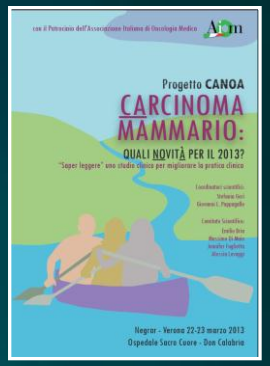
Negrar, 22 Marzo 2013



Lo studio Lapatinib e Trastuzumab vs Lapatinib EGF 104900

Nicla La Verde

ONCOLOGIA MEDICA E CHEMIOTERAPIA

A.O. FATEBENEFRATELLI E OFTALMICO

MILANO

VOLUME 28 · NUMBER 7 · MARCH 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

2010

Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer

Kimberly L. Blackwell, Harold J. Burstein, Anna Maria Storniolo, Hope Rugo, George Sledge, Maria Koehler, Catherine Ellis, Michelle Casey, Svetislava Vukelja, Joachim Bischoff, Jose Baselga, and Joyce O'Shaughnessy

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

2012

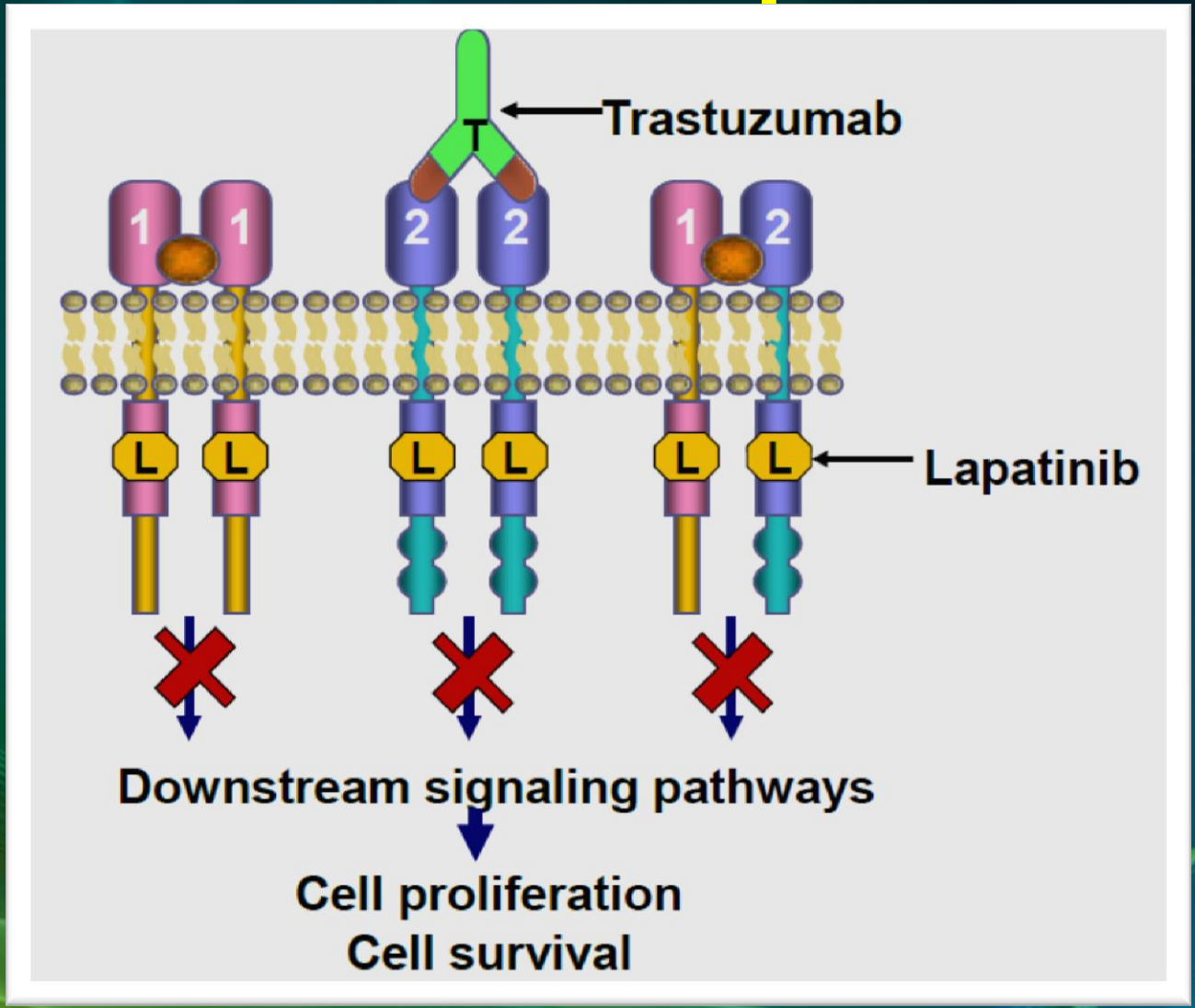
Overall Survival Benefit With Lapatinib in Combination With Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: Final Results From the EGF104900 Study

Kimberly L. Blackwell, Harold J. Burstein, Anna Maria Storniolo, Hope S. Rugo, George Sledge, Gursel Aktan, Catherine Ellis, Allison Florance, Svetislava Vukelja, Joachim Bischoff, José Baselga, and Joyce O'Shaughnessy

Objectives

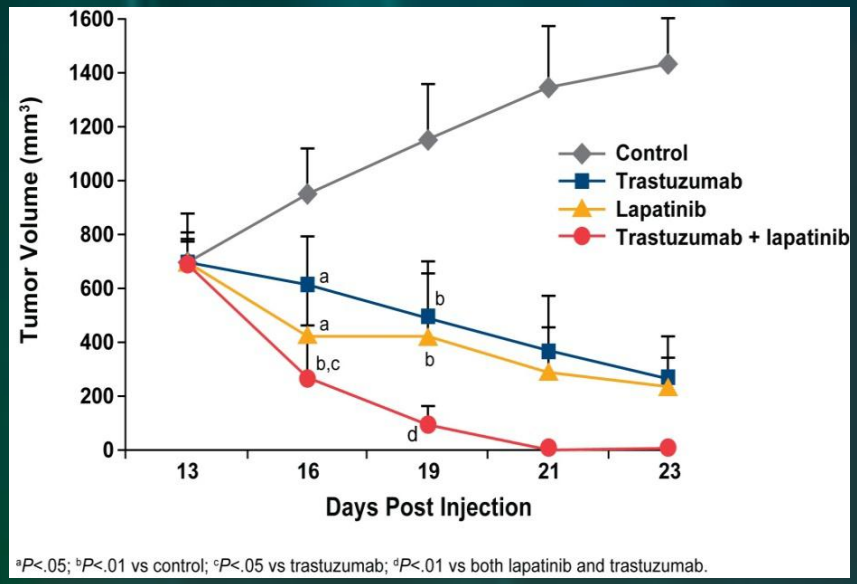
To determine whether treatment with the combination of **lapatinib and trastuzumab**, versus **lapatinib** alone would **enhance efficacy** in heavily pretreated ErbB2-positive patients

The rationale: dual targeting of the HER2 receptor

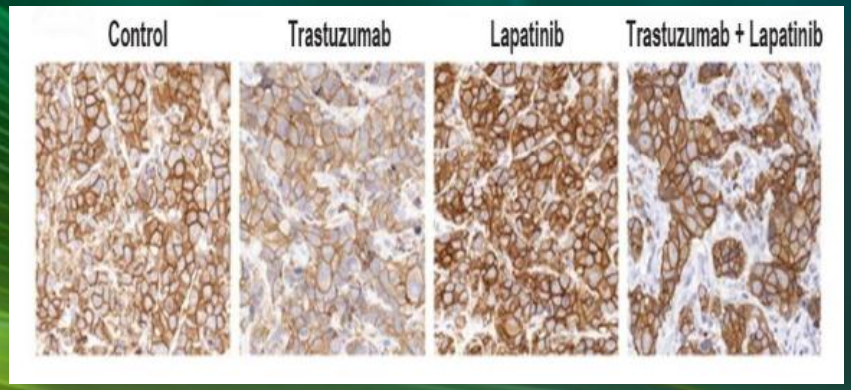


Scaltriti et al. Oncogene; 2009; 28:803-14

Preclinical data and scientific rationale



[a]*P*<.05; [b]*P*<.01 vs control; [c]*P*<.05 vs trastuzumab; [d]*P*<.01 vs both lapatinib and trastuzumab.

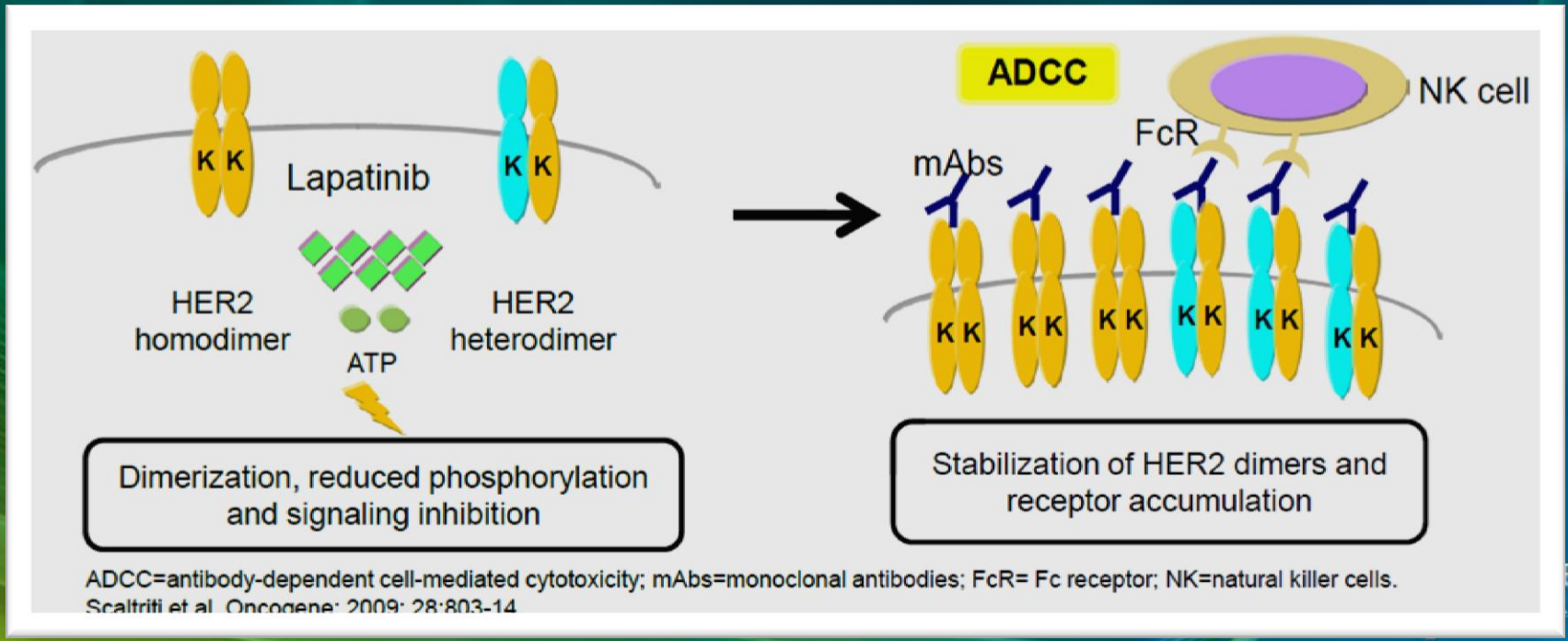


- Lapatinib plus trastuzumab resulted in complete tumor remission in xenografts (no tumor relapse after 8 months post treatment)
- Lapatinib induced accumulation of inactive HER2 at plasma membrane (Trastuzumab-mediated cytotoxicity was higher with the addition of lapatinib in MCF7/HER2 cells)
- In vivo activity was consistent with in vitro data demonstrating the combination as synergistic

D.O.M.E.C.
H. FBF - MI

Preclinical data and scientific rationale

- Lapatinib counteracts the phosphorylation, ubiquitination and degradation of HER2
- Lapatinib-induced cell surface accumulation of HER2 significantly enhances trastuzumab-mediated ADCC



ADCC=antibody-dependent cell-mediated cytotoxicity; mAbs=monoclonal antibodies; FcR= Fc receptor; NK=natural killer cells.
Scaltriti et al. Oncogene; 2009; 28:803-14

Clinical data and scientific rationale

VOLUME 26 · NUMBER 20 · JULY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Dose Escalation and Pharmacokinetic Study of Lapatinib in Combination With Trastuzumab in Patients With Advanced ErbB2-Positive Breast Cancer

Anna Maria Storniolo, Mark D. Pegram, Beth Overmoyer, Paula Silverman, Nancy W. Peacock, Suzanne F. Jones, Jill Loftiss, Nikita Arya, Kevin M. Koch, Elaine Paul, Lini Pandite, Ronald A. Fleming,

VOLUME 26 · NUMBER 20 · JULY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Dual-Agent Molecular Targeting of the ErbB2 Receptor: Killing One Bird With Two Stones

Hal W. Hirte, Department of Oncology, McMaster University, Hamilton, Ontario, Canada

Sebastien J. Hotte, Systemic Therapy Program, Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton,

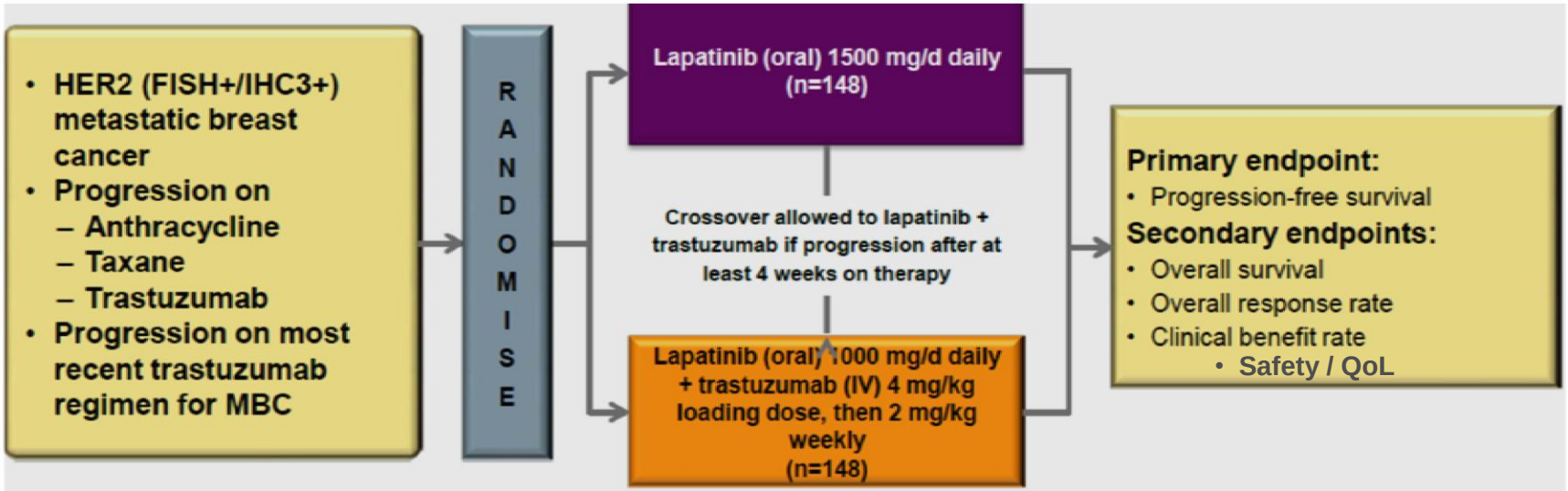
"The overall response rate (CR and PR) was 15% (eight of 54) based on the intent to treat population."

Blackwell KL et al. J Clin Oncol, 2012

D.O.M.E.C.
H. FBF - MI

Study design

phase III, randomized, open-label



- Tumour assessment occurred at 4, 8, 12, 16 weeks, and then every 8 weeks
- Independent review of response evaluation criteria in solid tumours (RECIST) data was performed

FISH=fluorescence insitu hybridization; IHC=immunohistochemistry; MBC=metastatic breast cancer; RECIST=Response Evaluation Criteria in Solid Tumours.

Blackwell KL et al. J Clin Oncol 2010;1124-30.

Inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Women aged ≥18 years with histologically or cytologically confirmed breast cancer • HER2 positive disease (overexpression or amplification confirmed by IHC3+ or FISH) • Metastatic disease that progressed on the most recent treatment regimen, which must have contained trastuzumab • Prior treatment with an anthracycline and a taxane in an adjuvant or metastatic setting • Measurable disease by RECIST • ECOG performance status ≤ 2	• Prior treatment with an ErbB1 and or HER2 inhibitor other than trastuzumab • Pre-existing malabsorption syndrome • A history of other malignancy

Blackwell KL et al. J Clin Oncol, 2010

Baseline Patients Clinical Characteristics

296 paz arruolati in 1 anno in 88 centri (3 paz x centro)

77 (52%) patients randomised to lapatinib crossed over to receive dual HER2 blockade:

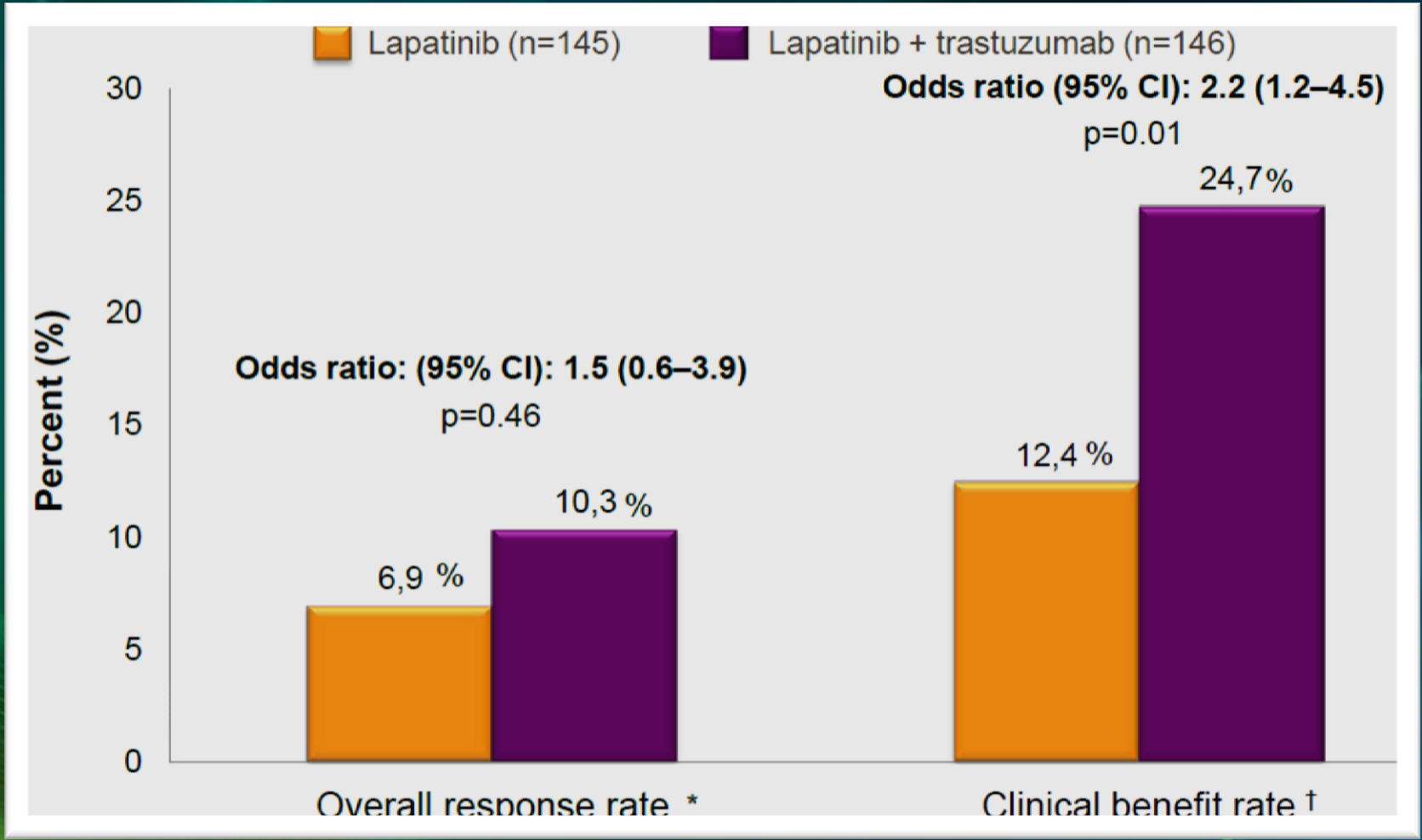
20 (27%) at week 4

20 (27%) at week 8

37 (46%) after week 8

Poststudy trastuzumab, %*	32	33
Poststudy lapatinib, %*	11	14

Tumour response



*Confirmed complete (CR) + partial response (PR)

†ConfirmedCR + PR + stable disease ≥ 6 mo

D.O.M.E.C. H. FBF - MI

Blackwell KL et al. J Clin Oncol, 2010

Lapatinib activity

original article

Annals of Oncology 19: 1068–1074, 2008
doi:10.1093/annonc/mdm601
Published online 17 February 2008

A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer

H. J. Burstein[1]*, A. M. Storniolo[2], S. Franco[3], J. Forster[4], S. Stein[4], S. Rubin[4], V. M. Salazar[4] & K. L. Blackwell[5]

	HER2+ ($n = 140$)		HER2− ($n = 89$)	
	Investigator review	Independent review	Investigator review	Independent review
Best response, *n* (%)				
CR	3 (2)	0	0	0
PR	3 (2)	2 (1)	0	0
SD	38 (27)	46 (33)	10 (11)	10 (11)
PD	85 (61)	64 (46)	76 (85)	49 (55)
Unknown	11 (8)	28 (20)	3 (3)	30 (34)
Response rate (CR or PR), % (95% CI)	4.3 (1.6, 9.1)	1.4 (0.2, 5.1)	0.0 (0.0, 4.1)	0.0 (0.0, 4.1)
Clinical benefit, % (95% CI)				
CR, PR, or SD ≥6 months	5.7 (2.5, 10.9)	5.7 (2.5, 10.9)	0.0 (0.0, 4.1)	0.0 (0.0, 4.1)
Time to progression, weeks, median	8.1	9.1	7.0	7.6
PFS, weeks, median (95% CI)		9.1 (8.0, 15.6)		7.6 (7.1, 7.7)
PFS ≥ 6 months, patients, % (95% CI)		18 (10, 25)		0 (0, 0)
Overall survival, weeks, median (95% CI)		29.4 (22.9, 37.7)		18.6 (16.0, 23.6)

ITT, intent-to-treat; HER2, human epidermal growth factor receptor type 2; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; CI, confidence interval.

Progression-free survival

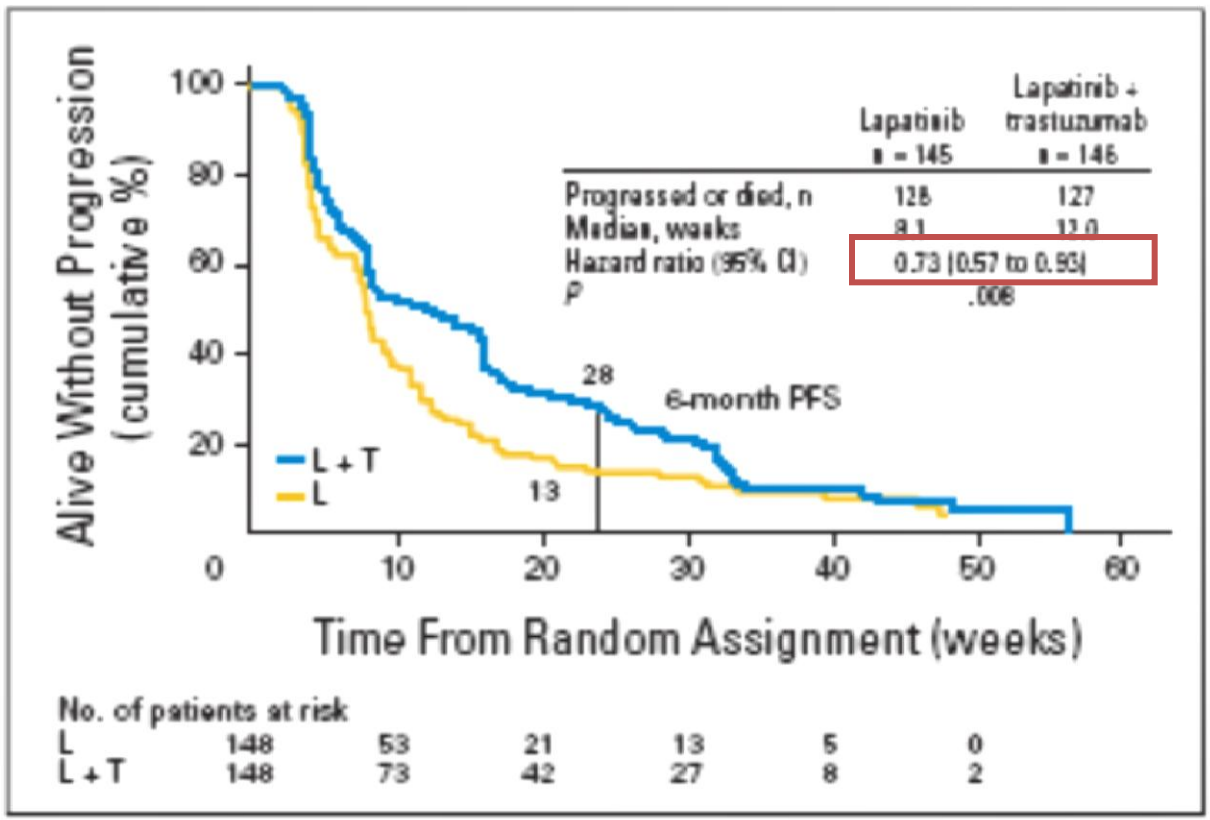
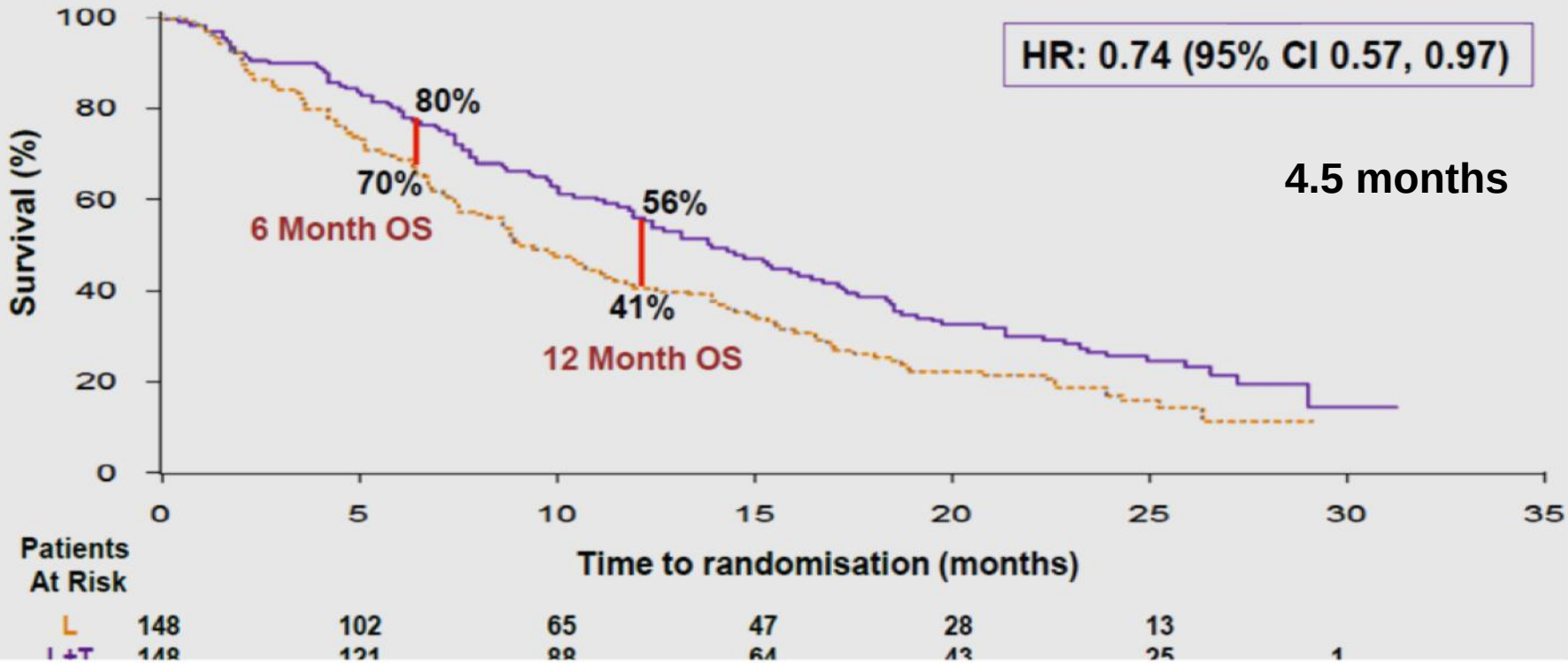


Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) in the intent-to-treat population. L, lapatinib; L+T, lapatinib plus trastuzumab.

Blackwell KL et al. J Clin Oncol, 2010

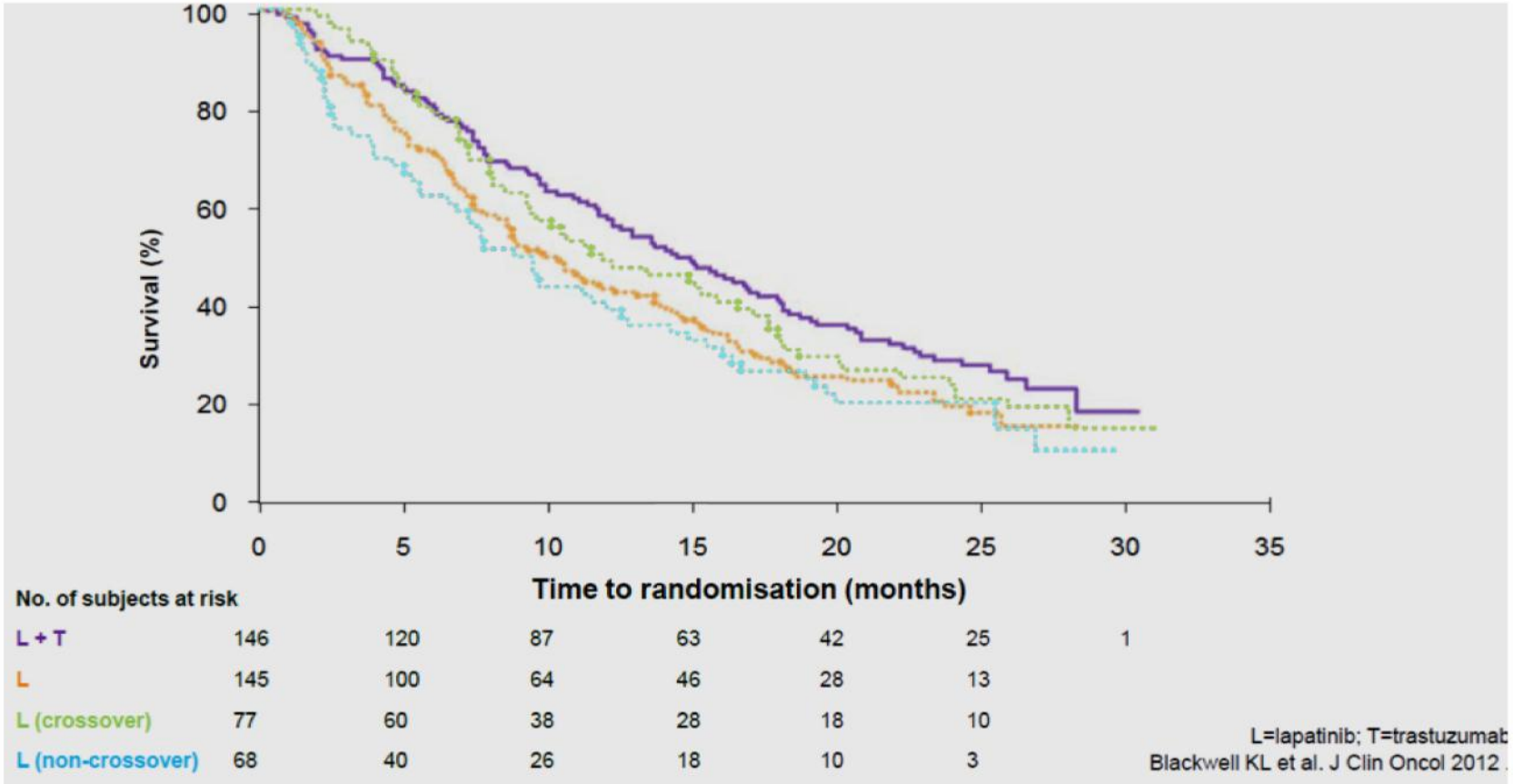
Overall survival

	Died n (%)	Median	P-value
Lapatinib (n=145)	113 (78%)	9.5 months	0.026
Lapatinib + trastuzumab (n=146)	105 (72%)	14 months	



Blackwell KL et al. J Clin Oncol, 2012

Overall survival with and without crossover



Blackwell KL et al. J Clin Oncol, 2012

Univariate analysis for Overall survival

Table 2. Summary of Univariate Analysis for OS

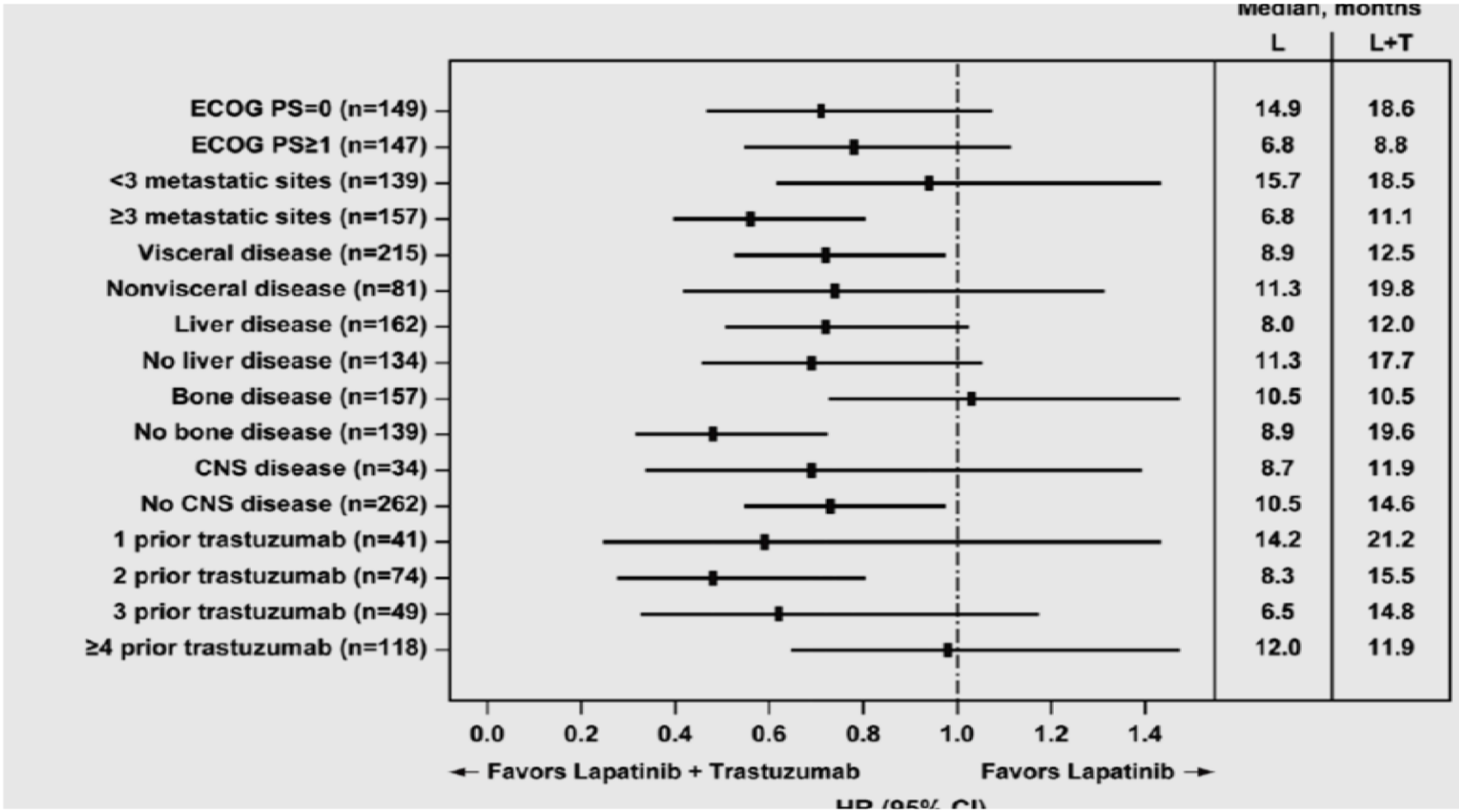
Baseline Factor	HR	95% CI	*P*
ECOG PS (0 *v* ≥ 1)	**0.44**	**0.34 to 0.58**	**< .001**
Age (continuous)	1.01	1.00 to 1.02	.1023
Hormone receptor status (ER negative/ PgR negative *v* ER positive or PgR positive)	0.93	0.71 to 1.21	.5665
Time from diagnosis to random assignment (continuous)	**0.95**	**0.91 to 0.99**	**.0285**
Time from metastasis to random assignment (continuous)	0.97	0.91 to 1.03	.2660
Last dose of trastuzumab (≥ 4 *v* < 4 weeks)	1.01	0.78 to 1.32	.9366
No. of prior trastuzumab regimens (≤ two *v* > two)	0.99	0.75 to 1.31	.9589
No. of prior metastatic trastuzumab regimens (≤ two *v* > two)	0.99	0.75 to 1.29	.9179
No. of prior regimens (≤ three *v* > three)	0.93	0.63 to 1.35	.6937
No. of prior metastatic regimens (≤ two *v* > two)	0.76	0.55 to 1.04	.0827
No. of metastatic sites (< three *v* ≥ three)	**0.44**	**0.33 to 0.57**	**< .001**
Disease site (nonvisceral or visceral)	**0.59**	**0.43 to 0.81**	**.0010**
Liver metastasis (no *v* yes)	**0.58**	**0.45 to 0.76**	**< .001**
Bone metastasis (no *v* yes)	**0.74**	**0.56 to 0.96**	**.024**
Skin metastasis (no *v* yes)	0.85	0.60 to 1.20	.3537
Brain metastasis (no *v* yes)	**0.64**	**0.44 to 0.92**	**.0175**

NOTE. Bold font indicates significant factors.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor.

D.O.M.E.C. H. FBF - MI

Blackwell KL et al. J Clin Oncol, 2012

Hazard ratios and 95% confidence intervals for overall survival analysis



Blackwell KL et al. J Clin Oncol, 2012

Common AEs

	Lapatinib (n=146)	Lapatinib + trastuzumab (n= 149)
Adverse events (all grades) n (%)		
Diarrhoea*	70 (48)	90 (60)
Rash**	43 (29)	33 (22)
Nausea	41 (28)	41 (28)
Fatigue	28 (19)	32 (21)
Vomiting	26 (18)	21 (14)
Dyspnoea	14 (10)	18 (12)
Anorexia	14 (10)	17 (11)
Cough	14 (10)	8 (5)
Dermatitis acneiform	14 (10)	8 (5)
Headache	13 (9)	15 (10)

AE=adverse event

*Includes diarrhoea, loose stools and frequent bowel movements.

**Includes acne, dermatitis, eczema, erythema, folliculitis, rash, rash papular and rash pustular

Blackwell KL et al. J Clin Oncol, 2010

Cardiac and hepatobiliary events

	Lapatinib (n=146)	Lapatinib + trastuzumab (n=149)
Decreased left ventricular ejection fraction		
Patients with events	**3 (2%)**	**9 (6%)**
Number of events	3	11
Serious events	3 (100%)	8 (73%)
Events leading to study withdrawal	1 (33%)	3 (27%)
Fatal events	0	1 (9%)
Hepatobiliary events		
Patients with events	**6 (4%)**	**3 (2%)**
Number of events	8	3
Serious event	3 (38%)	1 (33%)
Events leading to study withdrawal	2 (25%)	0
Fatal events	1 (13%)	0

Blackwell KL et al. J Clin Oncol, 2010

Authors conclusions

In heavily pre-treated metastatic breast cancer patients:

- This study demonstrated that lapatinib in combination with trastuzumab offers a chemotherapy-free option that has an acceptable tolerability profile and, versus lapatinib alone, reduced the risk of disease progression by 27% (2010)

- Dual blockade of the HER2 receptor with lapatinib + trastuzumab resulted in a statistically significant 4.5 months overall survival advantage (2012)

Authors conclusions

In heavily pre-treated metastatic breast cancer patients:

- These data strengthen the NCCN and ESMO clinical practice guidelines, which emphasize continued HER2 suppression for trastuzumab-exposed HER2-positive disease, either combined with chemotherapy agents or with the lapatinib plus trastuzumab combination (2012)

Authors conclusions

Exploratory analysis : Predictors of OS benefit

- (ECOG PS) of 0
- time from diagnosis to random assignment
- < three metastatic sites
- lack of visceral disease

Authors conclusions

- The overall incidence of adverse events was generally similar

✓ The incidence of diarrhoea was higher under lapatinib + trastuzumab dual blockade

✓ The incidence of rash was higher under lapatinib monotherapy

- Dual blockade with lapatinib + trastuzumab was associated with a manageable safety profile with no unexpected AEs

Personal conclusions

- Many reflections
- Some doubts
- Few anxieties
- Several questions

Thanks!!!

D.O.M.E.C.
H. FBF - MI