# Phase I Safety and Pharmacokinetic Study of Recombinant Human Anti-Vascular Endothelial Growth Factor in Patients With Advanced Cancer

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***Purpose:*** **We investigated the safety and pharmacokinetics of a recombinant human monoclonal antibody to vascular endothelial growth factor (rhuMAb VEGF) in patients with cancer.**

***Patients and Methods:*** **Cohorts of patients with metastatic cancer having failed prior therapy entered a phase I trial of rhuMAb VEGF administered by a 90-minute intravenous infusion at doses from 0.1 to 10.0 mg/kg on days 0, 28, 35, and 42. Patients underwent pharmacokinetic sampling on day 0 and had serum samples obtained during the subsequent 28 days. Response assessment was carried out on days 49 and 72.**

***Results:*** **Twenty-five patients with a median Eastern Cooperative Oncology Group performance status of 0 were accrued. There were no grade III or IV adverse events definitely related to the antibody. There were three episodes of tumor-related bleeding. Infusions of rhuMAb VEGF were well tolerated without significant toxicity. Grades I and II adverse events possibly or probably related to study drug included asthenia, headache, and nausea. Pharmacokinetics revealed a linear profile with a half-life of 21 days. There were no objective responses, though 12 patients experienced stable disease over the duration of the study.**

***Conclusion:*** **rhuMAb VEGF was safely administered without dose-limiting toxicity at doses ranging up to 10 mg/kg. Multiple doses of rhuMAb VEGF were well tolerated, and pharmacokinetic studies indicate that doses of ≥ 0.3 mg/kg have a half-life similar to that of other humanized antibodies. Subsequent trials will explore rhuMAb VEGF alone and in combination chemotherapy.**

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ANGIOGENESIS, OR new blood vessel formation, is critical to tumor growth, invasion, and metastasis.[1] Several humoral factors stimulate angiogenesis. These factors act either by inducing the enzymatic breakdown of the perivascular basement membrane or by inducing proliferation and chemotaxis of endothelial cells. Both components are critical for successful neovascularization, and the inhibition of either arm has been hypothesized as having a potential antitumor or antimetastatic effect on malignant cells. Vascular endothelial growth factor (VEGF) is a 43- to 46-kd glycoprotein that induces the proliferation and migration of vascular endothelial cells.[2,3] These activities are mediated via the two receptors for VEGF, flt-1 and KDR, which are found predominantly on vascular endothelial cells.[2] In preclinical models, VEGF is a potent neovascularization agent for both normal and malignant microvasculature.[4,5]

Many malignant cells produce VEGF, which serves as an autocrine factor for the induction of neovascularization. Several studies have demonstrated a correlation between high levels of VEGF and increased risk of metastatic disease and overall poor prognosis in a variety of malignancies including non–small-cell lung cancer and other cancers. In addition, increased expression of VEGF by malignant tumors is associated with a more invasive phenotype.[6-9] In preclinical animal models, the inhibition of VEGF is associated with stabilization of established tumors.[10] When administered in conjunction with chemotherapy, a synergistic antitumor activity can be seen in preclinical models.[11]

Recombinant human monoclonal antibody (rhuMAb) VEGF is a humanized monoclonal antibody that was generated by engineering the VEGF binding residues of a murine neutralizing antibody into the framework of a normal human immunoglobulin G (IgG).[12] This antibody binds and neutralizes all biologically active forms of VEGF (including VEGF165, VEGF121, and the thrombin split fragment VEGF110), because it recognizes the binding sites for the two VEGF receptors. The use of anti-VEGF antibodies has been extensively studied in preclinical in vivo models and has demonstrated an inhibition of tumor growth in a dose-dependent manner.[13] We now report on the first phase I study with anti-VEGF, which was performed to evaluate its safety and pharmacokinetic profile in patients

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with relapsed and refractory malignancies. These studies demonstrate that rhuMAb VEGF is safe in the doses and schedule used here and that serum concentrations attained with both single and multiple doses successfully reproduce concentrations necessary for antitumor activity based on preclinical models.

## PATIENTS AND METHODS

### *Inclusion Criteria*

From May 1, 1997, through July 31, 1997, 25 patients with measurable or assessable solid tumor malignancies were enrolled onto this phase I trial. Eligibility criteria included refractory advanced solid tumors for which no standard curative therapy existed, Eastern Cooperative Oncology Group (ECOG) performance status $\leq 1$, normal hematologic function as demonstrated by an absolute neutrophil count greater than 1,500 cells/$\mu$L, hemoglobin greater than 9 g/dL (transfusion allowed), and a platelet count greater than 100,000/$\mu$L, as well as normal renal function (creatinine less than 1.5 mg/dL) and hepatic function (bilirubin $<$ 1.5 times the upper limit of institutional normal). Patients were excluded if they had a known history of CNS metastatic disease with evidence of residual recurrent disease at study entry, had received chemotherapy or immunotherapy within the prior 4 weeks before study entry, or had taken any noncorticosteroidal anti-inflammatory agents within 10 days of study entry. Patients were also excluded if they had undergone invasive surgical procedures including organ biopsies within 2 weeks of study entry or were pregnant or lactating. The institutional review boards for the three participating centers approved the protocol, and voluntary written informed consent was obtained from all patients.

### *Study Drug Formulation and Administration*

RhuMAb VEGF was supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 100-mg (10 mg/mL) glass vial contained rhuMAb VEGF with histidine, trehalose, polysorbate 20, and sterile water for injection, USP, pH 5.5. Vials contained no preservative and were for single use only. Appropriate concentrations of rhuMAb VEGF were diluted into $D_5W$ for infusion. Patients received their infusion of rhuMAb VEGF over 90 minutes by calculated pump and underwent evaluation of vital signs including blood pressure, pulse, respiratory rate, and temperature before treatment, at intervals during infusion, and hourly for 3 hours after infusion. After their first infusion, patients were hospitalized for 24 hours, during which time they underwent serial pharmacokinetic sampling after infusion. During cycle 1 (days 0 to 28), patients underwent pharmacokinetic evaluation on day 0 as noted above and then subsequently had samples drawn on days 2, 4, 7, and 10 and weekly during routine visits for the duration of the study. After subsequent infusions on days 28, 35, and 42, patients were observed for 3 hours and subsequently discharged for outpatient follow-up. All patients were seen weekly during the 10 weeks of study therapy and follow-up and underwent evaluation with physical examination including ECOG performance status, vital signs, and laboratory evaluation with complete blood count with manual differential, chemistry evaluation, prothrombin time/partial thromboplastin time, and urinalysis. Toxicities were monitored using the National Cancer Institute Common Toxicity Criteria adjusted for biologic response modifiers.

Response assessment using either radiographic or physical examination evaluation was carried out on days 49 and 72. Patients with objective responses were to be offered continued therapy on a separate extension study.

### *VEGF and Anti-VEGF Levels*

Serum rhuMAb VEGF concentrations were determined using an enzyme-linked immunosorbent assay (ELISA), which uses truncated recombinant human VEGF for capture and a goat antibody to human IgG conjugated to horseradish peroxidase for detection. Concentrations of less than 78 ng/mL were considered less than reportable (LTR). Measurement of the serum levels of VEGF was performed with the ELISA using a monoclonal antibody to the heparin-binding domain of VEGF as both capture and detection. Therefore, it sees only full-length forms that contain this domain, ie, VEGF 165 and higher molecular weight forms. This format was chosen as it can detect free VEGF and VEGF bound to the therapeutic drug, rhuMAb VEGF. The LTR for this assay for VEGF is 20 pg/mL. Free VEGF was measured by passing serum through a Staphylococcus Protein A column to remove all IgGs, including antibody-bound VEGF. The flow-through fraction is measured as free VEGF. Percentage free VEGF (% Free VEGF) is determined by using this free VEGF as a percentage of total VEGF as assayed in the unfractionated serum. Anti rhuMAb VEGF antibodies were assayed by ELISA using rhuMAb VEGF Fab for detection and a goat antibody to human IgG conjugated to horseradish peroxidase for detection; a titer of 2 was considered the sensitivity limit.

### *Statistical Analysis*

This phase I study accrued five patients per dose level and planned to enroll an additional three patients if dose-limiting toxicity (defined as a grade III or greater adverse event using the biologic response modifier-adjusted common toxicity criteria) occurred in two patients in a given cohort. The toxic dose was defined as the dose level at which three or more patients in a given cohort experienced dose-limiting toxicity. The maximally tolerated dose was defined as one dose level below the toxic dose assuming that this level was well tolerated and fewer than two patients in the cohort experienced a dose-limiting toxicity.

Comparison of VEGF, rhuMAb VEGF, and other laboratory studies were performed using a two-sided paired student's *t* test. Individual and mean serum rhuMAb VEGF concentration-time data were plotted by dose group. Serum rhuMAb VEGF disposition was analyzed by compartmental methods. Individual parameter estimates were tabulated and summarized (mean, SD, range). RhuMAb VEGF pharmacokinetics was assessed for dose proportionality by graphic examination.

Serum VEGF concentration-time data were analyzed by noncompartmental methods and summarized by time and dose groups. Results are presented as the mean, SD, and minimum and maximum values.

## RESULTS

### *Patient Characteristics*

Twenty-five patients (eight male, 17 female) were accrued to this study. All were eligible and assessable for safety. Only one patient, treated at the 3-mg/kg dose level, did not receive all four doses of rhuMAb VEGF because of a hemorrhage into a previously undiagnosed cerebral metastasis during the month after the single dose administration. The diagnoses and demographic data are presented in Table 1. The median ECOG performance status was 0

**Table 1. Patient Characteristics**

| Characteristic | | No. of Patients |
|---|---|---|
| Total patients | | 25 |
| Men/women | | 8/17 |
| Age, years | | |
| Median | 55 | |
| Range | 21-70 | |
| ECOG performance score | | |
| 0 | | 17 |
| 1 | | 8 |
| Cancer type | | |
| Sarcoma | | 8 |
| Renal | | 7 |
| Breast | | 5 |
| Lung | | 2 |
| Other | | 3 |
| Prior therapy | | |
| Chemotherapy | | 22 |
| Radiation therapy | | 10 |
| Immunotherapy | | 10 |

(range, 0 to 1), and the mean age was 51 years (range, 21 to 70 years).

*Safety*

In general, rhuMAb VEGF was well tolerated at all doses studied. There were no Common Toxicity Criteria (CTC) grade 3 or 4 infusion-related toxicities. A small number of patients developed grade 1 or 2 adverse events characterized by asthenia, headache, nausea, or low-grade fever on the first day of rhuMAb VEGF administration (Table 2). Adverse events over the course of the entire study were similar in nature and predominantly of grades 1 to 2 in severity. These events are outlined in Table 3. Fever occurred in 10 patients, though the relationship to the study drug administration could not be determined in all cases. There was no relationship between the severity of the fever and dose of the rhuMAb VEGF.

No clinically significant changes were seen in biochemical, coagulation, or hematologic parameters. Although surgical interventions were limited to necessary procedures only, no patient demonstrated objective impairment of wound healing as a result of rhuMAbVEGF therapy. Minor changes in blood pressure were noted to be associated with rhuMAb VEGF administration. Systolic and diastolic blood pressures in patients treated at the 3 and 10 mg/kg dose levels increased an average of more than 10 mm Hg at some point during therapy. No significant changes in other vital signs were noted.

Adverse events graded as 3 or 4 on the CTC scale occurred in four patients (Table 3). These included a patient with anemia at the 0.1 mg/kg dose level and one patient with

**Table 2. Adverse Events Occurring in Over 20% of Patients on rhuMAb VEGF (all grades and attributions for 25 patients treated)**

| | No. of Subjects | |
|---|---|---|
| Adverse Event | Grade 1-2 | Grade 3-4 |
| Asthenia | 18 | 0 |
| Headache | 11 | 0 |
| Fever | 10 | 0 |
| Rash | 9 | 0 |
| Oral symptoms | 8 | 0 |
| Nausea | 7 | 0 |
| Arthralgias | 7 | 0 |
| Pain | 7 | 0 |
| Cough | 6 | 0 |
| Emesis | 6 | 0 |
| Dyspnea | 5 | 1 |

dyspnea at the 0.3 mg/kg dose level. In both of these cases, the events were attributable to progression of the patient's underlying malignancy. In addition, there were two episodes of serious bleeding, both at the 3.0 mg/kg dose level. The first of these patients was a 29 year-old female with a history of hepatocellular carcinoma. The patient had undergone a previous trisegmentectomy and subsequently developed multiple pulmonary metastases. She was treated with combination chemotherapy including carboplatin, doxorubicin, and cyclosporine with her best response being progressive disease. She received her first dose of rhuMAb VEGF at a dose of 3.0 mg/kg and on day 14 of cycle 1 was bicycling when she experienced a grand mal seizure and an acute cerebrovascular accident. She was evaluated with a CT scan of the head that demonstrated a cerebrovascular bleed and underwent emergent surgery for the evacuation of the hemorrhage. Pathologic evaluation of the surgical specimen revealed residual hepatocellular carcinoma consistent with hemorrhage into a previously unrecognized brain metastasis. An extensive review of the literature revealed a high-rate of tumor associated hemorrhage as the presenting sign in up to 87.5% in one series.[14] Based on these findings, it was decided in conjunction with the sponsor that the event was disease-related.

The second patient was a 38-year-old female with a primary diagnosis of an epithelioid sarcoma of the right thigh. Sites of disease included a large right thigh mass and multiple pulmonary metastases. She had received extensive prior therapy with multiple chemotherapy regimens as well as external beam radiation therapy and brachytherapy. On approximately study day 39, she noted increasing pain and swelling in her right thigh with discoloration of the tumor area. This area continued to expand and eventually ruptured resulting in a severe hemorrhagic complication requiring local therapy for control. This patient also experienced an

**Table 3. Adverse Event Profile (all grades)**

| Dose (mg/kg) | 0.1 | | 0.3 | | 1.0 | | 3.0 | | 10.0 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Grade | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 | 1-2 | 3-4 |
| Anemia | | 1 | | | | | | | | |
| Anxiety | | | | | | | | | | |
| Constipation | 2 | | | | 2 | | 1 | | | |
| Diarrhea | 1 | | | | | | 2 | | | |
| Dysphagia | | | 1 | | 1 | | | | 1 | |
| Dyspnea | | | | 1 | | | | | | |
| Edema | | | | | | | | | 2 | |
| HTN | | | 1 | | | | 1 | | | |
| IC bleed | | | | | | | | 1 | | |
| Myalgias | 1 | | | | | | | | 1 | |
| Nightmares | 1 | | 1 | | | | 1 | | | |
| Sinus | | | | | 2 | | 1 | | 2 | |
| Sweats | | | | | | | | | | |
| Tumor Hem | | | | | | | | 1 | | |

NOTE. All toxicities are listed, regardless of their potential relationship to study drug administration.
Abbreviations: HTN, hypertension; IC, intracerebral; Hem, hemorrhage.

uncomplicated episode of hemoptysis on day 57. Both of these episodes were related to the necrosis of existing tumors and were not believed to be reflect adverse events related to the study drug.

Based on the dose escalation schema defined in the protocol, expansion of the cohort was deemed as indicated if the two serious adverse events occurred in the first 28 days of the study. Although the event related to the CNS metastasis bleed was within this 28-day period, the second occurred beyond this point and therefore did not qualify to indicate a need for cohort expansion.

Two other patients (liposarcoma and breast cancer) reported episodes of minor hemoptysis. These occurred on days 57 and 2 of therapy, respectively, and spontaneously resolved. Both patients had recognized pulmonary metastases, and in both cases, it was believed that the bleeding was related to their underlying disease, though an association to the study drug could not be ruled out. Neither of the two premenopausal women experienced menstrual abnormalities during or after participation in this study.

### *Efficacy*

No patient treated on this phase I study experienced an objective partial or complete response. One patient with renal cell carcinoma, treated at the 10 mg/kg dose level, experienced a minor response with an approximately 20% to 30% reduction in the sum of perpendicular diameters of pulmonary and lymph node metastases. Among 23 patients who were assessable for response at 70 days, 12 experienced stable disease over the 70-day study interval, with the remaining 11 patients demonstrating progressive disease. The patients with stable disease included five with renal cell cancer and were otherwise distributed among the other previously noted diagnoses. Aside from the higher number of patients with renal cell cancer, no other definable association between stabilization and sites of metastases, age, sex, or prior therapy could be identified. The small numbers of patients, heterogeneity of tumor types, patient characteristics and durations of therapy, and lack of an established definition of stable disease preclude the determination of a meaningful association between the dose of rhuMAb VEGF dose and disease stability. Baseline serum VEGF levels in the patients with stable disease ranged from LTR to 281 pg/mL, with a mean of 98.4 compared with those patients with progressive disease who had baseline values of LTR to 122 pg/mL with a mean of 41.6. The patient with the minor response treated at the 10.0 mg/kg dose level was followed off therapy and progressed within 4 to 5 months of completion of treatment. He was subsequently retreated with rhuMAb VEGF and demonstrated another minor response with shrinkage of multiple pulmonary metastases and mediastinal nodal disease that lasted for 8 months until new bone metastases were identified. One additional patient with renal cell cancer developed objective minor regression of multiple hepatic metastases after completion of rhuMAb VEGF therapy (no change in an intact renal primary tumor). This response lasted 11 months before progressive disease with new bone metastases were identified.

### *Antibodies to rhuMAb VEGF*

No patient enrolled onto the trial developed antibodies to rhuMAb VEGF during the period of measurements (70 days).

**Table 4. Pharmacokinetic Profile for Single Dose rhuMAb VEGF**

| | Cmax (mcg/ml) | CL (ml/kg/day) | MRT | $AUC_{inf}$ (day*μg/mL) |
|---|---|---|---|---|
| 0.1 mg/kg | | | | |
| 1 | 3.97 | 2.3 | 10.9 | 43.5 |
| 2 | 1.92 | 16.4 | 3.14 | 6.09 |
| 3 | 2.68 | 3.8 | 9.79 | 26.3 |
| 4 | 1.44 | 16.6 | 4.16 | 6.03 |
| 5 | 2.37 | 6.55 | 7.77 | 15.3 |
| 0.3 mg/kg | | | | |
| 6 | 5.61 | 5.94 | 8.98 | 50.5 |
| 7 | 6.18 | 4.7 | 10.3 | 63.8 |
| 8 | 7.72 | 3.83 | 10.9 | 78.3 |
| 9 | 4.8 | 9.58 | 6.49 | 31.3 |
| 10 | 8.91 | 3.45 | 15.7 | 86.9 |
| 1.0 mg/kg | | | | |
| 11 | 29.9 | 4.17 | 7.99 | 240 |
| 12 | 39.3 | 2.62 | 16.7 | 382 |
| 13 | 23 | 3.87 | 17.1 | 259 |
| 14 | 24.6 | 4.13 | 17.6 | 242 |
| 15 | 21 | 2.95 | 24.6 | 339 |
| 3.0 mg/kg | | | | |
| 16 | ND | ND | ND | ND |
| 17 | 89.6 | 1.75 | 19.1 | 1720 |
| 18 | 75 | 2.07 | 30 | 1450 |
| 19 | 52.5 | 5.46 | 10.4 | 550 |
| 20 | 91.5 | 4.5 | 12.8 | 666 |
| 10.0 mg/kg | | | | |
| 21 | 186 | 4.02 | 13.3 | 2480 |
| 22 | 206 | 4.06 | 12 | 2490 |
| 23 | 294 | 1.91 | 17.7 | 5230 |
| 24 | 277 | 2.44 | 27.2 | 4100 |
| 25 | 294 | 1.66 | 54.3 | 6010 |

Abbreviations: Cmax, maximal concentration; CL, clearance; MRT, mean resonance time; AUCinf, area under the curve; ND, not done.

*Pharmacokinetic Studies of rhuMAb VEGF*

After administration of the first rhuMAb VEGF dose, mean observed $C_{max}$ ranged from 2.80 μg/mL for the 0.1 mg/kg group to 284 μg/mL for the 10 mg/kg group (Table 4). These changes were dose-related and there was no significant accumulation of rhuMAbVEGF during the multidosing portion of the study (data not shown). Mean kinetic profiles of the rhuMAb VEGF pharmacokinetics for the multiple administration portion of the study are show in Fig 1.

The mean rhuMAb VEGF clearance for the 0.1 mg/kg dose group (9.29 mL/kg/d) was higher than the clearance for all other dose groups (range 2.75-5.07 mL/kg/d); the larger mean resulted primarily from two of the patients whose clearances were greater than 14 mL/kg/d. Clearance values for the other three subjects were consistent with those estimated at higher doses. Over the range of doses of 0.3 to 10.0 mg/kg, the kinetics of rhuMAb VEGF seems to be linear, with a $t_{1/2}$ of approximately 21 days. Overall, the pharmacokinetic profile indicates that when rhuMAb VEGF was administered once followed by a 28-day washout period and then weekly for 3 weeks at doses ranging from 0.1 to 10 mg/kg, the disposition was characterized by a low clearance and a volume of distribution consistent with limited extravascular distribution.

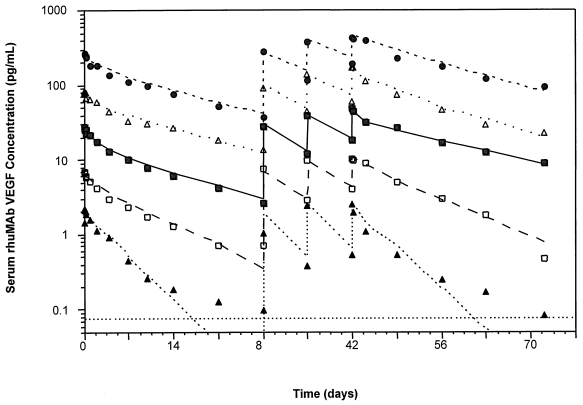


**Fig 1. Mean serum rhuMAb VEGF concentrations. Serum levels of rhuMAb VEGF after serial administrations (days 0, 28, 35, and 42) at doses of 0.1 (closed triangle), 0.3 (open square), 1.0 (closed square), 3.0 (open triangle), and 10.0 (closed circle) mg/kg. Cohorts consist of 4 to 5 patients.**

*Serum Levels of VEGF*

Before rhuMAb VEGF administration, individual serum VEGF concentrations ranged from less than 20 to 281 pg/mL. The two patients with major hemorrhagic events had pretreatment serum VEGF levels of 30.6 and 122 pg/mL, respectively. The latter of these was slightly elevated compared with the mean values across the different dose levels, though higher baseline levels were seen in a number of patients. Among the seven patients with renal cell carcinoma, the baseline serum VEGF concentrations ranged from LTR to 218 pg/mL (median 56.9 pg/mL). An increase in serum total VEGF concentration was observed across all dose groups; the increase was more consistent with doses of greater than 1.0 mg/kg with serum levels two to four times higher for the 1.0, 3.0, and 10 mg/kg dose groups than for the 0.1 and 0.3 mg/kg dose groups (Table 5). Free serum VEGF concentrations were found to be reduced and, at doses of ≥ 0.3 mg/kg, were below the detectable limit of the assay after the administration of rhuMAb VEGF and remained undetectable for the duration of the study (data based on eight patients not shown; personal communication, 2000, D. Fei, PhD, Genentech, Inc, South San Francisco, CA).

## DISCUSSION

The use of antiangiogenic agents as anticancer therapy has been the focus of numerous clinical investigations over the past several years. The ability to inhibit neovascularization and prevent tumor growth and metastases has the

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