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First-in-Human Study of AMG 820, a Monoclonal Anti-Colony-Stimulating Factor 1 Receptor Antibody, in Patients with Advanced Solid Tumors

Kyriakos P. Papadopoulos[1], Larry Gluck[2], Lainie P. Martin[3], Anthony J. Olszanski[3], Anthony W. Tolcher[4], Gataree Ngarmchamnanrith[5], Erik Rasmussen[6], Benny M. Amore[7], Dirk Nagorsen[5], John S. Hill[5], and Joe Stephenson Jr[2]

Abstract

Purpose: Binding of colony-stimulating factor 1 (CSF1) ligand to the CSF1 receptor (CSF1R) regulates survival of tumor-associated macrophages, which generally promote an immunosuppressive tumor microenvironment. AMG 820 is an investigational, fully human CSF1R antibody that inhibits binding of the ligands CSF1 and IL34 and subsequent ligand-mediated receptor activation. This first-in-human phase I study evaluated the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of AMG 820.

Experimental Design: Adult patients with relapsed or refractory advanced solid tumors received intravenous AMG 820 0.5 mg/kg once weekly or 1.5 to 20 mg/kg every 2 weeks until disease progression, adverse event (AE), or consent withdrawal.

Results: Twenty-five patients received $\geq$1 dose of AMG 820. AMG 820 was tolerated up to 20 mg/kg; the MTD was not reached. One dose-limiting toxicity was observed (20 mg/kg; nonreversible grade 3 deafness). Most patients (76%) had treatment-related AEs; the most common were periorbital edema (44%), increased aspartate aminotransferase (AST; 28%), fatigue (24%), nausea (16%), increased blood alkaline phosphatase (12%), and blurred vision (12%). No patients had serious or fatal treatment-related AEs; 28% had grade $\geq$3 treatment-related AEs. Grade 3 AST elevations resolved when treatment was withheld. AMG 820 showed linear pharmacokinetics, with minimal accumulation (<2-fold) after repeated dosing. Pharmacodynamic increases in serum CSF1 concentrations and reduced numbers of skin macrophages were observed. Best response was stable disease in 8 patients (32%).

Conclusions: AMG 820 was tolerated with manageable toxicities up to 20 mg/kg every 2 weeks. Pharmacodynamic response was demonstrated, and limited antitumor activity was observed. *Clin Cancer Res; 23(19); 5703–10. ©2017 AACR.*

Introduction

Tumor-associated macrophages (TAM) play an important role in supporting tumor growth and invasion and predominantly promote an immunosuppressive tumor microenvironment (1–4). TAMs support accumulation of regulatory T cells, which suppress cytotoxic natural killer and $CD8^+$ T cells, and facilitate metastasis through increasing angiogenesis (4). TAM recruitment and survival is regulated by binding of colony-stimulating factor-1 [CSF1, also known as macrophage colony-stimulating factor (MCSF)] to its cell-surface receptor (CSF1R, also known as MCSFR, FMS, or CD115; refs. 2, 3, 5). Multiple tumor types abnormally express CSF1R (6–8), which binds both receptor-specific ligands CSF1 and IL34 (5, 9, 10). Elevated serum CSF1, increased numbers of TAMs in tumors, and high expression of tissue CSF1 and/or CSF1R are associated with poor prognosis in patients with various cancers (1). CSF1R inhibitors can reduce tumor size in patients with diffuse-type giant cell tumors formed by aberrantly high expression of CSF1 and massive recruitment of CSF1R-expressing macrophages (11–13), and blocking CSF1R reduces TAM infiltration in various solid tumor models (14–17). Depletion of TAMs may modulate the negative influence of an immunosuppressive environment and provide an immunotherapeutic approach that is distinct from immune checkpoint inhibitors (18–21).

AMG 820 is an investigational, fully human immunoglobulin G2 mAb directed against human CSF1R that inhibits binding of the ligands CSF1 and IL34 and subsequent ligand-induced receptor activation. Preclinically, AMG 820 potently inhibited CSF1-driven proliferation of human bone marrow–derived monocytic

[1]Hematology/Oncology, START (South Texas Accelerated Research Therapeutics), San Antonio, Texas. [2]Medical Oncology/Hematology, Greenville Health System Cancer Institute, Greenville, South Carolina. [3]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania. [4]Clinical Research, START (South Texas Accelerated Research Therapeutics), San Antonio, Texas. [5]Early Development, Hematology and Oncology, Amgen Inc., Thousand Oaks, California. [6]Biostatistical Sciences, Amgen Inc., Thousand Oaks, California. [7]Clinical Pharmacology, Modeling and Simulation, Amgen Inc., South San Francisco, California.

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Current address for J.S. Hill: Translational Medicine, Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA.

Corresponding Author: Kyriakos P. Papadopoulos, South Texas Accelerated Research Therapeutics, 4383 Medical Drive, Suite 4021, San Antonio, TX 78229. Phone: 210-593-5270; Fax: 210-615-1121; E-mail: Kyri.Papadopoulos@start.stoh.com

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Translational Relevance

Tumor-associated macrophages (TAM) comprise a significant proportion of the cells in many tumors and may promote an immunosuppressive tumor microenvironment. TAM recruitment and survival is regulated by binding of colony-stimulating factor 1 (CSF1) or IL34 to the CSF1 receptor (CSF1R). Inhibition of CSF1R significantly reduces the number of TAMs and inhibits tumor growth in several but not all preclinical models. AMG 820 is a fully human mAb directed against human CSF1R that blocks ligand binding and receptor activation. We report the first-in-human clinical study of AMG 820 in patients with advanced solid tumors. AMG 820 was tolerated with manageable toxicities up to 20 mg/kg every 2 weeks. Pharmacodynamic response of reduced macrophages in skin biopsies was demonstrated and limited antitumor activity was observed. These data support continued investigation of AMG 820, with TAM depletion, providing an immunotherapeutic approach that is both distinct and potentially synergistic with immune checkpoint inhibitors.

cells, as well as CSF1- and IL34-driven proliferation of myelomonocytic AML-5 cells (Amgen Inc., data on file). Furthermore, the mouse surrogate antibody M279 significantly reduced TAMs in syngeneic mouse tumor models (AE5MG mesothelioma and Lewis Lung carcinoma; ref. 22), and depleted TAMs and inhibited tumor growth in a transgenic tumor model of aggressive breast cancer (23). The objective of this study was to assess the safety and tolerability [including dose-limiting toxicities (DLT) and MTD], and to evaluate the pharmacokinetics, pharmacodynamics, and antitumor activity of AMG 820 after multiple intravenous administrations in patients with advanced solid tumors.

Materials and Methods

This phase I, first-in-human, open-label, sequential dose-escalation study was conducted at three centers in the United States. This study was conducted in accordance with applicable Food and Drug Administration regulations and International Conference on Harmonization Good Clinical Practice regulations/guidelines. The study was reviewed and approved by the institutional review board of each study center. All patients provided written informed consent.

Patients

Eligible patients were $\geq$18 years old and had pathologically confirmed advanced solid tumors refractory to standard treatment; measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines; Eastern Cooperative Oncology Group performance status $\leq$2; and adequate hematologic, hepatic, cardiovascular, and renal function (24, 25). Exclusion criteria included primary central nervous system (CNS) tumors or CNS metastases; previous chemotherapy, radiotherapy, or investigational drug or immunotherapy within 28 days of first infusion; or anticoagulation therapy. A full list of the inclusion and exclusion criteria is provided in the Supplementary Methods.

Study design

This was a phase I, first-in-human, open-label, sequential dose-escalation study. Primary endpoints included the incidence of DLTs and adverse events (AE) and characterization of the AMG 820 pharmacokinetic profile. Secondary endpoints included tumor response as assessed per RECIST (24) and treatment-mediated changes in baseline levels of CSF1, IL34, and tartrate-resistant acid phosphatase isoform 5b (TRAP5b). Exploratory endpoints included the pharmacokinetic–pharmacodynamic relationship for safety and/or efficacy endpoints.

AMG 820 was administered by intravenous infusion over 60 minutes. The starting dose of AMG 820 was 0.5 mg/kg once weekly based on toxicologic, pharmacologic, and pharmacokinetic data obtained in cynomolgus monkeys; a protocol amendment was made to give all subsequent planned doses of AMG 820 (1.5, 3, 6, 10, and 20 mg/kg) once every 2 weeks. A standard 3+3 dose-finding design was used. The original study protocol included a dose-expansion phase; however, a decision was made to terminate the study (not related to safety reasons) after the completion of the dose-escalation phase. The MTD was defined as the highest dose with 0 out of 3 patients or $\leq$1 out of 6 patients in each cohort without DLTs. Dose escalation continued until the maximum tolerated or planned dose was reached.

A DLT was defined as any grade $\geq$3 hematologic or non-hematologic toxicity (except alopecia) occurring between days 1 and 28, unless clearly attributable to causes other than AMG 820 treatment. Patients experiencing a DLT between days 1 and 28 discontinued AMG 820. Patients withdrawn before day 28 for other than AMG 820–related reasons were replaced. Patients who experienced grade $\geq$3 periorbital edema or conjunctival swelling had AMG 820 withheld until resolution to grade $\leq$2; those who required >4 weeks to recover to grade $\leq$2 were withdrawn from the study. Patients received AMG 820 until disease progression, intolerable AEs, investigator decision, or consent withdrawal.

Study assessments

Safety assessments were performed at least every 2 weeks throughout the study treatment period and included vital sign measurements, physical examinations, clinical laboratory tests, 12-lead electrocardiogram, urinalysis, and collection of AE information. Baseline and end-of-study audiometry was instituted after an index patient experienced hearing loss. Treatment-emergent AEs were graded using Common Terminology Criteria for Adverse Events version 4.0 (26).

Radiologic assessments of tumor response by CT or MRI were conducted at baseline and approximately every 8 weeks thereafter according to RECIST (24). Tumor response was assessed locally at the sites and retrospectively at a central independent core laboratory.

Pharmacokinetics

Serum samples were collected on treatment days 1 and 43 at predose; 0.5 hours after beginning of infusion and end of infusion (EOI); at EOI +1, 6, 24, 96, 168, and 240 hours postdose; on day 15 at predose, EOI, EOI +1, 6, and 168 hours postdose; and for all other cycles predose and EOI +1 hour. AMG 820 concentrations were measured using an ELISA with a lower limit of quantification of 10 ng/mL (Amgen Inc., data on file). Noncompartmental analysis of AMG 820

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concentration–time data was conducted using Phoenix WinNonlin v.6.3 (Pharsight) to estimate maximum serum concentration (C_{max}), the time of C_{max}, last quantifiable drug concentration (C_{last}), elimination half-life ($t_{1/2}$), area under the concentration–time curve from time zero to last measurement (AUC_{last}), systemic clearance (CL), and steady-state volume of distribution (V_{ss}). Samples for anti-AMG 820 antibody testing were collected predose at cycle 1 day 1, every 2 weeks, and at study termination and were analyzed using a validated bridging antibody immunoassay.

Pharmacodynamics and biomarkers

Changes in macrophage populations after AMG 820 dosing were assessed in paired skin punch biopsies taken predose at screening, week 5, and week 13. Samples were processed for IHC analysis of CSF1R (CD115) and the macrophage markers CD68, CD163, and CD206 (Supplementary Methods). To assess the biomarkers CSF1, IL34, and TRAP5b, blood samples were collected and analyzed by standard sandwich ELISA methods. Blood samples for CSF1 and IL34 were collected concurrently with pharmacokinetic samples; for TRAP5b, a marker of osteoclast activity, the samples were collected predose at weeks 1, 3, 5, 9, every 8 weeks thereafter, and end of study.

Statistical analysis

The sample size in this study was determined empirically, and there was no formal hypothesis testing. Categorical and continuous data were summarized with frequencies and percentages or descriptive statistics, respectively. All patients who received at least one dose of AMG 820 were included in the safety analyses; the efficacy population included all patients in the safety population with a baseline assessment and at least one postbaseline tumor assessment.

Results

Patients

Twenty-five patients enrolled and received at least one dose of AMG 820 between March 31, 2008, and February 6, 2014. Patient demographics and baseline characteristics are listed in Table 1. The median age was 63 years. The most common tumor types were colorectal cancer (CRC; 44%) and non–small cell lung cancer (NSCLC; 12%). Patients discontinued treatment for the following reasons: 16 because of disease progression, 5 because of AEs (4 unrelated to AMG 820; 1 DLT related to AMG 820), 3 because of lack of clinical benefit, and 1 because of death.

Dose-limiting toxicity and MTD

One DLT, grade 3 irreversible bilateral hearing loss 12 days after the first dose of AMG 820, occurred in a female patient with anal cancer who received 20 mg/kg AMG 820 every 2 weeks (Table 2). This patient had previously received ≥5 cycles of potentially ototoxic cisplatin, the last of which was administered 1 month before the first dose of AMG 820. The patient did not report hearing loss at study entry nor was there a baseline audiology examination; thus, considering the temporal relationship between bilateral hearing loss and AMG 820 administration, this toxicity was attributed to AMG 820. The MTD was not determined; the preplanned 20-mg/kg dose was the highest dose tested, with both the 10- and 20-mg/kg doses showing sustained pharmacodynamic responses, as described in a later section.

Table 1. Demographics and key baseline characteristics

Characteristic	*N* = 25
Median (range) age (y)	63 (48–80)
Sex, *n* (%)	
Women	14 (56)
Men	11 (44)
Race, *n* (%)	
White	17 (68)
Hispanic or Latino	5 (20)
Black	3 (12)
ECOG performance status, *n* (%)	
0	5 (20)
1	19 (76)
2	1 (4)
Baseline disease stage, *n* (%)	
Stage 3	3 (12)
Stage 4	22 (88)
Primary tumor	
Colorectal	11 (44)
Non–small cell lung	3 (12)
Ovarian	2 (8)
Pancreatic	2 (8)
Anal	2 (8)
Cervix	1 (4)
Melanoma	1 (4)
Prostate	1 (4)
Neuroendocrine	1 (4)
Paraganglioma	1 (4)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Safety and tolerability

The median number of doses given for each dose group is shown in Table 2. Patients received between 1 and 21 doses of AMG 820. Treatment-related AEs occurred in 19 (76%) of the 25 patients (Table 3); the most common (≥5% of patients overall) were periorbital edema (44%; $n = 11$), increased aspartate aminotransferase (AST; 28%, $n = 7$), fatigue (24%, $n = 6$), nausea (16%, $n = 4$), increased blood alkaline phosphatase (12%, $n = 3$), and blurred vision (12%, $n = 3$). Seven patients (28%) had grade 3 treatment-related AEs that were not considered to be DLTs: four (16%) had increased AST, two (8%) had hypertension, and one (4%) had periorbital edema after three doses of AMG 820 10 mg/kg. Treatment-related increases in AST above baseline were apparent at the time of the second dose of AMG 820 (cycle 1 day 15), and resolved after AMG 820 was withheld or discontinued. Two of the four patients with grade 3 elevation of AST attributed to AMG 820 had concurrent progression of liver metastases. There were no grade 4, serious, or fatal treatment-related AEs. Three patients in the 10-mg/kg cohort and three patients in the 20-mg/kg cohort had their AMG 820 dose reduced or withheld for treatment-emergent AEs.

Of the 11 patients with periorbital edema, 10 were grade ≤2 (grade 1, $n = 7$; grade 2, $n = 3$) and were mostly managed without intervention. One patient with grade 3 periorbital edema had AMG 820 withheld until resolution to grade 2. One patient with grade 2 periorbital edema also had AMG 820 dosing withheld. Supportive measures, including steroids and diuretics, were instituted at the treating physician's discretion ($n = 4$).

Pharmacokinetics

The pharmacokinetic analysis included all 25 patients, with mean concentration–time profiles shown for all doses in

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Table 2. Dosing and DLTs

Dose group	Dose, mg/kg	*n*	Doses per patient, median (range)	DLTs
1	0.5	3	6 (4–10)	None
2	1.5	3	4 (2–4)	None
3	3	4[a]	3.5 (1–4)	None
4	6	3	3 (2–5)	None
5	10	4[a]	3.5 (2–21)	None
6	20	8	2 (1–6)	Grade 3 irreversible bilateral hearing loss[b] ($n = 1$)

[a]One patient was added to the noted dose groups to replace patients who did not complete the safety evaluation period for reasons unrelated to AMG 820.
[b]Patient with anal cancer previously treated with cisplatin.

Fig. 1A. Intravenous infusion at 0.5 mg/kg was characterized by apparent time and concentration dependency in AMG 820 elimination, possibly due to target-mediated drug disposition. With increases in dose level from 1.5 to 6 mg/kg, estimates of median $t_{1/2}$ and mean V_{ss} were increased, and mean CL was decreased after single intravenous administration (Supplementary Table S1). Although these trends suggest that AMG 820 was characterized by nonlinear pharmacokinetics up to 6 mg/kg, dose cohorts were small ($n = 3$ to 4) with large interindividual variability (%CV) estimates up to 65.2% and 23.6% for CL and V_{ss}, respectively. Over the 1.5- to 20-mg/kg dose range every 2 weeks, AMG 820 C_{max} and AUC_{last} exposures were increased approximately proportionally to increases in dose, with minimal accumulation (<2-fold) after repeated dosing. Following single intravenous infusion at 20 mg/kg, AMG 820 pharmacokinetics was characterized by a median estimated $t_{1/2}$ of 219 hours and mean estimates of C_{max} and AUC_{last} exposures of 619 μg/mL and 89,200 μg·h/mL, respectively (Supplementary Table S1). At the highest doses (10 and 20 mg/kg every 2 weeks), AMG 820 trough concentrations were at or above the target serum concentration of anti-mouse CSFR1 antibody found to be efficacious in a mouse NCI-H1650 tumor xenograft model (mean ± SD, 140 ± 56.5 μg/mL) to reduce tumor volume and deplete TAMs (Supplementary Fig. S1).

All 25 patients tested negative for anti-AMG 820–binding antibodies.

Pharmacodynamics

Serum CSF1 concentrations increased with increasing AMG 820 dose and concentration (Fig. 1B). CSF1 levels in the lowest dose cohort (0.5 mg/kg) were increased initially but returned to baseline before the next dosing cycle, reflecting concurrent decreases in circulating AMG 820 concentrations (Supplementary Fig. S2). At higher doses, elevated CSF1 levels were maintained over a 2-week dosing cycle with apparent maximal levels of approximately 1,500 ng/mL being reached at AMG 820 doses ≥6 mg/kg. AMG 820 demonstrated concentration- and dose-dependent modulation of circulating CSF1 concentrations, consistent with CSF1R saturation by AMG 820. Serum levels of the putative biomarkers IL34 and TRAP5b showed no significant treatment-related changes (Supplementary Fig. S3).

Eight paired predose and postdose skin biopsies from 8 patients were available for analysis of macrophage density. One patient in the 0.5-mg/kg once-weekly group showed little change from baseline in macrophage density at week 13. In the 7 patients treated with 10 mg/kg ($n = 3$) and 20 mg/kg ($n = 4$), AMG 820 dosing was associated with significantly reduced numbers of $CD68^+$, $CD163^+$, and $CD206^+$ skin macrophages as well as CSF1R levels at week 5 compared with baseline (Fig. 2A and B;

Table 3. Patient incidence of treatment-related AEs

	Dose group, mg/kg[a]						
Preferred term[b], *n* (%)	0.5 *n* = 3	1.5 *n* = 3	3 *n* = 4	6 *n* = 3	10 *n* = 4	20 *n* = 8	All patients *N* = 25
Patients reporting any treatment-related AEs	1 (33)	2 (67)	3 (75)	3 (100)	4 (100)	6 (75)	19 (76)
Grade 3	0	0	2 (50)[c]	1 (33)[d]	2 (50)[e]	2 (25)[f]	7 (28)
Treatment-related AEs in >5% of patients							
Periorbital edema	0	1 (33)	3 (75)	2 (67)	3 (75)	2 (25)	11 (44)
AST increased	0	0	1 (25)	2 (67)	2 (50)	2 (25)	7 (28)
Fatigue	0	1 (33)	2 (50)	0	2 (50)	1 (13)	6 (24)
Nausea	0	1 (33)	0	0	1 (25)	2 (25)	4 (16)
Blood alkaline phosphatase increased	0	0	1 (25)	2 (67)	0	0	3 (12)
Vision blurred	0	0	1 (25)	0	1 (25)	1 (13)	3 (12)
Decreased appetite	0	1 (33)	1 (25)	0	0	0	2 (8)
Hypertension	0	0	1 (25)	0	1 (25)	0	2 (8)
Lacrimation increased	0	0	1 (25)	0	1 (25)	0	2 (8)
Mucosal inflammation	0	1 (33)	0	0	0	1 (13)	2 (8)
Peripheral edema	0	0	1 (25)	0	1 (25)	0	2 (8)
Vomiting	0	0	0	0	0	2 (25)	2 (8)

[a]Dosing schedule was once weekly for 0.5 mg/kg and every 2 weeks for other groups.
[b]AEs were coded using Medical Dictionary for Regulatory Activities version 17.0 and graded using Common Terminology Criteria for Adverse Events version 4.0.
[c]One patient each for AST increased and hypertension.
[d]One patient with AST increased.
[e]One patient each for AST increased and periorbital edema.
[f]One patient each for AST increased and bilateral deafness.

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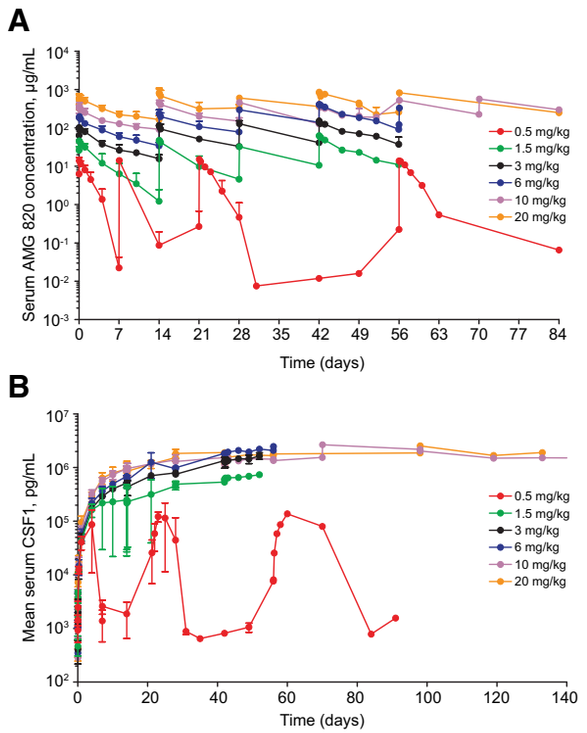

Figure 1.
A, Mean (SD) AMG 820 concentration–time profiles after AMG 820 intravenous infusion at 0.5 mg/kg once weekly or 1.5, 3, 6, 10, and 20 mg/kg every 2 weeks. **B,** Mean serum CSF1 concentration by the dose group.

Supplementary Fig. S4). The reduction in macrophage density between 10- and 20-mg/kg doses was not significantly different (Fig. 2A).

Antitumor activity

Fifteen patients were evaluable for tumor response. By central review, 8 patients (32%) had a best response of stable disease (SD). One patient with NSCLC previously treated with erlotinib who received 0.5 mg/kg AMG 820 once weekly showed a 25% reduction in sum of longest tumor diameters and remained on study for 12 weeks. Two patients, one with paraganglioma and liver metastases (10-mg/kg AMG 820 dose) and another with pancreatic neuroendocrine tumor who progressed on everolimus (20-mg/kg AMG 820 dose), experienced SD ≥16 weeks. Seven patients (28%) had progressive disease as best response. Ten patients (40%) ended the study before the first postbaseline scan (before week 9 dosing), and were therefore not assessable. Best tumor responses by primary tumor type and dose group are shown (Fig. 3).

Discussion

In this first-in-human phase I study, AMG 820 was tolerated with manageable toxicities at doses up to 20 mg/kg every 2 weeks. One DLT occurred at the maximum administered dose of 20 mg/kg; without baseline audiometry as reference, the toxicity of irreversible bilateral hearing loss was attributed to AMG 820. The MTD was not determined; doses ≥10 mg/kg resulted in trough serum concentrations higher than that found to be effective in preclinical models, and serum levels of the pharmacodynamic marker CSF1 rapidly increased and levels plateaued at

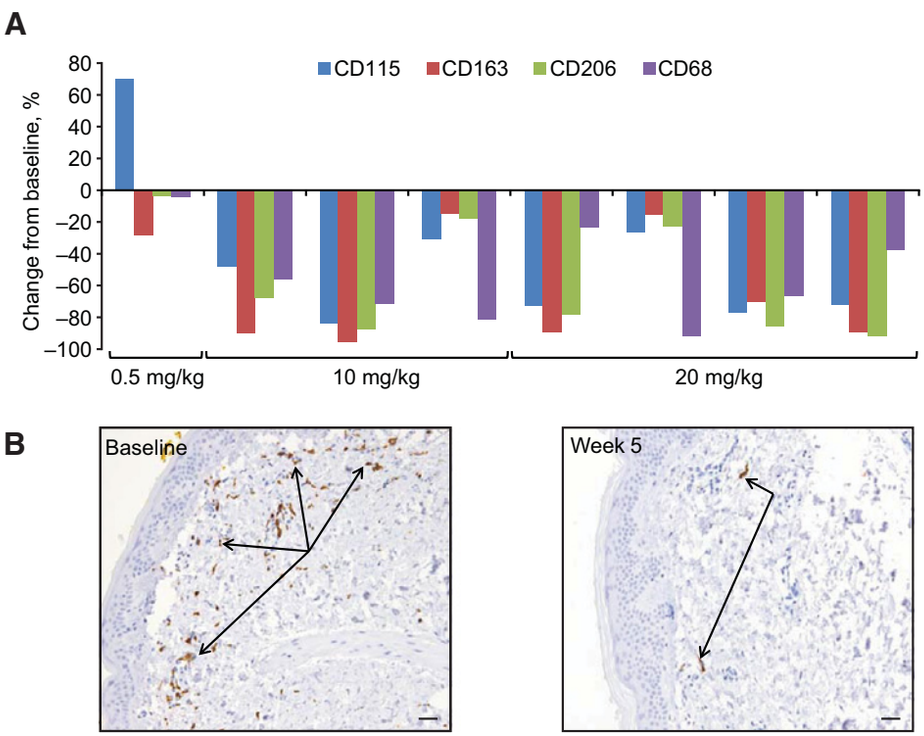

Figure 2.
A, Skin punch biopsies were collected from 8 patients at screening and at week 5, and the percentage change in density (cells per mm^2) of dermal macrophages that stained for CD115, CD163, CD206, and CD68 was calculated. Patients received AMG 820 at doses of 0.5 mg/kg once weekly ($n = 1$), 10 mg/kg every 2 weeks ($n = 3$), and 20 mg/kg every 2 weeks ($n = 4$). The number of macrophages infiltrating the dermis up to 2 mm from the epidermal border were enumerated using scanned images generated with an Aperio AT2 Digital Pathology Scanner (Leica Biosystems Inc.). Regions of interest were annotated, and the stained macrophages within the regions of interest were quantified (number of macrophages per square mm) using the IHC Nuclear algorithm of Aperio ImageScope Software (Leica Biosystems Inc.). **B,** Representative skin punch biopsy images showing skin macrophages (arrows) at week 5 compared with predose levels in a patient treated with AMG 820 10 mg/kg every 2 weeks; macrophages were detected by CD163 staining; scale bar, 50 μm.

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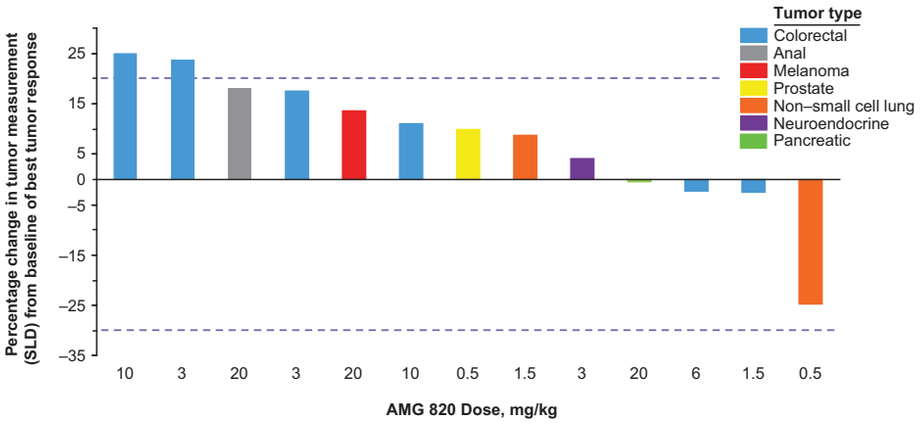

Figure 3.
Antitumor activity by independent central assessment in patients treated with AMG 820 with postbaseline scans. Two patients determined to have stable disease were considered to have nonmeasurable lesions by central assessment, and therefore are not shown; SLD, sum of longest diameter.

doses ≥6 mg/kg every 2 weeks. Safety and pharmacodynamic data support further development of AMG 820 at 20 mg/kg.

The most common treatment-related AEs with AMG 820 were periorbital edema (44%) and increased AST (28%). In the 11 patients with periorbital edema, all received AMG 820 doses ≥1.5 mg/kg every 2 weeks. All except one were grade ≤2 and resolved following drug discontinuation; most were managed without intervention or with diuretics and/or corticosteroids. In preclinical AMG 820 toxicology studies in cynomolgus monkeys, reversible periorbital or conjunctival swelling of generally minimal to moderate severity was observed in all animals. The mechanism leading to periorbital edema is unclear, although rearrangements in the extracellular matrix may be involved based on preclinical toxicology studies in cynomolgus monkeys (Amgen Inc., data on file). Treatment-related increases in AST resolved after withholding treatment. Half of the patients with treatment-related grade 3 AST increases had concurrent progression of liver lesions, which confounds attribution. Isolated elevation of AST may reflect depletion of Kupffer cells, which function to maintain serum enzyme homeostasis, rather than hepatotoxicity (22, 27). Furthermore, histologic findings in cynomolgus monkeys suggested that moderate increases in AST were not related to hepatotoxicity (Amgen Inc., data on file). Nevertheless, these results indicate that close monitoring of hepatotoxicity is warranted for future trials. Both of these AEs appear to be a class effect as they have been reported in clinical studies of the CSF1R-targeting agents, including the antibody emactuzumab (RG7155; Roche) and the small-molecule tyrosine kinase inhibitor pexidartinib (PLX3397; Plexxikon; refs. 12, 13).

AMG 820 showed linear increases in C_{max} and AUC_{last} exposures at doses ≥1.5 mg/kg every 2 weeks without marked accumulation after repeated dosing. A clear pharmacokinetic/pharmacodynamic relationship was observed between serum levels of AMG 820 and CSF1 as well as between AMG 820 and decreased macrophages in skin biopsies. Elevation in circulating CSF1 levels is presumably due to AMG 820 blocking CSF1 binding to CSF1R, preventing subsequent internalization and degradation (28). Notably, we did not observe a concordant pharmacodynamic response in serum levels of IL34, the second ligand for CSF1R. Baseline levels of IL34 were highly variable, which may have limited the ability to discern consistent changes in the small number of patients enrolled in this study. Furthermore, IL34 may simply be a poor biomarker of response to CSF1R blockade by AMG 820. Although anti-CSF1R antibodies have been shown to ablate osteoclasts in preclinical models (29), no consistent dose-related changes in TRAP5b were observed. Further studies are necessary to better understand the implications of these results.

Best response to AMG 820 treatment was SD. One patient with NSCLC had 25% tumor regression. Of note, another patient with paraganglioma and liver metastases who received AMG 820 10 mg/kg had a partial response (40% reduction) by local assessment; the patient was determined not assessable by central assessment because of poor baseline scan quality. This patient remained on study for 352 days before discontinuing for progressive disease. Patients with colorectal cancer, a tumor type considered less immune-responsive, comprised the majority of patients in this study and may account in part for the limited antitumor activity observed (30, 31).

This study was terminated before enrollment into the dose-expansion phase because the pharmacokinetic and pharmacodynamic studies indicated that CSF1R binding and suppression occurred without confirmed objective tumor responses. Limited antitumor activity of AMG 820 monotherapy is in accordance with results obtained preclinically and from clinical trials of the CSF1R inhibitors emactuzumab and pexidartinib in solid malignancies (12–16, 32). Consequently, to improve efficacy, preclinical studies have examined the effects of CSF1R inhibitors in combination with T-cell–targeted therapies, such as anti-programmed cell death protein 1 (anti–PD-1), anti-CTL–associated protein 4 (anti–CTLA-4), or adoptive cell transfer of tumor-targeted T cells (15, 16). The combination of CSF1/CSF1R blockade with anti–PD-1 and/or anti–CTLA-4 increased T-cell recruitment and antitumor activity compared with either anti–PD-1 or CSF1/CSF1R blockade therapy alone in a mouse model of pancreatic cancer (16).

In conclusion, this study demonstrates the safety and tolerability of the CSF1R antibody AMG 820 in patients with advanced solid tumors. AMG 820 showed proof of mechanism and limited single-agent antitumor activity. These results, together with preclinical data, support combination studies with other immunotherapeutic agents. However, recognizing the temporal association between AMG 820 and grade 3 elevations in AST in some patients, increased safety surveillance is warranted with combination partners. Accordingly, a phase Ib/II trial (NCT02713529) investigating the combination of AMG 820 and the PD-1 inhibitor pembrolizumab in patients with advanced solid tumors has been initiated.

Disclosure of Potential Conflicts of Interest

K.P. Papadopoulos reports receiving research funding from AbbVie, Amgen, ArQule, ARMO BioSciences, Daiichi Sankyo, GlaxoSmithKline, MedImmune, Novartis, Onyx, Regeneron, and Sanofi. L.P. Martin reports receiving research funding from AbbVie, Aduro Biotech, Amgen, Clovis Oncology, ImmunoGen, Millennium Pharmaceuticals, Novartis, Regeneron, and Tetralogic Pharmaceuticals; travel reimbursement from ImmunoGen; and is an advisory board member for ImmunoGen and Sanofi. A.J. Olszanski reports receiving compensation for serving as an advisor to Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck, and Takeda; research funding from Advaxis, Amgen, Bristol-Myers Squibb, EMD Serono, Ignyta, Immunocore, Incyte, Kyowa Hakko Kirin, Lilly, Mirati Therapeutics, Novartis, Pfizer, and Takeda; and travel, accommodation, or expense reimbursement from Takeda Pharmaceuticals. A.W. Tolcher is on the board of directors for Symphogen and reports receiving research funding from Akebia, AP Pharma, Arqule, Asana, Ascentage, Astex, Bayer, Bicycle Therapeutics, Bind, Birdie, Blend, Boehringer Ingelheim, Celator, Dicerna, Elekta, Eli Lilly, Endocyte, Fate Therapeutics, Genmab, Heron, Idea Pharma, Ignyta, Janssen, Johnson & Johnson, LiquidNet, Median, MedImmune, Merck, Mersana, Merus, Nanobiotix, OncoMed, Pharmacyclics, Pierre Fabre, Proximagen, Rigontec, Upsher-Smith, Valent, and Zymeworks. G. Ngarmchamnanrith, E. Rasmussen, B.M. Amore, and D. Nagorsen are employees of and hold stock in Amgen. J.S. Hill holds stock in AbbVie (Pharmacyclics) and Amgen, and holds patent or intellectual property interest with Amgen and Miravant Medical Technologies. J. Stephenson Jr. has participated on advisory committees or as a consultant to Bristol-Myers Squibb, Merck, and Pfizer, and has participated in speakers bureaus for Bristol-Myers Squibb, Celgene, Merck, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: K.P. Papadopoulos, A.W. Tolcher, G. Ngarmchamnanrith, E. Rasmussen, J.S. Hill

Development of methodology: G. Ngarmchamnanrith, E. Rasmussen, J.S. Hill

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.P. Papadopoulos, L. Gluck, L.P. Martin, A.J. Olszanski, A.W. Tolcher, G. Ngarmchamnanrith, J.S. Hill, J. Stephenson Jr

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.P. Papadopoulos, L. Gluck, A.J. Olszanski, G. Ngarmchamnanrith, E. Rasmussen, B.M. Amore, D. Nagorsen, J.S. Hill, J. Stephenson Jr

Writing, review, and/or revision of the manuscript: K.P. Papadopoulos, L. Gluck, L.P. Martin, A.J. Olszanski, A.W. Tolcher, G. Ngarmchamnanrith, B.M. Amore, D. Nagorsen, J.S. Hill, J. Stephenson Jr

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.P. Martin, J.S. Hill, J. Stephenson Jr

Study supervision: K.P. Papadopoulos, G. Ngarmchamnanrith, J.S. Hill, J. Stephenson Jr

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Kyriakos P. Papadopoulos, Larry Gluck, Lainie P. Martin, et al.

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