A Comparison of Lapatinib Plus Capecitabine Versus Capecitabine Alone for Quality-Adjusted Survival in Metastatic Breast Cancer: a Q-TWiST Analysis

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BACKGROUND

- Data source: Phase III randomized, open-label study comparing lapatinib plus capecitabine (L + C) to capecitabine (C) alone;
  - Included women with ErbB2 + refractory metastatic breast cancer (MBC), after prior therapy with an anthracycline, a taxane, and trastuzumab;
  - Study stopped early by Independent Data Monitoring Committee (IDMC) when planned interim analysis demonstrated significantly longer time to disease progression for patients taking L + C versus C.
- The Q-TWiST (Quality-Adjusted Time Without Symptoms or Toxicity) method is a technique to evaluate treatment toxicity and time-dependent clinical outcomes simultaneously.[1,2,3]
- The Q-TWiST method was used to examine the overall survival experience using patient-reported EQ-5D scores as utility weights.

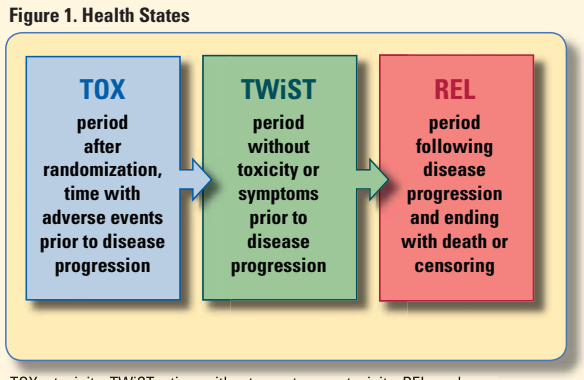
METHODS

- Survival curves for each treatment arm were partitioned into three health states, based on April 3, 2006 data (Figures 2 and 3).
- Individual utilities for each health state were determined from patient-reported health status on the EQ-5D[4] administered throughout study.
- Utilities collected during toxicity (TOX), time without symptoms or toxicity (TWiST), or relapse (REL), were averaged within health state for each subject.
- The utility-weighted sum of the mean health state durations was derived as:

$$Q\text{-}TWiST = \mu_{TOX} * TOX + TWiST + \mu_{REL} * REL$$

- Treatment comparisons of Q-TWiST were made at varying utility weight combinations, using trial-based EQ-5D scores.

Figure 1. Health States



TOX = toxicity; TWiST = time without symptoms or toxicity; REL = relapse.

RESULTS

Table 1. Unweighted Duration of Health States (weeks)

Health State	Lapatinib + Capecitabine (L + C) (n = 198)	Capecitabine (C) (n = 201)	Difference (L + C - C)	p value
TOX: Grade 3/4	1.7	1.5	0.2	0.5548
TWiST	32.1	21.3	10.8	0.0000
REL	19.0	26.6	-7.6	0.0019

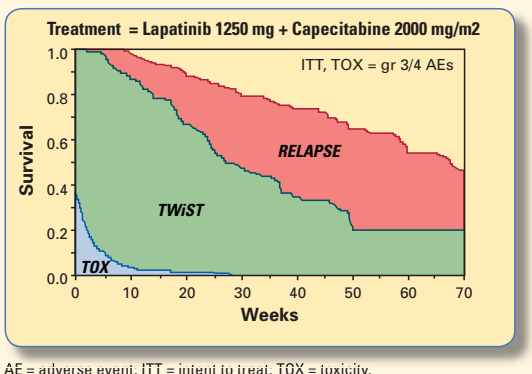
TOX = toxicity; TWiST = time without symptoms or toxicity; REL = relapse.

There was no significant difference in mean duration of serious adverse events prior to progression.

The combination therapy group spent more time in TWiST on average and less time in relapse than the group on capecitabine alone.

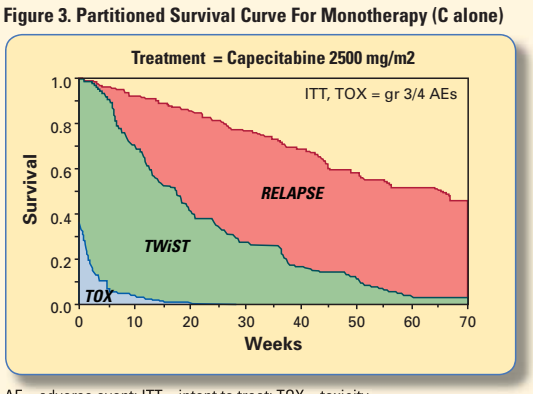
Partitioned survival curves are shown for three health states, restricted to median follow-up (67 weeks for ITT) with TOX defined to include only Grade 3/4 adverse events.

Figure 2. Partitioned Survival Curve for Combination Therapy (L + C)



AE = adverse event; ITT = intent to treat; TOX = toxicity.

Figure 3. Partitioned Survival Curve For Monotherapy (C alone)



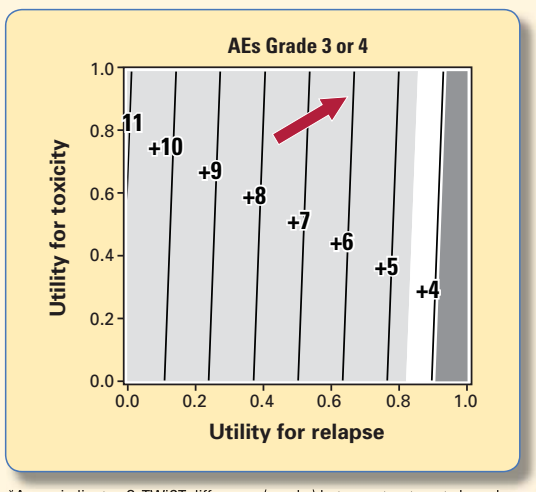
AE = adverse event; ITT = intent to treat; TOX = toxicity.

Table 2. Patient-Reported Utility Values Based on EQ5D

Mean Values	Lapatinib + Capecitabine	Capecitabine Alone
μTOX	0.60	0.59
μTWIST	0.66	0.66
μREL	0.41	0.44

TOX = toxicity; TWiST = time without symptoms or toxicity; REL = relapse.
For graphing comparisons, use utility values relative to TWiST: μTOX / μTWiST = .90; μREL / μTWiST = .65

Figure 4. Contour Graph*



*Arrow indicates Q-TWiST difference (weeks) between treatments based on mean observed utility values.

Over the 67-week time horizon, L + C combination therapy provided 6.1 weeks more quality-adjusted survival than capecitabine monotherapy (p = 0.006).

A threshold utility analysis (where uTWIST = 1 and uTOX and uREL = 0.5) produced a 7+ week difference in Q-TWIST favoring L + C vs C (p = 0.00013).

Combination therapy was favored across the entire matrix of possible utility weight combinations.

CONCLUSIONS

- Using patient-reported utility values, lapatinib plus capecitabine was shown to provide more quality-adjusted survival than capecitabine alone.
- Results were robust to sensitivity analyses.
- For MBC, a condition with generally poor prognosis, quality-adjusted survival greater than 5% of the 67-week time horizon can be considered clinically significant.

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