Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

Cancer Therapy: Clinical

Clinical Cancer Research

Safety, Pharmacokinetics, and Pharmacodynamics of AMG 102, a Fully Human Hepatocyte Growth Factor–Neutralizing Monoclonal Antibody, in a First-in-Human Study of Patients with Advanced Solid Tumors

Michael S. Gordon[1], Christopher J. Sweeney[2], David S. Mendelson[1], S. Gail Eckhardt[3], Abraham Anderson[4], Darrin M. Beaupre[4], Daniel Branstetter[4], Teresa L. Burgess[4], Angela Coxon[4], Hongjie Deng[4], Paula Kaplan-Lefko[4], Ian M. Leitch[4], Kelly S. Oliner[4], Lucy Yan[4], Min Zhu[4], and Lia Gore[3]

Abstract

Purpose: The aims were to assess the safety, pharmacokinetics, maximum tolerated dose, and antitumor activity of AMG 102, a fully human hepatocyte growth factor/scatter factor (HGF/SF)–neutralizing monoclonal antibody, in patients with solid tumors.

Experimental Design: Patients (N = 40) with refractory advanced solid tumors were enrolled into six sequential dose-escalation cohorts (0.5, 1, 3, 5, 10, or 20 mg/kg AMG 102 i.v. every 2 weeks) and a dose-expansion cohort (20 mg/kg AMG 102 every 2 weeks). Safety, anti–AMG 102 antibody formation, pharmacokinetics, tumor response, and exploratory biomarkers were assessed.

Results: AMG 102 was well tolerated up to the planned maximum dose of 20 mg/kg, and the maximum tolerated dose was not reached. Treatment-related adverse events were generally mild and included fatigue (13%), constipation (8%), nausea (8%), vomiting (5%), anorexia (5%), myalgia (5%), and hypertension (5%). Two patients experienced dose-limiting toxicities: one patient (0.5 mg/kg cohort) experienced grade 3 hypoxia and grade 3 dyspnea and one patient (1 mg/kg cohort) experienced grade 3 upper gastrointestinal hemorrhage. No anti–AMG 102 antibodies were detected, and AMG 102 had linear pharmacokinetics within the dose range investigated. Sixteen of 23 (70%) evaluable patients had a best response of stable disease with progression-free survival ranging from 7.9 to 40 weeks. Circulating levels of the biomarker HGF/SF (bound and unbound) increased in a dose-dependent manner, whereas soluble c-Met concentrations were generally similar across doses.

Conclusions: AMG 102 is safe and well tolerated, has a favorable pharmacokinetic profile, and will be further investigated as a monotherapy and in combination with other agents. *Clin Cancer Res; 16(2); 699–710. ©2010 AACR.*

Hepatocyte growth factor/scatter factor (HGF/SF) and its receptor c-Met regulate multiple cellular functions, including proliferation, survival, motility, and morphogenesis, particularly during wound healing and embryogenesis (1–4). Aberrant tumor expression of HGF/SF or c-Met has been linked to poor prognosis in multiple malignancies, including breast cancer, osteosarcoma, colorectal carcinoma, and glioma (5–9). HGF/SF-dependent autocrine and paracrine growth loops (6), overexpression of c-Met (7), activating mutations in c-Met (10–13), and amplifications of the *c-Met* gene resulting in the overexpression of c-Met (14–16) have also been observed in several tumor types. Taken together, these observations have made the HGF/SF–c-Met axis an important target for therapeutic intervention (17). In preclinical studies, HGF/SF antagonists inhibited tumor xenograft growth as well as *in vitro* tumor cell survival, migration, and invasion (18, 19). Several approaches targeting c-Met (small-molecule and peptide inhibitors, RNA-directed inhibitors, and monoclonal antibodies) have also shown antitumor activity in preclinical studies (20).

AMG 102 is a fully human HGF/SF-neutralizing monoclonal antibody (IgG2) that specifically targets HGF/SF. In cynomolgus monkeys, AMG 102 exhibited linear pharmacokinetics following a single dose, and there were no treatment-related cardiovascular, respiratory, or central nervous system toxicities (21). In addition, AMG 102 was well tolerated up to a dose of 150 mg/kg once weekly for up to 9 months in this species (22). The antitumor activity and

Authors' Affiliations: [1]Premiere Oncology of Arizona, Scottsdale, Arizona; [2]Indiana University School of Medicine, Indianapolis, Indiana; [3]University of Colorado Cancer Center, Aurora, Colorado; and [4]Amgen Inc., Thousand Oaks, California

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Michael S. Gordon, Premiere Oncology of Arizona, 9055 East Del Camino, Suite 100, Scottsdale, AZ 85258. Phone: 480-860-5000; Fax: 480-882-0130; E-mail: mgordon@premiereoncology.com.

doi: 10.1158/1078-0432.CCR-09-1365

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

Translational Relevance

In recent years, there has been increased interest in the development of biological agents that target human growth factors or their associated signaling components. The hepatocyte growth factor/scatter factor (HGF/SF)–c-Met axis has been implicated in the growth, survival, and migration of some human cancers. Clinical trials investigating monoclonal antibodies and small-molecule inhibitors directed at the HGF/SF–c-Met axis are currently under way. The recently characterized fully human IgG2 monoclonal antibody AMG 102 is unique among these because it specifically targets only HGF/SF. In this first-in-human study, AMG 102 was generally well tolerated at the doses tested and resulted in stable disease and tumor reductions in some patients. The findings presented in this study, therefore, warrant further investigation of AMG 102 for the treatment of solid tumors.

mechanism of action of AMG 102 have been evaluated in preclinical studies. AMG 102 inhibited tumor growth, induced tumor regressions, increased apoptosis, and decreased cell proliferation in human xenograft models of cancer (18). The objectives of this phase I, first-in-human, open-label study were to assess the safety, tolerability, pharmacokinetics, and maximum tolerated dose (MTD) of AMG 102 in adult patients with refractory advanced solid tumors. Circulating HGF/SF and soluble c-Met were also evaluated as potential biomarkers of response both in clinical samples and in a preclinical tumor xenograft model.

Materials and Methods

Eligibility criteria

Men and women ages ≥18 y were included in the study if they had a pathologically documented and definitively diagnosed advanced solid tumor refractory to standard treatment or for which no curative therapy was available. Patients had an Eastern Cooperative Oncology Group performance status of ≤2 or, for patients with a primary brain tumor, Eastern Cooperative Oncology Group performance status of 0 or 1.

Exclusion criteria included hematologic malignancies; unresolved toxicities from prior anticancer therapy; untreated or symptomatic brain metastases; myocardial infarction within the previous 6 mo; any condition affecting cardiac function (e.g., unstable angina or congestive heart failure) of New York Heart Association class >II; uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic blood pressure >160 mm Hg); cardiac arrhythmia; recent venous thrombosis (including deep vein thrombosis or pulmonary embolism within 1 y of study); history of upper gastrointestinal hemorrhage, peptic ulcer disease, or bleeding diathesis; iron deficiency anemia; antitumor treatment within 3 wk of study day 1 (or antibody therapy within 8 wk of study day 1); high-dose chemotherapy requiring hematopoietic progenitor cell support within 24 mo of study day 1; requirement for daily nonsteroidal anti-inflammatory drugs or corticosteroids (<325 mg aspirin was acceptable); absolute neutrophil count $<1.5 \times 10^9$/L (without granulocyte colony-stimulating factor support within 2 wk of study day 1); platelet count $<100 \times 10^9$/L (without transfusion within 2 wk of study day 1); hemoglobin <10 g/dL (without transfusion within 4 wk of study day 1); prothrombin time or partial thromboplastin time >1.5× the upper limits of normal (ULN); serum creatinine >1.5× ULN (unless 24-h creatinine clearance ≥60 mL/min); aspartate aminotransferase or alanine aminotransferase >2.5× ULN; aspartate aminotransferase or alanine aminotransferase >5× ULN in the presence of liver metastasis; total bilirubin >1.5× ULN; proteinuria >1+ on urine dipstick or >30 mg/dL; known positive test for HIV, hepatitis C virus antibody, or hepatitis B virus surface antigen; positive test for hepatitis B virus core antibody in the presence of a negative test for hepatitis B virus surface antibody; or documented cytomegalovirus or EBV infection within 6 mo of study day 1.

Institutional Review Board approval was obtained for all study procedures, and all study procedures were done in accordance with the Declaration of Helsinki. Each patient provided written informed consent before enrollment in the study.

Study design

This was a first-in-human open-label study with a dose-escalation and a dose-expansion component. The principal aims were to determine the incidence of adverse events, clinically significant changes in vital signs and clinical laboratory tests, the presence of anti–AMG 102 antibodies, pharmacokinetics, MTD, and tumor response and to conduct an assessment of exploratory biomarkers.

AMG 102 was administered as an i.v. infusion over approximately 30 to 60 min. In the dose-escalation phase, patients were enrolled sequentially into six dose cohorts receiving a single dose of AMG 102 (0.5, 1, 3, 5, 10, or 20 mg/kg; four patients per cohort). The maximum planned dose was 20 mg/kg. Following the first dose, patients entered a 4-wk treatment-free period to evaluate safety and pharmacokinetics. If no dose-limiting toxicity (DLT) was observed during the 4-wk period, AMG 102 administration was resumed at the same dose level every 2 wk and continued until patients experienced a DLT, an unacceptable adverse event, disease progression, or voluntary withdrawal. DLTs were defined as any treatment-related grade 3 or 4 hematologic or nonhematologic toxicity according to Common Terminology Criteria for Adverse Events, version 3.0. If no DLT was observed among the initial four patients during the first 4 wk of treatment, patients could be enrolled at the next dose level. If a patient experienced a DLT, up to two additional patients were added to that cohort. The MTD was defined as the highest dose level with DLTs in <33% of the patients enrolled in the cohort. After the completion of the dose

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

escalation, additional patients were to be enrolled into a dose expansion at the MTD, or the maximum planned dose (20 mg/kg every 2 wk) if the MTD was not reached, to further explore safety, tolerability, and pharmacokinetics and to support biomarker development. Nine patients were enrolled in the expansion cohort.

Evaluation of safety and formation of anti–AMG 102 antibodies

Adverse events (graded according to the Common Terminology Criteria for Adverse Events) were recorded for all patients who received one or more dose of AMG 102. During dose escalation and dose expansion, serum for anti–AMG 102 antibodies was collected before dose, before day 29 (second dose), before day 57 (fourth dose; dose escalation only), at each scheduled tumor assessment (every 8 wk within 3 d before dosing), and at 4 and 8 wk following the last dose of AMG 102. Anti–AMG 102-binding antibodies were assayed using an electrochemiluminescence-based immunoassay (see Supplementary Materials and Methods).

Pharmacokinetics

During the dose-escalation phase, serum samples were collected immediately before the first dose; at 30 min (during infusion) and 60 min (immediately after infusion); at 2, 8, 24, 48, and 96 h after dosing; at days 8, 15, and 29 (before the second dose); and at day 43 (before the third dose). Beginning on day 57, serum samples were collected before dosing (before the fourth dose) and at 0.5, 1, 2, 8, 24, 48, and 96 h after dosing. Serum was also collected before dosing at every dosing visit thereafter and at 4 and 8 wk following the last dose of AMG 102. During the dose expansion, serum was collected at baseline, at 1 h (immediately following infusion), at 2 and 24 h, at the time of each scheduled tumor assessment (every 8 wk within 3 d before dosing), and at 4 and 8 wk following the last dose of AMG 102.

Pharmacokinetic and exposure parameters of AMG 102 were estimated, including maximum observed serum concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration versus time curve in a dosing interval τ (AUC_τ; τ = 2 wk), systemic clearance, terminal elimination half-life ($t_{1/2}$), and accumulation ratio (AR). Noncompartmental analysis was used for pharmacokinetic assessment using WinNonlin Professional software version 5.1 (Pharsight Corp.). In the pharmacokinetic analysis, mean and SD of pharmacokinetic parameters were calculated for each dose level and for the first and fourth doses. The $t_{1/2}$ was estimated using the data collected in the single-dose study phase (sampled up to 4 wk). The AR was calculated based on the ratio of the AUC_τ after the first and fourth doses. Dose linearity was assessed using one-way ANOVA.

Serum AMG 102 measurement

Serum concentrations of AMG 102 were determined by an AMG 102–specific ELISA (see Supplementary Materials and Methods) using a recombinant human HGF/SF (capture reagent; Amgen Inc.) and a biotinylated polyclonal rabbit anti–AMG 102 antibody (Amgen Inc.) as previously described (21).

Preclinical biomarker measurement

Methods used to measure total circulating human HGF/SF and human soluble c-Met in mice bearing U-87 MG human glioblastoma xenografts are described in Supplementary Materials and Methods.

Clinical biomarker measurement

Plasma soluble c-Met and total HGF/SF. During dose escalation, plasma samples for the assessment of HGF/SF and soluble c-Met were collected before dosing; at 60 min (immediately after infusion); at 48 h; at days 8, 15, 29, and 57; and at 4 wk following the last dose of AMG 102. During the dose expansion, plasma samples were collected before dosing, before subsequent doses of AMG 102, and at 4 wk following the last dose of AMG 102. Plasma HGF/SF was measured using a quantitative sandwich ELISA kit that detects free and antibody-bound HGF/SF (including both pro-HGF/SF and mature HGF/SF; R&D Systems, Inc.). Color development was measured using a SpectraMax plate reader (Molecular Devices). An Amgen Molecular Sciences data analysis tool was used to calculate study sample and quality control sample HGF/SF concentrations using a linear regression model based on the eight-point standard curve. Standards consisted of HGF/SF protein reconstituted in assay diluent.

Plasma soluble c-Met was measured by a Meso Scale Discovery (MSD) electrochemiluminescence assay with a biotinylated, affinity-purified c-Met ectodomain-specific capture antibody (R&D Systems) and a MSD-conjugated antibody against recombinant human c-Met extracellular domain (MSD; ref. 23). A MSD Sector Imager 6000 was used to measure electrochemiluminescence, and unknowns were quantified by interpolation from the standard curve on each sample plate.

Tumor c-Met expression. Archival tumor samples were stained for cytoplasmic and membrane c-Met and scored on a scale of 0 to 4 (0 = no stain, 4 = maximal stain). Photomicrographs of c-Met immunohistochemical staining were generated as 8-bit RGB color images using a Nikon E600 microscope, Nikon DXM1200 digital camera, and MetaVue version 6.26 image software (MDS Analytical Technologies). Images were adjusted for brightness and converted to CMYK format using Adobe Photoshop, version 7.0.1 (Adobe Systems, Inc.). Complete staining methods are described in Supplementary Materials and Methods.

Evaluation of tumor response

To evaluate tumor responses, tumor imaging was done by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST; ref. 24). Positron emission tomography (PET) scanning with the ^{18}F-fluorodeoxyglucose tracer (^{18}F-FDG PET/CT) was included as an exploratory aim, although not used to judge patient response. During the dose-escalation phase, ^{18}F-FDG PET/CT scans were done

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

within 7 d before the first dose and at days 8 (±3 d) and 36 (±3 d), excluding patients with a primary brain tumor due to high baseline glucose uptake with ^{18}F-FDG in the brain. During the dose expansion, evaluations using ^{18}F-FDG PET/CT were done before dosing at day 1 (within 7 d before dosing) and once within 3 d of the third AMG 102 administration (excluding patients with a primary brain tumor). A metabolic response was defined as a 25% change threshold in total maximum standardized uptake value between baseline and day 8 or baseline and day 36 (25).

CT/MRI evaluations were done during initial patient screening and before dosing (within 3 d before dosing) every 8 wk thereafter.

Statistical analysis

Descriptive statistics were provided for selected demographic, safety, pharmacokinetics, preliminary efficacy, and biomarker data by dose and time as appropriate. To determine if levels of HGF/SF were dependent on the dose of AMG 102 or time on treatment (visits from day 1 to day 57) and to determine if there was an interaction between dose and time, log HGF/SF concentrations were analyzed using a linear mixed model (adjusted for baseline levels), with dose, time, and the interaction between dose and time as fixed effects and patient as a random effect.

Results

Patient demographics and disposition. Forty patients with refractory advanced solid tumors were enrolled in the study between December 16, 2004 and August 1, 2007. The last patient completed the study on August 29, 2007. Patient demographics and baseline characteristics are summarized in Table 1. Patients had a variety of relapsed and/or refractory cancers, including renal cell (13%), breast (10%), and ovarian (10%) cancer. Thirty-one patients received AMG 102 in the dose escalation: 0.5 mg/kg (n = 7), 1 mg/kg (n = 7), 3 mg/kg (n = 4), 5 mg/kg (n = 4), 10 mg/kg (n = 5), and 20 mg/kg (n = 4). Nine additional patients received 20 mg/kg AMG 102 in the dose-expansion portion, resulting in 13 total patients who received 20 mg/kg AMG 102 during the study. Patients were on study for 14 to 334 days. Reasons for discontinuing the study included disease progression (n = 29), discontinued to pursue alternative therapy (including patients who discontinued despite maintaining stable disease; n = 4), adverse event (n = 3), ineligibility (n = 1), death resulting from progressive disease (n = 2), and consent withdrawn (n = 1).

DLT and MTD. AMG 102 seemed to be well tolerated at all evaluated doses. Two patients experienced DLT and were discontinued from the study, receiving no additional AMG 102 (Table 2). In the 0.5 mg/kg cohort, a patient with non–small cell lung cancer experienced grade 3 treatment-related hypoxia and treatment-related dyspnea exacerbation following one dose (onset at day 2) of AMG 102. The patient received therapy for exacerbation of chronic obstructive pulmonary disease and was removed from the study at day 14. In the 1 mg/kg cohort, a patient with pancreatic cancer experienced a grade 3 treatment-related upper gastrointestinal hemorrhage following one dose (onset day 17) of AMG 102. The patient received lansoprazole,

Table 1. Demographics and key baseline characteristics

	All patients (N = 40)*
Sex, n (%)	
Women	23 (57.5)
Men	17 (42.5)
Race, n (%)	
White	35 (87.5)
Black	3 (7.5)
Hispanic or Latino	1 (2.5)
American Indian or Alaskan Native	1 (2.5)
Age (y)	
Median	59
Range	24-78
ECOG performance status, n (%)	
0	24 (60)
1	14 (35)
2	1 (3)
3†	1 (3)
Primary tumor type, n (%)	
Other‡	14 (35)
Renal cell	5 (13)
Breast	4 (10)
Ovarian	4 (10)
Melanoma	3 (8)
Non–small cell lung	3 (8)
Soft tissue sarcoma	3 (8)
Pancreatic	2 (5)
Uterine	2 (5)
Prior radiotherapy, n (%)	22 (55)
Regimens of prior therapy, n (%)	
0	6 (15)
1	5 (13)
2	6 (15)
≥3	23 (58)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Safety analysis set includes patients who received one or more dose of AMG 102.

†Patient was enrolled per protocol-specified eligibility criteria, but her condition deteriorated before the first dose of AMG 102. The patient was issued a postenrollment eligibility deviation and was removed from the study on day 15 as a result of progressive disease.

‡Includes two patients with hepatocellular carcinoma and one each with bladder, glioblastoma multiforme, colon, gallbladder, lung, lymph node metastasis, neuroendocrine, peritoneal adenocarcinoma, perivascular epithelioid, salivary gland, small bowel, and stomach cancers.

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

Table 2. DLTs and treatment-related adverse events

Patients reporting DLTs or AEs, *n* (%)	AMG 102 dose cohort (mg/kg)						
	0.5 (*n* = 7)	1 (*n* = 7)	3 (*n* = 4)	5 (*n* = 4)	10 (*n* = 5)	20 (*n* = 13)*	Total (*N* = 40)
DLTs							
Hypoxia, grade 3†	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Exacerbated dyspnea, grade 3†	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Upper gastrointestinal hemorrhage, grade 3	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
All treatment-related AEs	5 (71)	4 (57)	1 (25)	3 (75)	1 (20)	5 (38)	19 (48)
Gastrointestinal disorders							
Constipation	1 (14)	0 (0)	0 (0)	1(25)	0 (0)	1 (8)	3 (8)
Grade 1	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	2 (5)
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (3)
Nausea	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	1 (8)	3 (8)
Grade 1	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	1 (8)	3 (8)
Vomiting	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	1 (8)	2 (5)
Grade 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (3)
Grade 2	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
General disorders and administration site conditions							
Fatigue	2 (29)	1 (14)	0 (0)	1 (25)	1 (20)	0 (0)	5 (13)
Grade 1	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	2 (5)
Grade 2	1 (14)	1 (14)	0 (0)	0 (0)	1 (20)	0 (0)	3 (8)
Metabolism and nutrition disorders							
Anorexia/decreased appetite	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	1 (8)	3 (8)
Grade 1	1 (14)	0 (0)	0 (0)	1 (25)	0 (0)	1 (8)	3 (8)
Musculoskeletal and connective tissue disorders							
Myalgia	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	2 (5)
Grade 1	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	2 (5)
Vascular disorders							
Hypotension	0 (0)	2 (29)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
Grade 1	0 (0)	2 (29)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
Treatment-related AEs with a worst grade ≥3							
Colonic fistula, grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (3)
Dyspnea exacerbated, grade 3	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Hypoxia, grade 3	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Upper gastrointestinal hemorrhage, grade 3	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)

NOTE: Adverse events occurring in ≥5% of patients and adverse events with a worst grade ≥3 are shown. Safety analysis set includes patients who received one or more dose of AMG 102.

Abbreviation: AEs, adverse events.

*Includes patients from both dose escalation and dose expansion.

†Hypoxia and exacerbated dyspnea occurred in the same patient.

and the condition resolved 3 days after discontinuation of AMG 102. As a result of the DLTs, two additional patients were enrolled in the 0.5 mg/kg and in the 1 mg/kg cohorts. Additionally, two patients (one each in the 0.5 mg/kg and 1 mg/kg cohorts) who withdrew for reasons other than DLT were replaced, resulting in a total enrollment of seven patients in each of these cohorts. No further DLTs were observed in either cohort, and dose escalation continued to the 20 mg/kg dose. The MTD was not reached. Nine additional patients were enrolled in the dose expansion and received 20 mg/kg AMG 102 every 2 weeks.

Safety and tolerability. No dose-related trends were observed in the incidence or severity of adverse events. Nineteen patients (48%) experienced treatment-related adverse events (Table 2) during the study. The most common treatment-related adverse events included fatigue ($n = 5$), constipation ($n = 3$), anorexia/decreased appetite ($n = 3$), and nausea ($n = 3$). Three patients experienced grade 3 treatment-related adverse events. On day 203, one patient with ovarian cancer in the 20 mg/kg expansion cohort inadvertently received an investigational peptibody (AMG 386; ~4 mg/kg i.v.) in addition to 15 mg/kg AMG 102 i.v.; the patient subsequently experienced a grade 3

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

colonic fistula on day 236. The adverse event was determined to be treatment related, as it could not be ruled out that the possibility of receiving both AMG 102 and AMG 386 resulted in the fistula of the colon. The patient was hospitalized, discontinued AMG 102, and was removed from the study.

Thirty-nine patients (98%) experienced treatment-emergent adverse events during the study, 20 (50%) of whom experienced at least one grade 3 adverse event (Supplementary Table S1). The most common treatment-emergent adverse events (occurring in ≥10 patients) were fatigue (43%), nausea (40%), vomiting (33%), anorexia/decreased appetite (33%), peripheral edema (30%), and dyspnea (28%). Fourteen (35%) patients experienced serious treatment-emergent adverse events. Serious adverse events observed included pneumonia ($n = 3$), dyspnea ($n = 2$), hypotension ($n = 2$), and vomiting ($n = 2$), which were not considered related to treatment with AMG 102.

In total, five patients had adverse events that resulted in discontinuation of AMG 102 administration. In addition to the two patients who discontinued AMG 102 due to DLTs and the patient who discontinued AMG 102 as a result of a colonic fistula, one patient (1 mg/kg cohort) had deep vein thrombosis not considered related to study treatment that resulted in discontinuation of AMG 102, and one patient (1 mg/kg cohort) discontinued AMG 102 as a result of retroperitoneal sarcoma (patient died as a result of progressive disease). In addition to the patient with retroperitoneal sarcoma, one patient died due to progressive non–small cell lung cancer (20 mg/kg cohort). Thirteen patients had one or more adverse event (treatment emergent or treatment related) resulting in hospitalization. No patients had detectable anti–AMG 102-binding antibodies.

Pharmacokinetics. Pharmacokinetic parameters are shown in Table 3, and pharmacokinetic profiles are depicted in Fig. 1. Pharmacokinetic parameters were estimated from combined data from patients in the dose-escalation ($n = 31$) and dose-expansion ($n = 9$) phases. The C_{max} was observed mainly around the end of the 1-hour infusion, and the serum concentration of AMG 102 declined biphasically. The C_{max} and AUC_{τ}, which were assessed by one-way ANOVA, increased linearly with dose. The estimated clearance and $t_{1/2}$ were similar across doses, suggesting that AMG 102 exhibits linear pharmacokinetics in the dose range of 0.5 to 20 mg/kg. At the doses tested, the estimated mean clearance range was 0.104 to 0.176 mL/h/kg, and the $t_{1/2}$ range was 14.5 to 22 days. The mean clearance and $t_{1/2}$ of all dose levels were 0.141 mL/h/kg and 18 days, respectively. Following multiple-dose administration, accumulation of AMG 102 exposure was observed under the biweekly regimen. The trough concentration (C_{336h}) increased ~2-fold after the fourth dose compared with the first dose, and the AR based on the AUC ranged from 1.30 to 3.86.

Preclinical biomarkers. In mice bearing U-87 MG human glioblastoma xenografts, total plasma HGF/SF levels increased in a manner proportional to both AMG 102 dose and tumor volume (Supplementary Fig. S1A). Treatment with the selective c-Met tyrosine kinase inhibitor AMG 458 had no effect on total HGF/SF levels; however, HGF/SF levels within each treatment group were proportional to tumor size (Supplementary Fig. S1B). Soluble c-Met levels were not dependent on the dose of AMG 102 but increased in proportion to tumor weight (Supplementary Fig. S1C).

Clinical biomarkers. Total levels of HGF/SF increased from day 1 to day 57 and increased in a dose-dependent manner (Fig. 2A). Total HGF/SF levels were significantly dependent on dose ($P < 0.0001$) and study visit (i.e., time on treatment; $P < 0.0001$), and there was a significant interaction between dose and time on treatment ($P = 0.0089$). Plasma soluble c-Met levels were not dependent on dose level of AMG 102 or study visit (Fig. 2B).

Immunohistochemical analysis of archival tumor tissue samples (Fig. 2C; Supplementary Table S2) confirmed the expression of c-Met in the majority of available and evaluable specimens. Cytoplasmic expression of c-Met was observed in 14 of 16 (87%) viable specimens, with 2 patients having 0+ expression, 6 patients having 1+ expression, 4 patients having 2+ expression, and 4 patients having 3+ expression on a scale of 0 to 4. Membrane expression of c-Met was observed in 7 of 16 (43%) viable specimens, with 9 patients having 0+ expression, 1 patient having 2+ expression, 2 patients having 3+ expression, and 4 patients having 4+ expression on a scale of 0 to 4. Staining of c-Met was not observed in 2 of 16 (13%) specimens (Supplementary Table S2).

Antitumor activity. Imaging for the evaluation of tumor response per RECIST was available for 23 of 40 patients, and the remaining 17 patients did not have an evaluable postbaseline CT/MRI. Of the 17 unevaluable patients, 12 ended the study early (primarily due to disease progression; $n = 6$), and another 5 patients were evaluated with ^{18}F-FDG PET/noncontrast CT and thus could not be evaluated according to RECIST. There were no partial or complete responses. Sixteen patients had a best response of stable disease with progression-free survival (PFS) ranging from 7.9 to 40.0 weeks; 4 of these patients had shown prior progressive disease with other chemotherapies before enrollment into this study. The remaining seven evaluable patients had progressive disease with PFS ranging from 2.1 to 8.9 weeks (Fig. 3). A best response of stable disease per RECIST was achieved by 2 of 7 (28.6%) patients in the 0.5 mg/kg cohort, 3 of 7 (42.9%) patients in the 1 mg/kg cohort, 1 of 4 (25%) patients in the 3 mg/kg cohort, 1 of 4 (25%) patients in the 5 mg/kg cohort, 2 of 5 (40%) patients in the 10 mg/kg cohort, and 7 of 13 (53.8%) patients in the 20 mg/kg cohort (combined dose escalation and dose expansion). Interestingly, three patients with ovarian cancer receiving AMG 102 at 20 mg/kg had PFS >15 weeks. During the course of the study, levels of serum CA-125, a marker useful for following response to treatment for ovarian cancer (26), were assessed in two of the patients with ovarian cancer. CA-125 levels decreased

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

from 728 units/mL at baseline to 545 units/mL on day 114 in the first patient (22). In the second patient, CA-125 levels decreased from 450 units/mL at baseline to 260 units/mL (day 171) and then to 109 units/mL (day 228). However, it should be noted that the second patient incorrectly received an investigational peptibody, AMG 386, in addition to AMG 102 as a consequence of a dosing error on day 203.

Changes in the best-result sum of longest diameters of target lesions ranged from −19.0% to 24.0% (Fig. 3). Reduction in tumor dimensions was associated with the following primary tumor types: ovarian (n = 3), brain (n = 1), kidney (n = 1), hepatocellular carcinoma (n = 1), melanoma (n = 1), and pancreatic (n = 1). All eight patients who had a reduction in tumor dimensions achieved stable disease. ^{18}F-FDG PET/noncontrast CT revealed that 2 of 34 evaluable patients had metabolic responses: one patient with abdominal sarcoma had a response (−30%) at study day 8 but subsequently withdrew from the study on day 21, and one patient with appendiceal carcinoid had a response (−27%) at day 36.

Discussion

In this first-in-human study of AMG 102, a HGF/SF-specific neutralizing antibody, the MTD was not reached.

Table 3. AMG 102 pharmacokinetic parameters

	AMG 102 dose cohort (mg/kg)											
	0.5 (n = 1-7)		1 (n = 2-7)		3 (n = 1-4)		5 (n = 1-4)		10 (n = 2-5)		20 (n = 3-13)*	
Dose	**1**	**4**	**1**	**4**	**1**	**4**	**1**	**4**	**1**	**4**	**1**	**4**
t_{max} (h)												
n	7	2	7	3	4	2	4	1	5	2	13	3
Median	1.1	1.5	1.18	2.58	1.02	28.1	1.5	1	1	1.58	2	2
Range	1-8.42	1-2	1-170	1-8	1-24.5	8-48.1	1-2	1-1	1-2.85	0.5-2.65	0.917-24	1-2.62
C_{max} (μg/mL)												
n	7	2	7	3	4	2	4	1	5	2	13	3
Mean	15.4	18.7	18.1	38.2	95.1	118	77.2	192	234	372	443	695
SD	3.24	NC	5.29	6.46	44.8	NC	14.6	NC	76.2	NC	115	184
C_{336h} (μg/mL)												
n	7	1	6	2	4	1	4	1	4	2	12	3
Mean	3.99	6.32	5.54	12.6	24.3	45.9	25.1	65.3	73.5	151	140	356
SD	1.66	NC	1.74	NC	9.88	NC	5.64	NC	26.3	NC	45.7	125
$t_{1/2}$ (d)												
n	7	NC	7	NC	4	NC	4	NC	5	NC	4	NC
Mean	15.2	NC	14.5	NC	17.5	NC	20.0	NC	22.0	NC	21.6	NC
SD	10.0	NC	6.8	NC	3.81	NC	7.88	NC	11.3	NC	15.2	NC
AUC_T (h·μg/mL)												
n	7	1	6	2	4	1	4	1	4	2	12	3
Mean	2,320	3,520	2,690	6,920	11,800	17,700	12,500	42,100	36,000	55,900	75,900	147,000
SD	462	NC	553	NC	4,160	NC	2,340	NC	13,400	NC	18,900	35,700
$AUC_{0\text{-inf}}$ (h·μg/mL)												
n	5	NC	5	NC	3	NC	4	NC	4	NC	4	NC
Mean	5,600	NC	6,630	NC	26,800	NC	30,900	NC	91,300	NC	168,000	NC
SD	2,800	NC	1,950	NC	1,190	NC	10,500	NC	16,400	NC	112,000	NC
CL (mL/h/kg)												
n	5	NC	5	NC	3	NC	4	NC	4	NC	4	NC
Mean	0.104	NC	0.162	NC	0.135	NC	0.176	NC	0.112	NC	0.158	NC
SD	0.0378	NC	0.0497	NC	0.783	NC	0.0566	NC	0.0197	NC	0.0858	NC
AR												
n	NC	1	NC	2	NC	1	NC	1	NC	2	NC	3
Mean	NC	1.43	NC	2.39	NC	1.30	NC	3.86	NC	2.25	NC	2.45
SD	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	0.316

Abbreviations: $AUC_{0\text{-inf}}$, AUC from time 0 to infinity; CL, systemic clearance; C_{336h}, observed plasma concentration at 336 h after dose; NC, not calculated; r, 336 h with once-every-2-wk regimen.
*Cohort (20 mg/kg) includes samples from the dose escalation and dose expansion.

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

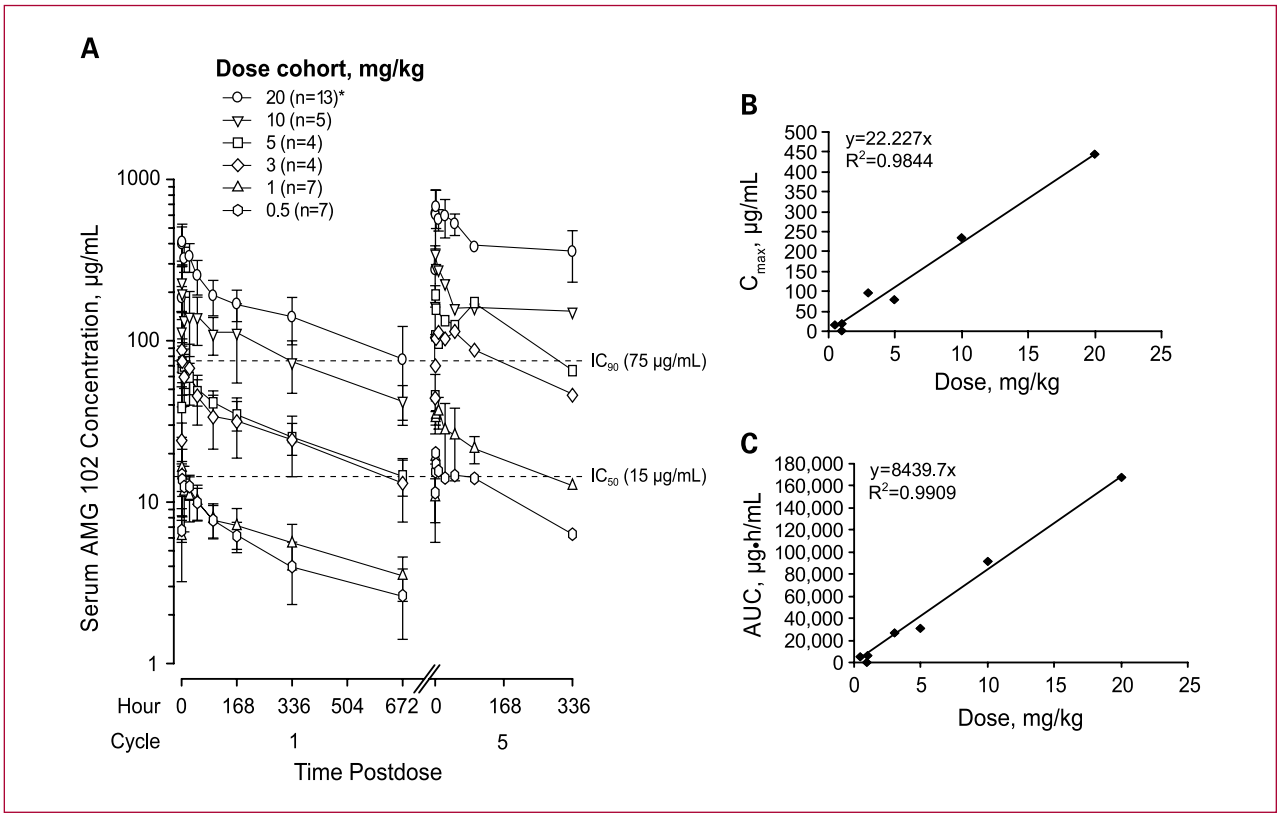


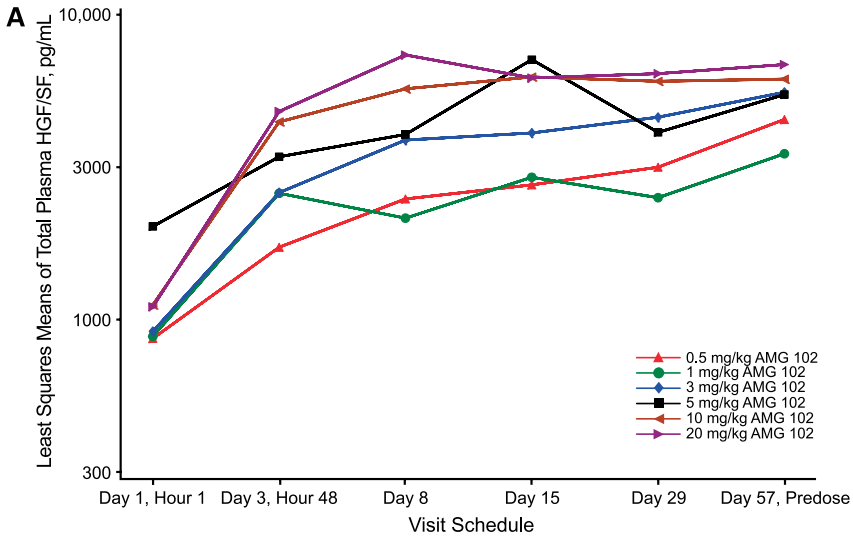
Fig. 1. Serum concentration and dose linearity of AMG 102. *A*, serum concentration versus time profiles. C_{max} (*B*) and AUC (*C*) were estimated by noncompartmental analysis and plotted against dose with linear regression. *, 20 mg/kg cohort includes samples from the dose escalation and dose expansion.

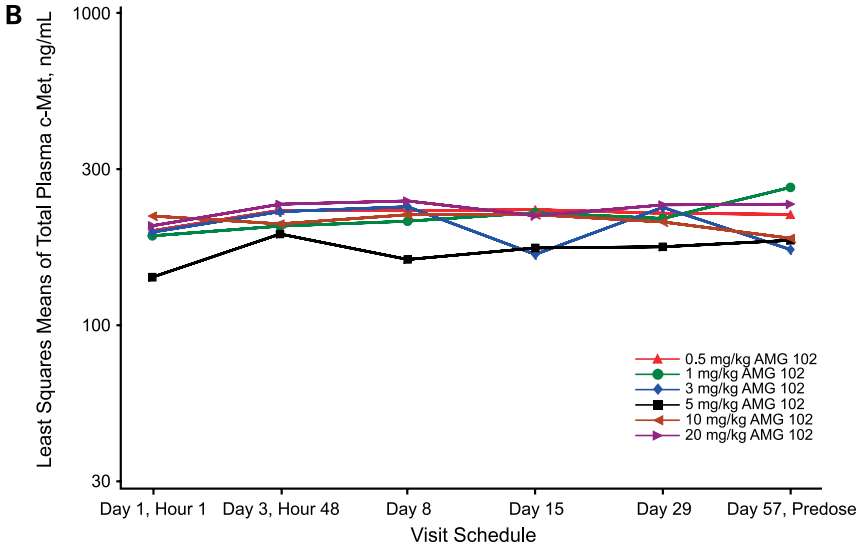
However, AMG 102 was generally well tolerated at doses up to the planned maximum dose (20 mg/kg) in heavily pretreated adult patients with refractory solid tumors. AMG 102–related adverse events were generally mild or moderate in severity, with the most frequently occurring (>5%) events being fatigue, constipation, and nausea. A total of two patients in the lowest dose cohorts (0.5 and 1 mg/kg) experienced DLTs. There were no other hematologic or nonhematologic DLTs observed in this trial. Indeed, there were no dose-related trends in the incidence of adverse events up to the highest dose tested (20 mg/kg). There were two deaths during the study resulting from disease progression. These were deemed to be unrelated to study treatment.

Recent studies have investigated the toxicity of small-molecule inhibitors of c-Met, some of which target kinases in addition to the c-Met protein. For example, in phase I and II studies, administration of XL880, an orally available small-molecule inhibitor of c-Met and vascular endothelial growth factor receptor 2, has been associated with mild to moderate hypertension, nausea, anorexia, vomiting, fatigue, and liver function abnormalities (27–30). Treatment with ARQ 197, a selective, non–ATP-competitive small-molecule inhibitor of c-Met, has been associated with fatigue, nausea, vomiting, diarrhea, and anorexia (30, 31), and treatment with XL184, a small-molecule inhibitor of c-Met, vascular endothelial growth factor receptor 2, Kit, Ret, Flt3, and Tie-2, has been associated with palmar/plantar erythema, mucositis, elevations of alanine aminotransferase and lipase, diarrhea, and hypopigmentation of the hair (32). Fatigue, nausea, vomiting, and anorexia were also observed during AMG 102 administration; however, hypertension and significant liver enzyme abnormalities were not observed. This may be due to the selectivity of AMG 102 for the c-Met ligand HGF/SF.

Although antitumor activity was not a primary objective of this study, a substantial proportion of the patients with refractory solid tumors who received AMG 102 in this study had stable disease, and a degree of tumor regression was observed in some patients. Of those evaluable for postbaseline tumor responses per RECIST, 16 of 23 (70%) achieved stable disease as a best response, 4 of whom had shown disease progression with chemotherapeutic intervention before entry into this trial. Three patients with ovarian cancer receiving AMG 102 at 20 mg/kg remained in the study with stable disease for a prolonged period (PFS >15 weeks) and showed reductions in tumor size. In addition, two of these patients with ovarian cancer had reductions in the tumor marker CA-125 (26). Although tumor c-Met data were not available for these two patients, this is an interesting observation because overexpression of c-Met among patients with advanced ovarian cancer has been associated with decreased overall survival (33).

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365





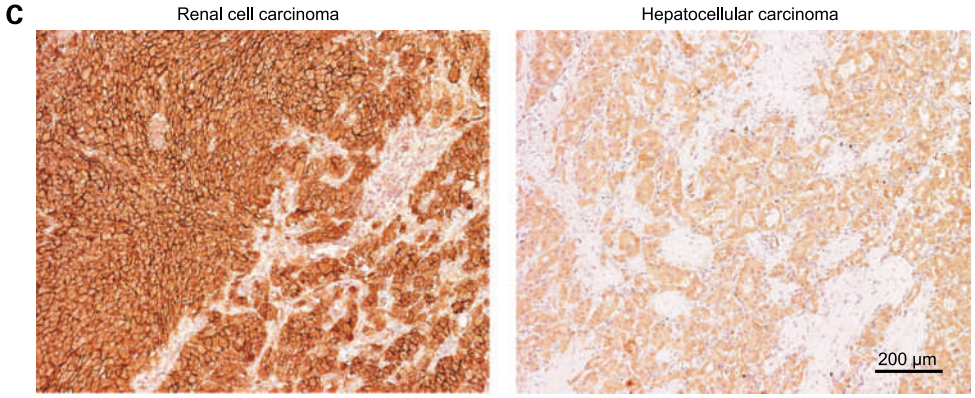


Fig. 2. Analysis of HGF/SF and c-Met as biomarkers. *A,* effect of AMG 102 on total plasma HGF/SF in patients with advanced solid tumors. *B,* effect of AMG 102 on plasma soluble c-Met in patients with advanced solid tumors. *C,* immunohistochemical staining of c-Met in a renal cell carcinoma, graded as 3 for cytoplasmic staining and 4 for membrane staining, and hepatocellular carcinoma, graded as 3 for cytoplasmic staining and 0 for membrane staining, using a relative scale of 0 to 4 (0 = no stain, 4 = maximal stain).

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

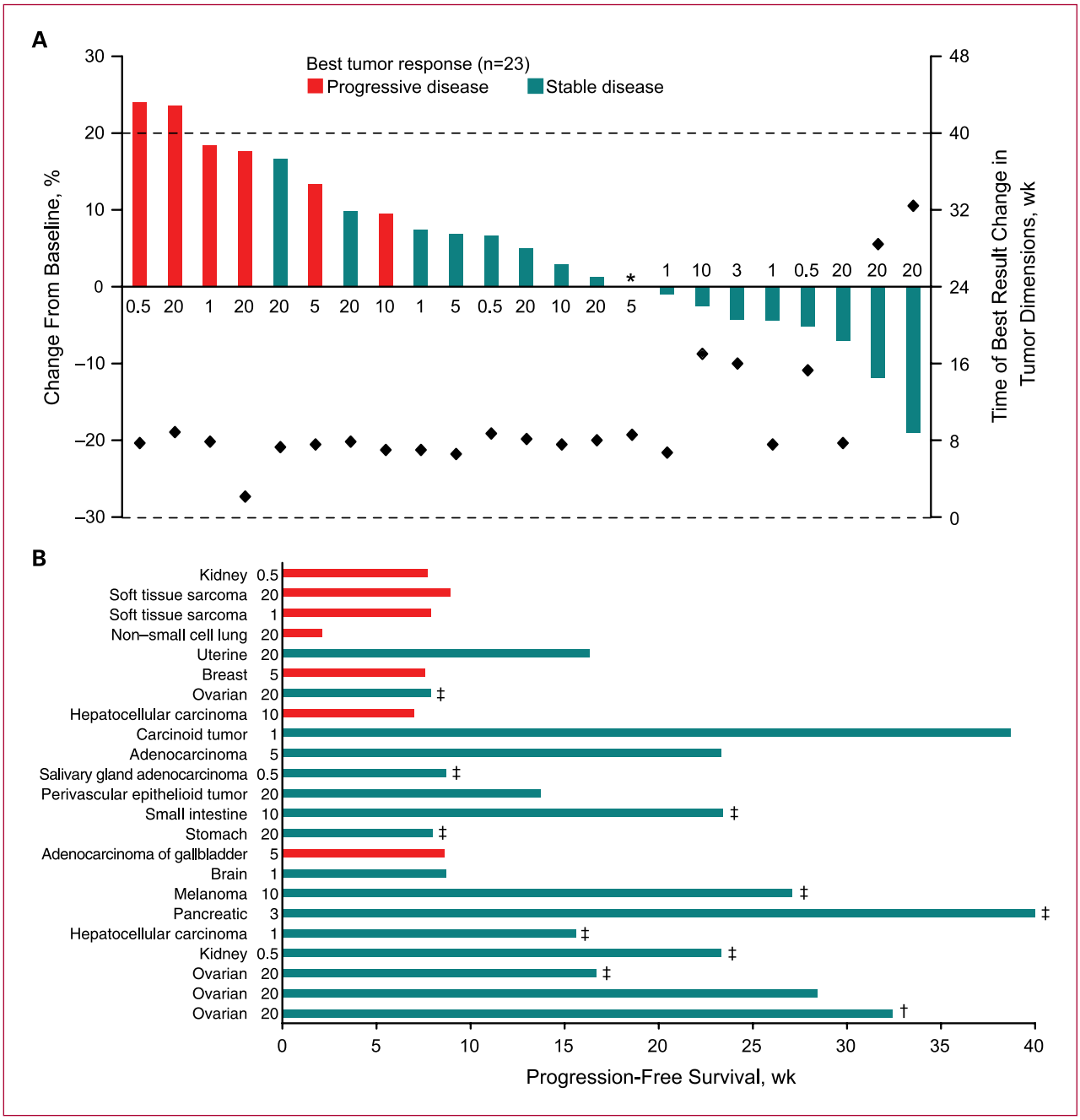


Fig. 3. Antitumor activity of AMG 102. *A,* best result of 23 evaluable patients according to modified RECIST (*bars*) and length of time on study (*diamonds*). The remaining 17 patients did not have an evaluable postbaseline CT/MRI scan. Dashed lines indicate the range of target lesion dimension changes from baseline that qualify as stable disease according to modified RECIST. Numbers indicate dose (mg/kg) of AMG 102. *, patient had no change in size of target lesions but had a determination of progressive disease based on development of new lesions. *B,* PFS and diagnosis for 23 evaluable patients according to modified RECIST. Numbers indicate dose (mg/kg) of AMG 102. †, patient received 3 mg/kg AMG 386 peptibody (dosing error) and 15 mg/kg AMG 102 on day 203; ‡, patients without progressive disease at the last disease assessment date were censored.

AMG 102 exhibited linear pharmacokinetics across all dose levels tested, with a mean $t_{1/2}$ of 18 days. Throughout the entire dosing interval, the mean trough concentrations (C_{336h}) of AMG 102 at 3 and 10 mg/kg exceeded the IC_{50} (~15 μg/mL) and IC_{90} (~75 μg/mL) values for inhibition of HGF/SF-stimulated proliferation of human umbilical vein endothelial cells and U-87 MG cells (18), suggesting that AMG 102 may have the potential for biological activity at this dose range. The exposure (C_{max}, AUC) of AMG 102 at the maximum planned dose of 20 mg/kg in the present

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

study was at least 6-fold lower than the no observed adverse event level dose (150 mg/kg) in the 40-week toxicity study in nonhuman primates, indicating that there was a sufficient safety margin in exposure. Although a MTD was not reached, a preliminary population pharmacokinetic model (22) developed with the pharmacokinetic data collected from this study suggested that dosing regimens of ≥10 mg/kg every 2 weeks, 15 mg/kg every 3 weeks, and 20 mg/kg every 4 weeks should maintain serum AMG 102 trough concentrations above the IC_{90} value in the human umbilical vein cell and U-87 MG cell proliferation assays described above in >90% of patients. Therefore, these regimens were chosen for ongoing phase 2 studies.

Biomarkers are important for identifying cancer subtypes, assessing metastatic potential, providing prognostic information, and predicting responses to therapeutic agents. To explore the potential of HGF/SF as a clinical biomarker, we first examined the effect of AMG 102 treatment on plasma total HGF/SF levels in a U-87 MG glioblastoma xenograft model. In this model, the total plasma level of HGF/SF (sum of free HGF/SF and HGF/SF bound to AMG 102) increased in proportion to AMG 102 dose and tumor size. Because the c-Met tyrosine kinase inhibitor AMG 458 had no effect on total HGF/SF levels, it is unlikely that the observed increases in HGF/SF levels were due to negative feedback from inhibition of c-Met. We hypothesize that increases in HGF/SF may be the result of AMG 102 stabilization of HGF/SF, resulting in increased HGF/SF half-life and/or HGF/SF redistribution from tissues (including tumors). At this time, we do not know why levels of soluble c-Met did not change after treatment with AMG 102.

The clinical biomarker data were similar to the preclinical data: in patients, plasma HGF/SF concentrations increased in a dose- as well as a time-dependent manner, and levels of soluble c-Met did not seem to be dependent on either dose or time on treatment. In addition, c-Met was expressed in the majority of available patient tumor samples. Although both HGF/SF and c-Met are well-documented prognostic markers of disease progression and survival (34–40), additional studies are required to determine whether these markers will be useful for predicting the efficacy of HGF/SF–c-Met axis–targeted therapies.

Overall, AMG 102 showed acceptable safety as a monotherapy at i.v. doses up to 20 mg/kg when administered every 2 weeks to patients with advanced solid tumors. Because of its favorable safety and pharmacokinetic profile and unique specificity to HGF/SF, the only known ligand of the c-Met receptor, there is a potential for incorporation of AMG 102 into combination therapy regimens both with cytotoxic chemotherapy and with other targeted agents. In a recent preclinical study, AMG 102 enhanced the efficacy of temozolomide or docetaxel in inhibiting growth of U-87 MG cells *in vitro* and U-87 MG tumor xenografts *in vivo* (41). In an ongoing phase Ib study, AMG 102 in combination with bevacizumab or motesanib (a small-molecule inhibitor of vascular endothelial growth factor receptors) led to durable stable disease in some patients (42). The most frequently occurring treatment-related adverse events were nausea and fatigue. Studies are ongoing to determine the clinical activity of AMG 102 both as monotherapy and in combination with other therapeutic regimens in several tumor types, including recurrent glioblastoma multiforme (43).

Disclosure of Potential Conflicts of Interest

A. Anderson, D.M. Beaupre, D. Branstetter, T.L. Burgess, A. Coxon, H. Deng, P. Kaplan-Lefko, I.M. Leitch, K.S. Oliner, L. Yan, and M. Zhu: employees/ownership interest, Amgen Inc. L. Gore: commercial research support, Merck and Co., Inc. S.G. Eckhardt: consultant, Amgen Inc. The authors acknowledge Benjamin Scott, Ph.D., who provided assistance in writing this manuscript with funding by Amgen Inc. The other authors declare no conflicts of interest.

Acknowledgments

We thank Jianfeng Lu, Mario Bejarano, and Mark Ma for pharmacokinetic assessment and sample analysis; Noelle Erbeck, Charity Scripture, Poornima Shubhakar, and Susan Glover for clinical support; Jim Gould for data management; Yao Zhuang for antibody analysis; Yuying Hwang for imaging support; Ronals Korn for ^{18}F-FDG PET/CT analysis; Jennifer Malella, Yun Lan, and Gwyneth Van for biomarker sample analysis; Karen Rex and Jan Sun for preclinical xenograft studies; Benjamin Scott, Ph.D., whose work was funded by Amgen Inc., for assistance in writing this manuscript; the research staff at each participating institution; and the patients who took part in this study.

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.

Received 5/28/09; revised 9/28/09; accepted 10/22/09; published OnlineFirst 1/12/10.

References

1. Stoker M, Gherardi E, Perryman M, Gray J. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature 1987;327:239–42.
2. Zarnegar R, Michalopoulos G. Purification and biological characterization of human hepatopoietin A, a polypeptide growth factor for hepatocytes. Cancer Res 1989;49:3314–20.
3. Montesano R, Matsumoto K, Nakamura T, Orci L. Identification of a fibroblast-derived epithelial morphogen as hepatocyte growth factor. Cell 1991;67:901–8.
4. Nakamura T, Nishizawa T, Hagiya M, et al. Molecular cloning and expression of human hepatocyte growth factor. Nature 1989;342:440–3.
5. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat Rev Mol Cell Biol 2003;4:915–25.
6. Ferracini R, Di Renzo MF, Scotlandi K, et al. The Met/HGF receptor is over-expressed in human osteosarcomas and is activated by either a paracrine or an autocrine circuit. Oncogene 1995;10:739–49.
7. Jin L, Fuchs A, Schnitt SJ, et al. Expression of scatter factor and

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

c-met receptor in benign and malignant breast tissue. Cancer 1997;79:749–60.
8. Fukuura T, Miki C, Inoue T, Matsumoto K, Suzuki H. Serum hepatocyte growth factor as an index of disease status of patients with colorectal carcinoma. Br J Cancer 1998;78:454–9.
9. Koochekpour S, Jeffers M, Rulong S, et al. Met and hepatocyte growth factor/scatter factor expression in human gliomas. Cancer Res 1997;57:5391–8.
10. Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene 1999;18: 2343–50.
11. Miller M, Ginalski K, Lesyng B, Nakaigawa N, Schmidt L, Zbar B. Structural basis of oncogenic activation caused by point mutations in the kinase domain of the MET proto-oncogene: modeling studies. Proteins 2001;44:32–43.
12. Di Renzo MF, Olivero M, Martone T, et al. Somatic mutations of the MET oncogene are selected during metastatic spread of human HNSC carcinomas. Oncogene 2000;19:1547–55.
13. Olivero M, Valente G, Bardelli A, et al. Novel mutation in the ATP-binding site of the MET oncogene tyrosine kinase in a HPRCC family. Int J Cancer 1999;82:640–3.
14. Di Renzo MF, Olivero M, Giacomini A, et al. Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. Clin Cancer Res 1995;1:147–54.
15. Nakajima M, Sawada H, Yamada Y, et al. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. Cancer 1999;85:1894–902.
16. Kijima Y, Hokita S, Yoshinaka H, et al. Amplification and overexpression of c-met gene in Epstein-Barr virus-associated gastric carcinomas. Oncology 2002;62:60–5.
17. Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nat Rev Drug Discov 2008;7:504–16.
18. Burgess T, Coxon A, Meyer S, et al. Fully human monoclonal antibodies to hepatocyte growth factor with therapeutic potential against hepatocyte growth factor/c-Met-dependent human tumors. Cancer Res 2006;66:1721–9.
19. Martin TA, Parr C, Davies G, et al. Growth and angiogenesis of human breast cancer in a nude mouse tumour model is reduced by NK4, a HGF/SF antagonist. Carcinogenesis 2003;24:1317–23.
20. Sattler M, Salgia R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. Curr Oncol Rep 2007;9:102–8.
21. Kakkar T, Ma M, Zhuang Y, Patton A, Hu Z, Mounho B. Pharmacokinetics and safety of a fully human hepatocyte growth factor antibody, AMG 102, in cynomolgus monkeys. Pharm Res 2007; 24:1910–8.
22. Data on file. Thousand Oaks (CA): Amgen Inc. 2008.
23. Athauda G, Giubellino A, Coleman JA, et al. c-Met ectodomain shedding rate correlates with malignant potential. Clin Cancer Res 2006; 12:4154–62.
24. Therasse P, Arbuck SG, Eisenhauer EA, et al. European Organization for Research and Treatment of CancerNational Cancer Institute of the United StatesNational Cancer Institute of Canada. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
25. Young H, Baum R, Cremerius U, et al. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Measurement of clinical and subclinical tumour response using [^{18}F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer 1999;35:1773–82.
26. Hogdall E. Cancer antigen 125 and prognosis. Curr Opin Obstet Gynecol 2008;20:4–8.
27. Jhawer MP, Kindler HL, Wainberg ZA, et al. Preliminary activity of XL880, a dual MET/VEGFR2 inhibitor, in MET amplified poorly differentiated gastric cancer (PDGC): interim results of a multicenter phase II study [abstract]. J Clin Oncol 2008;26:4572.
28. Ross RW, Srinivasan R, Vaishampayan U, et al. A phase 2 study of the dual MET/VEGFR2 inhibitor XL880 in patients (pts) with papillary renal carcinoma (PRC) [abstract]. In: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, November 14-18, 2007, San Francisco (CA). 2007.
29. Shapiro GI, Heath E, Malburg L, et al. A phase I dose-escalation study of the safety, pharmacokinetics (PK) and pharmacodynamics of XL880, a VEGFR and MET kinase inhibitor, administered daily to patients (pts) with advanced malignancies [abstract]. In: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, November 14-18, 2007, San Francisco (CA) 2007.
30. Yap TA, Harris D, Barriuso J, et al. Phase I trial to determine the dose range for the c-Met inhibitor ARQ 197 that inhibits c-Met and FAK phosphorylation, when administered by an oral twice-a-day schedule [abstract]. J Clin Oncol 2008;26:3584.
31. Rosen L, Senzer N, Nemunaitis J, et al. A phase I dose escalation study and signs of anti-metastatic activity of ARQ 197, A selective c-Met inhibitor [abstract]. In: AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, November 14-18, 2007, San Francisco (CA). 2007.
32. Salgia R, Sherman S, Hong DS, et al. A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC) [abstract]. J Clin Oncol 2008;26:3522.
33. Sawada K, Radjabi AR, Shinomiya N, et al. c-Met overexpression is a prognostic factor in ovarian cancer and an effective target for inhibition of peritoneal dissemination and invasion. Cancer Res 2007;67: 1670–9.
34. Ghoussoub RA, Dillon DA, D'Aquila T, Rimm EB, Fearon ER, Rimm DL. Expression of c-met is a strong independent prognostic factor in breast carcinoma. Cancer 1998;82:1513–20.
35. Kang JY, Dolled-Filhart M, Ocal IT, et al. Tissue microarray analysis of hepatocyte growth factor/Met pathway components reveals a role for Met, matriptase, and hepatocyte growth factor activator inhibitor 1 in the progression of node-negative breast cancer. Cancer Res 2003;63:1101–5.
36. Ren Y, Cao B, Law S, et al. Hepatocyte growth factor promotes cancer cell migration and angiogenic factors expression: a prognostic marker of human esophageal squamous cell carcinomas. Clin Cancer Res 2005;11:6190–7.
37. Srinivasan R, Choueiri TK, Vaishampayan U, et al. A phase II study of the dual MET/VEGFR2 inhibitor XL880 in patients (pts) with papillary renal carcinoma (PRC) [abstract]. J Clin Oncol 2008;26:5103.
38. Toi M, Taniguchi T, Ueno T, et al. Significance of circulating hepatocyte growth factor level as a prognostic indicator in primary breast cancer. Clin Cancer Res 1998;4:659–64.
39. Tuynman JB, Lagarde SM, Ten Kate FJ, Richel DJ, van Lanschot JJ. Met expression is an independent prognostic risk factor in patients with oesophageal adenocarcinoma. Br J Cancer 2008;98:1102–8.
40. Pena C, Shan M, Wilhelm S, Lathia C. Hepatocyte growth factor (HGF) is a prognostic biomarker for overall survival and a pharmacodynamic biomarker of sorafenib response in the SHARP phase III trial [abstract 460O]. Ann Oncol 2008;19:viii153–65.
41. Jun HT, Sun J, Rex K, et al. AMG 102, a fully human anti-hepatocyte growth factor/scatter factor neutralizing antibody, enhances the efficacy of temozolomide or docetaxel in U-87 MG cells and xenografts. Clin Cancer Res 2007;13:6735–42.
42. Rosen P, Sweeney C, Park D, et al. AMG 102, an HGF/SF antagonist, in combination with anti-angiogenesis targeted therapies in adult patients with advanced solid tumors [abstract]. J Clin Oncol 2008;26: 3570.
43. Reardon D, Cloughsey T, Raizer J, et al. Phase II study of AMG 102, a fully human neutralizing antibody against hepatocyte growth factor/scatter factor, in patients with recurrent glioblastoma multiforme [abstract]. J Clin Oncol 2008;26:2051.

Published OnlineFirst January 12, 2010; DOI: 10.1158/1078-0432.CCR-09-1365

Clinical Cancer Research

Safety, Pharmacokinetics, and Pharmacodynamics of AMG 102, a Fully Human Hepatocyte Growth Factor–Neutralizing Monoclonal Antibody, in a First-in-Human Study of Patients with Advanced Solid Tumors

Michael S. Gordon, Christopher J. Sweeney, David S. Mendelson, et al.

Clin Cancer Res 2010;16:699-710. Published OnlineFirst January 12, 2010.