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Long-term survivor characteristics in HER2-positive metastatic breast cancer from registHER

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Background: Data characterising long-term survivors (LTS) with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) are limited. This analysis describes LTS using registHER observational study data.

Methods: A latent class modelling (LCM) approach was used to identify distinct homogenous patient groups (or classes) based on progression-free survival (PFS), overall survival, and complete response. Demographics, clinicopathologic factors, first-line treatment patterns, and clinical outcomes were described for each class. Class-associated factors were evaluated using logistic regression analysis.

Results: LCM identified two survivor groups labelled as LTS ($n=244$) and short-term survivors (STS; $n=757$). Baseline characteristics were similar between groups, although LTS were more likely to be white (83.6% vs 77.8%) with oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) disease (59.4% vs 50.9%). Median PFS in LTS was 37.2 (95% confidence interval (CI): 32.9–40.5) vs 7.3 months (95% CI: 6.8–8.0) in STS. Factors associated with long-term survival included ER+ or PgR+ disease, metastasis to node/local sites, first-line trastuzumab use, and first-line taxane use.

Conclusions: Prognostic variables identified by LCM define a HER2-positive MBC patient profile and therapies that may be associated with more favourable long-term outcomes, enabling treatment selection appropriate to the patient's disease characteristics.

Breast cancer is the leading cause of cancer-related death in women, with ~40 000 US women expected to die from this disease in 2013 (Siegel *et al*, 2013). Amplification of the *human epidermal growth factor receptor 2 (HER2)* gene occurs in approximately 20% of patients with breast cancer (Ross *et al*, 2009; Dawood *et al*,

2010a), and this molecular subtype is associated with poor prognostic factors as shown by its highly proliferative and often high-grade histology (Eroles *et al*, 2012). In addition, patients with HER2-positive disease are more likely to develop central nervous system and visceral metastases than those with HER2-negative

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disease (Kallioniemi *et al*, 1991; Gabos *et al*, 2006; Pestalozzi *et al*, 2006; Bravo Marques, 2009; Leyland-Jones, 2009). Before the development of HER2-targeted therapies, HER2-positive breast cancer was associated with poorer patient outcomes when compared stage for stage with other breast cancer subtypes (Slamon *et al*, 1987; Awada *et al*, 2012). The introduction of HER2-targeted therapies has resulted in markedly improved clinical outcomes in both the early- and advanced-stage disease settings (Cobleigh *et al*, 1999; Slamon *et al*, 2001; Piccart-Gebhart *et al*, 2005; Romond *et al*, 2005; Geyer *et al*, 2006; Slamon *et al*, 2011; Baselga *et al*, 2012; Romond *et al*, 2012; Verma *et al*, 2012; Swain *et al*, 2013), with outcomes in HER2-positive metastatic breast cancer (MBC) similar to those of patients with HER2-negative disease (Dawood *et al*, 2010a). It was recently reported that the median overall survival (OS) in a cohort of patients with HER2-positive MBC who were treated with trastuzumab between 1999 and 2005 was 3.5 years from the time of initiation of therapy in the metastatic setting (Olson *et al*, 2013). However, despite improved patient survival times, the majority of patients with HER2-positive MBC ultimately relapse despite HER2-targeted treatment (Gajria and Chandralapaty, 2011).

Biomarkers with the potential to predict decreased sensitivity, early resistance, or relapse to HER2-directed therapies may include overexpression of truncated HER2 protein (p95^{HER2}); loss of the *phosphatase and tensin homolog* tumour-suppressor gene or activating mutations in the catalytic or regulatory subunits of phosphatidylinositol-3 kinase (PI3K), which is associated with upregulation of the PI3K/AKT/mTOR pathway; and overexpression of type 1 insulin-like growth factor receptor (Esteve *et al*, 2010). In patients with HER2-positive MBC, high levels of p95^{HER2} were found to correlate with decreased progression-free survival (PFS) and OS (Sperinde *et al*, 2010) and in patients with HER2-positive early-stage breast cancer, increased PI3K pathway activity was associated with a significantly worse OS (Jensen *et al*, 2012). Previously identified prognostic indicators in HER2-positive breast cancer include age, tumour size, axillary lymph node metastases, lymphovascular invasion, and the level of proliferation cell nuclear antigen (Liu *et al*, 2012). Predicting disease outcomes in patients with MBC is particularly complicated, as this is a biologically heterogeneous disease (Zidan *et al*, 2005) associated with variable clinical behaviour and survival times (Kennecke *et al*, 2010). Coupled with an incomplete understanding of the relationship between clinical characteristics and prognosis in HER2-positive MBC, the factors that predict outcome or response to HER2-targeted therapies are mostly exploratory.

Currently, data are limited regarding characteristics of long-term survivors (LTS) of HER2-positive MBC. RegistHER was a multicentre, prospective, observational, US-based cohort study of patients ($N=1023$) with HER2-positive MBC initiated in 2003. The objective of this analysis was to identify and describe homogeneous latent classes labelled as short-term survivors (STS) and LTS in the registHER study, in relation to demographics, disease characteristics, and treatment history, using a latent class modelling (LCM) approach. Additionally, we investigated the relationship between potential prognostic factors and long-term survival in this patient population.

MATERIALS AND METHODS

Study design. All of the patients who were recruited to the registHER study had HER2-positive MBC (newly diagnosed within 6 months) at the time of enrolment and were recruited to the registHER study from community and academic settings between December 2003 and February 2006 (ClinicalTrials.gov, NCT00105456; <http://www.clinicaltrials.gov/ct2/show/NCT00105456>). Details of the study

design, recruitment protocols, and study assessments have been described previously (Brufsky *et al*, 2011; Rugo *et al*, 2013). Previous or planned treatment with trastuzumab or any specific HER2-targeted therapy was not a requirement for enrolment, and patients received care in accordance with their physicians' standard practice, without study-specified evaluations. Upon enrolment, treatment history, sites of progressive disease, tumour response, survival, cardiac safety (grades 3–5), and any adverse events possibly related to the administration of trastuzumab were recorded. This information was updated every 3 months thereafter. In addition, the patients' demographic information, disease characteristics, history of breast cancer, history of metabolic disorders, cardiovascular disease (CVD), and cardiac safety data were collected. Cardiac safety events were defined using the Common Terminology Criteria for Adverse Events, v3.0 (National Cancer Institute, 2006), with selection based on physician opinion. No prespecified, scheduled assessments for tumour response were undertaken. Instead, tumour progression was reported by physicians according to their standard assessment schedule, judgment, and practice. The study was approved by all local institutional review boards, and all enrolled patients provided informed consent.

Statistical analysis. Statistical analyses were performed on all follow-up data for patients participating in registHER as of 15 June 2009 (database lock). The inclusion of data from 83 patients whose MBC diagnosis was made from 6 to –9 months before enrolment was permitted, and these data were included in all analyses. Of the 1023 patients in the registHER cohort, 22 were not reported as receiving any treatment for their MBC during the study, and data from these patients were therefore excluded from the analysis.

An LCM approach was used to identify one or more distinct homogeneous groups (latent classes) based on a simultaneous analysis of three response indicators: tumour response, PFS, and OS (Goodman, 1974; Vermunt 2009; Ross *et al*, 2012). The number of groups was determined by the Bayesian information criterion, and weights applied to the different indicators were estimated by maximum likelihood. Each patient was then assigned to the most likely group based on their posterior membership probabilities. Latent GOLD (Vermunt and Magidson, 2000) software was used for the LCM analysis.

Progression-free survival was defined as the time from MBC diagnosis to the first progression reported by the physicians' standard practice or death from any cause, whichever occurred first. Data for patients without disease progression or death as of the database lock were censored at the time of the last tumour response evaluation. OS was defined as the time from MBC diagnosis to the date of death from all causes. Data for patients without death as of the database lock were censored at the time of the last follow-up.

Baseline demographic and clinical characteristics were summarised by the two identified latent classes (STS and LTS) and the entire treated cohort. For continuous data, the number of observations, mean, s.d., median, minimum, and maximum were presented. Frequencies and percentages were calculated for categorical data. Comparability between LTS and STS was evaluated by the Wilcoxon rank-sum test for continuous data and by the chi-squared test for categorical data. When appropriate, 95% confidence intervals (CIs) were presented.

Frequencies and percentages of first-line treatment regimens, best first-line tumour response, and grade 3–5 cardiac adverse events were calculated. Trastuzumab-based first-line regimens were defined as patients receiving ≥ 21 days of trastuzumab in the first-line setting. The best first-line overall response was defined as the best response at any time during first-line treatment. Progression-free survival and OS were analysed using the Kaplan–Meier method to estimate median PFS and corresponding 95% CIs for

Table 1. Baseline demographic and clinical characteristics of STS, LTS, and all treated patients

Variable	STS (n = 757)	LTS (n = 244)	All treated patients (N = 1001)	P-value ^a
Age at enrolment, median years (range)	54 (20–92)	51 (26–82)	53 (20–92)	0.0049
<35 years	39 (5.2)	9 (3.7)	48 (4.8)	0.0117
35–64 years	545 (72.0)	199 (81.6)	744 (74.3)	
≥65 years	173 (22.9)	36 (14.8)	209 (20.9)	
Sex, n (%)				
Female	748 (98.8)	243 (99.6)	991 (99.0)	0.2873
Male	9 (1.2)	1 (0.4)	10 (1.0)	
Race, n (%)				
White	589 (77.8)	204 (83.6)	793 (79.2)	0.1157
Black	104 (13.7)	22 (9.0)	126 (12.6)	
Other	64 (8.5)	18 (7.4)	82 (8.2)	
BMI, n (%)				
<25 kg m ⁻²	254 (33.6)	76 (31.1)	330 (33.0)	0.7163
25 to <30 kg m ⁻²	236 (31.2)	82 (33.6)	318 (31.8)	
≥30 kg m ⁻²	267 (35.3)	86 (35.2)	353 (35.3)	
ECOG performance status at metastatic diagnosis, n (%)				
0–1	329 (43.5)	126 (51.6)	455 (45.5)	0.0791
2+	48 (6.3)	12 (4.9)	60 (6.0)	
Unknown/missing	380 (50.2)	106 (43.4)	486 (48.6)	
Serum albumin, n (%)				
≤3.5 g dl ⁻¹	108 (14.3)	24 (9.8)	132 (13.2)	0.0080
>3.5 g dl ⁻¹	365 (48.2)	145 (59.4)	510 (50.9)	
Unknown/missing	284 (37.5)	75 (30.7)	359 (35.9)	
ER/PgR status, n (%)				
ER+ or PgR+	385 (50.9)	145 (59.4)	530 (52.9)	0.0075
ER- and PgR-	348 (46.0)	86 (35.2)	434 (43.4)	
Unknown	24 (3.2)	13 (5.3)	37 (3.7)	
Site of metastatic disease at diagnosis, n (%)				
Any CNS	62 (8.2)	10 (4.1)	72 (7.2)	0.0131
Bone only or bone + breast	113 (14.9)	35 (14.3)	148 (14.8)	
Visceral	466 (61.6)	141 (57.8)	607 (60.6)	
Node/local	115 (15.2)	57 (23.4)	172 (17.2)	
Other sites	1 (0.1)	1 (0.4)	2 (0.2)	
Time to relapse after initial diagnosis, n (%)				
≤12 months	101 (13.3)	34 (13.9)	135 (13.5)	0.0066
>12 months	467 (61.7)	125 (51.2)	592 (59.1)	
Stage IV at initial diagnosis (<i>de novo</i> MBC)	189 (25.0)	85 (34.8)	274 (27.4)	
History of diabetes, n (%)				
Yes	65 (8.6)	13 (5.3)	78 (7.8)	0.0987
No/missing	692 (91.4)	231 (94.7)	923 (92.2)	
History of underlying CVD (any)^b, n (%)				
Angina	2 (0.3)	1 (0.4)	3 (0.3)	0.7174
Arrhythmia	18 (2.4)	4 (1.6)	22 (2.2)	0.4938
Congestive heart failure	13 (1.7)	2 (0.8)	15 (1.5)	0.3156
Hypertension with complications	41 (5.4)	7 (2.9)	48 (4.8)	0.1054
Myocardial infarction	14 (1.8)	5 (2.0)	19 (1.9)	0.8424
Peripheral vascular disease	9 (1.2)	4 (1.6)	13 (1.3)	0.5889
Other underlying cardiac disease	81 (10.7)	18 (7.4)	99 (9.9)	0.1305
History of underlying non-cardiac comorbidities (any), n (%)				
Yes	221 (29.2)	58 (23.8)	279 (27.9)	0.1003
No/missing	536 (70.8)	186 (76.2)	722 (72.1)	

Abbreviations: BMI = body mass index; CNS = central nervous system; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; LTS = long-term survivors; MBC = metastatic breast cancer; PgR = progesterone receptor; STS = short-term survivors.

^aP-values are from Wilcoxon two-sample test for continuous variables or chi-squared test for categorical variables for short-term vs long-term survivors.

^bPatients may be counted in multiple rows.

each group and overall. A logistic regression analysis on the latent class variable as a dependent variable with STS as the reference class was used to evaluate the effect of the following factors: age (age 35–64 years vs age <35 or age ≥65 years), race (white vs non-white), Eastern Cooperative Oncology Group (ECOG) performance status, serum albumin level, tumour oestrogen receptor/progesterone receptor (ER/PgR) status, stage of disease at initial diagnosis, site of metastatic disease (adjusted using a hierarchical approach, that is, (1) central nervous system (CNS), (2) bone and/or breast, (3) visceral/other, and (4) node/local), first-line trastuzumab use, first-line taxane use, history of underlying CVD, and history of other underlying non-cardiac comorbid conditions. A sensitivity analysis evaluating the effect of these factors on OS was also performed using Cox proportional hazards (PH) analysis.

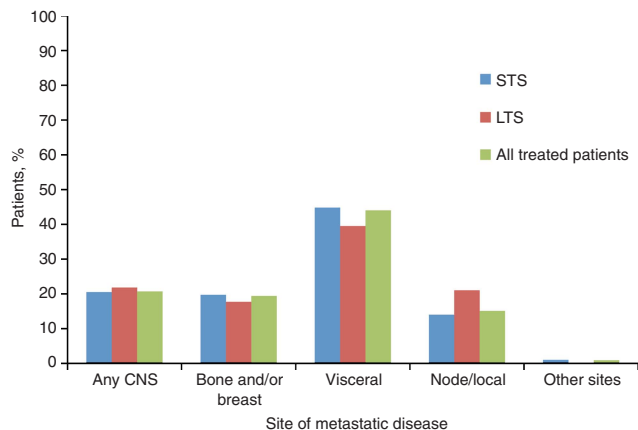


Figure 1. Site of first disease progression among short-term survivors (STS), long-term survivors (LTS), and all treated patients. Abbreviation: CNS = central nervous system.

RESULTS

LCM outcomes. LCM was used to identify one or more distinct homogeneous LTS group(s) and one or more STS group(s), based on a simultaneous analysis of complete first-line tumour response, PFS, and OS. A two-class LCM appeared to be the best model based on the lowest Bayesian information criterion value. The first class consisted of 244 (24.4%) of the 1001 patients and included 98.9% of patients (173 out of 175) who experienced a complete response (CR) as their best overall response. A total of 99.6% (243 out of 244) of patients in this group experienced CR or partial response (PR)/stable disease (SD) as their best overall response, and only 50.8% of patients within this class then later experienced progression following metastatic disease; therefore, this group was named the ‘LTS latent class’. The second patient group, consisting of 757 (75.6%) patients, was termed the ‘STS latent class’.

Patient characteristics. Baseline demographic and clinical characteristics for STS and LTS who were followed until death, withdrawal, or until database lock are shown in Table 1. There was a statistically significant difference in median age at enrolment between the two classes (51 years in LTS vs 54 years in STS; $P = 0.0049$). LTS and STS were similar in terms of the distribution of obese patients (body mass index ≥30) and history of diabetes. The proportion of non-white patients among LTS was lower than in STS (16.4% vs 22.2%, respectively). LTS were also more likely to have ER+ or PgR+ disease than STS (59.4% vs 50.9%, respectively) and a lower rate of underlying CVD (15.6% vs 19.9%, respectively). More specifically, patients within the LTS latent class had lower rates of congestive heart failure, hypertension with complications, arrhythmia, and other underlying cardiac disease than patients in the STS class (see Table 1), although these differences were not statistically significant.

Table 2. Treatment patterns before first disease progression

Treatment, n (%)	STS (n = 757)	LTS (n = 244)	All treated patients (N = 1001)
First-line trastuzumab-based regimens ^a	n = 613 (81.0)	n = 228 (93.4)	n = 841 (84.0)
With chemotherapy only	436 (71.1)	130 (57.0)	566 (67.3)
With hormonal therapy only	35 (5.7)	15 (6.6)	50 (5.9)
With chemotherapy and hormonal therapy	93 (15.2)	72 (31.6)	165 (19.6)
Trastuzumab alone	49 (8.0)	11 (4.8)	60 (7.1)
First-line non-trastuzumab regimens	n = 144 (19.0)	n = 16 (6.6)	n = 160 (16.0)
Chemotherapy only	72 (50.0)	7 (43.8)	79 (49.4)
Hormonal therapy only	53 (36.8)	4 (25.0)	57 (35.6)
Chemotherapy and hormonal therapy	8 (5.6)	5 (31.3)	13 (8.1)
<21 days of trastuzumab alone	11 (7.6)	0	11 (6.9)
Duration of trastuzumab in first line			
None or <21 days	144 (19.0)	16 (6.6)	160 (16.0)
21 days to 4 months	179 (23.6)	7 (2.9)	186 (18.6)
>4–8 months	193 (25.5)	27 (11.1)	220 (22.0)
>8–15 months	164 (21.7)	45 (18.4)	209 (20.9)
>15 months	77 (10.2)	149 (61.1)	226 (22.6)
First-line treatment with chemotherapy	n = 609 (80.4)	n = 214 (87.7)	n = 823 (82.2)
Taxane	404 (66.3)	169 (79.0)	573 (69.6)
Anthracyclines	38 (6.2)	14 (6.5)	52 (6.3)
Capecitabine	56 (9.2)	21 (9.8)	77 (9.4)
Any lapatinib treatment after MBC diagnosis	172 (22.7%)	38 (15.6%)	210 (21.0%)

Abbreviations: LTS = long-term survivors; MBC = metastatic breast cancer; STS = short-term survivors.

^aTrastuzumab-based regimens are defined as patients who received ≥21 days of trastuzumab as first-line therapy.

Although all patients enrolled in the study had stage IV MBC, at initial diagnosis a greater proportion of the LTS group had stage IV (*de novo*) disease than the STS group (34.8% vs 25.0%). The distribution of site of metastatic disease at diagnosis was similar, with visceral sites being the most common and CNS being the least common; however, fewer LTS presented with CNS metastases compared with STS (4.1% vs 8.2%, respectively), and a greater proportion of LTS had node/local metastasis vs STS (23.4% vs 15.2%) (see Table 1; Figure 1).

Treatment patterns for MBC before first disease progression.

First-line treatment patterns are defined as the therapeutic agents that patients received after MBC diagnosis and before first disease progression, and these may have been given either sequentially or concurrently. First-line trastuzumab use was higher in LTS (228 out of 244; 93.4%) than in STS (613 out of 757; 81.0%). Among patients who received chemotherapy as first-line treatment, LTS were more likely to receive a taxane (169 out of 214; 79.0%) compared with STS (404 out of 609; 66.3%), while anthracycline use was similar between these patient groups (6.5% vs 6.2%, respectively). Among those who received trastuzumab-based first-line treatment, LTS were more likely to receive hormonal therapy (15 out of 228; 6.6%) and combined chemotherapy/hormonal therapy (72 out of 228; 31.6%) compared with STS (35 out of 613; 5.7% and 93 out of 613; 15.2%, respectively) and less likely to receive chemotherapy and trastuzumab alone (Table 2).

Clinical outcomes. Before database lock, 15.2% of LTS had died compared with 65.3% of STS (Table 3). On average, LTS survived significantly longer without progressive disease than STS (median PFS, 37.2 months (95% CI: 32.9–40.5) vs 7.3 months (95% CI: 6.8–8.0) (Figure 2A). The median OS in STS was 27.2

months (95% CI: 25.4–29.3) but was non-estimable (NE) in LTS because the median OS was not reached (Figure 2B). The proportion of patients achieving physician-assessed first-line CR was much higher in LTS than in STS (70.9% vs 0.3%, respectively), and as a consequence, the proportion of patients achieving PR/SD was lower in LTS than in STS (28.7% vs 68.7%, respectively) (see Table 3). The time between MBC diagnosis and achieving CR/PR/SD was longer in LTS, with 52.7% of LTS achieving CR/PR/SD in <6 months compared with 91.0% of STS (see Table 3). The proportion of patients with disease progression was lower for LTS than for STS (50.8% vs 91.4% respectively). Although the distribution of metastasis to different body sites was similar between the two patient classes, the incidence of any CNS event was lower among LTS than among STS (18.9% vs 43.3%, respectively).

Cardiac safety outcomes. The incidence of any cardiac safety event (grades ≥ 3) was slightly lower in LTS (4.1%) than in STS (7.1%) (Supplementary Table 1). Left ventricular dysfunction was the most prevalent cardiac adverse event in both LTS (2.0%) and STS (2.0%).

Factors associated with short-term survival. Prognostic factors associated with the probability of short-term survival as an outcome were assessed using logistic regression analysis (Figure 3). Factors significantly associated with increased odds that a patient was classified as STS were older age at enrolment (≥ 65 years), non-white race, serum albumin (≤ 3.5 g dl⁻¹), recurrent MBC, and metastasis to the CNS. Conversely, factors associated with increased odds that a patient was classified as LTS included ER+ or PgR+ disease, metastasis to bone and/or breast or node/local sites (vs visceral/other metastasis), first-line

Table 3. Clinical outcomes stratified by survivor group

Parameter	Category/statistics	STS (n = 757)	LTS (n = 244)	All treated patients (N = 1001)
Number of deaths	n (%)	494 (65.3)	37 (15.2)	531 (53.0)
	Due to progression	458 (92.7)	34 (91.9)	492 (92.7)
	Other	36 (7.3)	3 (8.1)	39 (7.3)
PFS since metastatic diagnosis (months)	Median (95% CI)	7.3 (6.8–8.0)	37.2 (32.9–40.5)	10.2 (9.4–11.0)
Number of patients with first progression of disease	n (%)	692 (91.4)	124 (50.8)	816 (81.5)
OS since metastatic diagnosis (months)	Median (95% CI)	27.2 (25.4–29.3)	NE	35.9 (32.8–39.5)
Best first-line response, n (%)				
	CR	2 (0.3)	173 (70.9)	175 (17.5)
	PR/SD	520 (68.7)	70 (28.7)	590 (58.9)
	Unable to evaluate	20 (2.6)	1 (0.4)	21 (2.1)
	No assessment	215 (28.4)	0	215 (21.5)
Time between CR and MBC diagnosis, n (%)		n = 2	n = 173	n = 175
	≤ 6 months	2 (100.0)	69 (39.9)	71 (40.6)
	6 to ≤ 12 months	0	52 (30.1)	52 (29.7)
	12 to ≤ 18 months	0	22 (12.7)	22 (12.6)
	18 to ≤ 24 months	0	14 (8.1)	14 (8.0)
	>24 months	0	16 (9.2)	16 (9.1)
Time between CR/PR/SD and MBC diagnosis, n (%)		n = 522	n = 243	n = 765
	≤ 6 months	475 (91.0)	128 (52.7)	603 (78.8)
	6 to ≤ 12 months	45 (8.6)	59 (24.3)	104 (13.6)
	12 to ≤ 18 months	2 (0.4)	23 (9.5)	25 (3.3)
	18 to ≤ 24 months	0	14 (5.8)	14 (1.8)
	>24 months	0	19 (7.8)	19 (2.5)

Abbreviations: CI = confidence interval; CR = complete response; LTS = long-term survivors; MBC = metastatic breast cancer; NE = non-estimable; OS = overall survival; PFS = progression-free survival; PR, partial response; SD = stable disease; STS = short-term survivors.

trastuzumab use, and first-line taxane use. Prognostic factors associated with OS in all the treated patients were also assessed using Cox PH analysis (Figure 4). All of the factors that were associated with increased odds that a patient fell in the STS class in

the logistic regression analysis were also associated with an increased risk of mortality in the Cox PH analysis. However, in contrast to the logistic regression analysis, in the Cox PH model, an ECOG performance status of 2+ was associated with an increased risk of mortality (hazard ratio (HR), 2.022, 95% CI: 1.434–2.851).

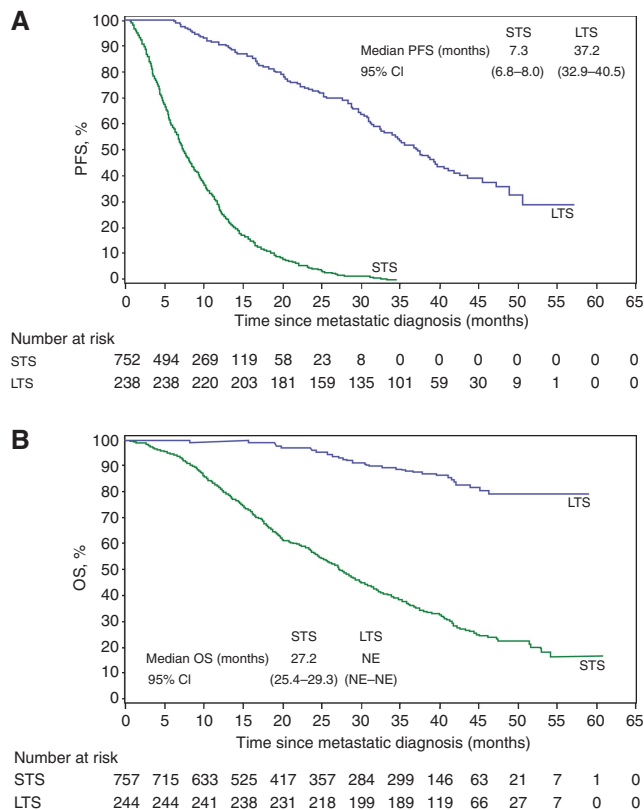


Figure 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) of the short-term survivor (STS) and long-term survivor (LTS) latent classes. Abbreviations: CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression-free survival.

DISCUSSION

Prolonged, relapse-free survival has previously been documented in a small subset (~2–3%) of MBC patients, regardless of HER2 status (Greenberg *et al*, 1996; Kobayashi *et al*, 2012); however, there is a paucity of data characterising long-term survival within the HER2-positive MBC population. In our study, baseline demographic and clinical characteristics in the LTS and STS patient cohorts classified by LCM were generally similar, although there were notable exceptions, suggesting that biological differences exist between these groups. For example, LTS were less likely to have ER/PgR-negative disease, which is consistent with previous studies demonstrating that patients with HER2-positive, ER/PgR-negative tumours have a poor prognosis (Carey *et al*, 2006; Largillier *et al*, 2008; Onitilo *et al*, 2009). However, this is in contrast with recent accumulating evidence that ER/PgR-positivity may confer a risk of late recurrence, which may not be captured within the follow-up time period of standard clinical trials. Another difference was the lower proportion of non-white patients in the LTS compared with the STS. Although socioeconomic factors and access to care may contribute to racial differences in the stage of breast cancer at diagnosis and subsequent treatment, underlying biological differences in breast cancer phenotypes between African-American and European-American women, irrespective of HER2 status, have previously been documented (Amend *et al*, 2006). Black race has previously been associated with poor prognosis and lower survival rates (Ooi *et al*, 2011; Sparano *et al*, 2012; Rugo *et al*, 2013), and this difference in survival persists following adjustment for socioeconomic factors (Newman, 2005; Du *et al*, 2011). In addition, a greater proportion of the LTS had stage IV disease at initial diagnosis (i.e., *de novo* metastatic disease) compared with STS and may be due to effects of

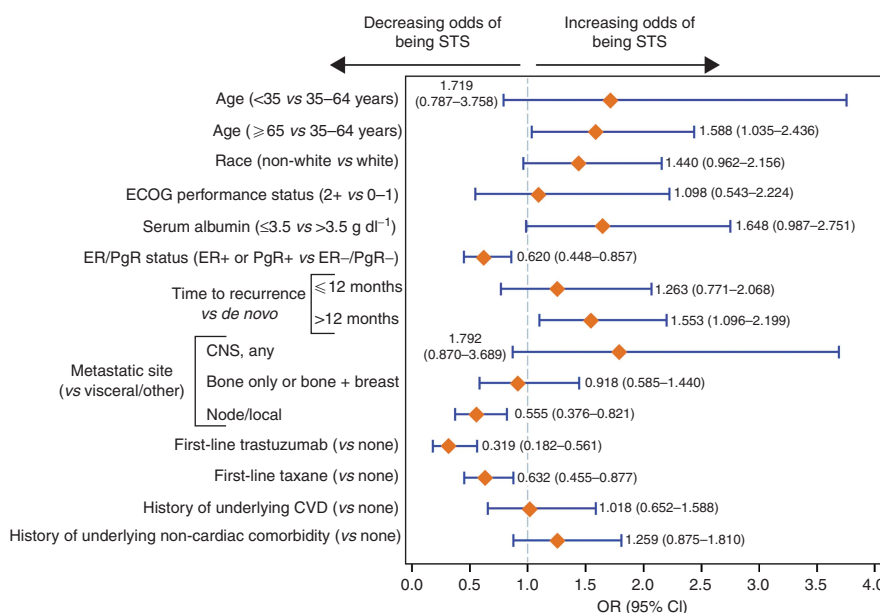


Figure 3. Logistic regression analysis examining prognostic factors associated with short-term survivors (STS). Abbreviations: CI = confidence interval; CNS = central nervous system; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; PgR = progesterone receptor; OR = odds ratio.

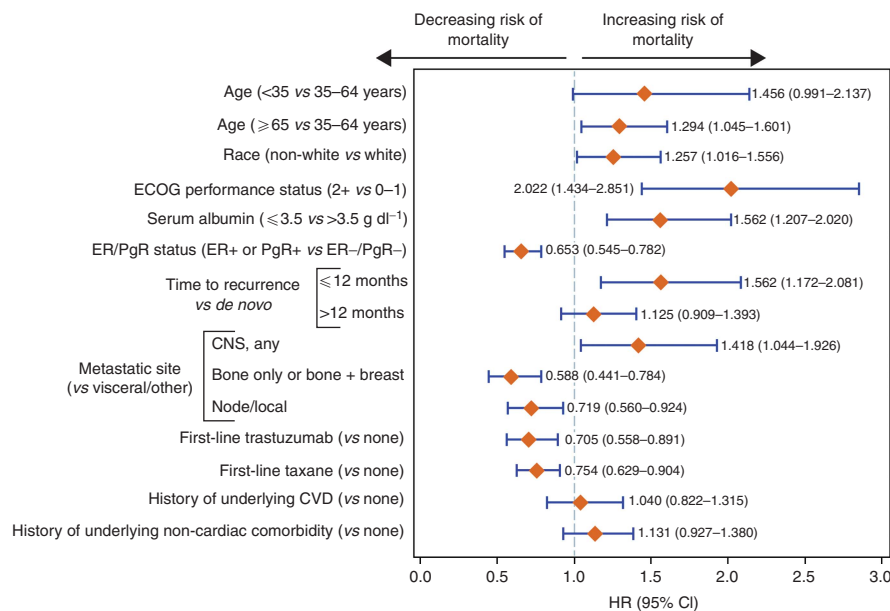


Figure 4. Cox proportional hazards model for overall survival. Abbreviations: CI = confidence interval; CNS = central nervous system; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; HR = hazard ratio; PgR = progesterone receptor.

previous drug exposure. This is consistent with results from a separate analysis from registHER comparing outcomes in patients with *de novo* vs recurrent MBC at initial diagnosis, which demonstrated that patients with *de novo* MBC had longer median OS than patients with recurrent MBC (Yardley *et al*, 2014).

Analysis of treatment patterns in LTS and STS found that LTS were more likely to have undergone first-line trastuzumab treatment (93.4% vs 81.0%, respectively) and were more likely to have been treated with a taxane (79.0% vs 66.3%, respectively). In addition, LTS were twice as likely to have been treated with a combination of trastuzumab, chemotherapy, and hormones as STS (31.6% vs 15.2%). It is unclear whether these differences result from treatment effects or are simply due to 'treatment selection bias' due to the observational non-randomised nature of this study. Additionally, as biological factors may influence both outcome and physician treatment choices, it is difficult to directly correlate treatment patterns with survival.

When examining outcomes, the proportion of patients achieving a first-line CR was significantly higher in LTS than in STS (70.9% (173 out of 244) vs 0.3% (2 out of 757), respectively). Additionally, the time between MBC diagnosis and achieving a response of SD or better was shorter in STS, suggesting that some intrinsic factors may result in more responsive disease that was not durable, with more rapid development of resistance; however, the exact factors are currently unknown. Likewise, PFS was significantly longer in LTS compared with STS (median PFS 37.2 months (95% CI: 32.9–40.5) vs 7.3 months (95% CI: 6.8–8.0), respectively). It has previously been suggested that achieving an initial CR is a prerequisite for long-term disease-free status following MBC diagnosis (Greenberg *et al*, 1996). In our analysis, 98.9% (173 out of 175) of the patients who achieved a CR following first-line treatment were in the LTS group, suggesting that in HER2-positive MBC CR to first-line therapy is strongly associated with survival and may partially account for the noted disparities in PFS between these two groups.

Prognostic factors associated with STS in our analysis were older age at enrolment (≥ 65 years), non-white race, serum albumin ≤ 3.5 g dl⁻¹, recurrent disease, and metastasis to the CNS. This is consistent with multiple previous reports in both HER2-positive and in unselected patients (Lis *et al*, 2003;

Brunetto *et al*, 2010; Dawood *et al*, 2010b; Ooi *et al*, 2011; Kaufman *et al*, 2012; Sparano *et al*, 2012), including a recent retrospective analysis of 1038 women noting that age at initial diagnosis of <50 years and hormonal receptor-positive status were the most relevant prognostic factors for longer survival, while the development of CNS, multiple, and/or hepatic sites of metastasis were prognostic for worse survival (Largillier *et al*, 2008).

In this study, an LCM approach was used to identify the two homogeneous survival groups labelled as STS and LTS, rather than selecting a survival time point to define them (Yardley *et al*, 2012). The use of LCM in this study enabled the identification of two groups that are biologically distinct in terms of clinical features (ER/PgR status), age, race, and also disease response (longer PFS and higher CR rates). LCM allows for the identification of distinct long-term and short-term survival sub-populations without the use of an arbitrary cutoff time point. In addition, LCM utilises information from multiple response variables, and right censoring is handled in a statistically appropriate way, because posterior membership probabilities are estimated for all subjects, regardless of the number of months of follow-up. Patients were assigned to the latent class (either STS or LTS) in which they have the highest posterior membership probability, and there is uncertainty associated with this unless the membership probability is 1. Although this uncertainty can be modelled (Vermunt, 2010), for simplicity, the latent class assignment was assumed to contain no error; therefore it is important to interpret the results with some caution.

In addition to limitations of the LCM analyses, further study limitations may have included 'confounding effects' resulting from the non-randomised and observational nature of the registHER study cohort. However, within each class the observed variables are statistically independent. This analysis may also have residual confounding owing to its inability to control for patient treatment compliance and previous treatment patterns, tumour size, and New York Heart Association Functional Classification. In addition, because patients could potentially have had a diagnosis of MBC for up to 9 months before enrolment, there is the possibility of selection bias for patients with a longer OS. The median OS for all treated patients in this study was 35.9 months; however, it has recently been reported that the median OS of HER2-positive MBC

now exceeds 3 years (Olson *et al*, 2013), suggesting that patients with a longer OS have not been selected for within this population.

Currently, approaches to managing MBC focus on individualising treatment to best target the patient's as well as the tumour's clinical and molecular characteristics. Physician's awareness regarding the variability in the prognosis for patients with stage IV disease is crucial in making optimal treatment recommendations.

In addition to guiding treatment decisions, a better understanding of prognostic factors in MBC, particularly in the increasingly smaller subgroup of patients with HER2-positive disease, may lead to improved clinical trial design to evaluate new therapeutic agents and/or concurrent and sequential treatment combinations as well as dual HER2-targeting strategies. As the outcomes for HER2-positive MBC continue to improve, long-term follow-up of these patients to capture prospective treatment patterns, such as in registHER and the subsequent SystHERs registry, are required to develop prognostic models for identification of patients who may expect to experience long-term disease control and potentially curative outcomes.

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CONFLICT OF INTEREST

AMB and PAK have received consulting fees from Genentech Inc./F. Hoffmann La-Roche, Ltd. DT has served in an uncompensated capacity on a steering committee and receives research funding (paid to his institution) for a registry study funded by Genentech, Inc./F. Hoffmann La-Roche, Ltd. MUY has served on an advisory board for Genentech, Inc. HSR has received research funding for her institution from Genentech, Inc. and GlaxoSmithKline; PAK has received research funding for his institution from Genentech, Inc. JM has received consulting fees from Genentech Inc. and has a financial interest in the Latent GOLD software package. BY and CQ are full-time employees of Genentech, Inc. and own stock in F. Hoffmann La-Roche Ltd. The other authors declare no conflict of interest.

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