Published in final edited form as:

Clin Breast Cancer. 2009 February ; 9(1): 16–22. doi:10.3816/CBC.2009.n.003.

A Phase I/II Trial of Trastuzumab plus Erlotinib in Metastatic HER2-Positive Breast Cancer: A Dual ErbB Targeted Approach

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Abstract

Background—This phase I/II trial was conducted to determine the toxicities, recommended dose, pharmacokinetics, and response rate of erlotinib plus trastuzumab in metastatic HER2+ breast cancer.

Patients and Methods—In phase I, sequential groups of patients with unlimited previous treatment received erlotinib at dose levels of 50, 100, and 150 mg plus standard dose weekly trastuzumab. In phase II, only patients with no previous chemotherapy or trastuzumab in the metastatic setting were allowed.

Results—The combination was well tolerated among the 16 patients enrolled in phase I, and the recommended phase II dose of erlotinib was initially set at 150 mg. After an interim review of the first 8 patients in phase II revealed a higher incidence of rash and diarrhea than expected from the phase I experience, the protocol was amended to treat new phase II patients at erlotinib 100 mg, with the opportunity to escalate to 150 mg after 3 weeks, based on individual patient tolerability. As a result of advances in other therapies aimed at HER2+ breast cancer, phase II closed before meeting its accrual goal. Among the 12 evaluable chemotherapy- and trastuzumab-naïve patients treated at the recommended phase II dose level, there were 4 partial responses, and the time to progression was 9.03 months (95% CI, 1.2-undetermined). No pharmacokinetic interaction between the 2 agents was observed.

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Disclosures

Bert Lum is an employee of and a major stock/investment holder in Genentech, Inc. Mubashira Malik is an employee of Genentech, Inc. Dr. Britten and Dr. Press have received research funding from Genentech, Inc. Dr. Britten and Dr. Bosserman have served as paid consultants or been on the Advisory Board of Genentech, Inc. Dr. Finn, Dr. Slamon, and Dr. Press are members of the Speaker's Bureau for Genentech, Inc.

Conclusion—The combination of erlotinib and trastuzumab was well tolerated when the dose of erlotinib was tailored to individual patient experience, and there was preliminary evidence of anticancer activity.

Keywords

Dose escalation; Epidermal growth factor receptor; Pharmacokinetics

Introduction

The standard treatment for HER2-positive breast cancer, whether in the metastatic or adjuvant setting, is the combination of trastuzumab and chemotherapy. Randomized trials have demonstrated that this approach results in prolonged disease-free and overall survival compared with chemotherapy alone.^{1–5} However, trastuzumab/chemotherapy combinations expose patients to toxic side effects, diminishing one of the potential benefits of a targeted approach. An alternative strategy involves the combination of trastuzumab with other targeted therapies, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), to reduce the need for chemotherapy.

The basic biology of the HER2 receptor suggests that the concurrent inhibition of EGFR and HER2 might be more effective than the inhibition of HER2 alone. The ErbB receptors, EGFR, HER2, ErbB3, and ErbB4, share common structural motifs, including an extracellular binding domain, a transmembrane domain, and an intracellular TK domain.⁶ ErbB receptors transmit signals across the cell membrane by binding ligand, triggering homo- and heterodimerization, and subsequently activating their intrinsic TKs. HER2 has no identified ligand and functions primarily as a coreceptor. In fact, the extracellular domain of HER2 is locked in an open configuration in which the dimerization site is left exposed, providing a structural explanation for the status of HER2 as the preferred ErbB dimerization partner.^{7,8} In addition, HER2 increases the affinity of its dimerization partner for ligand, decreases the rate of ligand-receptor complex internalization, and predisposes the receptor to recycling rather than degradation.^{6,9} In this way, HER2 cooperates with EGFR, and other ErbB receptors, to confer a growth advantage.

In HER2+ breast cancer models, the concurrent inhibition of HER2 and EGFR produces improved anticancer activity compared with the inhibition of HER2 alone. In 6 human breast cancer cell lines with increased levels of HER2 and variable levels of EGFR, trastuzumab and erlotinib demonstrated synergistic activity across a range of clinically relevant concentrations.¹⁰ Experiments in BT-474 and SKBR-3 cell lines have produced similar results with trastuzumab and gefitinib.^{11,12} Trastuzumab and gefitinib have also demonstrated enhanced antitumor activity against BT-474 xenografts.¹³ Furthermore, BT-474 cells selected for trastuzumab resistance demonstrate increased levels of phosphorylated EGFR and EGFR/HER2 heterodimers, suggesting that EGFR-mediated signaling is one possible mechanism of acquired resistance to trastuzumab.¹⁴ These results provide the rationale for combining trastuzumab with EGFR TKIs in the clinic.

Clinical trials with trastuzumab and EGFR TKIs were developed to examine the role of a dual- or pan-ErbB approach in the treatment of HER2+ breast cancer. The principal

objectives of this phase I/II trial of trastuzumab and erlotinib were to (1) establish the recommended dose of erlotinib administered orally once daily in combination with standard doses of weekly intravenous (I.V.) trastuzumab; (2) evaluate the safety profile of the 2 agents in combination; (3) determine the pharmacologic behavior of erlotinib and trastuzumab when used in combination; and (4) define the objective response rate (ORR) of trastuzumab and erlotinib in the first-line treatment of metastatic HER2+ breast cancer. Phase I of the trial proceeded as planned; however, during phase II, the science of HER2+ breast cancer evolved, and other targeted therapies became available for the treatment of this disease. Specifically, lapatinib, a dual EGFR and HER2 TKI, was found to improve the time to progression (TTP) achieved with capecitabine compared with capecitabine alone in women with advanced HER2+ breast cancer.¹⁵ In addition, the combination of trastuzumab plus the anti-VEGF antibody bevacizumab demonstrated an impressive RR of 54%, leading to further evaluation of trastuzumab and bevacizumab in phase III clinical trials.¹⁶ Mindful of the emerging data with other available therapies, this trial of trastuzumab and erlotinib was closed before meeting its accrual goal.

Patients and Methods

Patient Selection

Women with metastatic breast cancer (MBC) demonstrating HER2/*neu* gene amplification by fluorescence in situ hybridization were candidates for this trial. Previous chemotherapy and/or trastuzumab for the treatment of metastatic disease were only allowed for patients enrolled in phase I. Patients enrolled in phase II had no previous chemotherapy for metastatic disease and were trastuzumab naive. In addition, phase II patients were required to have bidimensionally measurable disease.

Patients were excluded if they had an abnormal left ventricular ejection fraction (LVEF), symptomatic or untreated brain metastases, liver metastases occupying > 30% of the liver parenchyma, albumin < 3 g/dL, or Eastern Cooperative Oncology Group (ECOG) performance status > 2. Patients were also excluded if they were pregnant. Concurrent administration of CYP3A4 inhibitors was prohibited. Written informed consent was obtained according to federal and institutional guidelines.

Escalation Scheme and Drug Dosing

In phase I, the recommended dose of oral erlotinib administered once daily when combined with standard dose I.V. trastuzumab was determined. Treatment consisted of trastuzumab I.V. 4 mg/kg on day 1, then 2 mg/kg per week beginning on day 8, and oral erlotinib beginning on day 2. At least 3 new patients were treated successively at each of the following erlotinib dose levels: 50, 100, and 150 mg daily. Inpatient erlotinib dose escalation was considered after 3 patients completed 1 course at the next dose level without dose-limiting toxicity (DLT). For practical purposes, a course was defined as a period of 4 weeks.

Dose-limiting toxicity was defined as any one of the following: (1) grade 4 neutropenia or thrombocytopenia; (2) grade 2 visual impairment; (3) grade 2 cardiac toxicity; or (4)

grade 3 nonhematologic toxicities. Nausea, vomiting, and diarrhea that could be controlled with medications were not considered dose limiting. The maximum tolerated dose (MTD) was defined as that dose level at which < 2 out of 6 patients experienced DLT. The recommended phase II dose was defined as either the MTD or erlotinib 150 mg, if the MTD was not reached. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria, version 2. During phases I and II, dose interruptions and/or reductions were permitted for erlotinib, but only dose interruptions were permitted for trastuzumab.

After 6 of the first 8 phase II patients required dose reductions for rash and/or diarrhea, the protocol was amended to dose phase II patients at erlotinib 100 mg for the first 3 weeks. Patients who had not experienced significant (intolerable grade 2 and/or grade 3) rash and/or (grade 2) diarrhea were eligible to receive erlotinib 150 mg beginning on day 22 of course 1. This approach tailored the dose of erlotinib for individual patients in phase II.

Toxicity and Response Assessments

Patient histories, physical examinations, complete blood counts, and biochemistry profiles were obtained at baseline, weekly during course 1, every 4 weeks for additional courses administered during the first year, and every 8 weeks thereafter, as long as the patient remained on study. An ophthalmologic assessment was performed at baseline, at study withdrawal, and at additional time points as clinically indicated. An echocardiogram was performed at baseline, every 8 weeks while on study, and at study withdrawal.

Appropriate radiographic studies for documentation of disease status were performed pretreatment and after every 2 courses (8 weeks). Disease was assessed according to World Health Organization guidelines.¹⁷

EGFR Analysis in Tumor Samples

Paraffin-embedded tissues from tumor biopsies at diagnosis were evaluated by immunohistochemistry (IHC) for EGFR expression using the EGFR pharmDx™ kit (DakoCytomation, Carpinteria, CA) according to the manufacturer's protocol.

Pharmacokinetic Sampling and Analysis

Erlotinib blood samples were obtained from 16 phase I patients at 4 sequential time points after the dose on day 2 and immediately preceding the dose (trough) on days 8, 15, and 22. Two patients were excluded from the analysis: one patient as a result of noncompliance, and a second patient because no concentration data were available beyond day 3. Plasma concentrations of erlotinib and its major active metabolite OSI-420 were analyzed using an isocratic reverse-phase high-performance liquid chromatographic tandem mass spectroscopy method with a lower limit of quantitation of 1 ng/mL for each analyte (MDS Pharma Services, Saint-Laurent, Quebec, Canada).^{18,19} Because the half-life of erlotinib is approximately 24 hours, the trough concentrations on days 8, 15, and 22 were assumed to be steady-state trough concentrations. To assess the effect of trastuzumab on erlotinib pharmacokinetics, erlotinib steady-state concentrations for each patient were averaged across days 8, 15, and 22 to provide one steady-state concentration value. Patients who received 50- and 100-mg doses had their concentration data dose-normalized to 150 mg (ie,

observed concentration $\times$ 150/actual dose) to allow comparison. Mean and 95% confidence intervals (CIs) were then calculated for these values and compared with mean and 95% CIs from a historical data set of 708 patients in phase II/III studies.

Trastuzumab peak and trough blood samples were also collected from 16 phase I patients during the first course of treatment on days 1, 8, 15, and 22. Trastuzumab serum concentrations were determined by a plate-binding enzyme-linked immunosorbent assay with a lower limit of quantitation of 0.156 mcg/mL (Genentech, Inc., South San Francisco, CA).²⁰ Because trastuzumab is best described as a 2-compartment pharmacokinetic model and concentration-time data collected in this study consisted of peak and trough determinations, traditional compartmental and noncompartmental pharmacokinetic analyses were not used as these data did not allow characterization of the distribution (α) phase. Rather, concentration-time data were analyzed by descriptive statistics at each time point, with data described as means and 95% CIs. To assess the effect of erlotinib on trastuzumab pharmacokinetics, a simulation was performed to produce a population of 50 trastuzumab individuals using population pharmacokinetic parameter estimates from an analysis of 265 trastuzumab patients²⁰; 95% CIs were calculated for these simulations and compared with the study patients. These simulations were performed using ADAPTII software (ADAPT II, release 4, Biomedical Simulations Resource, University of Southern California). Because of observations of trastuzumab concentrations at baseline ($n = 10$) and patients not receiving a loading dose ($n = 6$), data from day 1 were omitted from this analysis.

Statistical Methods

A classic 2-stage design was used to determine the phase II sample size.²¹ A previous trial of trastuzumab in HER2/*neu* positive MBC demonstrated a single-agent RR of 34%,²² and an increase in this ORR by 15% was of interest. A minimum of 27 patients were to be treated at the recommended dose level. The trial was to close to accrual if there were 9 responses in the first 27 patients in phase II. If there were > 9 responses, accrual was to continue to a total of 81 patients in phase II. Altogether, > 30 responses were required to demonstrate significant antitumor activity for the combination of trastuzumab and erlotinib. The α and α error rates were set at 0.05 and 0.20, respectively.

Descriptive statistics were used to summarize patient characteristics. The primary efficacy endpoint was the ORR. Time to progression was estimated by the Kaplan-Meier method, using JMP 6 statistical software (SAS institute, Cary, NC).

Results

In total, 27 patients, whose baseline characteristics are outlined in Table 1 were enrolled between September 2001 and June 2007. Two of the 16 patients enrolled in phase I were withdrawn and replaced because they were diagnosed with brain metastases during course 1 (on days 2 and 15, respectively). One patient enrolled in phase II developed complications from her disease following the first trastuzumab infusion and was withdrawn from study before receiving erlotinib.

Dose Escalation and Recommended Phase II Dose

Table 2 outlines the phase I dose escalation scheme. The erlotinib 50-mg dose level was expanded to 6 evaluable patients after the first patient on study developed DLT consisting of a grade 2 decrease in LVEF. With no additional DLTs, dose escalation continued to 100 mg, then to 150 mg. One patient at erlotinib 50 mg was subsequently escalated to 100 mg. Two patients at erlotinib 150 mg required dose reductions for intolerable grade 2 rash during course 1, one of whom required an additional reduction to erlotinib 50 mg for grade 3 rash during course 2. These dermatologic effects did not meet criteria for DLT. With this experience, the recommended phase II dose was erlotinib 150 mg daily combined with standard-dose weekly trastuzumab.

In an interim review of the first 8 patients enrolled at erlotinib 150 mg in phase II, 6 required erlotinib dose interruption and/or reduction for intolerable grade 2 or grade 3 rash and/or grade 3 diarrhea. Four patients required dose adjustments during course 1, and 2 patients required dose adjustments during course 3 or 4. One patient who had a dose reduction to 100 mg during course 4 for grade 3 diarrhea required a second dose reduction to 50 mg during course 8 for grade 3 paronychia. The overall frequency of dose reductions prompted a protocol amendment requiring new phase II patients to be dosed at erlotinib 100 mg, with the opportunity to escalate to 150 mg after 3 weeks, based on individual patient tolerability. Three patients were enrolled under this amendment: 2 were escalated to 150 mg, and 1 was withdrawn before receiving erlotinib.

Safety

The most common toxicities are outlined in Table 3. Almost all (23 of 26) patients who had both study medications experienced rash and/or diarrhea, which was usually grade 1 or 2 in severity and manageable with supportive care. The 8 patients who required dose modification for rash and/or diarrhea experienced improvement of symptoms upon dose interruption and/or reduction.

Two patients developed grade 2 decreased LVEF. The first patient, a 72-year-old trastuzumab-naïve woman who had received doxorubicin 360 mg/m² in the adjuvant setting, was withdrawn from study after 1 course at erlotinib 50 mg because of a dose-limiting decline in LVEF to 40%–45%. Within a month, the LVEF improved to 62%, and the patient was treated with trastuzumab plus taxane-based chemotherapy for 5 months, until she developed symptomatic congestive heart failure with an LVEF of 40%–45%. The second patient, a 59-year-old woman who had previously received docetaxel, carboplatin, and trastuzumab in the metastatic setting, developed an asymptomatic decrease in LVEF after 6 courses at erlotinib 100 mg. Within a month, the LVEF normalized, and the patient was successfully treated with liposomal doxorubicin.

Efficacy

A total of 12 patients with measurable disease and no previous trastuzumab in the metastatic setting were considered evaluable for response at the recommended phase II dose level, including 2 enrolled at erlotinib 150 mg in phase I and 10 enrolled in phase II. An additional patient enrolled in phase II was not evaluable for response because she was withdrawn

before receiving erlotinib. Among the 12 evaluable patients at the recommended phase II dose level, 4 had partial responses, and 1 had disease stabilization for 9 months. All 4 responses lasted > 6 months, with 2 responses lasting > 2 years. All responders experienced rash. One responder received erlotinib 150 mg throughout study participation, 2 responders required dose reductions for diarrhea and/or dermatologic toxicity, and 1 responder was escalated to 150 mg after 3 weeks at 100 mg. Only 1 of the 4 responders had a tumor that expressed EGFR by IHC.

The median TTP for the 12 evaluable patients at the recommended phase II dose level was 9.03 months (95% CI, 1.2-[unavailable]), depicted in Figure 1.

Among the other 14 patients enrolled in phase I, no responses were observed, although 2 patients experienced disease stabilization for > 6 months, including 1 trastuzumab-pretreated patient who was on study for 21 courses.

Pharmacokinetics

Dose-normalized erlotinib plasma concentrations are outlined in Table 4. The 14 patients included in this analysis had a mean erlotinib trough concentration of 1043 ng/mL, compared with a mean trough concentration of 1041 ng/mL from the historical comparative data set containing 708 patients. Overlapping 95% CIs for these 2 groups indicate no significant differences ($P > .05$), suggesting that erlotinib, when used in combination with trastuzumab, has similar pharmacokinetics as previously observed in phase II/III trials.

Observed trastuzumab serum peak and trough concentrations are also outlined in Table 4. Mean trastuzumab concentrations from the current study were higher than those predicted from the population pharmacokinetic analysis, reflecting 10 patients with baseline trastuzumab concentrations as a result of previous trastuzumab exposure. Dosing history data did not allow for adjustment for this previous exposure. The mean trough concentration on day 21 was 50.8 µg/mL, compared with an estimated 36.9 µg/mL from population-simulated data. Overlapping 95% CIs at each of the assessed time points indicate no statistically significant differences between the current study and historical data ($P > .05$) and suggest erlotinib caused no marked effects on trastuzumab concentrations.

Discussion

When this trial was initiated in 2001, TKIs capable of targeting multiple ErbB receptors were in the early stages of clinical development. The combination of erlotinib and trastuzumab provided an opportunity to target 2 interdependent ErbB receptors in HER2+ breast cancer, a disease that is driven by ErbB signaling. Over the years, accrual to the trial declined because of (1) negative results from the concurrent ECOG1100 trial with gefitinib and trastuzumab; (2) progress in the development of multitargeted TKIs, such as lapatinib; and (3) observations with other targeted strategies for HER2+ breast cancer, such as the combination of trastuzumab and bevacizumab. Nonetheless, the experience with erlotinib and trastuzumab provides insight into the development of a dual- or pan-ErbB approach for HER2+ breast cancer, which might influence future clinical trial design.

The combination of erlotinib and trastuzumab was well tolerated, particularly in trastuzumab-pretreated women. In phase I at the erlotinib 150-mg dose level, 1 of 4 trastuzumab-pretreated patients and 1 of 2 trastuzumab-naïve patients required dose reduction for intolerable grade 2 rash. When the trial was expanded to phase II in trastuzumab-naïve patients, the incidence of intolerable grade 2 or grade 3 rash and/or diarrhea was greater than expected from the phase I experience. There were no significant differences in baseline characteristics such as age, weight, or albumin to account for the difference in tolerability from phase I to phase II. It is unknown whether there was a difference in drug exposure between phase I and phase II because pharmacokinetic testing was not performed in phase II. The difference in tolerability could be explained by sampling error because of the small number of patients treated in phase I. Alternatively, inclusion criteria that permitted the participation of trastuzumab-pretreated patients in phase I might have led to the selection of patients who were less susceptible to toxicities from ErbB-targeted therapies. To address the potential for toxicity in a trastuzumab-naïve population, the protocol was amended to individualize erlotinib dosing based on dermatologic and gastrointestinal tolerability. Dosing to tolerability could be important with erlotinib, a drug that has consistently demonstrated an association between rash and response and/or survival.²³

Owing to the different clearance mechanisms of small molecules and monoclonal antibodies, as anticipated, there were no appreciable differences in the concentrations of erlotinib and trastuzumab when administered in combination (when normalized to administered dose and concentrations compared) compared with historical data from population pharmacokinetic studies. The phase I portion of the study demonstrated that the 2 agents might be safely combined at standard doses that achieve concentrations demonstrated to have single agent clinical activity in non-small-cell lung cancer and breast cancer, for erlotinib and trastuzumab, respectively. This verification of the anticipated pharmacokinetic results provides reassurance regarding the development pathway for other combinations of ErbB TKIs with trastuzumab.

Unfortunately, because the trial did not meet its accrual goal, no conclusions can be drawn regarding the efficacy of this regimen. It is unknown how the TTP of 9.03 months (95% CI, 1.2-[undetermined]) compares with the 3.1 to 3.8 months reported for single-agent trastuzumab.^{22,24} In addition, the results of this trial can neither confirm nor refute the ECOG1100 results, in which gefitinib 250 mg daily combined with standard-dose weekly trastuzumab in trastuzumab-naïve patients with HER2-positive breast cancer produced a TTP from 3 months (95% CI, 2.3–4.1) to 5.3 months (95% CI, 2.8–8.1), depending on previous exposure to chemotherapy for metastatic disease.²⁵ Erlotinib and trastuzumab did produce 4 responses among 12 patients, whereas there were only 3 responses among 32 patients enrolled in ECOG1100.²⁵ This apparent difference between RRs from the 2 trials combining EGFR TKIs with trastuzumab might be because of intrinsic differences between gefitinib and erlotinib, as gefitinib has produced disappointing results across malignancies. It is also possible that the 250-mg dose of gefitinib used in the ECOG1100 trial is insufficient to produce maximum antitumor activity. Nonetheless, any comparison between the 2 trials must be taken within the context of the small patient numbers.

With the approval of the dual ErbB TKI lapatinib, the combination erlotinib and trastuzumab has become outdated. Lapatinib has the advantage of providing both EGFR and HER2 coverage with a single oral medication. Other ErbB TKIs are in development that might offer improvements over lapatinib, based on half-life, increased potency to inhibit EGFR, ability to inhibit ErbB4, and irreversible enzyme inhibition. Also, the combination of a dual- or pan-ErbB TKI with trastuzumab might provide some incremental increase in anticancer activity. However, to date, none of the available evidence suggests that a dual- or pan-ErbB strategy will replace trastuzumab plus chemotherapy in the first-line treatment of HER2-positive MBC. Accomplishing the goal of abolishing chemotherapy will require the combination of agents that target distinct yet complementary molecular pathways.

Conclusion

Concurrent targeting of EGFR and HER2 with erlotinib and trastuzumab is well tolerated, particularly when the dose of erlotinib is individualized. As expected, there is no significant pharmacokinetic interaction between erlotinib and trastuzumab. These phase I results provide reassurance for the development pathway of other dual- or pan-ErbB TKIs in this population. Although the current trial does not adequately address the efficacy of a dual- or pan-ErbB approach, this approach alone is unlikely to be sufficient in the treatment of metastatic disease. Ongoing studies with lapatinib and newer generation ErbB TKIs will determine the role of a dual- or pan-ErbB approach as either a maintenance strategy and/or as a backbone regimen to which other targeted therapies could be added.

Acknowledgments

This work was supported by National Cancer Institute/Avon Foundation Progress for Patients Award 3 P30 CA016042-30S1 (C.B.).

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Figure 1. Time to Progression for Phase II Cohort

Among the twelve evaluable patients enrolled at the recommended phase II dose level, the median time to progression was 9.03 months (95% CI, 1.2–[unavailable]).

Table 1

Patient Characteristics

Characteristic	Value
Median Age, Years (Range)	54 (38–80)
Performance Status	
0	11
1	16
Site of Metastasis	
Visceral	22
Chest wall or lymph node only	3
Bone only	2
Estrogen Receptor Status	
Positive	9
Negative	18
HER2 Status by FISH	
Amplified	27
Not amplified	0
EGFR Status by IHC	
Expressed	4
Not expressed	18
Insufficient sample for testing	5
Previous Adjuvant Therapy	
Hormonal therapy	4
Chemotherapy	18
Trastuzumab	2
None	9
Previous Therapy for Metastatic Disease	
Hormonal therapy	6
Chemotherapy	9
Stem cell transplantation	1
Trastuzumab	10
None	15

Abbreviations: EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry

Table 2

Phase I Dose Escalation Scheme

Erlotinib Dose Level (mg/ day)	Number of Patients				Total Number of Courses	Number of Patients with DLT out of Total Number of Patients in Course 1
	New (Evaluable)	Escalated to This Dose	Reduced to This Dose	Total		
50	7 (6)	NA	1	8	18	1 of 6
100	3 (3)	1	2	6	37	0 of 3
150	6 (5)	0	NA	6	18	0 of 5
Total	16 (14)	–	–	–	73	1 of 14

Abbreviations: DLT = dose-limiting toxicity; NA = not applicable

Table 3

Most Frequent Toxicities

Toxicity, n (%)	Number of Patients* Experiencing Toxicity by Most Severe Grade			
	Grade 1	Grade 2	Grade 3	Total
Alopecia	4 (15)	0	0	4 (15)
Anemia	2 (8)	1 (4)	0	3 (12)
Anorexia	6 (23)	6 (23)	0	12 (46)
Diarrhea	14 (54)	4 (15)	4 (15)	22 (85)
Dry Skin	6 (23)	4 (15)	0	10 (38)
Dysgeusia	3 (12)	1 (4)	0	4 (15)
Dyspepsia	1 (4)	2 (8)	0	3 (12)
Elevated Transaminases	2 (8)	1 (4)	0	3 (12)
Epistaxis	3 (12)	0	0	3 (12)
Fatigue	9 (35)	2 (8)	0	11 (42)
Fever	2 (8)	1 (4)	0	3 (12)
Headache	0	4 (15)	0	4 (15)
Nausea	6 (23)	4 (15)	0	10 (38)
Pruritus	8 (31)	5 (19)	0	13 (50)
Stomatitis	8 (31)	2 (8)	0	10 (38)
Rash	11 (42)	9 (35)	2 (8)	22 (85)
Vomiting	2 (8)	1 (4)	0	3 (12)

* Among the 26 patients who received both medications.

Table 4

Comparison of Dose-Normalized Erlotinib Plasma and Observed Trastuzumab Serum Concentrations in the Current Study to Historical Data

Drug/Cohort		Mean Concentration (95% Confidence Interval)		
Time Point	Cohort	Day 7	Day 14	Day 21
Erlotinib[*]				
Trough	Current	–	1043 [†] (710–1377)	–
	Historical	–	1041 [†] (990–1093)	–
Trastuzumab[‡]				
Peak	Current	98.4 (64.8–132)	86 (67.4–105)	88.3 (66.9–110)
	Historical	77.8 (70.4–85.2)	81.2 (73.5–89)	86.2 (77.9–94.5)
Trough	Current	46 (32.2–59.8)	46.9 (31.4–62.4)	50.8 (35.6–66)
	Historical	28.4 (24.8–32)	31.9 (27.7–36.2)	36.9 (31.9–41.9)

^{*} Plasma concentration in ng/mL.

[†] Erlotinib data represented on day 14 are the average for concentrations obtained on days 7, 15, and 22.

[‡] Serum concentration in µg/mL.