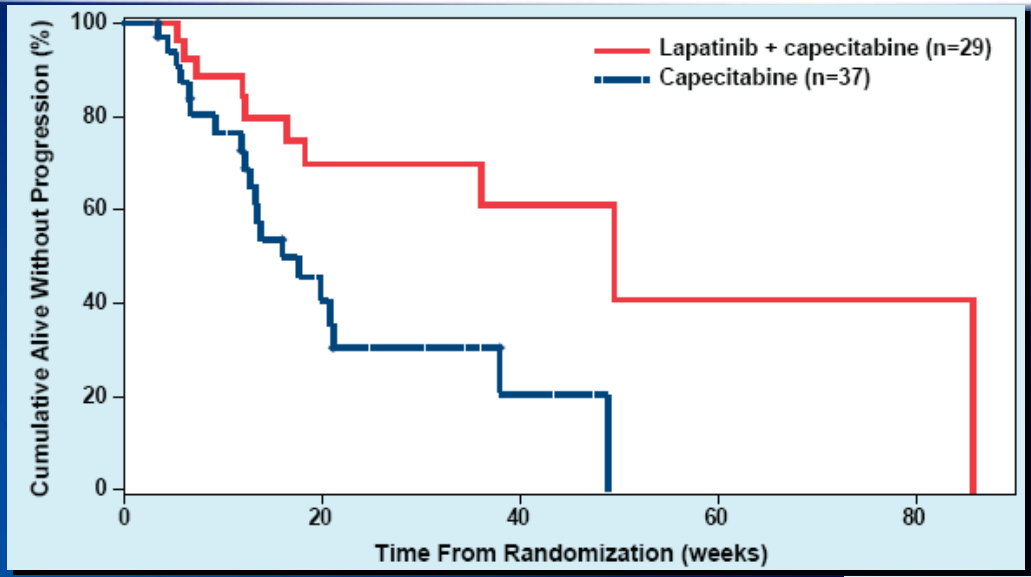
Time to Progression (TTP)



Overall Survival (OS)

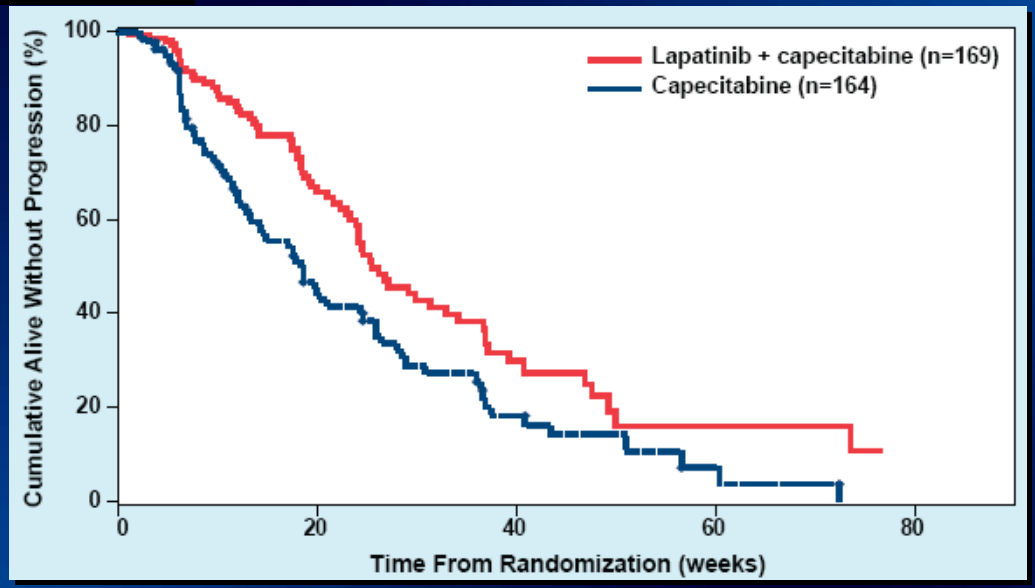


Time to Progression (TTP)
<3 prior vs. ≥3 prior chemotherapy regimens



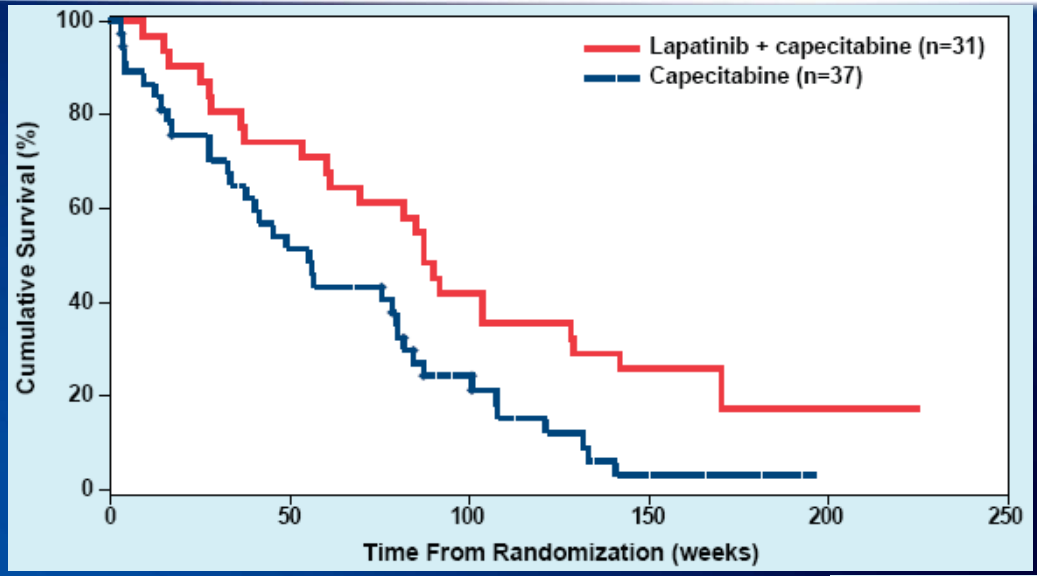
<3 prior chemotherapies

≥ 3 prior chemotherapies



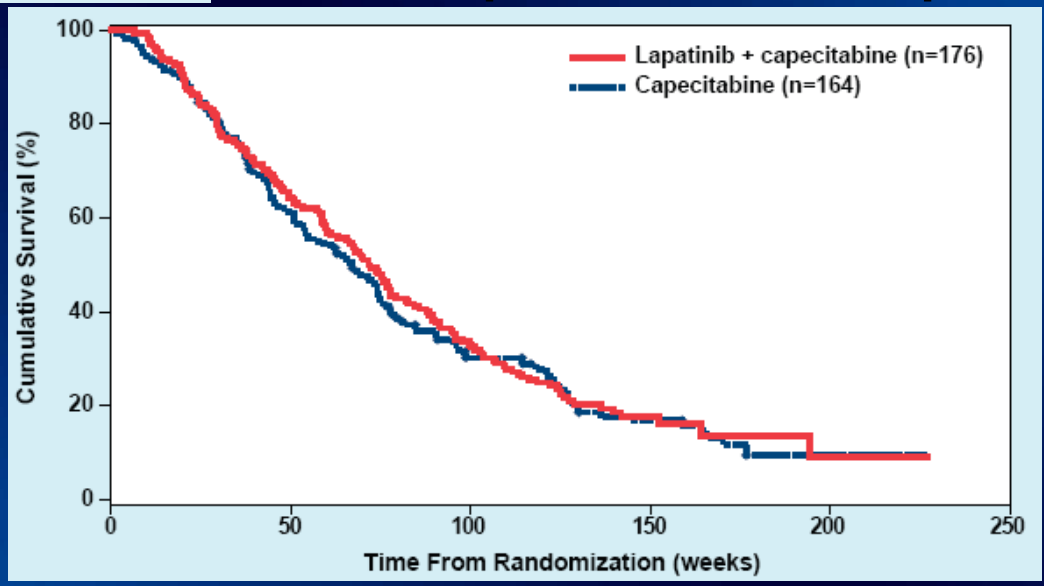
Crown et al.

Overall Survival (OS)
<3 prior vs. ≥3 prior chemotherapy regimens



<3 prior chemotherapies

≥ 3 prior chemotherapies



Crown et al.

LAPATINIB: Cardiac events observed in clinical trials

Prior therapy	Any cardiac event n (%)	Asymptomatic* n (%)	Symptomatic† n (%)
Anthracyclines (n=552)	**12 (2.2)**	**9 (1.6)**	**3 (0.5)**
Trastuzumab (n=826)	**14 (1.7)**	**13 (1.6)**	**1 (0.1)**
Neither of above (n=2311)	34 (1.5)	31 (1.3)	3 (0.1)
All patients (N=3689)	**60 (1.6)**	**53 (1.4)**	**7 (0.2)**

Perez et al. *Mayo Clin Proc* 2008; 83: 679

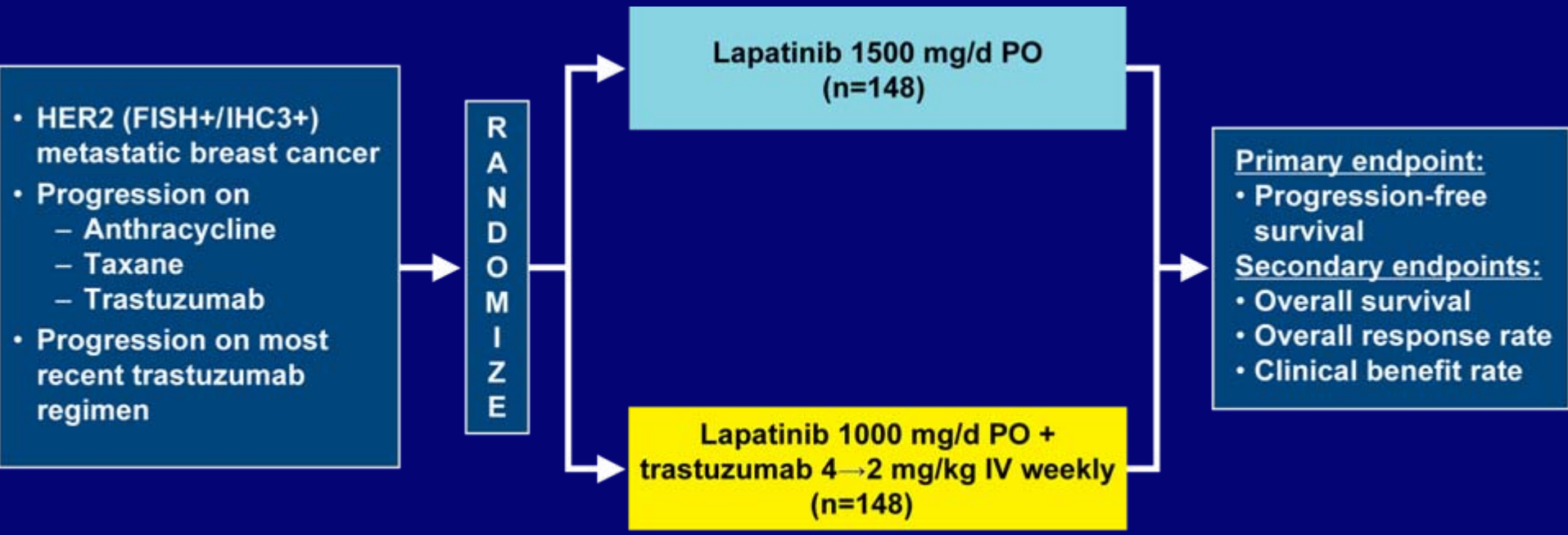
LAPATINIB

Wirksamkeit im GEHIRN

Lapatinib 1250/d + Capecitabin 2000/m2/d	**Pivotal study**	**Progression ZNS** **2%** versus **11%** (versus nur Capecitabin)
Lapatinib 1250/d + Capecitabin 2000/m2/d	N= 40	**20% Reduktion Gehirnmetastasen > 50%**
Lapatinib 750 mg/d	N= 104	**8% PR,** **16% Reduktion Gehirnmetastasen ≥ 20%**

Geyer JCO 24 (2006) 40s, Abstr 1035
Lin, JCO 25 (Suppl 18) (2007) 35s (Abstr. 1012)
Lin, Breast Cancer Res Treat 106 (Suppl 1) (2007) S272 (Abstr. 6076)

EGF104900: Phase III Study Evaluated Dual HER2 Blockade



FISH=fluorescence in situ hybridization; IHC=immunohistochemistry.

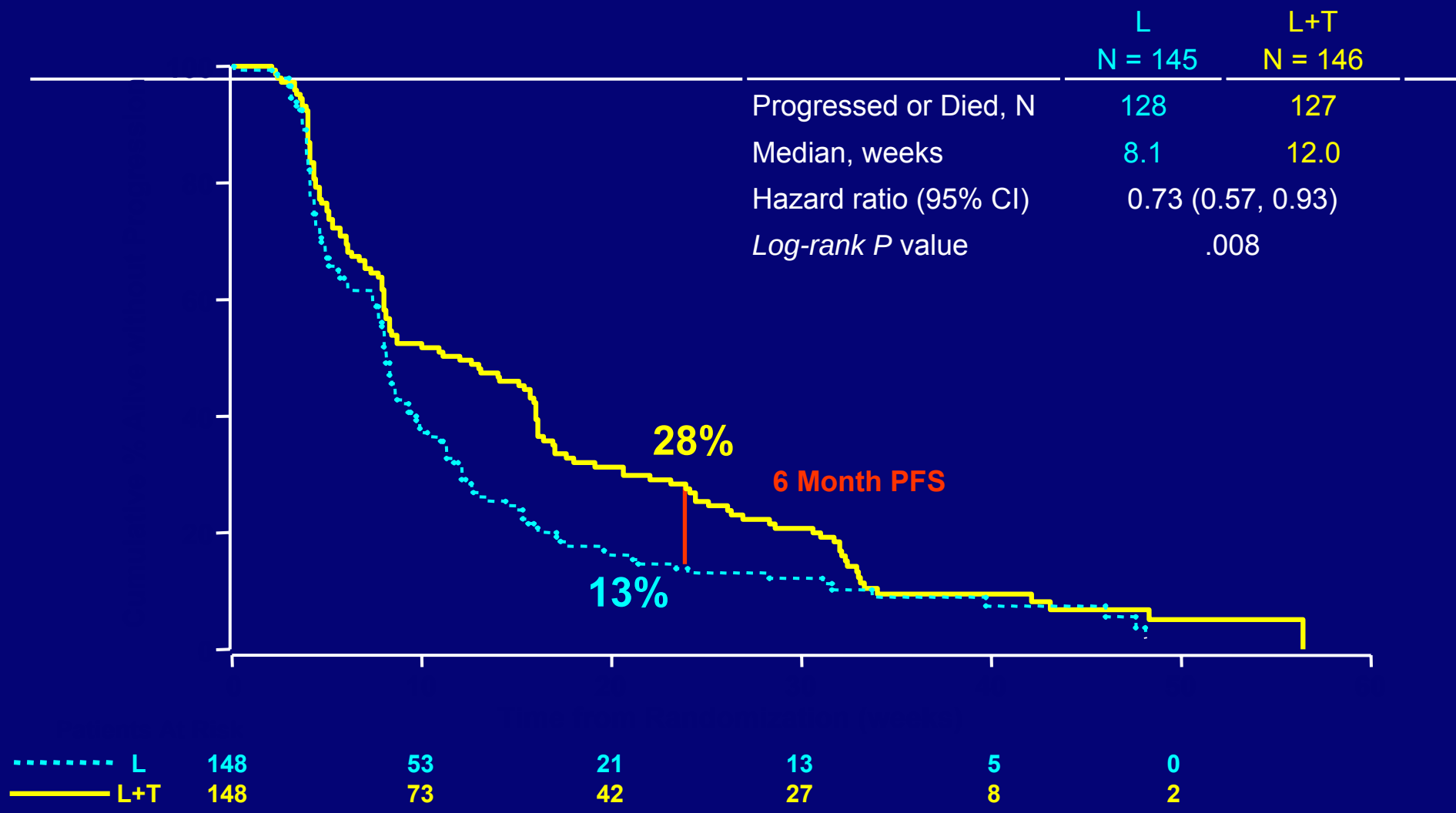
Blackwell, SABCS 2009

Patient and Tumor Characteristics

Study Arms ITT Population	Lapatinib N = 148	Lap+Trast N = 148
Median age, y (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 ≥ 6 prior regimens, %	28	34
Median prior trastuzumab regimens for MBC	3	3
Median time from last trastuzumab, days	25	27
ER- and PgR-negative, %	51	51
Visceral disease, %	74	71
Known Brain Metastasis	20	16

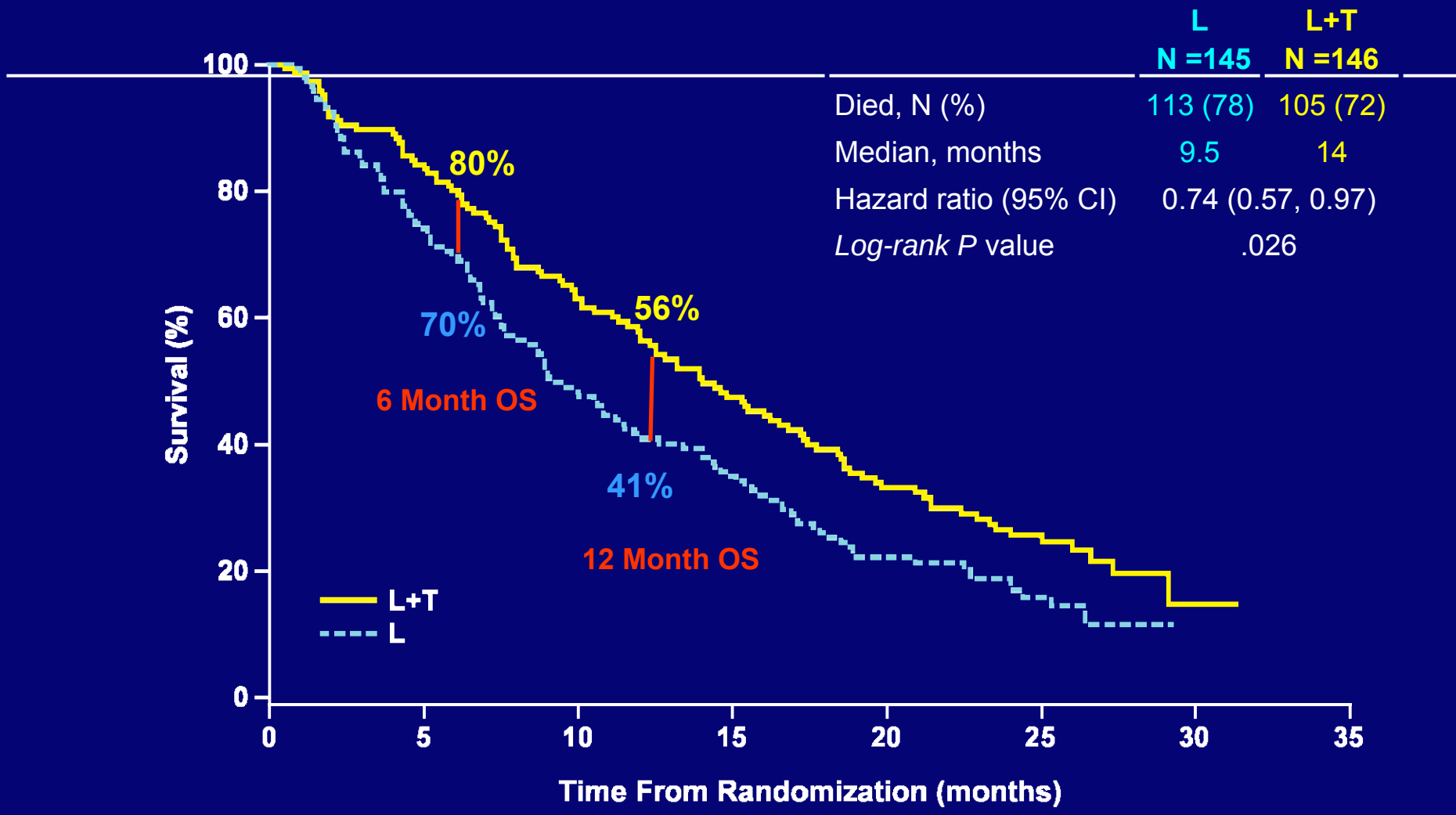
Blackwell, SABCS 2009

Progression-Free Survival in ITT



O'Shaughnessy, et al. ASCO 2008; Blackwell, et al. J Clin Oncol doi:10.1200/JCO.2008.21.4437 (In Press)

Updated Overall Survival in ITT



Phase III, Randomized, Double-Blind Controlled Trial FIRST LINE

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

RANDOMIZE

Letrozole 2.5 mg daily + Placebo

Letrozole 2.5 mg daily + Lapatinib 1500 mg daily

N=1286 (including n=219 HER2+)

Johnston et al.

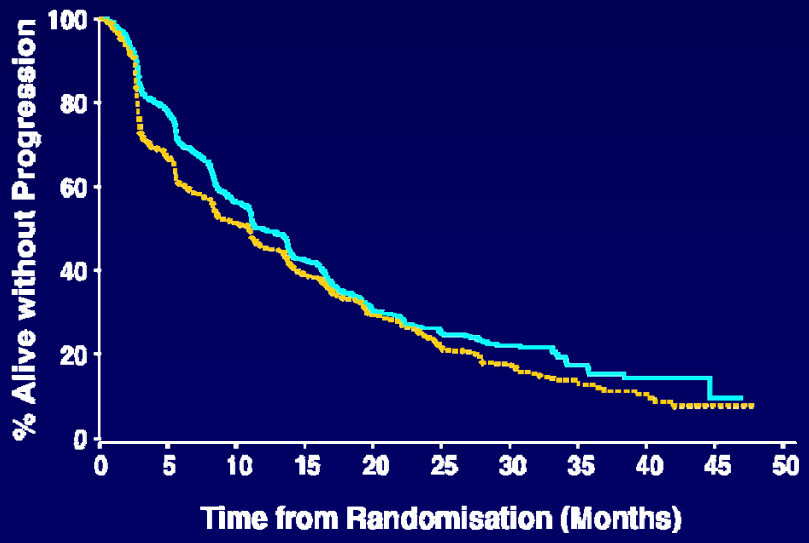
Patient Characteristics

	HER2+		ITT	
	Letrozole (N=108)	Letrozole + Lapatinib (N=111)	Letrozole (N=644)	Letrozole + Lapatinib (N=642)
Median age, y	59	60	63	62
Median time from initial diagnosis, mo	27.8	29.2	44.9	42.7
Interval since prior adjuvant tamoxifen				
≥ 6 Months / None	67 (62%)	73 (66%)	487 (76%)	501 (78%)
< 6 Months	41 (38%)	38 (34%)	157 (24%)	141 (22%)
Sites of disease				
Bone only	18 (17%)	16 (14%)	85 (13%)	94 (15%)
Visceral or soft tissue	90 (83%)	95 (86%)	559 (87%)	548 (85%)
Liver	37 (34%)	33 (30%)	171 (27%)	146 (23%)
Lung	40 (37%)	43 (39%)	242 (38%)	248 (39%)
Lymph node	43 (40%)	57 (51%)	304 (47%)	312 (49%)
Soft tissue	31 (29%)	35 (32%)	218 (34%)	212 (33%)
Other	18 (17%)	19 (17%)	127 (20%)	125 (19%)

Progression-Free Survival: ITT and HER2-ve Populations

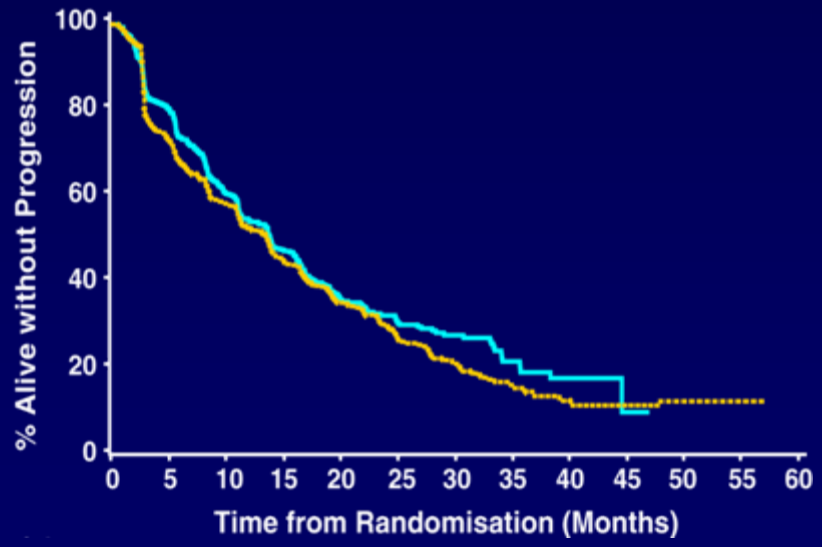
ITT

	Letrozole (N = 644)	Letrozole + Lapatinib (N = 642)
Progressed or died	476 (74%)	413 (64%)
Median PFS, mo	10.8	11.9
Hazard ratio (95% CI)	0.86 (0.76, 0.98)	
p-value	0.026	



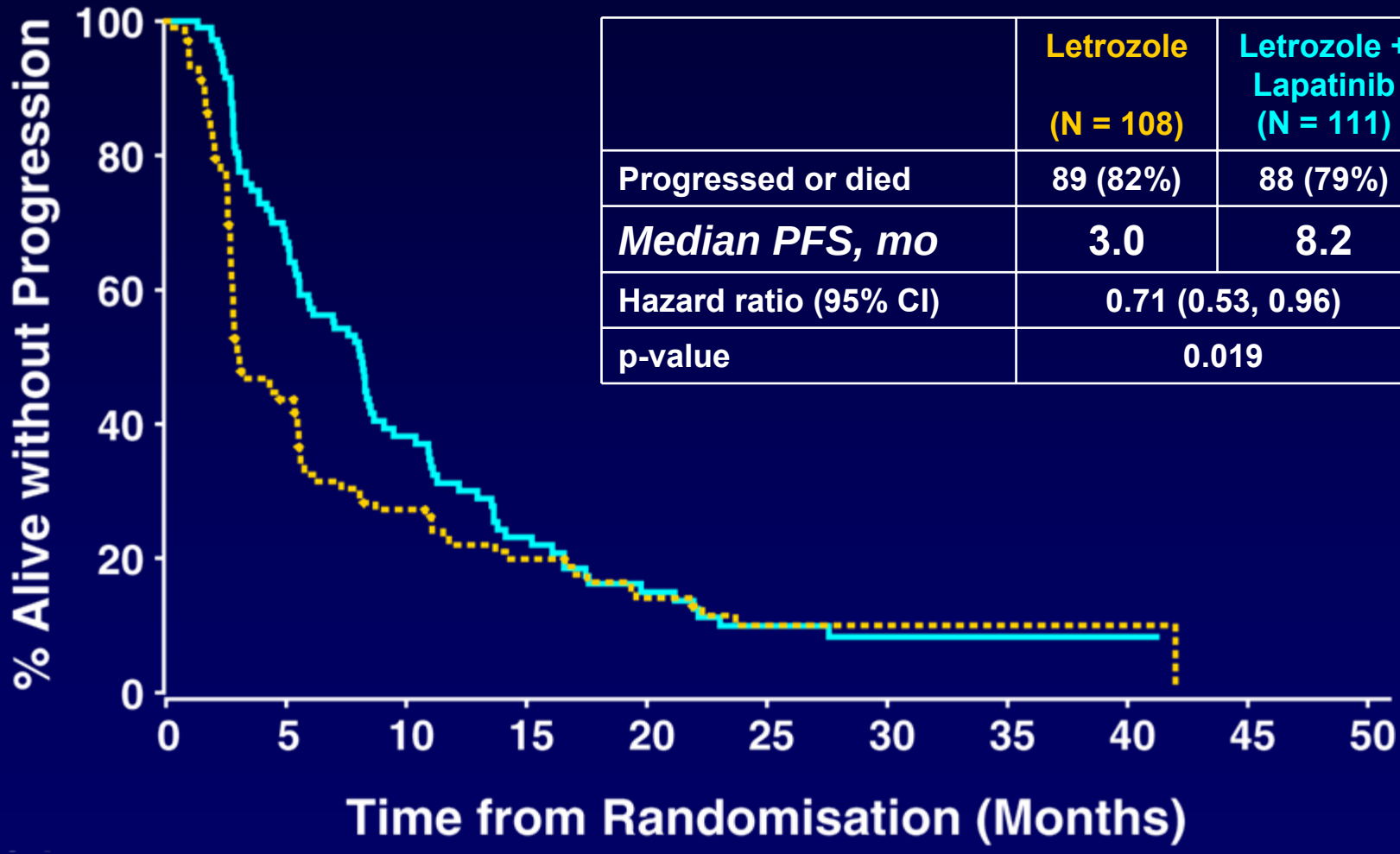
HER2-ve *

	Letrozole (N=474)	Letrozole + Lapatinib (N=478)
Progressed or died	342 (72%)	294 (62%)
Median PFS, mo	13.4	13.7
Hazard ratio (95% CI)	0.90 (0.77, 1.05)	
p-value	0.188	



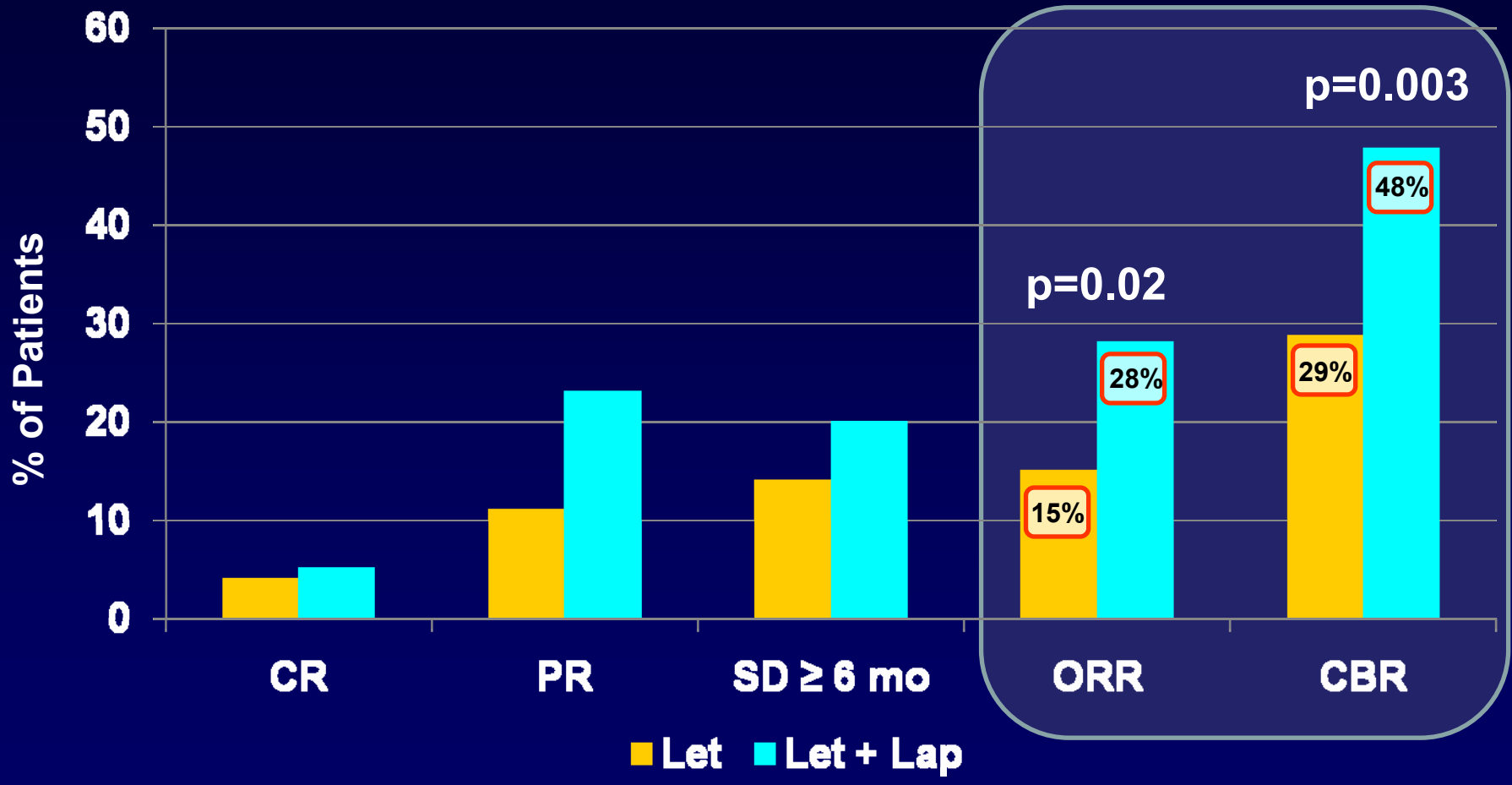
*Centrally confirmed

Progression-Free Survival: HER2+ Population



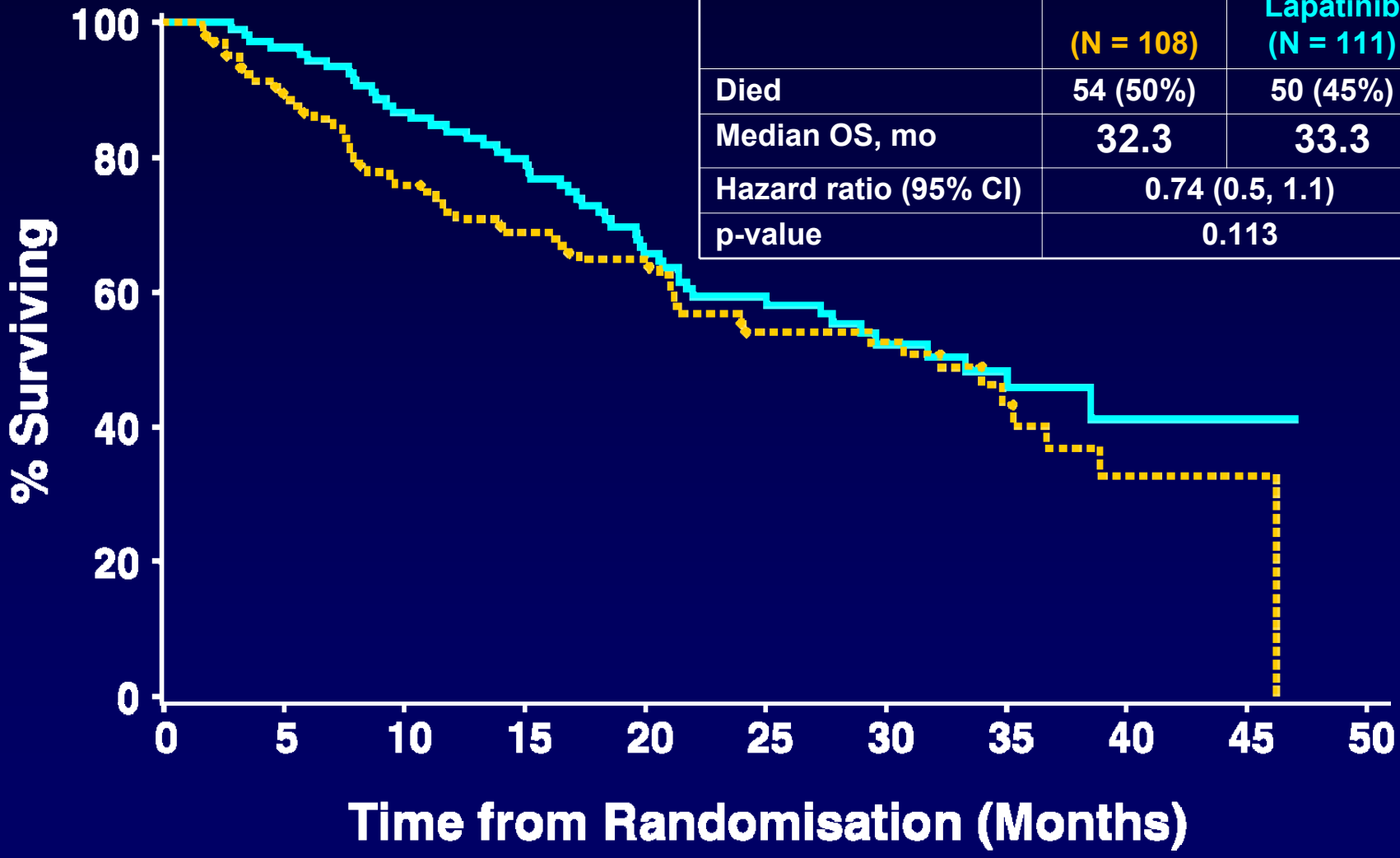
	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Progressed or died	89 (82%)	88 (79%)
Median PFS, mo	3.0	8.2
Hazard ratio (95% CI)	0.71 (0.53, 0.96)	
p-value	0.019	

Response: HER2+ Population (N=219)

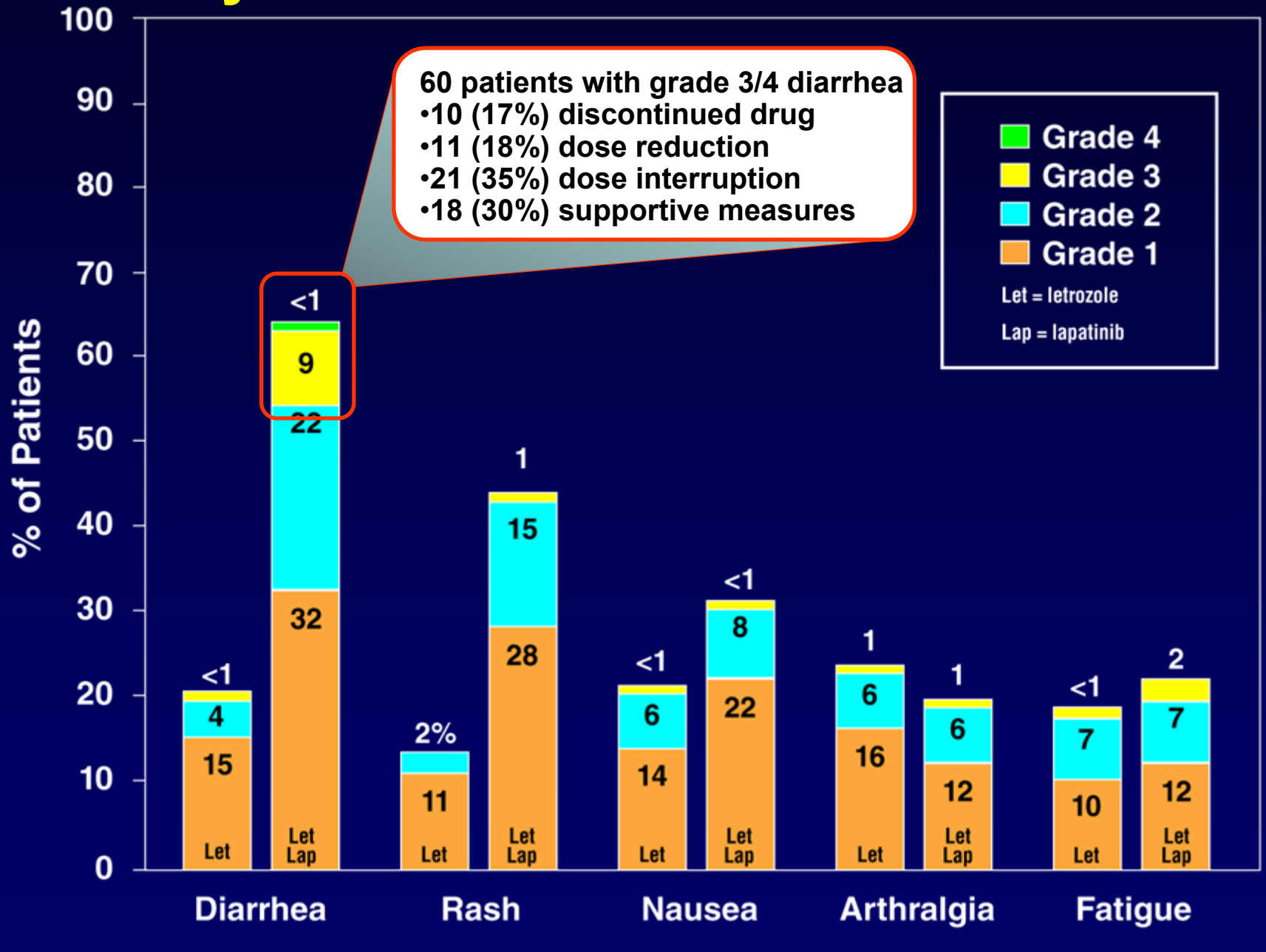


Overall Survival: HER2+ Population

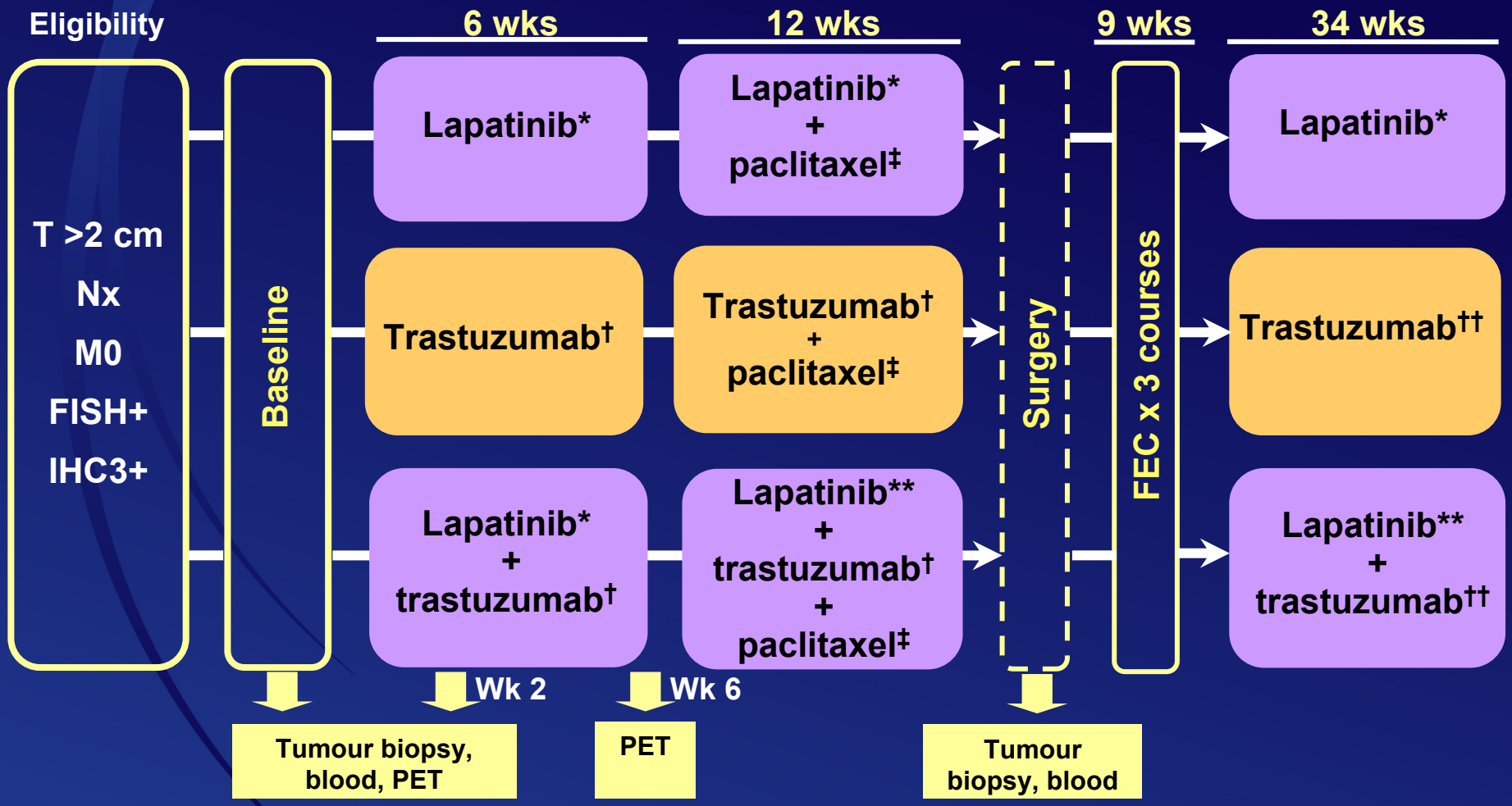
	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Died	54 (50%)	50 (45%)
Median OS, mo	32.3	33.3
Hazard ratio (95% CI)	0.74 (0.5, 1.1)	
p-value	0.113	



Safety: Most Common Adverse Events



NEO-ALTTO study design: lapatinib in neo-adjuvant setting



*1500 mg/day; †2 mg/kg q wk; ‡80 mg/m^2 q wk; **1000 mg/day; ††6 mg/kg q 3 wk

BIBW 2992 – LUX-Breast 1
Phase III metast. Her 2-pos.

EGFR + Anti Her2-TKI Nach 1 Vortherapie (= adj/pall) Trastuzumab, Zustand nach Anthrazyklin + Taxan N= 780	**BIBW 2992 + Vinorelbin**	**Trastuzumab + Vinorelbin**

Aktuelle Studie

NERATINIB
Her2-pos.

	Pan-ErbB Receptor TKI (1,2,4) 240 mg/Tag p.o. 16 Wo PFS	Medianes PFS
KEINE Vortherapie mit Trastuzumab	78%	40 Wo
Vortherapie mit Trastuzumab	59%	22 Wo
Diarrhö G3-G4	30% (Vortherapie) versus 13% (keine Vortherapie) Übelkeit, Erbrechen, Anorexie	

Burstein, JCO 28 (2010) 1301

NERATINIB + Trastuzumab
Her2-pos.

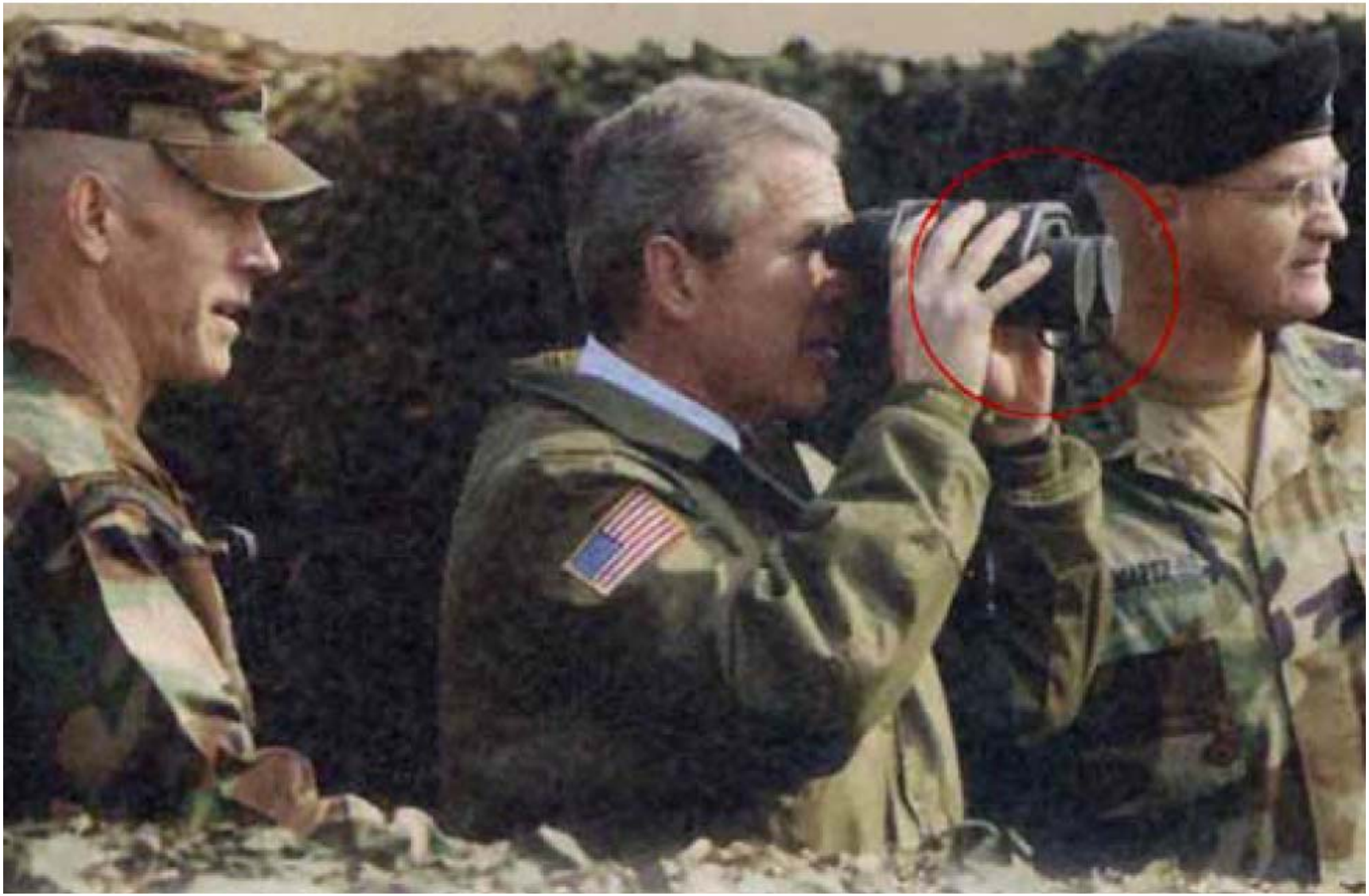
Phase I-II	**Neratinib 240 mg p.o. daily**
N= 37 (Trastuzumab-Vortherapie)	**+ Trastuzumab 4>2 mg/kg wöchentlich**
	Diarrhö 91% (≥ G3: 13%) Nausea 51% (≥ G3: 4%) Anorexie 40% Erbrechen 38% (≥ G3: 4%) Asthenie 27% KEINE relevante Kardiotoxizität
	27% Ansprechen Medianes PFS 6,2 Mon

Swaby, Proc ASCO (2009) Abstr. 1004

NERATINIB + Paclitaxel
Her2-pos.

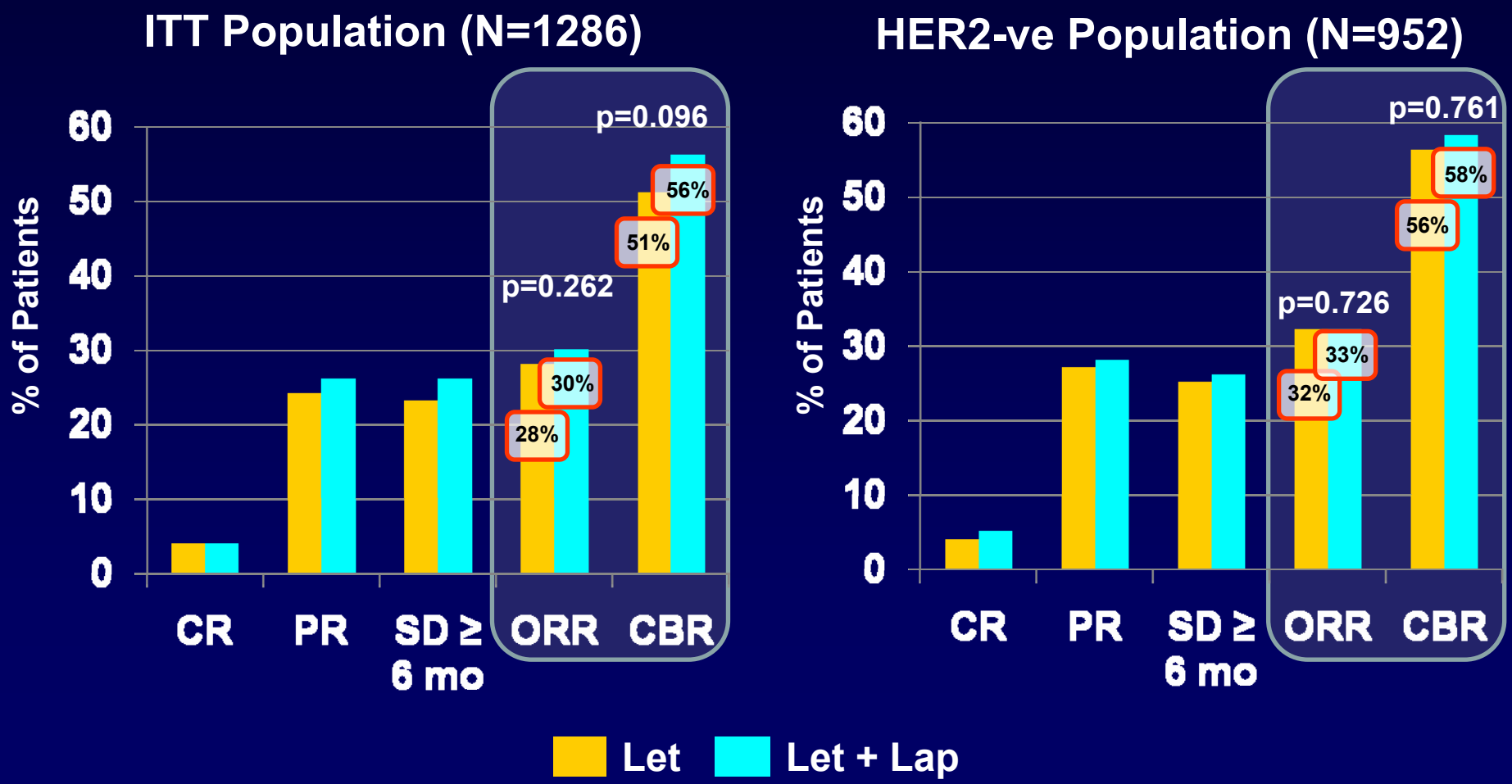
Phase I-II	**Neratinib (pan-erb-Inhibitor 1,2,4) 160-240 mg p.o. daily**
	+ Paclitaxel 80 mg/m2/d d 1,8,15 every 4 weeks
	Diarrhö 89% (≥ G3: 25%)(nach 3d) Neutropenie 42% (≥ G3: 17%) Hautveränderungen 26% Erbrechen 26%
N= 37 (AntiHer-Vortherapie)	**57%** Ansprechen (9/13 Lapatinib-Vortherapie)

Chow, Cancer Res 69 (Suppl)(2009) Abstr. 5081



ErbB-TKI: Perspektiven.
Lapatinib: Standard. ALLTO/Neo-ALLTO
Andere erbB-TKI: Optimale Komb. Partner ?

Response Rates: ITT and HER2-ve Populations



Response rates were compared using stratified Fisher's exact test.

Anti-EGFR and Anti Her-2 in ER+ MBC

Trial	Regimen	Population	No. of patients	Median PFS, mo	
				Endocrine therapy alone	Endocrine therapy + anti-ErbB
Osborne et al[2] Randomized, placebo-controlled phase II	**Tamoxifen +/- gefitinib**	**ITT**	**206†**	**8.8**	**10.9**
		HER2+ subset	**37**	**5.8**	**6.7**
Cristofanilli et al[3] Randomized, placebo-controlled phase II	**Anastrozole +/- gefitinib**	**ITT**	**93**	**8.2**	**14.5**

[2]Osborne K, et al. *Breast Cancer Res Treat.* 2007;106. Abstract 2067;
[3]Cristofanilli M, et al. *J Clin Oncol*. 2008;26(No 15S). Abstract 1012.