

An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer

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Background: The Lapatinib Expanded Access Program (LEAP) was designed to provide access to lapatinib plus capecitabine for HER2-positive metastatic breast cancer patients who previously received an anthracycline, a taxane, and a trastuzumab and had no other treatment options.

Patients and methods: LEAP opened globally and enrollment continued until lapatinib received regulatory approval in each participating country. Patients were assessed for progression-free survival (PFS) and overall survival (OS) and monitored for serious adverse events (SAEs).

Results: As of 30 September 2008, 4283 patients from 45 countries enrolled in LEAP. The median treatment duration was 24.7 weeks. The most common drug-related SAEs were diarrhea (9.7%), vomiting (4.3%), and nausea (2.4%) and were mainly grade 3 or higher. The incidences of special interest SAEs were decreased left ventricle ejection fraction (0.5%), interstitial lung disease/pneumonitis (0.2%), and serious hepatobiliary events (0.4%). This safety profile is consistent with the overall lapatinib program. The median PFS and OS were 21.1 [95% confidence interval (CI) = 20.1–22.3] and 39.6 (95% CI = 37.7–40.7) weeks, respectively ($n = 4006$). Subgroup analysis showed longer PFS and OS in patients who had not received prior capecitabine.

Conclusions: These results demonstrate the safety and efficacy of lapatinib in a broader patient population compared with a clinical trial.

Key words: capecitabine, EGFR, expanded access, HER2, lapatinib, metastatic breast cancer

introduction

Worldwide, breast cancer is the most common malignancy and cause of cancer-related death in women [1]. Despite improvements in early diagnosis and treatment, a significant portion of women relapse and die of metastatic breast cancer (MBC). In the 17%–30% of breast cancer patients who overexpress ErbB2 (HER2), the disease is associated with poorer prognosis, greater risk for disease progression, and

reductions in both progression-free survival (PFS) and overall survival (OS) [2–6].

Trastuzumab, a humanized HER2-directed monoclonal antibody, is an approved treatment of HER2-overexpressing breast cancer. However, treatment options for patients whose disease progressed while on or following trastuzumab therapy were limited until the availability of lapatinib [Tykerb[®]/Tyverb[®]; GlaxoSmithKline (GSK)]. Lapatinib is an orally bioavailable, small-molecule tyrosine kinase inhibitor that inhibits both ErbB1 [epidermal growth factor receptor (EGFR)] and HER2 receptors [7].

Several studies demonstrated the efficacy and safety of lapatinib either as monotherapy or in combination with either

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chemotherapy or endocrine therapy in patients with MBC [2, 8–11]. Of relevance to this report, the EGF100151 study was halted early after the Independent Data Monitoring Committee reviewed the prespecified interim analysis and concluded that the study met the criterion for superiority set for the study's primary end point of time to tumor progression in women receiving lapatinib plus capecitabine compared with capecitabine monotherapy [8, 9].

These interim results were expected to generate significant interest and increase demand for access to lapatinib because of the unmet medical need among these patients. While directing patients to ongoing lapatinib clinical trials could satisfy some of this demand, study population requirements or geographic limitations could have been obstacles to lapatinib access for many patients. Therefore, the Lapatinib Expanded Access Program (LEAP) and French Authorisation Temporaire d'Utilisation (ATU) were implemented in June 2006 and January 2007, respectively [12, 13].

The principle characteristics of LEAP were wide geographic distribution and a patient population similar to EGF100151. Moreover, LEAP enabled proper safety monitoring of the combination with adequate study conduct carried out within a clinical trial protocol. LEAP opened in countries where there was intent to file for the registration of the combination, and enrollment continued until lapatinib received regulatory approval in each participating country. To our knowledge, this is the first reported expanded access program (EAP) in breast cancer to have enrolled >4000 patients worldwide.

methods

LEAP was a single-arm, open-label trial. The primary objective of this study was to offer preapproval lapatinib access in combination with capecitabine. Secondary objectives were PFS and OS and evaluation of serious adverse events (SAEs). Compared with EGF100151, LEAP provided lapatinib access in a slightly broadened population [i.e. patients were eligible without measurable disease, with central nervous system (CNS) metastases, prior capecitabine therapy, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2] [14].

Eligible patients were male or female ≥ 18 years with HER2-positive (tested by local laboratory) locally advanced (stage IIIB or IIIC with T4 lesion) or MBC (stage IV) that had progressed (as assessed by modified RECIST) following treatment with an anthracycline, a taxane, and a trastuzumab alone or in combination either in the adjuvant or in the metastatic setting. Additional inclusion criteria included adequate hematologic, hepatic, and renal function and left ventricle ejection fraction (LVEF) within institutional limits of normal as measured by echocardiogram or multigated acquisition scans. Patients with CNS metastases were eligible, provided that lapatinib-prohibited medications were not required. The protocol was later amended to allow glucocorticoids for neurologic signs and symptoms of CNS metastases. Prior treatment with hormonal therapy, lapatinib (i.e. as part of another clinical trial), or capecitabine was also permitted. Patients eligible for other ongoing lapatinib clinical trials were not permitted to enroll in LEAP.

The main exclusion criteria were pregnancy or lactation during the study; any factor prohibiting the understanding or rendering of informed consent; any factor significantly affecting gastrointestinal function; prior history of allergic reaction to lapatinib, capecitabine, or fluorouracil therapies; and known dihydropyrimidine dehydrogenase deficiency. Patients with active cardiac disease <6 months from study entry, LVEF below institutional limit,

or uncontrolled or symptomatic congestive heart failure were ineligible. Although concurrent administration of nonstudy medications was not allowed, hormone therapy for ovarian suppression or concurrent bisphosphonate treatment was permitted.

treatments

Patients received lapatinib 1250 mg once daily at approximately the same time every morning and capecitabine 2000 mg/m²/day, days 1 to 14, every 21 days. The capecitabine dose was divided and given orally once in the morning and once in the evening. Dose reductions and delays for lapatinib- and/or capecitabine-related toxic effects were permitted.

assessments

Patients were monitored for SAEs. Disease progression was investigator assessed using the modified RECIST that included standard modalities of computed tomography and magnetic resonance imaging and others, such as positron emission tomography and ultrasound. Safety and efficacy assessments were carried out on all patients at 3- and 6-week intervals, respectively, and at the end of treatment. Assessments included physical examination, vital signs, ECOG performance status, clinical and laboratory evaluations to evaluate toxicity, LVEF evaluation, adverse event/toxicity monitoring, and tumor measurements.

statistical methods

safety. SAEs were summarized and categorized by toxicity grade. Although LEAP is ongoing, the SAE analyses for this publication are on the basis of the 30 September 2008 data cut-off. LVEF (%) was summarized for each scheduled assessment. Both the absolute change from baseline and the relative percentage change from baseline were summarized according to these categories: any increase, 0 to <20% decrease, $\geq 20\%$ decrease, or $\geq 20\%$ decrease and below institutional lower limit of normal.

efficacy. As the primary objective was to make lapatinib available during the preapproval period, no formal hypothesis testing was conducted. However, PFS and OS were assessed. OS was defined as the time from initiation of study medication until death due to any cause. PFS was defined as the time from initiation of study medication until the earliest date of disease progression or death from any cause. The protocol was amended in June 2008 to remove the PFS and OS end points because data collection ceased in countries where the combination received regulatory approval. Therefore, PFS and OS were censored if patients did not have disease progression or were alive by this date.

Because prior capecitabine use was allowed, PFS and OS were also analyzed by prior capecitabine exposure.

results

patients and treatments

As of 30 September 2008, 4283 patients from 45 countries were enrolled (Figure 1). The median age of patients was 52.1 years (range = 21–86), and most (99.4%) were female (Table 1). There were no reports of pregnancy. As per the baseline patient demographics population, of 4271 patients, 42.3% of patients had received prior capecitabine.

The median treatment duration of lapatinib plus capecitabine was 24.7 weeks. The maximum treatment duration was 131.3 weeks. During LEAP, 2112 (49.3%) patients discontinued therapy and entered the follow-up phase. While most patients discontinued therapy due to progressive disease (35.9%), additional discontinuation reasons included SAEs, withdrawal of consent, or switched to a commercial drug

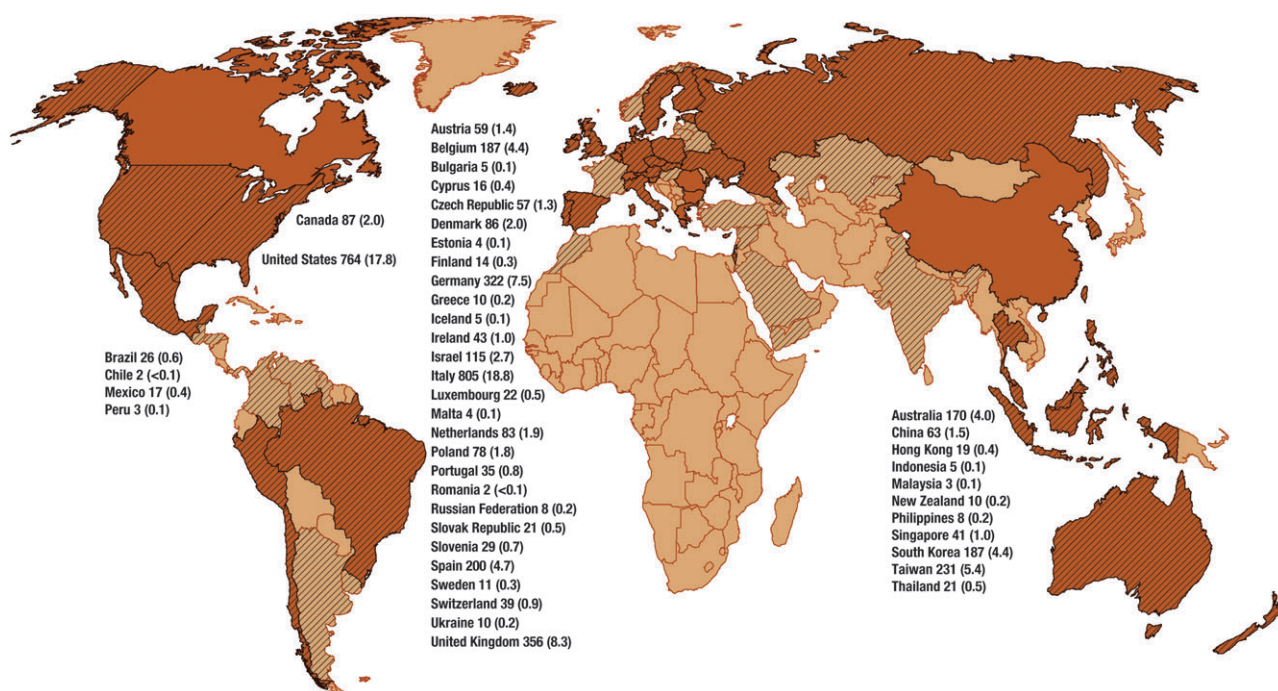


Figure 1. Countries participating (dark shaded) in the Lapatinitib Expanded Access Program (LEAP) and the number of patients recruited per country. Numbers in parentheses indicate the percent of patients per country of the total number of patients enrolled in LEAP. As of the 30 September 2008 data cut-off, 4283 patients were enrolled worldwide across 45 countries. As of January 2009, lapatinib was authorized for marketing (hatched pattern) in >70 countries in North America, Latin America, Europe, and Asia Pacific. In addition, marketing applications are under review in a number of international markets.

supply (Table 1). Approximately 39.6% (1694) of patients withdrew from LEAP primarily due to death (29.4%). The remaining patients were lost to follow-up or switched to a commercial drug supply.

As of 30 September 2008, there were four reports of accidental overdoses of lapatinib, all attributed to human error. Although asymptomatic, two patients received twice their prescribed daily dose of lapatinib (1250 mg/day), one patient for 2 weeks and another patient received a single double dose of lapatinib (2500 mg). The third patient accidentally received 50% of her capecitabine dose and 200% of her lapatinib dose for several days with no toxic effects reported. The fourth patient received an unreported overdose; both capecitabine and lapatinib were interrupted and the unspecified event was resolved.

safety

A total of 1478 SAEs were reported from 19.4% (829/4283) of patients. The most frequently reported SAE was diarrhea with 164 reports, 144 (87.8%) of which were assessed as treatment related (Table 2). Approximately 38.1% (563/1478) of the SAEs were assessed as related by the investigator. The most frequently reported drug-related SAEs were diarrhea (9.7%), vomiting (4.3%), and nausea (2.4%). These SAEs met protocol-defined serious criteria and were mainly grade 3 or higher.

As of 30 September 2008, 121 patients died due to events reported as SAEs. Of these, 104 were assessed as unrelated to lapatinib and the most commonly reported cause of these deaths was disease progression with associated complications (e.g. CNS metastases, respiratory failure, pleural effusion, or

failure to thrive). One patient scheduled to receive treatment suddenly died before lapatinib administration. The cause of death for this patient was unknown at the time of reporting and, therefore, was reported as unrelated. There was one death for which an investigator relationship was not reported. Of the remaining deaths, 15 (0.4%) were possibly lapatinib related, and all identified additional underlying factors that could have contributed to the patients' deaths (e.g. advanced cancer, concurrent medical conditions, and concomitant medications).

SAEs of special interest

cardiac safety. Overall, lapatinib plus capecitabine had limited effect on mean LVEF (Figure 2). However, 34 patients experienced decreased LVEF. Of these, 21 patients had decreased LVEF that met the protocol-specific serious definition (National Cancer Institute Common Terminology Criteria grade 3 or 4 LVEF decrease $\geq 20\%$ relative to baseline and below the institutional normal limits), yielding an incidence of 0.5% (21/4283). This is less than the overall incidence of decreased LVEF seen in the lapatinib program: 1.1% (143/12 795) or 1.3% (if 24 patients who remain blinded received lapatinib). The 21 patients who met the serious definition ranged in age from 38 to 74 years. The mean time to onset of decreased LVEF in these patients was ~ 79 days (range = 11–175). Thirteen of the 21 patients were asymptomatic. Eight patients displayed symptoms including dyspnea, vertigo, circulatory disturbance, and cardiac arrest. The mean nadir for LVEF decrease was 33% relative to baseline (range = 20%–65%). Treatment with lapatinib and capecitabine

Table 1. Summary of baseline patient demographics

Characteristics	N	Lapatinib + capecitabine
Median age, years (range)	4280 ^a	52.1 (21–86)
Sex (male/female), n	4272 ^a	25/4247
Ethnic origin, n (%)		
White	4266 ^a	3512 (82.3)
Asian		626 (14.7)
All others		128 (3.0)
Prior capecitabine, n (%)		
Yes	4271 ^{a,b}	1805 (42.3)
No		2466 (57.7)
Discontinued therapy	4283 ^c	2112 (49.3)
Progressive disease		1539 (35.9)
SAE		217 (5.1)
Withdrawal of consent		140 (3.3)
Switch to commercial drug supply		83 (1.9)
Protocol violation		8 (0.2)
Missing/other reason		125 (2.9)
Withdrew from study	4283 ^c	1694 (39.6)
Death		1258 (29.4)
Lost to follow-up		195 (4.6)
Switch to commercial drug supply		129 (3.0)
Missing/other reason		112 (2.6)

^aNumber of patients on the basis of available data.

^bNumber of patients on the basis of baseline demographic data and not the safety population.

^cNumber of patients who have received at least one dose of the study drug. SAE, serious adverse event.

Table 2. The most commonly reported SAEs

SAE	Drug-related SAEs ^a (%)	Total SAEs—all causalities (%)
Diarrhea	144 (9.7)	164 (11.1)
Vomiting	64 (4.3)	87 (5.9)
Nausea	36 (2.4)	47 (3.2)
Ejection fraction decreased	15 (1.0)	15 (1.0)
Neutropenia	11 (0.7)	15 (1.0)
Palmar–plantar erythrodysesthesia syndrome	10 (0.7)	12 (0.8)
Pulmonary embolism	10 (0.7)	55 (3.7)
Pyrexia	10 (0.7)	30 (2.0)
Asthenia	9 (0.6)	19 (1.3)
Mucosal inflammation	8 (0.5)	10 (0.7)
Hyperbilirubinemia	8 (0.5)	9 (0.6)

^aA total of 1478 SAEs were reported from 829 patients. SAE, serious adverse event.

was discontinued in 11 of 13 patients. Fifteen patients are known to have recovered and/or improved; two events were ongoing at the time of a patient's death due to disease progression, and the outcome was unknown for three patients. These patients' clinical conditions and low LVEF were complicated by previous cardiotoxic therapy, including anthracyclines and trastuzumab or concurrent medical

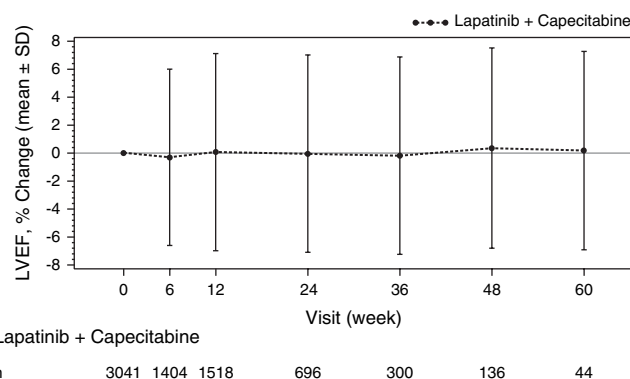


Figure 2. Percent change (mean \pm standard deviation) in left ventricle ejection fraction (LVEF) in patients receiving lapatinib plus capecitabine treatment during Lapatinib Expanded Access Program (LEAP). Thirty-four patients in LEAP experienced decreased LVEF and 21 of these met the protocol-specific definition of a serious decline in LVEF. Thirteen of these 21 patients were asymptomatic. Note: Week 0 is baseline.

conditions (e.g. hypertension, left-chest radiation, and cardiopulmonary disease). The 21st patient experienced a fatal event 110 days after initiating lapatinib and capecitabine. This patient developed grade 4 cardiac decompensation, hepatomegaly, and bilateral pleural effusion. Investigational products were discontinued and the patient withdrew and died 9 days later. The investigator assessed the event as possibly related to lapatinib and capecitabine.

interstitial pneumonitis. Seven patients developed pulmonary events possibly associated with interstitial pneumonitis: three patients experienced pneumonitis, two patients experienced interstitial lung disease, and two patients experienced lung infiltration. This gives an approximate incidence of 0.2% (7/4283) for pulmonary events for patients in LEAP, which is consistent with the overall incidence in the overall lapatinib program of 0.3% (36/12 795). The median time to onset was ~51 days (range = 6–157). Four patients recovered: two recovered at an unspecified date, one recovered in 14 days, and one recovered in 30 days. In addition, two patients died due to causes unrelated to lapatinib, and in one patient the event was ongoing at the time of reporting.

hepatobiliary events. Seventy-three patients in LEAP presented with serious hepatobiliary events regardless of causality. Of these, 15 patients experienced events assessed as possibly associated with lapatinib, yielding an incidence of 0.4% (15/4283). Of these, there were three deaths. Drug-induced liver injury was assessed by GSK as unlikely in one subject with hyperbilirubinemia who was withdrawn from the study with liver failure secondary to liver metastasis and in a second subject with hyperbilirubinemia secondary to cholestasis. In the third death, it was assessed unlikely in a subject who became jaundiced with increased hepatic enzymes although it could not be ruled out. The remaining 58 patients' reports were confounded by underlying medical condition, worsening of preexisting liver metastasis, alternative diagnoses (e.g. bile duct obstruction), or concomitant medications (e.g. capecitabine).

As of August 2008, the cumulative incidence of hepatobiliary events in the overall lapatinib program was 0.8% (101/12 309).

Of 20 deaths due to hepatobiliary events, nine cases (0.07%, 9/12 309) were considered associated with lapatinib, but there were confounding factors such as cirrhosis and underlying preexisting liver disease with metastases.

efficacy

At the time of the 30 September 2008 data cut-off, 4006 patients were available for efficacy analysis (Figure 3). In the OS analysis, 1265 patients (31.6%) had died and 2741 (68.4%) were censored. The median OS was 39.6 weeks [95% confidence interval (CI) = 37.7–40.7; Figure 3A]. In the PFS analysis, 1773 patients (44.3%) had progressed or died and 2233 (55.7%) were censored. The median PFS was 21.1 weeks (95% CI = 20.1–22.3; Figure 3B).

In the efficacy population, ~57.6% (2306/4006) of patients had no prior capecitabine exposure, while 42.3% (1693/4006) had prior capecitabine. For patients with no prior capecitabine exposure, 27.6% patients died and median OS was 41.7 weeks (95% CI = 40.0–44.0), while for patients receiving prior capecitabine, 37% died and median OS was 36.0 weeks (95% CI = 33.7–37.9; Figure 3C). In patients with no prior capecitabine exposure, 39.7% patients had PFS events and the median PFS was 23.9 weeks (95% CI = 22.3–25.0), whereas in patients with prior capecitabine exposure, 50.6% had PFS events and the median PFS was 18.4 weeks (95% CI = 17.9–19.4; Figure 3D).

discussion

Preapproval access programs such as LEAP and ATU enhance patient access to investigational agents while ensuring the scientific integrity of the pivotal trials important for regulatory approval [15]. Patients with life-threatening disease are often ineligible for entry into clinical trials because of specific inclusion criteria [16]. Thus, EAPs provide preapproval access for patients who could benefit from treatment yet have no other approved treatment options. Since the patient population tends to be more inclusive than patients enrolled in clinical trials, greater understanding of the range of safety data can be attained.

Although the design of LEAP does not permit formal hypothesis testing, the efficacy data indicate that median PFS, but not OS, shows similarities to previous findings. In LEAP, the median PFS and OS were 21.1 (95% CI = 20.1–22.3) and 39.6 (95% CI = 37.7–40.7) weeks, respectively. In EGF100151, median time to progression as assessed by the independent review committee (the time from randomization to disease progression or death from breast cancer) was 27.1 weeks (6.2 months) and median OS was 67.7 weeks (15.6 months) [9]. These differences could be due to patients with poorer prognoses being allowed to enroll in LEAP. In addition, in contrast to EGF100151, LEAP enrolled patients with prior capecitabine exposure. The data from the subgroup analysis showed that no prior capecitabine exposure results in a median PFS of 23.9 weeks, which is similar to the investigator-assessed

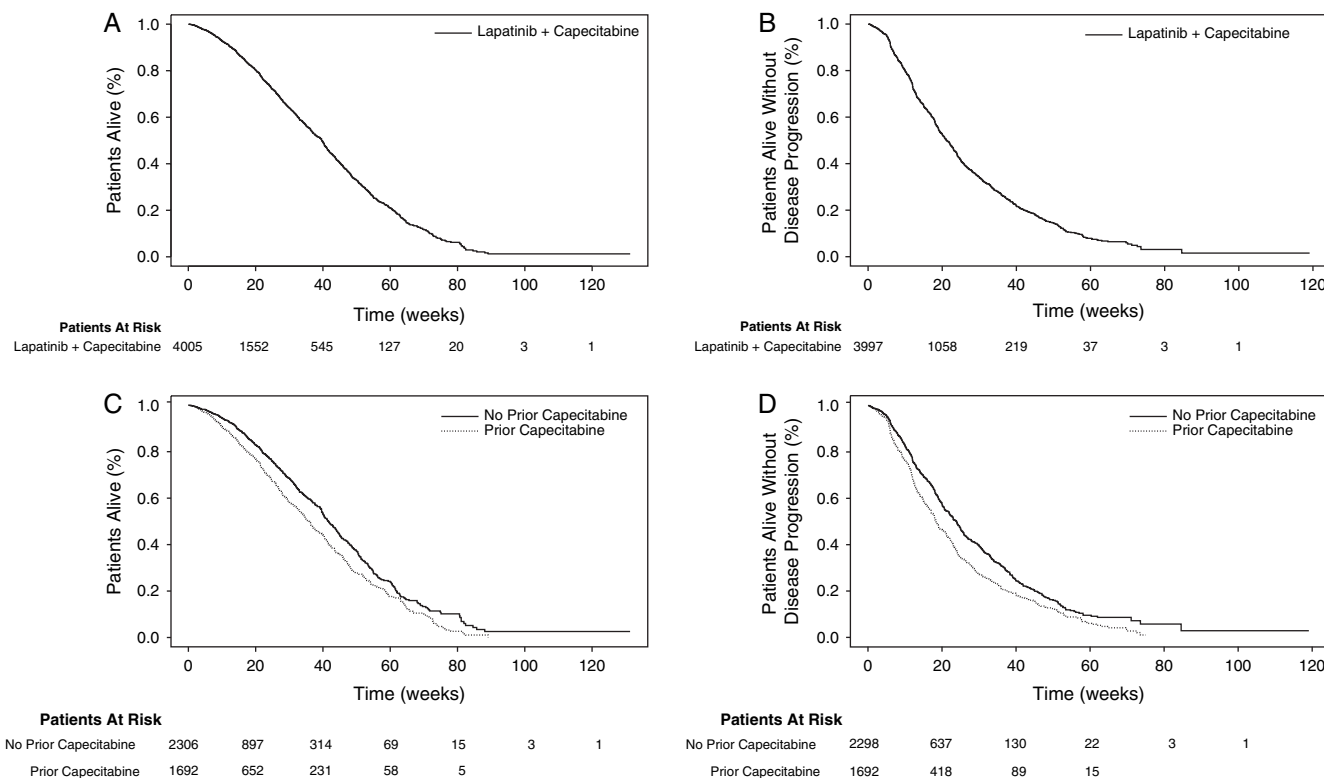


Figure 3. (A) Kaplan–Meier curve for overall survival (OS) for patients with HER2-positive metastatic breast cancer (MBC) treated with lapatinib plus capecitabine. (B) Kaplan–Meier curve for progression-free survival (PFS) for patients with HER2-positive MBC treated with lapatinib plus capecitabine. (C) Kaplan–Meier curve for OS for patients with HER2-positive MBC treated with lapatinib plus capecitabine and with/without prior exposure to capecitabine. (D) Kaplan–Meier curve for PFS for patients with HER2-positive MBC treated with lapatinib plus capecitabine and with/without prior exposure to capecitabine.

median time to progression of 27.1 weeks reported in EGF100151 as noted above [9]. It is noteworthy that these studies have key differences in the baseline population (i.e. unstipulated number of prior treatments of metastatic disease, performance status, and prior capecitabine therapy). While study designs may explain differences in median PFS and OS, the patients enrolled in an EAP are more indicative of a real-world patient population.

Unlike EGF100151, LEAP and ATU allowed enrollment of patients with CNS metastases. Preliminary exploratory analyses of 138 patients with CNS metastases from LEAP and ATU showed efficacy in terms of response and improvements in neurologic signs and symptoms [12]. Moreover, 42% of patients with progressive CNS metastases at study entry received prior capecitabine, while 36% of these patients experienced a CNS objective response. Despite the limitations of exploratory analyses, these data indicate that lapatinib plus capecitabine provide clinical benefit to HER2-positive breast cancer patients with progressive CNS metastases and are consistent with prior studies in HER2-positive patients with brain metastases treated with lapatinib [17].

The safety profile of lapatinib observed in LEAP is consistent with other trials involving lapatinib. Approximately 38.1% of the reported SAEs in LEAP were possibly related to lapatinib and the most frequently reported events were diarrhea, vomiting, and nausea. In EGF100151, the most common AEs (>25% incidence, any grade) reported for patients receiving lapatinib plus capecitabine were diarrhea, nausea, vomiting, hand-foot syndrome, and rash. Moreover, the most common grade 3 or 4 AEs in EGF100151 were diarrhea and hand-foot syndrome [8].

Cardiac toxicity is associated with HER2 inhibitors [18–20], and it is closely monitored in all lapatinib clinical trials. In LEAP, the estimated incidence for decreased LVEF was 0.5%. This is comparable to the low incidence of symptomatic (0.2%) and asymptomatic (1.4%) decreases in LVEF as seen in a meta-analysis of 3689 patients involved in 44 separate clinical studies of lapatinib [20].

Both the rapidity of enrollment and interest demonstrated by numerous investigators worldwide underscore the necessity for ensuring prompt access to new agents and addressing unmet medical needs. This study confirms that, in a large and geographically diverse patient population, these safety data are consistent with the overall lapatinib program and, importantly, the combination of lapatinib plus capecitabine offers clinical benefit to patients with MBC. It was noted that patients who received prior capecitabine have a shorter PFS and OS than patients with no prior capecitabine.

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