

First-Line Treatment With Lapatinib Plus Paclitaxel Versus Paclitaxel Alone for Patients With *ErbB2+* (HER2+) Metastatic Breast Cancer: Quality of Life Analyses Using Repeated Measures and Pattern Mixture Models

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BACKGROUND

- A phase 3, randomized, multicenter, double-blind, placebo-controlled study compared first-line treatment with lapatinib plus paclitaxel (L+P) to treatment with paclitaxel alone (P) in women with metastatic breast cancer.
- In the intent-to-treat population, median time to tumor progression (TTP) was longer in the L+P arm versus the P arm (29 vs. 22.9 weeks, respectively); however, differences were not significant (hazard ratio [HR] = 0.87; 95% confidence interval [CI], 0.72 to 1.05; $P = 0.142$) (Di Leo et al., 2008).
- In a preplanned subgroup analysis of *ErbB2+* patients, TTP for L+P was significantly improved (median, 36.4 vs. 25.1 weeks, HR = 0.53; 95% CI, 0.31 to 0.89; $P = 0.005$), with an emerging trend for survival benefit (Di Leo et al., 2008).

Study Treatment

- Patients were randomized to receive either oral lapatinib (1,500 mg once daily) plus intravenous paclitaxel (175 mg/m² over 3 hours every 3 weeks) or paclitaxel (175 mg/m² over 3 hours every 3 weeks) plus placebo.
- Treatment was administered until disease progression or withdrawal due to unacceptable toxicity or other reasons (e.g., consent withdrawal, noncompliance).

OBJECTIVE

This analysis models the quality of life (QOL) data in the subset of the randomized population that overexpressed *ErbB2+* (HER2+).

METHODS

- QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (Version 4) (Brady et al., 1997).
- The FACT-B consists of five subscale scores—physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and breast cancer subscale (BCS)—with higher scores indicating better QOL.
- Outcome measures are calculated as follows:
FACT-B total score = PWB + SWB + EWB + FWB + BCS
FACT-General (FACT-G) score = PWB + SWB + EWB + FWB
Trial outcome index (TOI) score = PWB + FWB + BCS
- A clinically meaningful change or minimum important difference has been estimated based on previous studies (2-3 points for the BCS, 7-8 points for the FACT-B total score, 5-6 points for the FACT-G and TOI scores) (Eton et al., 2004).
- Patients completed a FACT-B questionnaire at screening, at 9 weeks, at 12-week intervals thereafter, and at discontinuation of randomized therapy. The assessment at discontinuation was applied to the next scheduled visit for analyses.
- QOL changes from baseline analyses were performed on the FACT-B, TOI, and BCS using repeated measure models with baseline score as a covariate.
- A pattern mixture model was run as a sensitivity analysis to assess the impact of the missing data configuration.

RESULTS

- Of 579 randomized patients, 86 were *ErbB2+* based on FISH+, or IHC3+ if FISH status was unknown, and 85 completed at least one item from the FACT-B ($n = 48$, L+P; $n = 37$, P) (Table 1).
- More than 70% of *ErbB2+* patients had QOL information at study discontinuation. Analyses were restricted to 1 year because few patients remained on study after that time.

Table 1. Number of Patients Completing* FACT-B Questionnaire at Scheduled Visits

Visit	Lapatinib 1,500 mg + Paclitaxel 175 mg/m ² <i>ErbB2+</i> (n = 49)	Paclitaxel 175 mg/m ² + Placebo <i>ErbB2+</i> (n = 37)
Day 1, baseline	48 (98%)	37 (100%)
Week 9	42 (86%)	32 (86%)
Week 21	34 (69%)	19 (51%)
Week 33	23 (47%)	10 (27%)
Week 45	14 (29%)	3 (8%)
Week 57	3 (6%)	1 (3%)
Week 69	2 (4%)	1 (3%)
Week 81	1 (2%)	0 (0%)
Week 93	1 (2%)	0 (0%)
Week 105	1 (2%)	0 (0%)
Conclusion/withdrawal	35 (71%)	30 (81%)

*Complete was defined as completing at least one question in the FACT-B questionnaire.

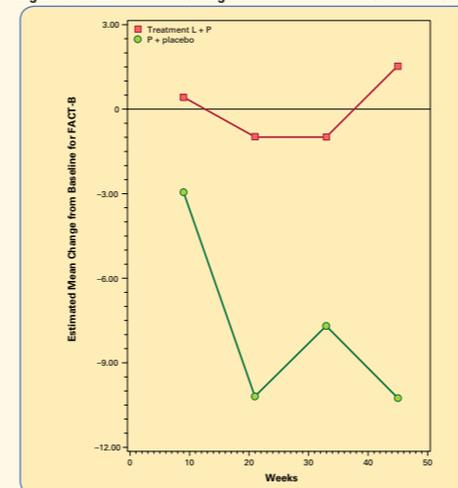
- The baseline characteristics of this subgroup were well-matched across treatment arms with regard to age, ECOG status, and prior anthracycline use. More patients in the L+P group than in the P group had visceral disease (69% vs. 51%) and more were at Stage IV (88% vs. 78%). The length of paclitaxel exposure during the treatment period was similar between arms, typically ending after 6 q3wk cycles.
- Table 2 presents baseline QOL subscales and scores for the *ErbB2+* subgroup. Compared with the P arm, on average, patients in the L+P arm had slightly smaller values in all the subscale scores and QOL scores at baseline. The smaller average values in QOL scores for patients receiving L+P are close to clinically meaningful differences, suggesting that patients receiving L+P had lower QOL at the beginning of treatment than patients who received P + placebo.

Table 2. Summary (Mean [Standard Deviation]) of Baseline for FACT-B Total, FACT-G Score, and TOI Score by Treatment

Score	Lapatinib 1,500 mg + Paclitaxel 175 mg/m ² (n = 48)	Paclitaxel 175 mg/m ² + Placebo (n = 37)
PWB	19.2 (6.63)	20.5 (5.84)
SWB	19.1 (5.82)	19.3 (5.64)
EWB	15.7 (4.32)	16.6 (4.17)
FWB	15.8 (6.49)	17.6 (5.36)
BCS	21.1 (5.30)	23.4 (6.06)
FACT-B total score	90.8 (19.67)	97.3 (18.74)
FACT-G score	69.8 (16.59)	74.0 (14.88)
TOI	56.1 (15.60)	61.5 (13.28)

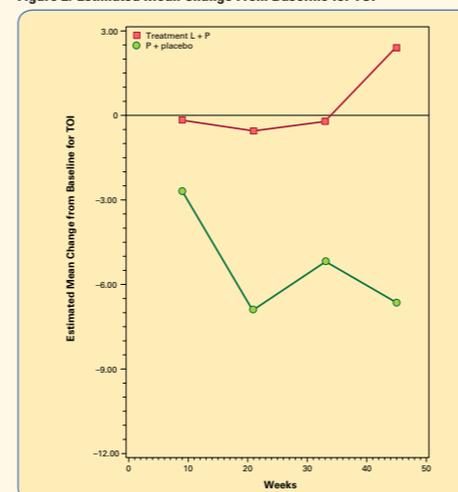
- Over the first year, the L+P arm demonstrated stable FACT-B scores over time, whereas average scores for patients on P monotherapy decreased, reaching a clinically meaningful and statistically significant decrease in QOL within 21 weeks of randomization (change from baseline: L+P, $P = 0.99$; P, $P = 0.01$) (Figure 1).

Figure 1. Estimated Mean Change From Baseline for FACT-B Total Score



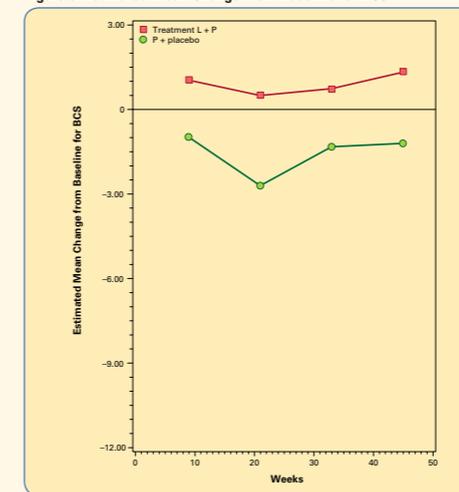
- Similar results are seen for the TOI, which focuses on the physical aspects of QOL (Figure 2). Again, the L+P group had stable QOL on average after baseline ($P = 0.82$), whereas the P + placebo group had statistically and clinically significant declines from the second assessment onward ($P = 0.01$).

Figure 2. Estimated Mean Change From Baseline for TOI



- On the BCS (Figure 3), the decline in the P + placebo group was statistically significant ($P = 0.03$) but reached a clinically meaningful decline of 2 to 3 points only at the second assessment.

Figure 3. Estimated Mean Change From Baseline for BCS



- Statistically significant differences were observed between treatment arms on the FACT-B ($P = 0.05$), TOI ($P = 0.03$), and BCS ($P = 0.01$). Table 3 provides estimated differences between groups at each time based on repeated measures models with discontinuation scores incorporated at next assessment time.

Table 3. Estimated QOL Treatment Differences* Based on Repeated Measures Models (*ErbB2+* Subgroup)

Week	FACT-B Score Difference (95% CI)	TOI Score Difference (95% CI)	BCS Score Difference (95% CI)
Week 9	3.4 (-4.2, 11.0)	2.5 (-2.8, 7.8)	2.0 (0.1, 4.0)
Week 21	9.2 (0.6, 17.9)	6.4 (0.6, 12.1)	3.2 (1.3, 5.1)
Week 33	6.7 (-2.1, 15.5)	5.0 (-1.0, 10.9)	2.1 (-0.3, 4.4)
Week 45	11.8 (0.6, 23.0)	9.1 (1.4, 16.7)	2.6 (-0.8, 5.9)

*Positive differences in scores indicate better QOL for L+P vs. P + placebo.

Note: Clinically meaningful differences: 7 to 8 points for FACT-B; 5 to 6 points for TOI; and 2 to 3 points for BCS.

- Pattern mixture models performed as sensitivity analyses suggested more QOL differentiation between treatments among patients who progressed or withdrew within 6 months of study start (data not shown). Sample sizes were too small to fully explore the impact of missing data configurations.

CONCLUSIONS

- Over the first year, on average, QOL was stable for patients in the L+P arm and decreased for patients in the P arm. Overall differences between the two treatment arms were statistically significant for several QOL scores.
- Although differences were not clinically meaningful at every visit, *ErbB2+* patients treated with L+P demonstrated consistently better QOL compared with patients treated with P alone.
- These findings represent clinically important differences between treatment groups regarding impact on QOL.

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