Phase I Dose-Escalation Study of 5-Day Intermittent Oral Lapatinib Therapy in Patients With Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer

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ABSTRACT

Purpose

The highly effective treatment of human epidermal growth factor receptor (HER) 2–amplified breast cancer has proven challenging because of a signal buffering capacity inherent in the functionally relevant HER2-HER3 target. HER2-HER3 signaling can be inactivated by doses of lapatinib that fully inactivate the HER2 kinase. In mouse models, such doses are not tolerable in continuous administration, but they are tolerable and highly effective in intermittent dosing. We pursued the clinical translation of this treatment hypothesis.

Patients and Methods

We conducted a phase I dose-escalation study in women with advanced HER2-overexpressing breast cancer. Lapatinib was administered on days 1 through 5 of repeating 14-day cycles. Dose escalation was conducted using a 3+3 design with plasma lapatinib level monitoring.

Results

Forty patients were evaluable for toxicity, and 34 patients were evaluable for dose-limiting toxicity (DLT). Lapatinib dose was escalated to 7,000 mg per day in twice-daily dosing with no DLTs; however, plasma lapatinib concentrations plateaued in this dose range. Additional cohorts evaluated strategies to increase lapatinib exposure, including the food effect, CYP3A4 inhibition, and dose fractionation. Of these, only ketoconazole was able to increase lapatinib exposure, despite highly variable lapatinib bioavailability. Intolerable exposure levels were not encountered. Eight patients (20%) experienced grade 3 diarrhea. Six patients achieved a response, and dramatic responses were seen in three patients with lapatinib concentrations approaching 10,000 ng/mL.

Conclusion

Lapatinib exposure can be safely and significantly increased through intermittent dosing but reaches a ceiling that currently impedes clinical translation of the treatment hypothesis. Preliminary efficacy data suggest that exposures approaching those seen in mouse models can result in highly significant tumor responses.

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INTRODUCTION

The treatment of kinase-driven cancers through the inactivation of their driving kinase is now a validated treatment paradigm producing monotherapy response rates of 95% in Bcr-Abl–driven leukemias,¹ 60% to 94% in EGFR-driven lung cancers,² 70% in Kit-driven GI stromal tumors,³ and 50% to 77% in BRAF-driven melanomas.^{4,5} Many of these responses are dramatic in their clinical presentations. However, this paradigm has not yet proven fruitful for the human epidermal growth factor receptor (HER) 2 target, and the clinical impact of [HER2 tyrosine kinase inhibitors](#) (TKIs) has been limited,⁶⁻⁸ falling far short of scientific expecta-

tions despite meeting expectations for biodistribution and with some evidence for target inhibition.⁹ Lapatinib is currently the only HER2 TKI approved for use; however, it is approved only in combination with chemotherapy or hormone therapy.^{10,11} The underperformance of HER2-targeting TKIs is not a result of the less potent nature of the available agents. In fact, lapatinib is one of the most potent and selective TKIs ever developed, with near singular selectivity against the HER family,^{12,13} a 9 nmol/L in vitro half-maximal inhibitory concentration against its target,¹³ and prolonged target inactivation as a result of an unusually slow off rate attributed to its unique mode of binding in the inactive conformation of the kinase¹⁴ and an energy-requiring mode of release.¹⁵

Furthermore, the clinical pharmacokinetic characteristics of lapatinib are similar, if not superior, to many other TKIs.¹⁶ Even irreversible HER2-targeting TKIs fail to achieve monotherapy efficacies seen with other kinase oncogene-driven cancers.¹⁷ Experimental science has recently begun to explain the underperformance of HER2-targeting TKIs, revealing this target to be far more complex and resilient than anticipated. HER2-driven tumorigenic growth requires its obligate partner **HER3**.^{18,19} Although kinase inactive, HER3 links HER2 in a reciprocal relationship with the downstream **PI3K/AKT** signaling pathway and a negative feedback signaling circuitry that can upregulate HER2-HER3 signaling in compensation for HER2 inhibitors.^{20,21} This endows the HER2-HER3 tumor driver with a signal-buffering capacity that protects it against a nearly two-log inhibition of HER2 catalytic activity, placing it beyond the therapeutic index of even the most potent TKIs.^{21,22} The inability to inactivate tumor HER2-HER3 signaling output in patients is entirely consistent with the modest clinical activity of HER family TKIs developed thus far.

The effective and durable inhibition of the HER2-HER3 tumor driver is possible with HER family TKIs but requires much higher concentrations that completely inactivate HER2 catalytic function, leaving HER3 unphosphorylated despite significant upregulation.²⁰ Although such high concentrations are feasible in vitro, they are not tolerable in continuous administration in vivo because of cutaneous and GI toxicities directly related to continuous EGFR and HER2 inactivation. Such doses, however, may be tolerable if administered intermittently. Because HER2-inactivating doses are expected to induce potent tumor apoptosis, we hypothesized that the repeated administration of intermittent high-dose therapy would have better efficacy than standard continuous dosing, which is known to be ineffective at target inactivation. This treatment hypothesis was tested in mouse models, and intermittent high-dose HER TKI therapy at its maximum-tolerated dose (MTD) was found to be far more efficacious than standard continuous low-dose therapy at its MTD.²² These data are entirely consistent with the hypothesis that near-complete in vivo inactivation of the HER2-HER3 tumor driver is required to produce highly effective antitumor responses. We proceeded to begin to translate this treatment hypothesis into the clinical realm in a phase I clinical study of intermittent high-dose oral lapatinib therapy in patients with HER2-overexpressing breast cancer.

PATIENTS AND METHODS

Patient Eligibility

Patients had a diagnosis of advanced HER2-overexpressing breast cancer with evaluable disease and a cardiac ejection fraction $\geq 50\%$ but without any restrictions on prior therapies including **trastuzumab** or lapatinib. Patients provided written informed consent on a study protocol approved by the University of California, San Francisco, Committee on Human Research.

Study Design and Treatment Plan

This was a phase I single-institution study conducted at the University of California, San Francisco. Patients self-administered lapatinib on days 1 through 5 of a repeating 14-day cycle. The morning dose of the first day of each 5-day course was a loading dose that was two times the other doses. Required prophylactic medications included ondansetron 8 mg three times per day and loperamide 4 mg three times per day between days -1 and 5, and octreotide 150 μg subcutaneously three times per day on days 2 through 6 starting from cohort 8. Additional antidiarrheals such as diphenoxylate and tincture of opium were prescribed as needed. Compliance with required prophylactic medications was greater than 90% based on study calendars and diaries.

Patients continued on therapy as long as they remained free of progression and unacceptable toxicities. Response was assessed clinically every four cycles (2 months), as well as on day 5 of cycle 1, to detect rapid or transient antitumor or cardiotoxic effects that fully reverse in the off-treatment period and would otherwise evade detection.

Dose/Exposure Escalation Design

This study used a 3+3 dose-escalation design with a starting dose cohort of 1,750 mg per day (in twice-daily fractions taken on an empty stomach) guided by toxicity evaluation. Dose levels 1 to 6 were predetermined. After six cohorts were accrued and based on interim lapatinib pharmacokinetic analyses, the study protocol was modified with the objective to escalate lapatinib exposure (instead of oral dose) in all subsequent cohorts (cohorts 7 to 10) through the following three modalities: concomitant intake of food shown previously to result in respective three- and four-fold increases with low-fat and high-fat meals²³; inhibition of lapatinib first-pass metabolism with the potent CYP3A4 inhibitor ketoconazole, shown previously to increase the area under the curve 3.6-fold and the half-life 1.7-fold²⁴; and further fractionation of the daily lapatinib dose from twice per day to four times per day administration, which was previously shown to double exposure from once per day to twice per day.¹⁶

Cohorts 7 to 10 were each individually designed based on the pharmacokinetic data obtained from prior cohorts. The dose and exposure escalation design for cohorts 1 to 10 is outlined in Table 1.

Ketoconazole 200 mg twice per day on days -1 to 5 was added starting from cohort 8. An additional three patients were enrolled into cohort 10 to better document the impact of ketoconazole on lapatinib concentrations.

Toxicity Assessment

Toxicity assessments, including history and physical exam and blood work, were performed every 14 days for the first four cycles and every other cycle thereafter. The 5-day course of cycle 1 was bracketed by safety and research procedures performed before day 1 and again on day 5. These procedures included a composite chest, abdominal, and pelvis computed tomography (CT) scan with cardiac gating, tumor biopsy, blood work for CBC with differential, chemistry panel, troponin I, and plasma lapatinib concentrations. All patients who received at least one dose of lapatinib were evaluable for toxicity. Only patients who took all scheduled lapatinib doses and completed toxicity evaluation for cycle 1 were evaluable for dose-limiting toxicity (DLT) unless missed doses were a result of a DLT. Restaging CT scans with cardiac gating were repeated every four cycles (2 months). Toxicity was assessed using the Common Terminology Criteria for Adverse Events (version 3.0). DLT was defined as toxicity occurring during the first cycle (14 days) of therapy attributable to lapatinib. DLTs were defined as any grade 3 or greater toxicity. In the case of diarrhea and nausea and vomiting, DLT was defined as grade 3 or greater toxicity on 3 consecutive days despite maximal use of supportive medications. In patients with liver metastases, DLT was defined as grade 3 or greater transaminitis with a $\geq$ two-fold increase over baseline. Grade 3 fatigue was a DLT if it persisted at the start of cycle 2.

Plasma Lapatinib Levels

Blood samples for measurement of lapatinib plasma concentration were obtained at baseline and 4 hours (approximate maximum concentration) after the morning dose on day 5 of cycle 1. Samples were also taken in cycle 2 of cohorts 9 and 10 after the treatment design was altered to administer cycle 2 as a control cycle in these cohorts. Samples were analyzed for lapatinib concentration using a previously described method,²⁵ with a sensitivity of 1 ng/mL and precision and accuracy within 15%. Concentrations from samples in 13 patients were corrected for sampling time errors more than an hour early or late to estimate the peak concentration at 4 hours for all patients. Correction involved linear scaling using a median dosing interval profile from previous twice per day dosing studies and assuming that variation was largely pre-systemic (bioavailability) and not post-systemic (curve shape). Of these 13 samples, 10 were corrected by 20% to 36%, two were corrected by 80%, and one was corrected by two-fold. Six patients with missing sample times were set to nominal, based on concentration values that seemed to be consistent with others in their cohort.

Table 1. Dose Exposure/Escalation Design

Cohort No.	No. of Patients	Daily Dose (mg)	Frequency	Exposure Enhancement Strategies		
				Food Effect	CYP3A4 Inhibition	Dose Fractionation
Dose-escalation cohort						
1	3	1,750	BID			
2	3	2,250	BID			
3	3	3,000	BID			
4	3	4,000	BID			
5	3	5,250	BID			
6	4	7,000	BID			
Protocol amendment, adaptive design						
7	3	3,000	BID	With food		
8	6	3,000	BID	With food	Ketoconazole	
9	3	3,000	QID	With food	Ketoconazole	QIDdosing
10	3	3,000	BID	With food	Ketoconazole	

NOTE. Lapatinib dose was initially escalated in predetermined serial cohorts 1 to 6 as shown. At that point, the protocol was amended to pursue strategies to increase lapatinib bioavailability. In cohort 7, patients took each lapatinib dose with a low-fat snack (250 kcal, 2 g of fat, according to a list of suggested snack options). In cohort 8, patients took lapatinib with a low-fat snack and ketoconazole 200 mg BID on days -1 to 5. In cohort 9, patients took lapatinib in four daily fractions (QID) with a low-fat snack and ketoconazole, except for cycle 2, where BID dosing was used for the purpose of additional pharmacokinetic data points and potential intrapatient pharmacokinetic comparison. Cohort 10 was added for additional ketoconazole data points from cycle 1 (with ketoconazole) and cycle 2 (no ketoconazole) to better document a ketoconazole effect.

Abbreviations: BID, twice a day; QID, four times a day.

Statistics

The effect of ketoconazole was assessed using a rank sum test. Linearity of the dose-concentration relationship was assessed with a power model: $\log(C_{\max}) = a + b \cdot \log(\text{dose})$, where $C_{\max}$ is maximum concentration, and response was assessed with a sigmoidal $E_{\max}$ model, using WINNonlin 5.2 software (Scientific Consultant, Apex, NC).

RESULTS

Patients

Forty-one patients were enrolled onto the study between January 2008 and January 2012. Forty patients received at least one dose of lapatinib and were evaluable for toxicity. Six patients were not evaluable for DLT (two patients developed rapid progression of disease, and four patients withdrew consent primarily because of low-grade toxicities that developed before the first 5-day course of lapatinib could be administered or completed). In total, 34 patients were evaluable for DLT. Patient characteristics are listed in Table 2. All patients had metastatic HER2-overexpressing breast cancer. Patients were heavily pretreated, as is typical for phase I trials. Nearly all patients had received prior trastuzumab therapy in the metastatic setting, and the majority had experienced progression on standard continuous-dose lapatinib.

Dose/Exposure Escalation and Toxicity

The median number of cycles completed per patient was six cycles (range, zero to 32 cycles). Lapatinib was escalated from 1,750 to 7,000 mg per day in the first six cohorts with no DLTs encountered. Although continued lapatinib dose escalation beyond 7,000 mg per day seemed feasible by tolerability criteria and protocol design, there was little scientific rationale for continuing dose escalation. This is because of the lapatinib concentration data, which showed that steady-state lapatinib plasma concentrations were not increasing proportionally with increasing lapatinib oral dose and, in fact, had plateaued (Fig 1A). Because the driving hypothesis for this study required

higher systemic and tumor lapatinib exposure, the protocol was redesigned at this point to implement and test the use of food, CYP3A4 inhibition, and dose fractionation as modalities that could be expected to increase lapatinib bioavailability and systemic exposure. These modalities were implemented using the 3,000 mg per day dose level because the data showed no increases in systemic exposure at doses greater than this dose. No DLTs were encountered in any of the cohorts. An oral MTD was not defined or pursued for this 5-day intermittent regimen. A maximum-tolerated systemic exposure was pursued but not defined because of the discovery of a systemic exposure ceiling associated with lapatinib, which precluded such a determination.

Table 3 lists all clinically significant grade 1 to 4 toxicities occurring in $\geq 10\%$ of patients that were possibly related to study treatment. The majority of toxicities were grade 1 and 2 and manageable with standard supportive care measures. As expected, the most common toxicity was diarrhea, which was transient and generally resolved

Table 2. Patient Clinical Characteristics

Characteristic	No. of Patients (N = 40)	%
Age, years		
Mean	50	
Range	29-69	
No. of metastatic sites		
Median	3	
Range	1-5	
No. of prior metastatic chemotherapy regimens		
Median	3	
Range	0-7	
Prior trastuzumab	37	93
Prior lapatinib	28	70
Hormone receptor positive	17	43

Fig 1. (A) All the plasma lapatinib concentrations obtained on this study are shown, plotted according to the treatment dose and strategy indicated. This data set includes both cycle 1 and 2 values obtained in cohorts 9 and 10, where cycle 2 was designed to function as a pharmacologic control cycle. (B) Plasma lapatinib concentrations are shown for patients taking lapatinib with or without ketoconazole (keto), but otherwise identically treated. Plasma lapatinib concentrations were sampled in cycle 1 or cycle 2 and are shown in different shapes to demonstrate the absence of any carryover effect. Plasma concentrations were compared in the presence and absence of ketoconazole using a rank sum test. BID, twice a day; QID, four times a day.

within 24 to 48 hours of completing each 5-day course of lapatinib. Of the 34 patients who completed cycle 1 and were evaluable for DLTs, 31 discontinued therapy because of progression of disease, and three patients withdrew consent. Five patients experienced serious adverse events requiring hospitalization, none of which were attributed to study treatment. Cardiac evaluation did not reveal any significant change in cardiac ejection fraction in any cohort or elevations in troponin I in any patient.

Plasma Lapatinib Concentrations

Lapatinib plasma concentrations were obtained from 39 patients and exhibited similar variability (coefficient of variation, 64% at 3,000-mg dose; $n = 15$) to previous data (coefficient of variation, 70%).¹⁶ Systemic exposure, although higher than previously reported

for doses up to 1,500 mg,¹⁶ did not increase proportionately with oral dose from 1,750 to 7,000 mg in the first six cohorts (Fig 1A). The power model gave an intercept of 2.46 ± 1.03 and a slope of 0.29 ± 0.28 , which was not significantly different from zero.

There was no increase in exposure with food or four times per day dosing at these doses (Fig 1A). However, coadministration of ketoconazole did increase lapatinib exposure (Fig 1B). The increases in lapatinib exposure were 2.7-fold in cycle 1 and 2.8-fold in cycle 2. In the absence of a carryover effect, the combined data gave a statistically significant 2.7-fold increase ($P = .004$; rank sum test).

Clinical Activity

Biologic activity was evident in a number of patients and was characterized as sufficient to produce clinical stability or clinical

Table 3. Clinically Significant Toxicities Encountered in $\geq 10\%$ of Patients (N = 40)

Toxicity	Toxicity Grade									
	Grade 1		Grade 2		Grade 3		Grade 4		All Grades	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Diarrhea	8	20	16	40	8	20	0	0	32	80
Nausea	13	33	13	33	1	1	0	0	27	68
Fatigue	12	30	10	25	0	0	0	0	22	55
Vomiting	8	20	9	23	1	3	0	0	18	45
Anorexia	4	10	13	33	0	0	0	0	17	43
Rash	10	25	6	18	0	0	0	0	16	40
Anemia	6	15	0	0	0	0	0	0	6	15
Dehydration	0	0	6	15	0	0	0	0	6	15
Transaminitis	5	13	1	3	0	0	0	0	6	15
Indirect hyperbilirubinemia	2	5	2	5	0	0	0	0	4	10
Headache	4	10	0	0	0	0	0	0	4	10

Table 4. Clinical Data of the Six Patients Who Had a Clinical Response

Patient No.	Cohort Level	Site of Largest Disease	Baseline Tumor Size (cm)	Best Tumor Response (cm)	Overall Response	PK (ng/mL)	Prior Trastuzumab	Prior Lapatinib
17	5	R axillary LN	4 × 3.6	3.1 × 3.6	PR	NA	Yes	Yes
18	6	Liver mass	2.6 × 2.0	Not measureable	PR	9,717	Yes	Yes
30	9	Anterior mediastinal LN conglomerate	7 × 3.3	Not measureable	CR	9,855	Yes	Yes
34	10	L axillary LN	2.7 × 1.1	1.7 × 0.8	PR	3,511	Yes	No
36	10	Lung nodule	1.6 × 1.3	0.6 × 0.6	PR	10,848	Yes	No
37	10	R breast mass	1.4 × 1.4 × 1.3	Not measureable	CR	5,703	Yes	No

Abbreviations: CR, complete response; L, left; LN, lymph node; NA, not available; PK, predicted peak lapatinib plasma concentration at 48 hours; PR, partial response; R, right.

response (complete or partial). Of the 34 patients evaluable for DLT, 30 were evaluable for response after 8 weeks of therapy. Of these, six patients achieved a partial or complete response. All six responders had previously experienced progression on trastuzumab in the metastatic setting (one patient on trastuzumab-emtansine and three patients with prior lapatinib). A number of other patients displayed evidence of transient biologic activity during the 5 days of therapy, as defined by a reduction in largest tumor size on day 5 CT scan, but progression during the off days, resulting in net stability in some and net progressive disease in others on the 2-month restaging scan (Tables 4 and 5). Five patients demonstrated clinical stability at the 8-week assessment, defined as a disease extent that was not significantly different than baseline. Patients experiencing a response or clinical stability remained on study for a median of 11.5 cycles (range, four to 32 cycles) and 6.5 cycles (six to 15 cycles), respectively.

There was no relationship between lapatinib oral dose and biologic activity; however, there was a relationship between lapatinib exposure and biologic activity (Fig 2A). The most striking responses were seen in the three patients who achieved a lapatinib plasma concentration approaching 10,000 ng/mL. One patient had complete and rapid resolution of a 2.6-cm liver metastasis after 2 months of treatment, a second patient achieved a complete response in bulky mediastinal metastases lasting almost 1 year (Fig 2B), and a third patient had a 63% reduction in a lung metastasis lasting 17 months. Both patients in Figure 2B had experienced progression on prior trastuzumab and standard lapatinib in the

metastatic setting. Of the 10 patients with lapatinib plasma concentrations of 3,500 ng/mL or less, none showed evidence of biologic activity on lapatinib therapy because all had progressive disease at 2 months.

DISCUSSION

We have demonstrated that the dose of lapatinib can be safely and significantly escalated through an intermittent dosing schedule beyond the current standard continuous MTD of 1,500 mg per day. The MTD for this intermittent dosing schedule remains undefined but, more importantly, was found to be clinically irrelevant because of a systemic exposure ceiling that precludes enhancing exposure through increasing dose. Although lapatinib systemic exposure in our study was higher than those reported for continuous dosing of up to 750 mg twice per day,¹⁶ exposure did not increase substantially across dose cohorts. The high degree of variability observed in this data is typical for lapatinib and seems to be largely related to intestinal absorption and its determinants.¹⁶

We tested the tenacity of the systemic exposure ceiling using adjunctive modalities with a rationale to increase lapatinib bioavailability. Of these, only the inhibition of CYP3A4 with ketoconazole was able to enhance exposure. The observed plateau in exposure may be a result of solubility-limited absorption, a property common to most small-molecule TKIs; plasma protein binding; or other unknown

Table 5. Clinical Data of the Seven Patients Who Showed Evidence of Transient Biologic Activity During the 5 Days of Lapatinib but Progression on the Off Days Leading to Overall Stable or Progressive Disease at the 2-Month Evaluation

Patient No.	Cohort Level	Site of Largest Disease	Baseline Tumor Size (cm)	Day-5 Response (cm)	2-Month Response	PK (ng/mL)	Prior Trastuzumab	Prior Lapatinib
4		Right lung apex mass	4.1 × 1.7	3.5 × 1.4	POD	4,447	Yes	Yes
5	2	RLL nodule	3 × 2.1	1.5 × 2.4	Mixed	Not available	Yes	No
7	2	RLL nodule	2.5 × 2.0	2	POD	3,597	Yes	Yes
20	6	RUL nodule	5.0 × 3.5	4.6 × 3.4	SD	3,801	Yes	No
25	7	Skin	14	Less erythema	NA	5,699	Yes	No
28	8	Chest wall	16	Less erythema	SD	3,082	Yes	Yes
29	8	Chest wall	Entire chest wall	Crusting over of lesions	POD	7,401	Yes	Yes

Abbreviations: NA, not applicable; PK, predicted peak lapatinib plasma concentration at 48 hours; POD, progression of disease; RLL, right lower left; RUL, right upper left; SD, stable disease.

Fig 2. (A) The lapatinib exposure values are plotted according to antitumor response status. The mean concentration values and 95% CIs are shown for each group. The mean lapatinib plasma concentrations between the no response and clinical benefit (defined as clinical response or stable disease [SD]) groups were compared using a two-tailed *t* test. Mean concentration was significantly higher in patients who derived clinical benefit than those who did not respond (5,727 ng/mL v 2,174 ng/mL, respectively; *P* < .001). (B) Computed tomography scan images of two patients who achieved high serum lapatinib concentrations and had rapid and dramatic antitumor effects from high-dose intermittent lapatinib therapy. One patient with a large liver metastasis before treatment (left; arrows) achieved serum lapatinib exposure of 10,857 ng/mL and complete resolution of her liver metastasis at the 2-month scan. Another patient with 7 cm of bulky mediastinal lymphadenopathy (right; arrows) achieved serum lapatinib exposure of 7,422 ng/mL and complete resolution of mediastinal lymphadenopathy. CR, complete response; PR, partial response.

pharmacokinetic processes. Lapatinib is highly bound to albumin, which is highly regulated but can vary substantially in patients with cancer. It is also bound to α 1-acid-glycoprotein, an acute reactant that binds lapatinib with high affinity but low capacity and is, therefore, an unlikely determinant. Thus, binding to albumin, which delivers lapatinib to the tumor, may account for the plateau and variability within it.

The presence of this exposure ceiling in humans impeded us from achieving the clinical translation of our scientific treatment hypothesis, developed in mouse models.²² Our clinical study does, however, provide informative observational data that are consistent with our underlying hypothesis. As a reference, the high efficacy seen in preclinical models using intermittent dosing was associated with plasma lapatinib concentrations in the 10,000 ng/mL range. The wide variability in lapatinib exposure seen in this study presents a range of exposure values that seem to correlate with antitumor efficacy with notable responses seen in patients approaching 10,000 ng/mL concentrations, similar to the experi-

ence in mouse models.²² This is consistent with our driving hypothesis that the highly effective treatment of HER2-driven cancer requires near-complete inactivation of the HER2 kinase, a bar much higher than that observed for other kinase-driven cancers. Such an endeavor must await the development of agents with even higher potencies and formulations that can provide much higher systemic exposure than current agents.

The development of novel formulations may be within the foreseeable future. There are now novel technologies with a proven track record in the systemic delivery of insoluble agents, and such technologies can be applied to the delivery of lapatinib.²⁶⁻³⁰ In fact, if feasible, an intravenous administration of HER family TKIs may overcome diarrhea as their principal dose-limiting toxicity. The experience with lapatinib suggests that the development of diarrhea as an adverse event is related to the oral dose but not to the plasma concentration.¹⁶ This suggests that this toxicity is enacted through direct GI luminal exposure to lapatinib, a mechanism that may be subverted by the development of intravenous agents. There

are also clinical data in support of this. In a phase I study of the HER family TKI CI-1033, an intravenously administered formulation achieved much higher systemic exposure and with much less diarrhea compared with the oral formulation.³¹ This agent has not been developed further because of toxicities, likely resulting from off-target effects typical of irreversible TKIs.

Clearly, we have not yet seen the full potential inherent in HER family TKIs for the treatment of HER2-amplified cancer. The complexity and resiliency of this target call for a degree of potency that is beyond the therapeutic index of current classes of HER2-targeting agents. The highly effective treatment of HER2-amplified cancer requires continued efforts to better understand the nature of HER2-HER3 signaling and innovative pharmaceutical technologies for the development of next-generation therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure

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GLOSSARY TERMS

HER2/*neu* (human epidermal growth factor receptor 2): also called ErbB2. HER2/*neu* 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.

HER3: a member of the epidermal growth factor receptor family of receptor tyrosine kinases that is encoded by the *ErbB3* gene. HER3 has a ligand binding domain but does not have an active kinase domain. HER3 heterodimerizes with HER2 and other members of the epidermal growth factor receptor family with active kinase domains to drive cell proliferation, transformation, and malignant pathogenesis.

PI3K/AKT pathway: signal transduction pathways involving the signaling molecules phosphatidylinositol-3 kinase (PI3K) and AKT, where PI3K generates phosphorylated inositides at the cell membrane, which are required for the recruitment and activation of AKT, a transforming serine-threonine kinase involved in cell survival.

trastuzumab: a humanized anti-ErbB2 monoclonal antibody approved for treating patients whose breast cancers overexpress the ErbB2 protein or demonstrate ErbB2 gene amplification. It is currently being tested in combination with other therapies.

tyrosine kinase inhibitors: molecules that inhibit the activity of tyrosine kinase receptors. Tyrosine kinase inhibitors are small molecules developed to inhibit the binding of ATP to the cytoplasmic region of the receptor (eg, gefitinib), thus further blocking the cascade of reactions that is activated by the pathway.