HER2 Positive Breast Cancer: Trastuzumab and Current Treatment Strategies

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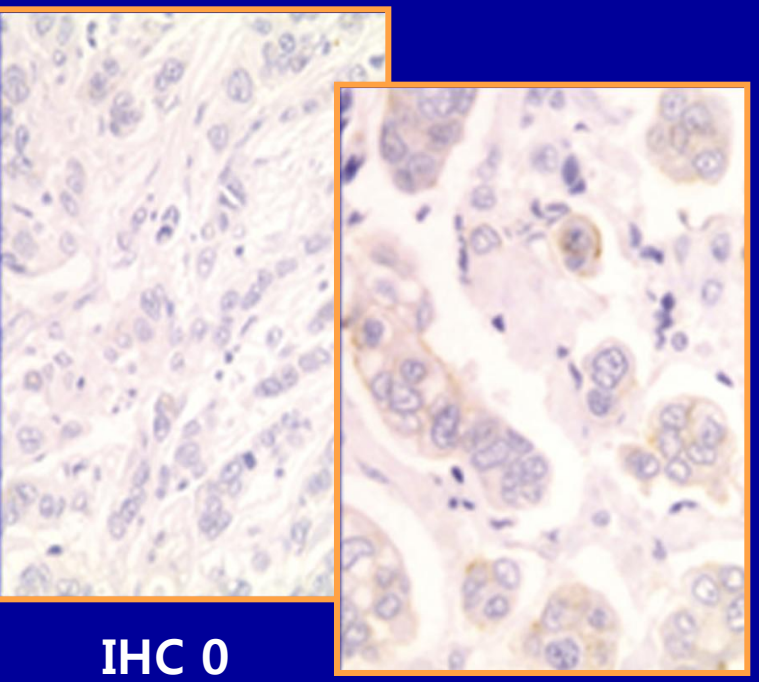
1) What is HER2 positive disease?

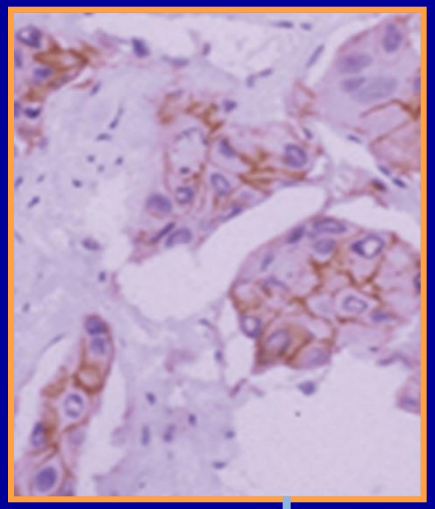
HER2 positivity



IHC 0

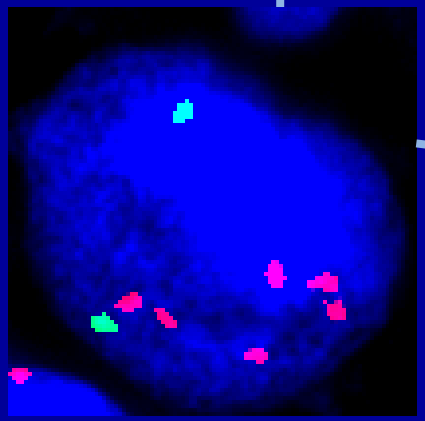
IHC I+

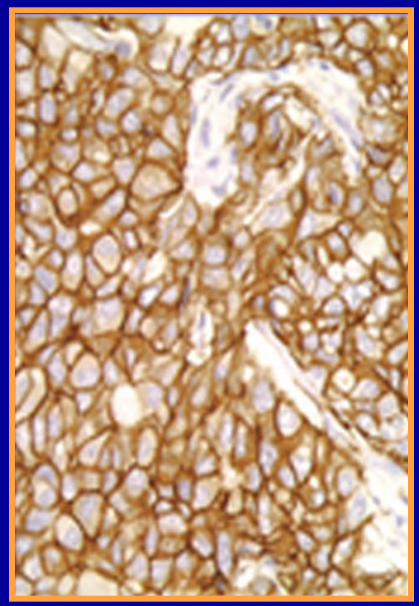
Negative



FISH

IHC 2+





IHC 3+

Positive

= CEP17 (control gene)

= HER2 gene

FISH ratio = number of red signal (HER2 gene number) / number of green signal (CEP17 gene number)

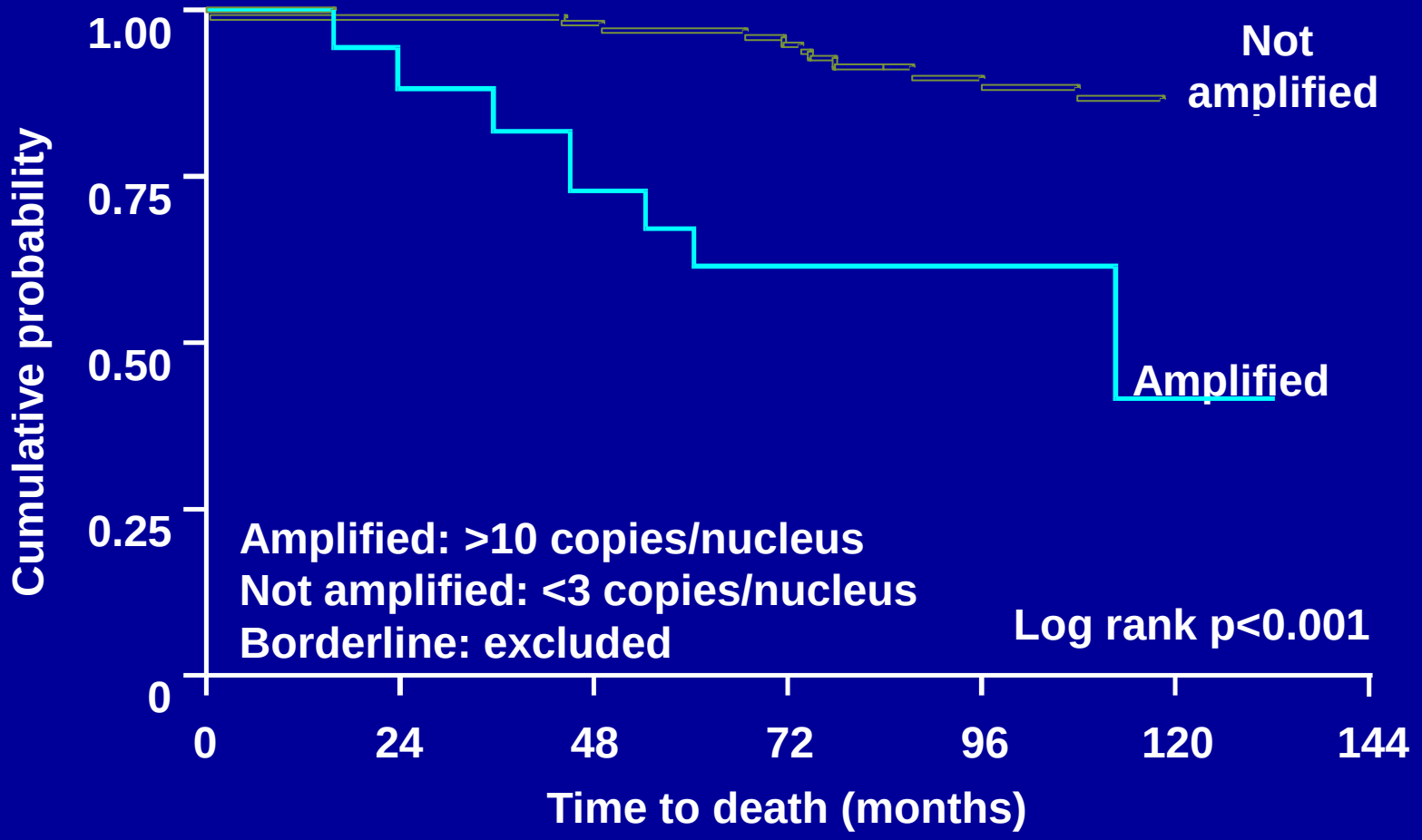
Receptor subtypes in breast cancer

Triple receptor status	EBC %	MBC %	BM %
ER or PR+, HER2-	57.6	45.7	18.2
ER or PR+, HER2 +	13.5	13.1	15.0
ER -, PR-, HER2+	12.7	16.4	29.4
ER -, PR-, HER2–	16.1	24.9	37.3

(8/2001 ~ 4/2006 at NCC)

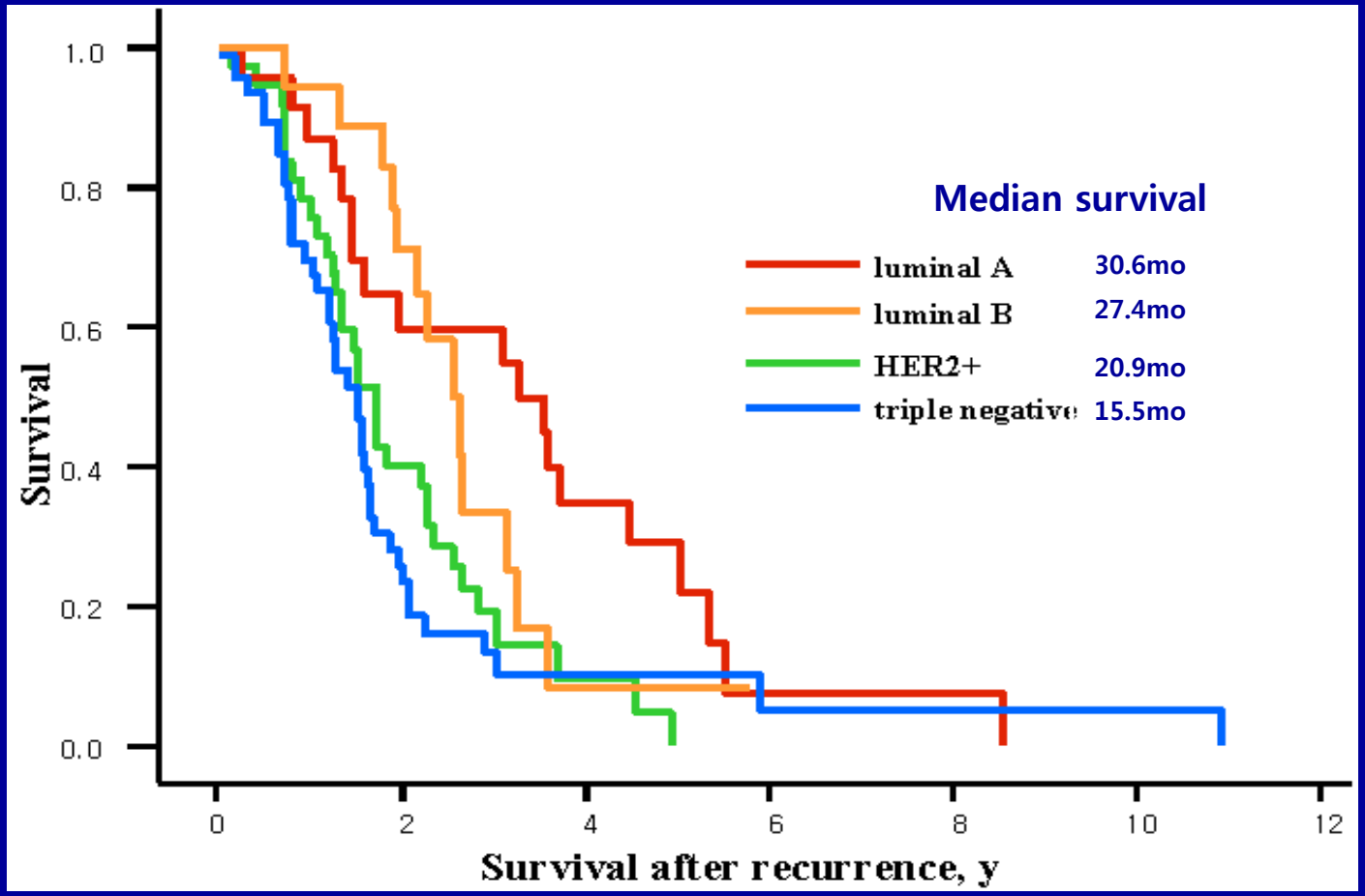
Nam BH et al. Breast Cancer Res 2008, 10:R20

Survival of node-negative BC patients related to HER2 status



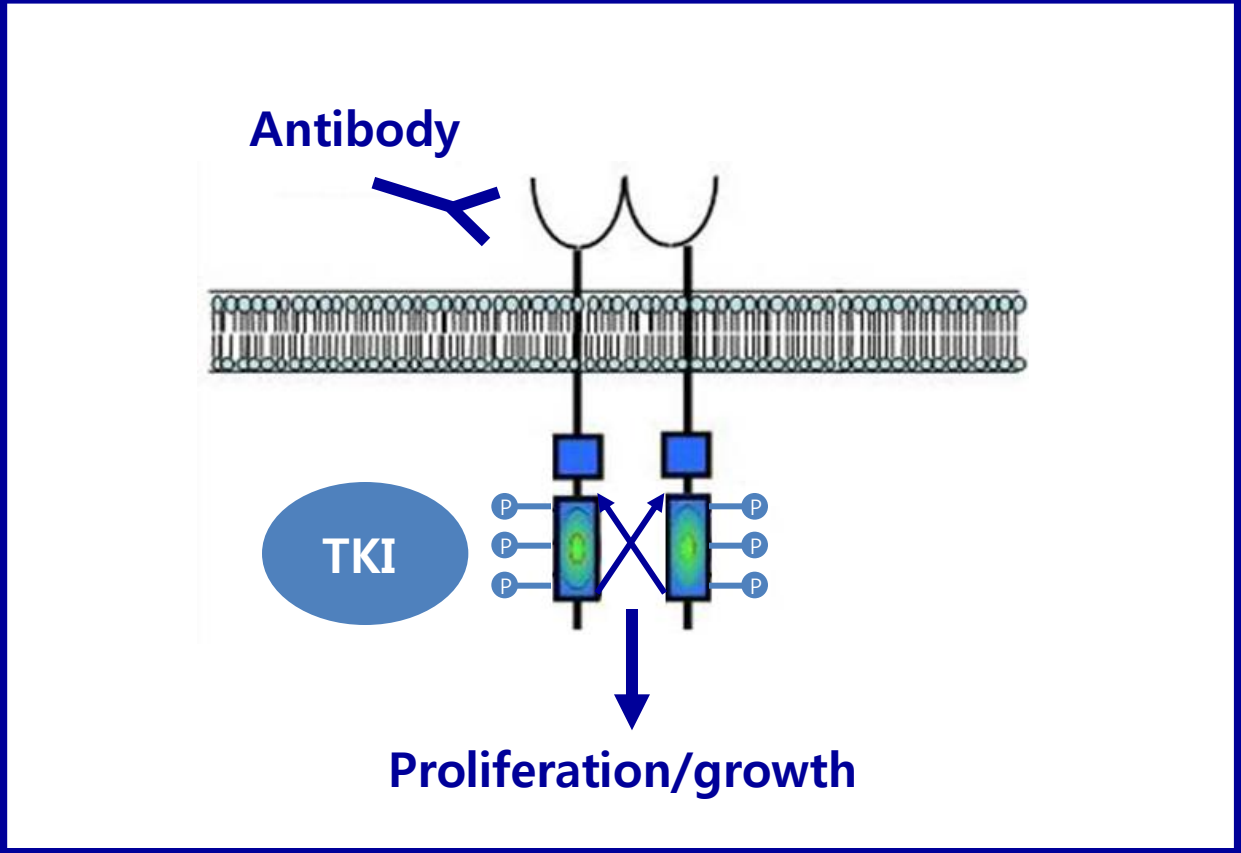
Ross and Fletcher. *Stem Cells.* 1998;16: 413–428.

Kaplan-Meier survival curves after metastasis according to receptor status

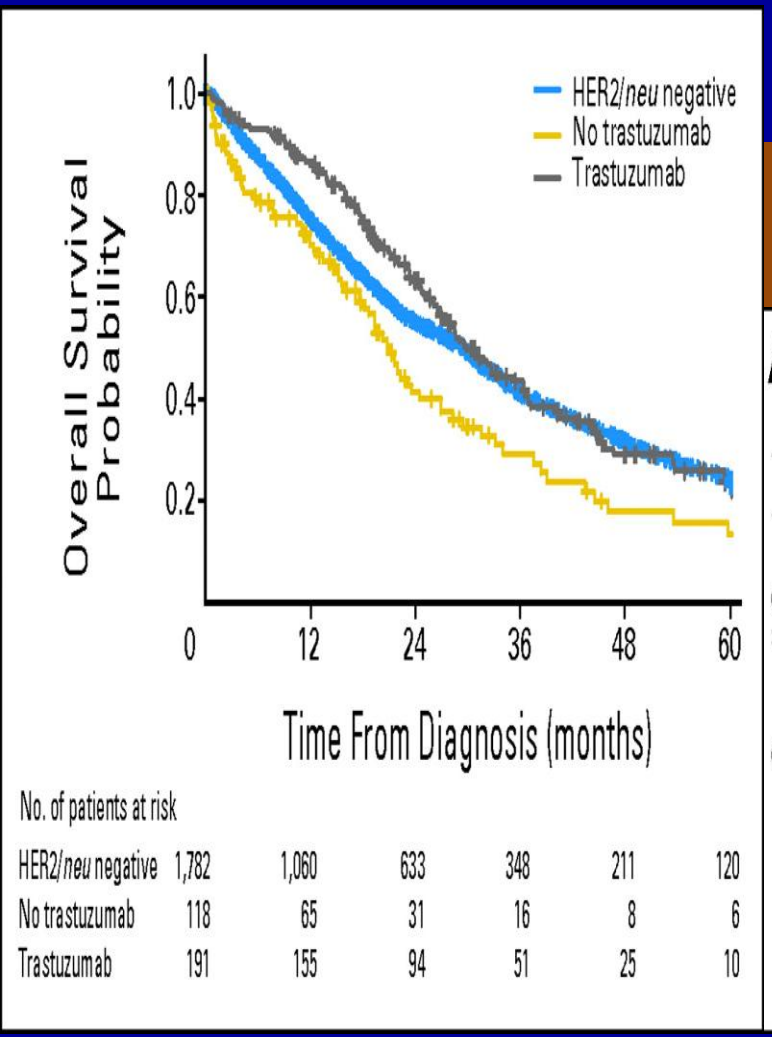


Nam BH et al Breast Cancer Res 2008, 10:R20

HER2 targeted agents: Trastuzumab and Lapatinib



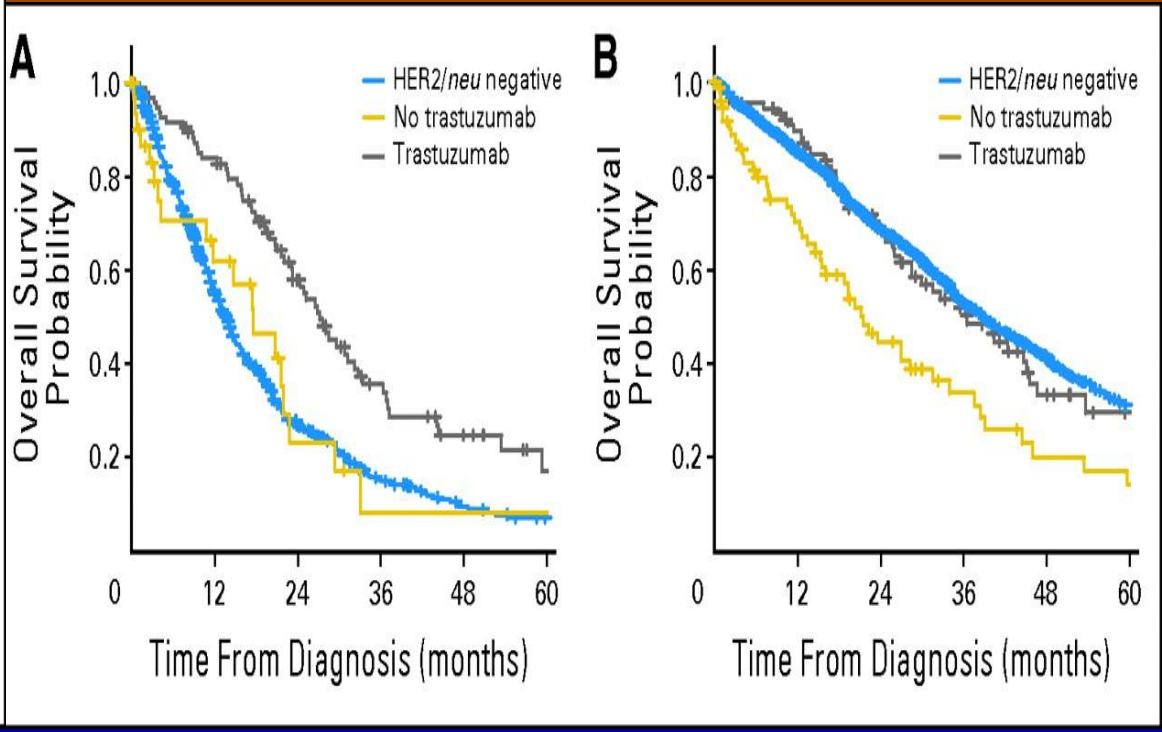
Overall survival by trastuzumab treatment



No. of patients at risk

HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

(A) HR-negative disease (B) HR-positive disease



Dawood et al. JCO 2010;28:92–98.

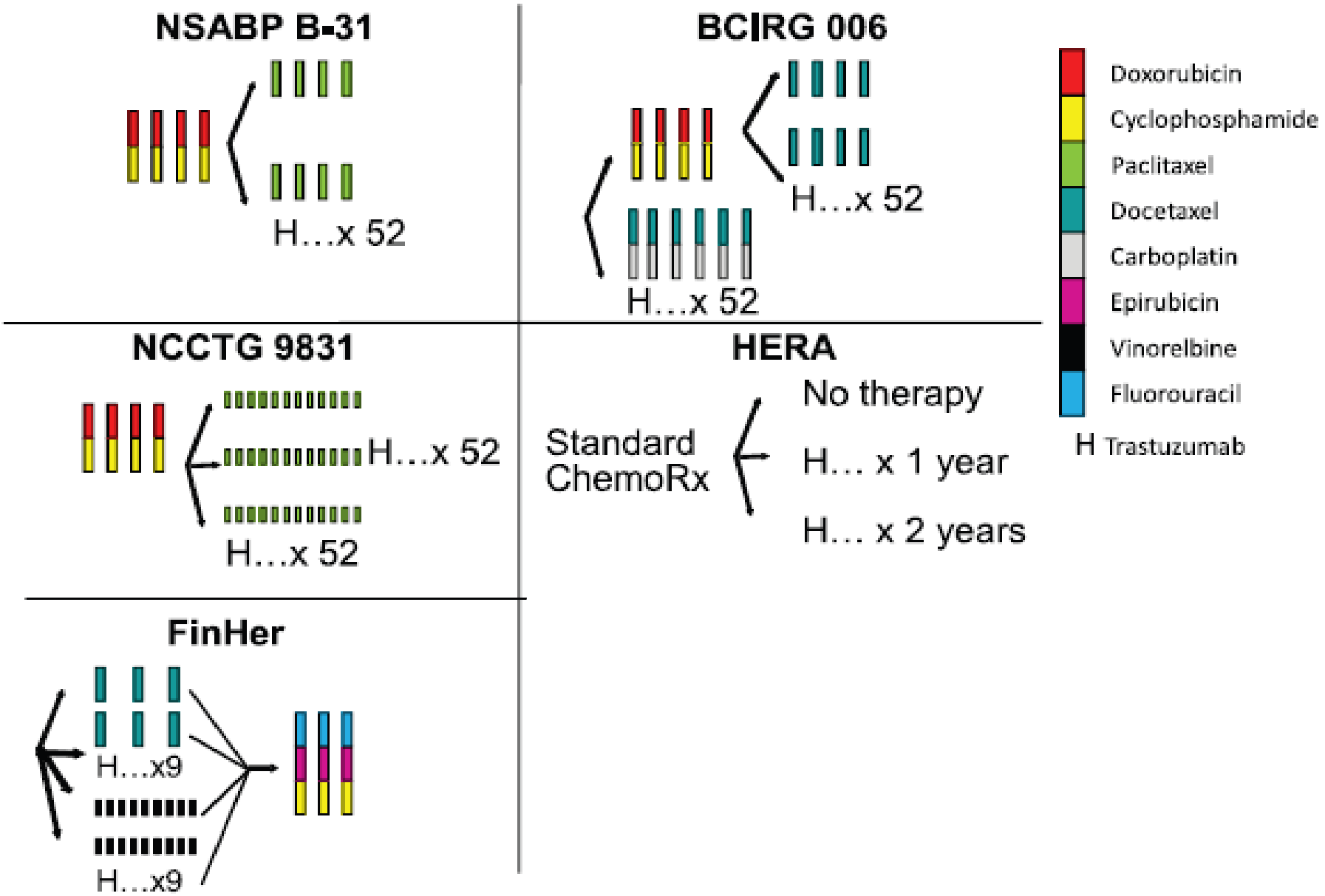
2) Anti-HER2 therapy in adjuvant setting

- Anti-HER2 therapy: trastuzumab
- Tumor <1cm, -LN
- Dual targeting

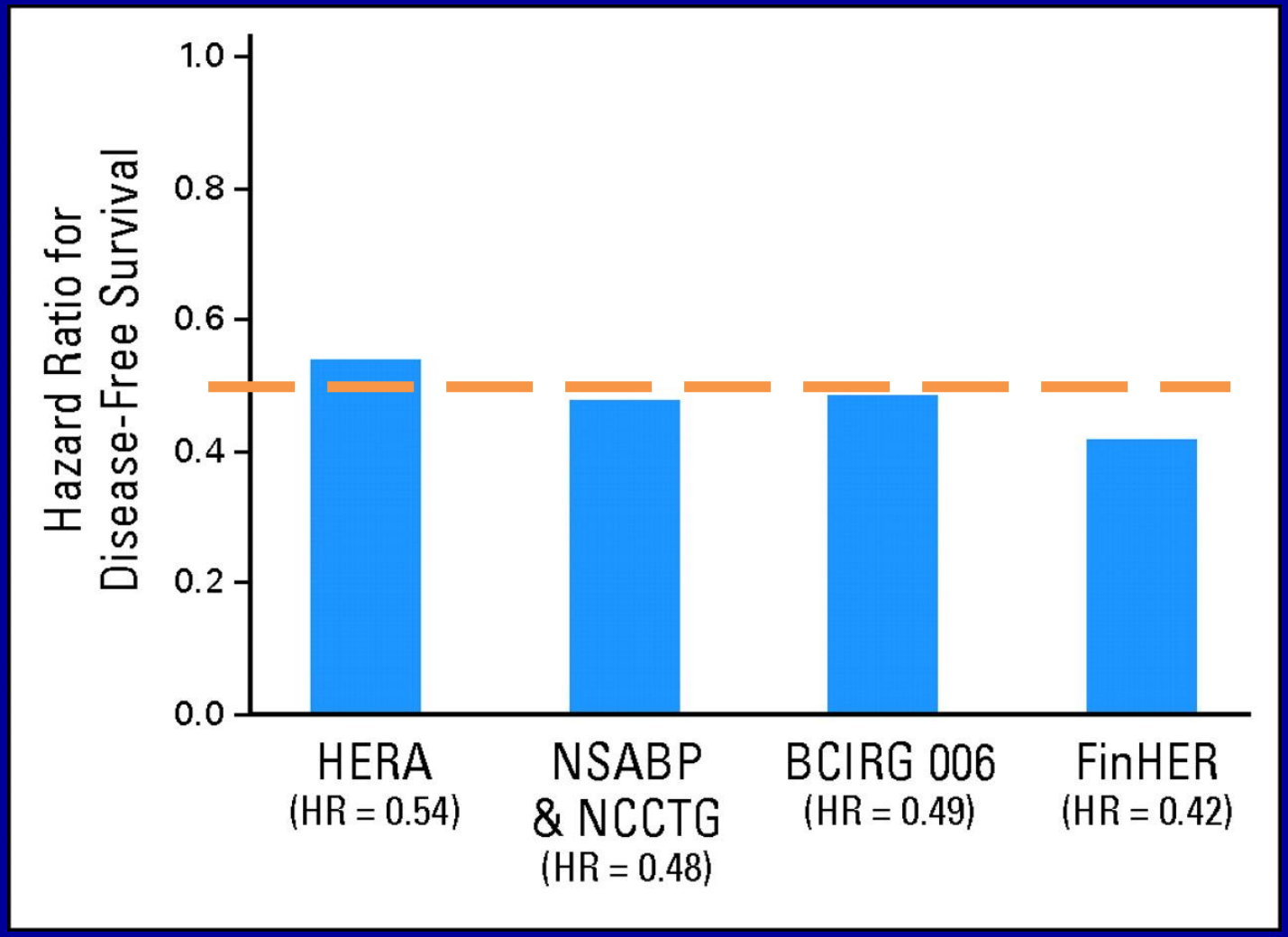
Adjuvant Therapy Trials with Trastuzumab and Chemotherapy

Group/Trial	Accrual	Design
NSABP B31	2,043	AC X 4 → P X 4 q 3 week AC X 4 → P X 4 q 3 week + H weekly X 1 year
NCCTG N9831	2,766	AC X 4 → P X 12 weekly AC X 4 → P X 12 weekly + H 1 year (concur with P) AC X 4 → P X 12 weekly + H 1 year (after P)
HERA	5,090	Any acceptable chemotherapy Chemotherapy → H q 3 week X 1 year Chemotherapy → H q 3 week X 2 year
BCIRG	3,222	AC X 4 → Docetaxel AC X 4 → D X 4 + H X 1 year DCb X 6 + H 1 year (H weekly with D → every 3 week)
FinHer	232	Vinorelbine or Docetaxel X 3 → FEC X 3 V or D X 3 + H X 9 weekly → FEC X 3

Adjuvant Trastuzumab

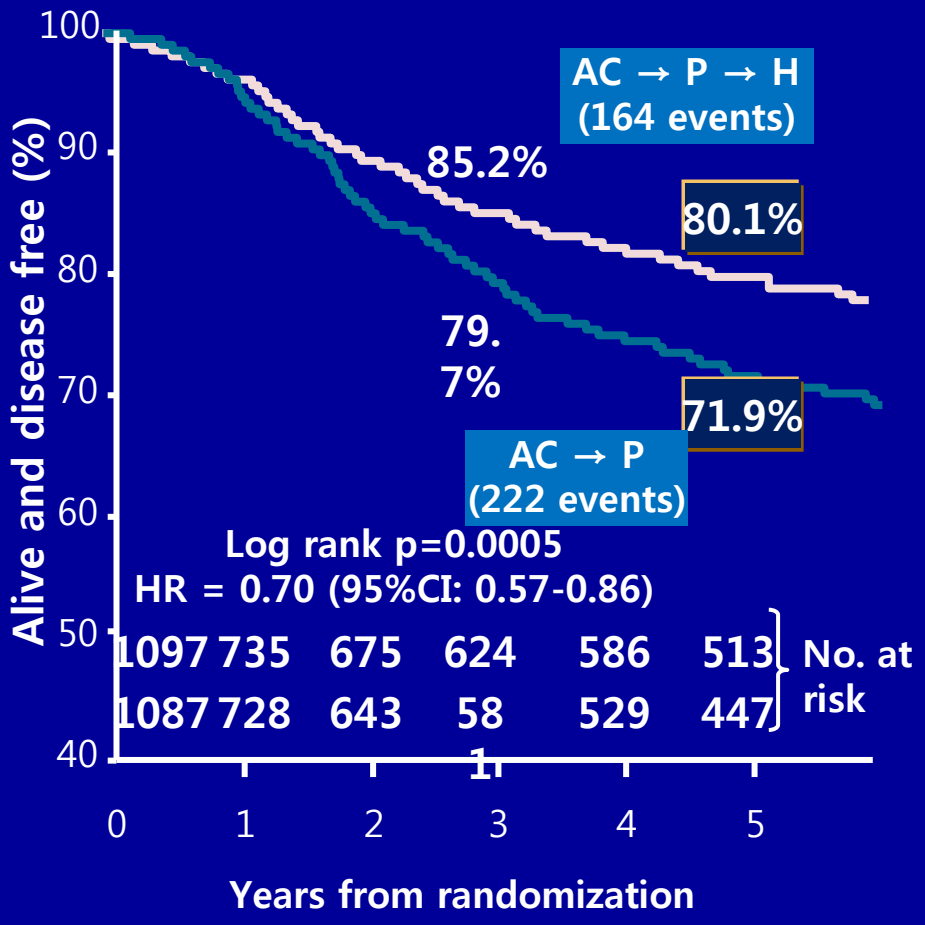


Overview of efficacy in adjuvant trastuzumab trials

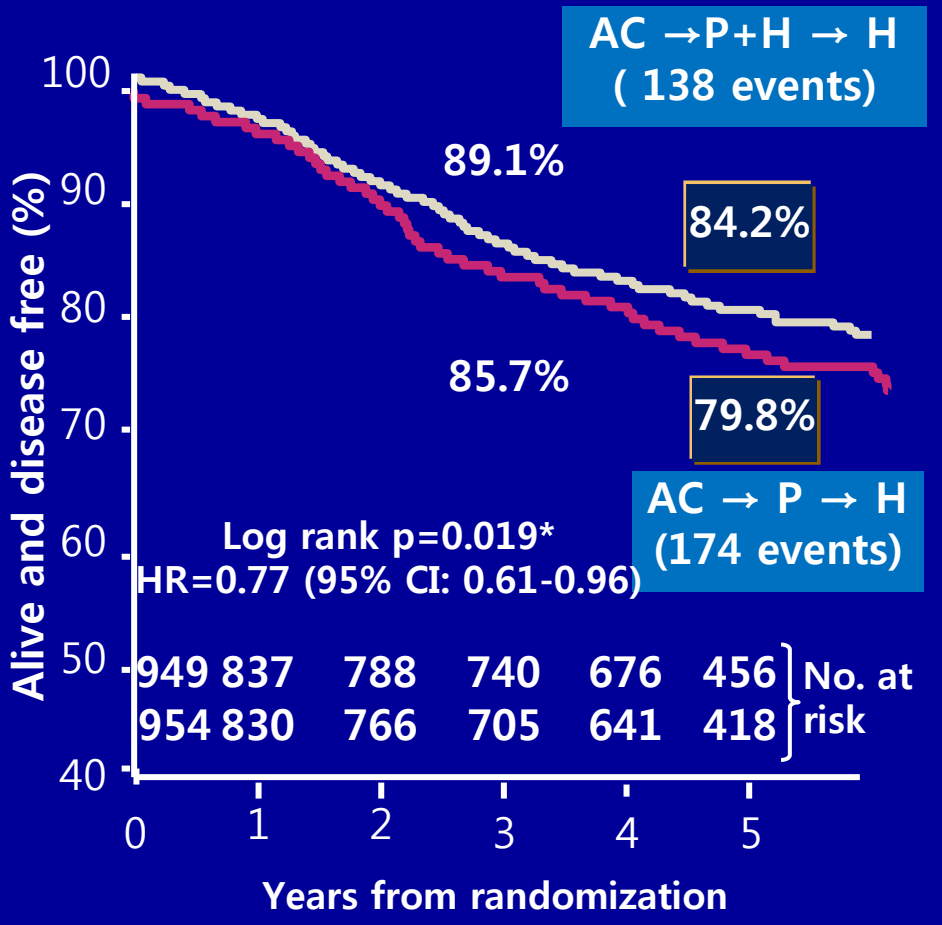


Telli M L et al. JCO 2007;25:3525-3533

N9831: Control vs Sequential
Median Follow-up 5.5 yr

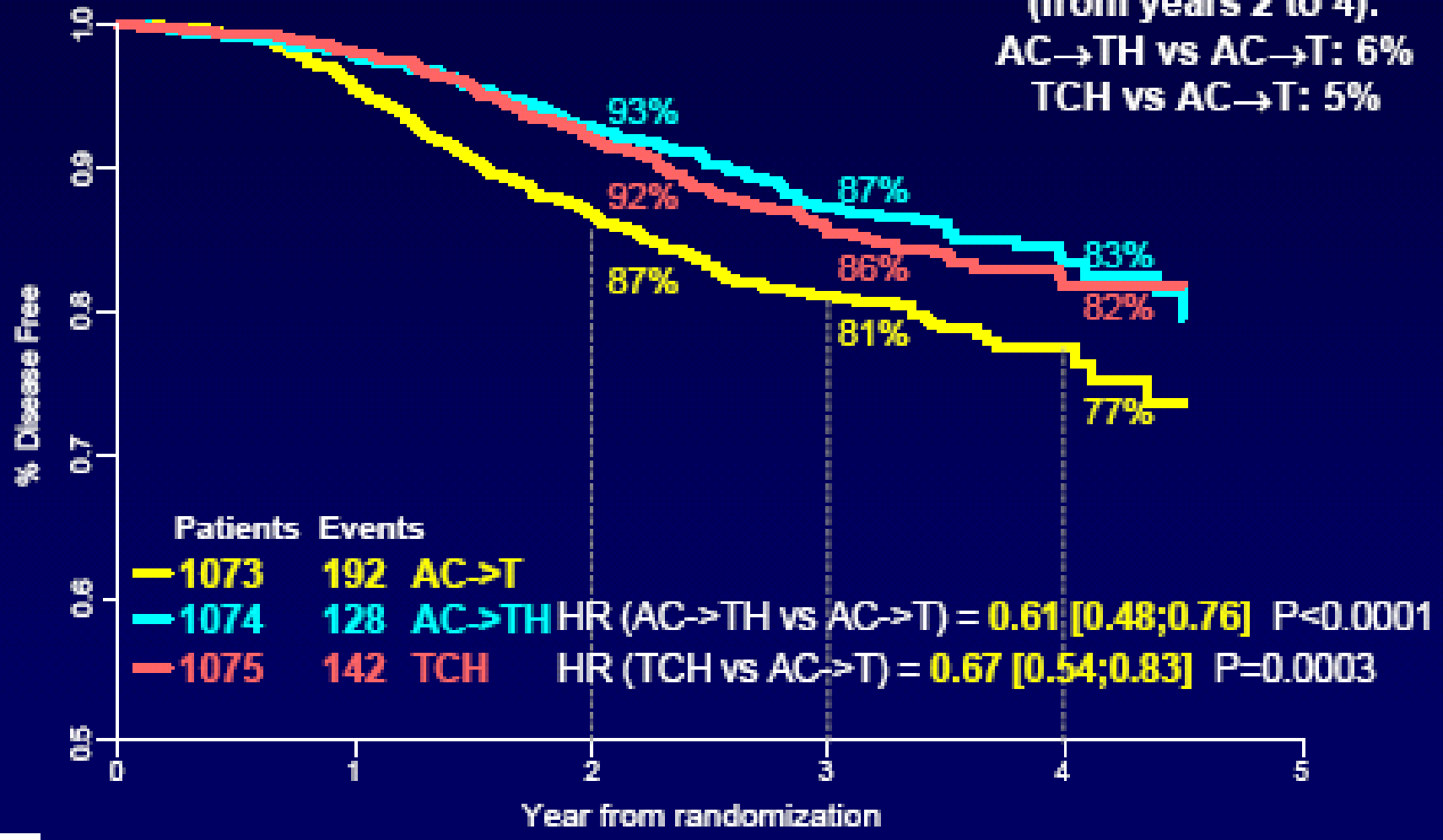


N9831: Sequential vs Concurrent
Median Follow-up: 5.3 yr



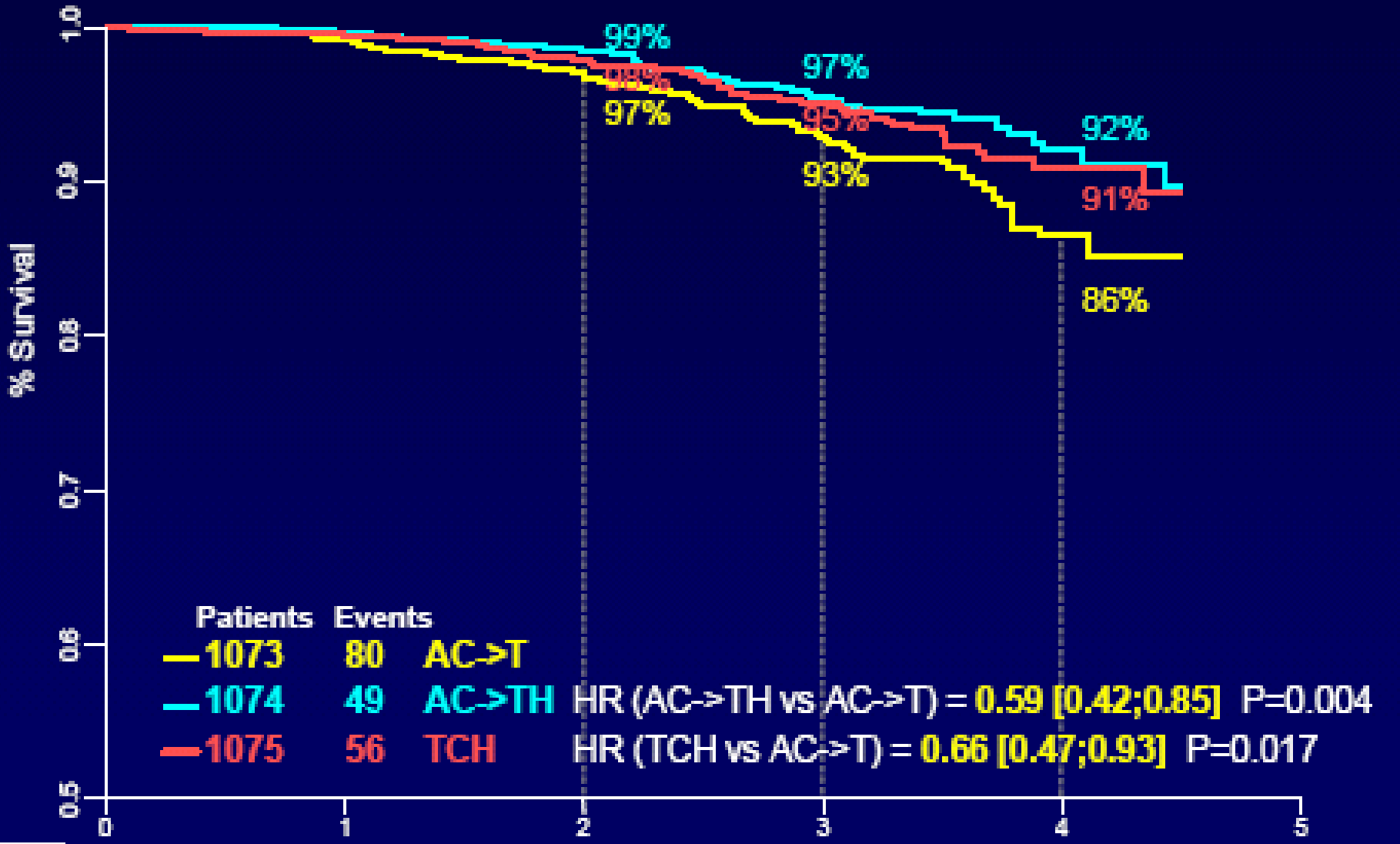
Perez EA, et al. SABCS 2009. Abstract 80.

Disease Free Survival - 2nd Interim Analysis



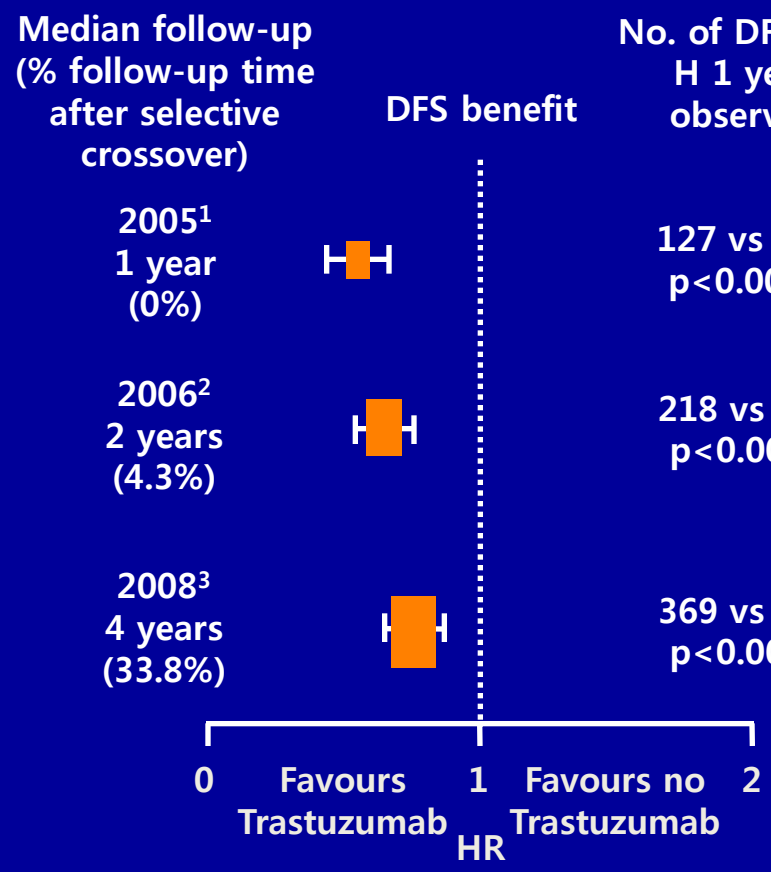
BCIRG 006
Slamon D., SABCS 2006

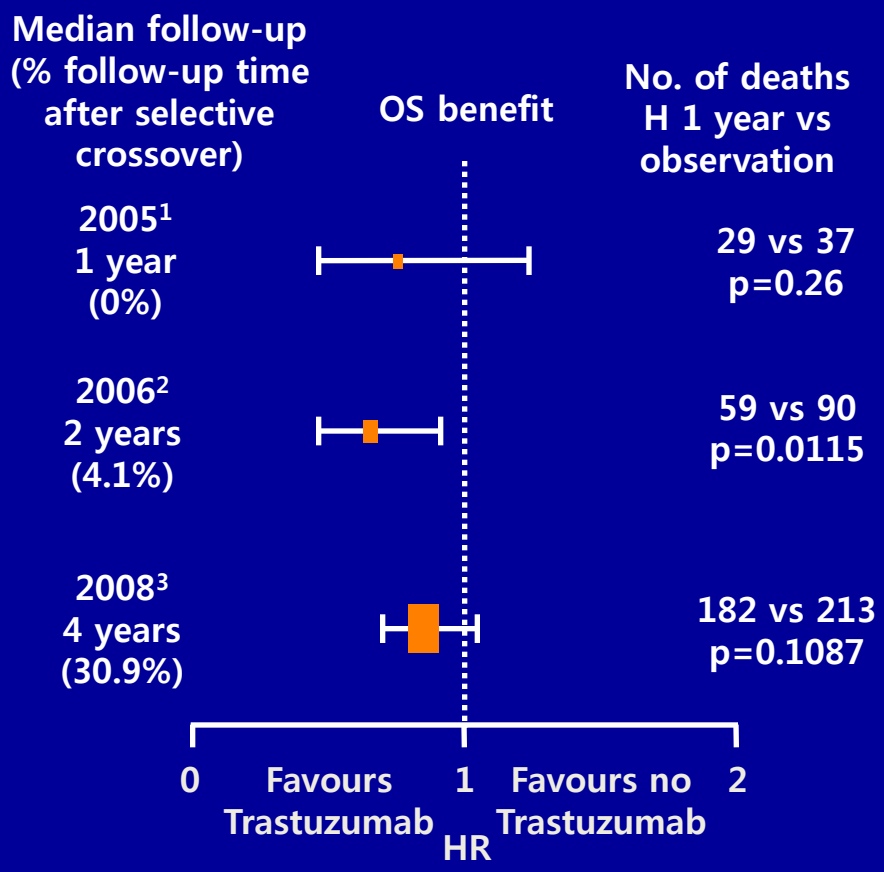
Overall Survival – 2nd Interim Analysis



BCIRG 006
Slamon D., SABCS 2006

HERA: DFS and OS Over Time





[1]Piccart-Gebhart et al NEJM 2005
[2]Smith et al Lancet 2007
[3]Gianni et al St Gallen 2009. Abstr S25.

Adjuvant trastuzumab trial results

Trial	ref		DFS HR	*p*	OS HR	*p*
NCCTG) N9831 (NSABP) B-31	Romond EH et al NEJM 2005 Perez EA et al JCO 2007	2 yrs 4 yrs	**0.48** **0.49**	**< 0.0001** **< 0.0001**	**0.67** **0.63**	**0.015** **<0.0004**
HERA	Piccart MJ et al NEJM 2005 Gianni L et al Breast 2009	2 yrs 4 yrs	**0.64** **0.76**	**< 0.0001** **< 0.0001**	**0.66** **0.85**	**0.0115** **0.108**
BCIRG 006	Slamon D et al SABCS 2006	AC-TH TCH	**0.61** **0.67**	**< 0.0001** **0.00003**	**0.59** **0.66**	**0.004** **0.017**
Fin HER	Joensuu H et al NEJM 2006 Joensuu H et al Breast 2009	3 yrs 5 yrs	**0.42** **0.65**	**0.01** **0.12**	**0.66** **0.55**	**0.15** **0.094**

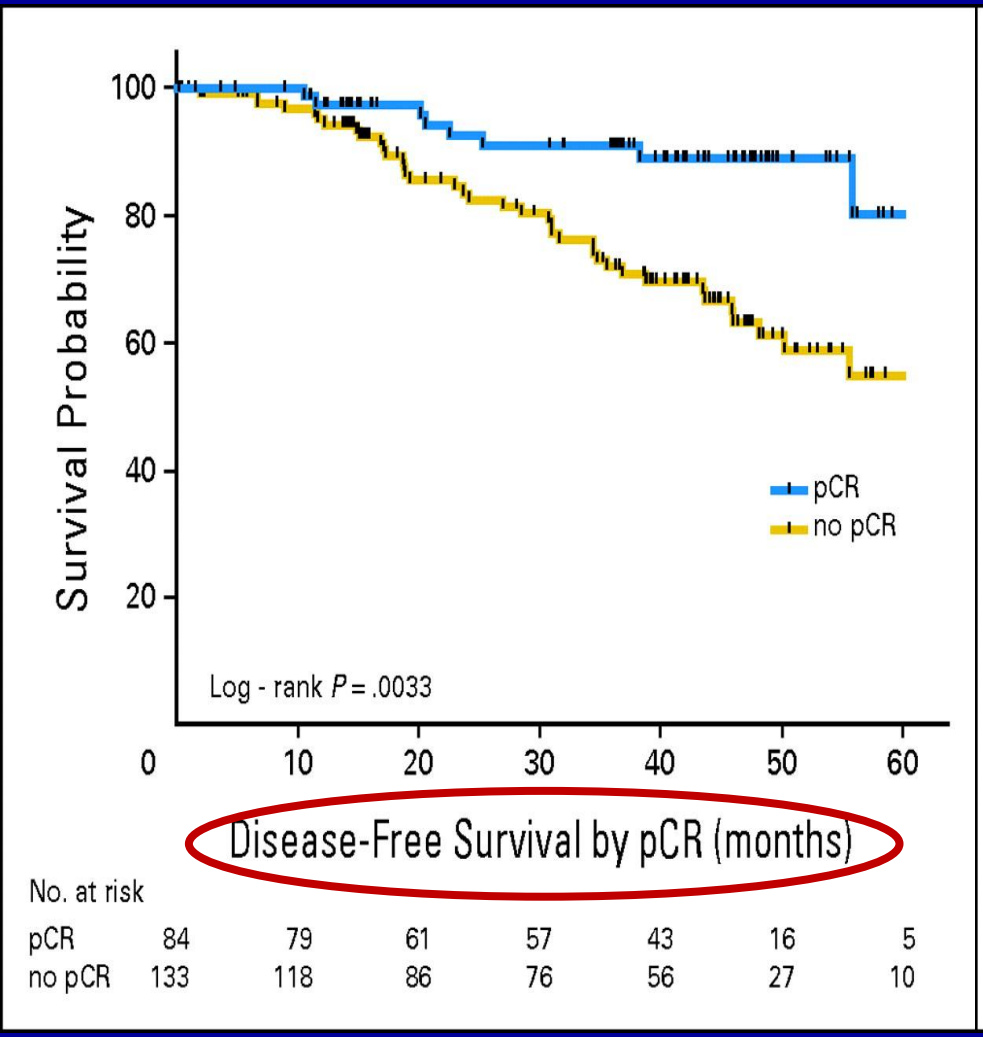
Neoadjuvant trials incorporating trastuzumab

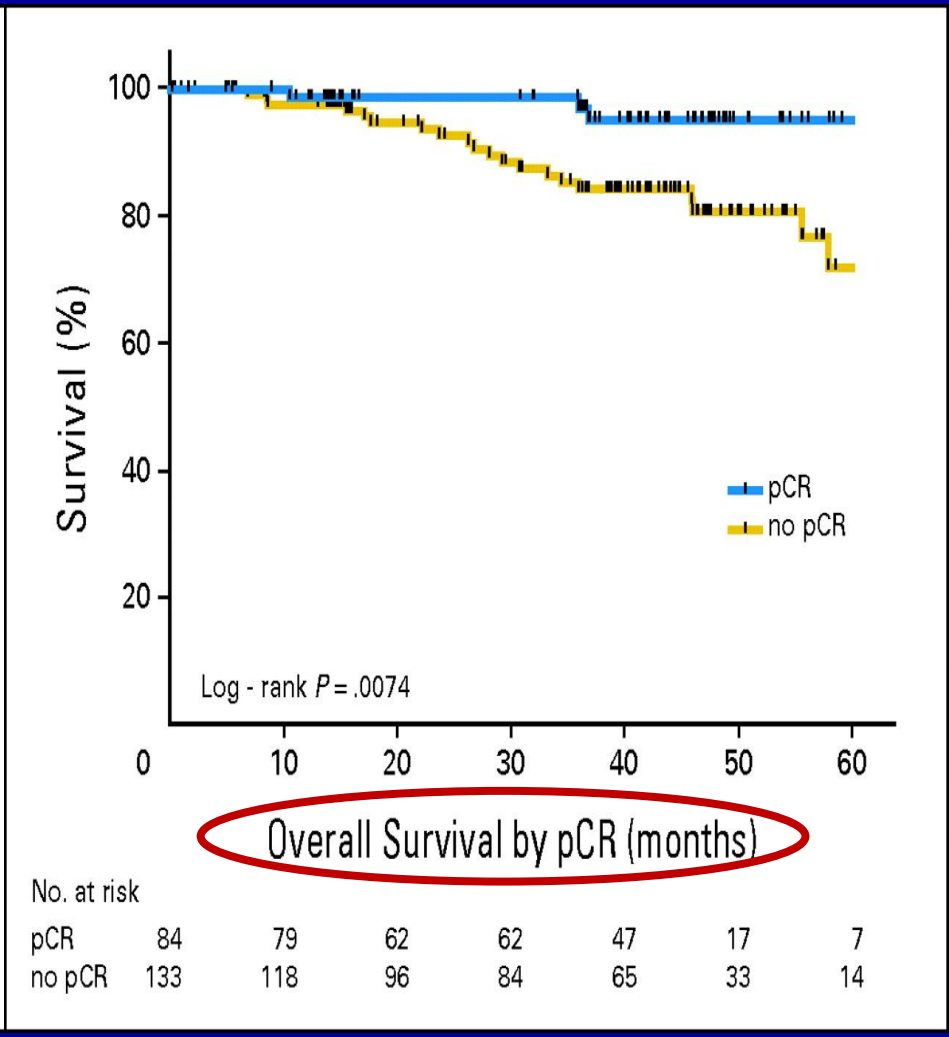
	PGH	P/FEC+H	DCH	TCH	NOAH
	(n=53) N (%)	(n=23) N (%)	(n=48) N (%)	(n=70) N (%)	(n=117) N (%)
pCR of the breast	37 (69.8)	15(65.2)	19(39.6)	33 (47.1)	50 (43)
pCR of the breast and LNs	31 (58.5)	15 (65.2)	8 (17.0)	27 (38.6)	45 (38)
Median age, (range)	43 (26-61)	52 (29-71)	51	47(24-67)	50
Primary tumor size (median) T1/T2 ($T \leq 5cm$) T3/T4 ($T > 5cm$)	5.3cm 30 (56.6) 23 (43.4)	NA 17 (73.9) 6 (26.1)	9.2 cm 0 48 (100)	4 cm 47(67) 23(33)	5.5 cm NA 71 (67)‡
LN involvement N0 N1 N2 or N3	 0 (0) 13 (24.5) 40 (75.4)	 10 (43.5) 12 (52.2) 1 (4.3)	 13 (27) 19 (40) 16 (33)	 33(47) 36(51) 1(1)	 16 (14) 50 (43) 50 (43)
Hormone receptor status Postitive (ER + or PR +) Negative (ER - and PR -)	24 (47.2) 28 (52.8)	13 (56.5) 10 (43.5)	26 (54) 22 (46)	NA	42 (36) 75 (64)
Grade 4 neutropenia	12 (22.6)	21 (91.3)	1 (2)*	1 (1.4)	3 (3)
Neutropenic fever	2 (3.8)	8 (34.8)	1 (2)*	2 (3) §	2 (2)

Im et al ASCO BCS, 2010 Buzdar et al J Clin Oncol 23:3676-3685. Hurley et al J Clin Oncol 2006; 24:1831-1838
Coudert et al J Clin Oncol 2007; 25:2678-2684. Gianni et al Lancet. 375:377-384.

TECHNO Trial of the AGO and GBG Study Groups

E90C x 4→Pac x 4 + trastuzumab (n=217)





Untch M et al. JCO 2011;29:3351-3357

Dual HER2 targeting neoadjuvant with trastuzumab and lapatinib

Trial	Treatment	N	Trastuzumab	Lapatinib	Combination
NEOALTTO	Paclitaxel x 12	450	29.5%	24.7%	51.3%;
CHER-LOB	Paclitaxel x 12 → FEC x 4	115	26%	28%	43%
US Oncology	FEC x 4 → Paclitaxel x 12	78	54%	45%	74%
Dual HER2 target	No chemo for HR- Letrozole for HR+	64	NA	NA	40% in HR- 21% in HR+

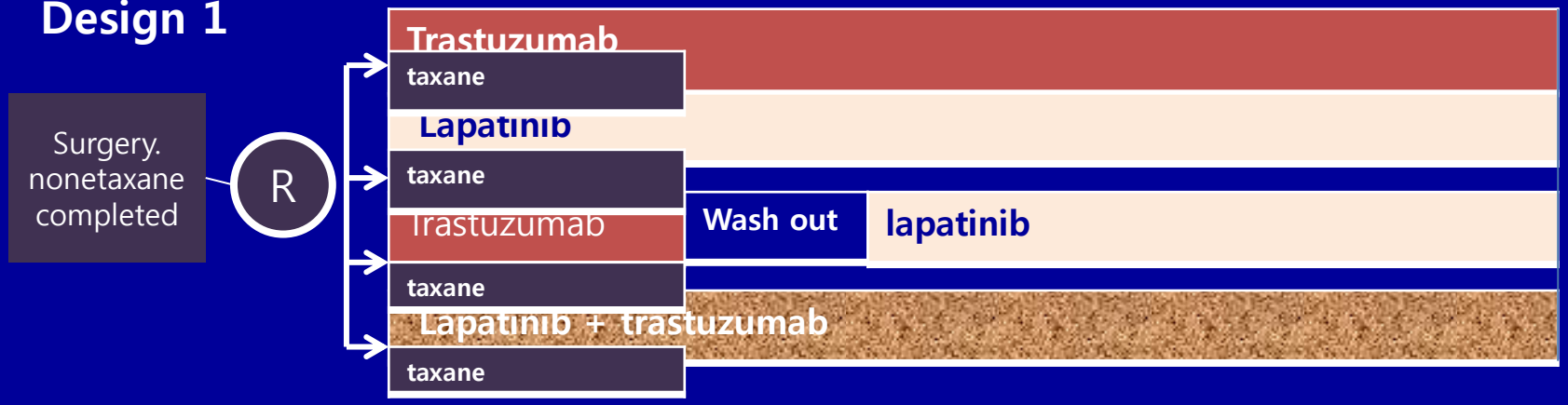
- Some patients achieve pCR w/o chemotherapy
- Final validation requires DFS results

NEOALTTO, SABCS 2010

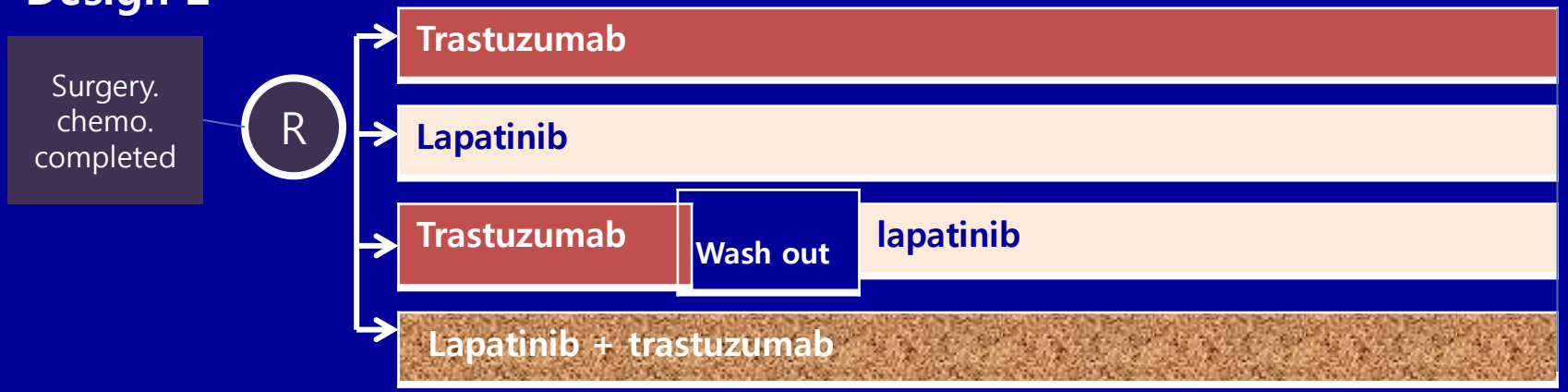
ASCO 2011,abst. 505, 506,507

ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Option) Study Design

Design 1

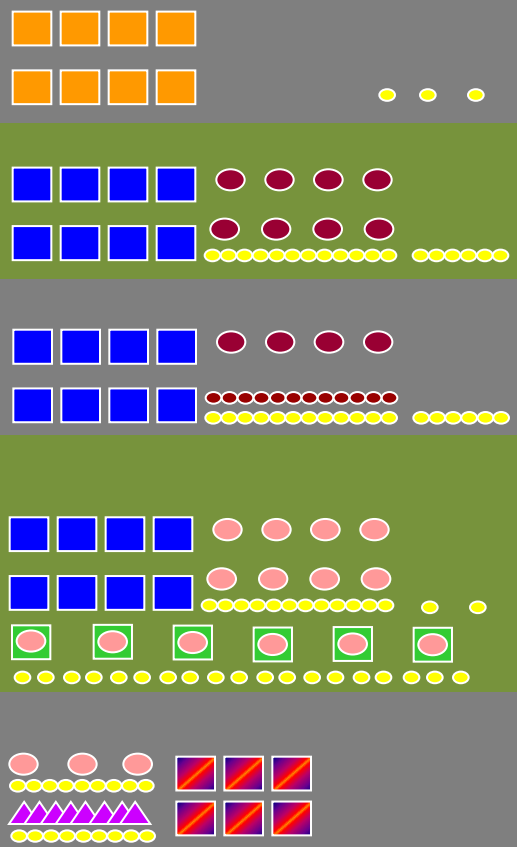


Design 2



Adjuvant Trastuzumab BC Trials

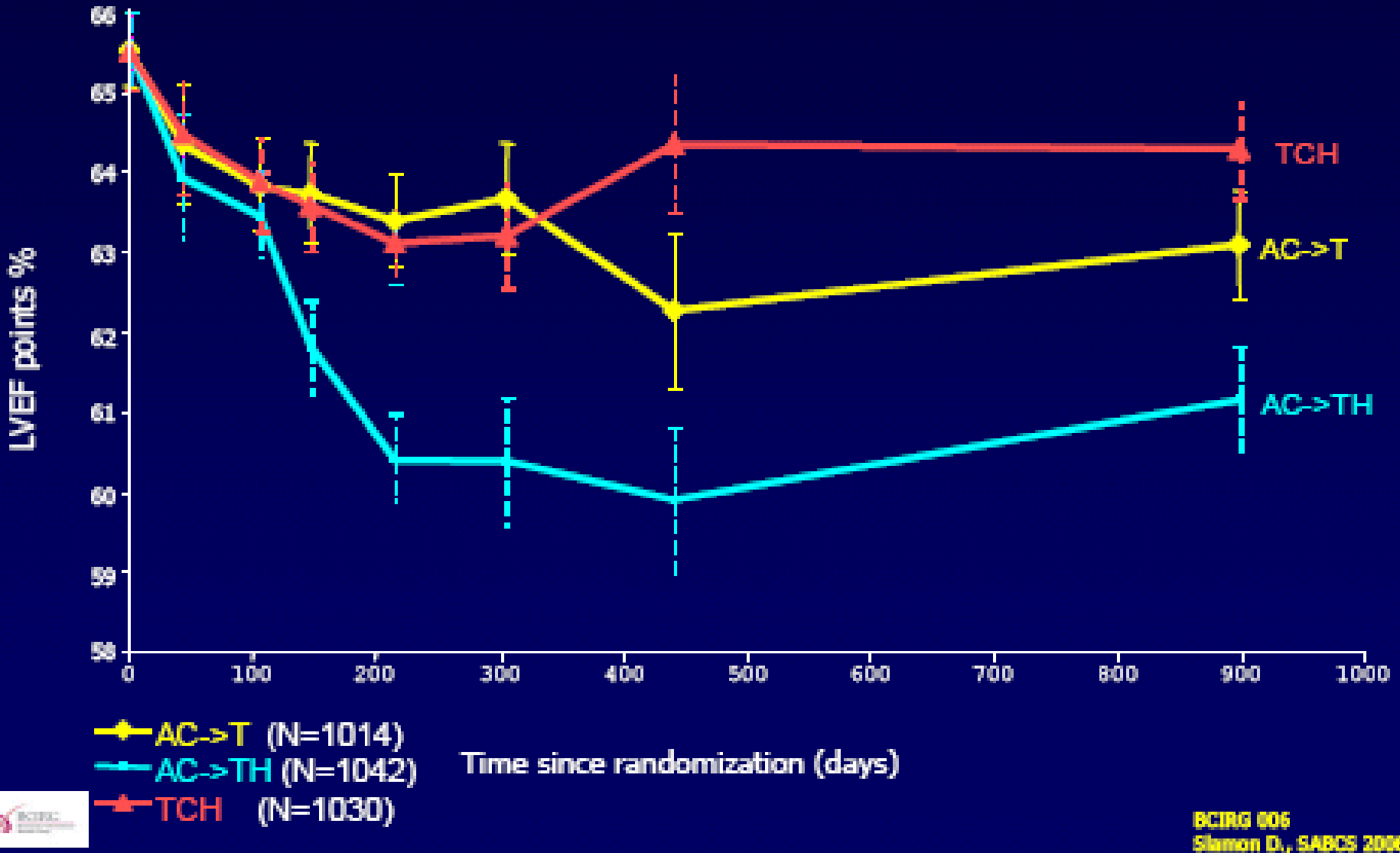
		Severe CHF	Systolic Dysfunction
HERA			
CT		0.6%	3.0%
CT → Trast			
NSABP B-31			
AC → Ptx		3.6%	15.9%
AC → Ptx+Trast			
NCCTG N 9831			
AC → Ptx		2.5 / 3.3%	14 / 17 %
AC → Ptx+Trast			
BCIRG 006			
AC → Docet		1.9 %	18.1 %
AC → Docet+Trast		0.4 %	8.6 %
TC+Trast → Trast			
FinHER			
Docet → +/- Trast		0 %	3.5 %
Vinblast → +/- Trast			



Risk factors for CHF:
Major: Hypertension
Other: age > 50, a "low normal" LVEF, and concurrent or prior anthracycline tx

Mean LVEF - All Observations

2nd Interim Analysis



BCIRG 006
Slamon D., SABCS 2006

3) Anti-HER2 therapy in metastatic setting:

- Rebiopsy?
- MBC: pivotal trial; mono or combination
- Trastuzumab or lapatinib by checking changes in the signaling pathways?

Rebiopsy of liver metastasis

1,250 sono-guided liver biopsies (1995 to 2008)

→ 255 matched primary and liver tissue samples for ER, PR, HER2 status

HER2: 13.9% discordant

- 31.5% of HER2 + primary tumor → HER2 - on metastasis biopsy
- 5.9% of HER2 – primary tumor → HER2 + on metastasis

ER: 14.5% discordant

- 25.9% of ER – primary tumor → ER + on metastasis
- 11.2% of ER + primary tumor → ER - on liver metastasis

Lindström **et al at the European Multidisciplinary Cancer Congress 2011**

Which of the following treatments would you recommend for patients who recurred after completion of adjuvant trastuzumab?

1. Rechallenge with trastuzumab + chemotherapy

2. Lapatinib and capecitabine

3. Trastuzumab and lapatinib

4. Clinical trial of trastuzumab or lapatinib + taxane

5. Clinical trial of new HER2-targeted agent (eg, pertuzumab + trastuzumab, trastuzumab-DM1, neratinib)

6. Clinical trial of everolimus in combination of trastuzumab and paclitaxel (BOLERO-1)

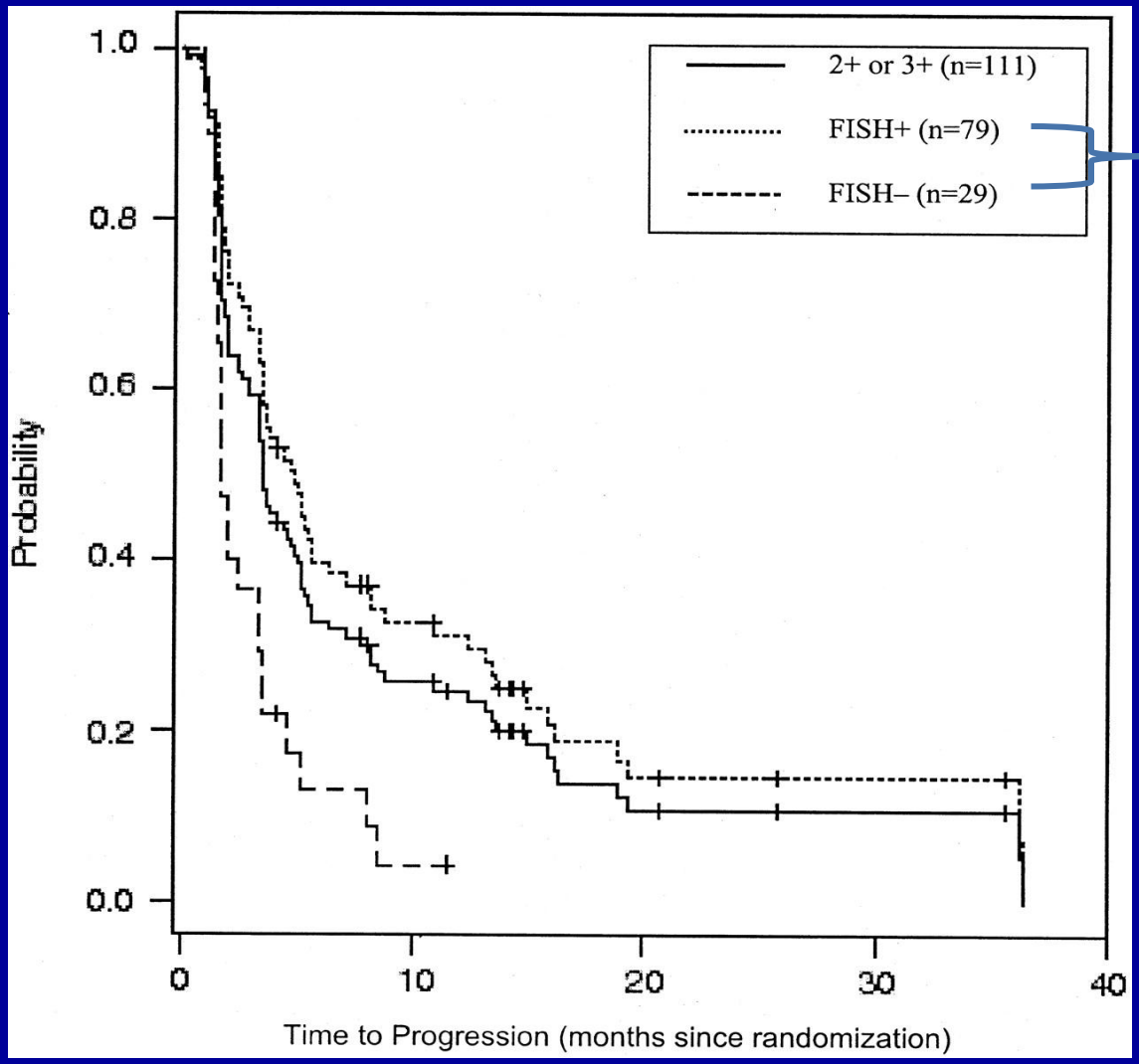
7. Clinical trial of vinorelbine + trastuzumab or BIBW 2992

Trastuzumab monotherapy in first-line treatment

	Objective Response		Clinical Benefit	
	No.	%	No.	%
All patients, n = 111 (95% CI)	29	**26** (18.0-34.3)	42	**38**
Estrogen receptor, Positive, n = 52	12	**23**	19	**36**
Negative, n = 54	16	**30**	21	**39**
Progesterone receptor, Positive, n = 46	10	**22**	16	**35**
Negative, n = 57	18	**32**	24	**42**
Lung or liver metastases, n = 74	16	**22**	24	**32**
Disease-free interval, ≤ 12 months, n = 30	6	20	9	**30**
> 12 months, n = 81	23	28	33	**41**
Previous adjuvant doxorubicin, n = 57	18	32	23	41
***HER2,* 3+, n = 84**	29	**35**	40	**48**
2+, n = 27	0	0	2	7
FISH, Positive, n = 79	27	**34**	38	**48**
Negative, n = 29	2	7	3	10

Vogel C L et al. JCO 2002;20:719-726

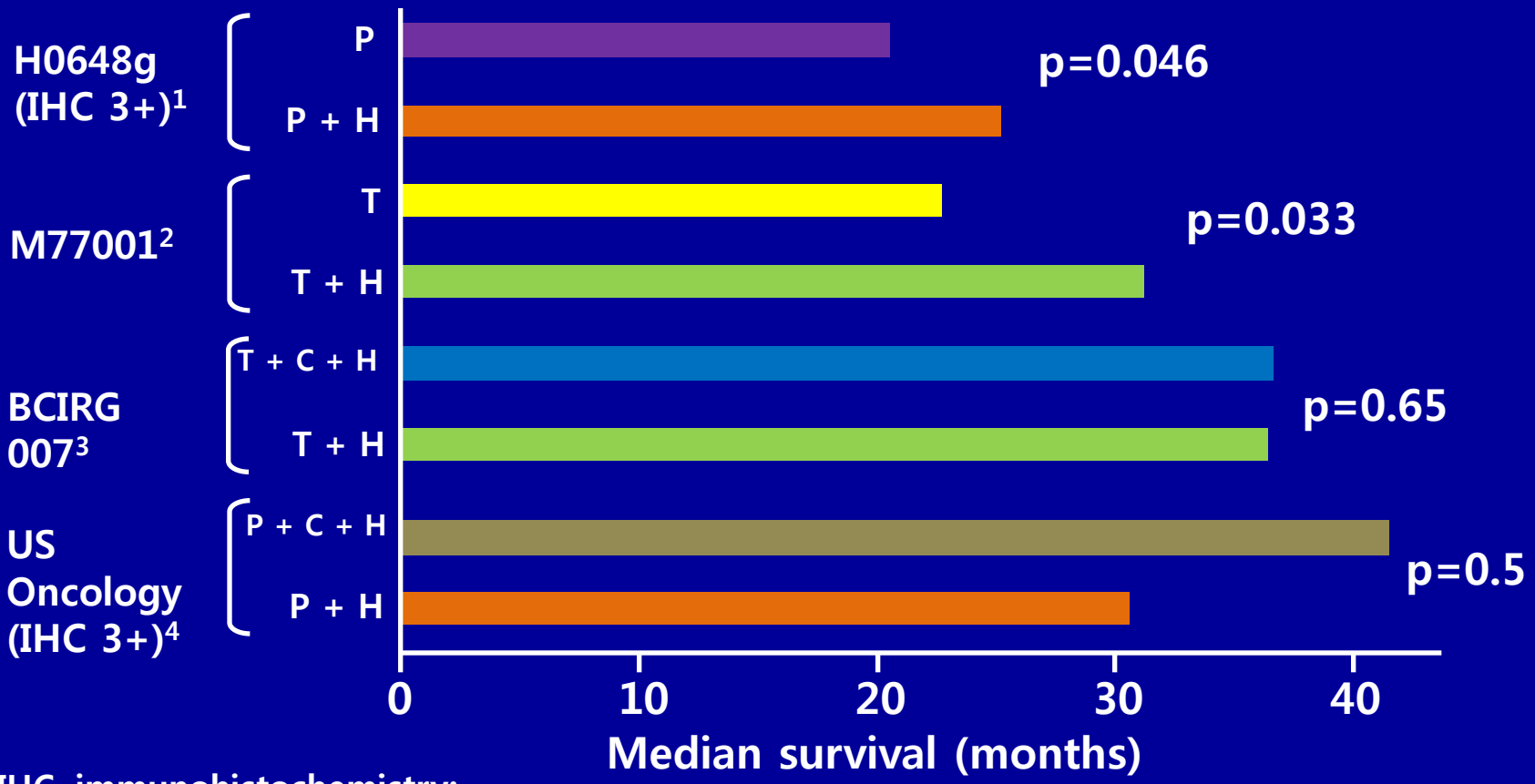
Kaplan-Meier estimates of TTP



$P < .0001$

Vogel C L et al. JCO 2002;20:719-726

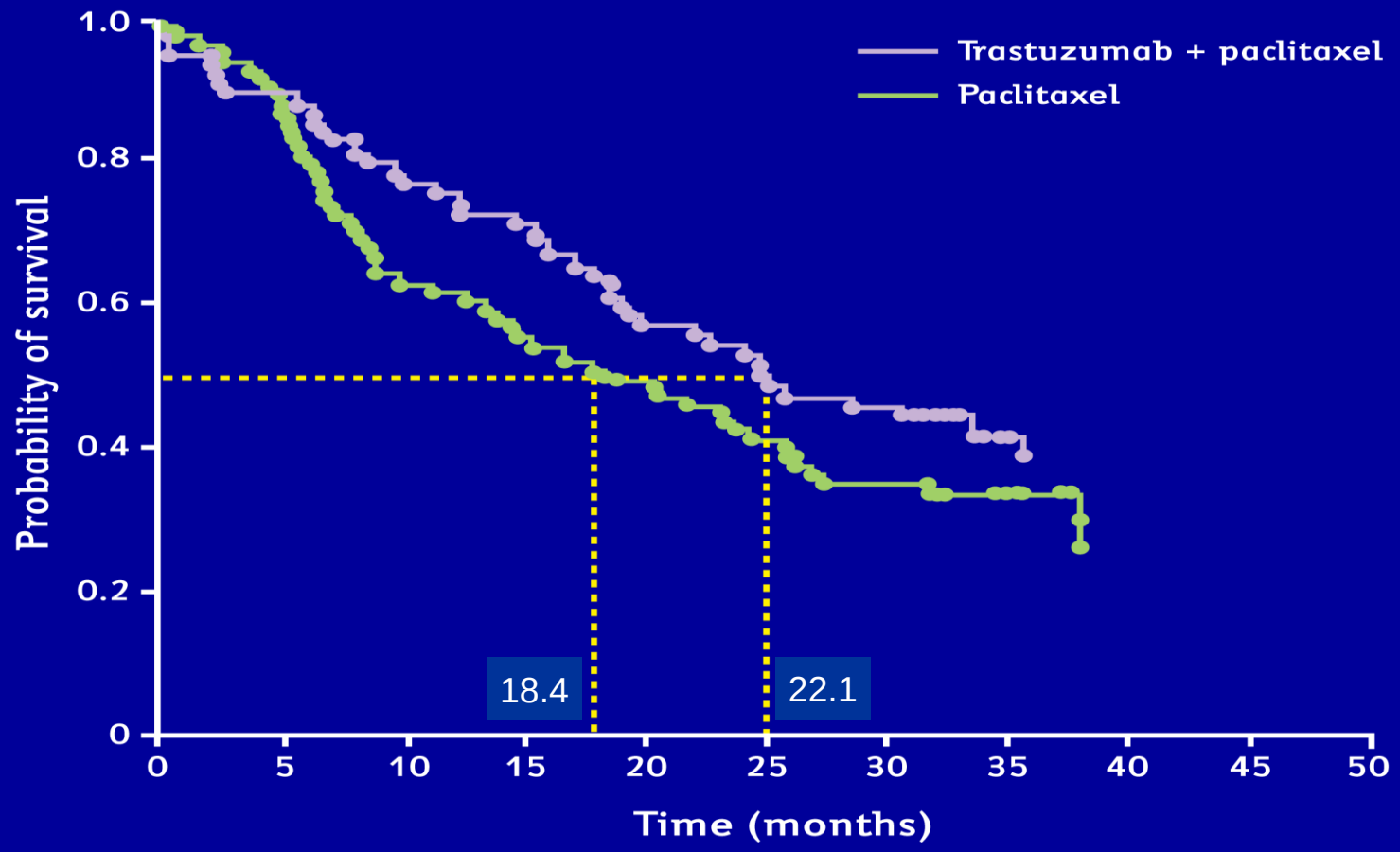
Trastuzumab provides proven OS benefit in first-line HER2-positive MBC



IHC, immunohistochemistry;
P, paclitaxel (Taxol); H, trastuzumab (Herceptin);
T, docetaxel (Taxotere); C, carboplatin

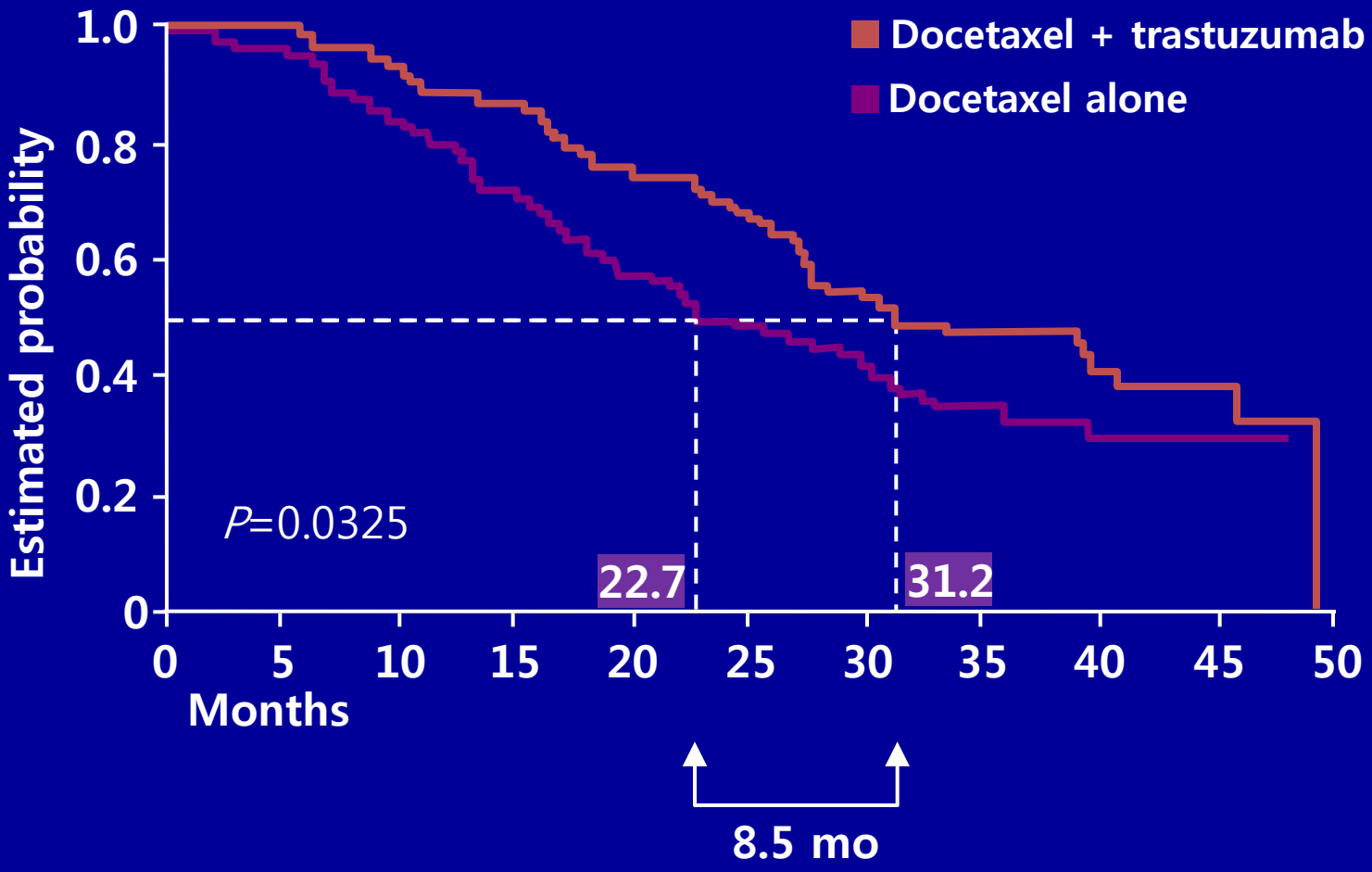
1. Slamon et al. NEJM 2001; 2. Marty et al. JCO 2005;
3. Pegram et al. JCO 2007; 4. Robert et al. JCO 2006

Trastuzumab – 1st targeted agent for ErbB2-positive Disease



Slamon et al. N Engl J Med 2001;344:783–9

First-Line Docetaxel ± Trastuzumab in MBC: Survival



Marty et al. J Clin Oncol. 2005;23:4265.

Primary and acquired resistance to first line trastuzumab therapy:

Trial	Treatment	ORR (%)	Median TTP (months)
(M77001) Marty et al, 2005[1] N=92	T + D vs D	61	11.7
(H0648g) Slamon et al, 2001[2] Smith et al, 2001[3] N=68	T + P vs P	49	7,1

*183 of 188 patients had received prior adjuvant chemotherapy and received T + P first-line for metastatic breast cancer; †Data are for retrospective subgroup of analysis of patients with ErbB2 IHC 3+ and treated with trastuzumab ± paclitaxel; ORR = overall response rate (complete or partial response); ORR = overall response rate; T = trastuzumab; D = docetaxel; P = paclitaxel

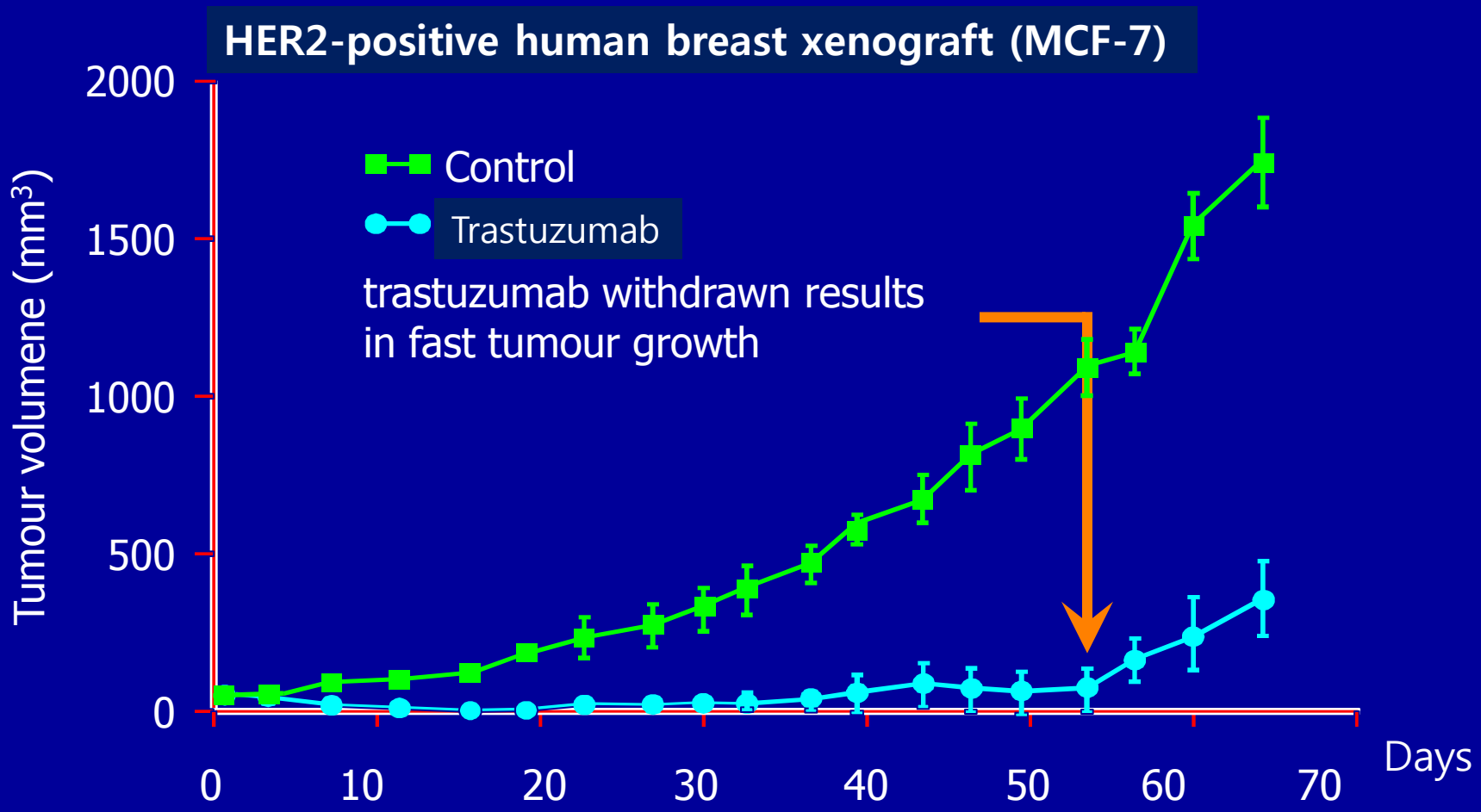
1. Marty et al. *J Clin Oncol* 2005;**23**:4265–74; 2. Slamon et al. *N Engl J Med* 2001;**344**:783–92;
2. 3.Smith et al. *Anticancer Drugs* 2001;**12(Suppl 4)**:S3–10

Which of the following treatments would you recommend for patients who progressed after first line trastuzumab?

1. Rechallenge with trastuzumab + chemotherapy
2. Lapatinib and capecitabine
3. Trastuzumab and lapatinib

Continuous suppression of HER2-signaling helps control tumour growth

- Overexpression of ErbB2 (HER2) is an early event in the development of breast cancer and is maintained **throughout the course** of the disease → **Continuous suppression of ErbB2 is needed**



Pietras R, et al. Oncogene 1998;17:2235–49

Clinical benefits from a 2nd trastuzumab-based regimen: non-randomised studies

Study	n	ORR, %	TTP, months
Montemurro et al 2006	40	18	6.3
Adamo et al 2007	26	23	9.0
Fountzilas et al 2003	80	24	5.2
Bartsch et al 2006	54	26	6.0
Bachelot et al 2007	17	29	NR
Metro et al 2007	37	29	6.7
Garcia-Saenz et al 2006	47	30	4.0
Gelmon et al 2004	65	32	6.0
Stemmler et al 2005	23	39	NR
Tokajuk et al 2006	14	50	5.1

ORR, overall response rate
TTP, time to progression; NR, not reported

GBG26: Trastuzumab + Capecitabine vs Capecitabine alone

Eligibility criteria

- Her2 +, locally/advanced/ metastatic BC
- PD during trastuzumab tx
  - Trastuzumab has to be given
  - previously (>=12 wks)
  - Tx free interval: maximum 6 wks
- No more than 1 palliative ctx
  - Taxanes/trastuzumab as 1st line
  - Trastuzumab alone or in combi w other 1st L ctx
  - Taxane/trastuzumab as adj tx
- LVEF >=50

RANDOMIZE

Capecitabine
2500 mg/m² d 1 – 14 q 22

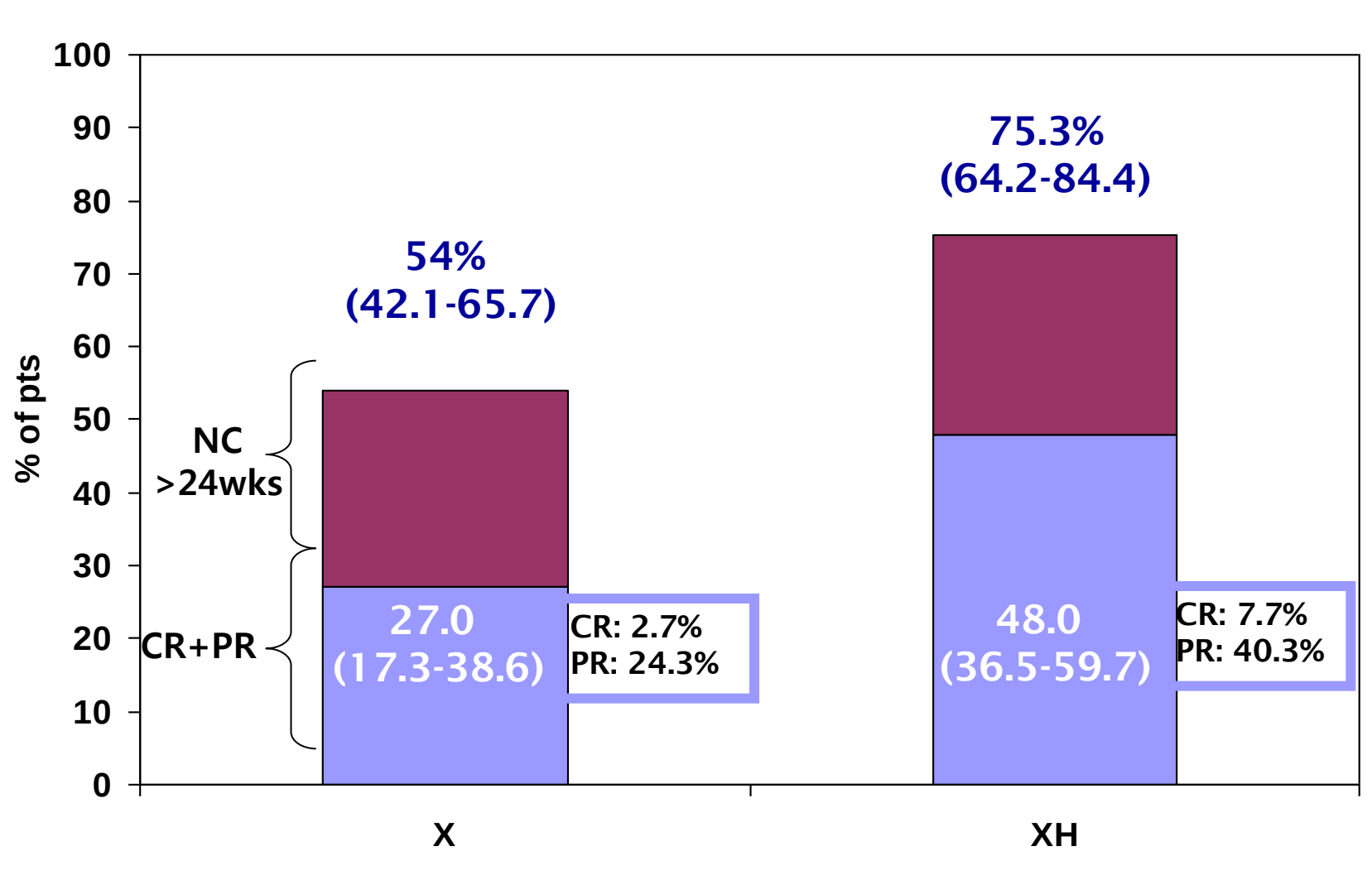
Capecitabine 2500 mg/m²/day, days 1-14 q 21 days
Continuation of Trastuzumab 6 mg/kg q22

N=482 (TTP from 4 to 5.1 mo)

- Primary objectives: TTP
- Secondary endpoint: Safety, ORR,Clinical benefit , OS

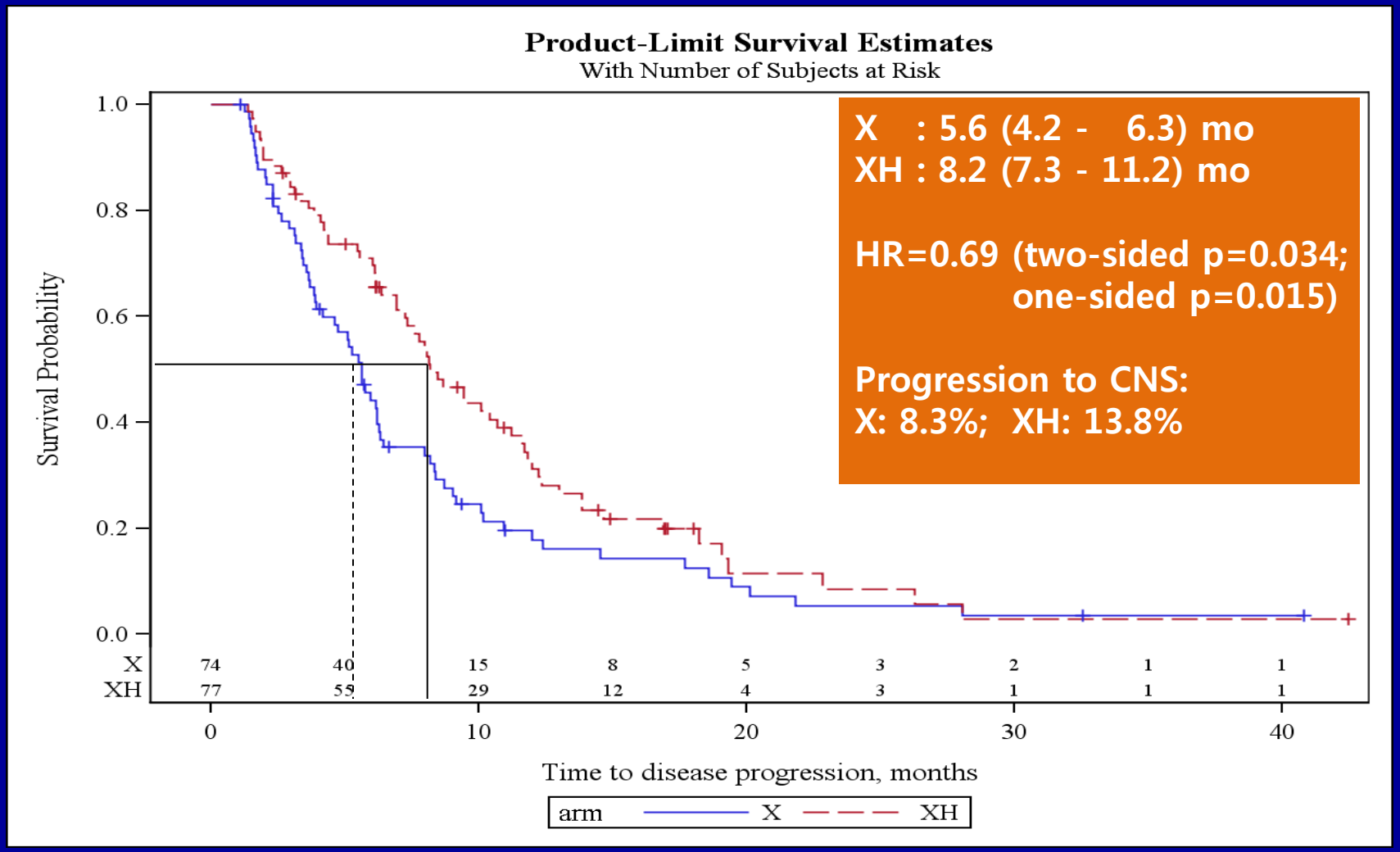
von Minckwitz G et al. J Clin Oncol 2008; 26;suppl; abstr 1025

Clinical Response



von Minckwitz G et al. J Clin Oncol 2008; 26;suppl; abstr 1025

Time To Progression



median follow-up: 15.6 mo

EGF100151: Phase III trial of capecitabine ± lapatinib in advanced or metastatic breast cancer

Eligibility criteria:

- Stage IIIB, stage IIIC with T4 lesion, or stage IV breast cancer that has progressed
- ErbB2 overexpression (IHC3+ or 2+ or FISH)
- Unlimited prior therapies, but no prior capecitabine
- Prior therapies must include:
  - Trastuzumab in metastatic setting
  - Anthracycline and taxane in either metastatic or adjuvant setting

RANDOMIZE

Arm 1

Lapatinib 1250 mg/day p.o.
Capecitabine 2000 mg/m^2/day, days 1-14
q 21 days

Arm 2

Capecitabine 2500 mg/m^2/day, days 1-14 *q 21 days*

Primary endpoint: TTP
Secondary endpoint: OS, PFS, ORR

Geyer C, et al. NEJM 2006;355:2733-2743.

Independent assessment efficacy results (ITT population)

End point	Lapatinib plus capecitabine (N = 163)	Capecitabine alone (N = 161)	Hazard ratio (95% CI)	P value
Median time to progression - mo	8.4	4.4	0.49 (0.34 - 0.71)	<0.001*
Median progression-free survival - mo	8.4	4.1	0.47 (0.33 - 0.67)	<0.001 †
Overall response % (95% CI)	22 (16 - 29)	14 (9 - 21)		0.09
Clinical benefit - no (%)	44 (27)	29 (18)		
Death - no (%)	36 (22)	35 (22)		

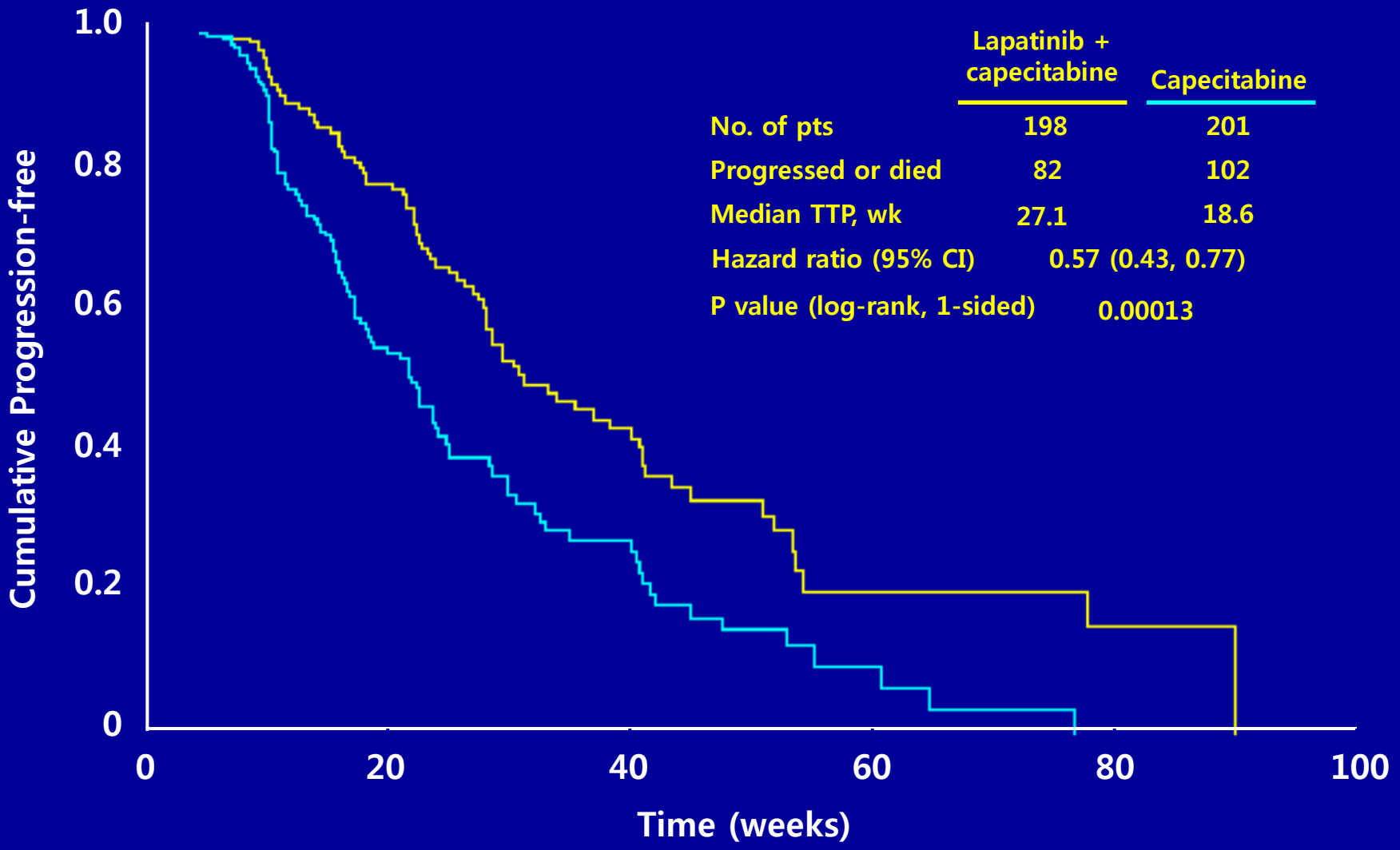
*End points are based on evaluation by the independent review committee under blinded conditions

†The p value was calculated with the log-rank test

‡The p value was calculated with Fisher's exact test

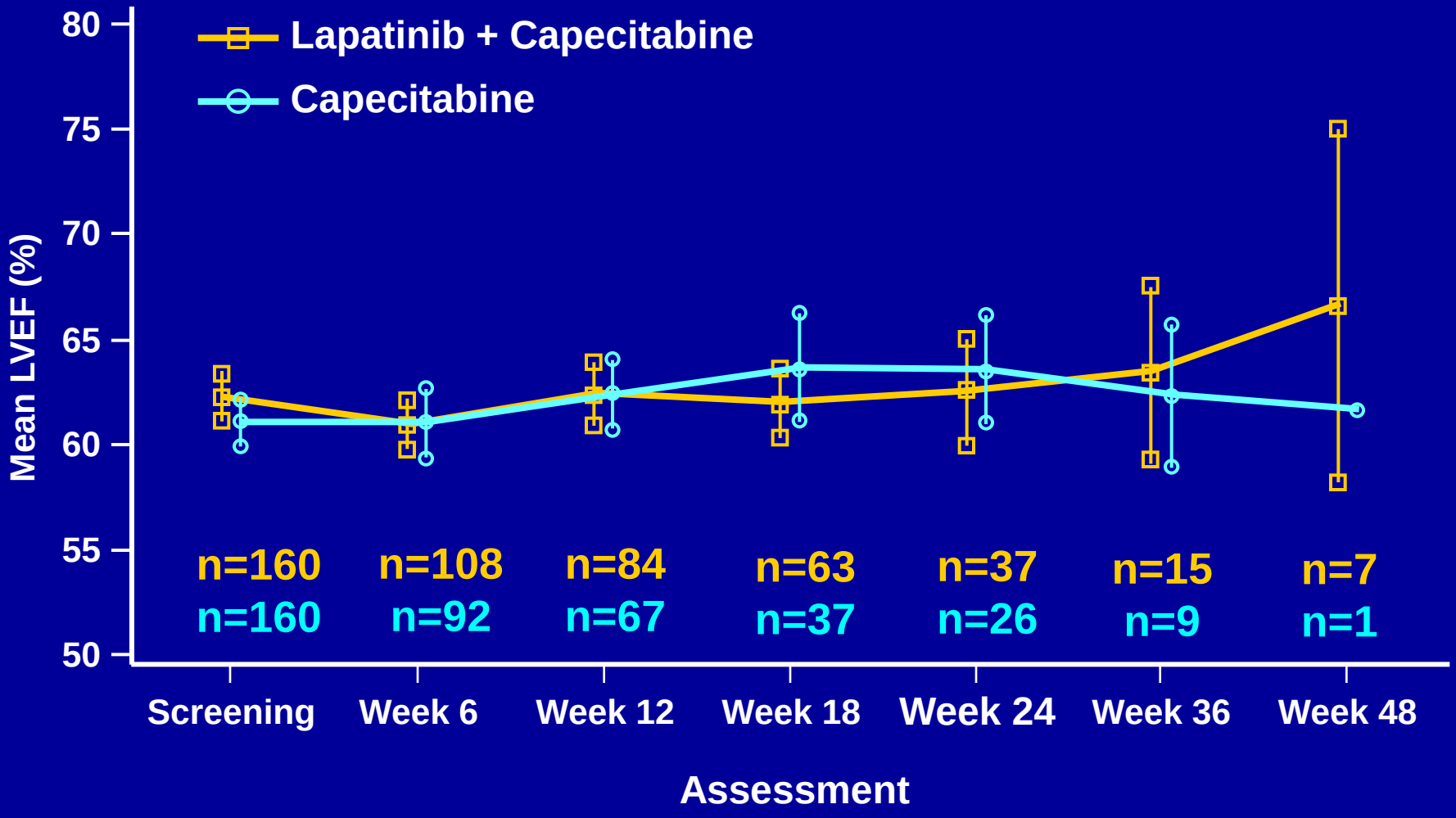
Geyer C, et al. NEJM 2006;355:2733-2743.

Ad hoc analysis - Time to Progression By Independent Assessment (n=399)

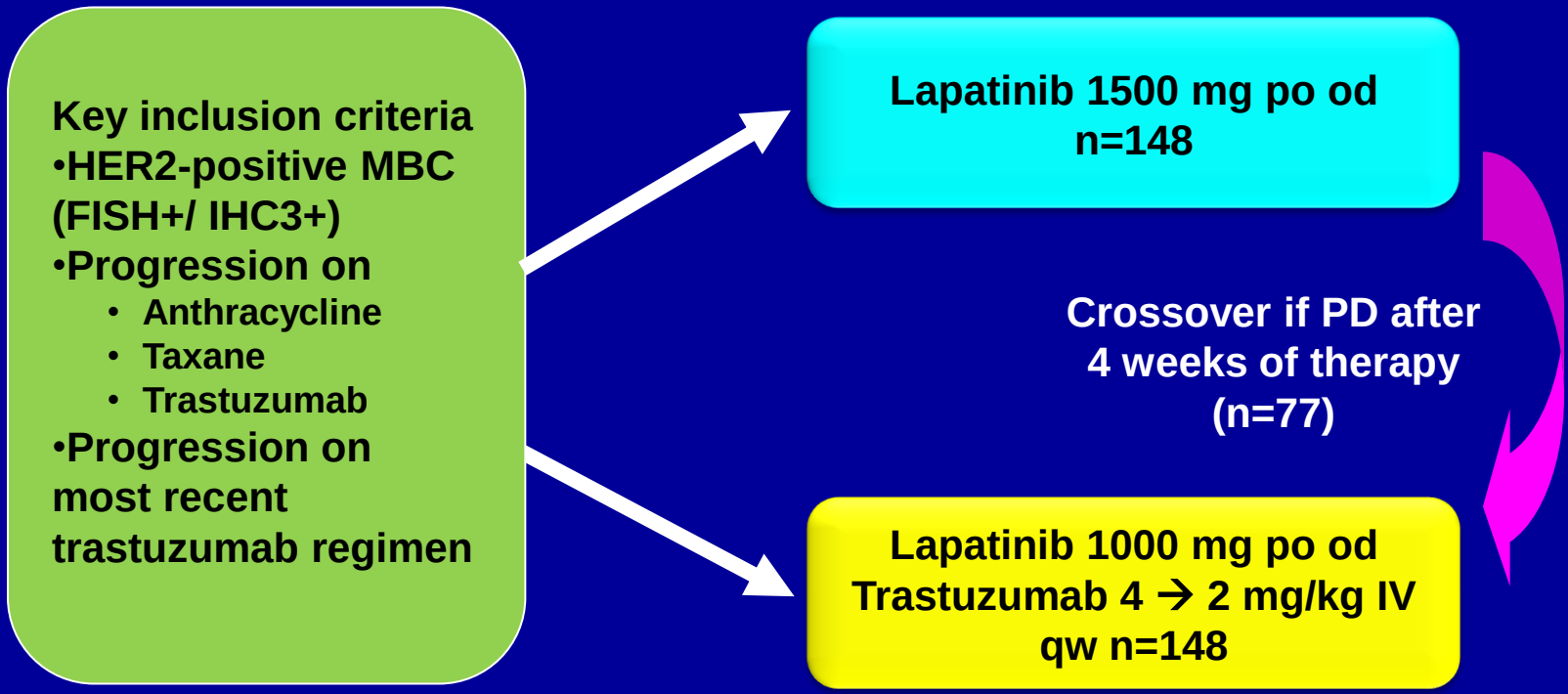


Cameron, Breast Cancer Res Treat. 2008 :112(3): 533-543

Mean LVEF at Scheduled Assessments



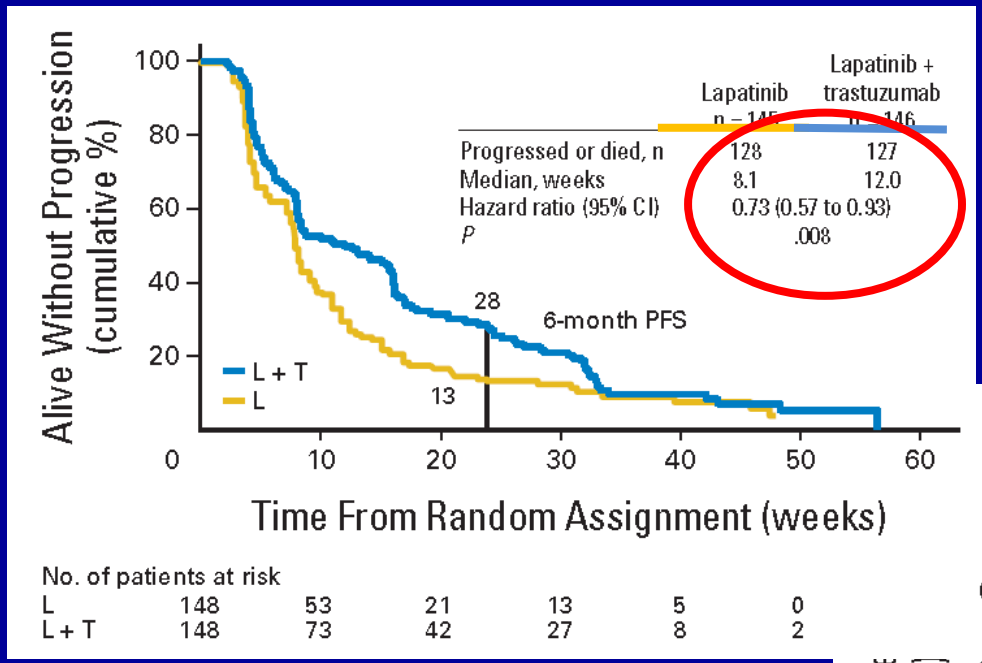
EGF104900: study design



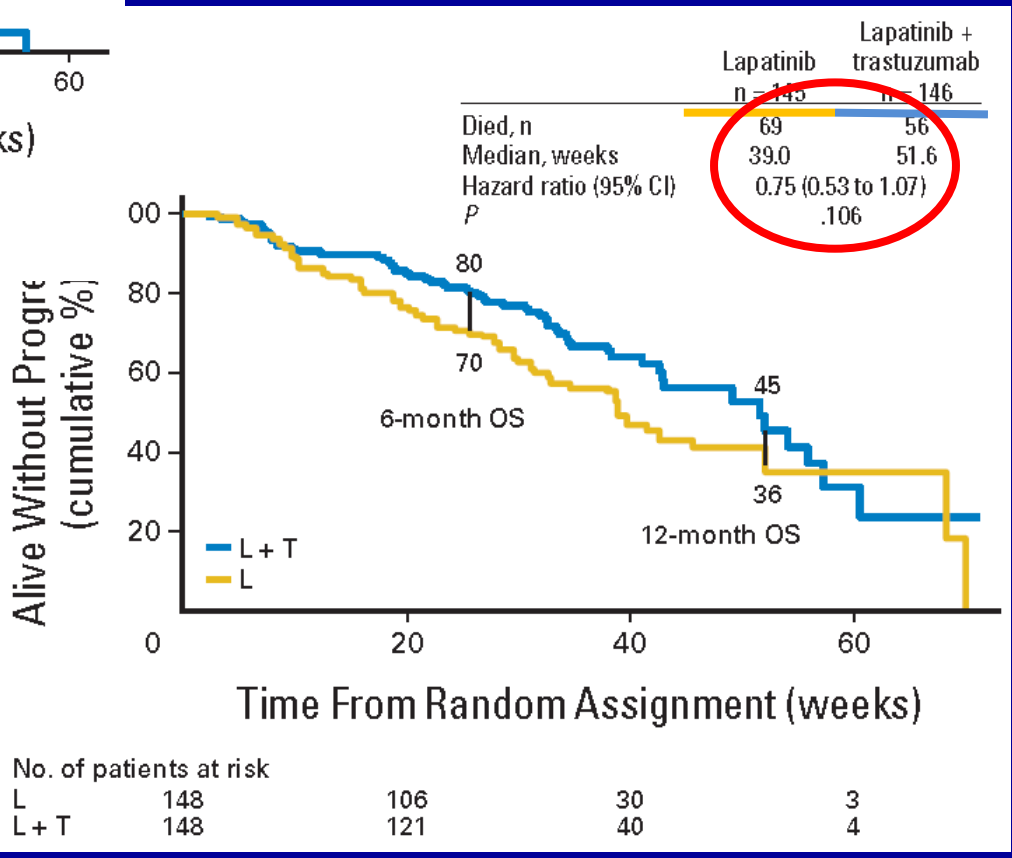
Primary endpoint: PFS
Secondary endpoints: OS, ORR and CBR

Blackwell et al. J Clin Oncol 28:1124, 2010

Progression-free survival



Overall survival



Blackwell et al. JCO 28:1124, 2010

EGF30008 Phase III Randomized, Double-Blind Trial

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

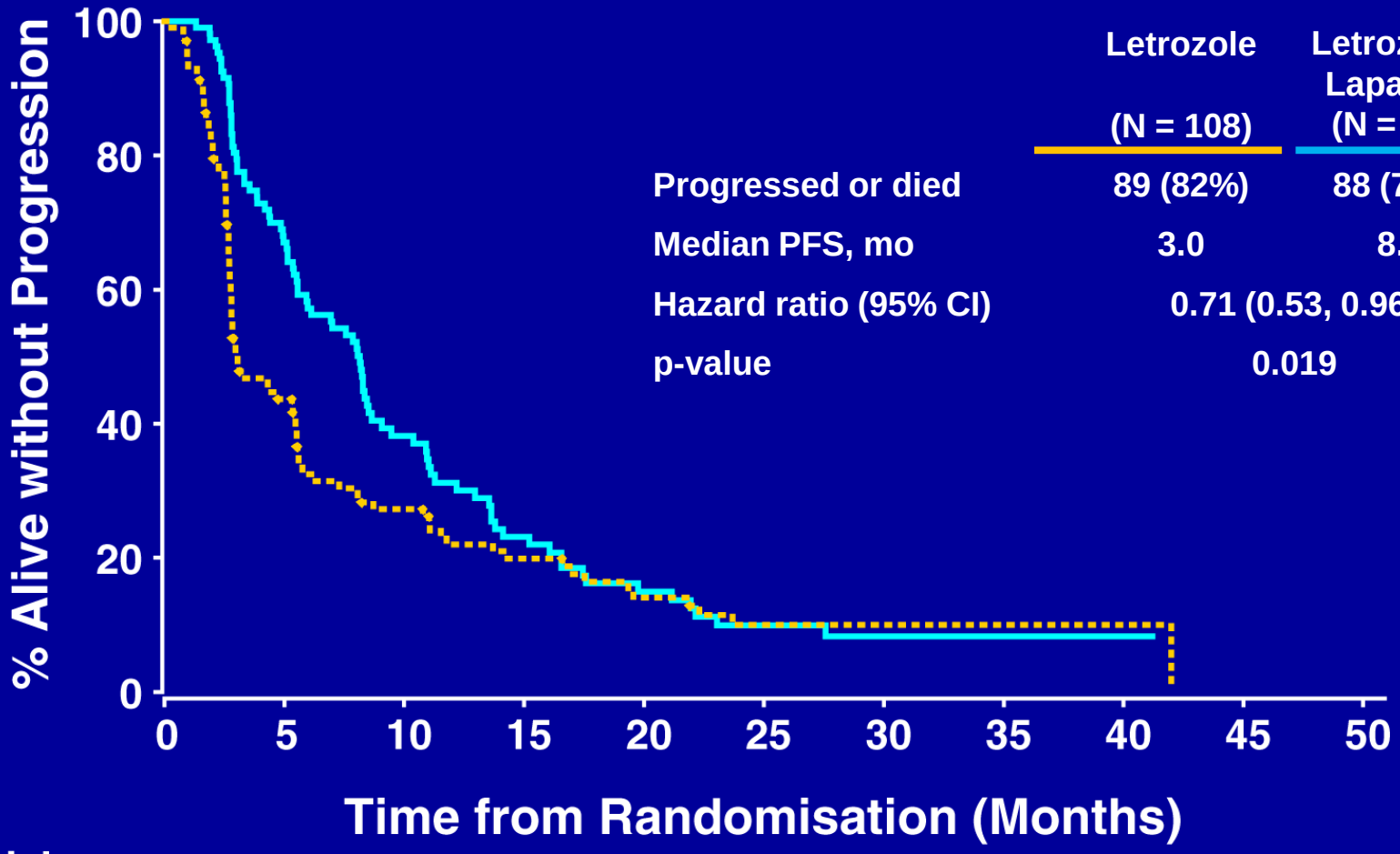
- Letrozole 2.5 mg daily + Placebo
- Letrozole 2.5 mg daily + Lapatinib 1500 mg daily

N=1286 (including n=219 HER2+)

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%)

Progression-Free Survival: HER2+ Population

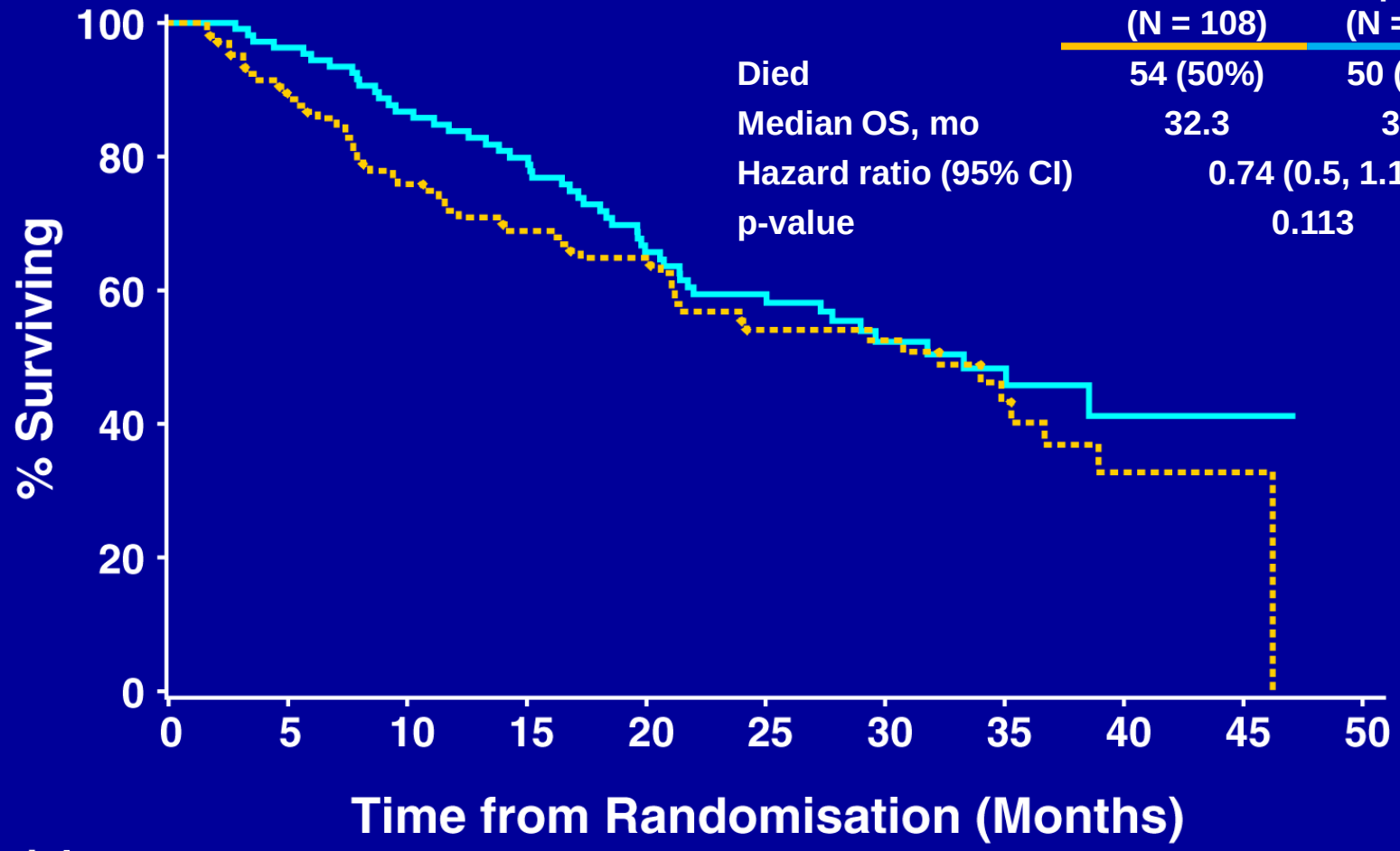


	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Progressed or died	89 (82%)	88 (79%)
Median PFS, mo	3.0	8.2
Hazard ratio (95% CI)	0.71 (0.53, 0.96)	
p-value	0.019	

Pts at risk:

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



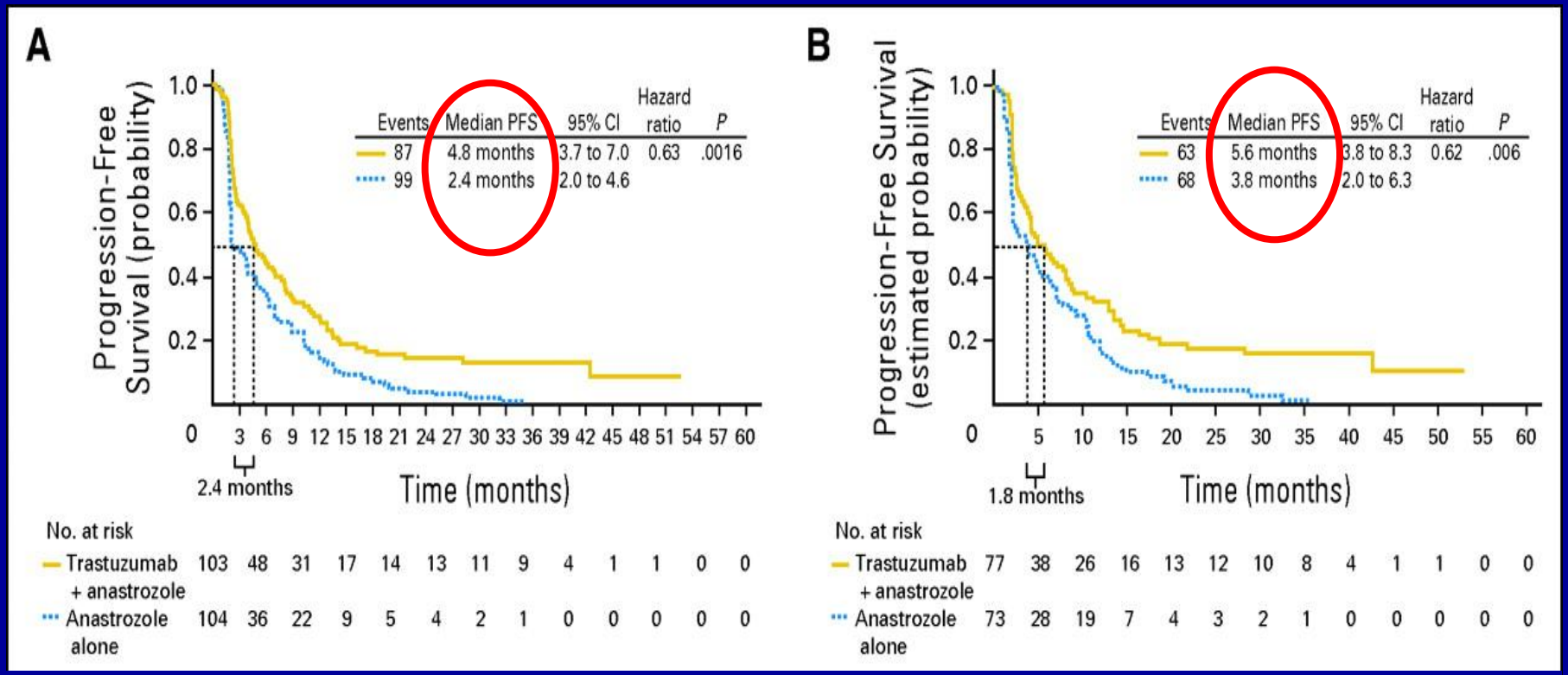
	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Died	54 (50%)	50 (45%)
Median OS, mo	32.3	33.3
Hazard ratio (95% CI)	0.74 (0.5, 1.1)	
p-value	0.113	

Pts at risk:										
Let + Lap	111	104	89	80	64	48	32	19	9	4
Let	108	93	76	69	59	38	31	15	8	2

Randomized Phase III TAnDEM Study

(A) PFS for the ITT population

B) PFS for centrally confirmed HR+ tumors



Kaufman B et al.JCO Nov 20, 2009:5529-5537

4) Brain metastasis:

- Korean EAP study
- Italian study by Metro
- LANDSCAPE study

Korean lapatinib expanded access(LEAP)

Single arm, open label lapatinib expanded access study

Enrolled between January 2007 and April 2008 in 6 centers

Eligible patients

- **locally advanced or metastatic breast cancer**
- Progression after anthracycline, taxane, trastuzumab given alone or in combination in either the metastatic or adjuvant setting
- **Patients with non-measurable disease, ECOG PS 2, prior capecitabine were included**
- Patients with CNS metastases were eligible if steroid requirement was minimal regardless of CNS symptom

Lapatinib 1250 mg po continuously + Capecitabine 2000 mg/m²/d po days 1-14 q 3 wk

Brain metastasis	vs	No Brain metastasis
Prior capecitabine	vs	No prior capecitabine
Positive HR	vs	Negative HR

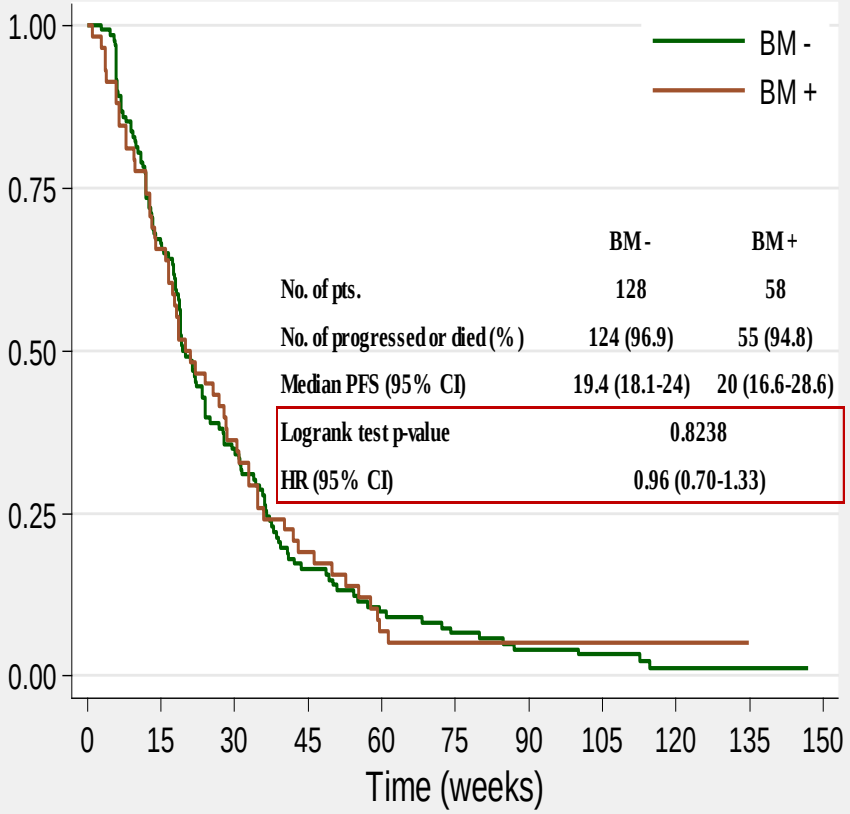
Ro J et al SABCS 2010 abstract

Synchronized brain response with systemic response in patients with brain metastasis

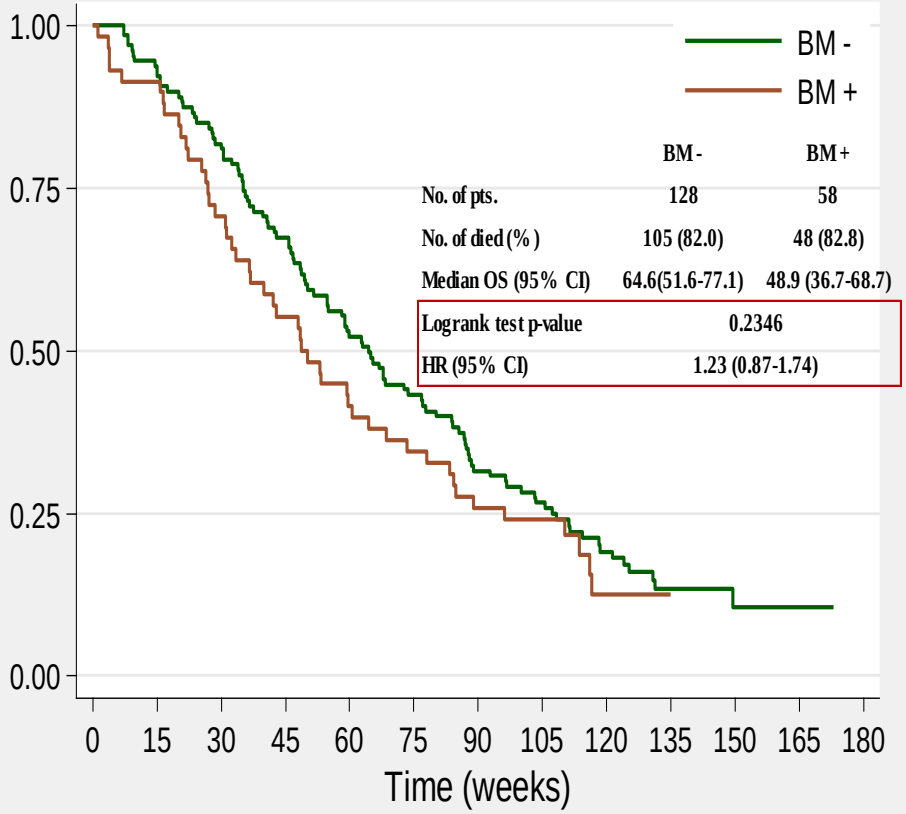
Brain response	CR	PR	Any Response	SD≥ 6mo	SD< 6mo	PD	total	P-value
Systemic response	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PR	2 (33.3)	1 (16.7)	13 (65.0)	2 (25.0)	0 (0.0)	1 (14.3)	19 (37.2)	
SD≥ 6mo	1 (16.7)	1 (16.7)	2 (10.0)	6 (75.0)	1(25.0)	0 (0.0)	11 (21.6)	
SD< 6mo	3 (50.0)	4 (66.7)	3 (15.0)	0 (0.0)	3 (75.0)	2 (28.6)	15 (29.4)	<0.0001
PD	0 (0.0)	0(0.0)	1 (10.0)	0 (0.0)	0 (0.0)	4 (57.1)	6 (11.8)	
total	6 (11.8)	6 (11.8)	20 (39.2)	8 (15.7)	4 (7.8)	7 (13.7)	51 (100.0)	

Kaplan-Meier Estimates by Brain Metastasis (all pts)

PFS



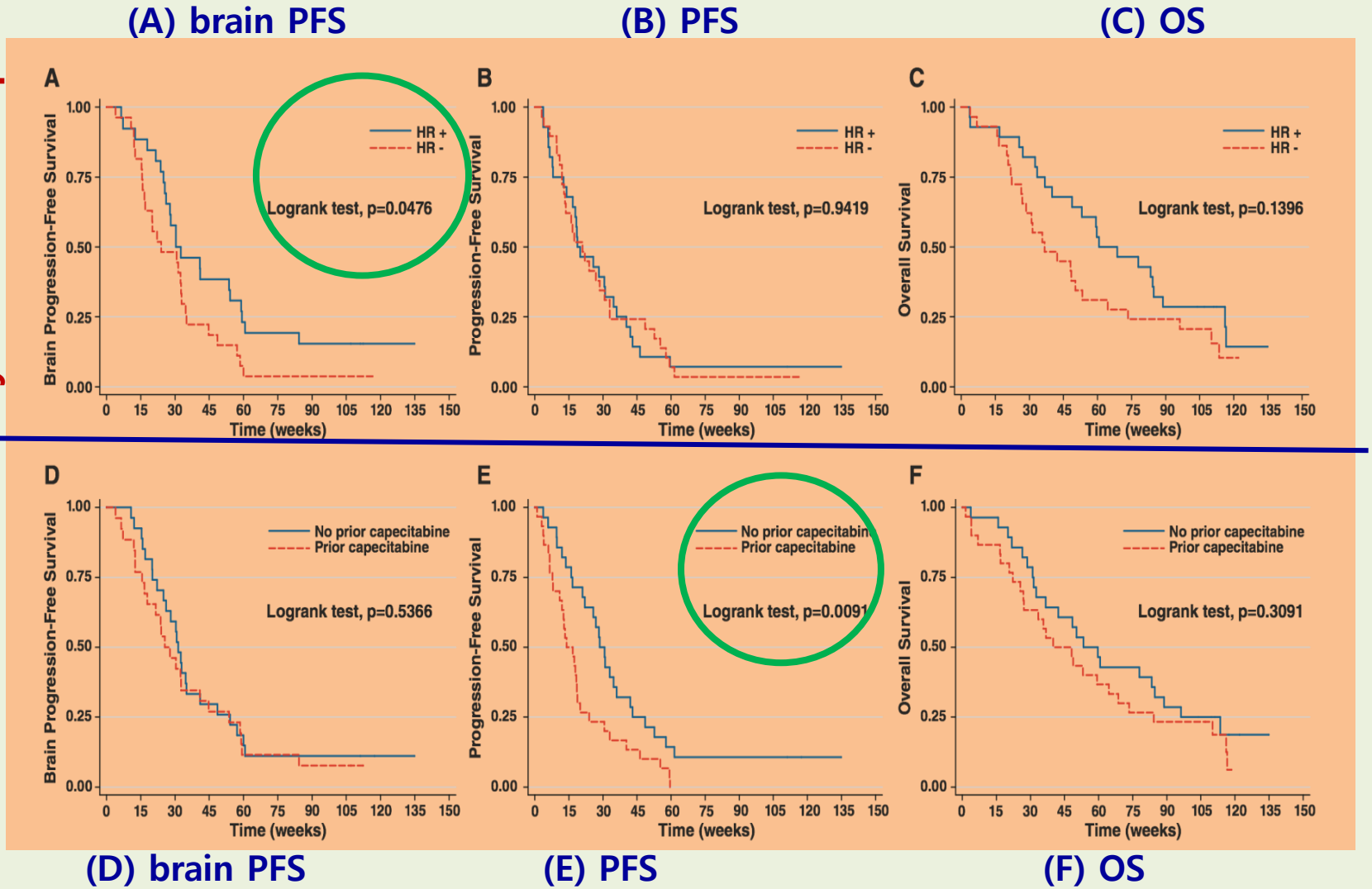
OS



Korean EAP data in patients with BM (n=58)

by hormone receptor

by prior capecitabine



Korean LEAP; Summary and Conclusion (2)

In patients with HER2-positive brain metastasis who received lapatinib plus capecitabine,

PFS: prolonged in patients with

Combined brain and systemic responders (P<.0001)

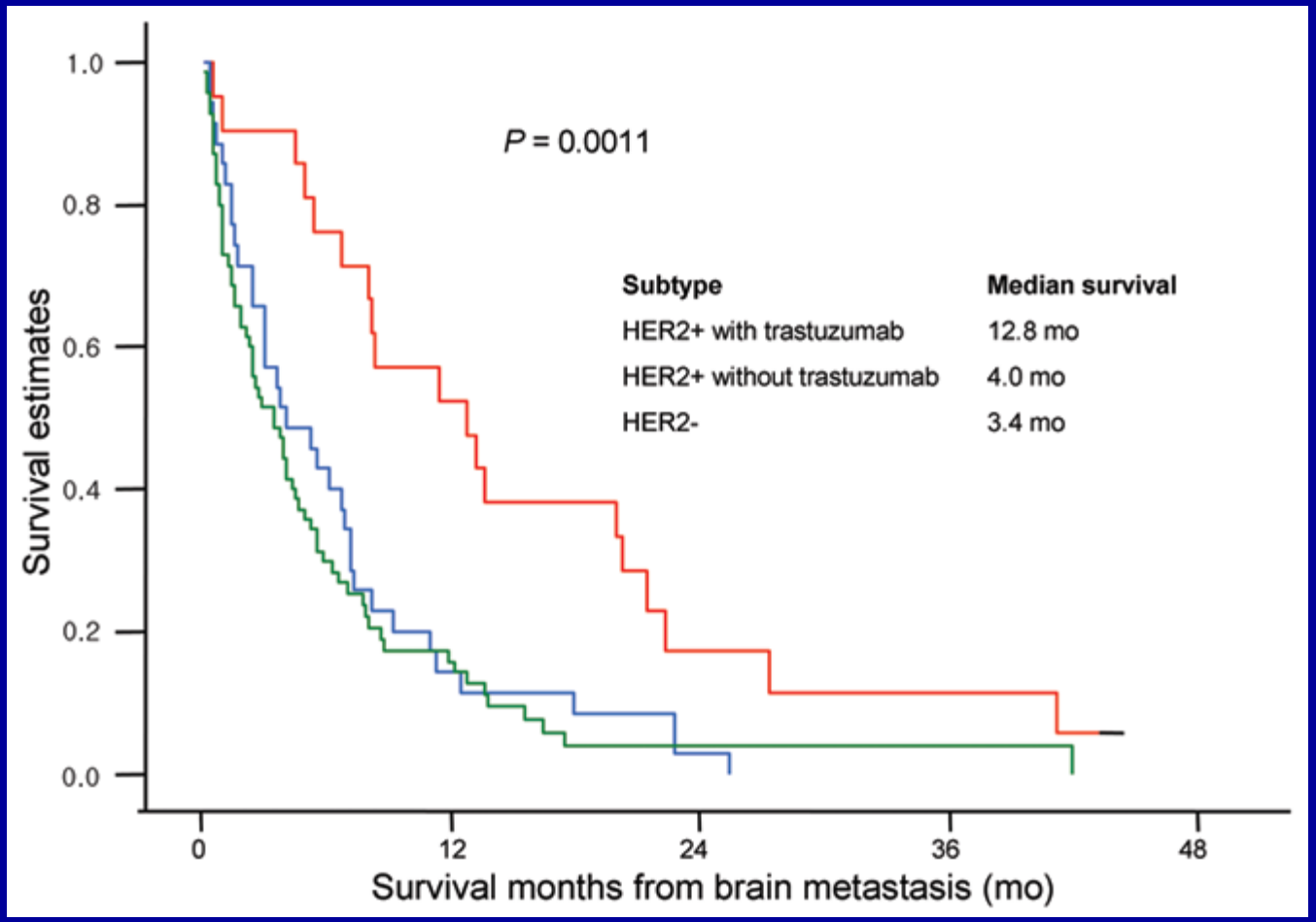
Hormone receptor-positive disease (P=.003)

OS: prolonged in patients with

Combined brain and systemic responses (P=.031)

History of longer use of prior trastuzumab
(median duration of ≥35.4 weeks, HR = 0.50,
95% CI: 0.25- 0.99; P=0.047)

Trastuzumab in HER2-positive BM



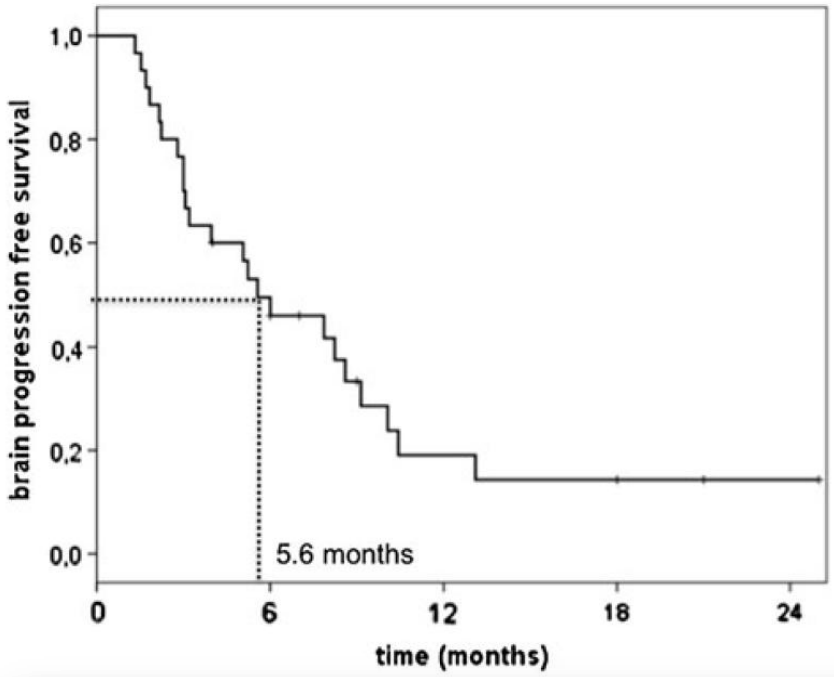
Nam et al. Breast Cancer Res 2008;10:R20.

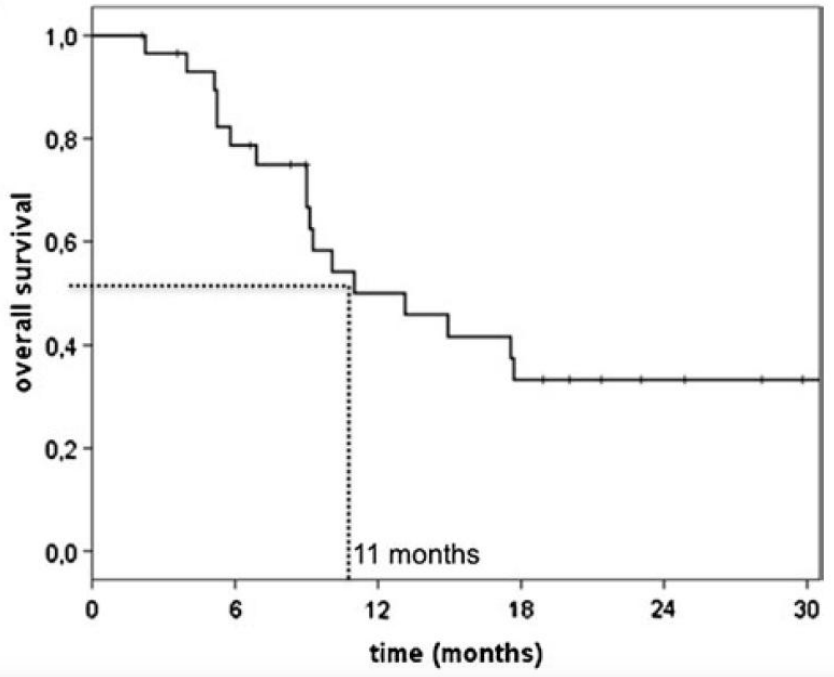
Lapatinib and Capecitabine for Brain Metastasis

Characteristics	
Median age, years (range)	**45 (24-75)**
ECOG	
0	**7 (23.3%)**
1	**14 (46.7%)**
2	**9 (30%)**
Median time from metastasis to BMs, mo	**12.4 (0-52.5)**
Median number of prior trastuzumab-based therapies	2 (1-5)
Extracranial metastasis	
No	**1 (3.3%)**
Yes	**29 (96.7%)**
Number of BMs	
>3	**12 (40%)**
≤3	**18 (60%)**
First systemic option after BMs	
Lapatinib + Capecitabine	6 (20%)
Trastuzumab-based therapy	24 (80%)

Metro G, et al. Ann Oncol 2010 Aug 19, Epub ahead of print.

Brain-specific PFS and OS from LC

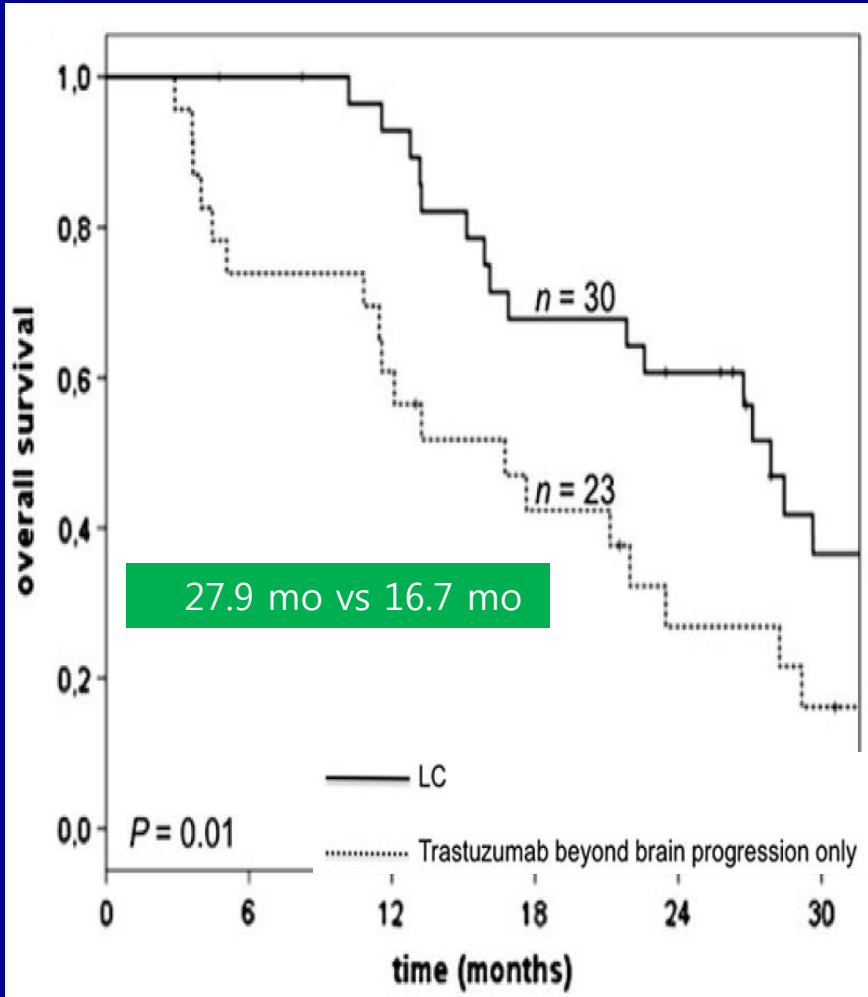


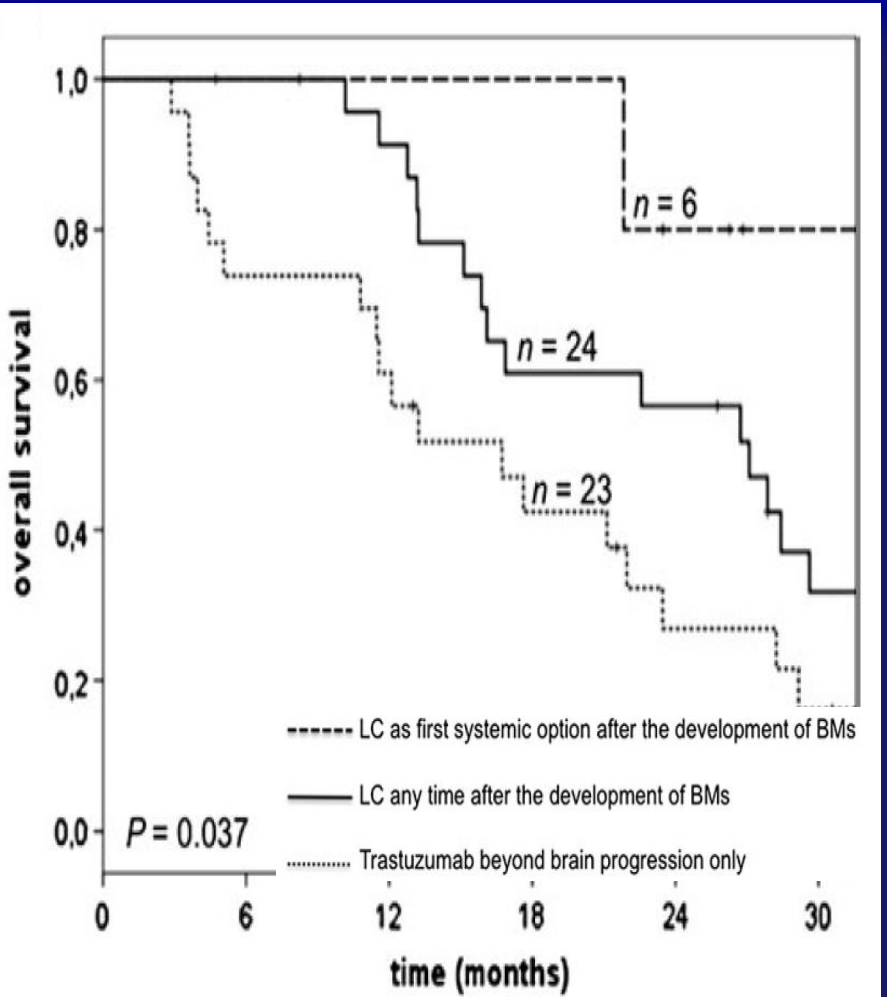


Best response for BMs	Local treatment for BMs			Total patients (n = 22), n (%)
	None (n = 4), n (%)	Radiotherapy (WBRT and/or SRS) (n = 17), n (%)	Neurosurgery with WBRT and/or SRS (n = 1), n (%)	
Partial response	3 (75)	3 (17.6)	1 (100)	**7 (31.8)**
Stable disease	1 (25)	5 (29.4)	—	**6 (27.3)**
Progressive disease	—	9 (53)	—	**9 (40.9)**

Metro G, et al. Ann Oncol 2010 Aug 19, Epub ahead of print.

OS from brain metastasis
L/C added *vs.* trastuzumab only





Metro G, et al. Ann Oncol 2010 Aug 19, Epub ahead of print.

- **LANDSCAPE: phase II study with lapatinib (L) and capecitabine (C) in patients with brain metastases (BM) from HER2-positive (+) metastatic breast cancer (MBC) before whole-brain radiotherapy (WBR).**

J Clin Oncol 29: 2011 (suppl; abstr 509)

LANDSCAPE

Background:

Capecitabine + lapatinib active in trastuzumab failures:
RR 23%, median time to PD = 6.2 months
Capecitabine + lapatinib active against previously irradiated brain mets (volumetric RR ≈ 20%)

Questions & Statistics

Whether WBRT could be delayed?
Volumetric RR of interest: 20% or more
N = 45 patients needed (power 85%, α = 5%)
Would this regimen control extra CNS disease efficiently?

CNS response definition

> 50% decrease in the volume of CNS lesions (≥ 1cm) in absence of progression of neurologic symptoms, increase of steroid dosage, progression outside CNS

J Clin Oncol 29: 2011 (suppl; abstr 509)

Landscape

N = 45 patients

not candidate for brain symptoms
not previously irradiated for their brain metastasis
pretreated with trastuzumab (93%)
not previously treated with capecitabine or lapatinib
ECOG PS 0-2

Results:

CNS-OR rate was 67% (95%CI 51-81),
Median TTP 5.5 months (95% CI 3.9-5.9)
median time to WBRT was 8.3 months (95% CI 5.1-11.7)
Early PD: 14%
Drop out due to toxicity: 7%
extra CNS RR:43%
1 yr OS: 70%
32 PD in brain
5 PD in brain and non brain (3 PD outside brain only)

J Clin Oncol 29: 2011 (suppl; abstr 509)

Landscape: Capecitabine + lapatinib as front line therapy for brain metastasis

"Capecitabine + lapatinib is not an unreasonable option as front line treatment for brain metastases occuring in HER2+ BC patients exposed to trastuzumab"

Summary

❖ **Overall,**

- Design up-front therapeutic strategies according to receptor subtype and stage of breast cancer
- Try to enroll patients to the clinical trials

❖ **In adjuvant and neoadjuvant settings,**

- Use concurrent trastuzumab with taxane containing regimen and complete 1 yr of anti-HER2 therapy

Summary

❖ **In metastatic setting,**

- Start combination therapy with chemo agent and continue both
- Treatment duration is unknown for patients who respond completely and maintain on trastuzumab monotherapy
- Continuation of anti-HER2 at the time of progression
- Combined administration with endocrine therapy is an option to treat for elderly or poorly tolerable comorbid patients

❖ **Brain metastasis,**

- Capecitabine + lapatinib may be an option as front line treatment for brain metastases
- Try to enroll patients for clinical trial of new TKI

Conclusion: ongoing issues

- Duration of therapy
- Optimal combination
- Optimal sequence
- Inaccurate diagnosis
- Resistance
- Drug access and cost
- Reimbursement coverage


Thank you for your attention!