Dual Inhibition of the Epidermal Growth Factor Receptor Pathway with Cetuximab and Erlotinib: A Phase I Study in Patients with Advanced Solid Malignancies

MICHAEL J. GUARINO,a CHARLES J. SCHNEIDER,a MARTHA A. HOSFORD,a JULIE R. BRAHMER,b CHARLES M. RUDIN,b FRIEDRICH GRAF FINCKENSTEIN,c ROBYN E. PHILIP-NORTON,d HAOLAN LU,e MARTIN R. WEBER,e DAVID S. ETTINGERb

aHelen F. Graham Cancer Center, Christiana Care, Newark, Delaware, USA; bThe Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA; cBristol-Myers Squibb Company, Princeton, New Jersey, USA; dOSI Oncology, Melville, New York, USA; eBristol-Myers Squibb Company, Wallingford, Connecticut, USA

Key Words. Cetuximab  Erlotinib  Phase I  Solid malignancies

Disclosures: Michael J. Guarino: None; Charles J. Schneider: None; Martha A. Hosford: None; Julie R. Brahmer: Consultant/advisory role: Abbott, Cephalon, Genentech, Eli Lilly, AstraZeneca; Charles M. Rudin: Consultant/advisory role: CTI Pharmaceuticals, Amgen; Research funding/contracted research: Pharmion; Friedrich Graf Finckenstein: Employment/leadership position: Bristol-Myers Squibb; Ownership interest: Bristol-Myers Squibb; Robyn E. Philip-Norton: Employment/leadership position: OSI Pharmaceuticals; Haolan Lu: Employment/leadership position: Bristol-Myers Squibb; Martin R. Weber: Employment/leadership position: Bristol-Myers Squibb; Ownership interest: Bristol-Myers Squibb; David S. Ettinger: Consultant/advisory role: AstraZeneca, Bristol-Myers Squibb; Eli Lilly, GlaxoSmithKline, Merck, MGI Pharma, Pfizer, Sanofi-Aventis; Research funding/contracted research: Bayer, Genentech, Pharmion.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Purpose. To determine the optimal dose of the antiepidermal growth factor receptor (EGFR) monoclonal antibody cetuximab that can be safely administered in combination with a standard daily dose of erlotinib in patients with advanced solid malignancies.

Patients and Methods. Patients with advanced solid malignancies who had failed standard chemotherapies received escalating doses of cetuximab without a loading dose (100, 200, 250 mg/m² i.v. weekly) in combination with a fixed dose of erlotinib (150 mg daily orally) until disease progression or unacceptable toxicity.

Results. Twenty-two patients were treated, including 14 patients (64%) with non-small cell lung cancer. Twenty patients received combination treatment at the highest dose level for a median of 5.5 weeks (range, 1–31 weeks). One dose-limiting toxicity was observed: grade 3 skin rash. Overall, the most common adverse events (any grade, grade 3/4) were consistent with the safety profiles of the individual drugs: acneform rash (100%, 9%), diarrhea (77%, 5%), and hypomagnesemia (59%, 12%). Seven of 18 evaluable patients (38.9%) had stable disease lasting for a median of 16.6 weeks (range, 6.1–25.1 weeks).

Conclusion. Dual EGFR inhibition with cetuximab

Correspondence: Michael J. Guarino, M.D., Medical Oncology Hematology Consultants, PA, Helen F. Graham Cancer Center, 4701 Ogletown-Stanton Road, Suite 2200, Newark, Delaware 19713, USA. Telephone: 302-366-1200; Fax: 302-366-1700; e-mail: mguarino@cbg.org Received May 29, 2008; accepted for publication December 1, 2008; first published online in The Oncologist Express on January 31, 2009. ©AlphaMed Press 1083-7159/2009/$30.00/0 doi: 10.1634/theoncologist.2008-0124

INTRODUCTION
The epidermal growth factor receptor (EGFR) is overexpressed in a variety of solid tumors; increased EGFR expression has been associated with poorer clinical outcomes in some of these malignancies [1–3]. The anti-EGFR chimeric monoclonal IgG1 cetuximab (Erbitux®; ImClone Systems Incorporated, New York, and Bristol-Myers Squibb Company, Princeton, NJ) is approved by the U.S. Food and Drug Administration for use in combination with irinotecan for the treatment of metastatic colorectal cancer and for use with radiotherapy for treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) [4, 5]. Single-agent cetuximab is also approved for metastatic colorectal cancer in patients intolerant to irinotecan and in SCCHN patients after failure of prior platinum-based therapy [6–9]. Clinical trials show that cetuximab may also have promising activity when used with chemotherapy in first-line treatment of non-small cell lung cancer (NSCLC) [10–15]. Erlotinib (Tarceva®; Genentech, Inc, South San Francisco, CA and OSI Pharmaceuticals Inc., Melville, NY) is a tyrosine kinase inhibitor (TKI) that improves the survival time of patients with advanced NSCLC who progress after one or two prior chemotherapy regimens [16]. Erlotinib is approved for use in advanced NSCLC after failure of previous chemotherapy, and in combination with gemcitabine in first-line treatment of advanced pancreatic cancer [16, 17].

The combination of an anti-EGFR monoclonal antibody and a TKI may enhance the inhibition of downstream signaling and lead to better treatment responses and outcomes [18–20]. This phase I study was designed to assess the feasibility and safety of administering an optimal dose of cetuximab in combination with a standard 150-mg/day dose of erlotinib in patients with advanced malignancies who had previously failed standard chemotherapy regimens.

PATIENTS AND METHODS

Eligibility Criteria
Patients were treated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD) and the Helen F. Graham Cancer Center (Newark, DE). Patients aged ≥ 18 years with advanced solid malignancies who had failed standard chemotherapy regimens and had Eastern Cooperative Oncology Group performance status score of 0–1, at least one bidimensionally measurable lesion, and a life expectancy ≥ 3 months were eligible. Prior chemotherapy, major surgery, or radiation therapy were acceptable (≥ 4 weeks, ≥ 3 months if radiation therapy to chest area). Patients with inadequate hematologic, hepatic, or renal function, symptomatic or uncontrolled central nervous system metastases, uncontrolled heart disease, or pulmonary fibrosis, and those who had received prior anti-EGFR therapy were excluded.

All patients provided written informed consent before any study procedures were performed. The study was approved by the investigational review board at both participating sites, and was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice and national regulatory guidelines.

Trial Design
This was an open-label, dose-escalation, phase I trial with an accelerated titration design. Cetuximab was administered once weekly, without an initial 400-mg/m2 dose, in sequential cohorts at dose levels of 100, 200, and 250 mg/m2, via 60-minute i.v. infusion after diphenhydramine premedication. After the first cetuximab dose, patients started erlotinib at a fixed dose of 150 mg/day orally. Each treatment cycle was 4 weeks regardless of omitted doses; doses could be omitted, but no delayed cycles were allowed. Treatment was continued until disease progression or unacceptable toxicity. Dose modifications of cetuximab or erlotinib were allowed in the event of severe toxicity.

One patient per cohort was to be treated until a dose-limiting toxicity (DLT) was observed during the first treatment cycle; that cohort was to be expanded to a total of six patients before further dose escalation was considered. If two instances of grade 2 toxicity were observed in the first cycle, the cohort was to be expanded to three patients before further escalation. The maximum-tolerated dose (MTD) was defined as the highest dose at which less than one third of the patients experienced a DLT during the first cycle. The recommended phase II dose (RPID) was to be defined by the MTD or the highest dose level (250 mg/m2) if an MTD was not reached. Up to 15 additional patients were to be enrolled at this RPID to confirm its safety. Intrasubject dose escalation to a new level shown to be safe was allowed provided the patient did not experience a DLT after at least 4 weeks on the lower dose level.
DLT was defined by any of the following events occurring during the first cycle only: any grade 4 toxicity other than infusion reaction; any grade 3 skin toxicity that required treatment interruption for >14 days; grade 3 or 4 diarrhea, vomiting, or nausea that could not be controlled with medical intervention or prophylaxis; any other grade ≥3 nonhematologic toxicity except for asthenia or infusion reaction; delayed recovery from toxicity (other than skin toxicity) resulting in withholding of retreatment >4 weeks; grade 4 neutropenia for at least five consecutive days or grade 3 or 4 neutropenia with sepsis or fever; or thrombocytopenia ≤25,000 cells/mm³ or bleeding requiring a platelet transfusion.

**Assessments**

High-resolution computed tomographic (CT) scans of the chest and of other tumor-bearing regions were performed within 4 weeks of the first dose of study treatment. All other baseline evaluations were performed within 14 days of the first dose.

The primary endpoint was identification of the RPIID for cetuximab in combination with erlotinib. Secondary endpoints included safety—defined by the MTD and incidence of adverse events (AEs) and abnormal laboratory parameters—and objective tumor response. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and coded to the Medical Dictionary for Regulatory Activities version 10.

Patients were evaluated for response according to modified World Health Organization criteria. CT analyses of tumor-bearing regions and other tumor response assessments were performed every 8 weeks, or more frequently if indicated. Responses to treatment required confirmation at least 4 weeks later. Criteria for stable disease (SD) had to be met ≥35 days after the first dose. The duration of SD was defined by the time between the first dosing date and the documented progression date in patients with SD as the best tumor response. Tumor measurements made by the investigator were reviewed by the study sponsor to determine the best tumor response and date of progression.

Evaluations for demographic and baseline characteristics, as well as safety, efficacy, and dosing, were carried out on the total group of treated patients, using descriptive statistics.

**RESULTS**

**Patient Disposition and Demographics**

From August 2005 to December 2006, 25 patients in total were screened and 22 patients were treated. One patient each was treated at the first two dose levels, and 20 patients were treated at the third dose level with cetuximab weekly at 250 mg/m² i.v. plus 150 mg erlotinib orally. All patients had been treated previously with chemotherapy in the adjuvant or metastatic setting, most of them (77.3%) with two or more prior regimens. Most patients (64%) had NSCLC (supplemental online data, supplemental Table S1).

**Treatment Exposure**

One patient was enrolled in each of the first two cohorts. Those patients received cetuximab for 8 weeks and erlotinib for 7.9 and 7.3 weeks, respectively, without dose modification or omission. In the third dose-level cohort, 20 patients were enrolled in total; cetuximab and erlotinib were each administered for a median duration of 5.5 weeks (range, 1.0–31.0 weeks and 1.0–30.1 weeks, respectively). In total, 135 infusions of cetuximab (250 mg/m²) were administered, and 28 planned infusions were omitted for toxicity or other reasons. Four cetuximab infusions were administered at a reduced dose: two because of skin toxicity, one as a result of delayed recovery from asthenia, and one because of an unknown reason. In total, 980 doses of erlotinib were administered, and 142 planned doses were omitted. The erlotinib dose was reduced in one patient for 11 days.

The most common drug-toxicity reasons for study treatment discontinuation were: five patients with acneform rash (four with grade 1 or 2 and one with grade 3), one patient with grade 3 diarrhea, one patient with grade 2 hypomagnesemia and hypocalcemia, and one patient with mild eye and skin pain.

**Safety**

No DLT was reported at the first two dose levels. One DLT (grade 3 rash) was reported in the third dose-level cohort. The cohort was expanded to six patients without another DLT, and subsequently to a total of 20 patients to collect additional safety data at this dose level. The MTD was not reached at the third dose level, and consequently, 250 mg/m² of cetuximab and 150 mg of erlotinib were determined to be the RPIIDs.

Overall, the safety profile of the combination was consistent with the individual safety profiles of each drug (Tables 1 and 2). The most common AEs were acneform rash and diarrhea. No grade 4 acneform rash was reported. Two patients (9.1%) had grade 3 acneform rash, whereas the rash was mild to moderate (grade 1 or 2) in the other 20 patients. Severe infusion reactions were not reported; three patients (13.6%) had grade 1 infusion reactions. Grade 3 or 4 hypomagnesemia was reported in two patients (12%).

Hematologic abnormalities were mostly mild to moder-
ate, with grade 3 leukopenia reported in one patient (4.8%),
grade 2 neutropenia in one patient (4.8%), and 16 patients
(76.2%) experiencing anemia (none of them severe). No grade
3 or 4 values in liver or renal function tests were reported.

**Efficacy**

Eighteen patients were evaluable for response. No objec-
tive responses were observed. Seven patients (38.9%)—
four with NSCLC and one each with colorectal cancer, cervical cancer, and an epithelial neoplasm with neuroen-
docrine features—had SD lasting for a median of 16.6
weeks (range, 6.1–25.1 weeks). All SD was seen in the
highest dose-level cohort.

**DISCUSSION**

This study demonstrates that the combination of cetuximab
and erlotinib is feasible and tolerable in patients with ad-
vanced malignancies who had previously failed standard
chemotherapies. The safety profile of the combination was
consistent with each of the individual drugs, with no unex-
pected toxicities seen during the study. The doses recom-
manded for phase II evaluation were 250 mg/m² weekly for
cetuximab and 150 mg daily erlotinib.

An accelerated-titration dose escalation design was
used for cetuximab. Given that the safety profile of each in-
dividual drug is well characterized, this design enabled us
to escalate doses rapidly, starting from a 100-mg/m² dose of
cetuximab that would allow detecting and monitoring po-
tentially prohibitive or unexpected safety signals, minimiz-
ing the number of patients treated with a dose below the
approved cetuximab standard (250 mg/m²). The interme-

tiate level (200 mg/m²) was included to merely avoid a dose
gap larger than twofold, because, with one single patient en-
rolled, potential interpatient variability could override any
relevant exposure difference between this and the highest
dose allowed (250 mg/m²).

Although the initial dose of cetuximab has been used in
other phase I studies of cetuximab plus TKI combinations
[21, 22], the 400-mg/m² initial cetuximab dose was not in-
cluded in this trial, an omission designed to curtail potential
overlapping toxicities. This approach was considered ac-
ceptable based on previous pharmacokinetic studies show-
ing that weekly administration of cetuximab at 250 mg/m²
[2] without the initial higher dose still resulted in serum lev-
els providing >50% target occupancy, and therefore would
not compromise activity [23].

This study did not include a pharmacokinetic analysis
for the potential interaction between the two drugs. This ap-

droach was based on the expected lack of drug interactions
between an antibody and an oral small molecule and the fact
that the individual pharmacokinetic profiles of cetuximab
and erlotinib were well characterized, as both agents were
already commercially available when the study was con-
ducted.

Rash affected every patient and was the most frequent
reason for toxicity-related treatment discontinuation; it may
therefore emerge as a relevant safety concern with this com-
bination. Even with the caveats implicit in any comparison
across trials, a 100% incidence with concurrent use appears

---

**Table 1. Adverse events of special interest (n = 22)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n (% of patients)</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acneform rash</td>
<td>22 (100)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (77.3)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>10 (58.8)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>3 (13.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

A Acneform rash was a composite of the Medical Dictionary for Regulatory Activities version 10 preferred terms: rash, rash pustular, rash erythematous, dermatitis acneform, dermatitis exfoliative, rash papular, rash pruritic, rash generalized, rash macular, rash maculopapular, acne, acne pustular, skin desquamation, and dry skin.

B Incidence of hypomagnesemia in 17 patients who had serum magnesium measured.

C Infusion reaction was a composite of the following preferred terms: infusion reaction, infusion-related reaction, hypersensitivity, anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. In addition, the terms dyspnea, pyrexia, and chills were grouped under infusion reaction when their onset occurred on the first day of study treatment.

---

**Table 2. Drug-related adverse events (n = 22)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n (% of patients)</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7 (31.8)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (31.8)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (22.7)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>3 (13.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

All drug-related adverse events are those occurring in two or more patients.
greater than the 76%–80% rates reported in studies of single-agent erlotinib or cetuximab; interestingly, however, there was no apparent increase in the rate of severe events [4, 6]. Whether a potential exacerbation of this toxicity may have a meaningful impact on the clinical use of this regimen will not be clear until larger trials are conducted.

Other studies have recommended more conservative dosing schemas, lowering the erlotinib dose to 50 mg in combination with the full dose of cetuximab [22]. In this trial, the tolerability of the highest dose in the 20 patients from the expansion cohort would validate cetuximab at a dose of 250 mg/m² weekly plus erlotinib at 150 mg daily as the recommended doses for future investigation. Although objective responses were not seen, seven of 18 evaluable patients had SD lasting for a median of nearly 4 months. In conclusion, this regimen warrants further evaluation in malignancies where either cetuximab or erlotinib is known to be active, including colorectal cancer, NSCLC, and SCCHN, with some studies already initiated.

ACKNOWLEDGMENTS
This study was supported in full by Bristol-Myers Squibb and ImClone Systems Incorporated, and partially by OSI Pharmaceuticals Incorporated.

REFERENCES


Baselga J, Schöffski, Rojo F et al. A phase I pharmacokinetic (PK) and molecular pharmacodynamic (PD) study of the combination of two anti-EGFR therapies, the monoclonal antibody (MAb) cetuximab (C) and the tyrosine kinase inhibitor (TKI) gefitinib (G), in patients (pts) with advanced colorectal cancer (CRC), head and neck (HNC) and non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2006;24(suppl 18):3006.

Preston GG, Calvo E, Papadopoulos K et al. Multi-targeted inhibition of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) pathways: A phase I study of cetuximab (C), erlotinib (E), and bevacizumab (B) in patients with solid tumors. Proc Am Soc Clin Oncol 2006;24(suppl 18):3005.