Effect of Lapatinib Plus Capecitabine on Quality of Life Compared to Capecitabine Alone in ErbB2-Positive Metastatic Breast Cancer: An Exploratory Analysis

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BACKGROUND

Study Design

A phase 3, randomized, open-label, multicenter study

Patient Population

Women with ErbB2+ refractory metastatic breast cancer (MBC) who had received prior therapy, including an anthracycline, a taxane, and trastuzumab

Study Treatment

L+C Arm	C Arm
Lapatinib: 1,250 mg/day, daily, continuously Capecitabine: 2,000 mg/m^2/day, days 1-14, every 21 days	Capecitabine: 2,500 mg/m^2/day, days 1-14, every 21 days

- Treatment was administered until disease progression or withdrawal due to unacceptable toxicity or other reasons (e.g., consent withdrawn, noncompliance).

Previous Results

- Combination therapy with lapatinib plus capecitabine (L+C) improved time to progression and progression-free survival relative to monotherapy with C.
- Higher point estimates for quality of life (QOL) scores among patients receiving L+C than among those receiving C suggest that there is no detriment to QOL for patients receiving combination therapy.

OBJECTIVES

The objectives of these exploratory QOL analyses were as follows:

- Evaluate and compare the proportion of patients treated with L+C who achieved minimum clinically important differences (MCID) in QOL scores, relative to patients treated with C
- Examine the relationship between QOL scores and tumor response status
- Examine the relationship between QOL scores and percentage reduction in tumor size

METHODS

- Quality of life was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) (Version 4) and EuroQol (EQ-5D) questionnaires.[2]
- Outcome measures are summarized below:
- Higher scores indicate a better QOL/health status for all outcome measures.

FACT-B total score = physical well-being + social/family well-being + emotional well-being + functional well-being + breast cancer subscale

FACT-General (FACT-G) score = physical well-being + social/family well-being + emotional well-being + functional well-being

Trial Outcome Index (TOI) score = physical well-being + functional well-being + breast cancer subscale

EQ-5D utility score: calculated from the five domain scores (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) using United Kingdom tariffs

EQ-5D visual analog scale (VAS) score: collected as a continuous measure using a "thermometer" scale

Analyses were performed for the intent-to-treat population using observed data.

- Proportions of QOL responders (i.e., patients achieving MCID[3] in QOL scores) were compared for patients receiving L+C and patients receiving C using Fisher's exact tests. The best response during follow-up (including scheduled and withdrawal visits) was used to determine the QOL response status.
- The relationship between QOL scores and tumor response status was examined using analysis of covariance adjusted for baseline score, with subjects in the L+C and C arms pooled together. Withdrawal visits were carried forward to the next scheduled visit, but not to later visits. A 2-week grace period was applied as appropriate (i.e., if a withdrawal visit occurred after the scheduled visit time but within 2 weeks, the withdrawal value was assigned to this scheduled visit).

Tumor response patients: subjects achieving either a complete response or a partial response

Stable disease patients: subjects with stable disease for at least 6 months

Progressive disease patients: subjects with disease progression or death due to breast cancer

- Pearson correlation coefficients (r) between change from baseline in QOL scores and percentage reduction in tumor size (best reported reduction) were calculated, and scatterplots were created. The change in QOL score was calculated from baseline to the date on which tumor size was reported. If a QOL score for the day tumor size was measured was not available, the score most recently taken prior to the measurement of tumor size was used.

RESULTS

- Study was closed to new enrollment early when the primary endpoint of the trial (time to progression) was achieved at an interim analysis, and patients receiving C alone were given the option to cross-over and receive L+C.
- At study closure (April 3, 2006), 399 subjects were randomly assigned to treatment (198 subjects to L+C and 201 subjects to C).
- Table 1 presents the questionnaire completion rates at various scheduled visits. The completion rates may be underestimated since per protocol patients who progressed were not required to complete the questionnaires for future visits.

Table 1. Number of Subjects Completing Questionnaire[a] at Scheduled Visits

Visit	Lapatinib 1,250 mg + Capecitabine 2,000 mg/m^2	Capecitabine 2,500 mg/m^2
Baseline	171 (100%)	168 (100%)
Week 6	118 (69%)	107 (64%)
Week 12	88 (51%)	68 (40%)
Week 18	71 (42%)	46 (27%)
Week 24	47 (27%)	30 (18%)
Week 36	21 (12%)	12 (7%)
Week 48	10 (6%)	2 (1%)
Week 60	3 (2%)	1 (1%)
Week 72	4 (2%)	0 (0%)
Week 84	1 (1%)	0 (0%)

[a]Completing at least one question in the FACT-B or EQ-5D questionnaire.
Note: percentage is of those who completed baseline questionnaire.

Quality-of-Life Responder Analysis

On average, subjects in the two treatment arms had similar baseline values in all the QOL scores (Table 2).

Table 2. Summary of Baseline Quality of Life Scores

	Lapatinib 1,250 mg + Capecitabine 2,000 mg/m^2		Capecitabine 2,500 mg/m^2	
QOL Score (Range)	n	Mean (SD)	n	Mean (SD)
FACT-B total (0-144)	163	95.7 (19.50)	166	96.4 (19.88)
FACT-G (0-108)	164	74.4 (15.45)	166	74.9 (16.35)
TOI (0-92)	164	59.0 (13.72)	165	59.1 (14.67)
EQ-5D utility (–0.594-1)	168	0.64 (0.258)	163	0.66 (0.240)
EQ-5D VAS (0-100)	163	65.3 (18.68)	163	67.5 (20.10)

SD = standard deviation.

In both treatment arms, approximately 40% of patients achieved the MCID for QOL outcomes (Table 3). A greater proportion of patients receiving L+C than those receiving C achieved an MCID for all five QOL scores, although the differences were not statistically significant. The largest difference was found in the EQ-5D VAS score (53% of patients in L+C arm vs. 41% in C arm, $P = 0.067$).

Table 3. Summary of Comparison of Quality of Life Response

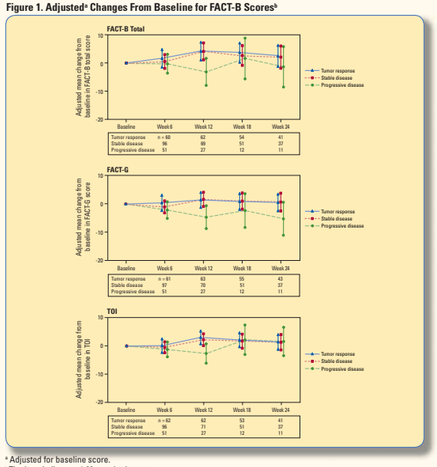
QOL Score		Lapatinib 1,250 mg + Capecitabine 2,000 mg/m^2	Capecitabine 2,500 mg/m^2	*P* value[a] for Treatment Difference
FACT-B Total	n[b]	139	132	
	≥ 8 (MCID upper bound)	61 (44%)	51 (39%)	0.391
	≥ 7 (MCID lower bound)	65 (47%)	54 (41%)	0.391
FACT-G	n[b]	142	132	
	≥ 6 (MCID upper bound)	55 (39%)	47 (36%)	0.618
	≥ 5 (MCID lower bound)	58 (41%)	52 (39%)	0.902
TOI	n[b]	140	132	
	≥ 6 (MCID upper bound)	58 (41%)	50 (38%)	0.620
	≥ 5 (MCID lower bound)	63 (45%)	55 (42%)	0.625
EQ-5D Utility	n[b]	144	131	
	≥ 0.05	59 (41%)	48 (37%)	0.536
EQ-5D VAS	n[b]	140	129	
	≥ 5	74 (53%)	53 (41%)	0.067

MCID = minimum clinically important difference.
[a]*P* values are from the Fisher's exact test.
[b]n is number of subjects with baseline and at least one postbaseline score.

Comparisons of QOL Among Patients With Tumor Response Versus Stable Disease Versus Progressive Disease

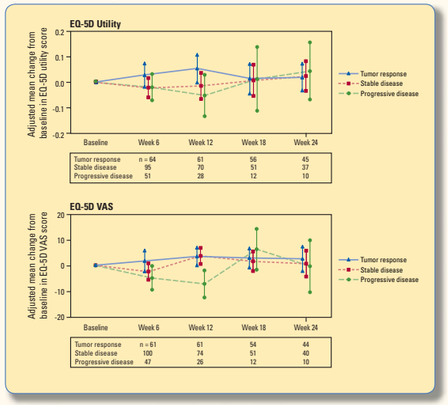
Patients who showed a tumor response had higher adjusted mean QOL change from baseline scores compared with those showing disease progression (significant at week 12: FACT-B total by 7.3, FACT-G by 6.1, TOI by 5.7, EQ-5D utility by 0.11, and ED-5D VAS by 10.7) (Figures 1 and 2). Since the sample sizes reduced during follow-up, especially among patients with progressive disease, the tests for later weeks have less power to detect the same effect.

Figure 1. Adjusted[a] Changes From Baseline for FACT-B Scores[b]



[a] Adjusted for baseline score.
[b]The bars indicate ± 1.96 standard errors.

Figure 2. Adjusted[a] Changes From Baseline for EQ-5D Scores[b]



[a] Adjusted for baseline score.
[b]The bars indicate ± 1.96 standard errors.

Correlation Between Changes in Quality of Life Outcomes and Tumor Size Reduction

Percentage reductions in tumor sizes were associated with improvement in the five QOL scores ($r = 0.15$-0.19, $P = 0.02$-0.07) (Table 3). Scatterplots for these relationships are shown in Figures 3 and 4.

Table 4. Summary of Correlation Between Change from Baseline in Quality of Life Scores and Percentage Reduction in Tumor Size

QOL score	n	Pearson correlation coefficient	*P* value
FACT-B Total	148	0.15	0.07
FACT-G	151	0.15	0.06
TOI	149	0.19	0.02
EQ-5D Utility	148	0.19	0.02
EQ-5D VAS	148	0.18	0.03

Figure 3. Change in Fact-B Total Score and Percentage Reduction in Tumor Size

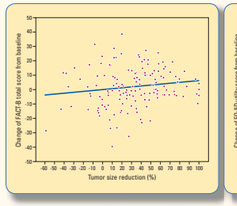
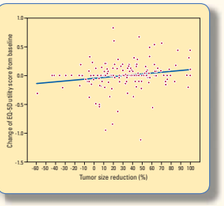


Figure 4. Change in EQ-5D Utility Score and Percentage Reduction in Tumor Size



CONCLUSIONS

- A greater proportion of patients receiving combination therapy with L+C achieved clinically important improvements in QOL scores relative to patients receiving monotherapy with C, although differences were not statistically significant.
- After 12 weeks of treatment, patients with stable disease or with tumor response showed clinically important differences in QOL scores compared to patients with progressive disease.
- QOL scores showed small, but significant, association with tumor reduction.
- The QOL benefits of the addition of lapatinib to capecitabine are positively related to the other clinical benefits provided by the combination to this heavily pretreated patient population.

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