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Academia–Pharma Intersect: Breast Cancer

Lapatinib Plus Capecitabine in Women with HER-2–Positive Advanced Breast Cancer: Final Survival Analysis of a Phase III Randomized Trial

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ABSTRACT

Objectives. **A planned interim analysis of study EGF100151 prompted early termination of enrollment based on a longer time to progression with lapatinib and capecitabine than with capecitabine alone in patients with human epidermal growth factor receptor (HER)-2$^+$ previously treated advanced breast cancer or metastatic breast cancer (MBC). Here, we report final analyses of overall survival.**

Patients and Methods. **Women with HER-2$^+$ MBC who progressed after regimens that included, but were not limited to, anthracyclines, taxanes, and trastuzumab, were randomized to lapatinib (1,250 mg/day) plus capecitabine (2,000 mg/m^2) or capecitabine monotherapy (2,500 mg/m^2) on days 1–14 of a 21-day cycle.**

Results. **At enrollment termination, 399 patients were randomized, and nine were being screened and were offered combination treatment. In total, 207 and 201 patients were enrolled to combination therapy and monotherapy, respectively. Thirty-six patients receiving monotherapy crossed over to combination therapy following enrollment termination. The median overall survival times were 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.71–1.08; $p = .210$). A Cox regression analysis considering crossover as a time-dependent covariate suggested a 20% lower risk for death for patients treated with combination therapy (HR, 0.80; 95% CI, 0.64–0.99; $p = .043$). The low incidence of serious adverse events was consistent with previously reported rates.**

Conclusions. **Although premature enrollment termination and subsequent crossover resulted in insufficient power to detect differences in overall survival, exploratory analyses demonstrate a trend toward a survival advantage with lapatinib plus capecitabine. These data continue to support the efficacy of lapatinib in patients with HER-2$^+$ MBC.** ***The Oncologist*** 2010;15:924–934

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Introduction

Increased expression and activation of human epidermal growth factor receptors (HERs) in breast cancer is associated with a higher risk for disease recurrence and poor prognosis [1]. HER-2 is overexpressed in 15%–20% of newly diagnosed breast cancer cases [1]. The anti–HER-2 monoclonal antibody trastuzumab has led to a longer time to progression (TTP) and overall survival (OS) time when added to chemotherapy in the first-line treatment of metastatic HER-2^+ breast cancer patients, and it produces longer disease-free survival and OS times when administered with or following chemotherapy in the adjuvant setting [2–6]. However, resistance to trastuzumab is present or eventually develops in patients with metastatic disease, and recurrences following trastuzumab-based adjuvant therapy still occur [7].

Lapatinib (Tykerb® or Tyverb®; GlaxoSmithKline, Research Triangle Park, NC) is a small-molecule, reversible tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor and HER-2 [8]. A planned interim analysis of a randomized, open-label, phase III trial (EGF100151) in women with HER-2^+, locally advanced breast cancer or metastatic breast cancer (MBC) who progressed following treatment with an anthracycline, a taxane, and trastuzumab in the adjuvant or metastatic setting demonstrated that the addition of lapatinib to capecitabine led to a significantly longer independently assessed TTP. Based on that analysis, the independent data monitoring committee (IDMC) recommended early termination of enrollment, notification of the patients of the results, and offering combination treatment to patients randomized to monotherapy. Efficacy and safety data from the interim analysis were reported at the time accrual was closed and a subsequent analysis of data through the termination of accrual was reported in 2008 [9, 10]. In the updated analysis, the hazard ratio (HR) for TTP, the primary endpoint, was 0.57 (95% confidence interval [CI], 0.43–0.77; $p < .001$) [10]. At that time, analysis of OS was immature, with 55 reported deaths in the combination arm and 64 deaths in the monotherapy arm (HR, 0.78; 95% CI, 0.55–1.12; $p = .177$) [10]. We now present mature survival analyses as well as exploratory analyses adjusted for baseline and disease history parameters and adjusted for crossover.

Patients and Methods

The study design, eligibility criteria, treatment plan, and statistical analyses have been detailed in prior publications but are summarized here [9, 10]. The institutional review board at each participating institution approved the study protocol, and all enrolled patients provided written informed consent.

Patient Eligibility

The study enrolled women with HER-2^+ locally advanced breast cancer or MBC who had progressed after treatment with regimens that included, but were not limited to, an anthracycline, a taxane, and trastuzumab [9]. Criteria for HER-2 positivity were a score of 3+ on the immunohistochemical (IHC) analysis or 2+ IHC staining intensity with demonstration of gene amplification by fluorescence in situ hybridization as determined by the local institution [9]. All patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (version 1.0) [11].

Treatment Plan

Patients were randomized 1:1 to treatment with lapatinib (1,250 mg) daily plus capecitabine (2,000 mg/m^2 in two divided doses) on days 1–14 of a 21-day cycle or capecitabine monotherapy (2,500 mg/m^2 in two divided doses) on the same cycle. The primary endpoint was independent assessment of TTP (defined as time from randomization to disease progression or death resulting from breast cancer). Secondary endpoints included progression-free survival (PFS) (the time from randomization to disease progression or death resulting from any cause), OS, the overall response rate, the clinical benefit rate (confirmed complete response plus confirmed partial response plus stable disease lasting ≥6 months), and safety measured according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0) [9].

Statistical Analysis

Enrollment was stopped on April 3, 2006, based on a recommendation by the IDMC [10]. Prior publications have detailed the sample size calculations, planned interim analysis, and stopping rules [9, 10]. This report provides updated survival analyses of all women ($n = 399$) who underwent randomization (intent-to-treat [ITT] population). In an effort to use data from all treated patients, the nine patients who were in screening when the study was halted were included in analyses conducted to explore baseline prognostic factors and the effects of crossover on overall survival ($n = 408$). Log-rank tests stratified by stage of disease and presence or absence of visceral disease were used to analyze time-to-event endpoints, and Fisher's exact tests were used for tumor response rates. All p-values were calculated as two sided.

To explore the effect of baseline disease history and prognostic factors on OS, a Cox proportional hazard model was employed. The 11 baseline and disease history factors that were investigated have been correlated with survival and are considered to be prognostic in the management of patients with MBC [12]. These factors were Eastern Cooperative Oncology Group (ECOG) performance status score (0 or ≥1),

number of metastatic sites (<3 or ≥3), site of disease (visceral or nonvisceral), liver metastases (yes or no), stage of disease (IIIB/IIIC or IV), hormone receptor status (estrogen receptor negative and progesterone receptor negative, estrogen receptor positive, or progesterone receptor positive), time from last dose of prior trastuzumab to randomization (≤8 weeks or >8 weeks), number of prior chemotherapy regimens (<3 or ≥3), age, time from diagnosis to randomization, and time from metastatic diagnosis to randomization.

A stepwise model-building approach was employed to evaluate the effects of these baseline prognostic factors. Treatment was retained in the model, whereas the prognostic factors identified as significant in univariate models were evaluated using stringent criteria for inclusion using entry/exit criteria of $\alpha \leq 0.05$.

RESULTS

Patient Population

When enrollment to the study ceased on April 3, 2006, there had been 399 patients randomized (ITT population) plus a further nine patients eligible who had not yet started treatment. Following unblinding of the results, these nine patients were all treated with the combination and their outcomes were not different from those patients randomized to the combination arm. Table 1 lists the patient baseline prognostic factors. The groups were balanced for all prognostic factors. As of October 1, 2008, 340 (83%) of the 408 patients had died. In the lapatinib plus capecitabine treatment arm, 168 (81%) of 207 patients had died, seven (3%) were censored when follow-up ended, and 32 (15%) were censored with ongoing follow-up. In the capecitabine monotherapy arm, 172 (86%) of 201 patients had died, seven (3%) were censored when follow-up ended, and 22 (11%) were censored with ongoing follow-up.

Efficacy

OS

The median OS times in the ITT population were 75.0 weeks for those treated with lapatinib plus capecitabine and 64.7 weeks for those treated with capecitabine alone, with an HR of 0.87 (95% CI, 0.70–1.08; $p = .206$) (Fig. 1A). An analysis of OS that included the nine additional patients in screening ($n = 408$) yielded identical results (75.0 weeks for combination therapy and 64.7 weeks for monotherapy, with an HR of 0.87; 95% CI, 0.71–1.08; $p = .210$).

A Cox regression model, using data from all 408 enrolled patients, evaluated the effects of treatment group along with baseline disease history and prognostic factors, described in Patients and Methods, on OS. Univariate analyses were conducted to evaluate prognostic factors in the presence of treatment. Significant factors were then analyzed in a stepwise fashion. Final model results are presented in Table 2. The adjusted HR of 0.81 (95% CI, 0.65–1.00; $p = .051$) represents a 19% lower risk for death for patients treated with lapatinib plus capecitabine than for those treated with capecitabine alone. The adjusted survival curves considering these main treatment effects show that the survival benefit was maintained over time in the combination arm (Fig. 1B).

Effect of Crossover Therapy

When enrollment for the study was halted, 39 patients were receiving capecitabine monotherapy. Of these, 35 patients (90%) crossed over to combination therapy. An additional patient who had discontinued capecitabine because of disease progression 6 days prior to the time enrollment was halted also received combination therapy. As a result, a total of 36 patients crossed over to the combination arm, thereby confounding the effect of treatment on OS. The baseline prognostic factors for patients who crossed over to lapatinib plus capecitabine were similar to those of the 165 patients on capecitabine alone who did not cross over. Because there is no optimal methodology to adjust for crossover in a survival analysis, several approaches were used to conduct exploratory analyses.

Exclusion of crossover patients from the analysis resulted in median OS times of 75.0 weeks in the combination group and 56.4 weeks in the monotherapy group, with an HR of 0.78 (95% CI, 0.62–0.97; $p = .023$) (Fig. 2). Although this approach discounts the benefit these patients may have received from capecitabine alone, it also excludes any benefit these patients may have received from combination therapy.

Censoring patients at the time of crossover to the combination arm resulted in median OS times of 75.0 weeks for lapatinib plus capecitabine and 62.6 weeks for capecitabine monotherapy, with an HR of 0.82 (95% CI, 0.66–1.02; $p = .074$). This analysis reflects the benefit these patients received from capecitabine monotherapy; however, it is a conservative analysis and potentially favors the capecitabine arm as a result of the fact that patients who died after crossover were censored.

A Cox regression model considering crossover as a time-dependent covariate was used to adjust for the effect of crossover without excluding the effect of capecitabine on OS for the patients who crossed over. The Cox regression with time-dependent crossover accounts for the effect of capecitabine as well as the effect of the combination following crossover. When crossover was used as a time-dependent covariate, the HR for the crossover effect was 0.63 (95% CI, 0.41–0.98; $p = .042$), suggesting that patients' risk for death was lower with

Table 1. Patient baseline prognostic factors

Baseline prognostic factor	Patients, *n* (%)	
	Lapatinib + capecitabine (*n* = 207)	**Capecitabine monotherapy (*n* = 201)**
Median age, yrs (range)	54 (26–80)	51 (28–83)
Disease site		
Visceral	153 (74)	158 (79)
Nonvisceral	54 (26)	43 (21)
ECOG performance status score		
0	127 (61)	117 (58)
≥1	79 (38)	77 (38)
Missing	1 (<1)	7 (3)
Median time from initial diagnosis, yrs (range)	3.8 (0–21)	4.1 (0–19)
Median time from diagnosis of metastasis, yrs (range)	1.7 (0–9)	1.6 (0–8)
Metastatic sites		
<3	104 (50)	105 (52)
≥3	103 (50)	96 (48)
Liver metastases at baseline		
Yes	111 (54)	102 (51)
No	96 (46)	99 (49)
Disease stage		
IIIB/IIIC	8 (4)	8 (4)
IV	199 (96)	193 (96)
Hormone receptor status		
ER^- and PR^-	101 (49)	101 (50)
ER^+ or PR^+	99 (48)	93 (46)
Unknown	7 (3)	7 (3)
Prior chemotherapy regimens		
<3	31 (15)	37 (18)
≥3	176 (85)	164 (82)
Time from last dose of trastuzumab to randomization		
≤8 wks	122 (59)	117 (58)
>8 wks	83 (40)	77 (38)
Missing	2 (<1)	7 (3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.

crossover to lapatinib plus capecitabine. The HR for the treatment effect ($n = 408$) was 0.80 (95% CI, 0.64–0.99; $p = .043$), suggesting a clinically relevant 20% lower risk for death for patients in the combination arm.

A final Cox regression model considered crossover as a time-dependent covariate and included the baseline prognostic factors identified as significant in the previous Cox regression analysis (i.e., ECOG performance status score, presence or absence of liver metastases, and number of metastatic sites). The model demonstrated an HR of 0.75 (95% CI, 0.60–0.94; $p = .013$) for the combination relative to monotherapy, suggesting a survival benefit (Table 3). Figure 3 provides a forest plot of the various exploratory analyses for OS adjusted for crossover. The results are consistent, regardless of the model, and are consistent with some attenuation of a demonstrable OS benefit resulting from the effects of crossover.

Exploratory Analyses of the Impact of Prior Trastuzumab Regimens on Efficacy

A previous analysis demonstrated that efficacy was not influenced by the interval from the last dose of trastuzumab

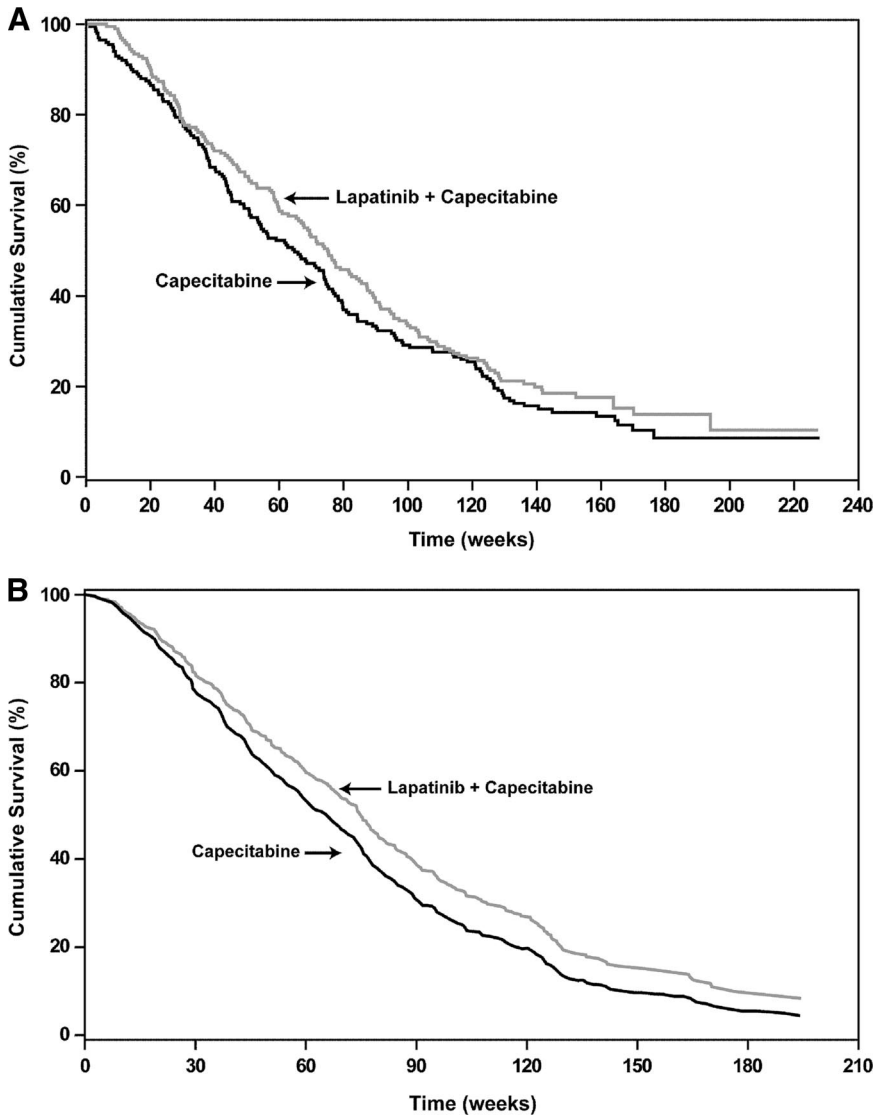

Figure 1. Kaplan–Meier estimates of overall survival (OS). **(A):** Intention-to-treat population. **(B):** OS curve adjusted for Eastern Cooperative Oncology Group performance status score, number of metastatic sites, and liver metastases.

Table 2. Summary of Cox regression model for OS ($n = 408$)

Covariate	Effect tested	HR (95% CI)[a]	*p*-value
Treatment group	Lapatinib + capecitabine versus capecitabine	0.81 (0.65–1.00)	.051
Metastatic sites	<3 versus ≥3	0.64 (0.51–0.79)	<.001
ECOG performance status score	0 versus ≥1	0.56 (0.45–0.70)	<.001
Liver metastases	No versus yes	0.52 (0.41–0.65)	<.001

[a]HR <1 indicates a lower risk.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

[10]. We elected to also conduct an exploratory analysis to determine if the number of prior metastatic trastuzumab-based regimens, regardless of the number of other prior treatment regimens, might influence TTP and OS. Exploratory subgroup analyses of TTP and OS data are presented for subgroups of patients treated with one or more than one prior regimen containing trastuzumab for metastatic disease.

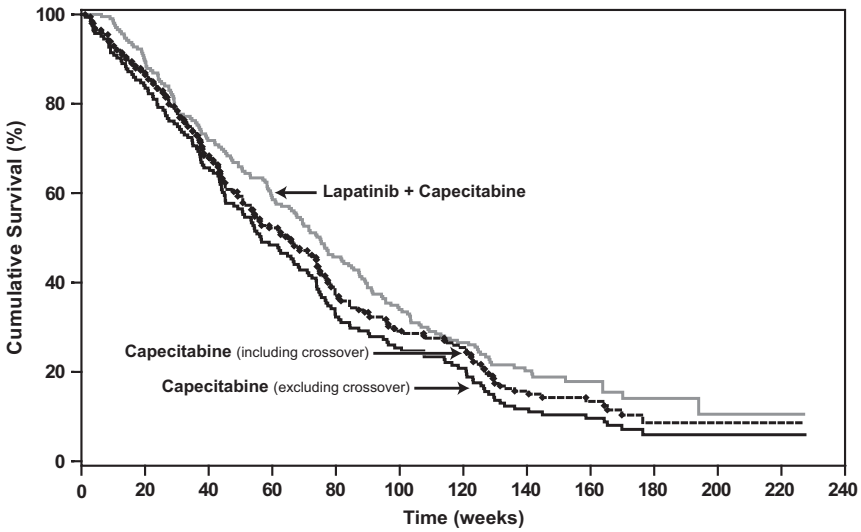

Figure 2. Kaplan–Meier estimates of overall survival including and excluding the crossover.

Table 3. Summary of Cox regression model for OS considering prognostic factors and crossover (N=408)

Covariate	Effect tested	HR (95% CI)[a]	*p*-value
Treatment group	Lapatinib + capecitabine versus capecitabine	0.75 (0.60–0.94)	.013
ECOG performance status score	0 versus ≥1	0.55 (0.44–0.69)	<.001
Liver metastases	No versus yes	0.52 (0.42–0.65)	<.001
Metastatic sites	<3 versus ≥3	0.64 (0.51–0.80)	<.001
Time-dependent crossover	Crossover versus not crossed over	0.65 (0.41–1.01)	.054

[a]HR <1 indicates a lower risk.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

Among patients receiving only one prior trastuzumab-based regimen, the median TTP were 31.3 weeks in the combination arm and 18.6 weeks in the monotherapy arm (HR, 0.50; 95% CI, 0.34–0.72; $p < .001$) (Fig. 4A). The median OS times in this group were 71.4 weeks and 56.6 weeks (HR, 0.79; 95% CI, 0.60–1.03; $p = .077$). A trend for a longer TTP was seen in patients who had been treated with more than one metastatic trastuzumab-based regimen, with median TTP of 24.4 weeks and 19.7 weeks in the combination and monotherapy arms, respectively (HR, 0.64; 95% CI, 0.38–1.07; $p = .09$) (Fig. 4B). However, in this group, the median OS times were similar in both the combination (77.1 weeks) and monotherapy (80.9 weeks) arms (HR, 1.09; 95% CI, 0.74–1.60; $p = .669$).

Update on Severe Adverse Events

As of the data cutoff of October 1, 2008, a total of 115 severe adverse events (SAEs) had been reported from 58 patients enrolled, including 47 events from 24 patients treated with lapatinib plus capecitabine, 11 events from six patients following crossover to combination therapy, and 57 events from 28 patients treated with capecitabine monotherapy (Table 4). The most frequently reported SAEs were diarrhea, dehydration, and vomiting.

Twelve deaths resulted from SAEs. In the combination arm, four patients died as a result of the following SAEs as assessed by the investigators: cardiorespiratory arrest, lymphedema, hyponatremia, and general deterioration in physical health. Two additional patients died from events that were later determined to be related to disease progression and central nervous system metastases, respectively. In the capecitabine arm, six patients died from the following nine SAEs (two patients experienced more than one fatal SAE) as assessed by the investigators: diarrhea, vomiting, cardiac arrest, intestinal obstruction, neutropenia, thrombocytopenia, pulmonary embolism, dyspnea, and respiratory arrest.

Cardiac Safety

A total of 11 patients experienced 12 events of decreased left ventricular ejection fraction (LVEF). Eight patients (mean age, 56 years; range, 46–68 years), four in each

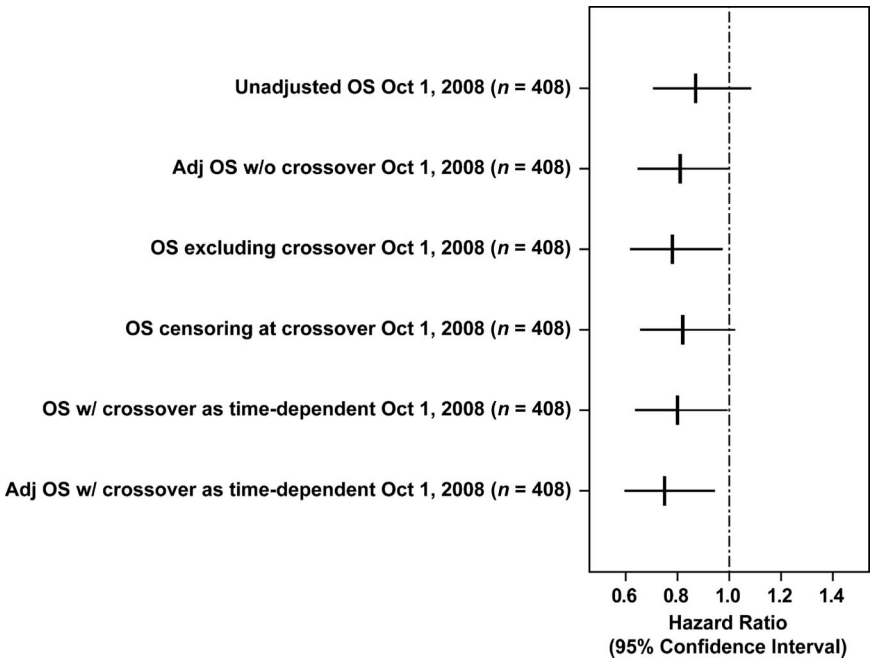

Figure 3. Hazard ratios and 95% confidence intervals for OS analyses.
Abbreviations: Adj, adjusted; OS, overall survival; w/, with; w/o, without.

treatment arm, met the protocol-specific serious definition (NCI CTCAE, version 3.0, grade 3 or 4 left ventricular systolic dysfunction or ≥20% absolute decrease in LVEF relative to the baseline value and below the institution's lower limit of normal). However, all eight patients were reported as asymptomatic. Of note, one crossover patient experienced two LVEF decrease events (once per treatment arm), but was asymptomatic during both episodes. Among the eight patients whose LVEF decrease met the protocol definition, the mean time to onset of decrease in LVEF was 63 days, with a range of 21–201 days, and the mean nadir absolute decline in LVEF was 26% relative to baseline, with a range of 20%–39%. LVEF effects in these patients were complicated by previous use of cardiotoxic medications (anthracyclines and trastuzumab) or concurrent conditions, such as hypertension, left chest radiation, and cardiopulmonary diseases.

Hepatobiliary Events

Oral TKIs have been associated with a low risk for hepatic toxicity as a possible class effect. Four patients (1.9%) in the lapatinib plus capecitabine arm and three patients (1.6%) in the capecitabine alone arm developed serious hepatobiliary events, with one capecitabine patient having two events. The hepatobiliary SAE reports were confounded by underlying medical conditions: worsening of pre-existing liver metastasis, alternative diagnoses (e.g., bile duct obstruction), and concomitant medications associated with hepatobiliary SAEs.

Discussion

The EGF100151 study was originally designed with a planned enrollment of 528 patients to provide 90% statistical power to detect a 50% longer TTP and 80% statistical power to detect a 30% longer OS time. The OS analysis was to be performed after 457 deaths had occurred. When the interim analysis demonstrated a significantly longer TTP (HR, 0.57; 95% CI, 0.43–0.77; $p = .001$) with the addition of lapatinib to capecitabine, patient enrollment was halted before the sample size of 528 patients was met. The 340 deaths in the final analyses provided only a 68% power to detect a 30% longer OS time. If crossover patients derived additional benefit with crossover to the combination treatment, the ability to detect a significant difference in OS may have been further hampered. Nevertheless, it is important to evaluate differences in OS recognizing the limitations of the analysis and to explore methods that attempt to address the potential impact of crossover.

The mature survival analysis performed when 83% of patients had died shows a trend for improvement with the combination. Although these data suggest that the addition of lapatinib to capecitabine led to a longer survival time, further research is needed to identify patients who may benefit the most from the addition of lapatinib to chemotherapy. However, it would be difficult to gather more information from the current study because of premature stoppage of accrual to the trial, crossover effects, and the effects of subsequent treatments on OS.

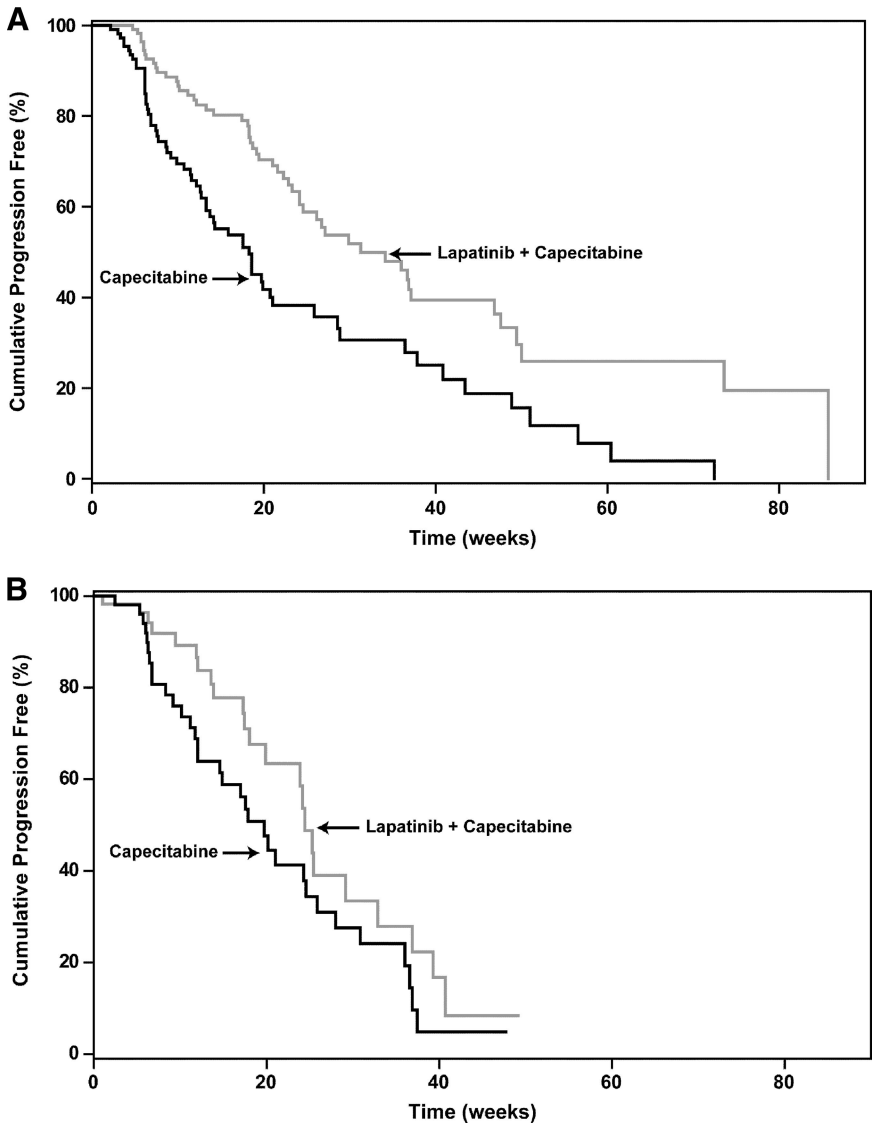

Figure 4. Kaplan–Meier estimates of time to progression in patients receiving: one prior metastatic trastuzumab-based regimen **(A)** or more than one prior metastatic trastuzumab-based regimen **(B)**.

Table 4. Most frequently reported serious adverse events (>3 reports)

Adverse event, *n*	Lapatinib + capecitabine (*n* = 207)	Lapatinib + capecitabine crossover patients (*n* = 36)	Capecitabine monotherapy (*n* = 191)
Diarrhea	7	1	5
Dehydration	3	0	3
Vomiting	2	1	3
Dyspnea	3	0	1
Nausea	0	1	3

Exploratory analyses adjusted for baseline disease history and treatment crossover were conducted using several methodologies to adjust for crossover. Each of the methods demonstrated a greater reduction in the HR for death than that determined by the ITT analysis, suggesting that the benefit from the combination following crossover from monotherapy may have impacted the ability of the ITT analysis to demonstrate a significant difference in the OS times. These updated survival analyses support the demonstrated efficacy of lapatinib in the TTP analysis in this heavily pretreated population.

Exploratory analyses have also been conducted to determine whether the interval from the last dose of prior trastuzumab [10] and the number of prior trastuzumab-based regimens would predict differential clinical benefit from lapa-

tinib. These analyses did not identify any subset of patients who did not benefit from the addition of lapatinib but suggested that lapatinib may be more effective in patients who had received only one prior trastuzumab-containing regimen. However, more research is needed to confirm these results because of the small number of patients in each subset.

The incidences of SAEs were similar in the capecitabine monotherapy and lapatinib plus capecitabine combination arms. Diarrhea was the most common SAE reported for this study. Lapatinib did not appear to be associated with a greater risk for key SAEs, including pneumonitis/pneumonia, LVEF, and hepatobiliary events.

CONCLUSIONS

An interim analysis of EGF100151 showed significant clinical benefits, including a trend toward OS in favor of combination therapy, versus monotherapy in patients with trastuzumab-pretreated HER-2^+ MBC. These results led to the premature termination of accrual to the study, and patients receiving monotherapy were permitted to cross over to combination therapy. Although premature termination and crossover resulted in insufficient power to detect an OS benefit, these updated analyses confirm a trend toward an OS advantage in the combination arm. A Cox regression analysis considering crossover as a time-dependent covariate suggested that there may have been a 20% lower risk for death in the combination therapy arm. In addition, the incidences of SAEs were largely consistent with previous reports [13, 14]. Overall, these updated analyses continue to support the clinical benefit and safety of lapatinib in patients with HER-2^+ MBC.

CONTRIBUTORS

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