Lapatinib e Trastuzumab vs Lapatinib:

Quale impatto sulla pratica clinica?

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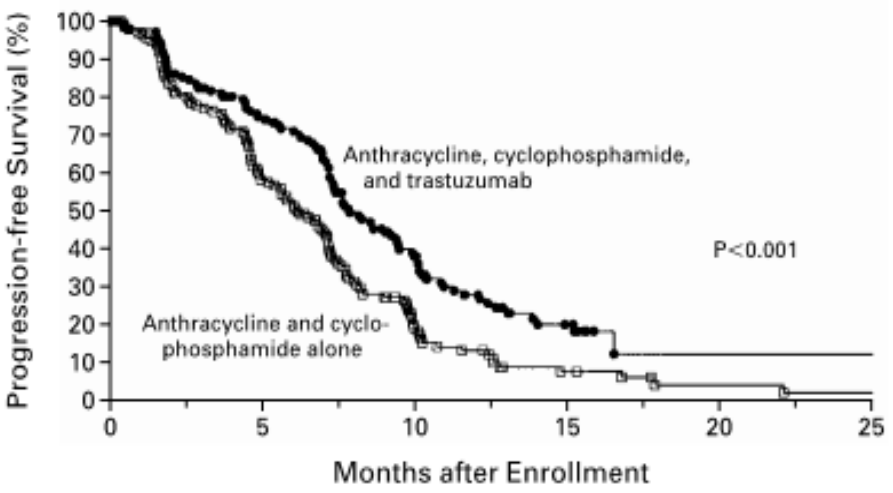
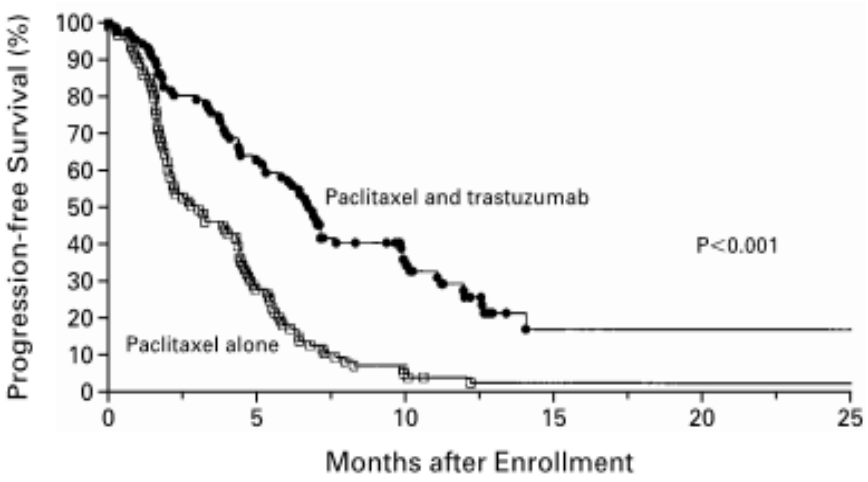
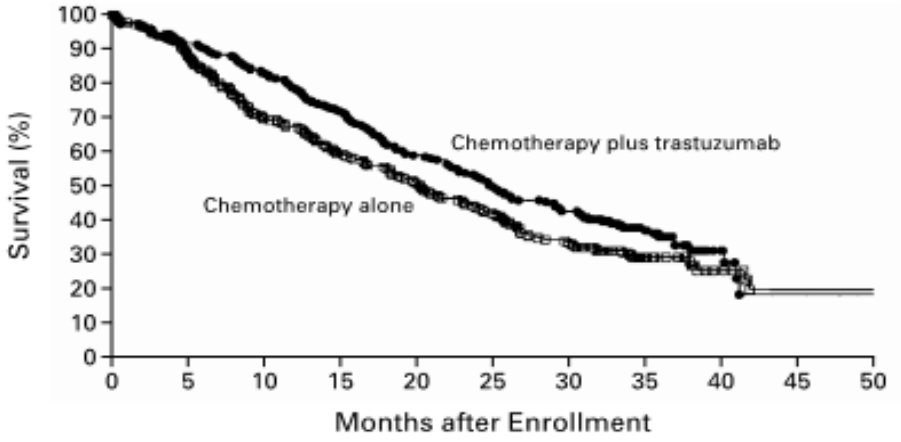
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2



AC 6.1 vs AC+T 7.8 $p < .001$



P 3.0 vs P+T 6.9 $p < .001$



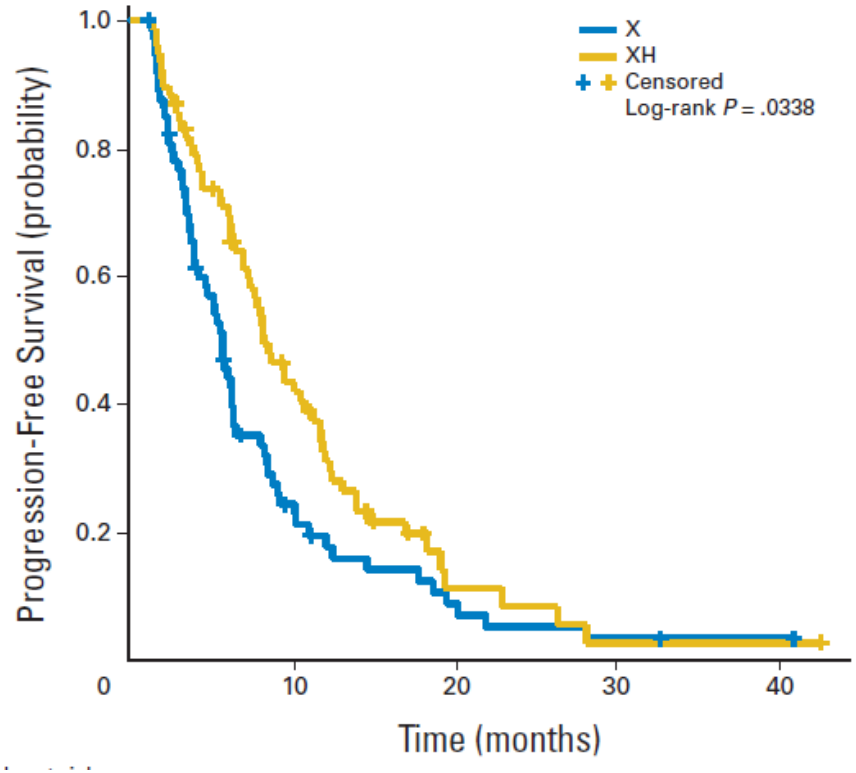
CT 20.3 vs CT+T 25.1 $p = .046$

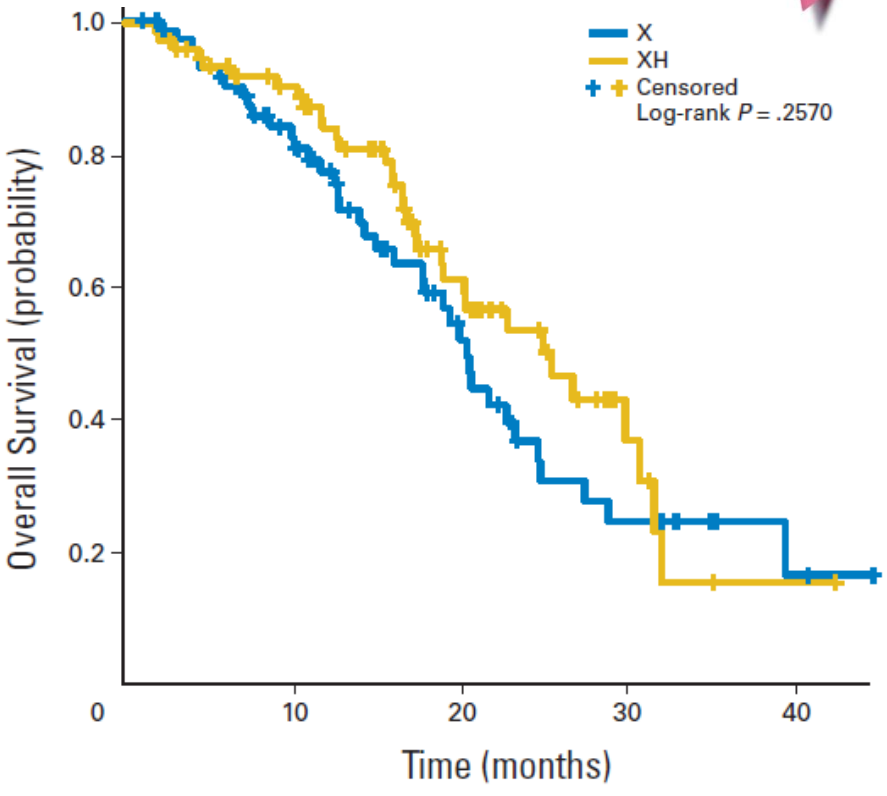
Beyond progression

An even greater controversy was the continuation of trastuzumab or other target therapy beyond progression of disease.

Laboratory data supported the concept that trastuzumab should be continued in this setting.

Trastuzumab plus capecitabine

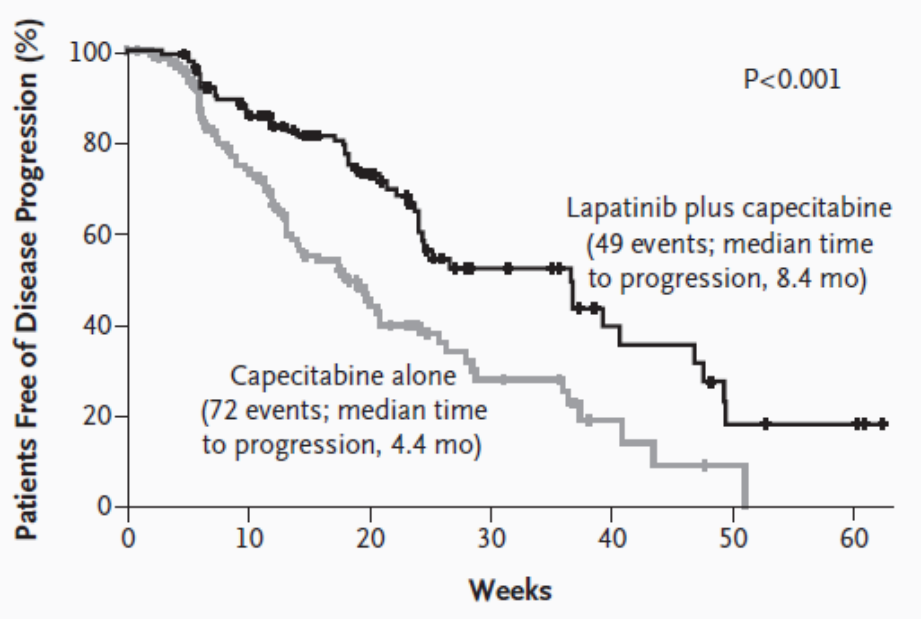


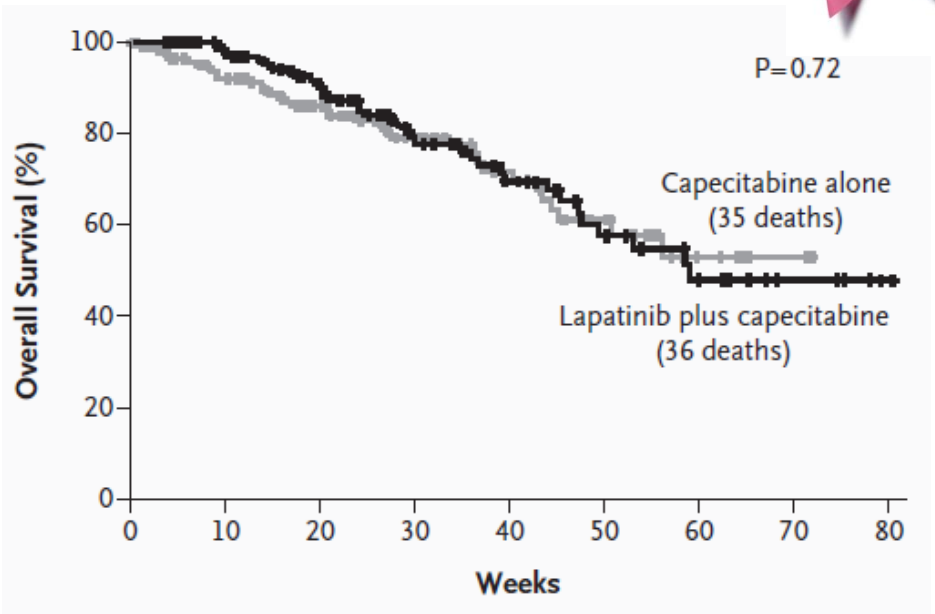


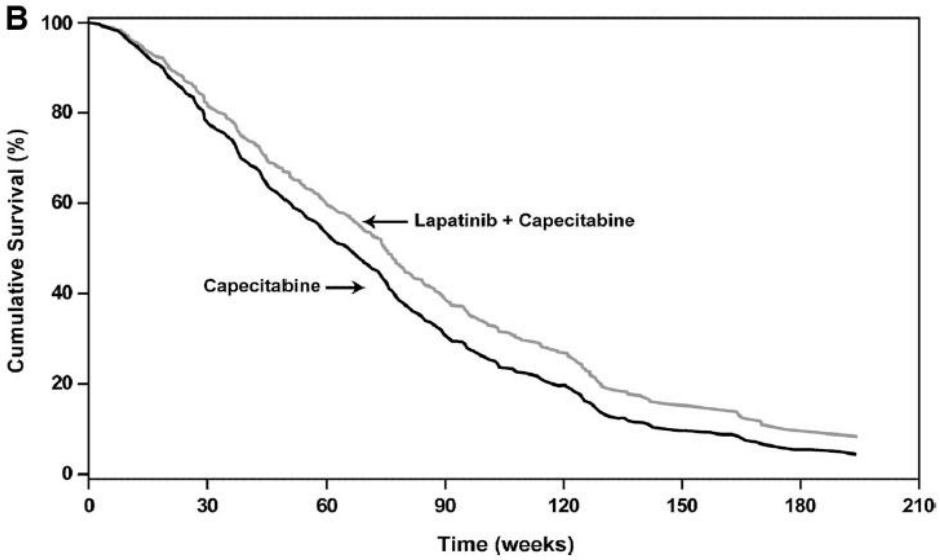
PFS = 5.6 vs 8.2 months, p = .0338, but OS was not statistically significanty different.

Open-label design with no indipendent assessment of response and small number of patients were important limitations.

Lapatinib plus capecitabine







OS curve adjusted for Eastern Cooperative Oncology Group performance status score, number of metastatic sites, and liver metastases.

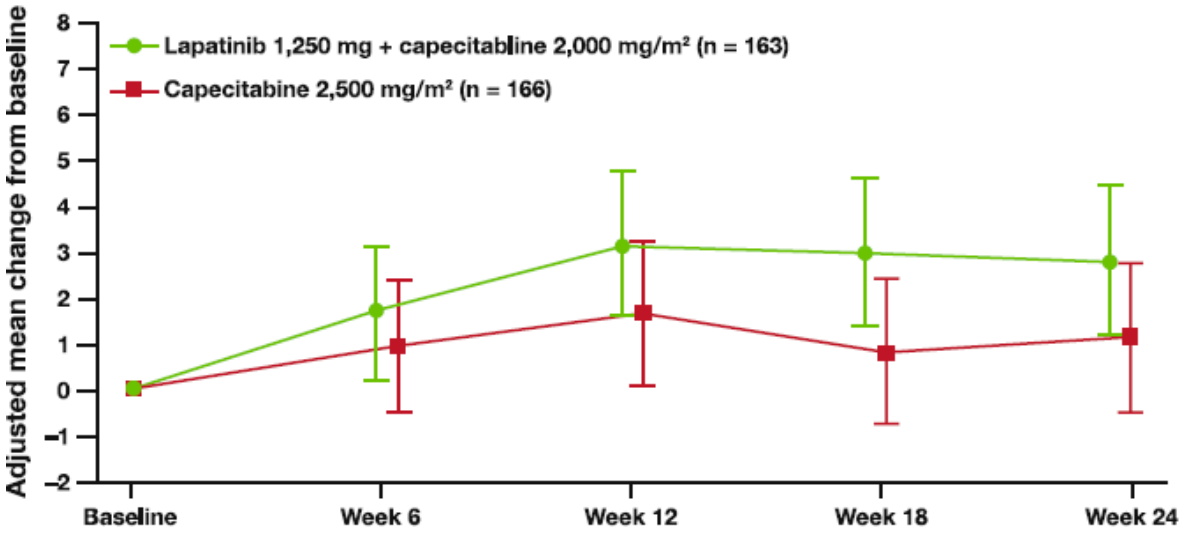
Lapatinib plus capecitabine [2]

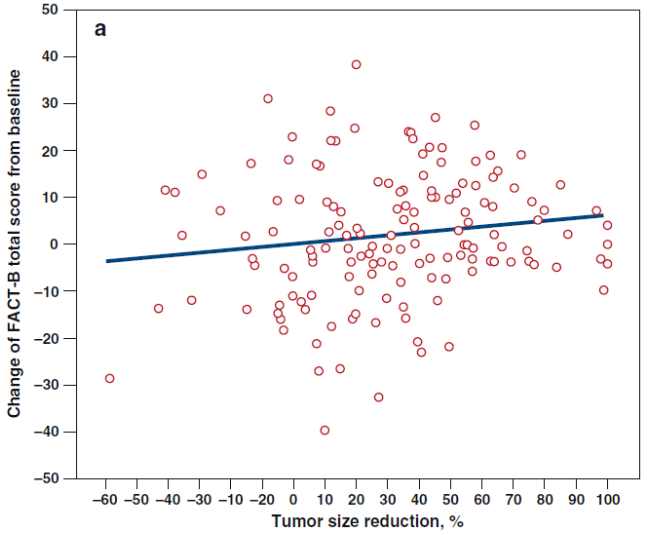
Progressive CNS metastases → 11 women in the monotherapy group vs 4 women in the combination-therapy group. This difference was not statistically significant (p = .10).

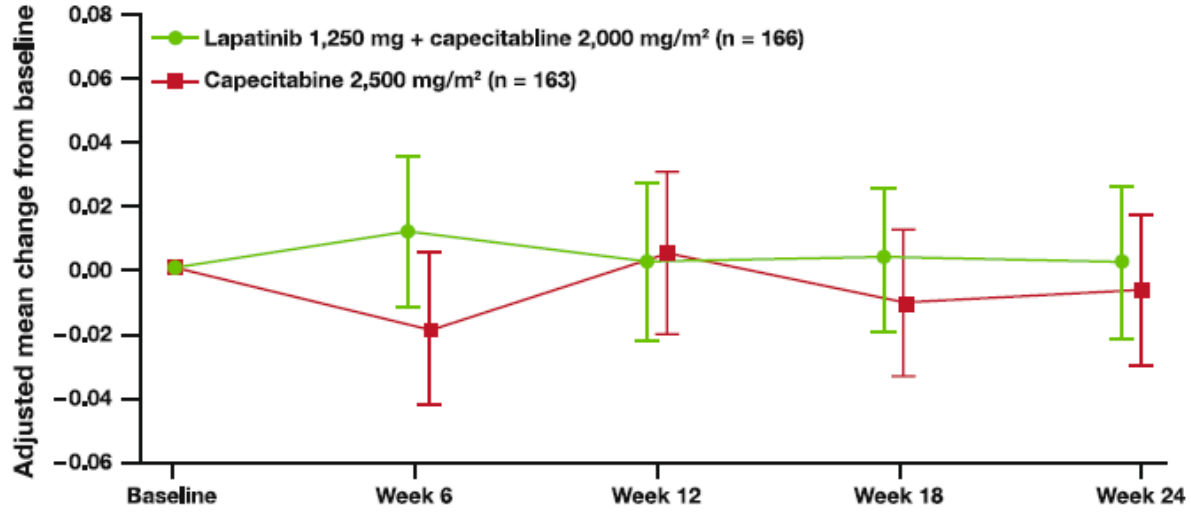
ADVERSE EVENTS:

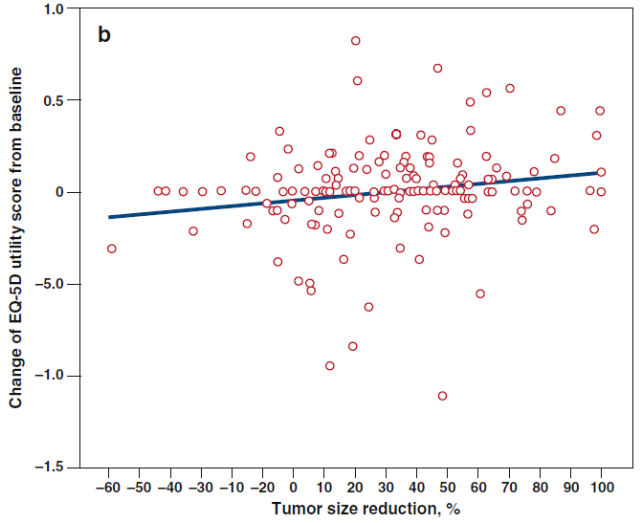
- Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy. Grade 4 diarrhea occurred in 2 women in the combination-therapy group (1%).
- 5 women had a fatal adverse event: 2 in the combination-therapy group and 3 in the monotherapy group.
- Adverse events led to discontinuation of treatment in 22 women in the combination-therapy group (13%) and in 18 women in the monotherapy group (12%).

Lapatinib plus capecitabine: QoL





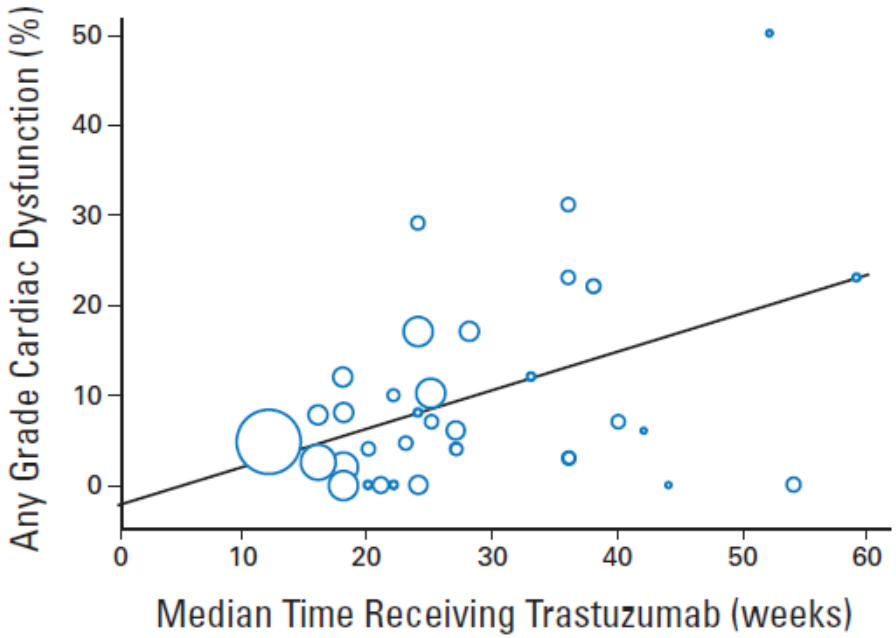




Cardiac safety

Trastuzumab plus capecitabine → 4 severe cardiac events: 1 congestive heart failure, 1 tachyarrhythmia, 1 hypertension, and 1 LVEF decrease > 10% from baseline. No therapy-related death occurred.

Lapatinib plus capecitabine → 4 asymptomatic cardiac events in combination-therapy group. No symptomatic cardiac events, no differences in mean LVEF values between capecitabine single agent and capecitabine plus lapatinb.



However, time receiving trastuzumab was associated with an increased risk of developing any grade of cardiac toxicity.

Lapatinib plus trastuzumab

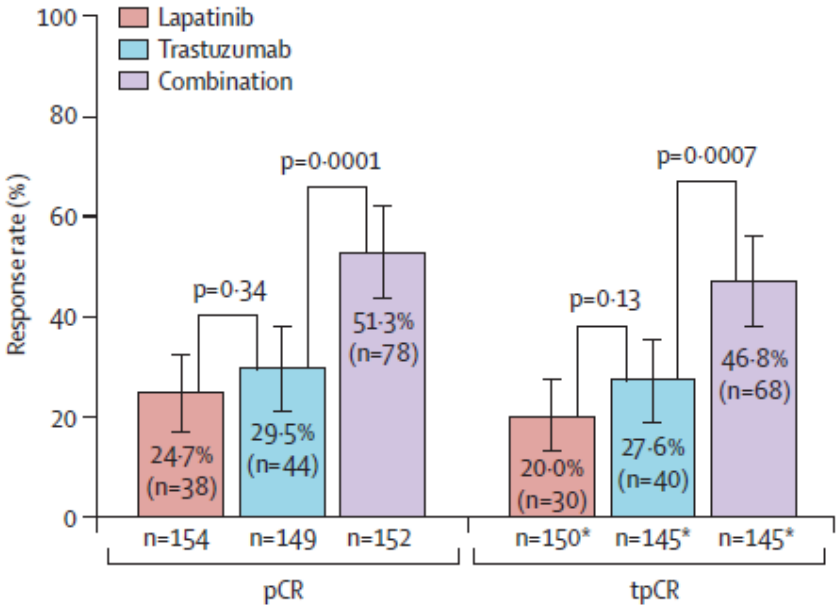
In ErB2-positive cells, lapatinib and trastuzumab have non-overlapping resistance mechanisms.

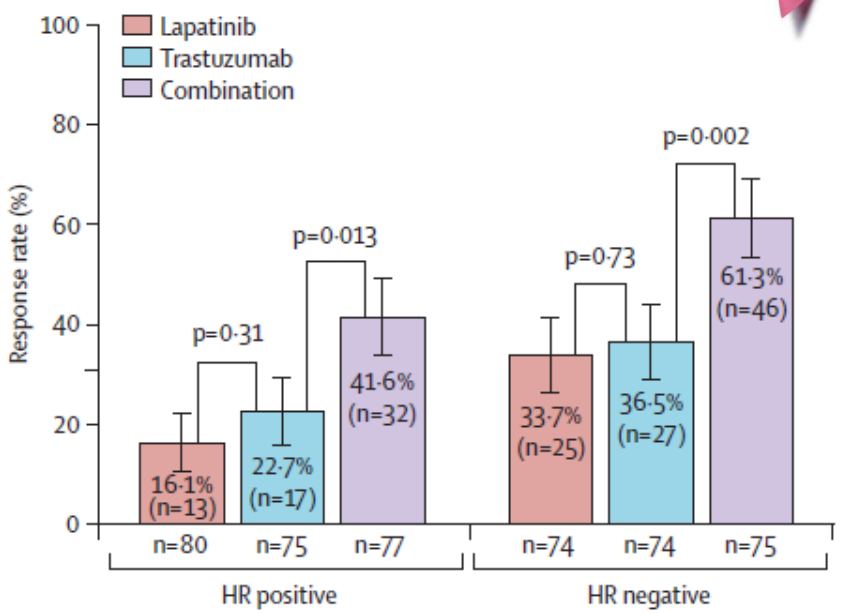
Preclinical models demonstrated the interaction of lapatinib with trastuzumab as synergistic and resulting in enhanced apoptosis in ErbB2-positive BC cells.

In xenograft models, lapatinib plus trastuzumab resulted in complete tumor regression within 10 days of treatment.

This preclinical data provide a rationale to pursue the combination in the clinical setting.

Lapatinib plus trastuzumab: neoadjuvant





NeoALTTO study → 3 treatments arms: oral lapatinib (1500 mg/d), trastuzumab (4 mg/kg loading dose, 2 mg/kg subsequent doses), or lapatinib (1000 mg/d) plus trastuzumab.

1 patient in each treatment arm had LVEF of less than 50% and a decrease of more than 10% from baseline. 1 patient in the combination group developed congestive heart failure and showed a LVEF decrease from 66% to 55%, but recovered after therapy was stopped.

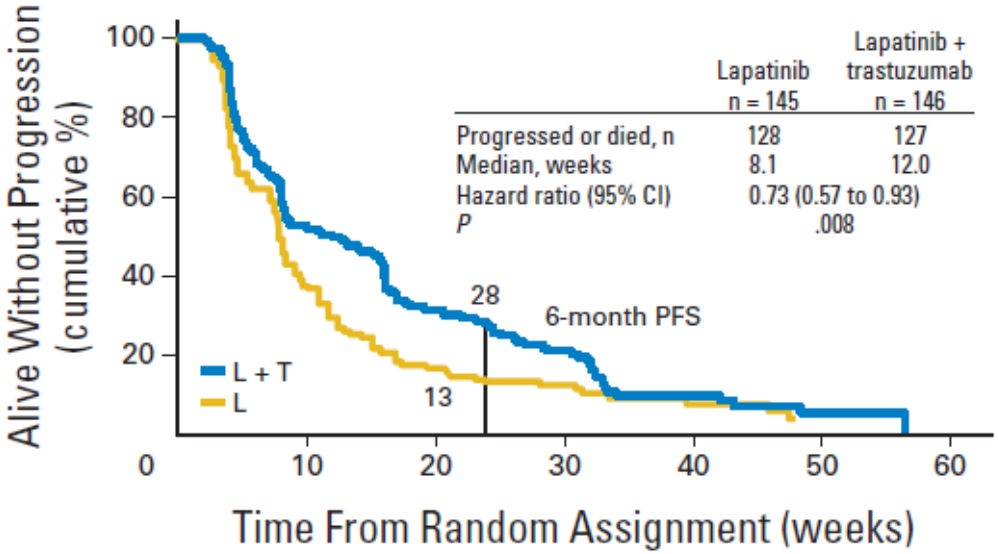
Lapatinib plus trastuzumab: neoadjuvant [2]

	Neoadjuvant treatment arms	Lapatinib dose (mg)	Duration of neoadjuvant HER2-targeted therapy	Number of patients	pCR (no invasive dz in breast and lymph nodes)	Treatment discontinuation rates
NeoALLTO	T × 6w, Pw + T × 12w	0	18	154	27.6%	1.3%
	L × 6w, Pw + L × 12w	1500	18	159	20.0%	18.8%
	TL × 6w, Pw + TL × 12w	750–1000	18	152	46.8%	21.0%
CHERLOB	(Pw × 12w, FEC75 × 4 over 12w) + T	0	26	39	25.0%	0%
	(Pw × 12w, FEC75 × 4 over 12w) + L	1250–1500	26	36	26.3%	17%
	(Pw × 12w, FEC75 × 4 over 12w) + TL	750–1000	26	46	46.7%	30%
NSABP B-41	AC × 4 over 12w, (Pw × 12w) + T	0	16*	173	49.1%	18%
	AC × 4 over 12w, (Pw × 12w) + L	1250	16*	178	47.4%	27%
	AC × 4 over 12w, (Pw × 12w) + TL	750	16*	173	60.4%	28%
Holmes et al	T × 2w, (FEC75 × 4 over 12w, Pw × 12w) + T	0	26	34	54.0%	9.4%
	L × 2w, (FEC75 × 4 over 12w, Pw × 12w) + L	750–1250	26	33	45.0%	11.7%
	TL × 2w, (FEC75 × 4 over 12w, Pw × 12w) + TL	750–1250	26	33	74.0%	25.8%

Average pCR of 53% for combination compared to 39% for trastuzumab alone (RR 1.39, 95% CI 1.20–0.63; p = .001).

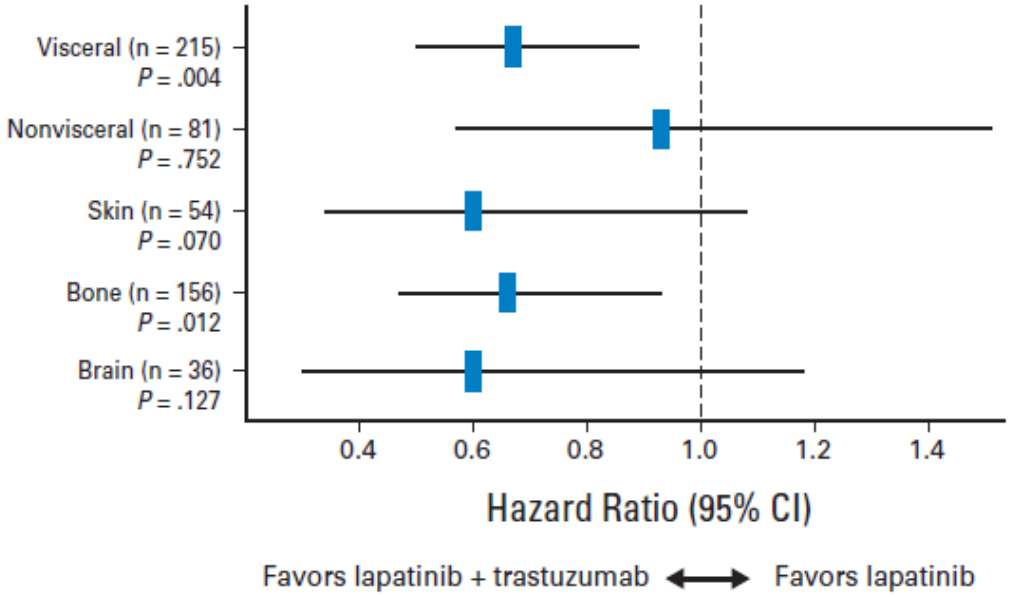
Diarrhea grade 3-4 had a frequency of 25.6%, dermatologic toxicity grade 3-4 was 7.6%, and discontinuation of treatment was 29.6%.
Cardiac toxicity was rare with only 1 of 198 patients (NeoALLTO and CHERLOB) having an LVEF of less than 50% or a decline greater than 10% from baseline in the combination arms.

Lapatinib + trastuzumab vs lapatinib: PFS

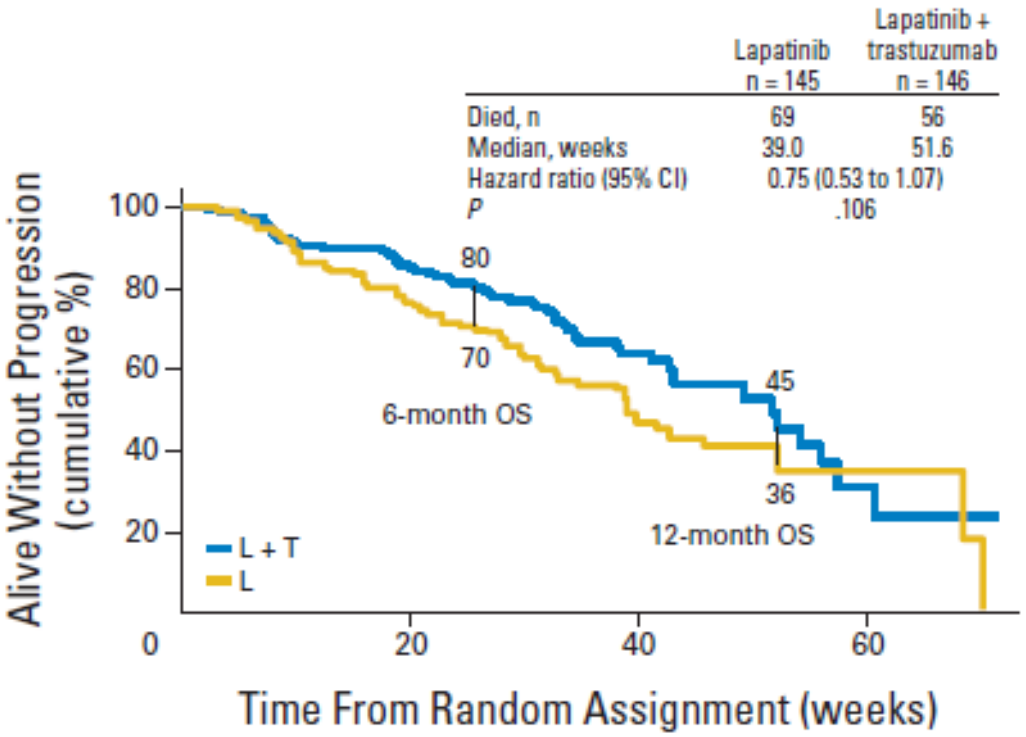


13% vs 28% of patients whose disease was progression-free at 6 months (p = .003)

Patients with visceral or bone disease at baseline = longer PFS.
PFS not significantly different in brain metastasis subgroup.



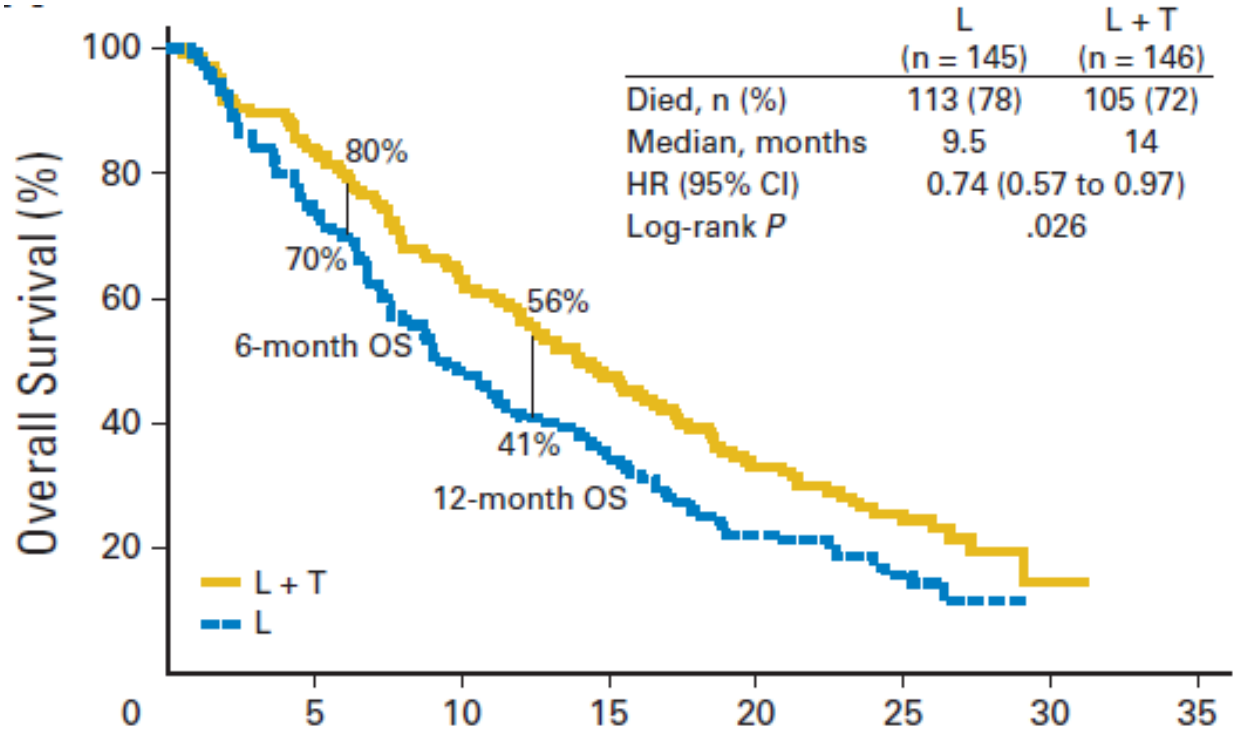
Lapatinib + trastuzumab vs lapatinib: OS



56% censoring rate → trend in improved OS after combination therapy.

6- and 12-months OS rates were 80% and 45% respectively, for combination therapy vs 70% and 36% for monotherapy.

Lapatinib + trastuzumab vs lapatinib: OS [2]



A total of 75% died → median OS was 14.0 months in combination arm vs 9.5 months in monotherapy arm (p = .026).

There was a 10% improvement in absolute OS rate at 6 months and 15% at 12 months.

Lapatinib + trastuzumab vs lapatinib: subgroups

Factor influencing OS (Cox Model):

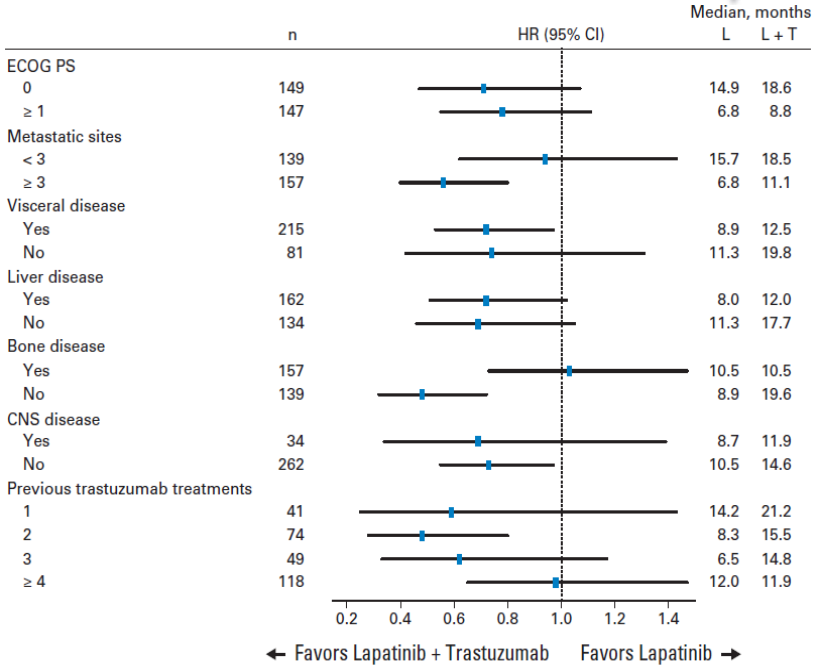
- ECOG PS 0 versus ≥1,
- greater time from diagnosis to random assignment,
- less metastatic sites,
- non-visceral versus visceral metastases.

Factor	Effect Tested	HR	95% CI	*P*
Treatment	Combination therapy *v* monotherapy	0.71	0.54 to 0.93	.0116
ECOG PS	0 *v* ≥ 1	0.46	0.35 to 0.60	< .001
Site of disease	Nonvisceral *v* visceral	0.68	0.49 to 0.94	.0181
No. of metastatic sites	< Three *v* ≥ three	0.48	0.36 to 0.63	< .001
Time from initial diagnosis until random assignment	Effect per 1-year increase	0.93	0.89 to 0.97	.0012

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival.

Lapatinib + trastuzumab vs lapatinib: subgroups

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**



Visceral disease, no bone and brain metastases, and ≥3 metastatic sites → significantly benefited from combination therapy.

Lapatinib + trastuzumab: CNS metastases

Studies on patients with HER2 positive breast cancer comparing treatment with lapatinib and trastuzumab.

Reference	Method	Study population	Characteristics of cohorts	Treatment after diagnosis of BM	OS (95% CI)
Bartsch (2012)[56]	Retrospective	Total 80			
		28	71% of all patients received prior	T ± CT	13.0 (8.9–17.2)
		15	T (3–57 months)	T + L ± CT	Not reached after 24 months
		9		CT only	
		28		RT only	
Kaplan (2012)[57]	Retrospective	111		T 58.5%	12.0
				L 41.5%	(p = 0.039)
					19.1
Yap (2012)[58]	Retrospective	280	Prior T: 55%	T ± CT and RT: 20%	10.5
			Prior L: <1%	L ± CT and RT: 11%	21.4
			Prior T + L: 7.5%	T + L ± CT and RT: 10%	25.9
				No anti-HER2 treatment ± CT and RT: 59%	5.7

CT, chemo therapy; CI, confidence interval; L, lapatinib; OS, overall survival; RT, radiotherapy; T, trastuzumab.

In the Yap study 63% of the patients were treated with anti-HER2 drugs prior to the diagnosis of CNS metastases.
After diagnosis of BM only 41% of the patients were offered anti-HER2 treatment.

OS differed markedly between treatment groups → 25.9 months observed for patients treated with trastuzumab + lapatinib, 10.5 months with trastuzumab, 21.4 months with lapatinib, and 5.7 months with chemotherapy alone ($p < 0.001$).

Lapatinib + trastuzumab: CNS metastases [2]

At the time of approval lapatinib was thought to cross the blood–brain barrier making this drug especially attractive for the prevention and treatment of BM. Emerging evidence now seem to indicate that lapatinib is not always distributed in high concentrations in CNS metastases.

No solid data exist on how to treat patients with HER2-positive disease and CNS metastases.

The choice of chemotherapy to accompany HER2- blockade is not obvious and we do not know if dual is better than single blockade.

Lapatinib + trastuzumab vs lapatinib: ER

Patients with ER+/HER2+ disease experienced no difference in median OS with dual therapy (12 versus 11.2 months; HR 0.85; 95% CI 0.57 to 1.26; *p* = .404), but those with ER-/HER2+ disease did (16.5 versus 8.9 months; HR 0.68; 95% CI 0.47 to 0.98; *p* = .012).

A likely explanation is that significant cross-talk between the ER and HER2 signaling pathways confounds sensitivity to HER2-targeted therapy. The relevance of ER expression in HER2+ disease to the probability of treatment response with HER2-targeted therapy is a theme that repeats itself in neoadjuvant trials.

Lapatinib + trastuzumab vs lapatinib: safety

Adverse Event, All Grades	Lapatinib (n = 146)		Lapatinib Plus Trastuzumab (n = 149)	
	No. of Patients	%	No. of Patients	%
Diarrhea*	70	48	90	60
Rash†	43	29	33	22
Nausea	41	28	41	28
Fatigue	28	19	32	21
Vomiting	26	18	21	14
Dyspnea	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

*Includes diarrhea, loose stools, and frequent bowel movements.
†Includes acne, dermatitis, eczema, erythema, folliculitis, rash, rash papular, and rash pustular.

Diarrhea any grade was more frequent in the combination arm (62% vs 48%), grade 3 was similar (7% versus 7%).

Rash was more frequent in the monotherapy arm (29% versus 23%).

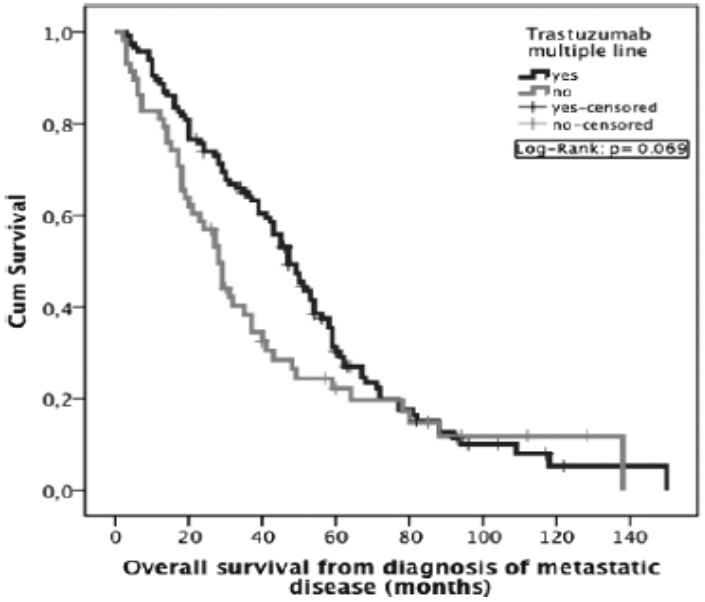
Lapatinib + trastuzumab vs lapatinib: Cardiac safety

Overall, 14 patients experienced cardiac events: 11 events in the combination arm and 3 in the monotherapy

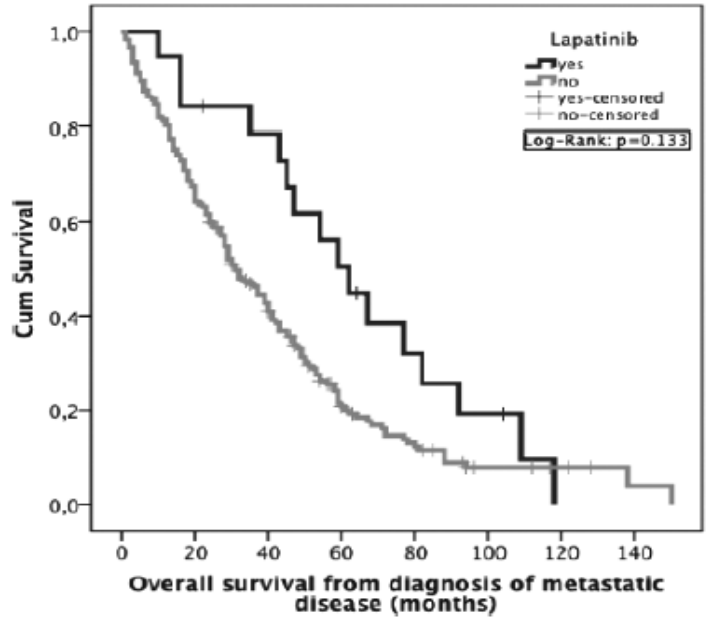
Of these serious cardiac events, 10 were related to the study drugs in the combination arm versus 2 in the monotherapy arm.

There was 1 fatal cardiac event (concurrent with pulmonary thromboembolism) in the combination arm.

Anti-HER2 therapy and OS [2]



Median OS in patients treated with multiple lines of palliative trastuzumab-based therapy was 47 months vs 28 months in patients who only received a single line of trastuzumab-based therapy (*p* = .069).



Median OS in patients treated with lapatinib was 62 months vs 47 months in patients with multiple-lines trastuzumab only (*p* = .133).

Prior lapatinib-based therapy did not result in a statistically significant reduction of incidence of CNS metastases.

Options

Three treatment options exist upon disease progression:

1) Trastuzumab therapy might be continued. Although safety and efficacy of this approach are proven, a potential impact on OS was not clearly demonstrated.

2) Switch from trastuzumab to lapatinib upon disease progression is a treatment option. Again, only a numerical improvement in terms of OS was observed.

3) Combination of trastuzumab with lapatinib showed a significant benefit in progression free survival and a significant longer OS.

International consensus guidelines

Guideline statement	LoE	Consensus
27) Anti-HER-2 therapy should be offered early to all patients with HER-2+ MBC, except in the presence of contra-indications to the use of such therapy.	1 A	91% (30) Yes 3% (1) Abstain (33 voters)
28) For patients with ER+/HER-2+ MBC for whom ET was chosen over CT, anti-HER-2 therapy + ET should be considered with the initiation of endocrine therapy (provided that further anti-HER-2 therapy is available) since anti-HER-2 therapy (either trastuzumab or lapatinib) in combination with ET has shown substantial PFS benefit (i.e., "time without CT") compared to ET alone. The addition of anti-HER2 therapy in this setting has not led to a survival benefit.	1 A	90% (27) Yes 10% (3) Abstain (30 voters)
29) Patients progressing on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway. The optimal duration of anti-HER-2 therapy for MBC (i.e. when to stop these agents) is currently unknown.	1 B	97% (29) Yes (30 voters)
30) It is currently unknown if the best option for patients progressing after receiving one line of trastuzumab + cytotoxic agent is to continue trastuzumab in conjunction with another cytotoxic agent or to change to lapatinib in combination with capecitabine. Therefore, both options are viable.	1 A	90% (26) Yes 10% (3) Abstain (29 voters)
31) In patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy, the best option remains unclear, but all such patients should be considered for further anti-HER-2 therapy. The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy that was administered, and the relapse free interval.	1 B	85% (23) Yes 15% (4) Abstain (27 voters)
32) Patients who have received any type of (neo)adjuvant anti-HER-2 therapy should not be excluded from clinical trials for HER-2+ MBC.	1 B	100% Yes (27 voters)
33) In case of progression on trastuzumab, the combination trastuzumab + lapatinib is a reasonable treatment option.	1 B	83% (24) Yes 10% (3) Abstain (29 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; ET: endocrine therapy; CT: chemotherapy; HR: hormone receptors.

Conclusions

In June 2012 the first international consensus guideline recommended early administration of HER2-directed drugs to all patients with HER2-positive MBC unless contraindicated and continuous blockade of the HER2 pathway even upon progression.

The EGF104900 study supports an important role for trastuzumab plus lapatinib combination therapy for HER2+ MBC.

It might be tempting to offer trastuzumab plus lapatinib as a chemotherapy-free approach to patients who already have significant declines in their ECOG performance score either from their disease, comorbid conditions, or prior chemotherapy, but on this point it is worth emphasizing that subset analyses in EGF104900 did not identify benefit in these patients.

Unanswered questions

- Could patients with HER2+ MBC benefit from a trastuzumab/lapatinib +/- capecitabine combination as first line therapy?

- What is the optimal sequential single-agent HER2 therapy?

- What could be the optimal regimen after progression through a chemotherapy-free approach with lapatinib/trastuzumab combination?