Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITÀ PER IL 2013?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Lo studio lapatinib e trastuzumab vs lapatinib:

Commento sulla metodologia

Emilio Bria

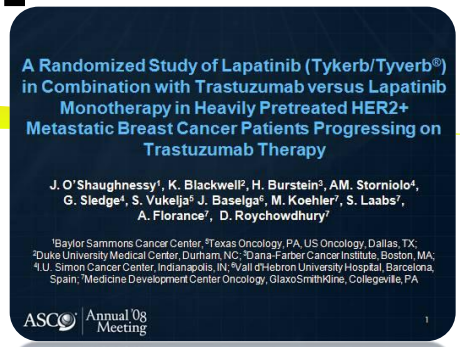
U.O.C. di Oncologia Medica d.U.

Azienda Ospedaliera Universitaria Integrata

Policlinico 'G.B. Rossi' - VERONA

Negrar (VR), 22 Marzo 2013

LAP + T *vs.* LAP



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 28 · NUMBER 7 · MARCH 1 2010

JOURNAL OF CLINICAL ONCOLOGY

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

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

‘Comments’ upon Methodology

- Protocol
- Efficacy assessment
- Eligibility
- Choice of end-point
- Statistics
- Data
- Updates

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

RANDOMIZATION

Lapatinib 1500 mg/day PO
N=148

Crossover if PD after 4wk therapy (N=73)

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

Study conducted and funded by GlaxoSmithKline

Study EGF104900

- **Primary Endpoint:**
  - PFS in ITT population by Investigator
- **Secondary Endpoints:**
  - Overall survival; overall response rate; clinical benefit rate; duration of response; time to response; safety; quality of life
- **Patient Accrual by Region:**
  - North America (62.5%)
  - Europe (37.5%)
- **Accrual:**
  - November 17, 2005 → November 21, 2006

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- EGF104900, a phase III, randomized, multicenter, **open-label** study
- Efficacy assessments were performed **every 4 weeks through week 16**, and then every 8 weeks thereafter.
  - ***Reproducibility bias?***
- Eligible patients had at least one **measurable** lesion……
- Cardiac ejection fraction **within the institutional normal range**
  - ***Selection bias?***

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- Primary End-point: **PFS**
  - …investigator assessed (*pros and cons*)
- Required PFS events: 192
  - 80% power (2-sided .05)
- Expected difference:
  - **HR 0.667**, 50% increase in median PFS
    - …..estimated ***8 weeks*** in the monotherapy group to ***12 weeks*** in the combination group…
      - ***Was that consistent with previous phase IIs?***

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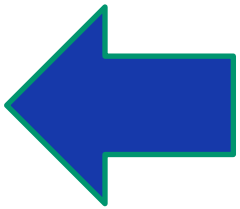
PFS……..why an issue?

Progression-Free Survival: Meaningful or Simply Measurable?

Christopher M. Booth and Elizabeth A. Eisenhauer

- Some trials showing improvement in PFS, without a corresponding increase in OS, have led to approval of new drugs and/or changes in standard of care.
- This suggests a growing belief in the oncology community that ***delaying progression in metastatic disease is a worthy goal, even if OS is not improved***.



Published Ahead of Print on February 27, 2012 as 10.1200/JCO.2011.38.7571
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.38.7571

Progression-Free Survival Remains Debatable Endpoint in Cancer Trials

By Rabiya Tuma

Nicholas Vogelzang, M.D.

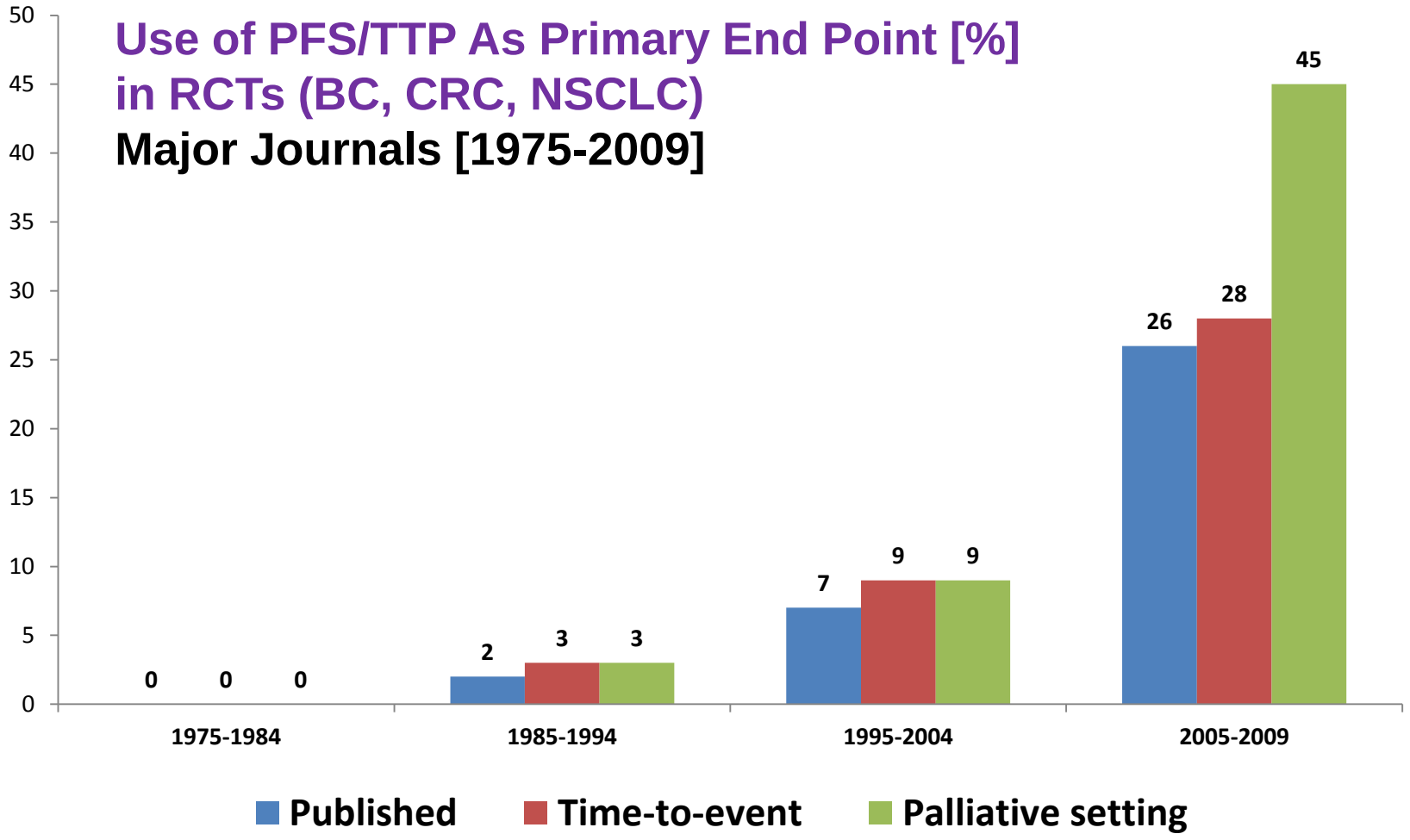
"PFS is a strong enough endpoint; it is the only reliable consistent endpoint that we have right now."

"Just demonstrating a statistically significant difference in PFS is not enough. It has to be clinically meaningful."

Richard Pazdur, M.D.

Progression-Free Survival: Meaningful or Simply Measurable?

Christopher M. Booth and Elizabeth A. Eisenhauer



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Why overall survival is NOT the only endpoint for drug approval.....and we need PFS ?

- May involve larger trials
- May require lenghty follow-up
- May be affected by:
  - ***Sequential treatments***
  - ***Crossover***
- Other endpoints can have intrinsic value

Courtesy of Di Maio M – ESMO 2011

Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma

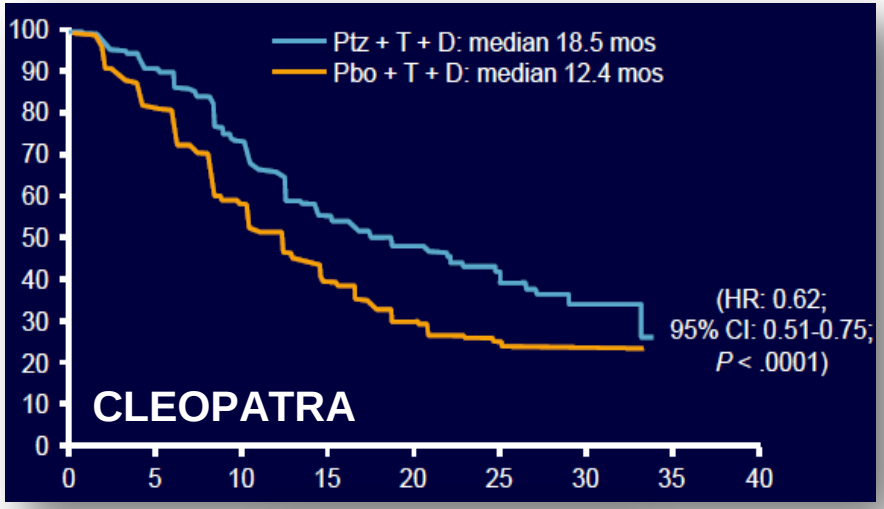
S.J. Hotte MD MSc, G.A. Bjarnason MD,† D.Y.C. Heng MD MPH,‡ M.A.S. Jewett MD,§ A. Kapoor MD,|| C. Kollmannsberger MD,# J. Maroun MD,** L.A. Mayhew MA,†† S. North MD MHPE,‡‡ M.N. Reaume MD MSc,§§ J.D. Ruether MD,|||| D. Soulieres MD MSc,## P.M. Venner MD,‡‡ E.W. Winquist MD MSc,*** L. Wood MD MSC,††† J.H.E. Yong MASc,‡‡‡ and F. Saad MD##*

TABLE III Quality requirements for use of progression-free survival as a primary endpoint

Randomized, blinded study
Defined and consistent assessments of response in each treatment arm
Central radiology review
Clinically relevant absolute gain in progression-free survival
Improvement in progression-free survival supported by other endpoints
Interval between progression and death expected to be 6 months or more
Sufficient data collected to evaluate impact on overall survival at a later date

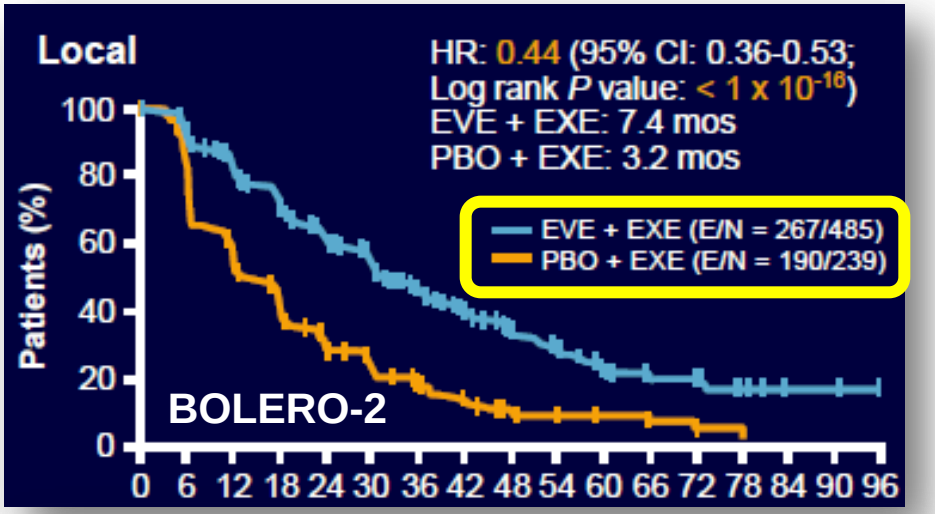
Local *vs* IRB Assessment

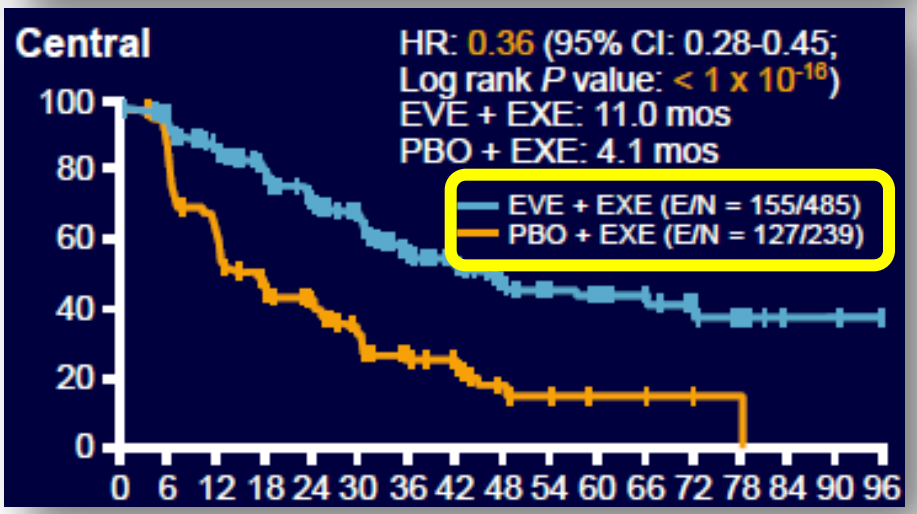
Primary: IRB



The NEW ENGLAND JOURNAL of MEDICINE

Primary: Local

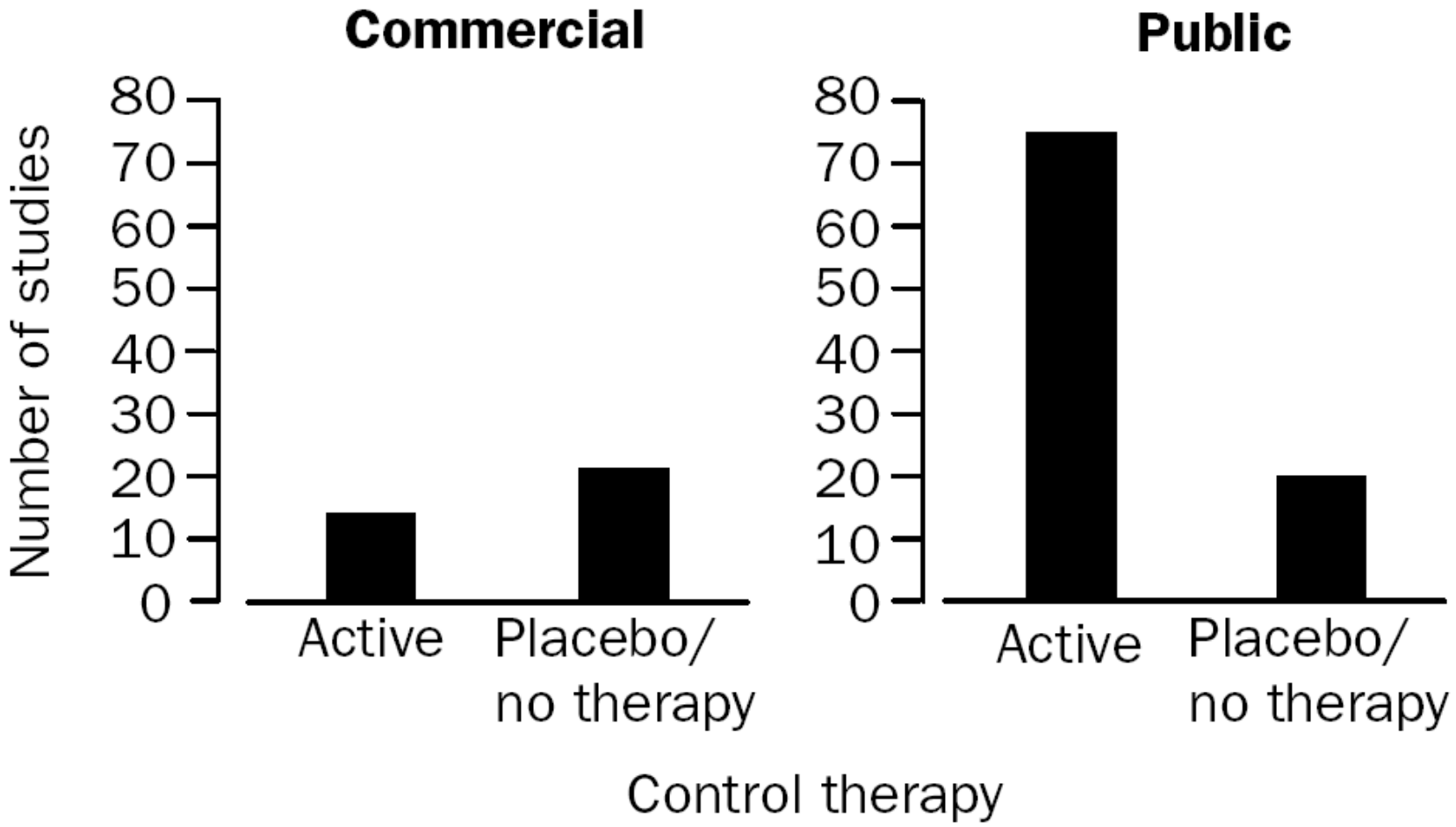




The uncertainty principle and industry-sponsored research

Benjamin Djulbegovic, Mensura Lacevic, Alan Cantor, Karen K Fields, Charles L Bennett, Jared R Adams, Nicole M Kuderer, Gary H Lyman

THE LANCET • Vol 356 • August 19, 2000



Previous Ph.IIs as quoted by authors

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]

Median PFS: 9.1 wks

ORR: 4.3%

Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens

K. L. Blackwell[1]*, M. D. Pegram[2], E. Tan-Chiu[3], L. S. Schwartzberg[4], M. C. Arbushites[5], J. D. Maltzman[5], J. K. Forster[5], S. D. Rubin[5], S. H. Stein[5] & H. J. Burstein[6]

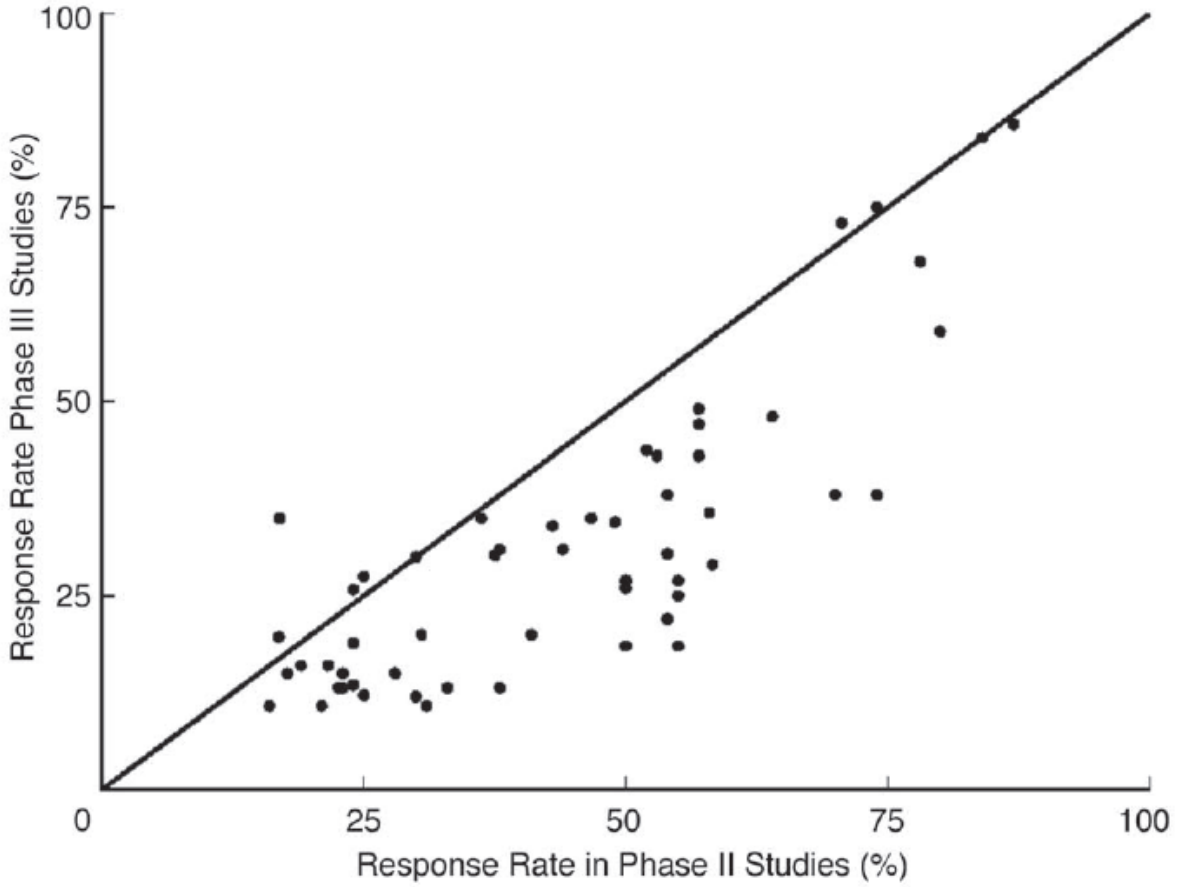
Median PFS: 15.3 wks

ORR: 14.1%

Tumor response		
Tumor response rate, %	6.9	10.3
95% CI	5.9 to 16.4	3.4 to 12.3

Comparison of Outcomes of Phase II Studies and Subsequent Randomized Control Studies Using Identical Chemotherapeutic Regimens

Mohammad I. Zia, Lillian L. Siu, Greg R. Pond, and Eric X. Chen



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JOURNAL OF CLINICAL ONCOLOGY

Patient and Tumor Characteristics

Study Arms ITT Population	L N = 148	L+T 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 ≥ 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

Between November 2005 and November 2006, 296 patients (148 per treatment arm), constituting the ITT population, were randomly assigned at 88 centers within North America (62.5%) and Europe (37.5%)

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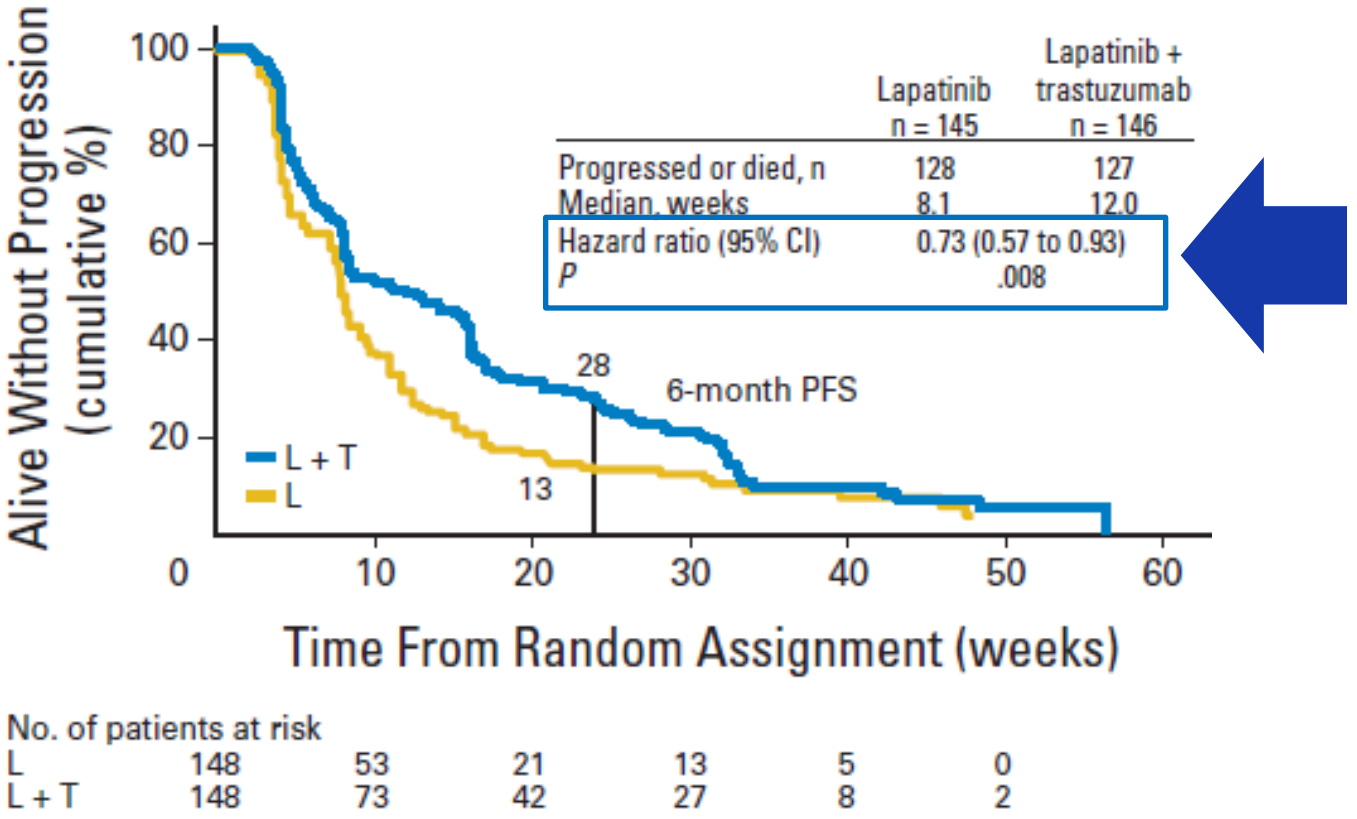

Independent review: HR 0.71; 95% CI, 0.52 to 0.98; *P=0.027*

Adjusted for significant covariates: HR 0.72; 95% CI, 0.56 to 0.92; *P=0.0095*

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JOURNAL OF CLINICAL ONCOLOGY

COMMENTARY | J Natl Cancer Inst 2011;103:16–20

When Are "Positive" Clinical Trials in Oncology Truly Positive?

Alberto Ocana, Ian F. Tannock

In some of the articles the magnitude of the reported values of δ were lower than the values predefined in the protocol.

We suggest that trials should not be declared positive based only on a statistically significant *P* value, but should also require detection of a difference in outcome that equals or exceeds a clinically important value that is specified in the protocol.

Courtesy of Pappagallo G – Perugia 2011

Statistical Design

	E2100	R1-Cap	R1-T/Anth	AVADO[1]
Sample size	685	600	600	705
PFS events	546	415	405	435
Power (%)	85	80	90	80
Effect in HR				
Targeted	0.75	0.75	0.70	0.70
Observed	0.48	0.69	0.64	0.62
P value	< 0.0001	0.0002	< 0.0001	0.0003

Cap = Capecitabine; HR = Hazard ratio; PFS = Progression-free survival; T/Anth = Taxane/anthracycline.
1. Sample size and PFS events include information from all 3 treatment arms. Effected size and p-value refer to the comparison between placebo and the standard dose.

Courtesy of Pappagallo G – Perugia 2011

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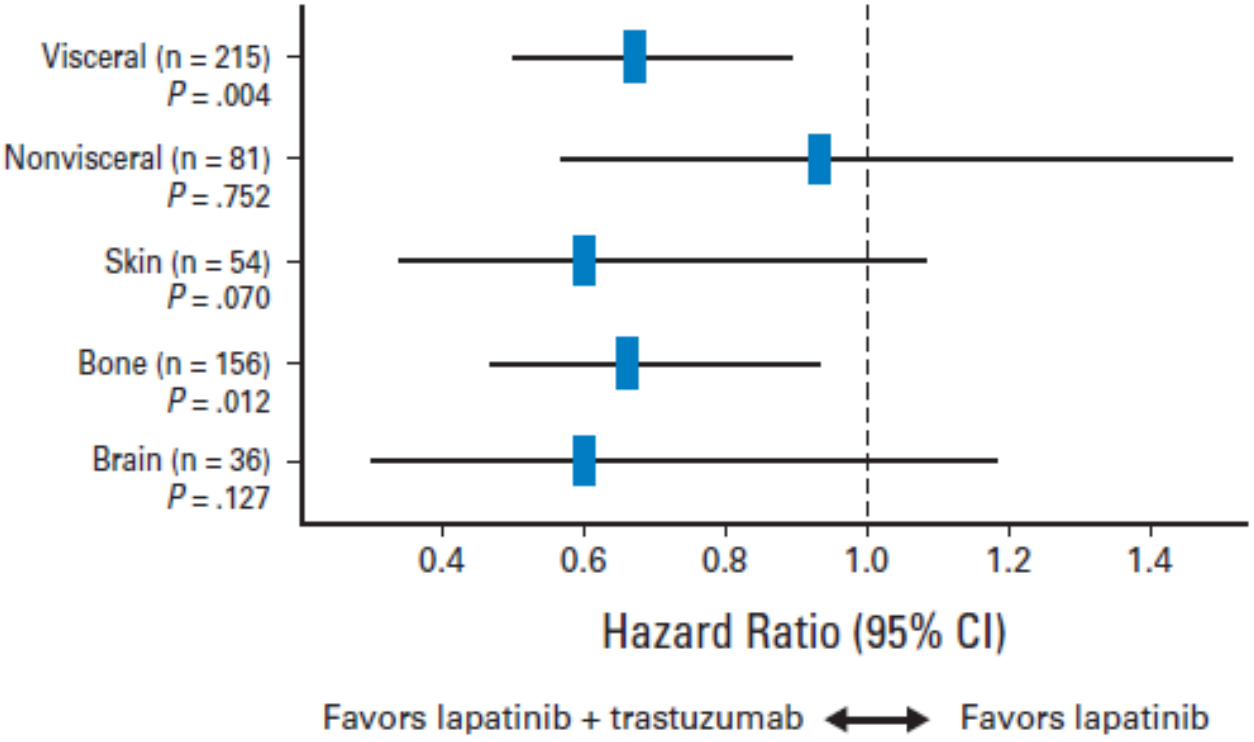
……Patients presenting with **visceral** or **bone** disease at baseline experienced a longer PFS if treated with the combination therapy……



No significant interaction!!!

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Subgroup analyses in randomized trials: risks of subgroup-specific analyses

Sara T. Brookes[a,*], Elise Whitely[a], Matthias Egger[b], George Davey Smith[a], Paul A. Mulheran[c], Tim J. Peters[d]

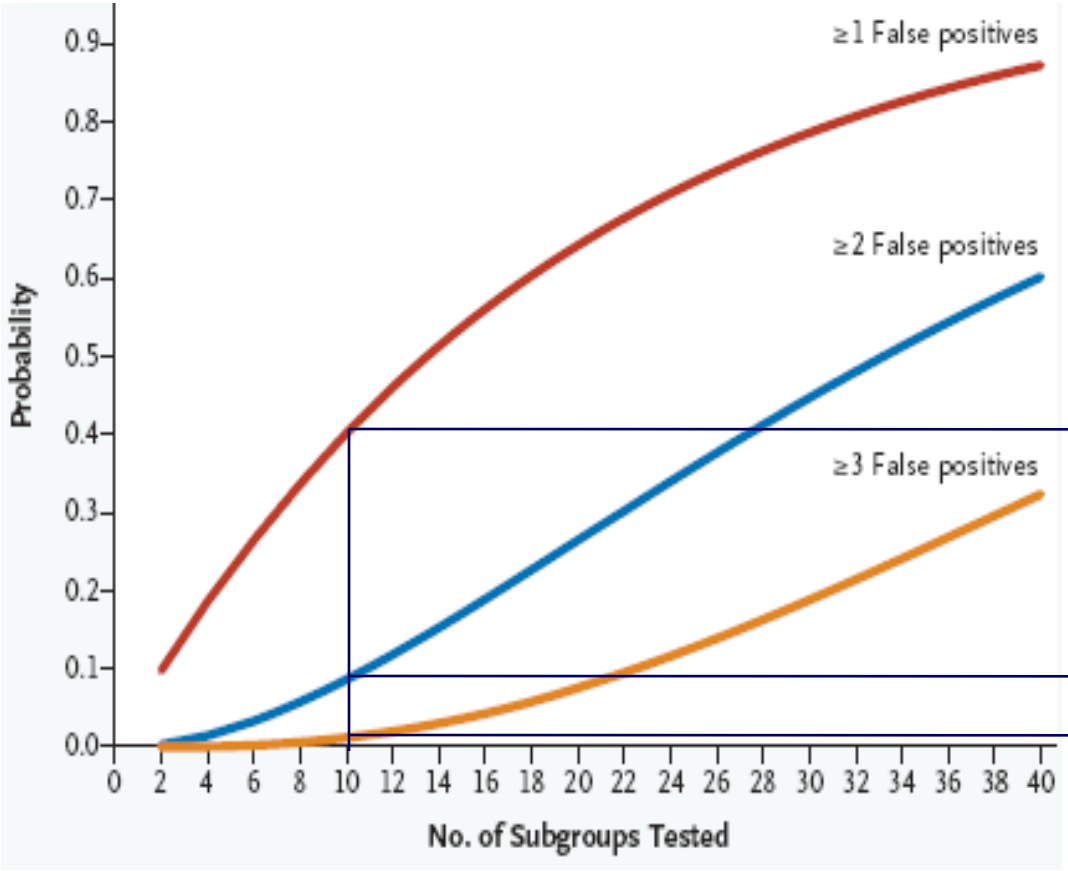
Journal of Clinical Epidemiology 57 (2004) 229–236

A test for interaction between treatment and subgroup is the appropriate way to examine whether treatment effects differ between subgroups [1,3,4,12–15]. This approach tests and estimates the difference between treatment effects across subgroups directly. It involves one statistical test irrespective of the number of subgroups, whereas subgroup-specific analyses involve two or more.

Courtesy of Pappagallo G – Perugia 2011

The Challenge of Subgroup Analyses — Reporting without Distorting

Ex.: if you test 10 subgroups, your F.P. chance is:



Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

N ENGL J MED 354;16 WWW.NEJM.ORG APRIL 20, 2006

Published Ahead of Print on October 13, 2009 as 10.1200/JCO.2009.22.4329
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.22.4329

Role of Sensitivity Analyses in Assessing Progression-Free Survival in Late-Stage Oncology Trials

Suman Bhattacharya, Gwen Fyfe, Robert J. Gray, and Daniel J. Sargent

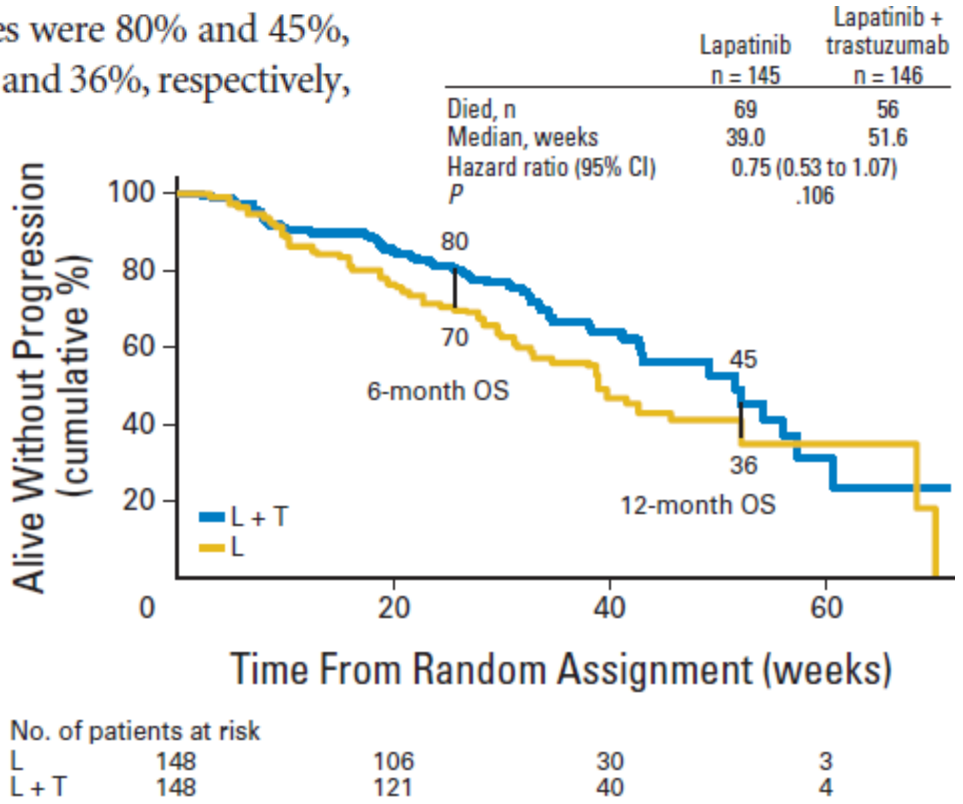
J Clin Oncol 27.

In a trial in which PFS is the primary end point, we recommend performing, at a minimum, sensitivity analyses to explore the impact of assessment time imbalances, nonradiologically confirmed PFS events, and missing data. In some cases, multiple assumptions may be violated simultaneously; analyses designed to explore the bias caused by multiple deviations should be included in a prospective sensitivity analysis plan. In general, sensitivity analyses should be included in the study protocol or statistical analysis plan and should optimally be reported alongside the primary results in study publications.

Courtesy of Pappagallo G – Perugia 2011

…..'Speculating' upon OS..

In total, 57 patients (39%) in the combination arm and 71 patients (48%) in the lapatinib monotherapy arm died by the time of data cutoff. The median OS time in the study was 51.6 weeks in patients receiving lapatinib plus trastuzumab compared with 39.0 weeks in patients receiving lapatinib monotherapy. Although these data are not mature (56% censoring rate), they show a trend in improved OS after combination therapy (HR = 0.75; 95% CI, 0.53 to 1.07; $P = .106$). The 6- and 12-month OS rates were 80% and 45%, respectively, for combination therapy and 70% and 36%, respectively, for monotherapy (Fig 3).



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

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1. **Mature OS data** (January 23, 2009), when 75% of patients died.
   - Overall 38 months
2. **Sensitivity analysis of OS** included a stratified log-rank test:
   - crossover patients censored at time of crossover
3. **Survival post progression** (SPP) analysis

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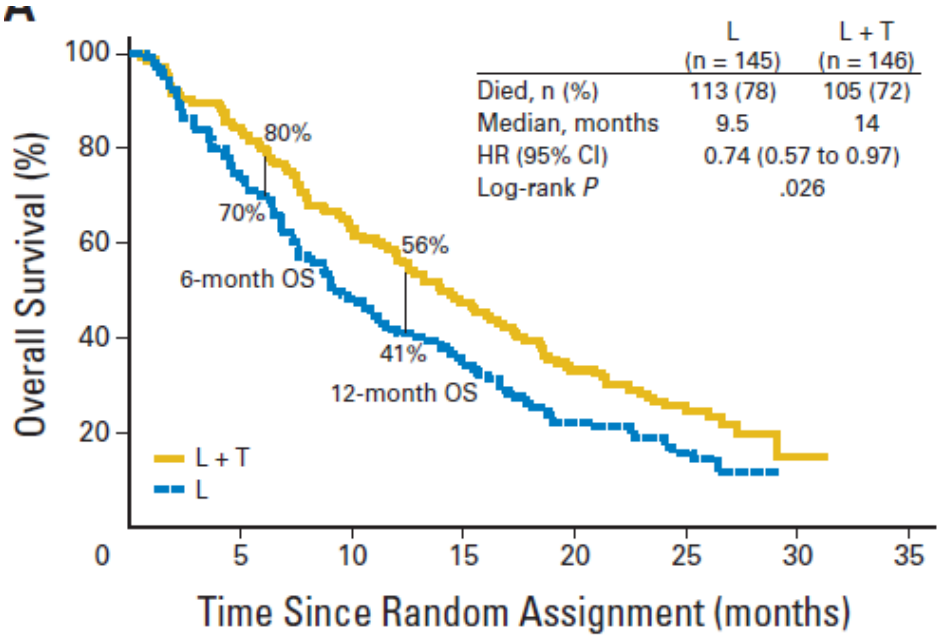
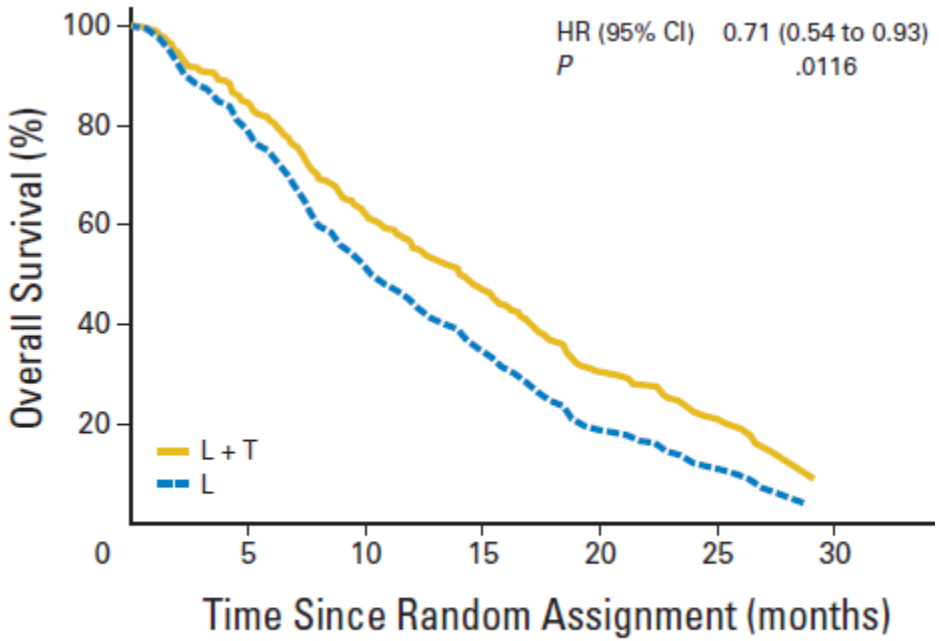
A



	L (n = 145)	L + T (n = 146)
Died, n (%)	113 (78)	105 (72)
Median, months	9.5	14
HR (95% CI)	0.74 (0.57 to 0.97)	
Log-rank *P*	.026	

No. at risk

L + T	146	120	87	63	42	25	1
L	145	100	64	46	28	13	



No. at risk

L + T	146	120	87	63	42	25	1
L	145	100	64	46	28	13	

SPP

Median SPP was 10.7 months for those receiving the lapatinib plus trastuzumab combination and 6.4 months for those receiving lapatinib (HR, 0.80; 95% CI, 0.61 to 1.05; $P = .106$).

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Conclusions

- Overall survival is the gold standard endpoint in metastatic breast cancer since it is both a safety and efficacy parameter.
- PFS may be an acceptable endpoint if measured properly and is of sufficient magnitude. Survival also should be measured to ensure that any new therapy does not lead to a decrement.
- Discussion of the appropriate setting to use PFS is encouraged by the FDA during trial design.

ASCO | Annual '08 Meeting

FDA approval overview.
Discussion: P. Cortazar

Courtesy of Pappagallo G – Perugia 2011

Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival

Kristine R. Broglio, Donald A. Berry

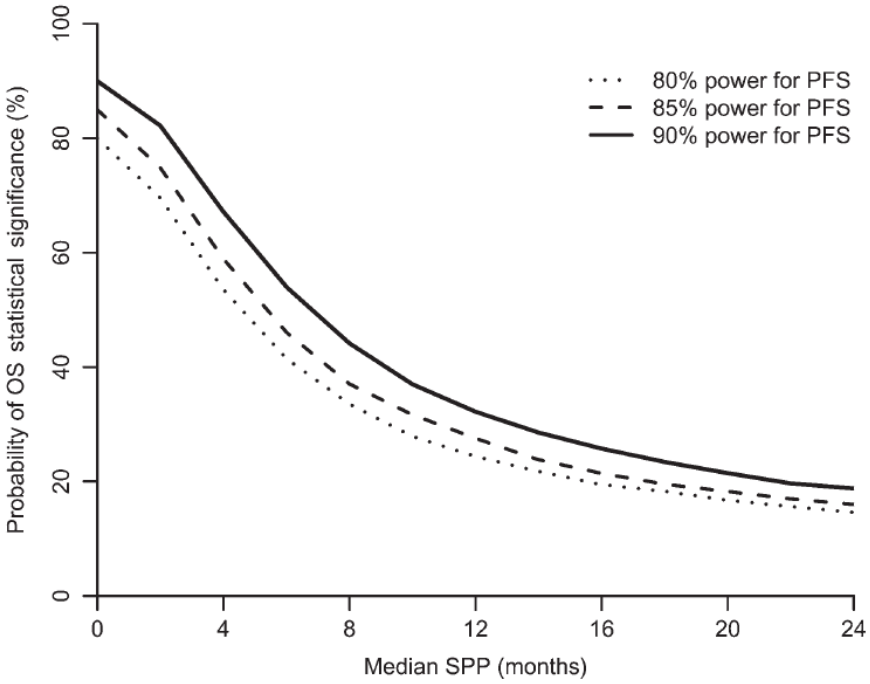


Figure 2. Probability of statistically significant differences in overall survival (OS) as a function of median survival postprogression (SPP). The **three curves** were indexed by the power for detecting the actual median progression-free survival (PFS) benefit that was simulated, 6 vs 9 months (ie, powers of 90%, 85%, and 80%).

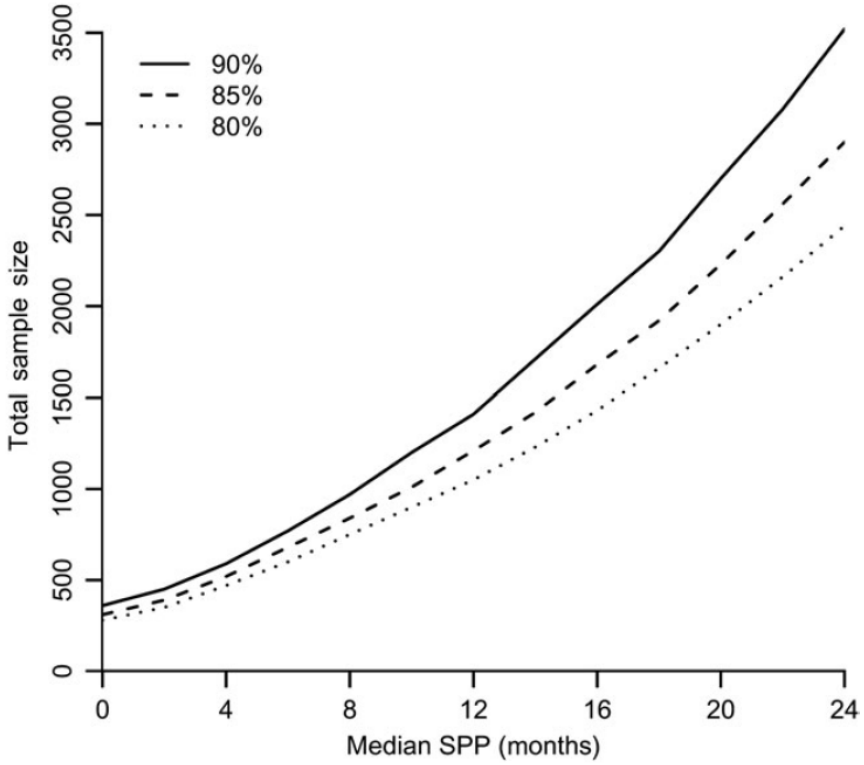


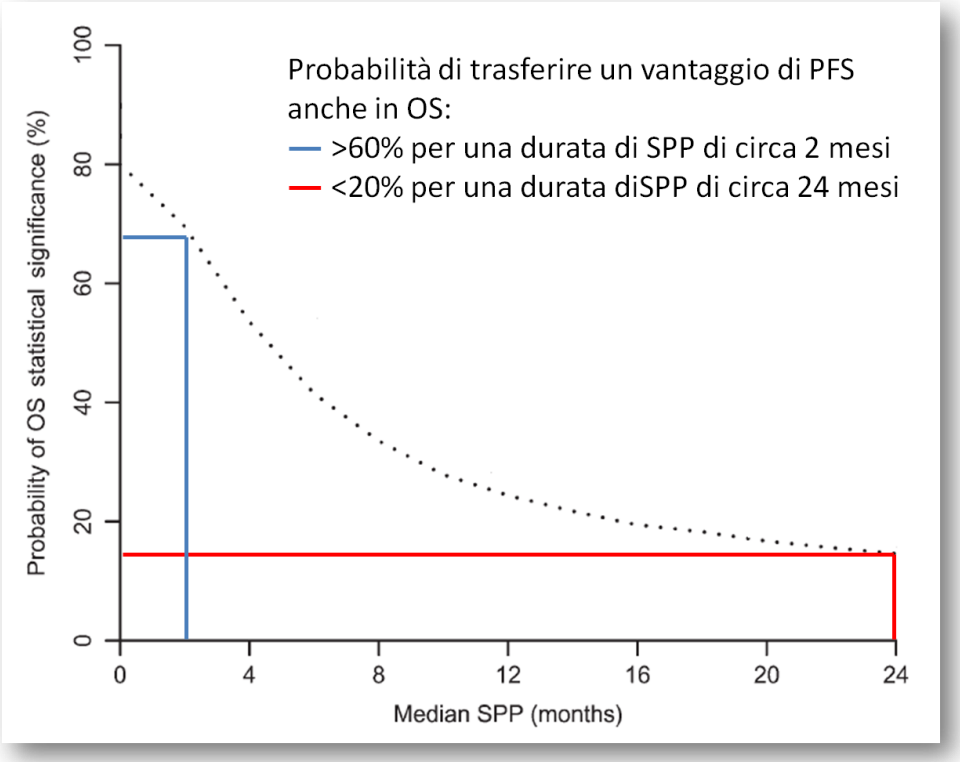
Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The **three curves** were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

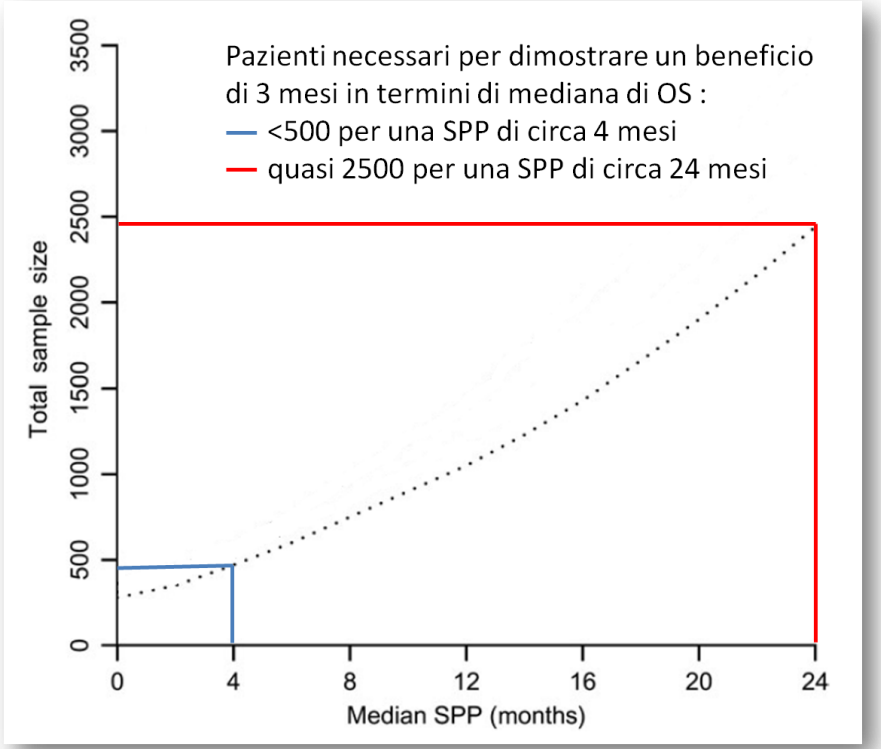
J Natl Cancer Inst 2009;101:1642–1649

Sopravvivenza post-progressione

OS = PFS + SPP

Se l'evento che determina la progressione è il decesso, allora SPP = 0





J Natl Cancer Inst 2009;101:1642–1649

Courtesy of Pappagallo G – Perugia 2011

Overall Survival and Post-Progression Survival in Advanced Breast Cancer: A Review of Recent Randomized Clinical Trials

Everardo D. Saad, Artur Katz, and Marc Buyse

Median PFS, OS, and PPS, and the Proportion of OS Accounted for by PPS for Selected Recent Studies in Breast Cancer

Trial	Median (months) PFS	OS	PPS	Proportion of OS Accounted for by PPS (%)
Paclitaxel (first-line)[8]	5.9	25.2	19.3	76.6
Paclitaxel + bevacizumab (first-line)[8]	11.8	26.7	14.9	55.8
Capecitabine (first-line)[10]	5.7	21.2	15.5	73.1
Capecitabine + bevacizumab (first-line)[10]	8.6	29.0	20.4	70.3
Anthracycline or taxane (first-line)[10]	8.0	23.8	15.8	66.4
Anthracycline or taxane + bevacizumab (first-line)[10]	9.2	25.2	16.0	63.5

Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

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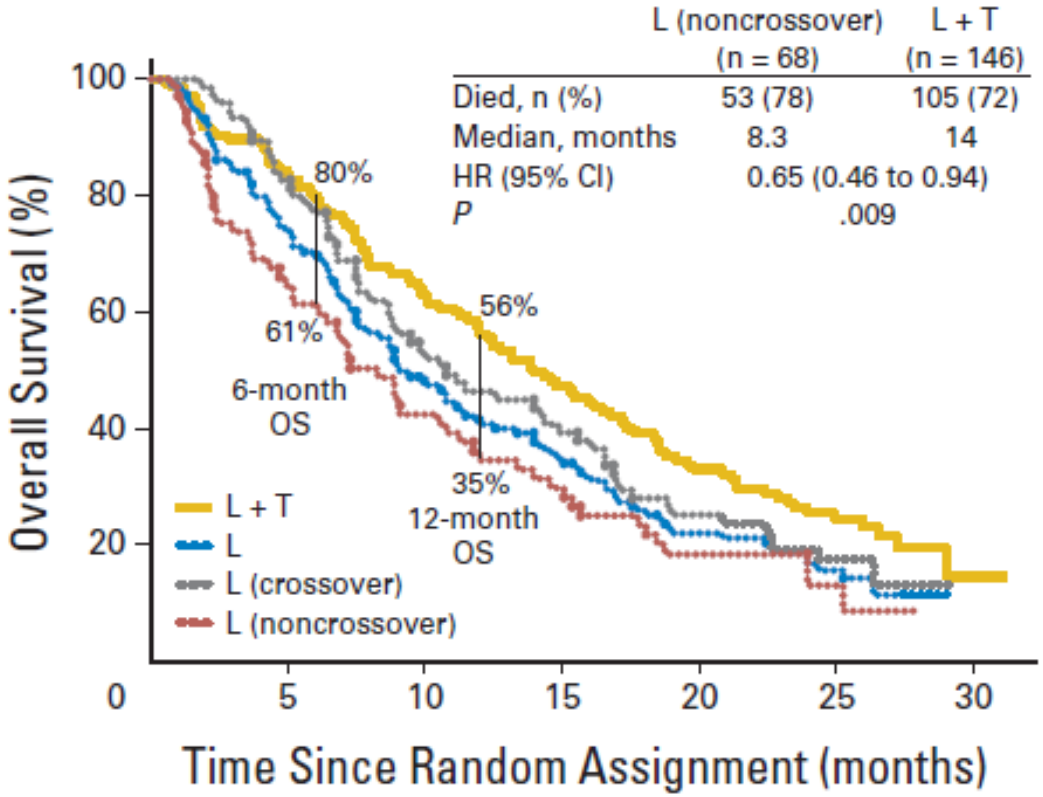

No. at risk

L + T	146	120	87	63	42	25	1
L	145	100	64	46	28	13	
L (crossover)	77	60	38	28	18	10	
L (noncrossover)	68	40	26	18	10	3	

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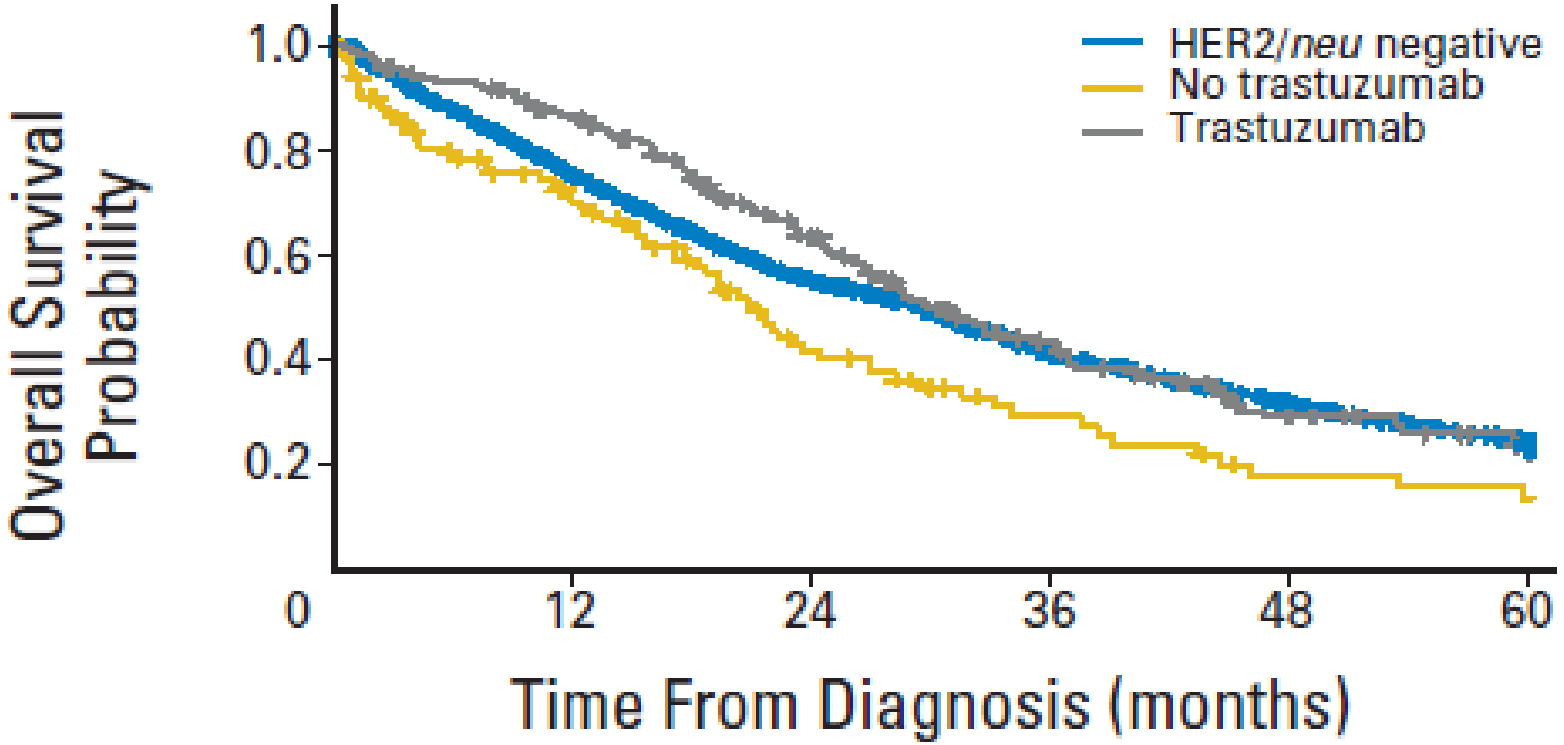
JOURNAL OF CLINICAL ONCOLOGY

Prognosis of Women With Metastatic Breast Cancer by *HER2* Status and Trastuzumab Treatment: An Institutional-Based Review

Shaheenah Dawood, Kristine Broglio, Aman U. Buzdar, Gabriel N. Hortobagyi, and Sharon H. Giordano



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

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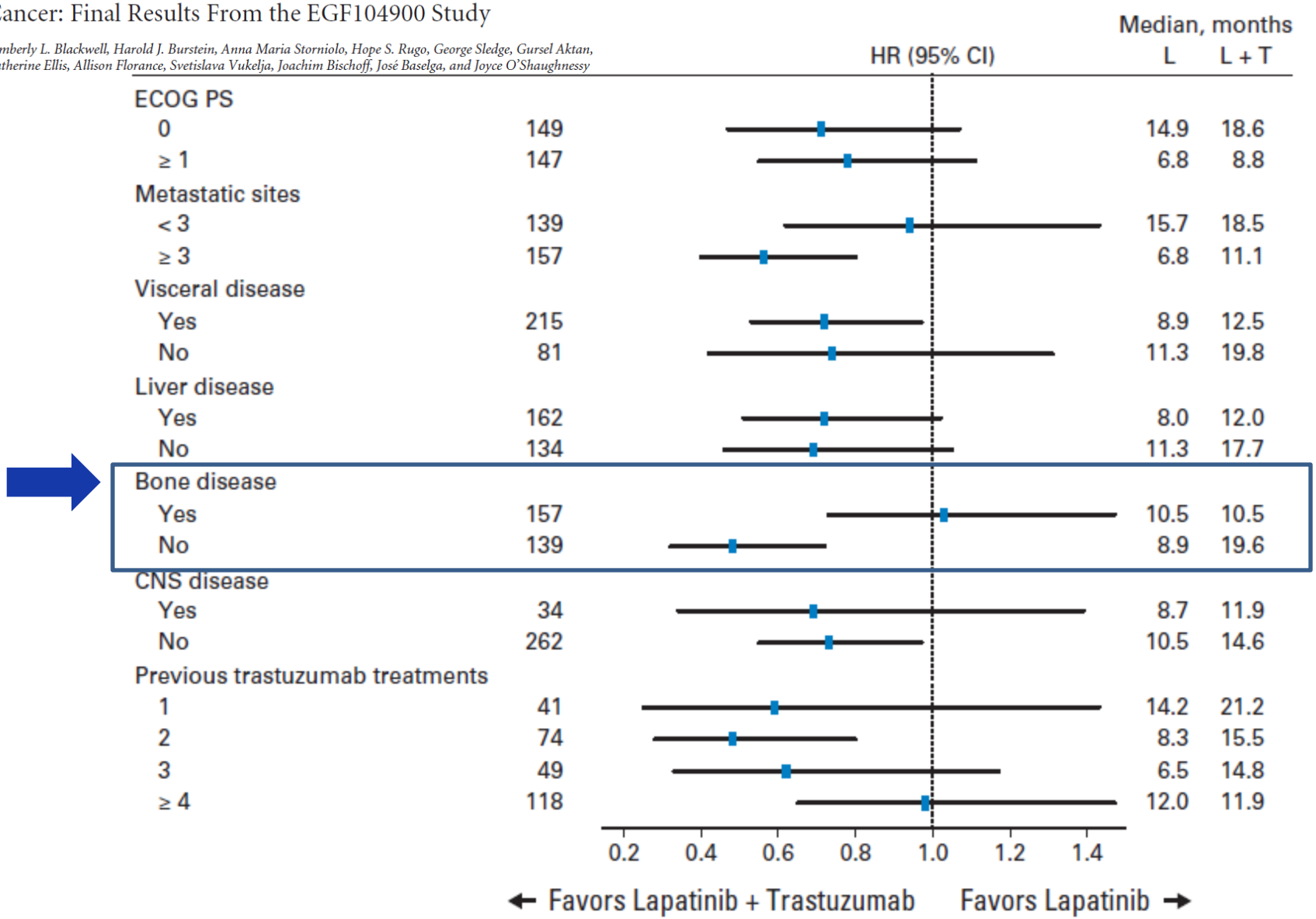
Overall Survival Benefit With Lapatinib in Combination With Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: Final Results From the EGF104900 Study

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



Interaction never mentioned!

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Types of Interactions

- **Qualitative Interaction:** the direction of true treatment differences varies among subsets of patients
  - also called *crossover interaction*
- **Quantitative Interaction:** variation in the magnitude but NOT direction of treatment effects among patient subgroups – also called a non-crossover interaction

Amy Wagaman, 2008

Conclusions

- Primary end-point (un)met?!?!!
  - **Less than what clinically expected**
- The effect of (adding) trastuzumab in the context of a extremely heavy pretreated patients' population seems documented
  - **How much is due to trastuzumab by itself?**
- OS advantage is certanily speculative, but,
  - **……as requested by agencies, the effect upon late survival is present**