Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC—A Randomized Phase III Trial


See accompanying editorial on page 401

ABSTRACT

Purpose
To evaluate the efficacy of adding lapatinib to capecitabine and oxaliplatin (CapeOx) in patients with previously untreated human epidermal growth factor receptor 2 (HER2)-amplified advanced gastroesophageal adenocarcinoma.

Patients and Methods
Patients with HER2-positive advanced gastroesophageal adenocarcinoma were randomly assigned at a one-to-one ratio to CapeOx plus lapatinib 1,250 mg or placebo daily. Primary end point was overall survival (OS) in patients with centrally confirmed HER2 amplification in the primary efficacy population.

Results
A total of 545 patients were randomly assigned, and 487 patients comprised the primary efficacy population. Median OS in the lapatinib and placebo arms was 12.2 (95% CI, 10.6 to 14.2) and 10.5 months (95% CI, 9.0 to 11.3), respectively. No correlation was observed between HER2 immunohistochemistry status and survival. Exploratory subgroup analyses showed OS in the lapatinib arm was prolonged in Asian and younger patients. No correlation was observed between HER2 immunohistochemistry status and survival. There were increased toxicities in the lapatinib arm, particularly diarrhea.

Conclusion
Addition of lapatinib to CapeOx did not increase OS in patients with HER2-amplified gastroesophageal adenocarcinoma. There were clear differences in the effect of lapatinib depending on region and age. Future studies could examine this correlation.

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INTRODUCTION

Gastric cancer is the third most common cause of cancer-related death worldwide.1 There is no standard first-line chemotherapy for this disease, but current treatment options include a combination of a fluoropyrimidine and platinum, such as cisplatin or oxaliplatin.2 Despite advances in cytotoxic therapies, survival for patients with metastatic disease remains poor, with few patients remaining alive 2 years after initiation of treatment.3,5

Human epidermal growth factor receptor 2 (HER2) is associated with approximately 20% of gastroesophageal adenocarcinomas,6,7 and targeted inhibition of HER2 has been shown to significantly improve outcomes in patients with breast cancer overexpressing or amplifying HER2.8,9 Lapatinib is a small-molecule tyrosine kinase inhibitor of
epidermal growth factor receptor and HER2, approved for the treatment of HER2-positive breast cancer. In vitro and in vivo studies with lapatinib in HER2-amplified upper GI cell lines have demonstrated significant antitumor effects.

A 9% response rate was seen with lapatinib monotherapy in patients with gastroesophageal adenocarcinoma. At the outset of this study, no anti-HER2 agent had demonstrated improved survival in this disease. Therefore, the TRIO-013 (Translational Research in Oncology)/LOGiC (Lapatinib Optimization Study in the HER2-Positive Gastric Cancer) trial was conducted to assess the clinical benefit and safety of adding lapatinib to capcitabine and oxaliplatin (CapeOx) as first-line chemotherapy.

Study Design and Treatment
TRIO-013/LOGiC was a multicenter, double-blind, randomized phase III study conducted at 186 centers in 22 countries in Asia, Europe, North America, and South America. The study was conducted in accordance with the current ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from each patient before the performance of any study-specific procedures. When deviations from GCP were detected, corrective and preventative actions were implemented, and the appropriate regulatory authorities and ethics committees were notified.

Patients were randomly assigned at a one-to-one ratio to CapeOx (capcitabine 1,700 mg/m² and oxaliplatin 130 mg/m²) plus lapatinib 1,250 mg (lapatinib arm) or to CapeOx plus placebo (placebo arm). Treatment was administered in 21-day cycles, consisting of intravenous oxaliplatin on day 1 (for up to eight cycles) and oral capcitabine in two daily doses (morning and evening) from day 1 to 14. Oral lapatinib or placebo were administered continuously and treated until progressive disease, unacceptable toxicity, or withdrawal; safety and disease assessments were performed throughout the study. If any study drugs were stopped, patients could continue receiving the remaining drugs. Random assignment was performed centrally and stratified by prior adjuvant and/or neoadjuvant chemotherapy (yes vs no) and by geographic region (North America, Asia, or rest of world [ROW]).

Patients
Eligible patients were age ≥ 18 years and had histologically confirmed unresectable adenocarcinoma of the stomach, esophagus, or gastroesophageal junction with radiologically evaluable disease according to RECIST; Eastern Cooperative Oncology Group performance status ≤ 2, and adequate organ function. No prior palliative chemotherapy was allowed, and prior treatment with oxaliplatin-based neoadjuvant or adjuvant chemotherapy could not have been completed < 12 months before study entry. Tumors had to have HER2 amplification by fluorescence in situ hybridization (FISH) assessed by local or designated central laboratory. If unavailable, immunohistochemistry (IHC; 3+) or HER2 amplification by chromogenic or silver in situ hybridization was permitted. The Appendix (online only) provides full inclusion and exclusion criteria.

End Points and Assessments
The primary end point was overall survival (OS), defined as the time from random assignment until death resulting from any cause. Previous analyses of studies with lapatinib in patients with breast cancer showed benefit only in patients with HER2 amplification, regardless of IHC status. Therefore, efficacy analyses were performed in the primary efficacy population (PEP), consisting of patients with disease confirmed for HER2 amplification as determined by FISH in the central laboratories (Appendix).

Secondary end points included progression-free survival (PFS), defined as the time from random assignment until the earliest date of disease progression or death resulting from any cause; best overall response rate, defined as the percentage of patients experiencing a confirmed complete response or partial response; duration of response (DoR); quality of life (QoL); and safety assessments (including drug exposure). Early deaths (ie, death < 30 days after first dose of study drug) were assessed in the safety population as post hoc analyses. Preplanned exploratory efficacy analyses included subgroup analysis of OS based on geographic region (Asia, North America, or ROW), prior adjuvant use, age, baseline Eastern Cooperative Oncology Group status, primary disease site, histologic cancer type, whether pylorus was intact, and HER2 FISH or IHC status.
RESULTS

Patients

A total of 545 patients were randomly assigned between June 2008 and January 2012 and comprised the intent-to-treat (ITT) population. The PEP included all randomly assigned patients with centrally confirmed HER2-positive status (lapatinib arm, n = 249; placebo arm, n = 238). There were 537 patients in the safety population (lapatinib arm, n = 270; placebo arm, n = 267). Patient flow is summarized in Figure 1.

Patient demographic and baseline characteristics in the PEP were similar between treatment arms (Table 1). In the lapatinib and placebo arms, respectively, 7% and 8% of patients had received prior adjuvant or neoadjuvant treatment, 40% and 39% patients were from Asia (majority from China or South Korea), and 57% (both treatment arms) were from the ROW (excluding North America). There were no major differences in baseline characteristics between the PEP and ITT population (data not shown).

Overall, 5% and 8% patients received trastuzumab as follow-up therapy (Asia, 9% and 12%; ROW, 1% and 4%) in the lapatinib and placebo arms, respectively. A majority of Asian patients receiving post-study trastuzumab were South Korean.

Efficacy

The cutoff date for primary efficacy analysis was September 24, 2012, after 350 deaths had occurred. Median follow-up was 12.2 months (95% CI, 10.6 to 14.2) in the lapatinib arm and 10.5 months (95% CI, 9.0 to 11.3) in the placebo arm (Fig 2A), which was not statistically significant (HR, 0.91; 95% CI, 0.73 to 1.12; P = .3492). ITT analysis of OS was consistent with the results in the PEP, with an HR of 0.91 (95% CI, 0.74 to 1.12; P = .3252). Because the trial missed its primary end point of OS, all other analyses are reported with a descriptive intent.

A significant difference between the lapatinib and placebo arms was observed for PFS in the PEP (HR, 0.82; 95% CI, 0.68 to 1.00; P = .0381). Median PFS values were 6.0 months (95% CI, 5.6 to 7.0) in the lapatinib arm and 5.4 months (95% CI, 4.4 to 5.7) in the placebo arm (Fig 2B). Similar PFS values were observed in the sensitivity analyses (HR, 0.82; 95% CI, 0.67 to 1.00; P = .0381). In the sensitivity analysis with censoring at the time a patient received nonprotocol therapy, median PFS values in the lapatinib and placebo arms were 6.0 (95% CI, 5.6 to 6.9) and 5.3 months (95% CI, 4.4 to 5.7), respectively;

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with such censoring, the difference was not statistically significant (HR, 0.84; 95% CI, 0.69 to 1.03; P = .0773).

A significant difference was observed in overall response rate between treatment arms: 53% (95% CI, 46.4 to 58.8) in the lapatinib arm and 39% (95% CI, 32.9 to 45.3) in the placebo arm (P = .0031 [Data Supplement]). Median DoR was 7.3 months (95% CI, 6.4 to 8.5) in the lapatinib arm and 5.6 months (95% CI, 4.6 to 6.0) in the placebo arm (Data Supplement). No significant difference was

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### Table: Subgroup Analysis of Overall Survival

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<th>Subgroup</th>
<th>n</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
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<td><strong>Primary efficacy population</strong></td>
<td>487</td>
<td>0.91 (0.73 to 1.12)</td>
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<tr>
<td><strong>Region</strong></td>
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<tr>
<td>Asia</td>
<td>193</td>
<td>0.68 (0.48 to 0.96)</td>
<td>.0261</td>
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<td>North America</td>
<td>17</td>
<td>1.61 (0.53 to 4.83)</td>
<td>.3651</td>
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<tr>
<td>Rest of World</td>
<td>277</td>
<td>1.04 (0.79 to 1.37)</td>
<td>.7791</td>
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<td><strong>Prior adjuvant use</strong></td>
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<tr>
<td>Yes</td>
<td>38</td>
<td>1.52 (0.68 to 3.41)</td>
<td>.2948</td>
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<tr>
<td>No</td>
<td>449</td>
<td>0.83 (0.67 to 1.04)</td>
<td>.0950</td>
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<td><strong>Age, years</strong></td>
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<td>&lt; 60</td>
<td>236</td>
<td>0.69 (0.51 to 0.94)</td>
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<tr>
<td>≥ 60</td>
<td>251</td>
<td>1.08 (0.81 to 1.45)</td>
<td>.5923</td>
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<td><strong>Baseline ECOG status</strong></td>
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<td>0-1</td>
<td>444</td>
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<td>≥ 2</td>
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<td><strong>Primary site</strong></td>
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<td>Intestinal</td>
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<td>Other</td>
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<td><strong>Pylorus intact</strong></td>
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<td>Yes</td>
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<td>0.80 (0.63 to 1.01)</td>
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<tr>
<td>No</td>
<td>114</td>
<td>1.06 (0.67 to 1.68)</td>
<td>.7944</td>
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<td><strong>HER2 status (all FISH+)</strong></td>
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<td>IHC 0</td>
<td>27</td>
<td>0.56 (0.24 to 1.31)</td>
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<tr>
<td>IHC 1+</td>
<td>54</td>
<td>1.16 (0.61 to 2.20)</td>
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<tr>
<td>IHC 2+</td>
<td>108</td>
<td>0.79 (0.50 to 1.25)</td>
<td>.3113</td>
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<tr>
<td>IHC 3+</td>
<td>297</td>
<td>0.90 (0.69 to 1.18)</td>
<td>.4603</td>
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<tr>
<td>IHC 0-1+</td>
<td>81</td>
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<td>.7082</td>
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<tr>
<td>IHC 2-3+</td>
<td>405</td>
<td>0.86 (0.68 to 1.09)</td>
<td>.2105</td>
</tr>
</tbody>
</table>

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### Figure 2

(A) Overall and (B) progression-free survival in primary efficacy population. CapeOx, capecitabine and oxaliplatin; HR, hazard ratio; L, lapatinib; P, placebo; PEP, primary efficacy population.

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### Figure 3

Forest plot for overall survival: subgroup analysis. CapeOx, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GE, gastroesophageal; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; L, lapatinib; P, placebo.
observed between the lapatinib and placebo arms in health-related QoL (Appendix).

Preplanned exploratory analyses included OS by geographic region and age. In the Asian subgroup, median OS was 16.5 months (95% CI, 13.3 to 20.2) in the lapatinib arm and 10.9 months (95% CI, 9.0 to 14.9) in the placebo arm (HR, 0.68; 95% CI, 0.48 to 0.96; $P = .0261$; Figs 3 and 4). In the ROW subgroup, however, median OS was 10.0 months (95% CI, 8.0 to 12.0) in the lapatinib arm and 9.1 months (95% CI, 8.3 to 10.9) in the placebo arm (HR, 1.08; 95% CI, 0.81 to 1.45; $P = .7781$; Figs 3 and 4A). In patients age < 60 years, median OS was 12.9 months (95% CI, 11.1 to 16.0) in the lapatinib arm and 9.0 months (95% CI, 7.8 to 11.3) in the placebo arm (HR, 0.69; 95% CI, 0.51 to 0.94; $P = .0141$; Figs 3 and 4B). In patients age $\geq$ 60 years, median OS was 11.3 months (95% CI, 8.4 to 13.8) in the lapatinib arm and 9.5 months (95% CI, 9.6 to 14.1) in the placebo arm (HR, 1.08; 95% CI, 0.81 to 1.45; $P = .5923$; Figs 3 and 4B).

Post hoc analysis of the OS data by region and age showed that patients age < and $\geq$ 60 years from Asia had HRs of 0.60 (95% CI, 0.38 to 0.94) and 0.80 (95% CI, 0.47 to 1.36), respectively. Outside of Asia, patients age < 60 years had an HR of 0.74 (95% CI, 0.49 to 1.11), whereas those age $\geq$ 60 years had an HR of 1.32 (95% CI, 0.91 to 1.90; Fig 5 [results of similar analyses for North American patients are shown in the Data Supplement]).

Multivariable Cox regression analysis of PFS and OS revealed statistically significant effects of region (favoring Asian patients), age (favoring younger patients), pylorus status (favoring pylorus intact), histology (favoring nondiffuse histology), and treatment (favoring lapatinib), as well as an interaction between age and treatment (larger effect of lapatinib in younger patients [Data Supplement]). In these multivariable analyses, the effect of lapatinib treatment on PFS had an HR of 0.176 (95% CI, 0.062 to 0.495; $P = .0010$) and on OS had an HR of 0.304 (95% CI, 0.099 to 0.936; $P = .0379$).

No correlation was observed between IHC status and OS benefit from lapatinib in this FISH-positive population. OS HR for IHC 0 to 1+ was 0.91 (95% CI, 0.55 to 1.51; $P = .7082$) and for IHC 2 to 3+ was 0.86 (95% CI, 0.68 to 1.09; $P = .2105$; Fig 3).

**Safety**

In the lapatinib arm, 255 patients (94%) experienced AEs, and 72 patients (27%) experienced serious AEs, compared with 236 (88%)

A

![Cumulative Survival](https://www.jco.org)

B

![Cumulative Survival](https://www.jco.org)

**Fig 4.** Overall survival in primary efficacy population by (A) region (left, Asia; right, rest of world) and (B) age (left, < 60 years; right, $\geq$ 60 years). CapeOx, capecitabine and oxaliplatin; HR, hazard ratio; L, lapatinib; P, placebo.
and 52 patients (19%) experiencing AEs and serious AEs, respectively, in the placebo arm (Table 2). Fifty-seven patients (21%) experienced an AE leading to study drug discontinuation in the lapatinib arm, compared with 50 (19%) in the placebo arm (Table 2). Overall incidence of AEs observed in the sensitivity analyses was similar.

The most common AEs in both arms were diarrhea, nausea, vomiting, and decreased appetite (Table 2). A majority of these AEs were grade 1 to 2 in severity. More patients experienced grade 1 to 2 and grade ≥3 AEs in the lapatinib arm. Diarrhea, in particular, was increased, with overall diarrhea experienced in 58% of patients in the lapatinib arm, compared with 29% of patients in the placebo arm. Grade ≥3 diarrhea was experienced by 12% of patients in the lapatinib arm and 3% in the placebo arm (Table 2).

Fifteen patients (6%) experienced fatal serious AEs in the lapatinib arm (Table 2), four of which were attributed to study treatment, whereas nine (3%) experienced serious AEs in the placebo arm, one of which was attributed to study treatment (Appendix). Post hoc analysis seemed to show numeric differences in early deaths (<30 days) between the lapatinib and placebo arms in patients in the ROW (12% v 5%), particularly in patients age ≥60 years (7% v 1% [Data Supplement]). Relative drug exposure was slightly lower in the lapatinib arm but was similar overall between treatments (Data Supplement).

Both lapatinib- and trastuzumab-based regimens improve outcomes in patients with HER2-positive breast cancer. Preclinical and early clinical studies also showed lapatinib to have activity in upper GI cancers with HER2 amplification.11 Although the addition of the anti-HER2 antibody trastuzumab to cisplatin-based therapy in the ToGA trial resulted in a significant improvement in OS,18 adding lapatinib to CapeOx in the first-line treatment of patients with advanced gastroesophageal adenocarcinoma in our study did not significantly improve OS, and a higher incidence of AEs was observed in the lapatinib arm. However, lapatinib treatment was not without effect, and preplanned subgroup and additional post hoc multivariable analyses revealed striking differences in outcomes in some populations, especially patients from Asia and younger patients (age <60 years).

**DISCUSSION**
There are several possible explanations for these results. Trastuzumab may have superior efficacy against HER2-positive cancers compared with lapatinib. Although the addition of lapatinib to capecitabine in patients with HER2-positive breast cancer, for whom trastuzumab-containing therapy had failed, was shown to improve survival, a recent breast cancer study showed lapatinib to be inferior to trastuzumab in combination with chemotherapy in the metastatic setting. There also may be biologic differences between HER2-positive breast and gastrointestinal cancers. Even with trastuzumab treatment, patients with HER2-positive gastric cancer have a relatively short survival, with few patients living > 3 years.

Lapatinib and trastuzumab have distinct toxicity profiles, and the addition of lapatinib to chemotherapy in the TRIO-013/LOGiC trial increased some specific toxicities, particularly diarrhea, which was not experienced frequently with the addition of trastuzumab. Patients with gastrointestinal cancer may be less able to tolerate GI toxicities than patients with breast cancer, leading to decreased efficacy or reduced patient compliance.

Despite the advantages of patient convenience with oral agents, concerns exist about absorption of such agents. Feeding alone has been shown to significantly change lapatinib absorption. Twenty-three percent of patients had their pylorus removed in this study, which could have affected emptying, and in this subgroup, there was no benefit in terms of OS (HR, 1.06; 95% CI, 0.67 to 1.68), as opposed to patients with an intact pylorus (HR, 0.80; 95% CI, 0.63 to 1.01). No pharmacokinetics were performed in this trial, but in the recently published second-line phase III TyTan (Tykerb With Taxol in Asian HER2-Positive Gastric Cancer) trial of paclitaxel with or without lapatinib, in a small subset of patients, those with an intact pylorus had higher plasma levels of lapatinib.

There was also significant variability of effect of lapatinib and patient location. In the 40% of patients from Asia, a clear benefit was observed in OS with the addition of lapatinib (HR, 0.68; 95% CI, 0.48 to 0.96), which was not seen in other patients (Fig 3). This difference between Asian and non-Asian patients was not observed in the ToGA trial, in which Asian patients had an HR of 0.82 (95% CI, 0.61 to 1.11), which was similar to the overall improvement (HR, 0.74; 95% CI, 0.60 to 0.91) and less than the improvement seen in Latin American and European patients. The TyTan trial, conducted only in Asian patients, showed a trend toward improved survival with the addition of lapatinib (especially in non-Japanese Asians) but did not reach statistical significance. Other trials with biologic agents, such as the AVAGAST (Avastin in Gastric Cancer) trial with bevacizumab, have also found differences between Asian and non-Asian patients, although in these cases, Asian patients did not benefit from the targeted therapy.

Gastric cancers in Asian populations differ from those in the West, and in some populations (including Chinese and Japanese patients), are more likely to occur in younger patients, be more distal, and have intestinal histology. There may be additional molecular differences, with recent studies showing lack of correlation between Lauren histologic classification and genetic alterations and the presence of multiple molecular subtypes. Other potential differences between Asian and non-Asian patients may include body mass, more frequent use of second- or third-line therapy, surgery type, toxicity tolerance, and physicians’ experience with patients with gastric cancer.

Another observation was the difference in the effect of lapatinib between older and younger patients. In lapatinib-treated patients age < 60 years, there was a significant improvement in OS (HR, 0.69; 95% CI, 0.51 to 0.94), which was not seen in older patients (HR, 1.08; 95% CI, 0.81 to 1.45). In a post hoc subgroup analysis, both younger and older Asian patients benefited, whereas there was a major difference in outcome between older and younger non-Asian patients. Possible explanations for this include differing biology between older and younger patients and tolerance of toxicities. However, a different effect on OS with age was observed in the ToGA trial (age < 60 years: HR, 0.84; 95% CI, 0.62 to 1.14; age ≥ 60 years: HR, 0.66; 95% CI, 0.49 to 0.88), with older

### Table 2. AEs (Safety Population)

<table>
<thead>
<tr>
<th>AE Summary</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Any on-treatment AE</td>
<td>255 (94)</td>
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<tr>
<td>Any serious AE</td>
<td>72 (27)</td>
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<tr>
<td>AE leading to study drug discontinuation</td>
<td>57 (21)</td>
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<td>Fatal serious AE</td>
<td>15 (6)</td>
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<table>
<thead>
<tr>
<th>AE by Maximum Grade*</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>156 (58)</td>
</tr>
<tr>
<td>Nausea</td>
<td>132 (49)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>118 (44)</td>
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<tr>
<td>Decreased appetite</td>
<td>111 (41)</td>
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<td>Fatigue</td>
<td>64 (24)</td>
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<td>Astenia</td>
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<tr>
<td>Neutropenia</td>
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<td>Dehydration</td>
<td>11 (4)</td>
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<tr>
<td>Anemia</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Ascites</td>
<td>2 (&lt; 1)</td>
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</table>

Abbreviations: AE, adverse event; CapeOx, capecitabine and oxaliplatin.

* ≥ 2% in either treatment arm.
patients (age > 60 years) experiencing an improved OS compared with younger patients after treatment with lapatinib.

The use of lapatinib in combination with CapeOx in patients with HER2-positive gastric cancer cannot be recommended. Future research may identify a subgroup of patients who benefit from such treatment, although there are several new anti-HER2 agents, such as pertuzumab and ado-trastuzumab, that are being tested in HER2-positive gastric cancer. Recently published Cancer Genome Atlas data revealed additional molecular subgroups in a population of Western and Asian gastric cancers. In breast cancer, lapatinib in combination with trastuzumab has activity superior to that of either single agent, which was also seen in preclinical gastric cancer models and may be worth examining in the future.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at www.jco.org.

**REFERENCES**


**AUTHOR CONTRIBUTIONS**

Conception and design: J. Randolph Hecht, Yung-Jue Bang, Paulo M. Hoff, Alberto Sobrero, Jin Li, Marc Buyse, Tomomi Kaneko, Michael F. Press, Dennis Slamon

Financial support: Dennis Slamon

Administrative support: Dennis Slamon

Provision of study materials or patients: J. Randolph Hecht, Yung-Jue Bang, Yaroslav Shparyk, Paulo M. Hoff, Alberto Sobrero

Collection and assembly of data: J. Randolph Hecht, Yung-Jue Bang, Shukui K. Qin, Hyun C. Chung, Jianming M. Xu, Joon O. Park, Krzysztof Tomaszewski, Yaroslav Shparyk, Paulo M. Hoff, Pamela Salman, Jin Li, Svetlana A. Protsenko, Karen Afenjar, Agathe Garcia, Tomomi Kaneko, Yingjie Huang, Sergio Santillana, Michael F. Press

Data analysis and interpretation: J. Randolph Hecht, Yung-Jue Bang, Shukui K. Qin, Hyun C. Chung, Jianming M. Xu, Alberto Sobrero, Zev A. Wainberg, Marc Buyse, Karen Afenjar, Vincent Houé, Tomomi Kaneko, Yingjie Huang, Saba Khan-Wasti, Sergio Santillana, Michael F. Press, Dennis Slamon

Manuscript writing: All authors

Final approval of manuscript: All authors

**Affiliations**

J. Randolph Hecht, Zev A. Wainberg, and Dennis Slamon, David Geffen School of Medicine, University of California Los Angeles, Santa Monica; Michael F. Press, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Yung-Jue Bang, Seoul National University College of Medicine; Hyun C. Chung, Yonsei Cancer Center, Yonsei Cancer Research Institute, Yonsei University College of Medicine; Joon O. Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; Shukui K. Qin, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Michael F. Press, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Paulo M. Hoff, University of California Los Angeles, Santa Monica; Yung-Jue Bang, Seoul National University College of Medicine; Jin Li, Marc Buyse, Tomomi Kaneko, Michael F. Press, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Dennis Slamon, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Qin, Shukui, Shukui K. Qin, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Buyse, Michael F. Press, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Slamon, Dennis, Dennis Slamon, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA.

**Disclosures provided by the authors are available with this article at www.jco.org.**
Qin, People’s Liberation Army Cancer Center, Nanjing Bayi Hospital, Jiangsu; Jianming M. Xu, Affiliated Hospital of the Military Medical Science Academy, Beijing; Jin Li, Cancer Hospital of Shanghai Fudan University, Shanghai, People’s Republic of China; Krzysztof Jeziorski, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; Yaroslav Shparyk, Lviv State Regional Oncology Medical and Diagnostic Center, Lviv, Ukraine; Paulo M. Hoff, Sociedade Beneficente de Senhoras–Hospital Sirio Libanês, Sao Paulo, Brazil; Alberto Sobrero, Istituto di Ricovero e Cura a Carattere Scientifico San Martino Istituto Scientifico Tumori, Genova, Italy; Pamela Salman, Fundación Arturo López Pérez, Santiago, Chile; Svetlana A. Protsenko, Petrov Research Institute of Oncology, St Petersburg, Russia; Marc Buyse, International Drug Development Institute, Leuven, Belgium; Karen Afenjar, Vincent Houé, and Agathe Garcia, Translational Research in Oncology, Paris, France; Tomomi Kaneko and Saba Khan-Wasti, GlaxoSmithKline, Brentford, United Kingdom; and Yingjie Huang and Sergio Santillana, GlaxoSmithKline, Philadelphia, PA.

**GLOSSARY TERMS**

**HER2neu (human epidermal growth factor receptor 2):**
also called ErbB2. HER2neu belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

**lapatinib:** a dual tyrosine kinase inhibitor. Lapatinib has been developed as an inhibitor of the tyrosine kinase activities of ErbB1 (EGFR) and ErbB2. Like other tyrosine kinase inhibitors, it competes with ATP binding to the intracellular regions of the receptors that are activated after tyrosine phosphorylation.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC—A Randomized Phase III Trial

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J. Randolph Hecht
Consulting or Advisory Role: Amgen, Roche/Genentech
Research Funding: GlaxoSmithKline (Inst), Amgen (Inst), Pfizer (Inst), Immunomedics (Inst), Gilead Sciences (Inst), Celgene (Inst), OncoMed (Inst)

Yung-Jue Bang
Consulting or Advisory Role: GlaxoSmithKline
Research Funding: GlaxoSmithKline (Inst)

Shukui K. Qin
No relationship to disclose

Hyun C. Chung
Consulting or Advisory Role: Celltrione, Eli Lilly, Taiho Pharmaceutical, Merck
Research Funding: Eli Lilly (Inst)

Jianming M. Xu
No relationship to disclose

Joon O. Park
Research Funding: GlaxoSmithKline

Krzysztof Jeziorski
No relationship to disclose

Yaroslav Shparyk
No relationship to disclose

Paulo M. Hoff
Honoraria: AstraZeneca (I)
Research Funding: GlaxoSmithKline, AstraZeneca, Roche

Alberto Sobrero
Honoraria: Amgen, Bayer, Merck Serono, Roche, Sanofi

Pamela Salman
No relationship to disclose

Jin Li
Honoraria: Roche, Pfizer
Research Funding: Merck

Svetlana A. Protsenko
No relationship to disclose

Zev A. Wainberg
Consulting or Advisory Role: Taiho Pharmaceutical, Sirtex
Speakers’ Bureau: Genentech
Research Funding: Novartis (Inst), Plexxikon (Inst), Pfizer (Inst), Biomarin (Inst)
Travel, Accommodations, Expenses: Genentech, Eli Lilly

Marc Buyse
Employment: IDDI
Stock or Other Ownership: IDDI

Karen Afenjar
Travel, Accommodations, Expenses: Roche

Vincent Houé
No relationship to disclose

Agathe Garcia
No relationship to disclose

Tomomi Kaneko
Employment: GlaxoSmithKline, Novartis Pharma
Stock or Other Ownership: GlaxoSmithKline

Yingjie Huang
Employment: GlaxoSmithKline
Stock or Other Ownership: GlaxoSmithKline

Saba Khan-Wasti
Employment: GlaxoSmithKline
Stock or Other Ownership: GlaxoSmithKline
Research Funding: GlaxoSmithKline

Sergio Santillana
Employment: GlaxoSmithKline, Takeda Pharmaceuticals
Stock or Other Ownership: GlaxoSmithKline, Takeda Pharmaceuticals
Travel, Accommodations, Expenses: GlaxoSmithKline, Takeda Pharmaceuticals

Michael F. Press
Honoraria: GlaxoSmithKline
Consulting or Advisory Role: GlaxoSmithKline
Research Funding: GlaxoSmithKline (Inst)

Dennis Slamon
Leadership: Biomarin
Stock or Other Ownership: Pfizer
Travel, Accommodations, Expenses: Biomarin, Novartis, Pfizer
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Appendix

Methods

Patients

Inclusion criteria: elapsed time period of $\geq 3$ weeks since any major surgery and $>5$ years since prior chemotherapy for malignancy (other than gastric carcinoma); unresectable gastric carcinoma or esophageal cancer resulting from locally advanced or locally recurrent disease; and elapsed time period of $\geq 3$ weeks since any major surgery and $>5$ years since prior chemotherapy for malignancy (other than gastric carcinoma).

Exclusion criteria: planned concurrent anticancer therapy; gastric carcinoid, epidermoid, sarcoma, or squamous cell carcinoma; known history of active CNS disease; malabsorption syndrome or uncontrolled inflammatory GI disease; known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure; current active hepatic or biliary disease; history of other malignancy during the last 5 years; and unresolved or unstable serious toxicity from prior administration of another investigational drug and/or prior cancer treatment.

All patients provided written informed consent before study participation.

Assessments

Human epidermal growth factor receptor 2 fluorescence in situ hybridization assay. Both biopsy and resection specimens were used for central human epidermal growth factor receptor 2 (HER2) fluorescence in situ hybridization (FISH) testing. The PathVysion HER2 FISH assay was used, with average HER2 gene copy number and chromosome 17 centromere copy number determined. HER2 amplification was defined as a ratio of HER2 gene copy number to chromosome 17 copy number of $\geq 2.0$, as discussed elsewhere.16

Tumor assessments. Tumor assessments were performed within 28 days before study entry and repeated every 6 weeks for 36 weeks and every 12 weeks thereafter using computed tomography scans of the chest, abdomen, and pelvis (or computed tomography of chest and magnetic resonance imaging of abdomen and pelvis).

Safety. Serious adverse events (SAEs) monitored included cardiac dysfunction, signs and symptoms of pneumonitis (grade $\geq 3$), any clinically or medically relevant grade 4 laboratory abnormality, increased ALT, and any new primary cancer. Cardiac, liver, and dermatologic assessments were also performed during the study.

Health outcomes. Patient questionnaires included: European Organisation for Research and Treatment of Cancer (EORTC) Health-Related Quality of Life Questionnaire Core 30 (QLQ C-30; version 3), the EORTC gastric cancer module (QLQ STO-22), or the EORTC esophageal cancer module (QLQ OES-18).

Treatment exposure. Treatment exposure was analyzed separately for each treatment (lapatinib or placebo, capecitabine, and oxaliplatin).

Sample Size and Statistical Analysis

The randomization code was created by the GlaxoSmithKline internal randomization system named Randall (block size, 6). A randomization code was generated, stratifying prior adjuvant or neoadjuvant use and region (North America, Asia, or rest of world), blinded to all project members and investigators and locked until unblinding in February 2013.

The Pike estimator of the hazard ratio was calculated based on the log-rank method and presented with an approximate 95% CI. Greenwood’s formula was used to calculate the SE of the overall and progression-free survival estimates.

A Cox proportional regression model was used for additional multivariable analyses. Type I error was fully allocated to primary analysis of overall survival only, and no adjustment was performed in the study.

Results

Safety

Fatal SAEs in the capecitabine and oxaliplatin (CapeOx) plus lapatinib arm included death (cause unknown; $n=2$ [<1%]), diarrhea and pneumonia aspiration (both $n=2$ [<1%]), and abdominal pain, impaired gastric emptying, gastric obstruction, vomiting, sepsis, abdominal infection, multiorgan failure, sudden death, cerebrovascular accident, epilepsy, acute myocardial
infarction, and cardiorespiratory arrest (all n = 1 [< 1%]). Fatal SAEs in the CapeOx plus placebo arm included sepsis, anemia, cellulitis, coma, drowning, infectious enterocolitis, hematemesis, large intestine perforation, and anemia (all n = 1 [< 1%]).

**Health Outcomes**

For the EORTC QLQ-C30 questionnaire, there was a difference in the attrition rate by week 36, with approximately 53% (102 of 192) of patients in the CapeOx plus lapatinib arm having discontinued and approximately 73% (143 of 195) in the CapeOx plus placebo arm having discontinued.

Few significant differences were observed between the CapeOx plus lapatinib arm and the CapeOx plus placebo arm regarding changes in EORTC QLQ-C30 results over time, except for role functioning and cognitive functioning scores at week 30 (better for CapeOx plus lapatinib), role functioning, nausea and vomiting, and constipation scores at week 36 (better for CapeOx plus lapatinib), and diarrhea over the first 30 weeks (worse for CapeOx plus lapatinib).

**Study Management**

The following study site staff provided study management oversight: Kaen Diego, Luis Fein, Juan A. Lacava, Guillermo L. Lerzo, Guillermo Mendez, Mirta Susana Varela, and Juan J. Zarba (Argentina); Kathia Abdalla, Mariangela Correa, Daniel de Iracema Gomes Cubero, André Murad, Yeni Veronica Neron do Nascimento, José Getúlio Martins Segalla, Guillerme Luiz Stelko Pereira, Fernando Meton de Alencar Camara Viera, Alberto Wainstein, and Juliana Yorimi Yamaguchi (Brazil); Neil Sun Chua, Richard Heng-Fu Shao, Wilson H. Miller, and Stephen Welch (Canada); Osvaldo Giannini and Eduardo Yañez (Chile); Yi Ba, Li Bai, Yuxian Bai, Zhendong Chen, Ying Cheng, Bi Feng, Jun Liang, Rongcheng Luo, Xuenong Ouyang, Hongming Pan, Yihong Sun, Jinwan Wang, and Liwei Wang (China); Anneli Elme and Krista Leppik (Estonia); Frank Wong and Thomas Chung Cheung Yau (Hong Kong); László Büdi, Csószí, Eva Somogyiné Ezer, László Mangel, and Gábor Pajkos (Hungary); Baruch Brenner, Efraim Idelevich, Einat Shacham-Shmueli, and Ido Wolf (Israel); Jaydip Biswas, Goswami Chanchal, Ajay Mehta, K. Pavithran, Arumugham Rajkumar, Mehta Shaesta, Atul Sharma, and Choondal Devan Sivanandan (India); Dino Amadori, Giuseppe Aprile, Andrea Ardizzoni, Sandro Barni, Carlo Barone, Vincenzo Catalano, Luigi Cavanna, Francesco Di Costanzo, Marina Faedi, Roberto Labianca, Luciano Latinì, Gabriele Luppi, Cora N. Sternberg, and Emiliano Tamburini (Italy); Ik-Joo Chung, Seok Yun Kang, Hoon Kyo Kim, Yeul Hong Kim, Seong-Hoon Shin, and Hong Suk Song (Korea); German Calderillo-Ruiz and Carlos Alberto Hernandez-Hernandez (Mexico); Marco B. Polee and Dirk J. Richel (the Netherlands); Krzysztof Krzemieniecki, Pawel Murawa, Joanna Pikiel, Pawel Rózanowski, Piotr Sawrycki, Magdalena Sikorska, and Zoran Stojcev (Poland); Fernando Hurtado de Mendoza, Paola Montenegro, and Patricia Pimentel (Peru); Svetlana Vladimirovna Averyanova, Oleg Aleksandrovich Gladkov, Vera Andreevna Gorbunova, Igor Leonidovich Kiselev, Nadezhda Vitalievana Kovalenko, Natalia Levchenko, Georgy Moiseyevich Manikhas, Vladimir Mikhailovich Moiseyenko, Dina Damirovna Sakaeva, Nailia Zagidovna Sherman, Marina Vasilievna Shomova, Dmitriy Petrovich Uдовitsa, and Dmitry Mikhailovich Vyushkov (Russia); Patrapim Sunpawerawong (Thailand); Alper Sevinc (Turkey); Wen-Liang Fang, Yan-Shen Shan, and Ming-Chin Yu (Taiwan); Igor N. Bondarenko, Yuriy Dumanskiy, Lurii S. Golovko, Yevhen S. Hotko, Volodymyr L. Komisarenko, Olexiy O. Kovalyov, Nataliy V. Martsynkovska, Viktor V. Paramonov, Tetiana M. Popovska, Alexander Y. Popovych, Roman V. Senyutovich, Vitaliy M. Sorkin, and Nataliia L. Voitko (Ukraine); David P. Chan, Sheldon J. Davidson, Eddie H. Hu, and David Park (United States).