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ORIGINAL ARTICLE

First-in-human study to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of the anti-CD27L antibody-drug conjugate AMG 172 in patients with relapsed/refractory renal cell carcinoma

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Abstract

Purpose This study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of the anti-CD27L antibody-drug conjugate AMG 172 in patients with relapsed/refractory clear cell renal cell carcinoma (ccRCC).

Methods This was an open-label, adaptive dose-exploration study in patients with relapsed/refractory ccRCC. The study was conducted in two parts for dose exploration and dose expansion on a biweekly dosing schedule. AMG 172 doses of 0.15, 0.3, 0.6, 1.2, 1.6, 1.8, and 2.4 mg/kg were studied in the dose-exploration phase.

Results The 1.6 mg/kg dose of AMG 172 was identified as the maximum tolerated dose (MTD). The most common adverse events were thrombocytopenia (59%), nausea (54%), decreased appetite (49%), vomiting (46%), and fatigue (35%). The most common dose-limiting toxicity (DLT) was thrombocytopenia. Thrombocytopenia and liver injury constituted DLTs that required discontinuation of treatment. Of the 10 patients treated at the MTD in part 2 of the study, 2 patients had grade 3 hepatocellular injury with aspartate aminotransferase or alanine aminotransferase elevation. Pharmacokinetic profiles indicated low levels of circulating unconjugated antibody and unconjugated cytotoxin. Dose-proportional increases in plasma exposure were observed over the dose range of 0.3–2.4 mg/kg. Following multiple biweekly doses, plasma accumulation was less than two-fold. Two patients (5.4%) had a partial response, 6 patients (16.2%) had stable disease, and 13 patients (35.1%) had progressive disease.

Conclusion AMG 172 exhibited a favorable pharmacokinetic profile in patients with relapsed/refractory ccRCC and showed evidence suggestive of limited antitumor activity. Safety and tolerability were as expected for a maytansinoid antibody-drug conjugate.

Keywords AMG 172 · CD27L · CcRCC · Antibody-drug conjugate · Phase 1 · Pharmacokinetics

Introduction

Treatment options for metastatic renal cell carcinomas (mRCC) include targeted therapies with an anti-angiogenic mechanism of action, mammalian target of rapamycin inhibitors, multityrosine kinase inhibitors, and more recently, checkpoint inhibitor immunotherapy [1]. The paradigm of treatment was completely modified recently by the approval of new targeted therapies (cabozantinib), and immunotherapy combinations [2]. Despite the use of these agents, a significant proportion of patients eventually progress and there is an urgent need to develop new therapeutic approaches for this indication.

CD27L, also known as CD70 or TNFSF7, is a type II integral membrane protein expressed on a subset of activated

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T cells, B cells, and mature dendritic cells [3]. The receptor for this ligand, CD27, is expressed on a large proportion of natural killer cells and on most resting T cells and B cells. Upon binding of CD27L, signalling through CD27 stimulates T-cell and B-cell activation [3–5]. CD27L is aberrantly expressed in certain solid tumors and hematologic malignancies [6–10], though the mechanisms for this are unclear. Due to its restricted expression in healthy tissues and, in the pathological situation, selective expression in cancerous tissue, this receptor exhibits properties consistent with those of a tumor-associated antigen [9, 11]. Published literature for CD27L mRNA and protein expression indicates that CD27L is expressed in the vast majority of clear cell RCC (ccRCC) [9, 12] and is rapidly internalized upon antibody binding [11, 13], making it a potential target for antibody-based cytotoxic drug delivery.

AMG 172 is an antibody-drug conjugate (ADC) comprised of anti–CD27L-MCC-DM1, where anti-CD27L is a fully human immunoglobulin (Ig) G1 monoclonal antibody, MCC is the non-cleavable linker 4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate conjugated to lysine residues in the antibody, and DM1 is a semisynthetic derivative of the ansamycin antibiotic, maytansine, conjugated to MCC. There is an average of five conjugated DM1 molecules per antibody. The antibody portion of AMG 172 consists of an IgG1k that binds with subnanomolar affinity to native CD27L and is internalized into CD27Lexpressing cells. Following internalization, AMG 172 is catabolized to release the intracellular active species, lysine-MCC-DM1, which inhibits microtubule assembly/disassembly dynamics and induces metaphase arrest. AMG 172 exhibits antitumor activity in preclinical models. There is little evidence that reverse signaling through CD27L occurs upon antibody binding; thus, AMG 172 is not expected to cause lymphocyte activation, but rather will serve as an ADC to induce the death of CD27L-expressing tumor cells. This report describes results from the first-in-human phase 1 study that evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of AMG 172 in patients with relapsed/refractory ccRCC.

Methods

Patients

Eligible patients were ≥ 18 years of age with a pathologically confirmed diagnosis of ccRCC that had relapsed or was refractory to systemic therapy (including at least one tyrosine kinase inhibitor). Key inclusion criteria were an Eastern Cooperative Oncology Group performance status of ≤ 1 and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria were baseline left ventricular ejection fraction < 50%, electrocardiogram QTcF > 470 msec, myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association greater than class 2), unstable angina, unstable cardiac arrhythmia requiring medication, or uncontrolled hypertension in the opinion of the investigator.

Study design and treatment

This was an open-label, adaptive, dose-exploration study of AMG 172 in patients with relapsed/refractory ccRCC conducted at four study centers in France, Germany, and the US. The study was conducted in two parts for dose exploration and dose expansion, respectively (Fig. 1). The primary objectives for both the dose-exploration and dose-expansion study parts were to assess safety, tolerability, and PK of AMG 172, and if possible, to determine the maximum tolerated dose (MTD) and evaluate the objective response rate (ORR) in patients treated at the MTD. Secondary objectives were to evaluate the incidence of

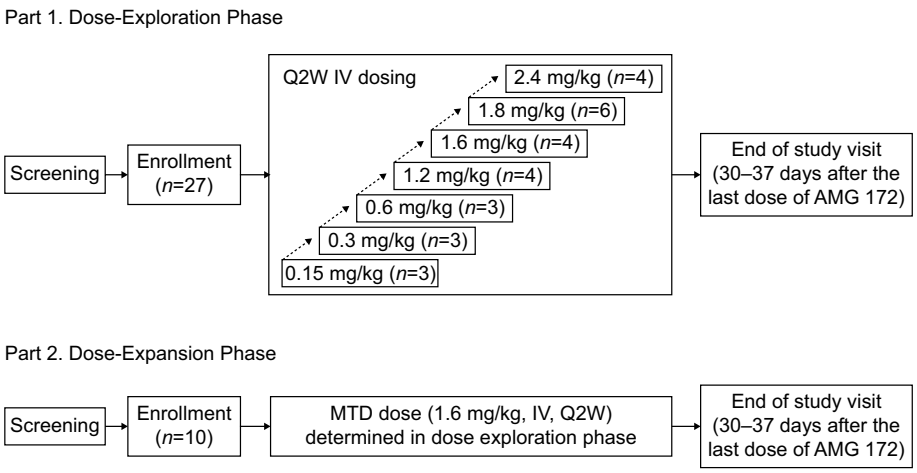

Fig. 1 Study design. IV intravenous, MTD maximum tolerated dose, Q2W once every 2 weeks

anti-AMG 172 antibody formation, duration of response (DOR) for patients treated at the MTD, and ORR for patients not treated at the MTD.

Each complete cycle lasted for 4 weeks, comprising two dose administrations of AMG 172. Eligible patients received AMG 172 intravenously (IV) as a 60-min infusion biweekly (Q2W) beginning on study day 1 and were assessed for dose-limiting toxicities (DLTs) during the initial safety window (days 1–28 of the 28-day cycle). A DLT was defined as a grade 3 or higher nonhematologic or a grade 4 hematologic adverse event that occurred during the DLT window (days 1–28) in part 1, unless clearly attributable to causes other than AMG 172 treatment.

Part 1 was an adaptive, dose-exploration design that used a continual reassessment method (CRM) [14, 15] to identify the MTD. The MTD was defined as the maximum dose at which the probability of a DLT was ≤ 25%. Patients were enrolled in cohorts of 3–4 patients according to the dose schedule. The adaptive design of the dose-exploration part using the CRM was preserved regardless of whether 3 or 4 patients were enrolled in a cohort. In part 1, the first patient enrolled for any specified dose level was treated and observed for a period of 24 h. Subsequent patients were treated after a period of 24 h, provided there were no safety concerns relating to the treatment of the first patient.

When the first DLT in a dose cohort was observed, the dose for the next cohort of patients was selected based on the prediction of the MTD using a model for the dose-toxicity curve. To ensure a safe dose exploration, the maximum dose increase at any point was ≤ 2 times the previous dose. Dose-exploration decisions were made during a Dose Level Review Meeting (DLRM). The prespecified nominal doses for use in the dose-exploration part were 0.15, 0.3, 0.6, 1.2, 2.4, and 3.6 mg/kg of AMG 172 (Q2W IV). Intermediate doses (e.g., 1.6 or 3.0 mg/kg) and alternative dose frequencies were permitted if required or supported by emerging data.

Patients who received the MTD in part 1 continued in part 2 at the same dosing schedule. The DLRM members reviewed safety data after half of the total number of patients required for dose expansion had enrolled and completed 28 days on study. An end-of-study visit occurred 30–37 days after the last dose of AMG 172.

All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol was approved by the relevant local Institutional Review Board/Independent Ethics Committee and informed consent was obtained from all individual participants included in the study. This study is registered with ClinicalTrials.gov (NCT01497821).

Pharmacokinetics

The components of AMG 172 were quantified in patients with relapsed/refractory ccRCC using validated bioanalytical methods. AMG 172 conjugated antibody (anti-CD27L antibody conjugated to at least one DM1 molecule) and the total anti-CD27L antibody (sum of unconjugated anti-CD27L antibody and AMG 172 conjugated antibody) were quantified using validated electrochemiluminescence (ECL) immunoassay with lowest limit of quantification (LLOQ) 20 ng/mL. The ECL immunoassay for measurement of AMG 172 conjugated antibody involved capture by the immobilized mouse anti-DM1 antibody and detection using the ruthenium conjugated mouse anti-AMG 172 1.23.1 antibody (SULFOTAG™ conjugated) (Amgen Inc.). The ECL immunoassay for measurement of total anti-CD27L antibody involved capture by the immobilized mouse anti-AMG 172 1.61.1 antibody and detection using the ruthenium conjugated mouse anti-AMG 172 1.23.1 antibody (SULFO-TAG™ conjugated) (Amgen Inc.). DM1 (total unconjugated DM1) was quantified using the microsampling dried blood spot sample collection with the liquid extraction sample preparation procedure, followed by liquid chromatography–tandem mass spectrometry (LC–MS/MS) detection with LLOQ 2.5 ng/mL. All samples analyzed using this method were below the lowest limit of quantification. Subsequently, a more sensitive bioanalytical method to improve the sensitivity by 10-fold (LLOQ 0.25 ng/mL) was developed to measure DM1 in plasma. This method, similar to the previous method, measured all unconjugated forms of DM1 (total unconjugated DM1) and included a tris (2-carboxyethyl) phosphine reduction process for sample preparation followed by *N*-Ethylmaleimide derivatization and LC–MS/MS detection. PK parameters, including the maximum observed concentration (C_{max}), and area under the concentration time curve (AUC) were summarized for AMG 172 conjugated antibody, total anti-CD27L antibody, and DM1. DM1 concentration data was collected for the starting dose (0.15 mg/kg) and MTD (1.6 mg/kg).

Efficacy

Best overall response for a patient was the best observed post-baseline disease/tumor response per RECIST version 1.1. ORR was defined as a tumor response assessment of either complete response (CR) or partial response (PR) per RECIST version 1.1 criteria and was determined only for patients with measurable disease at baseline. Any CR or PR was confirmed with a subsequent (consecutive) assessment no less than 28 days after the criteria for response were first met.

Statistical analysis

The PK parameters of AMG 172 conjugated antibody, total anti-CD27L antibody, and DM1 were estimated using standard noncompartmental PK methods [16]. The proportion of patients with an objective response with corresponding exact 80% confidence interval (CI) was calculated using the Clopper-Pearson method and tabulated for patients treated at the MTD and patients not treated at the MTD. The independent centrally reviewed response data were used as the primary assessment of tumor response. A sensitivity analysis using the investigator-reported response information collected on the case report form was conducted. For each patient and visit, the percentage change from baseline in the sum of the diameters of target lesions (SLD) was calculated. Descriptive statistics were provided for changes in tumor volume (based on independent central review), and selected pharmacodynamic and biomarker data by dose and time, as appropriate.

Results

Patient disposition

Baseline demographics and disease characteristics were as expected for this patient population, except for a greater proportion of men (Table 1). A total of 37 patients were treated with AMG 172; 27 patients in part 1 and 10 patients in part 2. The study explored seven doses (0.15, 0.3, 0.6, 1.2, 1.6, 1.8, and 2.4 mg/kg) of AMG 172 on a Q2W dosing schedule in part 1 to determine the MTD to be taken forward for part 2 (Fig. 1). The mean (standard deviation) number of infusions of AMG 172 administered per patient was 6.5 (8.4).

Table 1 Baseline demographics and disease characteristics

Characteristic	All patients ($N = 37$)
Age, *n* (%)	
< 65 years	22 (59.5)
≥ 65 years	15 (40.5)
≥ 75 years	4 (10.8)
Sex, *n* (%)	
Female	5 (13.5)
Male	32 (86.5)
Months since ccRCC diagnosis, median (min, max)	58.8 (5, 250)
Number of sites of metastatic disease, *n* (%)	
1	14 (37.8)
2	8 (21.6)
3	6 (16.2)
4	7 (18.9)
> 4	2 (5.4)
Disease stage at screening, *n* (%)	
II	1 (2.7)
III	1 (2.7)
IV	35 (94.6)
Number of prior anticancer therapies, *n* (%)	
1	5 (13.5)
2	3 (8.1)
3	9 (24.3)
≥ 3	28 (75.7)
Unknown	1 (2.7)
ECOG performance status, *n* (%)	
0	18 (48.6)
1	19 (51.4)

ccRCC clear cell renal cell carcinoma, *ECOG* Eastern Cooperative Oncology Group

Safety

Adverse events were reported for all 37 patients. The most commonly reported adverse events were thrombocytopenia, nausea, decreased appetite, vomiting, fatigue, anemia, asthenia, cough, and pyrexia (Table 2). Eight DLTs were reported in five patients across seven dosing cohorts in the dose-exploration phase. Three of four patients in the 2.4 mg/kg dose cohort and two of six patients in the 1.8 mg/kg dose cohort experienced DLTs. The adverse events reported as DLTs were thrombocytopenia (five patients), hepatocellular injury, myocardial infarction, and acute renal failure (all reported in one patient). All DLTs were considered treatment-related and none were fatal. The DLT of hepatocellular injury and three thrombocytopenia DLTs were grade 4; all other DLTs were grade 3. Two patients had three DLTs that resulted in discontinuation of AMG 172 (hepatocellular injury and thrombocytopenia [both reported in one patient], and thrombocytopenia [one patient]). No clinically meaningful trends in vital signs, electrocardiogram measurements, or body weight related to AMG 172 administration were observed during the study.

After review of the cumulative data from all patients enrolled in all dose-exploration cohorts, the 1.8 mg/kg Q2W dose was declared as not tolerated, and an MTD of 1.6 mg/kg Q2W was initiated in the part 2 dose expansion ($n = 10$). DLTs were reported in 3 patients in part 2 of the study (grade 3 hepatocellular injury and grade 4 thrombocytopenia [both reported in 1 patient], grade 3 hepatocellular injury [1 patient], and grade 3 thrombocytopenia [1 patient]). The 2 patients with grade 3 hepatocellular injury had aspartate aminotransferase (AST) or alanine aminotransferase elevations, and 1 patient had a grade 3 adverse event of increased AST after the second dose of AMG 172.

Table 2 Treatment-emergent any grade adverse events occurring in > 10% of patients

System organ class preferred term, *n* (%)	All patients (*N* = 37)
Thrombocytopenia	22 (59.5)
Nausea	20 (54.1)
Decreased appetite	18 (48.6)
Vomiting	17 (45.9)
Fatigue	13 (35.1)
Anemia	12 (32.4)
Asthenia	12 (32.4)
Cough	12 (32.4)
Pyrexia	12 (32.4)
Constipation	11 (29.7)
Hypophosphatemia	11 (29.7)
Aspartate aminotransferase increased	10 (27.0)
Alanine aminotransferase increased	8 (21.6)
Blood alkaline phosphatase increased	8 (21.6)
Epistaxis	8 (21.6)
Hypomagnesemia	8 (21.6)
Headache	7 (18.9)
Abdominal pain	6 (16.2)
Hepatocellular injury	6 (16.2)
Insomnia	6 (16.2)
Dyspnea	5 (13.5)
Hypercalcemia	5 (13.5)
Hypotension	5 (13.5)
Peripheral edema	5 (13.5)
Depression	4 (10.8)
Diarrhea	4 (10.8)
Hyperbilirubinemia	4 (10.8)
Night sweats	4 (10.8)
Wheezing	4 (10.8)

Pharmacokinetics and pharmacodynamics

All patients (*N* = 37) were included in the PK analysis set. Following Q2W IV administration of 0.15–2.4 mg/kg AMG 172 to patients with relapsed/refractory ccRCC, similar PK profiles were observed over the 2-week dosing interval for AMG 172 conjugated antibody and total anti-CD27L antibody, indicating low levels of circulating unconjugated antibody. In addition, low plasma levels were observed for unconjugated DM1 (C_{max} <2 ng/mL) (Fig. 2).

Plasma exposures for AMG 172 conjugated antibody and total anti-CD27L antibody increased in a dose-related manner in patients over the entire studied AMG 172 dose range (0.15–2.4 mg/kg). Following the first IV dose, AMG 172 conjugated antibody and total anti-CD27L antibody C_{max} and AUC_{336hr} increased approximately 20-fold for the 16-fold increase in dose (0.15–2.4 mg/kg). Based on a comparison of mean C_{max} and AUC_{336hr} across the dose range tested as well as linear regression analysis of dose-normalized log-transformed C_{max} and AUC_{336hr} values, AMG 172 conjugated antibody and total anti-CD27L antibody exposure increased dose proportionally from 0.30 to 2.4 mg/kg. Plasma accumulation was less than twofold following three IV doses of AMG 172 administered Q2W, with mean accumulation ratios ranging from 0.74 to 1.74 for AMG 172 conjugated antibody and from 0.73 to 1.99 for total anti-CD27L antibody. In patients who received AMG 172 doses ≥ 0.6 mg/kg, trough plasma concentrations of AMG 172 conjugated antibody remained above the 90% tumor cell–killing concentration (2800 ng/mL), determined from translational PK/pharmacodynamic modelling from a CD27L-expressing human tumor (786-O) xenograft mouse model [17].

AMG 172 bound and saturated the target expressed by B cells and T cells in the peripheral blood of patients at doses ≥ 0.3 mg/kg. T-cell, B-cell, and natural killer cell subsets were not altered directionally during treatment.

Efficacy

Efficacy data provided evidence suggestive of antitumor activity of AMG 172. Efficacy was evaluated using the safety analysis set (*N* = 37). Per the central read result using RECIST version 1.1, overall, 2 patients (5.4%) had a PR, 6 patients (16.2%) had stable disease (SD), and 13 patients (35.1%) had progressive disease (PD). Both patients with a PR were treated in the in 0.6 mg/kg dose cohort. One patient with a PR had a maximum decrease in SLD of 79% at week 39 and DOR of 12 months as per the central read result. The other patient with PR had a maximum decrease in SLD of 32% at week 38 and DOR was censored at 2 months. Of the 6 patients with SD, 4 had scans beyond the initial day 43 scan. Of these, 2 had progressed by the second scan (day 99), 1 was stable at day 99 but progressed after, and 1 had SD for all scans through day 435. Sixteen patients were not evaluable due to lack of follow-up scans per RECIST version 1.1. The overall ORR (80% CI) was 5.4% (1–14%) per central read result.

Discussion

AMG 172 is an anti-CD27L ADC being evaluated for the treatment of relapsed/refractory ccRCC. In this report, we determined the MTD for AMG 172 as 1.6 mg/kg Q2W IV, with thrombocytopenia being the most common DLT. Thrombocytopenia and liver injury constituted DLTs that required discontinuation of treatment. Thrombocytopenia may be a result of decreased platelet production consistent with the effect of microtubule inhibitors on the relevant hematopoietic precursor cells in bone marrow [18]. Additionally, we observed preliminary evidence suggestive of antitumor activity of AMG 172 in at least a subset

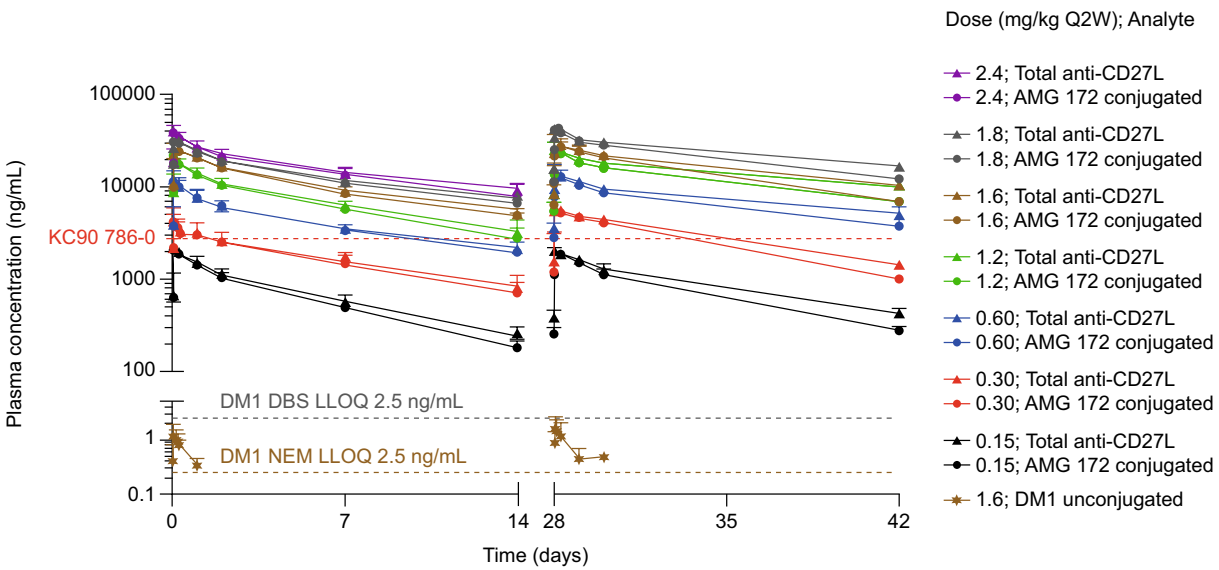

Fig. 2 Mean plasma concentration profiles for AMG 172 conjugated antibody, total anti-CD27L antibody, and DM1 in patients with clear cell renal carcinoma following Q2W administration of AMG 172. DBS dried blood spot, KC90 AMG 172–conjugated antibody plasma concentration (2800 ng/mL) estimated from translational pharmacokinetic/pharmacodynamic modeling to result in 90% killing of tumor cells in the CD27L-expressing human tumor (786-O) subcutaneous xenografts in mice, LLOQ lowest limit of quantification; NEM N-Ethylmaleimide; Q2W once every 2 weeks

of patients, with decreases from baseline observed in the mean SLD and the mean tumor volume in 2 patients.

Several ADCs are in various stages of preclinical and clinical development for solid tumors, including mRCC [19–23]. The results of this study are consistent with those of others involving CD27L-targeted ADC therapy for ccRCC. In a phase 1 trial of the CD27L-targeting SGN-75, Tannir et al. reported a similar efficacy profile to that observed in this study, with the majority of patients achieving SD (38%) or PD (38%) as best response, 6% achieving PR, and no CRs were observed [20]. Owonikoko et al. reported a best response of SD in 69% of patients during a phase 1 trial of another CD27L-targeting ADC, with no PR or CR observed [23]. The low proportion of patients achieving PR or CR with CD27L-targeting ADCs reported in the literature and in this current study indicates the potential need for preselection of patients based on the expression of CD27L in future studies.

The results of this study indicate that AMG 172 has a favorable PK profile in patients with ccRCC, consistent with the design of this ADC. Low levels of circulating unconjugated antibody suggest that competitive binding of these to target cells will not have compromised efficacy. Additionally, the low levels of circulating unconjugated DM1 indicate minimal exposure to the unbound anti-tubulin agent. Preclinical studies suggested AMG 172 doses $\geq$ 0.6 mg/kg Q2W to be potentially efficacious, which is in line with the preliminary response observed in this study.

AST elevations were reported for 3 patients (one after the second dose); a longer dosing interval may resolve this issue. Q2W PK data reported here were used to simulate responses to dosing frequency of once every 3 weeks (Q3W) using in silico PK modeling (unpublished data). PK modeling indicated that a Q3W schedule would provide sustained levels of AMG 172 that could have antitumor potential with reduced accumulation, which may alleviate the adverse event of increased liver enzymes observed after the second cycle.

In summary, we have identified an MTD for AMG 172 and have shown potential efficacy in a limited number of a patients with relapsed/refractory ccRCC. However, because of potential toxicity issues, additional treatment regimens, such as Q3W dosing, will need to be explored. Furthermore, because of the limited efficacy, any further exploration of this therapeutic strategy should involve preselection of patients based on CD27L expression levels or combination with other cancer therapies.

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Compliance with ethical standards

Conflict of interest CM has received fees for advisory boards, as a speaker or an investigator from Amgen, Astellas, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, and Orion. J-CS has received research funding from Amgen, and consultancy fees from AstraZeneca, Bristol-Meyers Squibb, Roche,

Sanofi, Pierre Fabre, and Servier. MG has a clinical trials selection process pending. ER, VVU, and GN are employees of Amgen and holders of Amgen stocks. SP was an employee of Amgen from 2005 to 2015. HH is an employee of Amgen. JK and ACL have nothing to disclose.

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