original article

Southwest Oncology Group study S0413: a phase II trial of lapatinib (GW572016) as first-line therapy in patients with advanced or metastatic gastric cancer

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Background: Lapatinib (GW572016) is a dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2/ErbB2), which are reported as overexpressed in 15%–45% of gastric cancers, making them potential targets.

Patients and methods: The primary objective of this study was to assess response rate. Secondary objectives included overall survival (OS), toxicity, and the relationship of EGFR, ErbB2, and markers of angiogenesis with clinical outcome. Lapatinib was administered to chemonaive metastatic gastric cancer patients at a dose of 1500 mg orally daily for 28 days.

Results: The study enrolled 47 patients from February 2005 until May 2006. Four patients (9%) had a confirmed partial response (PR), 1 (2%) had an unconfirmed PR, and 10 (23%) had stable disease. Median (95% confidence interval) time to treatment failure was 1.9 (1.6–3.1) months and OS was 4.8 (3.2–7.4) months. Significant adverse events: one grade 4 cardiac ischemia/infarction, one grade 4 fatigue, and one grade 4 emesis. One treatment-related death was due to central nervous system ischemia. An exploratory analysis of markers revealed gene expression of HER2, interleukin (IL)-8 and genomic polymorphisms IL-8, and vascular endothelial growth factor correlated with OS.

Conclusions: Lapatinib is well tolerated, with modest single-agent activity in advanced/metastatic gastric cancer patients. Potential molecular correlatives were identified which warrant further validation.

Key words: EGFR, gastric cancer, HER2, lapatinib

introduction

In 2010, there were an estimated 21 000 new cases of gastric cancer in the United States with 10 570 deaths and an overall 5-year survival rate of 22% [1]. Only 20% of cases are diagnosed at an early, potentially curable, stage.

Many chemotherapeutic drugs have single-agent activity in advanced disease, including fluoropyrimidines, platinums, irinotecan, taxanes, and adriamycin. Combination regimens have been shown to be more effective, with response rates ranging from 30% to 50%. However, there can be significant toxicity associated with these combinations and historically, median survival has been 6–9 months. There are more recent phase II and III studies that have reported longer survival, some >1 year [2]. Nevertheless, there remain limitations of traditional therapies and promising preliminary data with novel targeted therapeutics, newer agents are being investigated.

One potential therapeutic target is the epidermal growth factor receptor (EGFR). Both the EGFR and human epidermal growth factor receptor 2 (HER2) genes are amplified and overexpressed in a variety of solid human cancers and are associated with a poor prognosis in patients with gastric cancer. Preclinical studies have shown a significant number of gastric cancer cell lines express EGFR, which grow in response to EGF and transforming growth factor-α and show a greater degree of gastric wall invasion and lymph node metastasis, representing greater malignant potential [3–5]. Additionally, EGFR expression is significantly higher in gastric carcinoma than in adjacent normal gastric mucosa, with greater EGFR levels found in more advanced tumors [6]. Yasui et al. [7] evaluated gastric carcinoma samples for EGFR by 125-labeled EGF binding, with EGFR expression immunoreactivity detected in 33 (34%) of the 96 advanced gastric cancers. Similarly, evaluation by He et al. [8] of 104 specimens of gastric cancer revealed that 42% demonstrated expression of EGFR. Simultaneous EGF and EGFR expression was noted in 15% of gastric cancers, suggesting that these tumors may grow in an

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autocrine fashion. Twelve percent of specimens in this study were found to be positive for c-ErB2 [9].

HER2 has also been associated with poor prognosis, and expression of HER2 assessed in many trials and tissue series in gastric cancer specimens have shown conflicting results. This may be due to the differing methodology used in measuring HER2 status [6]. In fact, evaluations of both EGFR and HER2 have revealed varying expression, which may relate to the methods used to evaluate these markers [10–12]. Most recently, HER2 expression was noted to be ∼22% in the ToGA trial, carried out by both FISH and immunohistochemistry (IHC) [13].

In the laboratory, the combination of anti-EGFR and anti-ErB2 mAbs results in additive antiproliferative effects, suggesting a potential benefit of this combined therapy in the treatment of cancers stimulated by EGFR and HER2 signals.

Lapatinib was approved by the Food and Drug Administration in March 2007 for use in patients only in combination with capecitabine for HER2-positive breast cancer patients, who have completely responded to previous chemotherapy with anthracycline, taxanes, and trastuzumab [14]. Preclinical data have shown that lapatinib, an ErbB1 (EGFR) and ErB2 (HER2) inhibitor, may down-regulate thymidylate synthase in vitro.

The antitumor effect of lapatinib in gastric cancer cell lines has been reported to have the greatest effects in HER2-amplified cells [15]. Lapatinib inhibited phosphorylation of HER2, EGFR, and downstream signaling proteins resulting in G1 arrest and induction of apoptosis [16].

Lapatinib, a dual tyrosine kinase inhibitor of both EGFR and HER2/erbB2, is thought to react with the ATP binding site of protein kinases, competing with the ATP substrate inhibiting EGFR/HER2 autophosphorylation through this competition. Treatment with lapatinib in tumor xenografts that overexpressed both EGFR and HER2 resulted in reduced levels of phosphorylated tyrosine, which correlated with inhibition of tumor growth [17]. Apoptosis and arrest of tumor cell growth have been demonstrated with this agent, even in the presence of saturating concentrations of EGF [18]. Lapatinib has been shown to inhibit Erk1/2 and Akt phosphorylation (pErk and pAkt) in both EGFR and ErB2-expressing cell lines (BT474 and HN5). The ability of lapatinib to inhibit pAkt was associated with a 23-fold increase in the percentage of cells undergoing apoptosis compared with control cells. These results suggest that lapatinib treatment of EGFR/ErB2-expressing tumors could lead to inhibition of downstream signaling events [18].

Given evidence of expression of EGFR and potentially, HER2/ErB2 in patients with gastric cancer, and preclinical evidence that blockade of these receptors may lead to inhibition of cell growth and apoptosis, a phase II study using lapatinib as a single agent for patients with advanced or metastatic gastric cancer was conducted through the Southwest Oncology Group (SWOG) (ClinicalTrials.govIdentifier: NCT 00103324].

patients and methods

Study eligibility included the following: cytologically or pathologically verified diagnosis of advanced or metastatic adenocarcinoma gastric cancer not surgically curable; measurable disease by RECIST criteria; 2-week period between any surgery and study entry; completion of prior chemotherapy, hormonal therapy, immunotherapy, radiation therapy (to <25% of bone marrow), or chemoradiotherapy as neoadjuvant or adjuvant treatment at least 6 months before documented recurrence or advanced/metastatic disease; Zubrod's performance status from 0 to 1; ability to swallow and/or receive enteral medications via gastrostomy feeding tube (including ability to absorb medication); adequate bone marrow reserve as evidenced by absolute granulocyte count ≥1500/μl and platelets ≥100 000/μl; adequate hepatic function as evidenced by serum bilirubin ≤ institutional upper limit of normal (IULN), serum transaminases [serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT)] ≤2.5 × (IULN) [if liver metastasis were present, SGOT or SGPT had to be ≤5 × (IULN)]; measured or calculated creatinine clearance of >60 ml/min (utilizing G–K equation); cardiac ejection fraction within the institutional range as measured by echocardiogram or Multi Gated Acquisition (MUGA) scan. Patients must not have received previous treatment of metastatic disease or received any prior therapy with EGFR targeting therapies. Human immunodeficiency virus-positive patients were excluded because of possible pharmacokinetic interactions with antiretroviral therapy. HER2 amplification was not an entry criterion for this study. All patients must have signed the informed consent in accordance with institutional and federal guidelines.

study design

This was a phase II, open-label, multicenter trial administered and monitored by SWOG. The primary objective of this study was to assess the response rate of lapatinib in patients with advanced/metastatic gastric cancer. Secondary objectives included (i) assessment of overall survival (OS) in these patients; (ii) quantitative and qualitative toxic effects of this regimen; (iii) preliminary assessment of the relationship of protein expression and gene expression of EGFR, HER2, markers of angiogenesis [cyclooxygenase (COX)-2, vascular endothelial growth factor (VEGF), interleukin (IL)-8], and cell cycle (Cyclin D1) with clinical outcome in this study population.

Patients received lapatinib 1500 mg orally days 1 through 28. The drug was administered continuously, with one cycle defined as 28 days. Tablets were available in a strength of 250 mg, and a total of six were taken daily. Concomitant medications that were considered gastric pH modifiers were not permitted. The use of antacids was permitted, but these were administered within 1 hour before or after dosing. Dose adjustments were made for grade 3 toxicity or greater. The first dose reduction was from 1500 to 1000 mg/day, the second dose reduction 750 mg/day, and if a third dose reduction was required, patients were taken off study. Patients continued on protocol treatment until disease progression, symptomatic deterioration, unacceptable toxicity, treatment delay for any reason >4 weeks, or withdrawal of consent.

treatment assessments

Baseline assessments included medical history and physical examination, performance status, complete blood count with differential and platelet count, bilirubin, SGOT and SGPT, creatinine clearance, diagnostic tumor imaging, electrocardiogram and submission of paraffin-embedded tumor specimen, and a blood sample. An echocardiogram or MUGA was also carried out and required every 8 weeks. During the study, history, physical exam, performance status, blood counts, SGOT, SGPT, and creatinine clearance were evaluated every 4 weeks. Toxicity assessment, based on the National Cancer Institute Common Toxicity Criteria, version 2, was carried out every 4 weeks. Tumor response assessments were done after every two cycles. Disease assessment was mandated every 9 weeks while patients were on protocol treatment and every 3 months after they were off protocol

treatment but before progression. Measurable lesions were defined by RECIST. A second sample of blood for molecular correlates was collected 4 weeks after registration.

molecular correlates

genotyping. Peripheral blood or paraffin-embedded tissue samples were available from 41 eligible patients. Genomic DNA was extracted from white blood cells or paraffinized tissue using the QiAmp kit (Qiagen, Valencia, CA). Genomic DNA was obtained in 37 patients from peripheral blood and in four patients from paraffin-embedded tissue. These 41 genomic DNA samples were used to analyze all polymorphisms.

Single nucleotide polymorphisms were tested using PCR–RFLP technique as previously described. Briefly, forward and reverse primers were used for PCR amplification, PCR products were digested by restriction enzymes (New England Biolab, Massachussetts, MA), and alleles were separated on 4% NuSieve ethidium bromide-stained agarose gel. In case no restriction enzyme could be found, samples were analyzed by direct sequencing. For the EGFR (CA)n dinucleotide repeat, the 5′ end [33P-]γATP labeled PCR protocol was used.

gene expression levels. Thirty-seven paraffin-embedded tissue samples were available for gene expression assay. Laser captured microdissection, messenger RNA (mRNA) isolation, complementary DNA (cDNA) synthesis, and real-time PCR quantification of mRNA expression were carried out.

statistical design

The primary goal of this study was to evaluate the confirmed response probability (complete and partial) in patients with advanced/metastatic gastric cancer treated with lapatinib. Time to treatment failure (TTF) and OS were secondary end points. It is assumed that this therapy would be of no further interest if the true response probability was 5% or less and of interest if the true response probability was 20% or more. The study employed the two-stage design of Green and Dahlberg [19].

If, after the first 20 patients, at least one confirmed response was observed, an additional 20 patients were to be accrued. Five or more responses in the total of 40 were considered evidence that this regimen is of interest in the treatment of advanced/metastatic gastric cancer. This design had a power of 0.92 when the true response is 20%, at a significance level of 0.05. Forty patients were sufficient to estimate the probability of a particular toxicity to within ±16%. Any toxicity occurring with at least a 5% probability was likely (87%) to be seen at least once.

Additionally, the relationship of protein expression and gene expression of EGFR and HER2 and markers of angiogenesis and downstream regulatory markers were to be compared in a very preliminary fashion with clinical outcomes. The associations between gene polymorphisms and response were evaluated by Chi-squared test. The associations between gene polymorphisms and OS were examined using Kaplan–Meier plots and the log-rank test.

results

patient characteristics

From February 2005 to May 2006, 47 patients were accrued. Two patients did not receive any treatment and are not analyzable for any end point (one of whom was also ineligible due to no measurable disease). One other patient whose disease recurred too soon after adjuvant therapy was ineligible. Baseline characteristics for the 44 eligible and assessable patients are presented in Table 1.

treatment delivery

The median duration of protocol treatment was 1.9 months (range 0.3–12.5 months). Reasons for treatment discontinuation include progressive disease (84%), death (7%), toxicity (7%), and patient refusal (2%). Of the 44 eligible patients, 28 (64%) had their lapatinib dose reduced.

treatment efficacy

There were four partial responses (PRs) in 44 assessable patients, with no complete responses observed, for an overall confirmed response rate of 9% [95% confidence interval (CI) 3–22%]. There was also one unconfirmed PR for an overall response rate of 11%. There were 10 (23%) patients with stable disease. The remainder was not assessable for response ($N = 2$) or had early progression ($N = 27$). Patients who could not be assessed for response were treated as non-responders and included in the denominator. With all patients now off protocol treatment, the median TTF was 1.9 months (95% CI 1.6–3.1). Forty-three (98%) patients have died, with a median OS of 4.8 months (95% CI 3.2–7.4) (Figure 1).

toxicity

There were 15 (34%) grade 3 and 3 (7%) grade 4 adverse events. The most common grade 3 events were fatigue (8), anorexia (7), and diarrhea (4). There was one treatment-related death due to CNS ischemia. One patient each experienced grade 4 fatigue, cardiac ischemia/infarction, and vomiting. Of note, there were no left ventricular ejection fraction abnormalities recorded at baseline or during the course of the study.

Table 1. Patient and tumor characteristics ($N = 44$)

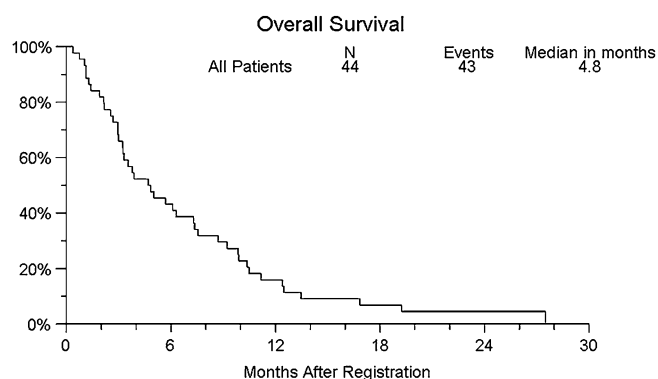| Age (years)	
Median	68.7
Range	38.9–90
Sex (%)	
Male	29 (66)
Female	15 (34)
Race (%)	
White	35 (80)
Black	4 (9)
Asian	4 (9)
Unknown	1 (2)
Zubrod performance status (%)	
0	15 (34)
1	29 (66)
Number of metastatic sites (%)	
0	1 (2)
1	15 (34)
2	15 (34)
3+	13 (30)
Prior therapy (%)	
Surgery	12 (27)
Chemotherapy	3 (7)
Radiation	8 (18)

Figure 1. Overall survival Kaplan–Meier curve in patients with advanced or metastatic gastric cancer treated with lapatinib as first-line therapy.

biologic markers

Genomic DNA from 41 patients was available for evaluation of eight polymorphisms in the seven genes of interest. Genotyping assays for the polymorphisms were successful as follows: 41 patients for COX-2, Cyclin D1, EGF, EGFR 497, HER2, and IL-8; 37 patients for EGFR (CA)n repeats; and 40 patients for VEGF. Table 2 describes patient outcomes within each polymorphism-based subgroup. There were four partial responders in the group of patients with IL-8 AA genotype compared with none in the group with AT or TT genotype. Patients with VEGF CC genotype had 3% (1/30) response rate, while patients with CT genotype had 22% (2/9) response rate and those with TT genotype had 100% (1/1) response rate. Patients with the IL-8 A/A genotype had median (95% CI) OS of 9.6 (3.0–11.2) months, longer than either the A/T [4.9 (3.2–7.4)] or the T/T [3.0 (2.5–4.8)] genotypes, although this result was not statistically significant ($P = 0.20$). None of the remaining polymorphisms tested were associated with either response or survival (Table 2).

Tumor cDNA from 36 microdissected tumor tissue specimens were available for the measurement of gene expression levels of six genes of interest. The median values used for the gene expression analyses were EGFR, 2.715; HER2, 0.065; IL-8, 16.59; VEGF, 5.88; COX-2, 1.94; and CYCLIN D1, 8.77. The gene expression assay was successful as follows: 33 patients for HER2, 34 patients for COX-2 and VEGF, 35 patients for EGFR and IL-8, 36 patients for CyclinD1, and 36 patients for EGFR gene expression levels. Table 3 summarizes tumor response and OS by intratumoral gene expression levels. Higher HER2 and lower IL-8 gene expression levels were significantly ($P < 0.05$) associated with improved OS, although these P values have not been adjusted for multiple comparisons. For none of the remaining genes were expression levels significantly associated with OS.

discussion

The current standard treatment of advanced gastric cancer includes two or three drug regimens, which can produce significant toxicity with limited efficacy. No targeted single-agent biologic therapy to date has demonstrated significant activity. In this study, single agent lapatinib demonstrated a confirmed response rate of 9% (overall response rate of 11%) and a median overall survival of 4.8 months.

Table 2. Response and overall survival by polymorphisms

Marker	N	RECIST response (%)		Overall survival	
		Yes	No	Median (95% CI), months	P^a
COX-2					
G/C	12	0 (0)	12 (100)	5.9 (3.0–9.9)	0.57
G/G	29	4 (14)	25 (86)	4.7 (3.0–8.7)	
Cyclin D1					
A/A	13	1 (8)	12 (92)	3.8 (3.0–9.9)	0.46
A/G	18	1 (6)	17 (94)	4.9 (3.3–7.4)	
G/G	10	2 (20)	8 (80)	4.5 (1.1–13.5)	
EGF					
A/A	10	0 (0)	10 (100)	4.9 (3.3–7.4)	0.92
A/G	22	3 (14)	19 (86)	3.4 (2.5–9.9)	
G/G	9	1 (11)	8 (89)	7.6 (3.0–9.9)	
EGFR					
A/A	21	2 (10)	19 (90)	3.3 (2.5–7.6)	0.38
A/G	13	2 (15)	11 (85)	6.1 (4.7–10.4)	
G/G	7	0 (0)	7 (100)	7.4 (1.3–13.5)	
EGFR (CA)n repeats					
At least 1 allele ≥20	17	0 (0)	17 (100)	4.7 (2.2–9.9)	0.94
Both alleles <20	20	3 (15)	17 (85)	4.9 (3.3–7.4)	
HER2					
Ile/Ile	28	3 (11)	25 (89)	4.8 (3.0–9.2)	0.86
Ile/Val	10	1 (10)	9 (90)	4.7 (2.2–9.9)	
Val/Val	3	0 (0)	3 (100)	5.0 (NA)	
IL-8					
A/A	14	4 (29)	10 (71)	9.6 (3.0–11.2)	0.20
A/T	18	0 (0)	18 (100)	4.9 (3.2–7.4)	
T/T	9	0 (0)	9 (100)	3.0 (2.5–4.8)	
TF A-603G					
A/A	14	2 (14)	12 (86)	4.2 (3.0–9.9)	0.37
A/G	18	2 (11)	16 (89)	5.3 (3.0–10.5)	
G/G	9	0 (0)	9 (100)	6.1 (2.1–9.2)	
VEGF					
C/C	30	1 (3)	29 (97)	4.9 (3.3–7.6)	0.79
C/T	9	2 (22)	7 (78)	3.0 (3.0–10.4)	
T/T	1	1 (100)	0 (0)	NA	

^{a}P values from Cox regression test for heterogeneity across subgroups; not adjusted for multiple comparisons.
CI, confidence interval; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IL-8, interleukin 8; N/A, not applicable; VEGF, vascular endothelial growth factor.

Clinically, single-agent activity with EGFR inhibitors have been evaluated in a very limited fashion in patients with gastric and gastroesophageal junction adenocarcinoma. Dragovich et al. [20] reported a phase II study using erlotinib in this population and did not find any significant activity in gastric cancer but did have a 9% confirmed response rate in gastroesophageal junction tumors. Other trials have shown limited efficacy of these agents in esophageal cancer and no significant efficacy in patients with gastric cancer. Combination therapy with cytotoxics plus EGFR inhibition, i.e. cetuximab has demonstrated promising results in esophageal and

Table 3. Response and overall survival by intratumoral gene expressions

Marker	N	RECIST response (%)		Overall survival	
		Yes	No	Median (95% CI), months	P^a
COX-2					
Above median	17	0 (0)	17 (100)	3.2 (2.1–8.7)	0.24
Below median	17	2 (12)	15 (88)	5.0 (3.0–9.9)	
Cyclin D1					
Above median	18	1 (6)	17 (94)	4.9 (3.0–9.2)	0.89
Below edian	18	2 (11)	16 (89)	4.0 (2.7–5.7)	
EGFR					
Above edian	18	2 (11)	16 (89)	3.3 (1.9–5.7)	0.17
Below edian	17	0 (0)	17 (100)	5.7 (3.0–8.7)	
Her2					
Above median	16	2 (13)	14 (87)	6.8 (3.3–12.4)	0.0031
Below median	17	0 (0)	17 (100)	3.0 (1.3–4.7)	
IL-8					
Above median	17	0 (0)	17 (100)	3.0 (2.2–5.7)	0.016
Below median	18	3 (17)	15 (83)	5.6 (3.3–10.5)	
VEGF					
Above median	17	1 (6)	16 (94)	3.8 (1.1–9.9)	0.63
Below median	17	1 (6)	16 (94)	4.8 (3.0–7.4)	

[a]P values from Cox regression; not adjusted for multiple comparisons.
CI, confidence interval; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IL-8, interleukin 8; VEGF, vascular endothelial growth factor.

gastroesophageal junction cancer [21]. In gastric cancer, encouraging responses have been reported in phase II studies with cetuximab in combination with 5-FU/lecovorin (LV)/ irinotecan with a time to progression of 8 months and combinations with 5-FU/LV and oxaliplatin with a reported time to progression of 7.6 months [22, 23].

HER2 amplification has been reported as an independent prognostic and potentially, predictive factor in gastric cancer. The utility of trastuzumab, the monoclonal antibody targeting HER2, has been limited in its evaluation and efficacy until recently. Van Cutsem et al. [13] presented data from the ToGA trial, a randomized phase III multicenter study, where more than 3800 patients with adenocarcinoma of the stomach or gastroesophageal junction were screened and 810 were positive for HER2 (22.1%). These patients were randomized to receive fluoropyrimidine with cisplatin and trastuzumab versus chemotherapy alone [13]. Patients were either HER2 positive by IHC3+ and/or FISH+. The OS for patients receiving chemotherapy with trastuzumab was 13.8 versus 11.1 months for patients receiving fluoropyrimine and cisplatin alone, hazard ratio 0.74 (0.60–0.91), $P = 0.0046$. The secondary end point of progression-free survival and response rate were also statistically superior in the patients receiving fluoropyrimidine, platinum, and trastuzumab. The combination was well tolerated. This is the first time a biological agent resulted in a survival benefit in advanced gastric cancer.

To explore potential molecular markers, we evaluated gene expression levels of six genes of interest in 36 patients and eight germ-line polymorphisms in seven genes of interest in 41 treated patients. These genes included those involved in EGFR

pathway (EGFR, EGF and HER2), angiogenesis pathway (COX-2, VEGF and IL-8), and cell cycle pathway (CyclinD1). We found that patients with higher HER2 or lower IL-8 gene expression levels had increased OS. These data are consistent with previously reported *in vitro* data published by Rusnak et al. [24], wherein lapatinib sensitivity is increased in human cell lines with high levels of HER2 expression [15, 16]. This has also been shown in previous reports for HER2 therapy with treatment with trastuzumab in breast cancer [25, 26]. HER2 evaluation by FISH was not carried out due to limitations with tissue samples in this study. HER2 gene expression has been correlated with amplification in prior reports [27]. Polymorphisms in IL-8 and VEGF, both involved in angiogenesis, showed some correlation with response and were significantly associated with OS. These data suggest that both EGFR and genes in the angiogenesis pathways may play a role in determining the efficacy of lapatinib. However, due to the small number of the patients involved in our biomarker study, our preliminary results should be interpreted cautiously, with these findings validated in a larger prospective clinical trial.

Evaluation of EGFR or HER2 status was not required for participation in this study. The patients were thereby not selected based on the tumor characteristics, which may have affected the potential efficacy of the drug. This may be particularly significant given that the lapatinib has demonstrated antitumor activity in HER2-amplified gastric cancer cell lines and HER2 amplification was found to be an important predictive factor for the growth inhibitory activity of lapatinib in gastric cancer [15, 16]. In terms of EGFR expression, there has not been association between EGFR protein expression and sensitivity to any of the HER-targeted agents [15]. Furthermore, preclinical data have shown lapatinib combined with 5-FU, cisplatin, oxaliplatin, or paclitaxel demonstrate an additive or synergistic effect [16, 28].

In this study, single-agent lapatinib demonstrated limited activity, although similar to some reports of treatment with single-agent chemotherapy in advanced/metastatic gastric cancer [2, 29]. Prior evaluation of single-agent 'targeted treatment' of EGFR or HER2 blockade as single agents has not demonstrated any significant responses. Dual inhibition of HER2 and EGFR did result in modest activity and provides support for combination treatment and screening for HER2 in advanced gastric cancer.

disclosure

H.-J.L.–stock/ownership interests and honoraria from Response Genetics, Inc; research funding from Glaxo Smith Kline. K.D. disclosures–stock/ownership interests and is an employee of Response Genetics, Inc. The other authors declare no conflict of interest.

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