Clinical Cancer Research

A Multicenter Phase II Study of AMG 337 in Patients with *MET*-Amplified Gastric/Gastroesophageal Junction/Esophageal Adenocarcinoma and Other *MET*-Amplified Solid Tumors

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Abstract

Purpose: *MET* gene amplification is associated with poor prognosis in gastric/gastroesophageal junction/esophageal (G/GEJ/E) cancers. We determined antitumor activity, safety, and pharmacokinetics of the small-molecule MET inhibitor AMG 337 in *MET*-amplified G/GEJ/E adenocarcinoma or other solid tumors.

Patients and Methods: In this phase II, single-arm study, adults with *MET*-amplified G/GEJ/E adenocarcinoma (cohort 1) or other *MET*-amplified solid tumors (cohort 2) received AMG 337 300 mg/day orally in 28-day cycles. The primary endpoint was objective response rate (ORR; cohort 1). Secondary endpoints included ORR (cohort 2), progression-free survival (PFS), overall survival (OS), and safety.

Results: Of 2101 patients screened for *MET* amplification, 132 were *MET*-amplified and 60 were enrolled: 45 in cohort 1, and 15 in cohort 2. Fifty-six patients (97%) had metastatic disease; 57 had prior lines of therapy (1 prior line, 29%; ≥2 prior lines, 69%). A protocol-permitted review showed efficacy that was lower-than-expected based on preliminary data from a first-in-human study, and enrollment was stopped. Fifty-eight patients received ≥1 AMG 337 dose. ORR in cohort 1 was 18% (8 partial responses). No responses were observed in cohort 2. Of 54 evaluable patients, median (95% CI) PFS and OS were 3.4 (2.2–5.0) and 7.9 (4.8–10.9) months, respectively. The most frequent adverse events (AEs) were headache (60%), nausea (38%), vomiting (38%), and abdominal pain, decreased appetite, and peripheral edema (33% each); 71% had grade ≥3 AEs and 59% had serious AEs.

Conclusions: AMG 337 showed antitumor activity in *MET*-amplified G/GEJ/E adenocarcinoma but not in *MET*-amplified non–small-cell lung cancer.

See related commentary by Ma, p. 2375

Introduction

Gastric and esophageal cancers are the fifth and eighth most common types of cancer worldwide, respectively (1). They are typically diagnosed at the locally advanced or advanced stage, when surgery is not an option (2). Systemic chemotherapy remains the primary mode of treatment for advanced disease; however, median overall survival (OS) for first-line treatment is approximately 9 to 11 months (3, 4).

The mesenchymal–epithelial transition (MET) receptor tyrosine kinase regulates cell survival, proliferation, and migration (5–9). MET overexpression and gene amplification have been observed in multiple solid tumors (10–14). MET overexpression has been reported in 46% to 74% of patients with gastric and esophageal cancers (15–18); *MET* amplification has been reported in 2% to 10% of this patient population (16–18). MET overexpression and amplification have been associated with poor prognosis, and MET overexpression has been correlated with depth of tumor invasion and lymph node metastasis, advanced stage, and shortened survival (18, 19); thus, MET inhibition represents a rational therapeutic strategy. Furthermore, MET pathway inhibitors (e.g., monoclonal antibodies and tyrosine kinase inhibitors) have shown activity in MET-overexpressing and *MET*-amplified gastric cancer (16, 20).

AMG 337 is a highly selective and potent small-molecule inhibitor of MET receptor signaling (21). In preclinical studies, AMG 337 inhibited phosphorylation of MET and downstream effectors in multiple *MET*-amplified cell lines, inhibited MET-dependent cell growth and induced apoptosis in those cell lines, and reduced tumor growth in MET-dependent xenograft models (21). In the phase I AMG 337 first-in-human study in solid

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Clinical Trial registration ID: ClinicalTrials.gov; NCT02016534

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Translational Relevance

A number of mesenchymal–epithelial transition (MET) pathway inhibitors have been assessed in clinical trials, but those trials have mainly focused on patients with high levels of MET protein expression. In this study, we assessed AMG 337, a highly selective small-molecule MET inhibitor, in patients with *MET* gene amplification, a relatively rare event. AMG 337 monotherapy in heavily pretreated patients with advanced stage *MET*-amplified tumors showed an objective response rate of 18% in the cohort of 45 patients with gastric/gastroesophageal junction/esophageal tumors and measurable disease. No responses were observed in patients with other solid tumors. The study was terminated after a protocol-permitted review showed lower-than-expected activity in a separate first-in-human study of AMG 337. Future studies are necessary to determine which biomarker(s) would be predictive of response to MET-targeted therapy, which signaling pathways contribute to resistance, and whether combination therapy would show greater efficacy than was observed in this study.

tumors, the maximum tolerated and recommended phase II dose was determined to be 300 mg orally once daily (QD), and the most common treatment-related adverse events (AEs) were headache, fatigue, nausea, and vomiting (22). In that study, AMG 337 showed an objective response rate (ORR) of 9.9% (11/111) in all patients, regardless of *MET*-amplification status, with a higher ORR (29.6%; 8/27) among *MET*-amplified patients. Based on the heightened antitumor activity in *MET*-amplified patients and acceptable toxicity profile observed in the first-in-human study, a decision was made to evaluate AMG 337 in additional trials, including the phase II study in patients with *MET*-amplified solid tumors reported here.

The objective of this phase II, multicenter, single-arm, 2-cohort study was to determine the antitumor activity, safety, and pharmacokinetics of AMG 337 in *MET*-amplified gastric/gastroesophageal junction/esophageal (G/GEJ/E) adenocarcinoma or other *MET*-amplified solid tumors (ClinicalTrials.gov Identifier: NCT02016534).

Patients and Methods

Patients

Adults with pathologically confirmed advanced G/GEJ/E adenocarcinoma or other solid tumors who had received prior therapy, for whom no standard therapy was available, or who had refused standard therapy, were included. Patients had tumor *MET* gene amplification as determined at a central laboratory; *MET* amplification was defined as a *MET*/*CEN-7* ratio $\geq$2.0. Patients also had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate organ function. Patients were excluded if they had known central nervous system metastases, arterial thrombosis, vascular ischemic events, venous thromboembolic events, peripheral edema grade >1, acute hepatitis B or detectable hepatitis C virus, or history of other malignancy within the previous 3 years. Patients with HER2-positive tumors were not excluded. All patients provided written informed consent. This study was conducted in accordance with the principles of the applicable country, US Food and Drug Administration, and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines. Compliance with ICH GCP guidelines provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki. The protocol was approved by an institutional review board or independent ethics committee at each study site.

Study design

This was a phase II, multicenter, single-arm cohort study. During screening, formalin-fixed, paraffin-embedded tumor samples were submitted for *MET*-amplification testing by a central laboratory. Tumor tissue submitted for testing was recent (preferred) or archival. Eligible patients with *MET*-amplified tumors were subsequently enrolled into 2 cohorts. Cohort 1 included patients with *MET*-amplified G/GEJ/E adenocarcinoma with measurable disease per RECIST version 1.1 (planned enrollment, $n = 100$). Cohort 2 included patients with other *MET*-amplified mixed solid tumors with measurable disease per RECIST version 1.1 (planned enrollment, $n = 40$); this cohort could include $\leq$10 patients with G/GEJ/E adenocarcinoma with nonmeasurable disease per RECIST version 1.1 (cohort 2A), $\leq$10 patients with G/GEJ/E adenocarcinoma with measurable disease who had received prior MET antibody therapy (cohort 2B), and patients with other types of *MET*-amplified solid tumors (cohort 2C).

Each treatment cycle consisted of a 28-day ($\pm$3 days) period. All patients self-administered AMG 337 300 mg orally QD on an empty stomach; at first, no food or drink (except water) was permitted 2 hours before/after administration. The protocol was later amended to allow caffeine (e.g., coffee) intake because caffeine use before dosing or during headache onset in the AMG 337 first-in-human study reduced the incidence of grade $\geq$3 headaches. Treatment continued for 12 months or until disease progression (per RECIST version 1.1), intolerance, consent withdrawal, initiation of a new systemic anticancer therapy, or study termination.

Treatment was withheld for patients who experienced grade $\geq$3 toxicity for which AMG 337 could not be excluded as the cause or grade $\geq$3 peripheral edema or headache until toxicity resolved. If resolution occurred within 4 weeks, patients resumed treatment at 200 mg QD. If toxicity recurred at the 200-mg QD dose, treatment was again withheld and patients could resume treatment at 150 mg QD. If resolution did not occur within 4 weeks or if toxicity occurred after the second dose reduction, treatment was discontinued.

Endpoints

The primary endpoint was ORR (proportion of patients with a complete response [CR] or partial response [PR]) per RECIST version 1.1 in cohort 1. Secondary endpoints included ORR in cohort 2, duration of response (DOR; time from first response to disease progression or death) and time to response (TTR; time from first dose to first response) in cohort 1 and patients from cohort 2 with measurable disease at baseline, progression-free survival (PFS; time from first dose to disease progression or death), OS (time from first dose to death), incidence and severity of AEs and significant laboratory abnormalities, AMG 337 exposure and dose intensity, and pharmacokinetics.

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Assessments

Radiologic tumor assessments (computed tomography or magnetic resonance imaging) per RECIST version 1.1 were conducted at screening, during week 8 (±3 days), and every 8 weeks thereafter until week 32. After week 32, assessments were conducted every 12 weeks until study end.

Adverse events and serious AEs were monitored throughout the study. Patients underwent a safety follow-up visit 30 (+3) days after the final administration unless the decision to discontinue treatment was made >30 days after the last AMG 337 dose or the patient was hospitalized at the time of the follow-up visit. In these instances, follow-up was conducted at the first available opportunity. Patients were contacted every 3 months (±14 days) after the safety follow-up visit or last response follow-up, whichever was later, until the final analysis or the last active patient had died, whichever occurred first. AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.

Pharmacokinetics

Approximately 20 patients at selected sites participated in intensive pharmacokinetic assessments. For these assessments, samples were collected predose and 0.5, 1.5, 3, and 6 hours postdose on cycle 1, day 1; predose on cycle 1, day 2; predose on cycle 1, day 15; predose and 0.5, 1.5, 3, and 6 hours postdose on cycle 1, day 28; predose on cycle 2, day 1; predose on day 1 of cycles 3, 5, 7, and 9; every 12 weeks thereafter; and at safety follow-up.

All patients participated in general pharmacokinetic assessments. Samples for pharmacokinetics were collected predose on days 1 and 15 of cycle 1; on day 1 of cycles 2, 3, 5, 7, and 9; every 12 weeks thereafter; and at safety follow-up. Samples were also taken 3 hours postdose on day 1 of cycles 1, 3, and 5.

Pharmacokinetic parameters were estimated by noncompartmental analysis of AMG 337 using Phoenix WinNonlin v.6.4 software (Centara; Princeton, NJ) based on individual plasma concentrations. The following parameters were estimated: maximum concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration–time curve from 0 to 24 hours (AUC_{0-24}), and accumulation ratio (AR), calculated as AUC on day 28 divided by AUC on day 1.

Biomarker analysis

To determine study eligibility, *MET* gene amplification status was assessed in a single central laboratory by IQFISH (Dako North America, an Agilent Technology Company; Carpinteria, CA). *MET* amplification was defined as a *MET/CEN-7* ratio ≥2.0. In exploratory analyses, *MET* gene copy number was evaluated. Biomarker assessments were conducted on archival tumor tissue.

Statistical analysis

No formal hypothesis testing was planned. The study focus was the estimation of the magnitude of treatment effect as assessed by ORR in cohort 1. The point estimate of ORR and the corresponding exact binomial 2-sided 95% CI were generated. The planned sample size was approximately 100 for cohort 1 and approximately 40 for cohort 2. With the planned sample size, the ORR could be estimated with a standard error not greater than 5%; the half-width of the 95% CI for the estimated ORR would be no more than 10%. Assuming an observed ORR of 50%, the lower bound of the 95% CI for the estimated ORR would exclude values <40%.

The full and safety analysis sets included all patients who received ≥1 AMG 337 dose. Response analyses included all patients with measurable disease who received ≥1 AMG 337 dose. Pharmacokinetic analyses included all patients from the safety analysis set with evaluable blood samples. All analyses were descriptive and focused on the estimation of the magnitude of treatment effect. Descriptive statistics were provided for safety and efficacy endpoints. Safety summaries were provided for all G/GEJ/E patients and overall.

The number and percentage of patients with a best overall response of CR, PR, stable disease, progressive disease, noncomplete response/nonprogressive disease were determined. The stable disease classification required patients to have a response of stable disease ≥6 weeks after the date of the first dose of AMG 337. ORR was calculated along with the corresponding exact 95% CI using the Clopper–Pearson method (23). For time-to-event variables, the Kaplan–Meier estimates and corresponding 2-sided 95% CI for the median were determined, and survival plots were prepared.

Results

Patients

Between February 14, 2014, and May 16, 2016 (data cutoff), 2,101 patients from 34 study centers were screened; 132 (6%) patients had *MET*-amplification, and 60 patients were enrolled (Fig. 1). Forty-five patients with measurable G/GEJ/E adenocarcinoma were enrolled in cohort 1; 10 patients with nonmeasurable G/GEJ/E adenocarcinoma were enrolled in cohort 2A; 1 patient with measurable G/GEJ/E adenocarcinoma who had received prior MET antibody therapy was enrolled in cohort 2B; and 4 patients with non–small-cell lung cancer (NSCLC) were enrolled in cohort 2C. Five patients were HER2-positive/amplified (cohort 1, $n = 4$; cohort 2A, $n = 1$).

Most patients were male (72%) and white (64%); median (range) age was 62 (25–85) years (Table 1). Fifty-six patients (97%) had metastatic disease, and 57 (98%) had received at least 1 prior line of therapy (1 prior line, 29%; 2 prior lines, 29%; and >2 prior lines 40%). Seventy-two percent of patients did not respond to the first line of chemotherapy, 67% of patients did not respond to any line of chemotherapy, 66% had prior curative surgery for their cancer, and 78% had prior radiotherapy for the current malignancy. Thirty-nine patients (67%) had an ECOG performance status of 1.

Of the 60 patients enrolled, 58 (97%) received ≥1 AMG 337 dose and were included in the efficacy and safety analyses; 2 patients (3%; 1 each from cohorts 2A and 2C) did not receive AMG 337. Forty-five (78%) had ≥1 dose reduction or dose withheld, most because of toxicity (59%). At data cutoff, 57 (95%) had discontinued treatment (disease progression, 57%; AEs, 17%; patient request, 8%; other, 8%; death, 3%; noncompliance, 2%); 1 from cohort 2A remained on study. Median (95% CI) time to treatment discontinuation was 2.6 (1.9–3.6) months. Reasons for study discontinuation included death (68%), administrative decision (17%), consent withdrawal (8%), and loss to follow-up (3%).

Enrollment in this and all AMG 337 studies was stopped and regulatory agencies were notified when a protocol-permitted review of this study found an ORR that was lower than expected based on preliminary data from the AMG 337 first-in-human

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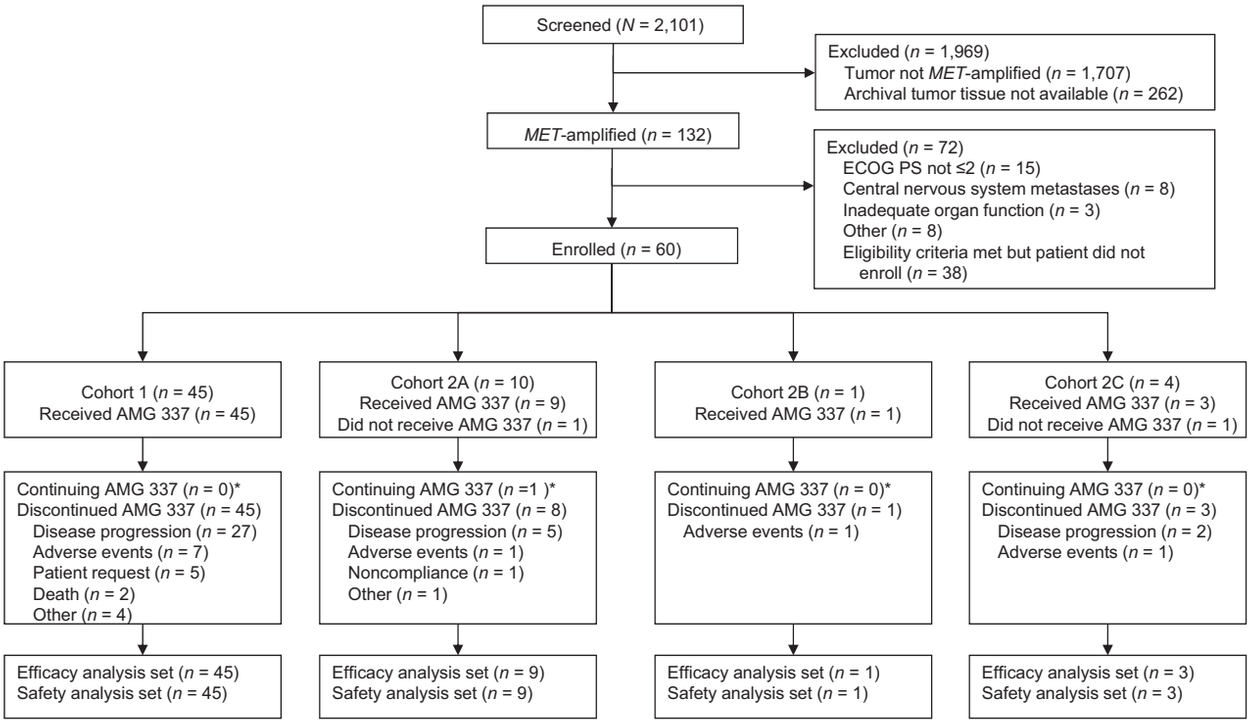

Figure 1.

Patient disposition. Cohort 1: patients with *MET*-amplified G/GEJ/E adenocarcinoma with measurable disease per RECIST; cohort 2A: patients with *MET*-amplified G/GEJ/E adenocarcinoma with nonmeasurable disease per RECIST; cohort 2B: a patient with *MET*-amplified G/GEJ/E adenocarcinoma with measurable disease per RECIST who had received prior MET antibody therapy; cohort 2C: patients with non–small-cell lung cancer. *At data cutoff, May 16, 2016.

study (22). As of July 2014, the first-in-human study had shown responses in 8 of 13 (62%) patients with *MET*-amplified G/GEJ/E adenocarcinoma (1 CR, duration of 141 weeks; 7 PRs, duration up to 85 weeks), suggesting that the response rate in this study, which only enrolled patients with *MET*-amplified tumors, would be high.

Efficacy

The maximum change in the sum of longest diameter (SLD) of target lesions for patients in cohort 1 is shown in Fig. 2A. Twelve patients had maximum percentage reductions >30%, and 7 patients had increases in SLD of their target lesion. Eight patients in cohort 1 achieved a best response of PR, for an ORR (95% CI) of 18% (8%-32%) in that cohort. Median (range) TTR was 7.6 (7.0–16.1) weeks, and median (95% CI) DOR was 6.0 (3.7–16.7) months in cohort 1. Of those who achieved a PR, 7 (88%) had disease progression, and 1 (13%) was censored. Sixteen patients in cohort 1 experienced a best response of stable disease (defined as neither sufficient target lesion shrinkage to be classified as PR nor sufficient increase to be classified as progression; Table 2); no responses were observed in the patients with G/GEJ/E adenocarcinoma in cohorts 2A or 2B or in the patients with NSCLC in cohort 2C.

Fifty-four patients (cohort 1, $n = 45$; cohort 2A, $n = 9$) were included in the PFS and OS analyses. Forty-five patients (83%) had a PFS event; median (95% CI) PFS was 3.4 (2.2-5.0) months (Fig. 2B). Thirty-six patients (66.7%) died; median (95% CI) OS was 7.9 (4.8–10.9) months (Fig. 2C).

Exposure

Across all cohorts, median (range) number of treatment cycles completed was 3.0 (1–21), and duration of treatment was 2.2 (0–20) months. Forty-five patients (78%) had ≥1 dose change or reduction, largely because of AEs ($n = 34$; 59%). Median (range) actual dose intensity was 297.8 (59–345) mg/day; relative dose intensity was 99% (20%–115%).

Adverse events

Fifty-seven patients (98%) had ≥1 treatment-emergent AE (Table 3). The most frequently reported AEs (≥30% of all patients) were headache (60%), nausea (38%), vomiting (38%), abdominal pain (33%), decreased appetite (33%), and peripheral edema (33%). Forty-one patients (71%) had grade ≥3 AEs, and 34 (59%) had serious AEs. Ten patients (17%) had AEs leading to AMG 337 discontinuation; these AEs were headache ($n = 2$ patients) and upper abdominal pain, increased blood bilirubin, cholangitis, fatigue, general physical health deterioration, increased hepatic enzyme, edema, peripheral edema, and vomiting ($n = 1$ patient each). Nine patients (16%) had fatal AEs; none were deemed treatment-related by investigators. Overall, AEs of interest were reported for 90% of patients; the most frequent was headache. Headache pain (worst level at onset) was evaluated on a scale from 1 (very mild pain) to 10 (extreme pain) for 35 patients who had any postbaseline headache pain; 9 (26%) had scores ≥6; the remaining (45%) had scores ranging from 1 to 5. AMG 337 is a potent inhibitor of the adenosine transporter, which was considered the underlying cause of headache. Other AEs of interest were

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Table 1. Patient demographics and disease characteristics[a]

Characteristic	Cohort 1 ($n = 45$)	Cohort 2A ($n = 9$)	Cohort 2B ($n = 1$)	Cohort 2C ($n = 3$)	All patients ($N = 58$)
Sex					
Female	11 (24)	3 (33)	1 (100)	1 (33)	16 (28)
Male	34 (76)	6 (67)	0	2 (67)	42 (72)
Median (range) age, years	62 (34–85)	58 (25–81)	59 (59–59)	64 (58–67)	62 (25–85)
Race					
White	27 (60)	6 (67)	1 (100)	3 (100)	37 (64)
Asian	17 (38)	3 (33)	0	0	20 (35)
Other	1 (2)	0	0	0	1 (2)
Ethnicity					
Hispanic/Latino	0	1 (11)	0	0	1 (2)
Not Hispanic/Latino	45 (100)	8 (89)	1 (100)	3 (100)	57 (98)
Region					
Asian	17 (38)	3 (33)	0	0	20 (35)
Europe/Australia	26 (58)	4 (44)	1 (100)	3 (100)	34 (59)
North America	2 (4)	2 (22)	0	0	4 (7)
ECOG performance status					
0	15 (33)	3 (33)	1 (100)	0	19 (33)
1	30 (67)	6 (67)	0	3 (100)	39 (67)
Disease stage at screening					
Locally advanced	2 (4)	0	0	0	2 (3)
Metastatic disease	43 (96)	9 (100)	1 (100)	3 (100)	56 (97)
Primary tumor location					
Stomach	33 (73)	7 (78)	0	0	40 (69)
GEJ	6 (13)	1 (11)	1 (100)	0	8 (14)
Esophageal	5 (11)	1 (11)	0	0	6 (10)
Other	1 (2)	0	0	3 (100)	4 (7)
Prior lines of therapy					
0	0	1 (11)	0	0	1 (2)
1	12 (27)	4 (44)	1 (100)	0	17 (29)
2	14 (31)	2 (22)	0	1 (33)	17 (29)
>2	19 (42)	2 (22)	0	2 (67)	23 (40)
MET/CEN-7 ratio, median (range)	6.2 (2.0–20.4)	4.7 (2.1–14.7)	2.5 (2.5–2.5)	4.7 (2.7–8.6)	5.4 (2.0–20.4)

NOTE: All data are *n* (%) unless otherwise stated.
[a]Full analysis set.

edema (57%), skin and subcutaneous disorders (35%), and drug-related hepatic disorders (35%).

Pharmacokinetics

The pharmacokinetic analysis set comprised 467 plasma samples from 58 patients; 16 with G/GEJ/E tumors underwent intensive pharmacokinetic sampling and had sufficient data for analysis (cohort 1, $n = 12$; cohort 2, $n = 4$). Pharmacokinetics were similar between cohorts, with no large variation from days 1 to 28 (Table 4). Mean C_{max} ranged from 3,080 to 4,110 ng/mL; mean t_{max} was approximately 3 hours; mean AUC_{0-24} ranged from 32,800 to 48,200 h·ng/mL, and accumulation was minimal: mean AR was 0.946 and 0.965 for cohorts 1 and 2, respectively.

Biomarkers

A tumor *MET/CEN-7* ratio $\geq$2.0 was a study eligibility criterion. Among the 58 patients included in the analysis, the mean (range) *MET/CEN-7* ratio was 7.0 (2.0–20.4), and mean (range) gene copy number was 16.4 (3.5–51.3). Among the 47 patients who were evaluable for treatment response, the mean (range) *MET/CEN-7* ratio was 7.7 (2.4–12.0) among the 8 responders (17.0%) and 7.1 (2.0–20.4) among the 39 nonresponders (83.0%).

Discussion

To our knowledge, this is the largest *MET*-amplification screen in G/GEJ/E cancer to date; 2,101 patients with G/GEJ/E cancer were screened using an analytically validated IQFISH assay. Previous MET pathway inhibitors assessed in clinical trials have focused on patients with high levels of MET protein expression (24, 25). In this study, we enrolled patients with tumors that exhibited *MET* gene amplification, a relatively rare event, as determined by *MET/CEN-7* ratio $\geq$2.0. *MET* amplification indicates pathway "addiction" and suggests that MET inhibition could be beneficial in *MET*-amplified patients (16, 20), a result supported by animal models (24). Resistance to MET inhibition can occur through activation of other pathways (24). For example, activation of HER2 or epidermal growth factor receptor pathways in *MET*-amplified GEJ tumor cell lines can overcome MET inhibition (24). This resistance may partially explain why an antitumor response to AMG 337 was not observed in more patients.

Of the 2,101 patients screened for eligibility for this study, including patients with G/GEJ/E adenocarcinoma and NSCLC, only 132 (6%) had *MET* amplification, which is consistent with previously reported rates of 2% to 10% (16, 18), yet this is a small percentage of the total G/GEJ/E population. In this study, which enrolled 60 of those eligible patients and evaluated AMG 337 as monotherapy, PRs as the best response were observed in 8 patients with G/GEJ/E tumors; no responses were observed in patients with NSCLC or in patients with nonmeasurable gastric cancer who had previously received MET inhibitors. Biomarker analysis did not uncover an association between the level of *MET* gene amplification and response to AMG 337 treatment; however, the total number of responders in this analysis was small.

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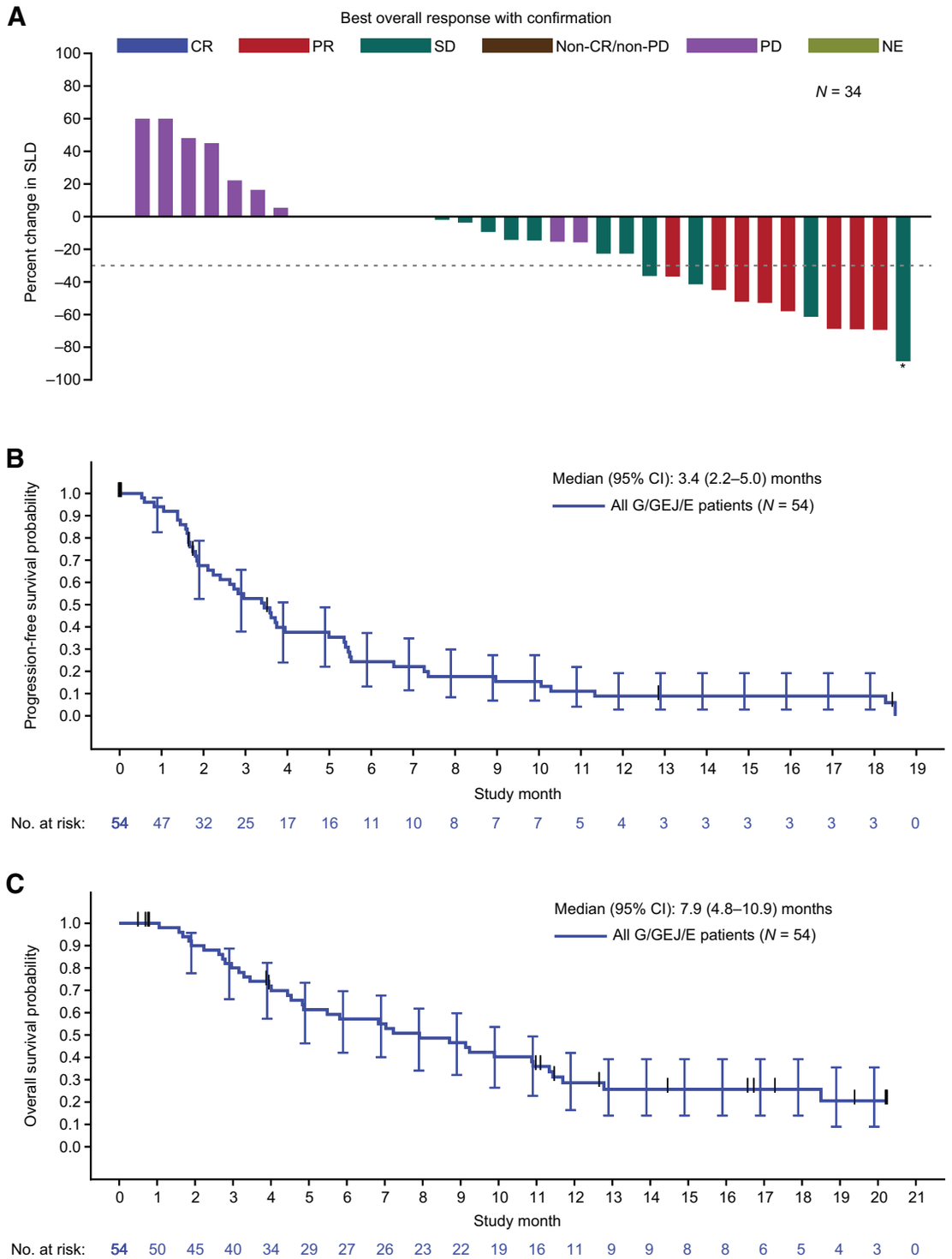

Figure 2.

Efficacy in patients with G/GEJ/E carcinoma. **A,** Maximum change in sum of longest diameter (SLD) of target lesion(s) in cohort 1, with bars shaded per RECIST response. **B,** PFS in all G/GEJ/E patients. **C,** OS in all G/GEJ/E patients. The dashed line in **A** marks 30% reduction in SLD; error bars in **B** and **C** indicate 95% CI. NE, not evaluable. *Unconfirmed PR graded as SD.

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Table 2. Efficacy analyses[a]

Efficacy, *n* (%)	Cohort 1 (*n* = 45)[b]	Cohort 2A (*n* = 10)[b]	Cohort 2B (*n* = 1)[b]	Cohort 2C (*n* = 4)[b]	All patients (*N* = 60)[b]
Response analysis set inclusion	45 (100)	0	1 (100)	3 (75)	49 (82)
Response analysis set exclusion[a]	0	10 (100)	0	1 (25)	11 (18)
No measurable tumor per RECIST at baseline	0	10 (100)	0	0	10 (17)
Did not receive AMG 337	0	1 (10)	0	1 (25)	2 (3)
Best response[a]					
CR	0	0	0	0	0
Partial response	8 (18)	0	0	0	8 (16)
Stable disease	16 (36)	N/A[c]	1 (100)	1 (33)	18 (37)
Non-CR/non-PD	0	N/A[c]	0	0	0
PD	12 (27)	N/A[c]	0	1 (33)	13 (27)
Not assessed	9 (20)	N/A[c]	0	1 (33)	10 (20)
ORR, %[d]	18	N/A	N/A	N/A	16
95% exact CI, %	8–32	N/A	N/A	N/A	7–30

Abbreviations: N/A, not applicable; PD, progressive disease.
[a]Response analysis set; defined as all enrolled patients with measurable tumor per RECIST at baseline who received ≥1 dose of AMG 337.
[b]All enrolled patients.
[c]No enrolled patients from cohort 2A met the criteria for inclusion in the response analysis set; however, among patients from cohort 2A excluded from response analysis set, 1 patient experienced stable disease, 5 patients experienced non-CR/non-PD, and 2 patients experienced PD; the response assessment was not conducted in 1 patient.
[d]Responses required confirmation.

Pharmacokinetics and rates/types of AEs were similar to those from previous AMG 337 studies (22); the most common treatment-emergent AEs were headache, vomiting, and nausea. Headache is a common adverse reaction to adenosine receptor agonists/transport inhibitors and may be reversed by adenosine antagonists such as caffeine (25, 26). AMG 337 pharmacokinetics was characterized by rapid absorption and no accumulation over 28 days of dosing.

Table 3. Treatment-emergent adverse events[a]

AE, *n* (%)	Patients (*N* = 58)
All AEs	57 (98)
Grade ≥3[b] AE	41 (71)
Serious AE	34 (59)
Serious treatment-related AE	12 (21)
Fatal AE	9 (16)
AEs of interest	52 (90)
AEs reported in ≥10% of patients	
Headache	35 (60)
Nausea	22 (38)
Vomiting	22 (38)
Abdominal pain	19 (33)
Decreased appetite	19 (33)
Peripheral edema	19 (33)
Fatigue	13 (22)
Asthenia	12 (21)
Diarrhea	12 (21)
Hypoalbuminemia	11 (19)
Back pain	10 (17)
Constipation	10 (17)
Dry skin	9 (16)
Dyspepsia	9 (16)
Edema	8 (14)
Pruritus	8 (14)
Pyrexia	8 (14)
Upper abdominal pain	7 (12)
ALT increased	7 (12)
Dizziness	7 (12)
Dyspnea	7 (12)
Rash	7 (12)
Ascites	6 (10)
Hypotension	6 (10)

Abbreviation: ALT, alanine aminotransferase.
[a]Safety analysis set.
[b]Per Common Terminology Criteria for Adverse Events version 4.

Results from preclinical studies and the phase I AMG 337 first-in-human study (ClinicalTrials.gov; NCT01253707) indicated that tumors with *MET* amplification had sensitivity to AMG 337 (21, 22, 27). However, an interim analysis of this study initiated when 30 patients had completed 2 28-day cycles found response rates that were lower than expected based on preliminary data from the AMG 337 phase I study. Responses had been observed in 62% of patients with *MET*-amplified tumors in the phase I study; responses were observed in only 13% of evaluable patients (3 of 24 patients with at least 1 postbaseline scan) in the analysis of this study that was available as of January 22, 2015. Consequently, this study was terminated early, and enrollment in all AMG 337 trials was discontinued. Reasons for the differences in response rates between the phase I study and the phase II study are unclear. The number of patients in the phase 1 study was small (111 enrolled, 27 *MET*-amplified), the response rates in the final analysis of the phase I study were lower (30%, 8 of 27 *MET*-amplified patients), and patients in the phase I study may have been enriched for factors other than MET that are not currently understood. The phase I study enrolled patients with a broader range of tumor types; the phase II study included patients who had received prior therapy for advanced disease (not just patients refractory to standard treatment or for whom no standard therapy was available), and the proportion of patients with metastatic disease was higher in the phase II study (97% vs. 89%). Future studies are necessary to determine which biomarker(s) would be predictive of response to MET-targeted therapy, which signaling pathways contribute to resistance, and whether combination therapy with a MET inhibitor and another targeted agent would show greater efficacy than was observed here.

The MET inhibitors onartuzumab (a monovalent monoclonal antibody that binds the extracellular domain of MET, blocking interaction with the MET ligand HGF) and rilotumumab (a monoclonal antibody that selectively targets HGF) have been examined in MET-IHC–positive G/GEJ cancer (28, 29). The phase

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Table 4. Pharmacokinetics[a]

	Cohort 1							Cohort 2						
	Day 1			Day 28				Day 1			Day 28			
Statistics	t_{max}, h (n = 12)	C_{max}, ng/mL (n = 12)	AUC_{0-24}, h·ng/mL (n = 12)	t_{max}, h (n = 8)	C_{max}, ng/mL (n = 8)	AUC_{0-24}, h·ng/mL (n = 7)	AR (n = 7)	t_{max}, h (n = 4)	C_{max}, ng/mL (n = 4)	AUC_{0-24}, h·ng/mL (n = 3)	t_{max}, h (n = 3)	C_{max}, ng/mL (n = 3)	AUC_{0-24}, h·ng/mL (n = 3)	AR (n = 3)
Mean (SD)	3.2 (1.4)	4,110 (1,850)	48,200 (22,000)	3.0 (1.4)	3,260 (832)	36,800 (11,800)	0.946 (0.389)	3.0 (2.1)	3,080 (535)	36,000 (7,530)	1.8 (1.3)	3,100 (448)	32,800 (9,020)	0.965 (0.404)
Median	3.0	3,700	42,200	3.0	3,520	39,100	1.07	2.3	3,160	34,100	1.9	3,330	37,400	1.13
(range)	(1.5–6.1)	(1,570–7,170)	(17,600–94,300)	(1.5–6.0)	(2,040–4,380)	(21,000–54,900)	(0.328–1.37)	(1.5–6.0)	(2,410–3,570)	(27,900–44,300)	(0.4–3.0)	(2,580–3,380)	(22,400–38,500)	(0.504–1.26)
CV%	41.9	45.0	47.6	45.2	25.5	32.1	41.1	69.7	17.4	20.9	70.8	14.5	27.5	41.9

Abbreviation: CV, coefficient of variation.
[a]Pharmacokinetic analysis set.

III METGastric and RILOMET-1 studies demonstrated no PFS or OS benefit with either MET inhibitor in combination with chemotherapy (28, 29). The phase II YO28252 study of onartuzumab plus FOLFOX in patients with metastatic GEJ or gastric adenocarcinoma reported a median PFS of 5.95 months for onartuzumab plus FOLFOX versus 6.80 months for placebo plus FOLFOX in all patients, a median OS of 8.51 months versus 8.48 months in the MET-positive subset, and an ORR of 60.5% in the intent-to-treat population (30). In the present single-arm, phase II study of AMG 337 as monotherapy in patients with *MET*-amplified solid tumors, median PFS and OS were 3.4 and 7.9 months, respectively, and the ORR was 16% overall (18% in patients with measurable *MET*-amplified G/GEJ/E adenocarcinoma [cohort 1]).

This study had several limitations. This was a single-arm study; thus, within-study comparison of the response rate with standard of care was not possible. Additionally, early termination likely influenced the final results. Although patients were enrolled based on *MET* amplification status, testing of *MET* amplification was conducted using archival tumor tissue, and the test result may not have been reflective of tumor status during the study. It is possible that some tumors may have changed between the time archival tumor samples were collected and the time patients were enrolled and treated, or that other genomic alterations in some tumors may have affected response to inhibition of the MET signaling pathway. In the future, this may be addressable using novel diagnostic tools (e.g., liquid biopsy) to evaluate dynamic changes occurring during therapy (30).

In conclusion, this study of AMG 337 monotherapy demonstrated an ORR of 18% in heavily pretreated patients with advanced *MET*-amplified G/GEJ/E adenocarcinoma and a median duration of response of 6.0 months (cohort 1). Although it is unlikely that monotherapy would be beneficial in unselected patients, it is possible that a select group of patients could benefit from AMG 337 or that combination therapy strategies could be useful; however, such approaches would require further study.

Disclosure of Potential Conflicts of Interest

E. Van Cutsem is a consultant/advisory board member for Bayer, Bristol-Myers Squibb, Celgene, Lilly, Merck KgA, MSD, Novartis, Servier, and reports receiving commercial research support from Amgen, Bayer, Boehringer, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, MSD, Merck KgA, Novartis, Roche, and Servier. V. Shankaran reports receiving commercial research grants from AstraZeneca, Bayer, and Bristol-Myers Squibb. S. Siena is a consultant/advisory board member for Amgen, Bayer, Bristol-Myers Squibb, Incyte, Merck, Novartis, Roche, and Seattle Genetics. Ning F. Go and Hui Yang are employees and stockholders of Amgen Inc. Marco Schupp is an employee of Amgen (Europe) GmbH and is a stockholder of Amgen Inc. D. Cunningham reports receiving commercial research grants from 4SC, Amgen, AstraZeneca, Bayer, Celgene, Clovis, Eli Lilly, Janssen, MedImmune, Merck, Merrimack, and Sanofi. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Van Cutsem, B. Karaszewska, Y.-K. Kang, H.C. Chung, S. Siena, N.F. Go, H. Yang, M. Schupp
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Data Sharing Statement

There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (i) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or (ii) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews requests. If not approved, requests may be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/.

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