

# registHER: An Observational Cohort Study of Survival of Patients with HER2-Positive Metastatic Breast Cancer and Use of Trastuzumab Following Progression

Hope. S. Rugo,<sup>3</sup> Peter A. Kaufman,<sup>4</sup> Marianne Ulcickas Yood,<sup>5</sup> Adam M. Brufsky,<sup>1</sup> Musa Mayer,<sup>2</sup> Elizabeth Tan-Chiu,<sup>6</sup> Denise A. Yardley,<sup>9</sup> Merrill D. Birkner,<sup>8</sup> Lisa I. Wang,<sup>8</sup> Melissa G. Brammer,<sup>8</sup> Debu Tripathy<sup>7</sup>

<sup>1</sup>University of Pittsburgh Cancer Center, Pittsburgh, PA; <sup>2</sup>Patient Advocate, New York, NY; <sup>3</sup>UCSF Comprehensive Cancer Center, San Francisco, CA; <sup>4</sup>Dartmouth-Hitchcock Medical Center, Lebanon, NH; <sup>5</sup>EpiSource, LLC and Yale University School of Medicine, New Haven, CT; <sup>6</sup>Florida Cancer Care, Tamarac, FL; <sup>7</sup>University of Texas Southwestern Medical Center, Dallas, TX; <sup>8</sup>Genentech, Inc., South San Francisco, CA; <sup>9</sup>Sarah Cannon Research Institute, Nashville, TN

## BACKGROUND

- Trastuzumab (T; Herceptin®, Genentech, Inc.) has demonstrated clinical activity in advanced HER2-positive breast cancer.
- When administered in combination with chemotherapy until progressive disease (PD), T extends the survival of women with HER2-positive metastatic breast cancer (MBC).<sup>1,2</sup>
- Most HER2-positive MBC patients who initially respond to T-based therapies will eventually experience PD.
- registHER, a US-based multicenter prospective observational study of 1023 patients, is the largest study population of patients with newly diagnosed HER2-positive MBC.
- This prospective study offers a unique opportunity to describe treatment patterns and outcomes associated with use of T either initially or after PD following use of T in a real-world HER2-positive MBC study population.

## OBJECTIVE

- To describe treatment patterns and outcomes associated with use of T either initially or after disease progression following use of T among patients with newly diagnosed HER2-positive MBC enrolled in the registHER study

## PATIENTS AND METHODS

### Study Population

- Male and female patients with newly diagnosed (within 6 months) HER2-positive MBC treated in community and academic settings were recruited from December 2003 to February 2006.
- Patients will be followed for at least 3 years, or until death or disenrollment from the study.
- Treatments for MBC are administered according to standard of care by the treating physician; prior or planned treatment with T was not required for enrollment.

### Treatment Regimen (Lines) Definition

- Therapies received before a patient experienced his or her first PD were classified as part of the patient's first-line regimen; therapies received between 1<sup>st</sup> and 2<sup>nd</sup> PD were classified as part of the 2<sup>nd</sup>-line regimen (Figure 1).
- Patients were classified as "ever" receiving T in a 1<sup>st</sup>-line regimen if they received T any time prior to their 1<sup>st</sup> PD.
  - The subset of patients who received ≥21 cumulative days of T as part of each regimens (i.e., 1<sup>st</sup>-line, 2<sup>nd</sup>-line, was identified; this subset was identified and used for analysis of T beyond 1<sup>st</sup> PD (Figure 3).
- Duration of T therapy was calculated as the time from the date of first administration to the date the treatment was discontinued. Given the prolonged half life of T following administration, short breaks in treatment lasting for ≤30 days were counted as part of a continuous treatment regimen
- Patients were classified as not receiving T if they had no T exposure following their first PD event or following subsequent progressive events.

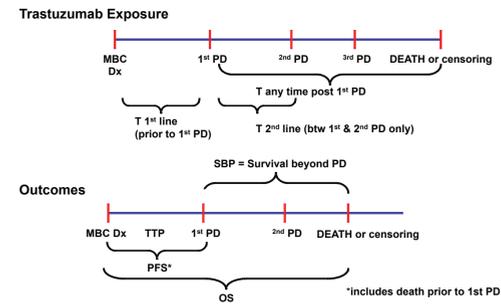
### Clinical Outcome Definitions

- Tumor progression was determined according to physician-reported assessments of radiologic and clinical data.
- Overall survival (OS) was defined as the time from the patient's initial MBC diagnosis to the date of death from any cause (Figure 1).
- Progression-free survival (PFS) was defined as the time from the date of the patient's initial MBC diagnosis to date of their 1<sup>st</sup> reported PD or death of the patient from any cause (Figure 1).
- Survival beyond progression (SBP) was defined as the time from the date of the patient's first PD to the date of death from any cause (Figure 1).
- For all of the above outcome measures, if followup ended for a reason other than PD or death, the patient's data were censored on that date (Figure 1).

### Covariates

- Covariates evaluated to determine their effects on predicting the choice of treatment following initial PD and as clinically-relevant prognostic factors of survival beyond progression included:
  - Age, race, ECOG performance status, hormone receptor status, number of metastatic sites and location of metastases, and presence of underlying co-morbid conditions.
- Additional clinical events developing during treatment that were evaluated included:
  - Time to first progression, development of serious T-related adverse events, site of PD (e.g., CNS, visceral), the type and duration of treatment regimen received prior to the patient's first PD, and the use of the dual HER1/HER2 tyrosine kinase inhibitor lapatinib (Tykerb®, GlaxoSmithKline) following 1<sup>st</sup> PD.

Figure 1. Definition of Treatment Periods and Endpoints



### Statistical Methods

- Analyses incorporate all follow-up data on registHER patients as of January 2, 2008.
- OS, PFS, and SBP were estimated using the Kaplan-Meier product-limit method and are presented as medians and ranges.
- For analysis of T use beyond 1st PD (population in Figure 3):
  - Cox proportional hazard models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for the independent effects of baseline and post-baseline clinical and treatment factors on SBP.
  - SBP, comparing the two treatment groups (T vs. no T beyond first progression), was estimated using Cox proportional hazards models, both unadjusted, and adjusted for the covariates determined to be either significant predictors of treatment with T beyond progression or prognostic of survival.
  - Backward and forward selection methods, using a criterion of p=0.1, were used to determine the covariates included in the final adjusted multivariate models.
  - The following sensitivity analyses were conducted: 1) restricting the comparison group of patients who did not receive T beyond progression in the analysis to those who survived at least 21 days and received therapy post-progression, and 2) using T beyond progression as a time-varying covariate.

## RESULTS

### Patients and Tumor Characteristics

- 1,023 patients enrolled in registHER. As of the January 2, 2008 data cut-off:
  - 491 (48%) remain in the study.
  - 453 (44%) have died.
  - 46 (4%) were lost to follow-up for reasons other than death
- Median patient follow-up time from metastatic diagnosis was 25 months.
- 983 (96%) patients had known HR status at the time of MBC diagnosis, 543 (55%) patients were hormone receptor (HR)-positive for either estrogen receptor (ER), and/or progesterone receptor (PR), and 440 (45%) were HR-negative.

### Course of Treatment and PD for the Study Cohort

- 1009 patients received systemic treatment for MBC (Figure 2).
  - 87% (879) of patients received a first-line treatment regimen that contained T.
  - 13% (130) of patients received first-line treatment that did not contain T.
- 685/879 (78%) of patients receiving T 1<sup>st</sup> line experienced PD.
  - 79% (539/685) of these patients were treated with T in the 2<sup>nd</sup> line setting.
  - 21% (146/685) of patients were not treated with T post progression.
- 420 patients treated with T in the 1<sup>st</sup> and 2<sup>nd</sup> line settings experienced a 2<sup>nd</sup> PD.
  - 83% (347/420) received additional T in a 3<sup>rd</sup> or later line of therapy.
- Since the U.S. approval of lapatinib in March 2007, the current data base cut-off includes newly-reported lapatinib use.
  - A greater number of patients treated with T following progression on 1<sup>st</sup> line T received lapatinib than those who did not receive T beyond progression.
    - 21.8% (115/527) of patients treated with T following 1<sup>st</sup> PD received lapatinib; 12 received lapatinib in 2<sup>nd</sup> line, and 103 in 3<sup>rd</sup> or later lines.
  - 13% (15/115) of patients not treated with T after 1<sup>st</sup> PD received lapatinib, 12 received lapatinib in 2<sup>nd</sup> line, and 3 in 3<sup>rd</sup> or subsequent lines.

Figure 2. Flowchart of HER2-positive MBC Patients Receiving or Not Receiving Trastuzumab Therapy during the Course of Their Disease

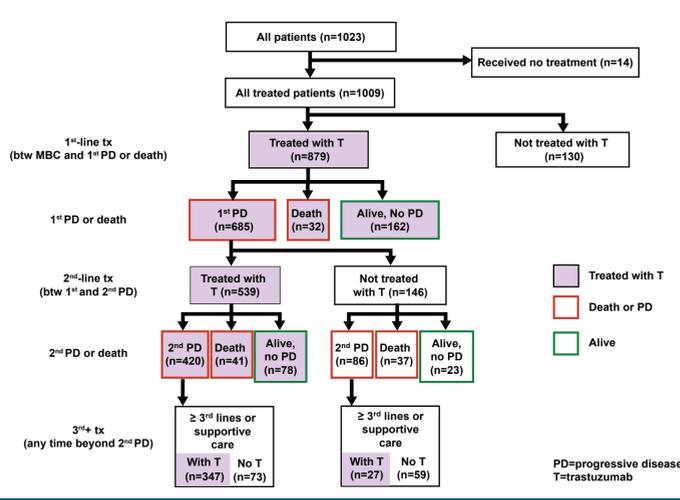


Table 1. First-line Treatments\* Received for MBC, by HR Status and Site of Metastases

| Characteristic                | Total N | Trastuzumab Treated (n=879) |              |                        | Non-Trastuzumab Treated (n=130) |                     | Untreated (n=14) |
|-------------------------------|---------|-----------------------------|--------------|------------------------|---------------------------------|---------------------|------------------|
|                               |         | T Alone                     | T+ E Therapy | T+ Chemo +/- E Therapy | E Therapy Only                  | Chemo +/- E Therapy |                  |
| Overall, n (%)†               | 1023    | 74 (7.2)                    | 51 (5.0)     | 754 (73.7)             | 59 (5.8)                        | 71 (6.9)            | 14 (1.4)         |
| HR status                     |         |                             |              |                        |                                 |                     |                  |
| ER+ and/or PR+                | 543     | 24 (4.4)                    | 50 (9.2)     | 365 (67.2)             | 58 (10.7)                       | 41 (7.6)            | 5 (0.9)          |
| ER- and PR-                   | 440     | 45 (10.2)                   | 0 (0)        | 362 (83.3)             | 1 (0.2)                         | 25 (5.7)            | 7 (1.6)          |
| Unknown                       | 40      | 5 (12.5)                    | 1 (2.5)      | 27 (67.5)              | 0 (0.0)                         | 5 (12.5)            | 2 (5.0)          |
| Metastatic sites at diagnosis |         |                             |              |                        |                                 |                     |                  |
| Any CNS                       | 75      | 15 (20.0)                   | 4 (5.3)      | 48 (64.0)              | 1 (1.3)                         | 3 (4.0)             | 4 (5.3)          |
| Bone only                     | 136     | 10 (7.4)                    | 18 (13.2)    | 76 (55.9)              | 24 (17.6)                       | 8 (5.9)             | 0 (0)            |
| Any Visceral                  | 623     | 39 (6.3)                    | 22 (3.5)     | 487 (78.2)             | 24 (3.9)                        | 44 (7.1)            | 7 (1.1)          |
| Node/local                    | 173     | 10 (5.8)                    | 5 (2.9)      | 134 (77.5)             | 8 (4.6)                         | 14 (8.1)            | 2 (1.2)          |
| All other sites               | 16      | 0 (0.0)                     | 2 (12.5)     | 9 (56.3)               | 2 (12.5)                        | 2 (12.5)            | 1 (6.3)          |

CNS=central nervous system E=endocrine ER=estrogen receptor HR=hormone receptor PR=progesterone receptor  
T= trastuzumab  
\* First-line metastatic treatment was defined as all treatment received by the patient before PD.  
† Percentages are calculated from the N of each row.

Table 2. PFS and OS from MBC Diagnosis for All Patients and by Use of Trastuzumab as First-Line Therapy

|   | No. of patients | Median Unadjusted OS,* months (quartiles) | Total # deaths | Median Unadjusted PFS,† months (quartiles) | Total No. of PD |
|---|-----------------|---|----------------|--|-----------------|
| All patients                                  | 1023            | 35.2 (18.0–63.1)                          | 450            | 10.2 (4.9–21.3)                            | 840             |
| All treated patients                          | 1009            | 35.6 (18.6–63.1)                          | 439            | 10.2 (5.0–21.6)                            | 829             |
| Patient ever treated with trastuzumab         | 879             | 35.9 (18.7–49.6)                          | 376            | 11.0 (5.4–22.0)                            | 716             |
| ≥21 days of trastuzumab duration              | 836             | 37.3 (19.5–50.6)                          | 346            | 11.4 (6.0–23.2)                            | 674             |
| <21 days of trastuzumab duration              | 43              | 17.3 (5.8–30.0)                           | 30             | 1.3 (1.0–3.5)                              | 42              |
| Patients not receiving first-line trastuzumab | 130             | 31.4 (16.1–89.5)                          | 63             | 5.4 (3.2–15.8)                             | 113             |

PFS= progression-free survival OS=overall survival  
\* OS is defined as time from metastatic diagnosis to death or censoring.  
† PFS is defined as time from metastatic diagnosis to first PD, death or censoring.

### Predictors of Treatment beyond Progression

- In patients who received ≥21 days of T prior to their first progression, we evaluated clinical and first-line treatment factors that may have influenced whether a patient received a T-containing regimen in subsequent treatment lines (Figure 3).
- Patients who received T beyond first progression compared with those who did not were generally younger (<50 years old, 45% vs. 29%), non-White (22% vs. 17%), HR positive (51% vs. 43%), and had fewer cardiac co-morbidities (15% vs. 22%).
  - Patients who developed T-related serious adverse events were less likely to receive T beyond progression.

Figure 3. Patient Population Used to Analyze Trastuzumab Use Beyond 1<sup>st</sup> PD. Boxes indicate populations compared.

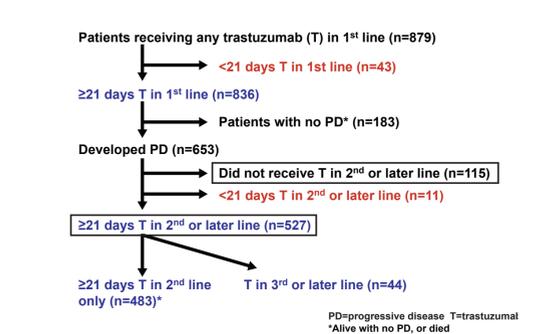


Table 3. Trastuzumab Treatment and SBP\*

|  | No. of deaths | Median SBP, months (range) |
|--|---------------|----------------------------|
| In patients who received T in 1 <sup>st</sup> line   |               |                            |
| T beyond 1 <sup>st</sup> PD† (n=527)   | 247           | 21.1 (0.9–45.8)            |
| No T beyond 1 <sup>st</sup> PD (n=115)   | 77            | 5.9 (0–30.9)               |
| SBP  |               |                            |
| T received beyond 1 <sup>st</sup> progression vs. no T received beyond 1 <sup>st</sup> progression |               |                            |
| Unadjusted HR  | 0.25          | 0.19–0.33                  |
| Adjusted HR  | 0.23          | 0.17–0.31                  |
| Covariates in multivariate model   |               |                            |
| Age (yr)   |               |                            |
| 50–64 vs. <50  | 1.08          | 0.84–1.39                  |
| 65+ vs. <50  | 1.37          | 1.01–1.85                  |
| Race (White vs. non-White)   | 1.32          | 1.01–1.73                  |
| ECOG performance status at metastatic diagnosis  |               |                            |
| ≥ 2 vs. 0 or 1   | 2.67          | 1.75–4.08                  |
| Unknown/missing vs. 0 or 1   | 1.02          | 0.81–1.29                  |
| HR status at metastatic diagnosis  |               |                            |
| ER-/PR- vs. ER+ and/or PR+   | 1.55          | 1.23–1.95                  |
| Unknown/missing vs. ER+ and/or PR+   | 2.03          | 1.18–3.49                  |
| Site of 1st PD   |               |                            |
| Any CNS vs. any visceral   | 1.51          | 1.15–1.97                  |
| Bone only vs. any visceral   | 0.46          | 0.29–0.72                  |
| Node/local vs. any visceral  | 0.63          | 0.43–0.94                  |
| Other vs. any visceral   | 0.86          | 0.56–1.31                  |
| Time to 1 <sup>st</sup> PD (vs. 12 months)   |               |                            |
| 0 to <3 months   | 0.83          | 0.57–1.21                  |
| 3 to <6 months   | 0.62          | 0.43–0.90                  |
| 6 months to <12 months   | 0.39          | 0.26–0.59                  |

ECOG=Eastern Oncology Group PD=progressive disease PS=performance status  
SBP=survival beyond progression T=trastuzumab  
\* SBP is defined as the time from first PD to death or censoring.  
† In patients who received ≥21 days of trastuzumab after their 1st PD.

### Treatment With Trastuzumab beyond Progression (Multivariate Analysis)

- The unadjusted HR comparing SBP in patients receiving T beyond progression with those who did not was 0.25 (95% CI: 0.19–0.33), suggesting improved SBP in patients who received T (Table 3).
- The adjusted HR, based on a multivariate model that included significant predictors of survival, was similar to the unadjusted HR (HR, 0.23; 95% CI: 0.17–0.31) (Table 3).
- When lapatinib use was added to the multivariate model, the estimate for reduction in risk of death associated with use of T beyond progression did not change (HR=0.25; 95% CI: 0.19–0.34).
- Of the 115 patients who did not receive T beyond progression, 43% (50) either survived <21 days after developing PD (n=16) or received no treatment following PD (n=34).
- There was little difference in the adjusted reduction in risk of death beyond progression when these patients were excluded (adjusted HR, 0.25; 95% CI: 0.17–0.36).
- Similarly, evaluation of T beyond progression as a time-varying covariate resulted in an adjusted HR of 0.30 (95% CI: 0.23–0.41).

## CONCLUSIONS

- In registHER, an observational cohort study of patients with HER2-positive MBC, 87% of patients were treated with trastuzumab (T) in the 1st-line setting.
- Median survival from MBC diagnosis for all patients was 35.2 months; 35.9 months for those receiving T in their 1st-line treatment regimen, and 31.4 months for those who did not.
- The unadjusted HR comparing survival beyond progression (SBP) in patients receiving T beyond progression with those who did not receive T was 0.25 (95% CI: 0.19–0.33), suggesting improved SBP in patients who received T.
- An adjusted HR including significant predictors of survival was similar (HR, 0.23; 95% CI: 0.17–0.31).
- Strengths of this study were high participation, minimal patient loss to followup, a predominance of patients (>80%) having been seen at non-academic centers (representing community practice patterns), and a geographic distribution of registHER patients that was fairly representative of the overall U.S. population of breast cancer patients.
- Despite the use of an adjusted multivariable model to account for bias due to potential confounding factors, the presence of unmeasured confounding variables in this observational study may still exist.
- These registHER data show that for patients who continued use of T following progression on a prior T-containing first-line regimen had reduced risk of death and a longer survival than patients who did not continue with T.

## REFERENCES

- Slamon DJ, Leyland-Jones B, Shak S, et al. 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 344:783-92.
- Marty M, Cognetti F, Maraninchi D, et al. 2005. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 23:4265-74.

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