Phase I Study of E7820, an Oral Inhibitor of Integrin α-2 Expression with Antiangiogenic Properties, in Patients with Advanced Malignancies

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Abstract

**Purpose:** This phase I study was conducted to characterize the safety profile, pharmacokinetics, pharmacodynamics, dose-limiting toxicity (DLT), and the maximum-tolerated dose of E7820, a novel oral sulfonamide derivative with antiangiogenic properties, when administered to patients with advanced solid malignancies.

**Patients and Methods:** Patients received single daily doses of E7820 orally for 28 days in cycle 1, followed by a 7-day no-treatment period, after which time-uninterrupted daily dosing ensued. The starting dose of E7820 was 10 mg/d, which was increased to 20, 40, 70, 100, and 200 mg/d in cohorts of new patients.

**Results:** Thirty-seven patients [21 male; median age 65 (40–82)] were enrolled. At 100 mg/d, 1 patient experienced a DLT consisting of grade 3 neutropenia, thrombocytopenia, and elevated liver enzymes. At the 200-mg dose level, 2 patients experienced grade 4 thrombocytopenia and neutropenia. No partial or complete responses were observed; 8 patients had stable disease (>4 months), including 5 patients with protracted stable disease exceeding 6 months. Mean time to maximum plasma concentration values ranged from 1 to 12 hours, whereas mean terminal half-life values ranged from 5.6 to 8.6 hours. Flow cytometric analysis of platelet integrin α-2 expression showed a sustained greater than 50% decrease beyond day 28 in 3 of 4 patients at 200 mg, whereas moderate (<30%) decreases were observed at 70- and 100-mg dose levels.

**Conclusions:** The recommended phase II dose of E7820 is 100 mg/d, based on a fasting schedule. E7820 downregulates integrin α-2 expression in surrogate tissues (platelets) and is associated with stable disease in a wide variety of heavily pretreated malignancies. Clin Cancer Res; 17(1); 193–200. ©2011 AACR.

Introduction

Integrins are transmembrane glycoprotein receptors that play key roles in angiogenesis and are essential for endothelial cell migration, proliferation, and survival (1). They control cellular adhesion to extracellular matrix proteins found in intercellular spaces and basement membranes and also transduce signals that promote cell proliferation, migration, and cell survival (2). These effects are mediated by inhibition of caspase activation, anchoring of actin filaments to the basement membrane, and stimulation of cyclins (3, 4).

Integrins regulate angiogenesis by promoting the proliferation and survival of endothelial cells (5). Embryonic deletion of key integrins results in defects in the organization and proliferation of early vasculature and the ability of endothelial cells to form blood vessels (6, 7). The therapeutic potential of integrins as a drug target became clear when it was shown that small peptide and antibody antagonists of integrins could inhibit tumor angiogenesis, growth, and metastasis (8, 9). Several integrin inhibitors have been evaluated in clinical trials including cilengitide, a cyclic peptide antagonist of integrins αvβ3 and αvβ5 used as a treatment option for glioblastoma, and etaracizumab a humanized monoclonal antibody against αvβ3 integrin receptor (10, 11).

E7820 [N-(3-cyano-4-methyl-1H-indol-7-yl)-3-cyano-benzene-sulfonamide] is a first-in-class, orally available aromatic sulfonamide derivative that inhibits the proliferation and tube formation of human umbilical vein cells induced by either basic fibroblast growth factor or VEGF (12). This inhibition seems to be mediated through suppression of endothelial integrin α-2 mRNA and to a lesser extent integrin α-3, α-5, and β-1 mRNA expression. Preclinical studies have shown that oral administration of
E7820 inhibits tumor growth and reduces angiogenesis in subcutaneously implanted human colon, breast, and kidney cells in mice (12). Similar effects were seen in orthotopically implanted human pancreatic KP-1 and colon Colo320DM tumors (13). Furthermore, administration of E7820 resulted in a decrease in platelet integrin α2 expression at the maximum-tolerated dose. Although no objective responses were observed, E7820 treatment was associated with prolonged stable disease in a substantial number of heavily pretreated patients. Higher doses were associated with toxicities such as grade 3 or 4 thrombocytopenia, neutropenia, and bleeding.

Translational Relevance

Integrins are transmembrane glycoproteins that are important in angiogenesis and cell proliferation, migration, and survival. The realization that integrin inhibition impairs tumor growth and metastasis prompted the development of integrin inhibitors some of which are now in clinical use. E7820 is an orally available, aromatic sulfonamide derivative that has shown antitumor and antiangiogenic effects in preclinical models of human colon, breast, and renal cancer. This effect is believed to be mediated through the suppression of integrin α2 mRNA. We report the first in human phase I study of E7820 in patients with refractory solid tumors. Treatment with E7820 resulted in significant decreases in platelet integrin α2 expression at the maximum-tolerated dose. Although no objective responses were observed, E7820 treatment was associated with prolonged stable disease in a substantial number of heavily pretreated patients. Higher doses were associated with toxicities such as grade 3 or 4 thrombocytopenia, neutropenia, and bleeding.

Patients and Methods

Patient selection

Patients with solid malignancies for whom standard treatment failed or for whom adequate therapy was not available were eligible for this study. Relevant eligibility criteria included: an age at least 18 years; a Karnofsky performance status (KPS) of at least 70%; a life expectancy of at least 3 months; and adequate renal (creatinine ≤1.5 mg/dL or creatinine clearance ≥60 mL/min/1.73 m²), hematopoietic (absolute neutrophil count ≥1,500/mm³ and platelets ≥100,000/mm³) and hepatic function (bilirubin ≤1.5 mg/dL and aspartate transaminase ≤2.5 times upper limit of normal or ≤5 times upper limit if due to liver metastases). Study exclusion criteria included the following: a history of prior hypersensitivity to sulfonamide derivatives; treatment with chemotherapy or radiation involving at least 25% of hematopoietic reserves within 4 weeks; the persistence of any clinically significant side effects to prior chemotherapy or radiotherapy; clinically or radiologically progressive central nervous system metastasis, active infection with hepatitis B or C, or human immunodeficiency virus active, uncontrolled, intercurrent infection; major surgery within 4 weeks; a history of unstable ischemic disease, clinically significant thrombosis, documented vascular headache with neurologic changes; antithrombotic therapy or therapeutic anticoagulant therapy; pregnancy or breast-feeding; less than 30% of ideal weight for height and age; or other significant disease that in the investigator opinion would contraindicate the participation in the study. Patients provided written consent according to the federal and institutional requirements.

Trial design and dose escalation

Patients received daily dosing of E7820 for 28 days in cycle 1, followed by a 7-day no-treatment rest period. Thereafter, patients had continuous daily dosing. One cycle was defined as a 28-day treatment period. Patients received fixed doses of E7820 beginning at 10 mg. The 10-mg starting dose was chosen, as it represented one tenth of the exposure level (as mg/kg) that showed minimal reversible effects in dogs. Additional dose levels explored were 20, 40, 70, 100, and 200 mg. At least 3 patients were enrolled in each cohort according to the following rules: if no patient experienced DLT, the dose escalation continued; if 1 of 3 patients experienced DLT, the dose escalation continued; if 1 of 3 patients experienced DLT, an additional 3 patients were treated at the same dose level; if no additional patient experienced DLT, the dose escalation was continued; and if at least 2 patients in any cohort of up to 6 patients experienced DLT, dose escalation was terminated and additional patients were to be entered at the next lower dose level. MTD was defined as the highest dose that does not meet the DLT dose-level definition. The DLT dose level was defined as the lowest dose level at which DLT was experienced in 2 or more patients of a maximum of 6 patients.

Inpatient dose escalation was permitted on a case-by-case basis. DLT was defined as grade 3–4 nonhematologic toxicity excluding untreated nausea and vomiting and untreated diarrhea; grade 3–4 thrombocytopenia and neutropenia and failure to administer 75% or greater of the planned dose of E7820 to an individual patient due to drug-related toxicities. Patients were requested to complete a daily medication administration log and to report any side effects to study site personnel as soon as possible. Side effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3. Patients remained on study until they no longer experienced clinical benefit, had progressive disease, or experienced unacceptable toxicity.

Pharmacokinetic studies

Blood sample collection for pharmacokinetic analysis were done on cycle 1 day 1 and 28 at predose and at 0.25,
0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after drug administration. A blood sample for plasma protein binding study was also collected on cycle 1 day 1. A 24 hours urine collection for pharmacokinetic analysis was done on cycle 1 day 1 through day 2. Bioanalysis of urine and plasma samples was done using liquid chromatography-tandem mass spectrometry (LC-MS/MS) on a reversed-phase system using a C18 column and a Perkin Elmer Sciex API 3000 mass spectrometer for detection (14). The upper limit of quantitation was established at 250 ng/mL and the lower limit of quantitation was 1 ng/mL. Accuracies were within the 85% to 115% interval and precision was less than 15%. The calibration curve was linear over this concentration range. The concentration of free and bound E7820 was determined using modified Scatchard equations as previously described (15). Patients were required to fast overnight before dosing for pharmacokinetic analysis. Food effect was assessed in 7 patients receiving 100 mg of E7820 and 1 patient receiving 200 mg on day 1 of cycle 2 by fasting overnight and then consuming a standard high-fat breakfast 30 minutes before the dose of E7820 and repeating the same pharmacokinetic analysis done on day 1 of cycle 1.

Pharmacodynamic studies
Blood samples for integrin α-2 assay were collected at predose and at 6 hours postdrug dosing on day 1, at 24 hours postdrug dosing on day 2, and at predose dosing on day 28 of cycle 1. Beyond cycle 1, for each subsequent cycle, samples were collected on day 28 only. Platelet integrin α-2 expression was measured using flow cytometry as previously described (13).

Response criteria
The effect of E7820 on tumor size was assessed by tumor measurements and clinical assessments. Clinical assessments were done at screening and during every cycle. Tumor assessments (computed tomography and/or magnetic resonance imaging) were done at baseline and every 2 cycles thereafter, while on treatment, and at study termination. To ensure consistency, the same imaging technique was used throughout the study in individual patients. Criteria for evaluating tumor response were modified from the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) guidelines (16). As E7820 was expected to slow tumor growth rather than induce tumor regression, progressive disease was defined in the protocol as at least a 50% increase in the sum of the largest diameter (LD) of target lesions, taking as reference the smallest summed LD recorded since the treatment started or the appearance of 1 or more new lesions.

Results
General
Thirty-seven patients with advanced or refractory malignancies were enrolled and received 107 cycles of treatment. The overall mean duration of exposure to E7820 was 88.6 days (range, 1–448). The duration of treatment ranged from 0 to 16 cycles, with the majority of patients completing 1 to 2 cycles. All patients received at least 1 dose of E7820 and all patients were included in the safety population, pharmacokinetic, and pharmacodynamic data. Patient characteristics are summarized in Table 1. A broad range of tumor types was represented. Thirty-five patients received prior chemotherapy, including 3 patients who had previously received bevacuzimab. Fourteen patients received prior radiotherapy.

Patients were enrolled in cohorts of 3, starting with a dose of 10 mg/d. The dose was doubled up to 40 mg/d and then increased to 70 mg/d. Four patients were then enrolled at 100 mg/d (1 patient was replaced for not completing 21 days of therapy due to disease-related decreased performance status). No DLTs were noted in these 4 patients. As there were no significant changes in pharmacokinetic parameters between the 70- and 100-mg groups, the next cohort of treated patients were treated at 200 mg. Six patients were then enrolled at 200 mg/d, and 2 patients experienced DLTs at this dose level.

An additional 13 patients (17 patients in total) were enrolled at 100 mg. Only 1 patient experienced a DLT at this dose level and therefore the DLT dose level was established as 200 mg/d and the MTD and the recommended dose for further testing of E7820 was 100 mg/d based on a fasting schedule.

Safety
All treated patients were assessed for safety. The toxicities of all grades considered possibly or probably related to study medication are summarized in Table 2. Toxicities were reported at all dose levels. The most common side effects were nausea, fatigue, diarrhea, and anemia and most were Common Terminology Criteria grade 1 or 2. Grade 3 or 4 toxicities were reported only at the 100- and 200-mg dose levels. Most grade 3 or 4 toxicities were hemato logic. Toxicities leading to study discontinuation occurred in 1 patient in the 100-mg dose level and 2 patients in the 200-mg dose level, and no patients discontinued the study due to toxicities at the lower dose levels.

In the 100-mg dose level, a 74-year-old male patient with colon cancer and initially normal bone marrow function developed grade 4 thrombocytopenia and neutropenia, renal and liver dysfunction (grade 4 hyperbilirubinemia), and urosepsis 21 days after starting study medication that was subsequently fatal. A 62-year-old patient treated in the 200-mg dose level with a history of cervical cancer developed grade 3 mucositis and pancytopenia (grade 4 thrombocytopenia and neutropenia and grade 3 anemia). She later died with uncontrolled uterine bleeding secondary to advanced cervical cancer and thrombocytopenia. A 75-year-old female patient who was also treated at the 200-mg dose level, with a history of metastatic breast cancer, developed grade 2 thrombocytopenia resulting in interruption of study drug at day 14 for the remainder of cycle 1. Her platelet count returned to normal, and she restarted E7820 at 200 mg for cycle 2 of therapy but stopped at day 47 when she developed grade 4 thrombocytopenia (platelet count 23 × 10^9/L). The study medication was...
Among the 37 treated patients, 29 were evaluated for response. Fourteen patients (37.8% of total) experienced stable disease lasting 8 (n = 2, 5.4%), 16 (n = 4, 10.8%), 20 (n = 1, 3.7%), 24 (n = 2, 5.4%), 32 (n = 2, 5.4%), 40 (n = 2, 5.4%), and 52 weeks (n = 1, 3.7%) based on the protocol definition of response. On the basis of the protocol definition of response, patients with a greater than 25% but less than 50% increase in the sum of longest diameters (RECIST definition of progression) were not considered as having progressive disease. There were no complete or partial responses and 15 patients (40.5%) had progressive disease. Tumor response was not evaluated in 8 patients due to early cessation of treatment.

**Pharmacokinetics**

E7820 is rapidly absorbed following oral administration. After a single dose, mean peak plasma concentrations ranging from 0.19 μg/mL (10-mg dose level) to 1.86 μg/mL (200-mg dose level; ref. Table 3 and Fig. 1) were achieved within 2.17 to 5.33 hours postdosing [mean time to maximum plasma concentration (tmax)]. The maximum concentration (Cmax) and area under the curve (AUC) values increased with escalating doses, although less than proportional dose increases were observed over the 70- to 200-mg dose range (Fig. 1A and B). Mean AUC0–24 values ranged from 1.2 (10-mg dose level) to 21.6 (200-mg dose level) μg h/mL (Table 3 and Fig. 1B). The mean terminal half-life of E7820 ranged from 5.6 to 8.6 hours. The pharmacokinetic parameters were similar on days 1 and 28 following continuous E7820 administration (Fig. 1A and B). A small degree of drug accumulation occurred after 28 days of continuous dosing of E7820 as expected from the observed half-life. On days 1 and 28, the mean Cmax values at 100 mg/d were 1.49 and 2.07 μg/mL, respectively. The day 1 and 28 AUC values were 14.8 and 20.3 μg h/mL, respectively. In vivo assessment of protein binding showed that E7820 is highly protein bound and all patients had free concentrations of E7820 of less than 1%. As expected, less than 1% of the dose was excreted in the urine. A summary of E7820 pharmacokinetics after a single, oral dose of E7820 is presented in Table 3. The patient treated with 200 mg of E7820 who developed grade 4 thrombocytopenia and uncontrolled vaginal hemorrhage on day 14 of treatment had an abnormally high Cmax after cycle 1 day 1 of 2.65 μg/mL compared with a mean of 1.86 μg/mL for all the 200-mg dose patients.

The derived pharmacokinetic parameters for cycle 1 day 1 (fasting) and cycle 2 day 1 (fed) subjects were compared. The geometric mean AUC0–τ increased by approximately 58% and the geometric mean Cmax increased by approximately 43% during the fed period for subjects in the 100-mg dose group. A full study investigating the safety and pharmacokinetics of E7820 under fed conditions is planned.

**Pharmacodynamics**

Cell-surface expression of integrin α-2 on circulating platelets at predose baseline was compared with that found predose on cycle 1 day 28. As shown in Figure 2, expression

### Table 1. Patient characteristics

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<th>No. (N = 37)</th>
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</tr>
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</tr>
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<tr>
<td>80%</td>
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<td>100%</td>
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<td>5.4</td>
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<tr>
<td>Carcinoid</td>
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<td>5.4</td>
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<tr>
<td>Othera</td>
<td>8</td>
<td>21.6</td>
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</tr>
</tbody>
</table>

**Table 1. Patient characteristics**

4Melanoma, Ewing sarcoma, breast, cervix, thyroid, penis, anus, and peritoneal.

discontinued and her platelet count returned to normal 3 weeks later. This was considered a DLT because the subject received less than 75% of the planned dose of E7820 due to thrombocytopenia during cycle 1.

Six patients died during the study or within 30 days after the last treatment, 4 due to progressive disease, 1 due to sepsis, and 1 due to vaginal hemorrhage as described earlier.

**Tumor response**

Among the 37 treated patients, 29 were evaluated for response. There were no objective responses. Among the 37 treated patients, 29 were evaluated for response. Fourteen patients (37.8% of total) experienced stable disease lasting 8 (n = 2, 5.4%), 16 (n = 4, 10.8%), 20 (n = 1, 3.7%), 24 (n = 2, 5.4%), 32 (n = 2, 5.4%), 40 (n = 2, 5.4%), and 52 weeks (n = 1, 3.7%) based on the protocol definition of response. On the basis of the protocol definition of response, patients with a greater than 25% but less than 50% increase in the sum of longest diameters (RECIST definition of progression) were not considered as having progressive disease. There were no complete or partial responses and 15 patients (40.5%) had progressive disease. Tumor response was not evaluated in 8 patients due to early cessation of treatment.
### Table 2. Toxicities considered E7820 related

**E7820 daily dose at start date of toxicity (no. of patients treated)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>10 mg (3)</th>
<th>20 mg (4)</th>
<th>40 mg (3)</th>
<th>70 mg (4)</th>
<th>100 mg (17)</th>
<th>200 mg (6)</th>
<th>Overall (37)</th>
</tr>
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<tbody>
<tr>
<td>1/2</td>
<td>1 (25)</td>
<td>4 (23)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>6 (16)</td>
<td>1 (3)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>3/4</td>
<td>1 (6)</td>
<td>2 (33)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>2 (33)</td>
<td>3 (8)</td>
<td></td>
</tr>
</tbody>
</table>

**Hematologic toxicity**

- Anemia: 1 (25) 4 (23) 1 (17) 1 (17) 6 (16) 1 (3)
- Neutropenia: 1 (6) 2 (33) 3 (8)
- Thrombocytopenia: 1 (6) 2 (33) 3 (8)

**Nonhematologic toxicity**

- Abdominal pain: 1 (33) 1 (6) 2 (5) 4 (11)
- Constipation: 2 (67) 1 (25)
- Diarrhea: 2 (67) 3 (75) 1 (25) 4 (23) 3 (50) 13 (35)
- Dry mouth: 1 (6) 1 (3)
- Nausea: 2 (67) 2 (50) 3 (100) 2 (50) 6 (35) 16 (43)
- Stomatitis: 1 (33) 1 (25) 1 (6) 1 (17) 3 (8) 2 (6)
- Vomiting: 1 (33) 1 (33) 4 (23) 6 (16)
- Chest pain: 1 (6) 1 (17) 2 (5)
- Fatigue: 2 (66.6) 1 (25) 1 (33) 1 (25) 7 (41) 2 (33) 14 (38)
- Peripheral edema: 2 (12) 1 (17) 2 (5)
- Pyrexia: 1 (6) 1 (17) 2 (5)
- Palpitations: 2 (12) 1 (17) 3 (8)
- Elevated alanine aminotransferase: 1 (25) 1 (6) 1 (17) 3 (8)
- Elevated aspartate aminotransferase: 1 (25) 2 (12) 1 (17) 4 (11)
- Elevated alkaline phosphatase: 1 (33) 1 (25) 1 (6) 1 (17) 4 (11)
- Hyperbilirubinemia: 1 (6) 1 (17) 1 (3) 1 (3)
- Vaginal hemorrhage: 1 (3) 1 (3)
- Hemoptysis: 1 (6) 1 (17) 1 (3)

**NOTE:** All toxicities that were felt to be possibly, probably, or definitely related to E7820. The values given are number of patients (% of patients) with toxicity.
of integrin α-2 was decreased as a function of increasing E7820 dosing. Decreases in platelet integrin α-2 expression were not observed in the 10 and 20 mg/d cohorts, however, patients treated at 100 mg showed a decrease of approximately 25% by day 28. Consistent with known kinetics of platelet turnover, decreased integrin α-2 expression was not observed on cycle 1 day 8 (8 days after beginning dosing; data not shown), whereas reductions in integrin α-2 expression seen at the end of cycle 1 were retained in the 100- and 200-mg cohorts 8 days after cycle 1 dosing was stopped (samples obtained cycle 2 day 1; data not shown).

Discussion

This trial shows that E7820 can be safely administered to patients with advanced cancer at doses up to 100 mg/d. Pharmacokinetic analysis showed that E7820 is rapidly adsorbed following oral administration, with an apparent median terminal elimination half-life of less than 8.6 hours. Hematologic abnormalities (neutropenia and thrombocytopenia) were the most common DLTs. Platelet integrins are necessary for platelet aggregation and clot formation (17). Preclinical studies have shown that oral administration of E7820 induced a dose-dependent reduction in platelet integrin α-2 expression as measured by flow cytometry, but it did not affect the absolute platelet count (13). Bleeding episodes did occur in this study in association with thrombocytopenia, and hemorrhagic events will need to be monitored closely in future studies of E7820. The effects of E7820 on platelet function as measured by the PFA 100 system are being studied in the phase II study of E7820 in combination with cetuximab, and so far no toxicities with E7820 have been observed.

Other adverse events were generally mild to moderate and reversible. Gastrointestinal (nausea, diarrhea, constipation, abdominal pain, and vomiting) and constitutional side effects (fatigue) were the most commonly reported toxicities with E7820.

Prolonged stable disease was seen at all dose levels but was more common at higher doses. Stable disease lasting greater than 6 cycles was observed in patients with bladder, colon, carcinoid, melanoma, and non–small cell lung

Table 3. Relevant E7820 pharmacokinetic parameters (mean values ± SD)

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<th>Dose, mg/d</th>
<th>No. of patients</th>
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<th>AUC_0–24, μg h/mL</th>
<th>t_1/2</th>
<th>V_ss/f, L</th>
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<td>100</td>
<td>17</td>
<td>1.49 ± 0.68</td>
<td>3.21 ± 3.12</td>
<td>14.8 ± 7.7</td>
<td>6.58 ± 1.71</td>
<td>76.7 ± 46.5</td>
<td>8.4 ± 5.2</td>
</tr>
<tr>
<td>200</td>
<td>6</td>
<td>1.86 ± 0.74</td>
<td>3.42 ± 3.34</td>
<td>21.6 ± 10.5</td>
<td>8.60⁵</td>
<td>75.2⁵</td>
<td>6.1⁵</td>
</tr>
</tbody>
</table>

Abbreviations: AUC_0–24, area under the curve; t_1/2, half-life; V_ss, volume of distribution; Cl, clearance.

¹Mean t_max for each group.

²No standard deviations are available for the last 3 parameters.

Figure 1. Maximum plasma concentrations (C_max) and AUC of E7820 after single doses. A, the indicated amount of E7820 was administered to fasted subjects and plasma E7820 concentrations were determined as described in the Patients and Methods section. Plasma C_max were determined and the mean values (SD) for C_max after dosing on day 1 (*) and day 28 (■) were calculated. B, the indicated amount of E7820 was administered to fasted subjects and plasma E7820 concentrations were determined as described in the Patients and Methods section. AUC of E7820 was determined and the mean values for AUC after dosing on day 1 (*) and day 28 (■) were calculated.
targeting angiogenesis. As E7820 is unlikely to cause early tumor shrinkage, measurement of biomarkers such as integrin α-2 expression may instead provide evidence of an early objective vascular response. Our exploratory pharmacodynamic analysis suggests that at the MTD, E7820 inhibits the expression of integrin α-2 in a normal tissue surrogate when administered under clinical conditions and that expression of platelet integrin α-2 is readily measurable in patients receiving E7820. These results have been confirmed in a small dose-escalation study of E7820 administered in combination with cetuximab (19). Larger patient numbers of patients would be needed to determine whether treatment-related decreases in platelet integrin α-2 expression are statistically significant and correlate with clinical response. The optimal use of antiangiogenesis agents is likely to be in combination with other chemotherapies or radiotherapy as shown by the benefit of bevacizumab in combination with standard chemotherapy in metastatic colorectal and lung cancer (20, 21). Potential synergism of E7820 with standard chemotherapy will be investigated in future studies. Cross talk between integrin α-2 expression and EGFR pathways has been shown, and E7820 is now being investigated in combination with cetuximab in advanced malignancies (22). Preliminary results suggest that the combination is well tolerated and is associated with stable disease in a proportion of patients (19).

This trial suggests that up to 100 mg/d of E7820 has a reasonable safety profile and may be associated with disease stabilization in a wide variety of heavily pretreated malignancies. On the basis of these promising findings, E7820 is being now being investigated in a phase II study in combination with the epidermal growth factor inhibitor cetuximab in colorectal cancer (19). Targeting of integrin α-2 expression represents a novel mechanism of inhibiting angiogenesis and is a promising new strategy in anticancer treatment.

Disclosure of Potential Conflicts of Interest


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Phase I Study of E7820, an Oral Inhibitor of Integrin α-2 Expression with Antiangiogenic Properties, in Patients with Advanced Malignancies

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