Lapatinib Plus Letrozole Compared With Letrozole Alone as First-Line Therapy in Hormone Receptor Positive HER2+ Metastatic Breast Cancer: A Quality of Life Analysis

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BACKGROUND

In a study comparing first-line lapatinib plus letrozole (L+Let) with letrozole plus placebo (Let), HER2+ metastatic breast cancer patients who were hormone-receptor positive and received L+Let experienced significantly longer progression-free survival (8.2 vs. 3.0 months, hazard ratio [95% CI] = 0.71 [0.53, 0.96], *P* = 0.019) (Johnston et al., 2008).

OBJECTIVE

This analysis focuses on quality of life (QOL) among HER2+ patients (the primary analysis population).

METHODS

Study Design

- The study was a phase 3, randomized, double-blind, multicenter trial.
- Eligible patients were postmenopausal women with hormone receptor positive (ER+ and/or PgR+) advanced or metastatic breast cancer, who had not received previous therapy for advanced or metastatic disease.
- The subgroup of HER2+ patients was prospectively defined for the primary endpoint analysis for this study.

Study Treatment

- Patients were randomized to receive either Let (2.5 mg once daily [QD]) with L (1,500 mg QD) or Let (2.5 mg QD) with a matching placebo.
- Treatment was administered daily until disease progression or withdrawal from study due to unacceptable toxicity or other reasons (e.g., consent withdrawn, noncompliance).

QOL Assessments

- QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (Version 4) (Brady et al., 1997), which measures multidimensional QOL in patients with breast cancer over a recall period of 7 days.
- FACT-B produces 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)—which 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

- Higher scores on the FACT-B scales indicate a higher QOL.
- A clinically meaningful change or minimum important difference (MID) 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 the TOI scores) (Eton et al., 2004).
- The FACT-B questionnaire was completed on day 1 predose, every 12 weeks, and at study withdrawal.
- All withdrawals were included in analyses up to the time of withdrawal. Analyses based on observed data and also using the last observation carried forward (LOCF) method were performed (no imputation applied to the data at discontinuation).
- Baseline scores were summarized by treatment group for each of five subscales and for the FACT-B total score, FACT-G score, and TOI score.
- Changes from baseline in the FACT-B total score, FACT-G score, and TOI score were analyzed in the HER2+ population using analysis of covariance with baseline value as a covariate.
- In a responder analysis, patients achieving MID in QOL scores (QOL responders) were compared using Fisher's exact test.

RESULTS

- Among 1,286 patients, 219 were identified as HER2+ (L+Let, n = 111; Let, n = 108).
- Because QOL assessments were stopped after treatment termination, few patients completed the questionnaire after week 48, and the results reported here are only for the visits up to week 48.
- Table 1 presents the questionnaire completion rates at scheduled visits.

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

Visit	L+Let (n = 111)	Let (n = 108)
Day 1, baseline	110 (99.1%)	101 (93.5%)
Week 12	87 (78.4%)	65 (60.2%)
Week 24	63 (56.8%)	39 (36.1%)
Week 36	40 (36.0%)	25 (23.1%)
Week 48	31 (27.9%)	23 (21.3%)
Week 60	21 (18.9%)	15 (13.9%)
Week 72	18 (16.2%)	17 (15.7%)
Week 84	12 (10.8%)	13 (12.0%)
Week 96	11 (9.9%)	10 (9.3%)
Week 108	7 (6.3%)	6 (5.6%)
Week 120	6 (5.4%)	5 (4.6%)
Week 132	4 (3.6%)	2 (1.9%)
Week 144	2 (1.8%)	2 (1.9%)
Week 156	1 (0.9%)	2 (1.9%)
Week 168	1 (0.9%)	2 (1.9%)
Week 180	1 (0.9%)	0 (0.0%)
Conclusion/ withdrawal	78 (70.3%)	67 (62.0%)

[a] Completed was defined as completing at least 1 question in the FACT-B questionnaire.

- On average, patients in the two treatment arms had similar baseline values in all the FACT-B scores (Table 2).
- Baseline QOL scores on the physical, functional, social, and emotional subscales in these patients untreated for metastatic disease were generally comparable to those of ambulatory patients with zero or some symptoms (Cella et al., 1993).

Table 2. Summary of Baseline FACT-B Subscale Scores, FACT-B Total Scores, FACT-G Scores, and TOI Scores by Treatment Arm (HER2+ Population)

Assessment	L+Let (n = 111)		Let (n = 108)	
	n	Mean (SD)	n	Mean (SD)
PWB subscale (0-28)	106	21.8 (5.05)	99	21.2 (5.22)
SWB subscale (0-28)	109	20.9 (5.86)	98	22.4 (5.95)
EWB subscale (0-24)	110	15.6 (4.50)	100	16.0 (4.85)
FWB subscale (0-28)	110	17.5 (5.68)	100	17.7 (5.93)
BCS (0-36)	108	23.2 (5.19)	98	23.6 (5.98)
FACT-B total (0-144)	104	99.3 (19.16)	96	101.1 (19.31)
FACT-G (0-108)	105	75.9 (15.65)	98	77.4 (15.64)
TOI (0-92)	103	62.5 (12.77)	97	62.4 (13.65)

SD= standard deviation.

- In both treatment arms, 30% to 40% of patients had minimally important improvements in QOL during the study (Table 3).
- There were no significant differences between the two treatment arms in percentage of QOL responders.

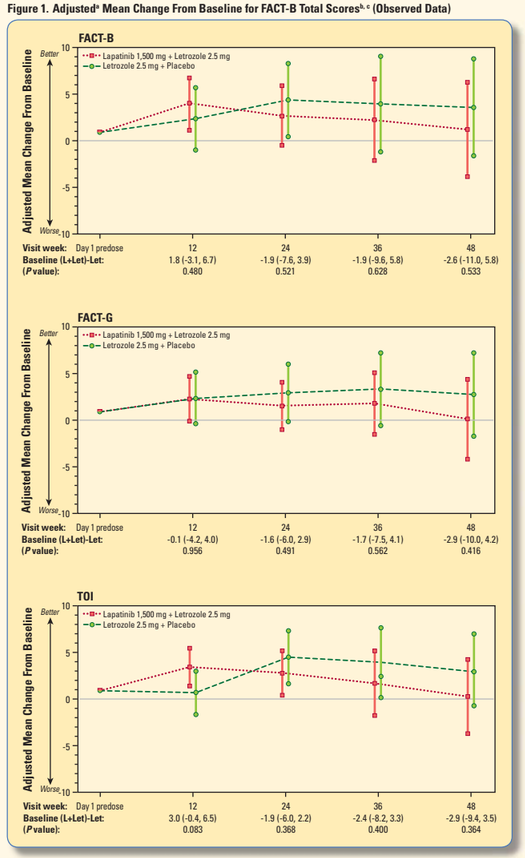
Table 3. Summary of Comparison of QOL Response

QOL Score		L+Let	Let	*P* Value for Treatment Difference[a]
FACT-B total	n[b]	98	85	
	≥ 8 (MID upper bound)	33 (34%)	29 (34%)	> 0.99
	≥ 7 (MID lower bound)	36 (37%)	29 (34%)	0.758
FACT-G	n[b]	99	87	
	≥ 6 (MID upper bound)	38 (38%)	29 (33%)	0.54
	≥ 5 (MID lower bound)	41 (41%)	34 (39%)	0.766
TOI	n[b]	97	87	
	≥ 6 (MID upper bound)	33 (34%)	29 (33%)	> 0.99
	≥ 5 (MID lower bound)	36 (37%)	30 (34%)	0.759

[a] *P* values are from Fisher's exact test.
[b] n is number of subjects with baseline and at least 1 postbaseline score.

- The mean changes in subscale and total QOL scores were generally stable over time in both treatment arms for patients who stayed in the study (Figure 1), with no significant differences between groups.
- Over the first year, no MIDs were observed in average change from baseline in either group on subscale or total scores.

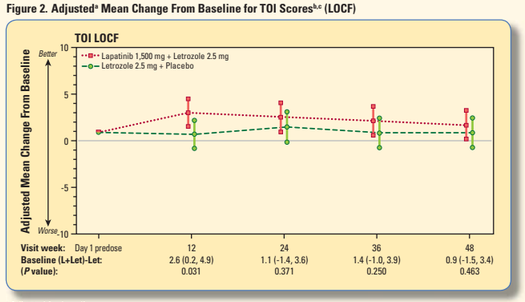
Figure 1. Adjusted[a] Mean Change From Baseline for FACT-B Total Scores[b,c] (Observed Data)



[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard error.
[c] The analysis was performed based on observed data.

- The analyses of changes from baseline for FACT-B, FACT-G, and TOI were repeated using the LOCF approach. The differences between groups were small and not significant, except TOI score at week 12, which was statistically significant (*P* = 0.031) but did not reach MID (Figure 2). Otherwise, results for the FACT-B, FACT-G, and TOI were consistent with observed data.

Figure 2. Adjusted[a] Mean Change From Baseline for TOI Scores[b,c] (LOCF)



[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard error.
[c] Missing post-baseline data were imputed using LOCF method.

CONCLUSIONS

- The addition of L to Let significantly increases progression-free survival while maintaining QOL when compared with Let alone, thus confirming the clinical benefit of the combination therapy in the HR+, HER2+ metastatic breast cancer patient population.
- The L+Let combination provides an effective option in this patient population by maintaining QOL and delaying the need for chemotherapy and its accompanying side effects.

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