A Review of the Impact of Lapatinib on Health-Related Quality of Life of Patients With Newly Diagnosed and Refractory Metastatic Breast Cancer

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BACKGROUND

- Lapatinib, an oral dual tyrosine kinase inhibitor, has demonstrated clinical activity as monotherapy and as combination therapy for both trastuzumab-naïve and pretreated human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC).
- Four phase 3 randomized multicenter studies evaluating lapatinib (LAP) as combination therapy (with letrozole [LET], paclitaxel [P], capecitabine [C], or trastuzumab [T]) for first-line or refractory/relapsed MBC were used for this review.[1-4]
  - EGF30008: The combination of LAP + LET as first-line therapy for MBC significantly prolonged median progression-free survival (PFS) relative to LET monotherapy in HER2+ patients who were hormone-receptor positive (LAP + LET: 8.2 months; LET: 3.0 months; hazard ratio [HR] = 0.71 [95% confidence interval [CI], 0.53-0.96]; $P = 0.019$).[5]
  - EGF30001: In the subgroup of HER2+ patients among women untreated for MBC, the median time to tumor progression (TTP) for LAP + P was significantly improved relative to P monotherapy (LAP + P: 36.4 weeks; P: 25.1 weeks; HR = 0.53 [95% CI, 0.31-0.89]; $P = 0.005$), with an emerging trend for survival benefit despite the lack of statistical significance for the improvement in the overall sample of women with MBC.[6]
  - EGF100151: The combination of LAP + C significantly prolonged the median time to disease progression by 43% compared with C monotherapy in heavily pretreated patients with HER2+ advanced breast cancer or MBC (LAP + C: 27.1 weeks; C: 18.6 weeks; HR = 0.57 [95% CI, 0.43-0.77]; $P < 0.001$) and provided a trend toward improved overall survival.[7]
  - EGF104900: The combination of LAP +T significantly prolonged median PFS relative to LAP monotherapy in women with HER2+ MBC who had received a median of three prior trastuzumab-containing regimens (LAP +T: 12.0 weeks; LAP: 8.1 weeks; HR = 0.73 [95% CI, 0.57-0.93]; $P = 0.008$), and showed a trend for improved overall survival.[8]
- Besides clinical activity, the impact of LAP on health-related quality of life (HRQoL) is a critical consideration for treatment: patients with advanced MBC often undergo numerous rounds of treatment, and both side effects from treatment and symptoms associated with disease progression can reduce patients' HRQoL.
- The assessment of HRQoL, including pain, fatigue, anxiety, and the effects of disease on physical and social functioning, contributes to the overall risk benefit profile of new drugs for the treatment of cancer.

OBJECTIVE

- The objective of this review was to summarize the impact of LAP (as combination therapy) on the HRQoL of HER2+ MBC patients in four clinical studies.

METHODS

- HRQoL was assessed in each study using the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire.
  - The FACT-B includes five subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and the breast cancer subscale (BCS). FACT-B total score (range: 0 to 144) is calculated as follows:

    FACT-B total score = PWB + SWB + EWB + FWB + BCS
  - Higher scores on the FACT-B scales indicate better HRQoL.
  - A clinically meaningful change or minimum important difference (MID) was 7 to 8 points for the FACT B total score based on previous studies.[9]
- For all four studies, the FACT-B questionnaire was completed on day 1 (predose), at regular follow-up visits during treatment, and at therapy discontinuation (withdrawal).
- Treatment was administered until disease progression or withdrawal due to unacceptable toxicity or other reasons.
- In all four studies, changes from baseline in FACT-B total score were analyzed using analysis of covariance (ANCOVA) or a repeated-measures model with baseline value as a covariate. In two studies, HRQoL responders were determined based on published MIDs, and Fisher's exact test was performed for treatment difference.

RESULTS

Study Characteristics

- All four studies were phase 3 randomized multicenter studies (Table 1).

Table 1. Study Characteristics[1-4]

Study Number	Blinding	Patients	HER2 Status	Treatment Arms	
				Combination	Monotherapy
EGF30008	Double-blinded	Postmenopausal, ER+/PgR+, no prior therapy for MBC	HER2+ subgroup	**LAP + LET** LAP 1,500 mg/day + LET 2.5 mg/day	**LET + placebo** LET 2.5 mg/day + placebo
EGF30001	Double-blinded	No prior therapy for MBC	HER2+ subgroup	**LAP + P** LAP 1,500 mg daily + P 175 mg/m^2 IV over 3 hours every 3 weeks	**P + placebo** P 175 mg/m^2 IV over 3 hours every 3 weeks + placebo
EGF100151	Open-label	Refractory to prior therapy for MBC	HER2+	**LAP + C** LAP 1,250 mg daily + C 2,000 mg/m^2/day, days 1-14 of each 21 day cycle	**C** C 2,500 mg/m^2/day, days 1-14 of a 21-day cycle
EGF104900	Open-label	Refractory to prior T-containing therapy for MBC	HER2+	**LAP + T** LAP 1,000mg daily + T 4 mg/kg IV followed by 2 mg/kg IV weekly	**LAP** LAP 1,500 mg daily[a]

HER2+ = human epidermal growth factor receptor 2–positive; ER+ = estrogen receptor–positive; PgR+ = progesterone receptor–positive; MBC = metastatic breast cancer.
Treatment: LAP = lapatinib; LET = letrozole; P = paclitaxel; IV = intravenous; C = capecitabine; T = trastuzumab.
[a] Patients receiving LAP monotherapy, who experienced documented radiologic disease progression after at least 4 weeks of treatment, were allowed to cross over to treatment with LAP + T remaining in the study until further disease progression was noted.

Baseline HRQoL Scores

- Baseline HRQoL scores were generally comparable between treatment arms (Table 2).

Table 2. Baseline Quality-of-Life Subscales and Total Scores[1-4]

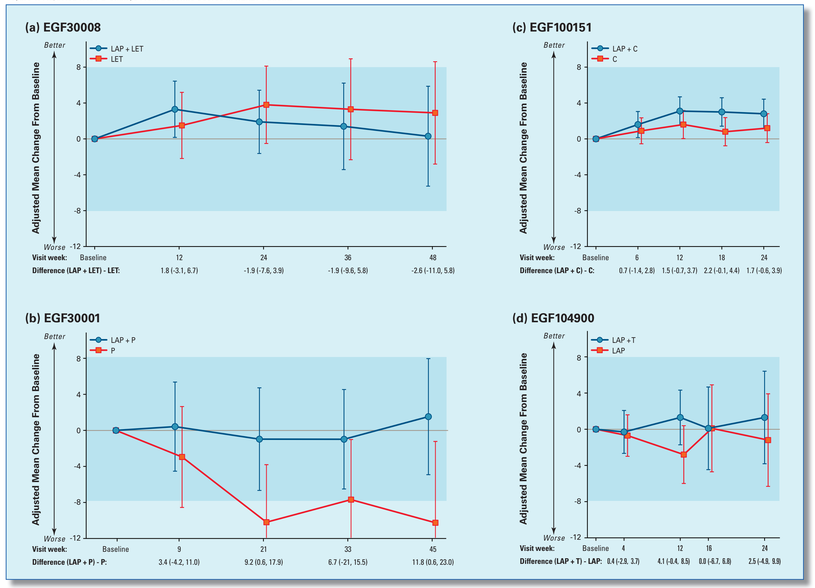
Subscale[a] (Range)	EGF30008		EGF30001		EGF100151		EGF104900	
	LAP + LET (n = 111) Mean (SD)	LET + Placebo (n = 108) Mean (SD)	LAP + P (n = 49) Mean (SD)	P + Placebo (n = 37) Mean (SD)	LAP + C (n = 198) Mean (SD)	C (n = 201) Mean (SD)	LAP + T (n = 148) Mean (SD)	LAP (n = 148) Mean (SD)
PWB (0-28)	21.8 (5.05)	21.2 (5.22)	19.2 (6.63)	20.5 (5.84)	20.3 (5.62)	20.5 (5.68)	20.5 (5.30)	20.0 (6.20)
SWB (0-28)	20.9 (5.86)	22.4 (5.95)	19.1 (5.82)	19.3 (5.64)	21.6 (5.08)	22.3 (5.00)	22.7 (4.93)	22.3 (5.46)
EWB (0-24)	15.6 (4.50)	16.0 (4.85)	15.7 (4.32)	16.6 (4.17)	15.0 (4.85)	15.1 (5.00)	15.5 (4.97)	15.1 (5.37)
FWB (0-28)	17.5 (5.68)	17.7 (5.93)	15.8 (6.49)	17.6 (5.36)	17.6 (5.71)	17.2 (6.34)	17.6 (6.21)	17.4 (6.29)
BCS (0-36)	23.2 (5.19)	23.6 (5.98)	21.1 (5.30)	23.4 (6.06)	21.2 (6.54)	21.5 (6.19)	22.7 (5.85)	22.3 (5.68)
FACT-B total score (0-144)	99.3 (19.16)	101.1 (19.31)	90.8 (19.67)	97.3 (18.74)	95.7 (19.50)	96.4 (19.88)	98.7 (21.17)	97.2 (21.85)

SD = standard deviation.
Treatment: LAP = lapatinib; LET = letrozole; P = paclitaxel; C = capecitabine; T = trastuzumab.
Subscale: PWB = physical well-being; SWB = social/family well-being; EWB = emotional well-being; FWB = functional well-being; BCS = breast cancer subscale; FACT-B = Functional Assessment of Cancer Therapy–Breast.
[a] Higher scores indicate better HRQoL.

Adjusted Change From Baseline in HRQoL Scores

- Adjusted mean changes relative to baseline in HRQoL scores were generally stable over time for all treatment arms within each study and in some instances were higher for the LAP combination arm.
- The following observations were made for patients with no prior therapy for MBC (Figures 1a and 1b):
  - Patients receiving combination therapy with LAP (LAP + LET and LAP + P) had stable FACT-B total scores over the first year, whereas the adjusted scores for patients on P monotherapy decreased, reaching a clinically meaningful and statistically significant decrease in HRQoL within 21 weeks of randomization.
  - The addition of LAP to LET did not significantly affect FACT-B total scores over the first year. Furthermore, the patients taking LAP + P had significantly higher HRQoL scores at weeks 21 and 45 on average than patients taking P monotherapy.
- The following observations were made for patients refractory to prior therapy for MBC (Figures 1c and 1d):
  - Patients receiving LAP combination therapy (LAP + C, LAP +T) or LAP monotherapy had stable FACT-B total scores over the first 24 weeks.
  - Adjusted point estimates of the treatment differences between LAP + C and C over the first 24 weeks ranged from 0.7 to 2.2 for FACT-B total score. None of the differences were statistically significant or achieved the MID.

Figure 1. Adjusted FACT-B Change From Baseline Scores in HER2+ Patients[1-4]

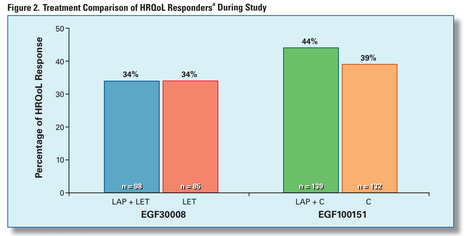


Treatment: LAP = lapatinib; LET = letrozole; C = capecitabine; P = paclitaxel; T = trastuzumab.
Based on the intent-to-treat (ITT) principle, patients were analyzed in the treatment group to which they were randomized. Vertical bars stand for ± 1.96 × standard error. Dark zones indicate within the MID upper bound.
LAP + LET, LET: ANCOVA (adjusting for baseline score); observed data, not including withdrawal visit.
LAP + P, P: Repeated measures with autoregressive covariance structure (adjusting for baseline score); observed data, with scores from discontinuation assessments assigned to the next scheduled visit.
LAP + C, C: ANCOVA (adjusting for baseline score); last observation carried forward (LOCF), not including withdrawal visit.
LAP + T, LAP: ANCOVA (adjusting for baseline score); observed data, not including withdrawal visit but including crossover data.

HRQoL Responder Analysis

- There were no significant differences between treatment arms in percentage of HRQoL responders in studies where this endpoint was evaluated.
- In all evaluated treatment arms (i.e., LAP + LET, LET, LAP + C, C), 30% to 45% of patients had minimally important improvements in HRQoL (based on the upper bound of the MID range) during the study (Figure 2). There was no significant difference in the HRQoL response rate with the addition of LAP to LET (no prior therapy for MBC) or C (refractory to prior therapy for MBC) (LAP + LET vs. LET: $P > 0.99$; LAP + C vs. C: $P = 0.391$)
- Similar results were obtained in analysis using the MID lower bound to define HRQoL responders.

Figure 2. Treatment Comparison of HRQoL Responders[a] During Study



HRQoL = health-related quality of life.
Treatment: LAP = lapatinib; LET = letrozole; C = capecitabine.
[a] HRQoL responders were defined as change from baseline score ≥ the MID upper bound (i.e., 8 for FACT-B total score).
n is the number of patients with baseline and at least one postbaseline score.

CONCLUSION

- The addition of LAP to other treatments (LET, P, C, T) has shown clinical benefit without compromising HRQoL in patients with HER2+ MBC.

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