2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 102

Name of Active Ingredient: AMG 102

Title of Study: A Global, Multicenter, Open-label, Single Agent, Two-stage, Phase 2 Study to Evaluate the Efficacy and Safety of AMG 102 in Subjects with Advanced Renal Cell Carcinoma

Investigators and Study Centers: This study was conducted at 2 sites in Belgium and 5 sites in the United States. Two other sites were identified however they were not initiated and did not enroll subjects.

[redacted] MD, [redacted]
[redacted], MD, [redacted]
[redacted], MD, [redacted]
[redacted], MD, [redacted]
[redacted], MD, [redacted]
[redacted], [redacted]
[redacted], MD, [redacted]

Publication: Kabbinavar F, Garcia JA, Stadler WM, Gil T, Jonasch E, Tagawa ST. Efficacy and safety of AMG 102 in patients with advanced renal cell carcinoma (RCC). ECCO 15-ESMO, Sep2009.

Study Period: 04 January 2007 (Date first subject enrolled) 29 May 2009 (Data cut-off date for this report).

Development Phase: 2

Introduction and Objectives:

An estimated 190,000 new renal cancer cases and 91,000 deaths from renal cancer occur in the world each year (Parkin et al, 2001). Surgical excision is the primary treatment for RCC. Metastatic RCC has a varied clinical course. About 50% of patients survive less than 1 year and only 10% survive over 5 years (Motzer et al, 2004). Chemotherapy ineffectively treats RCC (Motzer et al, 1996). Until recently, the only effective treatment for metastatic disease was cytokine-based immunotherapy with interferon or interleukin with response rate of approximately 15% (Rosenberg et al, 1987) with the combination of interferon alfa and nephrectomy being superior to interferon alfa (Flanigan et al, 2001).

Hepatocyte growth factor (HGF), also referred to as scatter factor, is a multifunctional protein with a strong mitogenic effect on hepatocytes. Accumulating data suggests that dysregulation of HGF/mesenchymal epithelial transition factor (c-Met) signaling may play an important role in many human malignancies. HGF overexpression has been found in many types of solid tumors including kidney tumors (Stuart et al, 2000; Trusolino et al, 2000).

AMG 102 is a fully human monoclonal antibody (IgG2) against human HGF that blocks the binding of HGF to its receptor c-Met, thus inhibiting HGF/c-Met-signaling activities in cells. In phase 1 studies, AMG 102 has an acceptable safety profile at doses up to 20 mg/kg every 2 weeks (Q2W), and the maximum tolerated dose was not reached.

The primary objective in this study was to assess the objective response rate in subjects with advanced RCC receiving AMG 102 treatment.

Secondary objectives were to estimate the overall survival and progression-free survival rates in this population; to assess duration of response and time to response in this population; and to assess the pharmacokinetics of AMG 102 in subjects with advanced RCC.

The safety objective was to assess the safety of AMG 102 in subjects with advanced RCC.

[redacted]

Methodology:

A global, multicenter, open-label, single agent, 2-stage, phase 2 study to assess the efficacy and safety of AMG 102 to treat subjects with advanced RCC. AMG 102 was administered intravenously (IV) once Q2W until documented radiological disease progression, intolerable adverse event, documented clinical progression, or consent withdrawal. The primary response evaluation was based on the confirmed objective response as determined by a review of radiographic responses and clinical assessments based on the RECIST with modifications, from all subjects by independent central reviewers.

For pharmacokinetic assessment, blood samples were to be collected in cycles 1, 3 and 5 following intravenous infusion for the measurement of serum concentrations of AMG 102 at pre-infusion (Cmin) and end-of infusion (Cmax).

This study used version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events as a guide to assess severity for grading adverse events that were experienced by research subjects.

Number of Subjects Planned: The estimated planned enrollment in this study was approximately 80 subjects. A maximum of 2 dose levels were to be tested in up to approximately 40 subjects per dose, depending on the response rate observed (see study schema, Figure 7-1).

Number of Subjects Enrolled: 61 (40 subjects at the 10-mg/kg dose level and 21 subjects at the 20-mg/kg dose level)

Sex: 43 (70.5%) men and 18 (29.5%) women

Age: median 59 years (range 39 to 84)

Ethnicity (Race): 58 (95.1%) white, 1 each (1.6%) Black, Hispanic, and Asian

Diagnosis and Main Criteria for Eligibility: Subjects were men and women ≥ 18 years old who had documented histologically confirmed advanced or metastatic RCC with the primary tumor in place or following nephrectomy

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 102 was administered IV Q2W until documented radiological disease progression, intolerable adverse event, documented clinical progression, or consent withdrawal. The manufacturing batch numbers used in this study are [redacted].

Duration of Treatment: The planned minimum duration of therapy for this evaluation was 8 weeks. Each subject was to be on study for approximately 9 months, and the total study duration was estimated to be approximately 2.5 years.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: This was an open-label study with no reference therapy.

Study Endpoints

Primary Endpoint: objective best confirmed response rate at any time

Secondary Endpoints: adverse events, overall survival, progression-free survival, duration of response (for responders only), time to response, pharmacokinetics of AMG 102 (C_{max} and C_{min})

[redacted]

Statistical Methods:

The primary efficacy analysis was performed when the last subject at a given dose level had been treated for at least 12 weeks from the first dose of AMG 102. All subjects were either off protocol directed therapy or had been followed until at least week 13. The primary response evaluation was based on confirmed objective response rate per the response evaluation criteria for solid tumors (RECIST) with modifications, as determined by a review of the imaging scans for all subjects by an independent reviewer. Each subject's best confirmed (ie, confirmed on a subsequent scan) response (at any time) was used in the primary analysis.

Analyses of the primary and secondary efficacy endpoints were conducted on the safety analysis set/subject treated analysis set separately for each dose level. The analysis of the safety endpoint was conducted for each dose level separately and again for both groups combined.

Kaplan-Meier estimates and 2-sided 95% confidence interval for landmark times by 8-week intervals were produced for the endpoints of overall survival and progression-free survival time. Descriptive statistics for the duration of and time to response for the responding subjects were calculated. Other than the efficacy evaluation required to determine whether to proceed to the second stage of accrual, no planned formal interim analysis was performed.

Safety was continually monitored, and the study may have been discontinued at any time for safety concerns.

All reported adverse events were assigned a body system and preferred term within a body system according to MedDRA version 12.0, the adverse event preferred term dictionary. The number and percent of subjects reporting adverse events (all, serious, and related) were tabulated by dose levels.

The pharmacokinetic parameters (Cmax, Cmin) of AMG 102 were tabulated by dose levels and treatment cycles. Descriptive statistics were computed for mean and standard deviation (SD) of each pharmacokinetic parameter.

Summary of Results:

Subject Disposition:

A total of 61 subjects were enrolled in this study (40 subjects at the 10-mg/kg dose level and 21 subjects at the 20-mg/kg dose level). All subjects enrolled in the study received at least 1 dose of AMG 102. The most common reason for discontinuation of study drug was disease progression (25 subjects, 59.3%). Other reasons for discontinuation were adverse event (11 subjects, 18.6%), consent withdrawn (5 subjects, 8.5%), other (4 subjects, 6.8%), ineligibility determined, noncompliance, subject request, and death (1 subject, 1.7% each). The overall median (range) duration of treatment and follow-up time were 10.00 weeks (2.1 to 101.9) and 40.00 weeks (2.1 to 101.9), respectively. The duration of treatment was similar between subjects receiving 10 and 20 mg/kg AMG 102; however, the duration of follow-up was different (the median follow-up for the 10-mg/kg group was roughly 18 weeks longer than for the 20-mg/kg group), possibly due to the fact that the 20 mg cohort recruited after the 10 mg cohort. There were 2 subjects (both in the 10-mg/kg group) still in treatment at the time of the data cut off (29 May 2009).

Efficacy Results:

According to the central assessment and the investigator assessment, the response rate (95% CI) for the 10-mg/kg dose level was 2.5% (0.1, 13.2). There was 1 confirmed partial response (PR) at the 10-mg/kg dose level and no confirmed responses at the 20-mg/kg dose level.

Most subjects at the 10-mg/kg dose level had a best response of stable disease (SD) (18 subjects 45.0%); followed by progressive disease (PD) (16 subjects, 40.0%), not done (5 subjects, 12.5%), and PR (1 subject, 2.5%). There were equal amounts of subjects who had a best response of SD and PD at the 20-mg/kg dose level (central assessment: 8 subjects, 38.1% each; investigator assessment: 9 subjects 42.9% each); and assessments were not done for 3 subjects, 14.3%.

Per central assessment, the median (95% CI) progression free survival time was 32.0 (16.9, 46.1) weeks at the 10-mg/kg dose level and 8.6 (8.0, 16.0) weeks at the 20-mg/kg dose level. The median (95% CI) progression free survival time per investigator assessment was 16.0 (7.9, 33.1) weeks for the 10-mg/kg dose level and 8.6 (8.0, 16.1) weeks for the 20-mg/kg dose level. Differences in patient demographics and evolution in standards of care may have been reflected in observed PFS differences between the 10 and 20 mg/kg cohorts, namely the time to metastatic disease and the prior use of sunitinib."

The median (95% CI) Kaplan-Meier estimates for overall survival were 14.9 (9.4, not estimable [NE]) months for subjects at the 10-mg/kg dose level and NE (7.1, NE) months at the 20-mg/kg dose level. The NE values were due to the fact that more than 50% of the subjects were still alive at the time of the analysis.

Pharmacokinetic Results: Evaluable AMG 102 serum concentrations from 58 subjects were available for data analysis (40 and 18 subjects from the 10- and 20-mg/kg dose groups, respectively). Pre-infusion and end-of-infusion concentrations were estimated for cycles 1, 3, and 5. The C_{max} accumulation ratio was approximately 2 fold between cycle 5 and cycle 1, similar to that found in Study 20040167 (Q2W, monotherapy in patients with solid tumors), in which AMG 102 exposure was expected to attain stead state in cycle 5. In addition, the mean C_{max} and C_{min} values of AMG 102 estimated in this study were also comparable to those reported in Study 20040167 [Table 10-1]). The mean C_{min} values in cycle 5 were 176 and 375 μg/mL at 10 and 20 mg/kg, respectively, which exceeded the inhibitory concentration IC_{50} (15 μg/mL) and IC_{90} (75 μg/mL) from both HGF stimulated U87-MG-glioblastima cell proliferation (autocrine) and human

umbilical vein endothelial cell (HUVEC) proliferation (paracrine) assays, respectively, and were well above the IC_{90} value (8.6 μg/mL) observed in a U87-MG established xenograft model.

Antibody Results: No anti-AMG 102 antibodies were detected in any of the samples tested.

Safety Results:

All 61 subjects (100%) had at least 1 treatment emergent adverse event. There were 25 subjects (41.0%) who had a worst grade of 3; 6 subjects (9.8%) had a worst grade of 4, 2 subjects (3.3%) had a worst grade of 5. Twenty-five subjects (41.0%) had an adverse event that was considered serious, and 9 subjects (14.8%) had an adverse event that led to permanent discontinuation of study drug. No infusion reactions were reported.

The most common adverse events (≥ 20% of subjects) were fatigue (37.7%), peripheral edema (36.1%), nausea (27.9%), constipation (24.6%), anorexia (23.0%), and dyspnea (21.3%). Overall, individual adverse events were experienced by a higher percentage of subjects in the 10-mg/kg cohort than in the 20-mg/kg cohort, most likely due to the increased number of infusions of AMG 102 and longer observation time in the 10 mg/kg group.

Forty-five subjects (73.8%) had adverse events reported as possibly related to AMG 102. The most common (≥ 10% of subjects) treatment-related adverse events were fatigue (24.6%); peripheral edema, and nausea (19.7% each); and anorexia and edema (11.5% each). The incidence of individual treatment-related adverse events by preferred term was generally similar between the 10-mg/kg and 20-mg/kg dose cohorts with the exception of edema, nausea, rash, vomiting, and diarrhea.

A total of 25 subjects (41.0%) had adverse events reported as serious. Serious adverse events occurred in 1 subject each except for abdominal pain and dyspnea (3 subjects, 4.9% each); and general physical health deterioration, generalized edema, and edema (2 subjects, 3.3% each). Eight subjects had serious adverse events reported as being treatment related. All serious treatment-related adverse events occurred in 1 subject each except dyspnea and edema (2 subjects [3.3%] each).

Eleven subjects withdrew from the study and/or permanently discontinued AMG 102 due to adverse events. Five subjects withdrew from the study due to adverse events; 3 of these subjects (subjects [redacted]) were also reported as withdrawing from the study due to these adverse events. One subject (1.6%) each withdrew due to supraventricular tachycardia, abdominal pain, pathological fracture, pulmonary embolism, and deep vein thrombosis. Nine subjects (14.8%) had adverse events leading to permanent discontinuation of AMG 102. Of these, 5 subjects (41.0%) had grade 2 or 3 edema events that were not reported as serious; however 3 of these events were reported as possibly related to AMG 102. One subject (1.6%) had a grade 3 adverse event of deep vein thrombosis that was reported as serious and possibly related to AMG 102, 1 subject had a grade 4 adverse event of supraventricular tachycardia that was reported as serious and possibly related to AMG 102, 1 subject had a grade 3 adverse event of pathological fracture that was reported as serious and not related to AMG 102, and 1 subject had a grade 4 adverse events of sepsis that was reported as serious and not related to AMG 102.

Twenty-eight subjects (45.9%) had adverse events of edema. Using specific terms pertaining to edema, peripheral edema was reported in 22 subjects (36.1%), edema was reported in 10 subjects (16.4%), and generalized edema was reported in 2 subjects (3.3%). All other types of edema events (fluid retention and periorbital edema) were reported in single subjects (1.6%). Most edema events were grade 1 or 2. Six subjects reported grade 3 edema events with 2 subjects each having 2 different types of edema events. Grade 3 edema was reported in 4 subjects (6.6%), grade 3 peripheral edema was reported in 2 subjects (3.3%), grade 3 generalized edema was reported in 1 subject (1.6%), and grade 3 brain edema was reported in 1

subject (1.6%). There were no grade 4 or 5 edemas reported. Five subjects discontinued investigational product due to edema events.

A total of 25 subjects (41.0%) died on study (19 subjects [47.5%] 10 mg/kg, 6 subjects [28.6%] 20 mg/kg). One of the deaths was a subject at the 20-mg/kg dose level who died in the first 8 weeks of the treatment period. Nineteen of the deaths occurred more than 8 weeks after the last dose of AMG 102 (17 subjects [42.5%] 10 mg/kg, 2 subjects [9.5%] 20 mg/kg). None of the deaths were attributed to AMG 102.

Conclusions:

AMG 102 demonstrated limited single-agent response in the setting of renal carcinoma as there was only 1 objective PR on study. A subset of patients experienced prolonged stable disease. AMG 102 was generally safe and well tolerated with edema as an identified risk. At the 10- and 20-mg/kg dose levels, AMG 102 concentrations exceeded the IC_{90} values obtained from nonclinical studies. The pharmacokinetics of AMG 102 in subjects with advanced RCC appeared to be similar to that in subjects with advanced solid tumors.