An Exploration of the Association of QOL Scores With Tumor Progression Status in First-Line HR+, HER2+ MBC Patients Treated With Lapatinib Plus Letrozole or Letrozole Alone

Poster # 5106

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BACKGROUND

- A phase 3, randomized, double-blind study found that median progression-free survival was significantly prolonged for a group of *ErbB2*-positive (HER2+) postmenopausal patients receiving lapatinib plus letrozole (L+Let) as first-line therapy for hormone receptor positive (HR+) metastatic breast cancer (MBC) compared with patients on Let plus placebo (Let) (8.2 months vs. 3.0 months; hazard ratio [95% CI] = 0.71 [0.53, 0.96]; $P = 0.019$).[1]
- Previous reports showed that quality of life (QOL) was generally stable for patients who stayed on study and that the proportion of QOL responders in the two treatment arms was similar.[2]

OBJECTIVE

- Exploratory analyses were performed to examine the extent to which QOL scores reflected tumor progression events by assessing QOL changes by progression status at consecutive timepoints among patients in the study with HER2+ tumors (the primary analysis population).

METHODS

Study Design

- The study (EGF30008) was a phase 3, randomized, double-blind, multicenter trial.
- Eligible patients were postmenopausal women with HR+ (ER+ and/or PR+) advanced or MBC, who had not received previous therapy for advanced or metastatic disease.
- The subgroup of HER2+ patients was prospectively defined for the primary endpoint analysis.

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daily until disease progression or withdrawal from study due to unacceptable toxicity or other reasons (e.g., consent withdrawn, noncompliance).

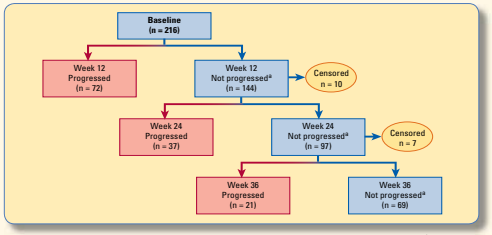
Assessments

- Disease progression was determined by investigators according to definitions established in the modified Response Evaluation Criteria in Solid Tumors (RECIST 1.0). Radiographic and clinical disease assessments were obtained within 4 weeks prior to the first dose and every 12 weeks or sooner if clinically indicated.
- QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (Version 4)[3] at baseline, every 12 weeks, and at study withdrawal.
  - Five subscale scores—physical, social/family, emotional, functional well-being, and breast cancer subscale (BCS)—are summed to give the FACT-B total score.
  - The trial outcome index (TOI) score is the sum of the physical, functional, and BCS subscores.
  - Higher scores on the FACT-B scales indicate a higher QOL.
- Patients had to have baseline and postbaseline QOL scores to be included in the analyses; withdrawal QOL assessments were analyzed when they occurred.
  - At weeks 12, 24, and 36, QOL scores were stratified based on investigator assessment of progression before or up to 1 week after scheduled disease assessment.
  - For those patients whose disease had not progressed by week 12, QOL scores were then examined at week 24, stratified by whether the patient had disease progression or not during the interim. This approach was continued through week 36 after which too few patients with QOL data remained on study.
- The QOL score change from baseline was compared using least squared means from analysis of covariance (ANCOVA), adjusted for baseline value.
- Distribution of QOL responses, stratified by whether change from baseline represented minimally important declines, increases, or stability, were compared using Fisher's exact test. A clinically meaningful change or minimum important difference (MID) was 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 TOI scores).[4]

RESULTS

Among 1,286 patients, 219 were identified as HER2+ (L+Let, n = 111; Let, n = 108). Three patients did not complete any FACT-B questionnaires and were excluded from this exploratory analysis. Figure 1 shows the number of patients whose disease progressed at any point, up to and including 1 week after scheduled visit.

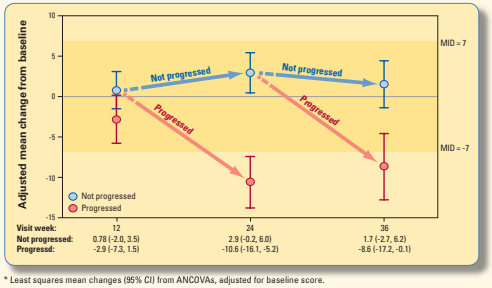
Figure 1. Number of Patients With Disease Progression as of Each Scheduled Visit (+ 1 Week), Pooled Across Treatment Arms



[a]For this analysis, nonprogressed withdrawn patients were included in the next scheduled visit but not beyond (n = 10 at week 12; n = 7 at week 24).

- For patients without disease progression over a 36-week period, changes from baseline in FACT-B total scores remained stable and within MID levels (represented by highlighted area on Figure 2).
- Average QOL declines reached clinically and statistically significant levels for patients whose disease progressed after week 12, but not for patients whose disease progressed earlier.

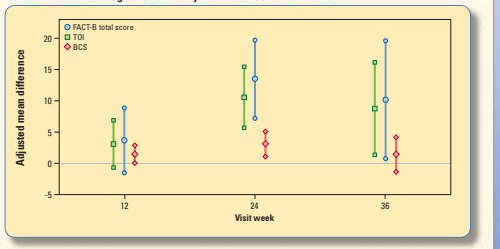
Figure 2. Adjusted* Mean Changes From Baseline for FACT-B Total Scores



* Least squares mean changes (95% *CI*) from ANCOVAs, adjusted for baseline score.

- Differences in average changes from baseline in FACT-B total scores were statistically and clinically significant between patients whose disease progressed and those whose disease did not at week 24 ($P < 0.0001$) and week 36 ($P = 0.04$) but not at week 12 ($P = 0.16$) (Figure 3).
- The pattern of differences was consistent for the TOI and BCS subscores.

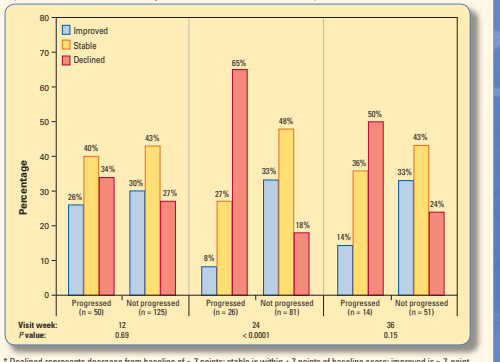
Figure 3. Differences in Adjusted Mean Changes* From Baseline for QOL Scores Between Patients Whose Disease Had Progressed or Not by the Time of Scheduled Visits



* Differences of 7-8 points are considered minimally important for the FACT-B total score, 5-6 points for the TOI, 2-3 points for the BCS. Differences shown are least squares means (95% CI) from ANCOVA adjusted for baseline score. Positive values indicate higher QOL scores for patients who did not progress compared to patients who did progress.

- At week 12, the distribution of patients by FACT-B response level was similar between patients whose disease progressed and those whose disease did not ($P = 0.69$) (Figure 4).
- For patients with disease progression between weeks 12 and 24, 65% had FACT-B declines more than 7 points from baseline vs. 19% of patients without disease progression ($P < 0.0001$).
- Results were similar at week 36, but not statistically significant ($P = 0.15$).

Figure 4. Distribution of QOL Response Based on MID FACT-B Change* From Baseline



* Declined represents decrease from baseline of ≥ 7 points; stable is within ± 7 points of baseline score; improved is ≥ 7-point increase from baseline. *P* values are from Fisher's exact test using patients with baseline and postbaseline QOL scores.

CONCLUSIONS

- Results show that tumor progression is associated with clinically meaningful declines in QOL scores in patients with HR+, HER2+ MBC.
- These hypothesis-generating analyses suggest that QOL declines may take more than a few months to evolve.
- Hence, the longer progression-free survival for L+Let versus Let is expected to translate into a QOL advantage.

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