#4090

A Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) Analysis Comparing First-Line Therapy With Lapatinib Plus Paclitaxel Versus Paclitaxel Alone for Patients With HER2+ Metastatic Breast Cancer (MBC)

Beth Sherrill[1], Angelo Di Leo[2], Mayur Amonkar[3], Maria Koehler[3], Michael Arbushites[3]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Sandro Pitigliani Medical Oncology Unit, Prato, Italy; [3]GlaxoSmithKline, Collegeville, PA, United States

BACKGROUND

- The objective of this study was to compare the quality-adjusted survival experience among patients with HER2+ refractory advanced or metastatic breast cancer (MBC) treated with either lapatinib plus paclitaxel (L+P) or paclitaxel (P) alone.
- Data source:
  - Phase 3, randomized, multicenter, double-blind, placebo-controlled study (EGF30001) comparing L+P with P.
  - Women with MBC who had not received prior therapy for metastatic disease.
- In a subgroup analysis of HER2+ (ErbB2+) patients, time to tumor progression for L+P was significantly improved, with an emerging trend for survival benefit.
- The Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) method was used to compare the tradeoff between toxicities (TOX) and delayed progression in a prospectively defined subset of the randomized intent to treat (ITT) population that overexpressed HER2.

METHODS

- Overall survival (OS) was calculated for each treatment group using the product limit method. This method accounts for dropouts and differential follow-up; it is typically used to estimate the median time to event and a descriptive curve. The area under this curve represents the mean time to event.
- Curves were generated for progression-free survival (PFS) and for time with TOX. These curves were overlaid onto the OS curve. Table 1 presents definitions for health states.

Table 1. Definitions for Health States

Health State	Definition
TOX	• Time after randomization with grade 3/4 AEs before progression • Truncated if AE duration was greater or equal to time to progression (i.e., censored as of progression or censoring for progression) • Zero if no qualifying AEs prior to disease progression
TWiST	• Remaining time after TOX before progression • Derived as the difference between mean PFS and mean TOX • Censored at the time of the last independently assessed radiologic scan preceding the initiation of any alternative anticancer therapy
RELapse (REL)	• After progression, period until death from any cause or end of follow-up • Derived as the difference between mean OS and mean PFS • Censored as of last available contact with patient or data lock date (February 5, 2007)

- A sensitivity analysis was performed by redefining the TOX state to include all adverse events (AEs) of all grades.
- Analyses were performed on the prospectively defined HER2+ subgroup. The HER2+ population was composed of all randomized patients who received at least one dose of randomized therapy and who at baseline had documented amplification of ErbB2 by fluorescence in situ hybridization (FISH) or 3+ IHC3+ irrespective of FISH. A further subset of this population excluded patients for whom FISH status was unknown.
- The Q-TWiST score was calculated as follows:

$$\text{Q-TWiST} = (\mu\text{TOX} \times \text{TOX}) + \text{TWiST} + (\mu\text{REL} \times \text{REL})$$

where the multiplication of utility and time results in a quality-adjusted duration.

- Survival time is discounted under the assumption that days of sickness are of lower use to a patient than days without sickness.

Threshold Utility Analysis

- The threshold utility analysis was carried out to determine combinations of utility weights under which Q-TWiST is statistically different between treatment groups.
- Treatment comparisons of Q-TWiST were made for a matrix of possible utility weight combinations where:
  - μTWIST held constant at 1.
  - μTOX and μREL varied from 0 to 1 by 0.25, resulting in 25 combinations.

RESULTS

The ITT population included 579 patients ages 23-87 years of which 91 were HER2+ (n = 52 L+P, n = 39 P) based on FISH+ or IHC3+ irrespective of FISH (86 patients based on FISH+ or IHC3+ if FISH unknown; n = 49 L+P, n = 37 P). Table 2 presents number of patients experiencing each event. Figures 1 and 2 show survival curves. Analyses were restricted to the overall median survival of 96 weeks based on data through February 5, 2007.

Table 2. Patient Status by Treatment Group in HER2+ Subgroup (n = 91)

Event	L+P (n = 52)	P (n = 39)
Grade 3/4 AEs	31	17
PFS event (progression or death due to any cause)	44	34
Deaths—all causes	20	19

Figure 1. Partitioned Survival Curve for Combination Therapy (L+P) in HER2+ Subgroup (n = 52)

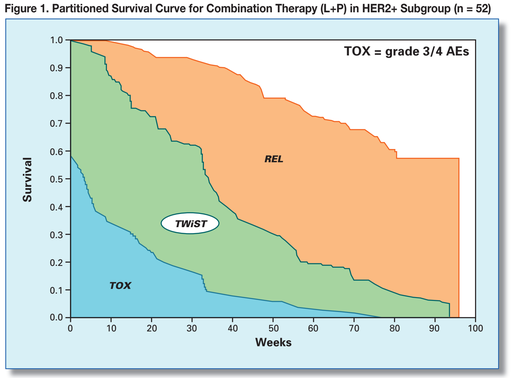


Figure 2. Partitioned Survival Curve for Monotherapy (P) in HER2+ Subgroup (n = 39)

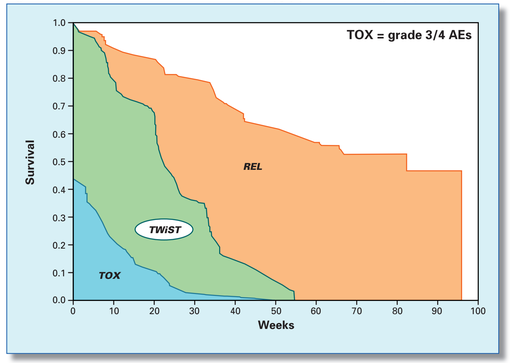


Table 3 presents the unweighted mean durations of health states.

Table 3. Mean Duration of Health States (Weeks) in the HER2+ Subgroup (n = 91)

Health State	L+P (n = 52)	P (n = 39)	Difference (L+P – P)	$P > \lvert Z \rvert$ [a]
TOX: Grade 3/4 AEs	12.8	6.2	6.5	0.0265
TWiST	27.3	20.5	6.8	0.1790
REL	38.4	39.7	–1.3	0.8171

[a] Null hypothesis: Difference [(L+P) – P] = 0.

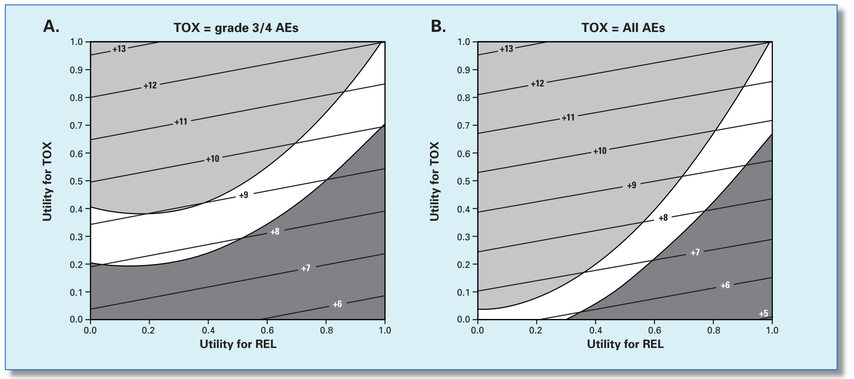
Figure 3 illustrates the combinations of utility weights for TOX and REL that result in statistically significant Q-TWiST differences between groups. Q-TWiST differences between the arms ranged from 5 to 13 weeks across utility weight combinations, with most tests providing a statistically significant advantage of L+P over P (Figure 3A and Table 4). Results were similar in a sensitivity analysis regardless of grade (Figure 3B) and in a subset of the HER2+ population (n = 86) with patients excluded if FISH status was unknown (not shown).

Table 4. Q-TWiST Differences (Weeks) in the HER2+ Subgroup With TOX = Grade 3/4 AEs (n = 91)[a]

Utility for TOX	1.0	13.3	13.0	12.7	12.3	12.0
	0.75	11.7	11.4	11.0	10.7	10.4
	0.50	10.1	9.7	9.4	9.1	8.7
	0.25	8.4	8.1	7.8	7.4	7.1
	0	6.8	6.5	6.1	5.8	5.5
		0	0.25	0.50	0.75	1.0
		Utility for REL				

[a] Light gray, $P < 0.05$; white, $0.05 < P < 0.1$; dark gray, $P > 0.1$.

Figure 3. Contour Graphs Showing Q-TWiST Difference (in Weeks) Between Treatments (L+P vs. P) at Varying Utility Levels for Sensitivity Analysis in HER2+ Subgroup (n = 91)[a, b]



[a] Positive numbers on slanted lines indicate more Q-TWiST (weeks) for patients taking L+P versus P.

[b] Shading represents P values from the test of Q-TWiST differences between groups: light gray, $P < 0.05$; white, $0.05 < P < 0.1$; dark gray, $P > 0.1$.

CONCLUSION

- Among patients with HER2+ MBC, treatment with lapatinib plus paclitaxel resulted in more quality-adjusted survival than with paclitaxel monotherapy.
- When utilities for periods of TOX and REL were valued at half the utility of TWiST, the Q-TWiST difference was approximately 9 weeks, approximately 10% of the 96-week median OS in favor of lapatinib plus paclitaxel.
- These findings represent clinically important differences between treatment groups in quality-adjusted survival.

REFERENCES

Di Leo A, Gomez HL, Aziz Z, Zvirbule Z, Bines J, Arbushites MC, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 2008 Oct 27. [Epub ahead of print]

Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Stat Med 1990;9(11):1259-76.

CONTACT INFORMATION

Beth Sherrill, MStat
Director of Statistics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

http://www.rtihs.org
Telephone: +1.919.541.1233
E-mail: bsherrill@rti.org

Presented at: 2008 San Antonio Breast Cancer Symposium (SABCS)
December 10-14, 2008
San Antonio, Texas, USA