Phase I Trial of Irinotecan, Infusional 5-Fluorouracil, and Leucovorin (FOLFIRI) with Erlotinib (OSI-774): Early Termination Due To Increased Toxicities

Wells A. Messersmith,1 Daniel A. Laheru,1
Neil N. Senzer,2 Ross C. Donehower,1
Paula Grouleff,1 Theresa Rogers,1
Sean K. Kelley,3 David A. Ramies,3
Bert L. Lum,3 and Manuel Hidalgo1

1Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; 2Mary Crowley Medical Research Center, Dallas, Texas; and 3Genentech, Inc., South San Francisco, California

ABSTRACT

Purpose: This phase I study was conducted to establish the dose-limiting toxicities and maximum-tolerated dose of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in combination with FOLFIRI, a standard regimen of irinotecan, leucovorin, and infusional 5-fluorouracil (5-FU) in patients with advanced colorectal cancer.

Experimental Design: The trial used a dose-escalation design beginning with 100 mg/day erlotinib continuously and dose-reduced FOLFIRI (150 mg/m² i.v. day 1 irinotecan, 200 mg/m² i.v. leucovorin, 320 mg/m² i.v. bolus days 1 to 2 5-FU, and 480 mg/m² i.v. 5-FU infusion over 22 hours, days 1 to 2) administered in 6-week cycles (three FOLFIRI treatments). Plasma sampling was performed for irinotecan, erlotinib, and 5-FU for pharmacokinetic analysis during cycle 1.

Results: The study was halted after six patients at the lowest dose level due to unexpectedly severe toxicities, including disfiguring grade 2 rash (three patients), grade 3 diarrhea (three patients), and grade ≥ 3 neutropenia (three patients). All patients required some dose interruption or reduction of either erlotinib or FOLFIRI, and only one patient completed two 6-week cycles of therapy. Five patients had stable disease after one cycle, and one patient had a partial response. No plasma pharmacokinetic interaction was observed that could explain the observed increased toxicity.

Conclusions: FOLFIRI combined with erlotinib causes excessive toxicity at reduced doses. These findings contrast with available data regarding the optimal safety profile of trials combining small molecule epidermal growth factor receptor inhibitors with other conventional chemotherapy and highlight the need to perform safety-oriented studies of such combinations.

INTRODUCTION

The epidermal growth factor receptor (EGFR) is one of a family of growth factor tyrosine kinases in which ligand binding initiates a signaling cascade that influences tumor cell growth and survival. EGFR is deregulated in a number of human malignancies, including ~75% of colorectal adenocarcinomas (1). Overexpression of EGFR has been associated with poor survival and chemoresistance in other tumor types (2), and deregulation of the EGFR signaling network has been associated with tumor growth, metastasis, and angiogenesis (3). Recently, activating mutations in the EGFR tyrosine kinase domain were found in tumors from a subgroup of non–small-cell lung cancer patients who responded to the EGFR inhibitor gefitinib (Iressa), indicating a possible genetic determinant of response (4, 5).

Overall, trials combining EGFR inhibitors with conventional chemotherapy for solid tumors such as the lung cancer INTACT studies have been disappointing in terms of improved efficacy (6, 7), but early reports have been more promising in advanced colorectal cancer. A response rate of 78% has been reported in a phase II study combining gefitinib with FOLFOX-4 in the first-line setting (8). In addition, the EGFR antibody cetuximab (Erbitux) showed an improved response rate and time to progression when combined with irinotecan in patients with irotexican-resistant colorectal cancer (9). In general, these studies also demonstrated that combining EGFR-targeting agents with conventional chemotherapy does not significantly increase toxicities.

Erlotinib (Tarceva; OSI-774) is an oral, selective, and reversible small-molecule inhibitor of the EGFR tyrosine kinase. Phase I and II studies have shown a good safety profile, tolerability, and encouraging preliminary activity in a variety of solid tumors (10). FOLFIRI, consisting of infusional 5-fluorouracil (5-FU), leucovorin, and the topoisomerase I inhibitor irinotecan (Camptosar), is one of the standard first- or second-line regimens in advanced colorectal cancer after demonstrating a survival benefit compared with 5-FU/leucovorin alone (11). We undertook at phase I trial combining erlotinib with FOLFIRI in patients with advanced colorectal cancer.

Because erlotinib and irinotecan are both metabolized in part by P450 3A4 (CYP3A4), drug interactions between these agents were of theoretical concern. The majority of the antitumor activity of irinotecan is attributed to an active metabolite SN-38, which is 100-fold more cytotoxic than parent compound (12). Although SN-38 is generated directly from irinotecan via enzymatic cleavage by carboxylesterase, CYP3A4 activity pro-

Received 4/20/04; revised 5/19/04; accepted 6/2/04.

Grant support: Genentech, Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Manuel Hidalgo, 1650 Orleans Street, Room M88, Baltimore, MD 21231. Phone: (410) 502-9746; Fax: (410) 614-9006; E-mail: mhidalg1@jhmi.edu.

©2004 American Association for Cancer Research.
duces another irinotecan metabolite called 7-ethyl-10-[(1-piperidino)-1-amino]-carbonyloxy camptothecin (NPC), which can be converted to SN-38. For this potential safety concern, reduced initial doses and pharmacokinetic analyses were incorporated into the trial.

PATIENTS AND METHODS

Eligibility. After Institutional Review Board approval, patients with histologically confirmed advanced colorectal adenocarcinoma without previous treatment were enrolled in this study. Eligibility criteria also included: age ≥ 18 years; Eastern Cooperative Oncology Group performance status of 0 or 1; life expectancy > 3 months; measurable disease (defined as > 1 cm on spiral computed tomography scan); adequate organ function, including bone marrow (absolute neutrophil count ≥ 1500/μL), hemoglobin ≥ 9 g/dL, platelets > 100,000/μL; liver (total bilirubin < 1.6 mg/dL, international normalized ratio < 1.5, aspartate aminotransferase/alanine aminotransferase < 2.5× upper limit of normal for patients without liver metastases, <5× upper limit of normal for patients with liver metastases); and kidneys (serum creatinine ≤ 1.5× upper limit of normal). Exclusion criteria included prior chemotherapy other than adjuvant fluoropyrimidines in combination with leucovorin, levalsole, and/or irinotecan; prior treatment with EGFR-targeted agents; administration or fluoropyrimidines as a radiation sensitizer within 6 months; brain metastases; other malignancies within 5 years; uncontrolled medical illnesses; inability to take oral medications; surgery within 28 days; HIV positivity; and inability to take full-dose anticoagulation. Written informed consent was obtained as per federal and institutional guidelines before treatment.

Dosage and Drug Administration. The original plan was to enroll cohorts of six patients with escalating doses of FOLFIRI and erlotinib until the maximum-tolerated dose was reached, followed by enrollment of an additional six subjects at the maximum-tolerated dose, but the trial was stopped at the lowest dose level because of excessive toxicity. Tolerability at a particular dose level was defined as the occurrence of dose-limiting toxicity (DLT) in ≤33% of the subjects during the first 6-week cycle (less than or equal to two subjects in a six-subject cohort). The first dose level began with a dose of erlotinib that was 33% lower than the standard single-agent dose, and doses of the cytotoxic study drugs (FOLFIRI) that were ~20% reduced from standard doses. This dose-escalation design began with 100 mg/day erlotinib continuously and dose-reduced FOLFIRI (150 mg/m² i.v. day 1 irinotecan, 200 mg/m² i.v. leucovorin, 320 mg/m² i.v. bolus days 1 to 5-FU, and 480 mg/m² i.v. 5-FU infusion over 22 hours days 1 to 2) administered in 6-week cycles (three FOLFIRI treatments). Each cycle lasted 6 weeks (three FOLFIRI treatments).

Toxicity Assessment. Toxicity was assessed every 2 weeks using the National Cancer Institute Common Toxicity Criteria, version 2, and responses were determined clinically and radiologically before and after each cycle of therapy using RECIST. DLT was defined as treatment-related National Cancer Institute Common Toxicity Criteria grade ≥ 3 nausea, vomiting, or diarrhea despite maximal supportive treatment, other grade ≥ 3 nonhematologic toxicities, grade 4 neutropenia > 7 days, grade 4 thrombocytopenia, or grade 3 or 4 febrile neutropenia (>38.5°C).

Drug Assay and Pharmacokinetic Analysis

Plasma Sampling. At prespecified time points, serial plasma samples were collected to measure the plasma concentrations of erlotinib and its major active metabolites (OSI-420/413), irinotecan and its metabolite (SN-38), and 5-FU. Six serial plasma samples were obtained after the first irinotecan dose (before erlotinib therapy) to evaluate irinotecan disposition in the absence of erlotinib. After the second irinotecan dose (on day 14 of erlotinib therapy), plasma samples were collected using the same design to determine any impact of erlotinib on irinotecan disposition. Steady-state concentration profiles for erlotinib were obtained on study days 13 (after a 13-day washout of irinotecan) and day 14 after coadministration with irinotecan, with six serial plasma samples obtained after each dose. Intermittent plasma samples were also taken throughout the study to confirm exposure to 5-FU but were not subjected to a formal pharmacokinetic analysis.

Drug Assay. Drug and metabolite concentrations in plasma were quantitated using validated methods by a contract laboratory (MDS Pharma, Montreal, Quebec, Canada). Erlotinib and its metabolites (OSI-420/413) were analyzed using liquid chromatography tandem mass spectrometry methods. The lower limit of quantitation was 1.09 and 1.0 ng/mL for erlotinib and OSI-420/413, respectively. Irinotecan and its metabolite (SN-38) were also analyzed using liquid chromatography tandem mass spectrometry methods. The lower limit of quantitation was 5.01 and 0.0504 ng/mL for irinotecan and SN-38, respectively. 5-FU was analyzed using gas chromatography with mass selective detection methods. The lower limit of quantitation was 5.01 ng/mL. In all three assays, the intrabatch coefficient of variation at the lower quality control concentration were <12% (data on file; Genentech, Inc., South San Francisco, CA).

Pharmacokinetic Analysis. Individual patient plasma drug concentration data were analyzed by traditional noncompartmental methods (WinNonlin version 3.2; Pharsight Corporation, Mountain View, CA). For erlotinib, this included a model for extravascular input at steady state, where the area under the plasma concentration-time curve (AUCtau, from time 0 to 24 hours (AUC0–24), was calculated using the linear trapezoidal rule. The maximum plasma concentration (Cmax) and the time to the maximum plasma concentration (Tmax) were determined by visual inspection of the plasma concentration-time data. Oral clearance at steady-state (Cl/Fss) was determined by dividing the dose by AUC0–24 and the elimination half-life estimated by dividing 0.693 by λz. For irinotecan, this included an i.v. infusion model, where clearance (Cl) was determined by dividing the dose by AUC0–infinity and the elimination half-life estimated by dividing 0.693 by λz.

The impact of erlotinib on irinotecan disposition was determined by comparison of irinotecan and SN-38 profiles on study days 1 (irinotecan alone) and 14 (irinotecan + erlotinib). Changes in erlotinib pharmacokinetics in the presence of irinotecan were determined by comparison of erlotinib and OSI-420/413 profiles on study days 13 (erlotinib alone) and 14 (erlotinib + irinotecan). Historical pharmacokinetic data for erlotinib and
OSI-420/413 after a single agent erlotinib treatment were also considered for comparison (13).

RESULTS

Six patients (four males, two females; mean age, 56 years; range, 37–74 years; Eastern Cooperative Oncology Group performance status 0 to 1) with advanced colorectal cancer were enrolled on the study at the first dose level: 100 mg/day erlotinib continuously and dose-reduced FOLFIRI (150 mg/m² i.v. day 1 irinotecan, 200 mg/m² i.v. days 1 to 2 leucovorin, 320 mg/m² i.v. bolus day 1 to 2 5-FU, and 480 mg/m² i.v. 5-FU infusion over 22 hours days 1 to 2). Full-dose FOLFIRI consists of 180 mg/m² irinotecan, 200 mg/m² leucovorin, 400 mg/m² bolus 5-FU, and 600 mg/m² infusional 5-FU days 1 to 2, and erlotinib is typically dosed at 150 mg/day continuously. One patient was dose-escalated to full-dose FOLFIRI with the same dose of erlotinib for cycle 2 but came off-study on day 14 due to toxicity which required hospital admission.

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (y/sex)</th>
<th>Total cycles*</th>
<th>Toxicity†</th>
<th>Adjustments</th>
<th>Response‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60/F</td>
<td>1.3‡</td>
<td>G3 vomiting (DLT), G3 diarrhea, G2 abdominal pain</td>
<td>Erlotinib held 15 days; FOLFIRI held until off-study due to toxicity</td>
<td>SD</td>
</tr>
<tr>
<td>2</td>
<td>74/M</td>
<td>1.6</td>
<td>G2 rash (severe), G3 neutropenia, G3 diarrhea</td>
<td>FOLFIRI held and reduced; erlotinib held 14 days and reduced</td>
<td>SD</td>
</tr>
<tr>
<td>3</td>
<td>37/M</td>
<td>2</td>
<td>G2 rash (severe)</td>
<td>Erlotinib held for 17 days and reduced</td>
<td>SD</td>
</tr>
<tr>
<td>4</td>
<td>62/F</td>
<td>1.3</td>
<td>G3 neutropenia, G2 rash</td>
<td>FOLFIRI reduced</td>
<td>SD</td>
</tr>
<tr>
<td>5</td>
<td>42/M</td>
<td>1.3</td>
<td>G4 neutropenia, G2 rash (severe), G3 diarrhea (DLT)</td>
<td>FOLFIRI and erlotinib reduced; erlotinib held 8 days</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>1</td>
<td>G3 diarrhea, G3 dehydration, G4 pulmonary embolus</td>
<td>Erlotinib held 3 days; off-study after cycle 1 due to toxicity/study closure</td>
<td>SD</td>
</tr>
</tbody>
</table>

‡Response after cycle 1 (SD, stable disease; PR, partial response, as measured per RECIST criteria).

§This patient was dose escalated to full-dose FOLFIRI for cycle 2 but came off study on day 14 due to toxicity which required hospital admission.

* One cycle consisted of 6 weeks (i.e., three FOLFIRI treatments, given every 2 weeks).
† Only grade 3 to 4 toxicities and/or grade 1 to 2 toxicities that caused dose delays/modifications are listed. Note that National Cancer Institute Common Toxicity Criteria, version 2, grade rash based on proportion of body involved; thus, rashes could be grade 2 (<50% body involved) but sufficiently severe and/or disfiguring to necessitate dose reduction. Severe grade 2 rashes in Common Toxicity Criteria, version 2, could be classified as grade 3 in Common Toxicity Criteria, version 3.

Pharmacokinetic analysis did not show a significant interaction between the chemotherapy agents and their major metabolites (Table 2; Figs. 1–3). Pharmacokinetic parameter estimates for irinotecan were not statistically different when irinotecan was given in the absence (d1) or presence (d14) of erlotinib (ANOVA; P > 0.05). Plasma profiles for SN38 were nearly identical on days 1 and 14, suggesting that erlotinib did not impact irinotecan metabolism, nor the disposition of SN38 (Fig. 1). The ratio of SN38 to its parent increased from ~1 to 9% over the 24-hour sampling period.

Table 2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose level (mg/day)</th>
<th>Day</th>
<th>No. of patients</th>
<th>Cmax (μg/mL)</th>
<th>Tmax (hours)</th>
<th>CI/F (L/hour)</th>
<th>t1/2* (hour)</th>
<th>AUC0–24 (hour*μg/mL)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>100</td>
<td>13</td>
<td>5</td>
<td>2.12 ± 0.52</td>
<td>1.65 ± 1.42</td>
<td>1.12 ± 0.91</td>
<td>35.0 ± 9.02</td>
<td>36.0 ± 12.4</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>100</td>
<td>14</td>
<td>4</td>
<td>2.32 ± 0.37</td>
<td>9.88 ± 10.6</td>
<td>1.34 ± 0.90</td>
<td>28.5 ± 23.5</td>
<td>44.5 ± 16.5</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>150</td>
<td>1</td>
<td>6</td>
<td>1.29 ± 0.28</td>
<td>1.13 ± 0.41</td>
<td>19.2 ± 4.31</td>
<td>5.35 ± 0.43</td>
<td>7.85 ± 1.59</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>150</td>
<td>14</td>
<td>6</td>
<td>0.98 ± 0.29</td>
<td>1.13 ± 0.41</td>
<td>25.3 ± 11.4</td>
<td>5.70 ± 0.60</td>
<td>6.65 ± 2.65</td>
</tr>
</tbody>
</table>

NOTE. Parameters calculated using non-compartmental analysis.
* Elimination half-life = 0.693/Lz.
† AUC calculated from start if irinotecan infusion to 24 hours after completion of infusion.

Abbreviations: AUC, area under the plasma concentration versus time curve; Cmax, maximum plasma concentration; t1/2, elimination half-life; Tmax, time to the maximum plasma concentration; CI/F, oral clearance.
Pharmacokinetic parameter estimates for erlotinib were not statistically different when erlotinib was given in the absence (day 13) or presence (day 14) of irinotecan (ANOVA; \( P < 0.05 \)). Plasma profiles for the major metabolite (OSI-420/413) of erlotinib paralleled erlotinib profiles and showed that OSI-420/413 levels were consistently 9–10% of the parent (Fig. 2). These results suggest that irinotecan did not impact the disposition or metabolism of erlotinib or OSI-420/413. However, because a true erlotinib control was not included in this study, we also compared results obtained here to those reported by Hidalgo et al. (13) that described erlotinib pharmacokinetic after multiple daily administrations to cancer patients. In this earlier study, patients were given 100 mg erlotinib/day for 24 days. Reported daily exposure to erlotinib at steady state (\( \text{AUC}_{0-24, \text{day} 24} = 38.2 \pm 37.1 \)) was similar to exposure seen in the current study (\( 36.0 \pm 12.4 \) to \( 44.5 \pm 16.5 \)), suggesting no drug-drug interactions between irinotecan and erlotinib.

5-FU plasma concentrations were consistent with previously published values and were not markedly affected by coadministration of erlotinib (Fig. 3).

**DISCUSSION**

FOLIRI is a standard first- or second-line regimen for advanced colorectal cancer, with published response rates ranging from 40 to 50%. The most common side effects from this regimen in published trials include diarrhea (grade 3 to 4, 13%), neutropenia (46%), anemia (6%), and mucositis (4%). Rash, including hand-foot syndrome, occurs in <1% (13). Erlotinib also causes diarrhea at 150 mg (typically easily controlled with loperamide), but the other major toxicity is a dose-dependent, reversible acneiform rash primarily affecting the face and upper trunk (13). The rash is rarely greater than grade 2 at the 100 mg daily dose level; even at 150 mg, the rash rarely causes termination of treatment. Other toxicities (typically mild) of erlotinib include headache, nausea/vomiting, elevated bilirubin, and mucositis; bone marrow suppression is not typically seen.

Although the limited number of patients restricts the ability to reach any definitive conclusions, this phase I trial combining erlotinib and FOLFIRI was halted early at the first dose level because of unexpectedly high incidence of toxicity, especially gastrointestinal symptoms and rash. The two DLTs were grade 3 vomiting (requiring hospital admission) and grade 3 diarrhea, both despite supportive measures. Three other patients developed grade 3 diarrhea as well. Although nausea/vomiting...
and diarrhea are overlapping toxicities of erlotinib, 5-FU, and irinotecan, the frequency and severity at reduced dose levels was unexpected.

Another surprisingly severe toxicity seen in this trial was acneiform rash, which necessitated dose reductions or discontinuations of erlotinib in three patients despite the reduced starting dose of 100 mg daily. These rashes did not meet criteria for DLT but were dose limiting from a clinical perspective with regards to patient tolerability. Given the extensive experience of one investigator (M. Hidalgo) with erlotinib in clinical trials, the severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual. The National Cancer Institute Common Toxicity Criteria, version 2, severe rashes seen at this dose level were highly unusual.

REFERENCES


Phase I Trial of Irinotecan, Infusional 5-Fluorouracil, and Leucovorin (FOLFIRI) with Erlotinib (OSI-774): Early Termination Due To Increased Toxicities


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/19/6522

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.