**Featured Article**

**Administration of CI-1033, an Irreversible Pan-erbB Tyrosine Kinase Inhibitor, Is Feasible on a 7-Day On, 7-Day Off Schedule: A Phase I Pharmacokinetic and Food Effect Study**

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**ABSTRACT**

**Purpose:** To determine the maximum tolerated dose of administrating CI-1033, an oral 4-anilinoquinazoline that irreversibly inhibits the tyrosine kinase domain of all erbB subfamilies, on an intermittent schedule, and assess the interaction of CI-1033 with food on the pharmacokinetic behavior.

**Experimental Design:** Escalating doses of CI-1033 from a dose level of 300 mg/day for 7 days every other week were administered to patients with advanced solid malignancies. Plasma concentration-time data sets from all evaluable patients were used to develop a population pharmacokinetic model. Noncompartmental methods were used to independently assess the effect of a high-fat meal on CI-1033 absorption and bioavailability.

**Results:** Twenty-four patients were treated with 69 twenty-eight day courses. The incidence of unacceptable toxicity, principally diarrhea and skin rash, was observed at the 300 mg/day dose level. At the 250 mg/day level, toxicity was manageable, and protracted administration was feasible. A one-compartment linear model with first-order absorption and elimination adequately described the pharmacokinetic disposition. CI/F, apparent volume of distribution (Vd/F), and kα (mean ± relative SD) were 280 L/hour ± 33%, 684 L ± 20%, and 0.35 hour±1 ± 69%, respectively. Cmax values were achieved in 2 to 4 hours. Systemic CI-1033 exposure was largely unaffected by administration of a high-fat meal. At 250 mg, concentration values exceeded IC50 values required for prolonged pan-erbB tyrosine kinase inhibition in preclinical assays.

**Conclusions:** The recommended dose on this schedule is 250 mg/day. Its tolerability and the biological relevance of concentrations achieved at the maximal tolerated dose warrant consideration of disease-directed evaluations. This intermittent treatment schedule can be used without regard to meals.

**INTRODUCTION**

The frequency of overexpression and/or aberrations of at least one member of the erbB receptor family in human nonhematological epithelial malignancies is high, approaching almost 90% in some studies (1, 2). Ligand binding to the extracellular domain of the erbB receptor results in phosphorylation of tyrosine residues in the tyrosine kinase (TK) domain, which mediates cell proliferation, survival, angiogenesis, and metastasis (3–5). Additionally, the magnitude of erbB expression has been consistently shown to be an adverse prognostic determinant in patients with carcinomas of the breast (6–10), ovary (11, 12), prostate (13, 14), stomach (15, 16), head and neck (17), lung (18), brain (19), and melanoma (20), and has served in part as the rationale for developing various therapeutic strategies against erbB (21).

On the basis of the results of disease-directed studies with both monoclonal antibody and small-molecule therapeutics targeting erbB1, it is clear that the magnitude of the resultant anticancer activity is disproportionately less than the magnitude of target expression, and both erbB signaling and determinants of therapeutic response are complex (21). This complexity is illustrated by extensive cooperation and interactions between erbB subfamily members, particularly cross-activation, heterodimerization, and cross-talk, in proliferative signal transduction and malignant transformation, which challenges the notion of developing broadly effective therapeutic strategies by targeting any single erbB subfamily member. Targeting erbB1 alone in malignancies that are not driven by constitutive erbB1 aberrations neglects the importance of other erbB subfamily members such as erbB2 and erbB3 that play unique roles as receptor dimerization partners and also neglects their importance in...
tuning, amplifying, and diversifying signals (22). The multiplicity of erbB receptors and their ability to engage in cross-talk also confers redundancy in the signaling pathway and resistance against attempts to target specific pathway elements. Furthermore, although the advent of potent and specific quinazoline-based small molecules that competitively inhibit ATP binding in the TK domain of erbB has provided the foundation for developing many of the erbB TK inhibitors in clinical development, the high intracellular concentration of ATP has been raised as a potential impediment in achieving sustained inhibition of erbB signaling with competitive inhibitors (23).

CI-1033 (canertinib dihydrochloride; Pfizer Global Research and Development, Ann Arbor, MI; Fig. 1), an orally available 3-chloro, 4-fluoro, 4-anilinoquinazoline, was developed to irreversibly bind to the TK domain of all erbB members. When bound into the ATP pocket, the acrylamide side-chain at position C6 of CI-1033 is brought into close proximity with cysteine 773 of erbB1 (or the analogous cysteines 784 and 778 of erbB2 and erbB4, respectively), which facilitates the rapid formation of a covalent bond that permanently inactivates the catalytically active erbB1, erbB2, and erbB4 family members and effectively blocks erbB3-dependent signaling because of the unavailability of catalytically active heterodimerization partners. The covalent binding of CI-1033 within the ATP pocket of the receptor results in a more prolonged suppression of erbB activity compared with reversible inhibitors in preclinical studies (24, 25). Furthermore, although CI-1033 binds covalently to erbB, it retains selectivity and is inactive against an extensive panel of other protein kinases (5). Moreover, the irreversible inhibition of erbB by CI-1033 has been shown to facilitate receptor tagging with ubiquitin and degradation (26). In this setting, the reversibility of downstream proliferative signaling may be more dependent on the resynthesis of receptors rather than on pharmacokinetic parameters (e.g., clearance). In essence, these features may afford a greater therapeutic advantage to CI-1033 relative to other erbB TK inhibitors, which have reversible actions and target one specific erbB subfamily (27). In addition, given the multiplicity of erbB receptor expression in individual cancers, the broad and highly specific inhibition of the entire family of erbB receptors (28) by CI-1033, including inhibition of the constitutively active mutant epidermal growth factor receptor vIII (29), and the potential of CI-1033 to sequentially signal partners from other signaling-competent receptors by stabilizing inactive erbB homo- and heterodimers (3, 30, 31), the agent could theoretically provide greater efficacy and a broader spectrum of antitumor activity.

In preclinical studies, CI-1033 showed prominent antitumor activity in a broad range of in vivo and in vitro assessments. In the human tumor cloning assay, CI-1033 inhibited the growth of clonogenic cells derived from a variety of tissue types. Broad and impressive activity against human tumor xenografts of colon, lung, breast, and glial origin was also observed (3). Furthermore, notable regression of well-established erbB1-dependent A431 human vulvar carcinoma xenografts associated with near-maximal suppression of erbB1 tyrosine phosphorylation occurred, even at the lowest dose tested, which was associated with C_{max} values approaching 66 ng/mL. Antitumor activity was shown to be independent of dose fractionation, with significant in vivo activity noted on both intermittent (weekly) and continuous daily treatment schedules (3).

The toxicological and pharmacologic profiles of CI-1033 have been evaluated in rodents and monkeys. In both species, toxicity was consistent with modulation of the intended targets. Diarrhea and emesis, which were associated with erosion/atrophy of the gastrointestinal mucosa and blunting of intestinal villi, were the principal toxicities that precluded dose escalation of CI-1033 on single- and multiple-dose oral schedules. With protracted treatment, cutaneous toxicity was prominent in rodents but not in monkeys. Absolute oral bioavailability ranged from moderate in the rat (35%–39%) to low in the monkey (7%), and C_{max} values were achieved within 3 hours after treatment. At CI-1033 doses up to 100 mg/kg, pharmacokinetics were proportional to dose. CI-1033 was highly bound to plasma proteins (>99%) and biliary elimination was the principal route of excretion of radioactivity in radiolabeled drug disposition studies.

The unique mechanistic features of CI-1033 as an irreversible pan-erbB inhibitor, as well as its impressive preclinical activity, served as the impetus for its clinical development. The feasibility of administering CI-1033 on both daily protracted and intermittent schedules has been evaluated in patients with advanced solid malignancies (5). Although intermittent schedules are appealing from a mechanistic standpoint, thrombocytopenia and rare hypersensitivity reactions have been noted in patients treated on an intermittent weekly dosing schedule (32, 33). The principal objectives of this study were to (a) determine the maximal tolerated dose of CI-1033 administered on an intermittent schedule in which CI-1033 is administered daily for 7 days every 2 weeks (7 days-on, 7 days-off) and recommend a dose for disease-directed trials, (b) characterize the toxicities associated with this schedule of administration, (c) describe the pharmacology including the effect of food on absorption, and (d) seek preliminary evidence of antitumor activity.

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Fig. 1 Chemical structure of CI-1033. Note: The chemical groups in the dotted circles represent the reactive groups responsible for alkylation of cysteine in the TK domain of the erbB receptors. They are attached to a condensed quinazoline backbone.
PATIENTS AND METHODS

Patient Selection. Patients with histologically documented advanced-stage nonhematological malignancies that were refractory to standard therapy, or for whom no effective therapy existed, were candidates for this study. Eligibility criteria also included the following: (a) age ≥18 years; (b) Karnofsky performance status ≥50%; (c) life expectancy of at least 12 weeks; (d) no chemotherapy within 4 weeks before the first dose of CI-1033 and no hormonal therapy, immunotherapy, or radiotherapy within 2 weeks; (e) adequate hematopoietic (absolute neutrophilic count ≥ 1500/μL, platelet count ≥ 100,000/μL), hepatic (total bilirubin ≤ 1.5 times institutional upper normal limit, aspartate transaminase and alanine transaminase ≤ 3 times institutional normal upper limit), and renal (calculated creatinine clearance ≥ 45 mL/minute according to the method of Cockcroft and Gault; ref. 34) functions; (f) no history of swallowing disorders or gastrointestinal malabsorption that could interfere with bioavailability of the study drug; and (g) no concurrent serious infection or coexisting medical problem of sufficient severity to potentially limit full compliance with the protocol. All patients gave written informed consent before entry into the study in accordance with federal and institutional guidelines.

Dosage and Drug Administration. The starting dose of CI-1033 was 300 mg daily for 7 days every other week, which is equivalent to 66% of the maximal tolerated dose achieved when CI-1033 is administered for 14 consecutive days every 3 weeks (35). Each 28-day period, which consisted of two 7-day treatment periods, was arbitrarily defined as one course of treatment. Because this dose level closely approximated those doses associated with toxicity on alternate, albeit not widely disparate, CI-1033 schedules (33), a moderately conservative dose escalation scheme in which the maximal dose escalation increment was 40% was used. At least three patients were to be treated at CI-1033 dose levels that did not result in dose-limiting toxicity (DLT) during first courses. If one of the first three patients experienced a DLT in course 1, at least three additional patients were enrolled at the same dose level to verify its validity. The maximal tolerated dose was defined as the highest dose at which less than two of the first six patients experienced consistent DLT during the first course of treatment. If the incidence of dose-limiting events was shown to be unacceptably high in the first course of treatment at the first dose level, the next cohort of new patients was to be treated with 250 mg of CI-1033, which represents a 17% dose reduction. DLT was defined as (a) any grade 4 hematologic toxicity; (b) an absolute neutrophilic count < 1000/μL with a documented infection or fever ≥38.5°C; (c) any grade 3 or 4 nonhematological toxicity (excluding nausea, vomiting, or diarrhea associated with suboptimal premedication and/or management or tolerable cutaneous toxicity); and (d) a delay exceeding 14 days in the initiation of a 7-day treatment period of CI-1033 because of toxicity that did not resolve to grade ≤1 or pretreatment levels. Patients were permitted to begin each successive 7-day treatment period as long as drug-related toxicities had resolved to the levels specified previously, and there was no evidence of disease progression. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (36). In the event of DLT, patients could be retreated with CI-1033 at the next lower dose level. Intrapatient dose escalation was not permitted.

All patients were asked to refrain from eating for 2 hours before and after treatment. The subset of patients that participated in an evaluation of the effects of food on CI-1033 absorption and bioavailability were required to abstain from ingesting food and liquids for 8 hours before the administration of CI-1033 with 6 fluid ounces (180 mL) of tap water on day 1 of courses 1 and 2 (study day 29). On both days, the dose of CI-1033 was to be given at approximately the same time of day. On day 1 of course 1, continued fasting from food and liquids was required for 2 additional hours, after taking the study drug. On day 1 of course 2, CI-1033 was administered with a high-fat, high-calorie breakfast. This meal was adopted from the Food and Drug Administration Draft Guidance for Industry “Food-Effect Bioavailability and Bioequivalence Studies,” first issued in October 1997 (37). Patients had 30 minutes to complete the meal and were then immediately given CI-1033 (within 5 minutes) with tap water. Additional food and liquids were prohibited for 2 hours after administration of the drug.

CI-1033 was supplied by Pfizer Global Research and Development (Ann Arbor, Michigan) as 5-mg, 25-mg, and 250-mg tablets. An absolute dose was administered irrespective of the body surface area and weight of the patient based on the results of previous pharmacokinetic studies that did not show a relationship between clearance and either body weight or body surface area.2 Doses were to be rounded down to the nearest available capsule strength. Patients were instructed to self-administer CI-1033 at the same time of day according to the treatment schedule and to refrain from consuming food and beverages other than water for 2 hours before and 2 hours after each CI-1033 dose. A diary that detailed the dates and times of drug administration as well as relevant pretreatment events and possible toxicities was kept by each patient and was required to be submitted before dispensing drug for each successive course.

Pretreatment and Follow-Up Studies. Histories that included recording of performance status and concurrent medications, physical examination, and routine laboratory evaluations were done before treatment and weekly. Routine laboratory evaluations included complete blood counts, differential white blood cell count, electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, transaminases, coagulation profile, and urinalysis. Pretreatment studies also included an electrocardiogram, and relevant radiological studies for evaluation of all measurable or evaluable sites of malignancy, as well as an assessment of relevant tumor markers. An ophthalmological examination consisting of measurement of visual acuity and slit lamp microscopy was done before treatment and after every other course. Radiological studies for disease status assessments were also done after every other course or as needed to confirm response. Patients were able to continue treatment if they did not develop progressive disease. A complete response was scored if there was disappearance of all active disease on two measurements separated by a minimum period of 4 weeks and a PR required at least a 50% reduction in the sum of the product of the bidimensional measurements of all lesions documented separated by at least 4 weeks. Any concur-
rent increase in the size of any lesion by $\geq 25\%$ or the appearance of any new lesion was considered disease progression. Stable disease was defined as best response if the criteria for either a complete or partial response were not met during the study, and if the criteria for progressive disease were not met during the first 8 weeks the patient was in the study.

**Plasma Sampling and Assay.** Except for the food effect component, pharmacokinetic profiling was accomplished with sparse blood sampling. Blood samples in EDTA/ascorbic acid-containing tubes were collected on day 15 of the first course, just before the beginning of the second 7-day treatment period, and then 1, 3, and 6 hours after treatment. Those patients who participated in the food effect component of the study underwent blood sampling before and at 1, 2, 4, 6, 8, 12, and 24 hours after administration of CI-1033, on day 1 of course 1 (without food) and day 1 of course 2 (with food), which corresponded to study day 29.

The samples were centrifuged at 3,000 rpm for 15 minutes immediately after collection. The plasma was then transferred to a sample tube, which was frozen at $-20^\circ C$ until assayed for CI-1033. An acetonitrile protein precipitation reaction with an alkene deuterated CI-1033 internal standard was used to isolate the serum from a 0.2-mL aliquot of plasma. Supernatant compound separation was accomplished on an YMC Cyanopeak 3.0 x 50-mm column (YMC Co. Ltd., Milford, MA), and subsequent mass spectrometric analysis was done on a SCIEX Triple Quadrupole API 3000 (MDS Sciex, San Francisco, CA). The resulting range of quantitation for CI-1033 was 1 to 500 ng/mL. Overall precision [percentage of coefficient of variation (%CV)] of quality control samples averaged 9.9%, with an overall accuracy [percentage of relative error (%RE)] of $-7.7\%$ to $-1.6\%$.

**Pharmacokinetic Analysis.** Population pharmacokinetic (PK) methods were used to pool and analyze all data, including that obtained from patients participating in the food effect portion of the study. We conducted the population analysis with a one-compartment linear model with first-order absorption and elimination together with an absorption lag time using NONMEM V and PREDPP ADVAN2 (38). Bayesian estimates were obtained by conditioning on the individual concentrations with allowance for interaction between subject level and residual effects. Model dependent parameters included $V_d/F$, apparent clearance (CI/F), and $k_e$ as well as their interindividual variances. We assessed the effect of food on CI-1033 absorption using noncompartmental methods. $C_{max}$ and $T_{max}$ were recorded as observed. Area under the concentration-time curve extrapolated to infinity (AUC$_{0\rightarrow\infty}$) was determined by linear trapezoidal approximation. All descriptive summaries were generated with SAS Version 8.0 (SAS Institute, Inc. Cary, NC, 1989–1996).

**RESULTS**

**General.** Twenty-four patients, whose pertinent characteristics are displayed in Table 1, received 69 four-week courses of CI-1033 at two dose levels. All patients were fully evaluable for toxicity. The total numbers of new patients treated at each dose level, number of evaluable courses, rates of DLTs as functions of the numbers of first and total courses at each dose level, and dose escalation scheme are depicted in Table 2. The median number of courses administered to each patient was two (range, 1–10). Ten patients required dose reduction (six patients) or discontinuation (four patients) for intolerable toxicity.

At the starting dose level of CI-1033, 300 mg/day, the planned patient cohort size of three was increased to six after the occurrence of DLT in course 1 in one of the first three individuals treated with CI-1033. Although three of the first six patients experienced dose-limiting events [grade 3 asthenia (1 patient), grade 3 diarrhea (1 patient), and grade 3 rash (1 patient)], the lack of consistency in the nature of the events permitted dose escalation according to the protocol. Instead, the cohort size was increased to nine subjects to broaden the experience at the dose level. However, two of the final three patients developed grade 2 events, consisting of diarrhea and rash, after the first 7-day treatment period. Although these events did not meet the strict definition of DLT as established in the protocol a priori, the relatively high incidences of both moderate and severe events, many of which were subjectively intolerable, in the first course of treatment were unacceptably high and projected to preclude chronic treatment with CI-1033 at this dose. Therefore, new patients were treated at a reduced dose level of CI-1033, 250 mg/day. At 250 mg/day, 3 (20%) of 15 patients experienced grade 3 events in course 1, consisting of diarrhea (1 patient), skin rash (1 patient), and both diarrhea and malaise (1 patient), but prophylactic and/or supportive anti-diarrheal measures had not been optimally used in both individuals who experienced isolated diarrheal events and further treatment was feasible in one patient after dose reduction and such measures were instituted. Of 15 patients treated with CI-1033 at the 250 mg/day dose level, three patients experienced DLT in course 1, four patients experienced DLT at any time during treatment, and 5 of 40 courses were associated with DLT. Only one patient had CI-1033 discontinued because of toxicity. On the basis of these results, the maximal tolerated dose of CI-1033 was determined to be 250 mg/day.

**Toxicity.** Cutaneous toxicity and diarrhea were the most common toxicities of CI-1033 and precluded dose escalation on
Phase I and Food Effect Study of CI-1033

dose reduction and/or treatment interruption, and were therefore considered dose-limiting.

The distributions of severest grades of the most common adverse events experienced by each study patient as a function of dose level are displayed in Table 3.

**Gastrointestinal.** Adverse gastrointestinal events, particularly nausea, vomiting, and diarrhea were the most common toxicities reported during the study. With regard to both dose cohorts, diarrhea was the most pertinent toxicity of CI-1033. Nineteen (79.2%) of 24 patients experienced diarrhea at some time during treatment. The onset of symptoms was typically on the 3rd day of the 7-day treatment period and symptoms generally resolved completely or to a minimal severity level within 2 to 3 days after the 7-day treatment period (median duration, 6.5 days). Most events were either self-limited or ameliorated with specific antidiarrheal measures such as loperamide. The majority of episodes were mild to moderate (grade 1 or 2) in severity. Although 6 (25%) patients experienced grade 3 diarrhea, including 3 of 9 patients treated at the 300-mg/day and 3 of 15 patients treated at the 250-mg/day dose levels, respectively, these events generally occurred in the absence of optimal antidiarrheal medication and/or support in the first course of treatment. Retreatment was usually feasible with greater tolerability and/or support in the first course of treatment.

Nausea and vomiting were also common in patients treated with CI-1033, with 18 (75%) and 9 (37.5%) patients experiencing nausea and/or vomiting, respectively, at some time during treatment. However, these toxicities were not mutually exclusive and were usually reported simultaneously. The preponderance of episodes were mild or moderate (grade 1 or 2); however, two (8.3%) patients experienced grade 3 nausea and vomiting in the absence of premedication. Most events were brief in duration, typically beginning on the first day of the 7-day treatment period and lasting a median of 2.5 days. Nausea and vomiting were also prevented and/or managed successfully with prochlorperazine or serotonin 5HT3 receptor antagonists, but routine premedication was not necessary because most events were nausea alone, mild in severity, brief, and sporadic.

**Cutaneous Toxicity.** Cutaneous toxicity was the most common adverse event. It was experienced by 20 (83.3%) of 24 patients. The cutaneous manifestations were qualitatively similar in most affected individuals. The rash typically involved the face in a periorificial distribution, as well as the upper trunk. Cutaneous manifestations were initially noted rostrally with progression caudally to involve the upper trunk. The typical appearance was that of an erythematous macular-papular rash. The onset of the rash and/or worsening of residual manifestations because of previous treatment were generally on the 5th day on the 7-day treatment period, with worsening for 3 to 4 days into the 7-day rest period. Next, the cutaneous lesions receded as manifested by decreased erythema and development of crusting, scar formation, and hyperpigmentation. This cycle of progression and recession of lesions was noted throughout the intermittent therapy; however, the magnitude and severity of the cutaneous lesions progressively decreased with chronic administration. In most patients, the intensity of the rash was maximal during weeks 2 to 4, followed by gradual resolution despite

**Table 2** Dose-de-escalation scheme

<table>
<thead>
<tr>
<th>Dose*</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>N of patients with DLTs</th>
<th>Type of DLTs</th>
<th>Toxicity grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First course</td>
<td></td>
<td>All courses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg</td>
<td>9</td>
<td>29</td>
<td>5*/9</td>
<td>Asthenia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rash</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rash</td>
<td>2</td>
<td>Non-DLT †</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>2</td>
<td>Non-DLT †</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea, asthenia</td>
<td>3, 3</td>
<td>Same patient</td>
</tr>
</tbody>
</table>

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; No., number.
* The starting dose of CI-1033 was 300 mg daily for 7 days every other week. Each 28-day period was defined as one course of treatment.
† Two episodes of grade 2 diarrhea and skin rash that were grade 2 by NCI-CTC; however, both events were considered intolerable, required dose reduction and/or treatment interruption, and were therefore considered dose-limiting.

this 7-day-on, 7-day-off schedule. The distributions of severest grades of the most common adverse events experienced by each study patient as a function of dose level are displayed in Table 3.

**Table 3** Summary of toxicity during the study (all courses)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Patient no.</th>
<th>Diarrhea grade</th>
<th>Rash grade</th>
<th>Nausea grade</th>
<th>Vomiting grade</th>
<th>Asthenia grade</th>
<th>Stomatitis grade</th>
<th>Thrombocyt. grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>250</td>
<td>15</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Totals (patients)</td>
<td>24</td>
<td>13</td>
<td>6</td>
<td>18</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>(%)</td>
<td>100</td>
<td>54</td>
<td>25</td>
<td>75</td>
<td>8</td>
<td>67</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>

Abbreviations: Thrombocyt., thrombocytopenia.
further treatment with CI-1033 on this 7-day-on, 7-day-off schedule.

Symptoms attributable to the cutaneous effects of CI-1033 were disproportionately less than appearance of the rash itself. Nevertheless, the maximal severity of the cutaneous toxicity was grade 1 or 2 in most individuals. However, grade 3 cutaneous toxicity that required interruption of treatment was experienced by one patient each at the 250 and 300 mg/day dose levels. In addition, one patient who was treated with CI-1033, 300 mg/day, developed an intolerable rash that was considered dose-limiting, albeit grade 2 in severity as defined by the National Cancer Institute Common Toxicity Criteria. This was based on a subjective appreciation of the cosmetic appearance of the cutaneous lesions, as well as discomfort. Although various topical medications, including corticosteroids, were used to hasten the resolution of the cutaneous effects in patients, it is not clear whether any specific topical therapy was truly effective because the skin lesions tended to inherently recede over time.

Miscellaneous. Mild to moderate (grade 1 or 2) mucositis, thrombocytopenia, and ocular manifestations that did not seem related to dose in the relatively narrow dose range were common. Seven (29.1%) patients developed mucositis, characterized by swelling and soreness of the oral mucosa. These manifestations typically peaked in severity at the end of the 7-day treatment period and resolved during the 7-day rest period without any specific measures. Eleven (45.8%) patients, including 7 and 4 patients at the 250 and 300 mg/day dose levels, respectively, experienced thrombocytopenia, which resulted in neither dose reduction nor treatment interruption. Thrombocytopenia occurred at a median of 4 days into each treatment period, and its duration coincided closely with the duration of CI-1033 treatment. In affected subjects, platelets usually returned to pretreatment levels during the 7-day rest period, and there was no evidence of cumulative toxicity on this schedule. Two patients, both treated with CI-1033 at the 250 mg/day dose level, complained of dryness of their eyes, which was diagnosed as keratitis sicca (grades 1 and 2) and felt to be related to study drug. The symptoms responded to lubricating solutions and treatment disruption was not required. No other ophthalmic findings were evident on visual acuity and slit lamp microscopic examinations. In addition, no clinically significant electrocardiographic abnormalities, hypersensitivity phenomena, or manifestations compatible with drug-induced pulmonary toxicity were evident.

Other events that were possibly related to CI-1033 included anemia, coagulation abnormalities, elevations in hepatic transaminases and/or alkaline phosphatase, and various abnormalities in clinical chemistry tests. Ten (41.7%) patients developed anemia, but most events were mild or moderate (grade 1 or 2) in severity. One patient developed grade 4 anemia (nadir hemoglobin, 6.4 g/dL) concurrent with progressive disease after two courses of CI-1033 at the 300-mg/day dose level. These effects were noted in patients treated at both dose levels of CI-1033, and definite temporal relationships could not be established for any of these potential toxicities, indicating that the underlying malignant process may have contributed. Most changes in blood chemistry characteristics were also mild or moderate (grade 1 or 2). The most frequently occurring changes included hyperglycemia ($n = 15, 62.5\%$), hypomagnesemia ($n = 10, 41.76\%$), hypoalbuminemia ($n = 11, 45.58\%$), hypocalcemia ($n = 8, 33.3\%$), and decreased bicarbonate ($n = 8, 33.3\%$). Grade 3 events included hypoalbuminemia (four patients), elevated aspartate aminotransferase, hyperglycemia, hypermagnesemia, hypokalemia, and hypophosphatemia (two patients each). One patient experienced grade 4 hyponatremia. Occult hematuria and/or proteinuria ($\geq 2+$) were observed in 10 patients across both dose levels in the study. These abnormalities were often present before treatment, suggesting that underlying disease was a contributory factor. No relationship to administration of the investigational drug could be established.

**Antitumor Activity.** No patient had objective evidence of a major response. Three of the 10 evaluable patients with colorectal carcinoma and the single patient with an advanced mesothelioma, all of whom had experienced progressive disease before treatment with CI-1033, had stable disease as their best response. Two of the colorectal carcinoma patients were treated with CI-1033, 300 mg/day, whereas the two other individuals were treated with CI-1033 at the 250-mg dose level. The median time to progression for these four patients was 6.5 months (range, 4.2–11). Another subject with colorectal carcinoma with liver and lung metastases that had progressed during prior treatment with 5-fluorouracil, leucovorin, and irinotecan experienced a 44% reduction in measurable disease that lasted 11 months on CI-1033 treatment at the 300 mg/day dose level.

**Pharmacokinetics.** Consistent with its rapid clearance, there was no evidence of drug accumulation over time. After oral administration, absorption was slightly delayed; the absorption lag-time averaged 25 minutes, and maximal concentrations were attained 2 to 4 hours after treatment. Estimated mean ± relative SD values for $C_{L/F}$, $V_{a/F}$, and $k_{a}$ were 280 L/h ± 33%, 684 L ± 20%, and 0.35 hours$^{-1}$ ± 69%, respectively. Table 4 shows CI-1033 empirical Bayesian pharmacokinetic parameter estimates by administered dose. At any given dose level, there was moderate variability in systemic exposure among patients and between study days. Both $C_{L/F}$ and $V_{a/F}$ values were dose-independent, suggesting dose-proportional drug disposition within the relatively narrow dose range evaluated in this study. At the recommended dose of 250 mg/day, mean $C_{max}$ of the 12 patients with available PK data, including those participating in the food effect study, was 175.2 ± 79.2 ng/mL.

The administration of CI-1033 with a high-fat meal had little effect on its PK behavior when compared with administration under fasting conditions as shown by the mean CI-1033

<table>
<thead>
<tr>
<th>Dose given, number of patients (%)</th>
<th>200 mg, 3 pt*</th>
<th>250 mg, 14 pt</th>
<th>300 mg, 4 pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V/F$ (liters)</td>
<td>667 (2)</td>
<td>670 (7)</td>
<td>675 (7)</td>
</tr>
<tr>
<td>$C_{L/F}$ (L/hour)</td>
<td>270 (39)</td>
<td>266 (18)</td>
<td>319 (6)</td>
</tr>
<tr>
<td>$k_{a}$ (hrs$^{-1}$)</td>
<td>0.39 (27)</td>
<td>0.50 (94)</td>
<td>0.42 (49)</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>1.9 (33)</td>
<td>1.8 (18)</td>
<td>1.5 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{L/F}$, apparent clearance; RSD, relative SD; pt, patient; $V/F$, apparent volume of distribution.

* These patients were dose reduced because of adverse events during first week of treatment, before plasma sampling for PK analysis.

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**Table 4** Mean ($%RSD$) CI-1033 empirical Bayesian pharmacokinetic parameter estimates by administered dose
concentration versus time plots done under fed and fasting conditions in Fig. 2. A slightly $>1$ hour increase in the mean $T_{\text{max}}$ value from 3 to 4.3 hours, with no change in either AUC$_{0\text{-}t}$ or $C_{\text{max}}$ values indicates that a high-fat meal delays the absorption of CI-1033 but does not affect the extent of its absorption. High variability as well as a limited sample ($n = 6$) precluded a rigorous statistical analysis.

**DISCUSSION**

The erbB family of extracellular receptors mediates the transduction of proliferative signals that are essential for cell proliferation of many types of human cancer (39). Today, targeted therapy against these TK receptors is a reality with the availability of both monoclonal antibodies targeting the extracellular domains of erbB1 and erbB2 and various small-molecule, ATP-mimetic inhibitors of erbB1 TK. However, the objective antitumor activity of these agents is disproportionately lower than expectations based on the high rates of expression, overexpression, and aberrations of erbB1 in human malignancies, particularly carcinomas, with the robust responses limited to patients with gene mutations that drive tumor proliferation (29, 40, 41).

The rationale for developing the 4-anilinoquinazoline CI-1033 that irreversibly inhibits all erbB TK is based on both in vitro and in vivo evidence that the antitumor activity of erbB-targeted therapeutics is maximum after prolonged suppression of the receptor TK activity. It was felt that irreversible inhibitors might be more advantageous than reversible inhibitors in permanently eliminating existing receptor TK activity that would regenerate only when new receptors are synthesized. Furthermore, it was hypothesized that even reversible receptor TK inhibitors with favorable pharmacokinetic characteristics such as wide and protracted tissue distribution would have to overcome high intracellular ATP concentrations to impart protracted inhibition of receptor TKs. As an irreversible inhibitor of receptor TK, CI-1033 has the potential advantage of lowering the minimal plasma concentration at which activity occurs, minimizing the requirements for continuous drug administration and eliminating the requirements for therapeutics with long plasma half-lives without compromising efficacy. As expected based on its receptor binding characteristics, the activity of CI-1033 has been shown to be independent of dose fractionation in preclinical studies, with substantial activity achieved on dosing regimens ranging from once daily to once weekly. All of these considerations could also reduce toxicity because of any nonspecific interactions that may occur at high or prolonged plasma levels. Another major impetus for developing CI-1033 is its potential to irreversibly bind to the ATP-binding pocket of all erbB TKs, thereby inhibiting activation, cross-activation, and downstream signaling emanating from erbB1, erbB2, erbB3, and erbB4. Cross-activation or heterodimerization may occur between distinct erbB receptors despite the inactivation of the TK domain of one of the receptors.

This phase I and pharmacologic study was designed to evaluate the feasibility of administering CI-1033 daily on a 7-day-on, 7-day-off schedule because intermittent schedules have been associated with prominent activity in preclinical studies, possibly due in part to the irreversible binding of the agent to erbB TK. Furthermore, schedules in which CI-1033 is administered either daily on a less interrupted schedule with lower doses or weekly with higher doses have been associated with preclusive toxicity (33, 42). The incidence and severity of
toxicities associated with CI-1033 at the recommended phase II dose, 250 mg/day, were tolerable. Furthermore, there was adequate safety experience over multiple courses in patients treated at this dose level, with most of the adverse effects noted being of grade 1 or 2. In contrast, an unacceptably high incidence of early dose-limiting events occurred in patients treated with CI-1033 at the next higher dose level, 300 mg/day. The principal toxicities of CI-1033 were cutaneous effects and diarrhea. Similar toxicities, mainly rash and diarrhea, have been observed with other erbB TK inhibitors, which suggests an erbB-mediated mechanism of action for the pharmacodynamic effects of these drugs (43). At the recommended dose of 250 mg/day, adverse events were prevented or managed successfully in most cases without the need for interruption of treatment. In most cases, diarrhea was well controlled by the intake of loperamide, and skin rash generally improved or resolved within 3 weeks after therapy without any need for interruption of the treatment. There were no treatment-related deaths or grade 4 toxicity during the study. Disease progression was the primary reason for discontinuation and only four (16.7%) patients withdrew because of treatment-related adverse effects.

No treatment-related hypersensitivity reactions were noted in the present study, but manifestations of hypersensitivity phenomena have occurred in patients treated with other dosing schedules of CI-1033 (32, 33). Although thrombocytopenia was not observed previously in preclinical toxicology evaluations in animals, it was an unexpected severe side effect in patients receiving higher doses of CI-1033 administered on days 1, 8, and 15 every 28 days (33), possibly because of the greater chemical reactivity and kinase promiscuity of CI-1033 compared with more restricted and reversible erbB1 TK inhibitors. The occurrence of thrombocytopenia in the present study was generally grade 1 or 2 and not clinically relevant at the dose levels explored. Thrombocytopenia was noncumulative, with similar nadirs noted with each successive treatment and with complete recovery before the beginning of each successive course. Finally, although CI-1033 did not seem to be associated with substantial cardiac, ocular, neurologic, renal, hepatic, or pulmonary side effects when given on this schedule, additional safety monitoring is warranted and will be continued in the ongoing phase I and II clinical trials.

The clinical PK of CI-1033 have been evaluated after administration of doses ranging from 50 to 1,000 mg in 225 patients from different phase I studies with this agent (42, 44, 45). Systemic exposure in the patients analyzed in the present study was consistent with that observed in the parental population. Estimates of the clearance rates are higher than observed previously, most likely because of the truncated profile in which the last sample is collected just 6 hours after dosing for most patients. Only those six patients completing the food effect component of the study contributed complete 24-hour concentration time profiles that in turn led to an underestimation of the terminal phase t1/2 at approximately 2 hours. Although the plasma sampling scheme makes cross study comparisons difficult, it does not prevent assessment of dose proportionality and accumulation potential within this study. Absorption was rapid with Cmax values observed 2 to 4 hours after treatment. There was no evidence of accumulation on repeated dosing, as would be expected given the 2-hour elimination half-life estimate. This PK behavior is not unexpected and is congruent with that observed in other studies (42, 44, 45). In the absence of accumulation, Cmax values still exceed by 10-fold the IC50 values for prolonged pan-erbB TK inhibition and/or transactivation of all erbB receptor subfamily members, in vitro studies. Furthermore, these concentrations almost triple the concentrations that produce maximal suppression of erbB-TK phosphorylation in animal models.4

The results of this phase I and pharmacological study indicate that daily oral treatment with CI-1033 on a 7-day-on, 7-day-off schedule is well tolerated and devoid of relevant hematologic toxicity and hypersensitivity reactions. In fact, the principal toxicities of CI-1033 on this schedule, cutaneous toxicity and diarrhea, are similar to those of monoclonal antibodies and small-molecule inhibitors of erbB1 TK. Furthermore, CI-1033 plasma concentrations at the recommended phase II dose of 250 mg/day exceed biologically relevant concentrations by at least one order of magnitude. Although major tumor regression was not noted in the 14 patients evaluable for tumor response, antitumor activity was not a primary end point in this phase I study done in a heterogeneous patient population with malignancies that undoubtedly possess a wide range of erbB expression and activation profiles. Large, multicenter disease-directed studies in patients with advanced carcinomas of the lung, breast, and ovary will provide an opportunity to benchmark the antitumor activities of CI-1033 relative to those of more specific inhibitors of erbB1 TK as well as an opportunity to evaluate the potential for antitumor activity outside the range of specific inhibitors of erbB1 TK that might be conferred by the pan-erbB inhibitory properties of CI-1033.

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Administration of CI-1033, an Irreversible Pan-erbB Tyrosine Kinase Inhibitor, Is Feasible on a 7-Day On, 7-Day Off Schedule: A Phase I Pharmacokinetic and Food Effect Study


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