GlaxoSmithKline Oncology

Impact of Lapatinib Plus Trastuzumab Versus Single-Agent Lapatinib on Quality of Life of Patients With Trastuzumab-Refractory HER2+ (ErbB2+) Metastatic Breast Cancer

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OBJECTIVE

- The objective of this study was to evaluate and compare the safety and efficacy of lapatinib (L) + trastuzumab (T) versus L monotherapy. This analysis focuses on the impact of treatments on health-related quality of life (QOL).

BACKGROUND

Study Design

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

Patient Population

- Eligible patients were women with metastatic breast cancer (MBC) who had progressed on prior treatment with anthracyclines, taxanes, and T. Patients had documentation of disease progression on their most recent treatment regimen, which must have contained T.
- A total of 296 patients were randomized in a 1:1 ratio to either receive oral L (1000 mg qd) with T (4 mg/kg intravenous [IV] load followed by 2 mg/kg IV weekly) (L + T arm) or L (1500 mg qd) (L arm).
- Treatment was administered until disease progression or withdrawal due to unacceptable toxicity or other reasons (e.g., consent withdrawn, noncompliance).
- A total of 73 patients randomized to L who experienced objective disease progression after receiving at least 4 weeks of study treatment elected to crossover to receive L + T until further disease progression or withdrawal due to other reasons.
- The combination of L + T significantly prolonged progression-free survival (PFS) in women with ErbB2 + MBC who had received a median of five prior chemotherapy-based regimens (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.57-0.93; $P = 0.008$). The clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD] for 6 months) was 24.7% in the L + T arm and 12.4% in the L alone arm.[1]

METHODS

- QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (Version 4),[2] which measures multidimensional QOL in patients with breast cancer.
- FACT-B is a 37-item (27 general questions and 10 breast-cancer-specific questions), self-reporting instrument with 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).

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

- Outcome measures include the FACT-B total score, FACT-G score, and TOI score.
- Higher scores on the FACT-B scales indicate a higher QOL.
- A clinically meaningful change has been estimated based on previous studies (2-3 points for the breast cancer subscale, 7-8 points for the FACT-B total score, 5-6 points for the FACT-G and the TOI scores).[3]
- The FACT-B questionnaire was completed at baseline, weeks 4, 12, 16, and then every 8 weeks, and at discontinuation of therapy.
- 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 intent-to-treat (ITT) population using analysis of covariance with baseline value as a covariate.

RESULTS

- Baseline QOL assessment in both arms (N = 148/arm) was completed in more than 95% of patients. Approximately 40% of patients in the L + T arm and 36% in the L arm completed the week 12 assessment; 20% in both arms completed the week 24 assessment (Table 1). Since relatively few patients completed the questionnaire in the scheduled visits after week 24, the results reported here are only for the visits up to week 24.

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

Visit	L 1000 mg + T (n = 148)	L 1500 mg (n = 148)
Day 1, baseline	142 (96%)	141 (95%)
Week 4	108 (73%)	120 (81%)
Week 12	60 (41%)	54 (36%)
Week 16	46 (31%)	41 (28%)
Week 24	30 (20%)	29 (20%)
Week 32	19 (13%)	20 (14%)
Week 40	13 (9%)	11 (7%)
Week 48	7 (5%)	5 (3%)
Conclusion/withdrawal	69 (47%)	75 (51%)

Note: "Complete" was defined as completing at least one 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).

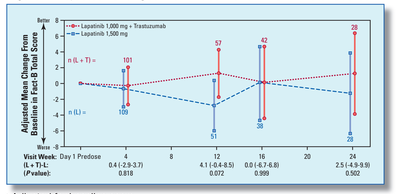
Table 2. Summary of Baseline FACT-B Subscale Scores, Total Scores, FACT-G Scores, and TOI Scores by Treatment

	L 1000 mg + T (n = 148)		L 1500 mg (n = 148)	
	n	Mean (SD)	n	Mean (SD)
Physical well-being subscale (0-28)	141	20.5 (5.30)	141	20.0 (6.20)
Social/family well-being subscale (0-28)	141	22.7 (4.93)	141	22.3 (5.46)
Emotional well-being subscale (0-24)	142	15.5 (4.97)	141	15.1 (5.37)
Functional well-being subscale (0-28)	142	17.6 (6.21)	141	17.4 (6.29)
Breast cancer subscale (0-36)	138	22.7 (5.85)	137	22.3 (5.68)
FACT-B total (0-144)	137	98.7 (21.17)	137	97.2 (21.85)
FACT-G (0-108)	141	76.3 (16.92)	141	74.8 (18.56)
TOI (0-92)	137	60.7 (14.70)	137	59.8 (15.03)

SD = standard deviation.

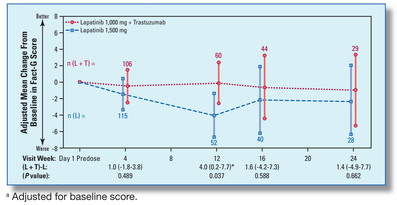
- At postbaseline visits, patients who remained on study in both treatment arms displayed little decline in QOL.
- Adjusted point estimates of the treatment differences were generally in favor of the L + T arm, although none of the differences achieved the minimum clinically important difference. Differences ranged from 0 to 4.1 for FACT B total score, 1 to 4.0 for the FACT G score, and 0.4 to 2.7, for the TOI score. Only the difference for the FACT G total score at Week 12 was statistically significant (4.0, $P = 0.037$). (Figures 1-3).

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



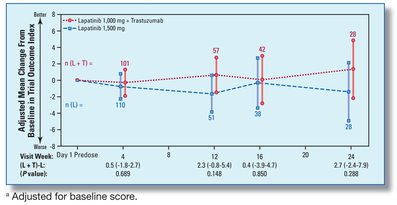
[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard errors.
[c] The analysis is performed based on observed data.

Figure 2. Adjusted[a] Changes From Baseline for FACT-G Scores[b, c]



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

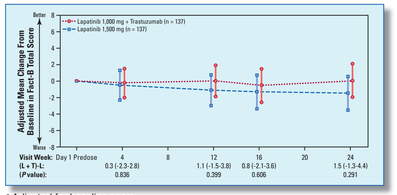
Figure 3. Adjusted[a] Changes From Baseline for TOI Scores[b, c]



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

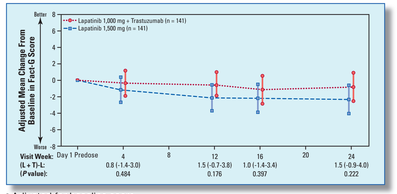
- Overall, the results using the LOCF approach were comparable to the results using the observed data. (Figures 4-6).

Figure 4. Adjusted[a] Changes From Baseline for FACT-B Total Scores with LOCF [b, c]



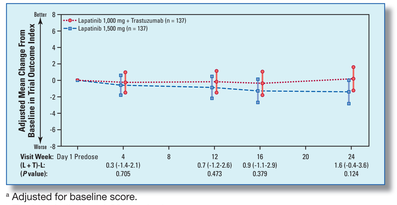
[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard errors.
[c] Missing postbaseline data were imputed using the LOCF method.

Figure 5. Adjusted[a] Changes From Baseline for FACT-G Scores with LOCF [b, c]



[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard errors.
[c] Missing postbaseline data were imputed using the LOCF method.

Figure 6. Adjusted[a] Changes From Baseline for TOI Scores with LOCF [b, c]



[a] Adjusted for baseline score.
[b] The bars indicate ± 1.96 standard errors.
[c] Missing postbaseline data were imputed using the LOCF method.

- For the assessment at discontinuation, both treatment arms had average decreases from baseline that were clinically meaningful (or approaching clinically meaningful) in all the FACT-B scores indicating patients experienced substantial worsening of QOL after discontinuation of treatment. In addition, few differences between the two treatment arms were observed in change from baseline in all the FACT-B scores (Table 3).

Table 3. Adjusted Changes from Baseline for FACT-B Total Scores, FACT-G Scores, and TOI Scores, for the assessment at discontinuation

	L 1000 mg + T		L 1500 mg		Treatment Difference	
	n	Adjusted Mean	n	Adjusted Mean	Mean (95% CI)	*P* Value
FACT-B total score	63	-7.5	67	-7.7	0.2 (-5.2-5.5)	0.947
FACT-G score	66	-7.7	71	-7.5	-0.2 (-4.6-4.2)	0.920
TOI score	63	-4.7	67	-5.2	0.5 (-3.4-4.4)	0.813

CONCLUSION

- The analysis suggests that the QOL for patients treated with the combination therapy was comparable to those patients treated with monotherapy L.
- The combination of L + T prolonged PFS and improved the clinical benefit response rate for patients with relapsed ErbB2+ MBC over treatment with L alone.

REFERENCES

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