Clinical Cancer Research

Andecaliximab/GS-5745 Alone and Combined with mFOLFOX6 in Advanced Gastric and Gastroesophageal Junction Adenocarcinoma: Results from a Phase I Study

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Abstract

Purpose: Matrix metalloproteinase-9 (MMP9) is implicated in protumorigenic processes. Andecaliximab (GS-5745, a monoclonal antibody targeting MMP9) was evaluated as monotherapy and in combination with mFOLFOX6.

Patients and Methods: Three dosages of andecaliximab monotherapy [200, 600, and 1800 mg i.v. every 2 weeks (q2w)] were investigated in patients with advanced solid tumors ($n = 13$ in a 3+3 design). After determining a recommended dose, patients with advanced HER2-negative gastric/gastroesophageal junction (GEJ) adenocarcinoma ($n = 40$) received 800 mg andecaliximab + mFOLFOX6 q2w. Pharmacokinetics, pharmacodynamics, safety, and efficacy were assessed.

Results: Andecaliximab monotherapy demonstrated no dose-limiting toxicity (DLT) in any cohort, displaying target-mediated drug disposition at the lowest dose (200 mg) and linear pharmacokinetics at higher doses. Based on target engagement, recommended doses for further study are 800 mg q2w or 1,200 mg q3w. Maximal andecaliximab target binding, defined as undetectable andecaliximab-free MMP9 in plasma, was observed in the gastric/GEJ adenocarcinoma cohort. We observed no unusual toxicity, although there were four deaths on study not attributed to andecaliximab treatment. In first-line patients ($n = 36$), median progression-free survival (PFS) was 9.9 months [95% confidence interval (CI), 5–13.9 months], and the overall response rate (ORR) was 50%. Among all patients ($n = 40$), median PFS was 7.8 (90% CI, 5.5–13.9) months, and ORR was 48%, with a median duration of response of 8.4 months.

Conclusions: Andecaliximab monotherapy achieved target engagement without DLT. Andecaliximab + mFOLFOX6 showed encouraging clinical activity without additional toxicity in patients with HER2-negative gastric/GEJ adenocarcinoma. A phase III study evaluating mFOLFOX6 ± andecaliximab in this setting is ongoing. *Clin Cancer Res; 24(16); 3829–37.* *©2018 AACR.*

Introduction

Matrix metalloproteinases (MMP) comprise a family of at least 23 Zn^{2+}-dependent proteases involved in degradation and remodeling of the extracellular matrix and basement membranes. MMPs also play a role in activation or inactivation of growth factors, cytokines, and chemokines, in normal and pathologic biological processes (1). MMP9 is an inducible MMP expressed heterogeneously by tumor epithelia as well as infiltrating macrophages, neutrophils, other inflammatory cells, fibroblastic stroma, and tumor-associated endothelial cells. MMP9 activation can release cytokines, growth factors, and bioactive protein fragments that modulate inflammation, neovascularization, and matrix remodeling (2–4).

Tumor expression of MMP9 is implicated in many protumorigenic processes. During invasion and proliferation processes, MMP9 expression has been associated with loss-of-tumor suppression activity, as well as with gain-of-oncogenic activity. In addition, MMP9 appears to contribute to temporal responses to changes in local tumor environment (3–5). MMP9

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Translational Relevance

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases involved in remodeling of the extracellular matrix and modulating growth signals in normal and pathologic processes. Andecaliximab, a recombinant chimeric immunoglobulin G_4 monoclonal antibody, blocks the protumorigenic activities of MMP9. A safe dose of andecaliximab was determined, at which pharmacokinetics was linear and free circulating MMP9 was undetectable, demonstrating target engagement. Combination of andecaliximab with mFOLFOX6 chemotherapy appeared well tolerated with no new or unexpected safety signals. Andecaliximab + mFOLFOX6 demonstrated encouraging results, especially in chemotherapy-naïve (first line) patients with advanced gastric/gastroesophageal adenocarcinoma or those who had completed adjuvant/neoadjuvant treatment at least 6 months prior to initiating this combination. The addition of andecaliximab to mFOLFOX6 was associated with encouraging clinical activity without increased apparent toxicity. Andecaliximab + mFOLFOX6 is being evaluated in a multicenter, random assignment phase III study in first-line gastric and gastroesophageal junction adenocarcinoma.

expression by infiltrating inflammatory cells in the tumor microenvironment is associated with local protumorigenic immune suppression, blunting T- and natural killer (NK)–cell responses via several potential mechanisms. MMP9 promotes local activation of TGFβ and other immune-suppressive factors, inactivation of chemokines necessary for trafficking of effector T cells, and cleavage of factors that enable tumor cell recognition by NK cells, such as major histocompatibility complex class I polypeptide-related sequence A and other NK group 2, member D ligands (6–9). Elevated MMP9 protein or RNA levels are associated with reduced overall survival in gastric and other cancers (10–12).

Early clinical experience with pan-MMP inhibitors in cancer demonstrated potential efficacy but was associated with dose-limiting musculoskeletal syndrome (13, 14). Andecaliximab is a recombinant chimeric immunoglobulin G_4 monoclonal antibody that demonstrates high affinity and selectivity for MMP9 (15, 16). The mitigation of both immunogenicity and off-target effects may overcome major shortcomings that have hindered the therapeutic success of MMP inhibition in the past. Andecaliximab was engineered without T-cell epitopes to reduce the risk of immunogenicity (17, 18). A murine monoclonal antibody targeting the same MMP9 epitope as andecaliximab significantly reduced primary tumor growth in a murine colorectal cancer xenograft mode. In addition, targeting either stromal or epithelial MMP9 in the same model reduced the incidence of metastases (15).

The negative prognostic effects and patterns of MMP9 expression and the precedents of prior pan-MMP inhibitors provided a rationale for evaluating andecaliximab + chemotherapy in advanced solid tumors, including gastric and gastroesophageal junction (GEJ) adenocarcinoma. We initiated a phase I study (ClinicalTrials.gov Identifier: NCT01803282) in two parts: a monotherapy dose-finding stage (part A), and a combination treatment stage (part B) in patients with selected tumor types. Here, we present data from part A and the gastric/GEJ adenocarcinoma cohort of part B.

Patients and Methods

Study design

This phase I study was divided into two parts: part A, dose-finding monotherapy phase enrolling patients with advanced solid tumors, and part B, andecaliximab + chemotherapy in specific patient expansion cohorts, including patients with advanced pancreatic adenocarcinoma, non–small cell lung cancer, gastric/GEJ adenocarcinoma, colorectal adenocarcinoma, or HER2-negative breast cancer (see Supplementary Fig. S1). Data from cohorts other than gastric/GEJ will be published separately. Planned enrollment included 12 to 48 patients in part A and 15 to 40 patients per cohort in part B. The determination of the final sample size followed the principles of a two-stage design, whereas the decision to enroll 40 patients was contingent on the safety and efficacy signals from the initial 15 patients. Enrollment of 40 patients would be sufficient to assess pharmacokinetics (PKs) and safety, and to give a reasonably precise estimate of efficacy, that is, tumor response. For an estimated overall response rate of 50%, a sample size of 40 patients would allow the 95% confidence interval (CI) to be ±15%. The study was conducted in accordance with the Declaration of Helsinki; local ethics committees/institutional review boards at all participating centers approved the study. All patients provided written informed consent before entering the study.

Patient eligibility

Key inclusion criteria for all patients included age ≥18 years; Eastern Cooperative Oncology Group Performance Status of ≤1; life expectancy of >3 months; adequate hematologic, hepatic, and coagulation function; serum creatinine ≤1.5 × upper limit of normal; and willingness to follow adequate precautions to prevent pregnancy. For part A, patients were required to have histologically or cytologically confirmed advanced malignant solid tumors refractory to or intolerant of standard therapy, or for which no standard therapy was available. For the gastric/GEJ adenocarcinoma cohort of part B, patients were required to have histologically confirmed, HER2-negative, inoperable advanced gastric/GEJ adenocarcinoma treatment-naïve in the metastatic setting (prior systemic therapy in the nonmetastatic setting was allowed). Key exclusion criteria for all patients included significant comorbid medical conditions that posed a risk to patient safety or limited study participation; pregnancy or lactation in women; untreated central nervous system metastases; and known HIV, HBV, or HCV infection.

Study treatment

Monotherapy cohorts. Andecaliximab was administered at 200 (cohort 1), 600 (cohort 2), and 1,800 mg (cohort 3) via i.v. infusion over 30 minutes every 2 weeks (q2w) following a 3 + 3 design. If dose-limiting toxicities (DLTs) were experienced by ≥2 patients in a cohort, dose de-escalation would occur to an intermediate dose. The MTD was defined as the highest andecaliximab dose level at which ≤33% of patients experienced a DLT during days 1 to 28 (cycle 1). The following adverse events (AEs) occurring during cycle 1 (possibly related

to andecaliximab) were considered DLTs: grade 4 neutropenia [absolute neutrophil count (ANC) < 500/μL] for >7 days; febrile neutropenia (ANC < 1,000/μL with fever >101°F (38.5°C)]; grade 4 thrombocytopenia; grade 3 thrombocytopenia with bleeding; grade 3 or 4 nonhematologic toxicity (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive care); treatment delay of ≥14 days due to unresolved toxicity and nonhematologic toxicity of ≥grade 2 that was dose-limiting. Andecaliximab was permanently discontinued for recurrent toxicities meeting the definition of a DLT or for toxicities that did not resolve within 28 days.

Combination cohort (gastric/GEJ adenocarcinoma). The combination with 5-fluorouracil + leucovorin + oxaliplatin (mFOLFOX6) was selected based on U.S. treatment guidelines for patients with advanced HER2-negative gastric/GEJ adenocarcinoma (19). Andecaliximab (800 mg) was administered on days 1 and 15 of each 28-day cycle. mFOLFOX6 was administered immediately following andecaliximab on days 1 and 15 of each 28-day cycle as follows: *l*-leucovorin (200 mg/m^2) or *dl*-leucovorin (400 mg/m^2), oxaliplatin (85 mg/m^2), 5-fluorouracil bolus (400 mg/m^2), followed by a 46-hour infusion of 5-fluorouracil (2,400 mg/m^2).

Patients were treated until unacceptable toxicity, withdrawal of consent, disease progression, or death.

Pharmacokinetics

Blood was collected for evaluation of plasma concentrations of andecaliximab at scheduled times following infusion. Plasma drug levels were determined with a validated proprietary electrochemiluminescence immunoassay method. PK parameters were calculated using standard noncompartmental methods with Phoenix WinNonLin software. Data were listed and summarized using descriptive statistics by cohort and treatment.

Pharmacodynamic MMP9-binding assay

Total (bound and free) MMP9 and free MMP9 were measured as described in Supplementary Material. Maximal andecaliximab binding to MMP9 was achieved when levels of andecaliximab-free MMP9 were below the limit of detection.

Collagen neoepitope assay

The collagen I cleavage fragment C1M was measured in serial serum samples by immunoassay (Nordic Bioscience A/S, Herlev, Denmark). Interpatient and intrapatient variabilities (measured at two time points prior to drug treatment) were 101% and 39%, respectively, in the gastric cohort.

Efficacy assessments

Efficacy data are available from part B only. Disease burden was evaluated at screening by physical examination and radiographic assessment (contrast-enhanced CT or MRI) and then every 8 weeks. Responses were assessed by investigators per the RECIST version 1.1 criteria (20). Objective response rate (ORR) was defined as the proportion of patients with complete response (CR) or partial response (PR) as best overall response during combination therapy. The Clopper–Pearson method was used to calculate the exact CIs of ORR. Progression-free survival (PFS) was defined as the time interval from the first dose of andecaliximab to the earlier of the first documentation of definitive disease progression or death from any cause, analyzed using Kaplan–Meier methods. A *post hoc* analysis of efficacy was performed in first-line patients enrolled in the combination cohort, defined as patients who were treatment-naïve or >190 days from prior treatment

Table 1. Patient demographics and baseline characteristics

	Part A			Part B
	Cohort 1	**Cohort 2**	**Cohort 3**	**Gastric/GEJ cohort (andecaliximab+ mFOLFOX6)**
Andecaliximab dose	200 mg q 2 weeks	600 mg q 2 weeks	1,800 mg q 2 weeks	800 mg q 2 weeks
Patients, *n*	4	3	6	40
Male, *n* (%)	3 (75)	3 (100)	4 (67)	31 (78)
Median age (range), y	61.5 (53–81)	67 (66–77)	61 (39–81)	61 (37–84)
ECOG status at screening, *n* (%)				
0	3 (75)	2 (67)	3 (50)	12 (30)
1	1 (25)	1 (33)	3 (50)	28 (70)
Disease histology, *n* (%)				
Pancreatic	1 (25)	0	1 (17)	
Adenocarcinoma of the lung	1 (25)	0	2 (33)	
Other	2 (50)[a]	2 (66)[b]	2 (33)[c]	
Gastroesophageal junction	0	1 (34)	1 (17)	23 (58)
Gastric				17 (43)
Diffuse				12 (30)
Intestinal				5 (13)
Disease stage at screening				
Locally advanced, unresectable				3 (8)
Metastatic				37 (92)
Treatment-naïve patients, *n* (%)	0	0	0	29 (73)
Patients with ≥1 prior systemic chemotherapy, *n* (%)	4 (100)	3 (100)	6 (100)	11 (27)[d]
Median prior chemotherapy regimens (range)	3.5 (2–5)	3 (2–3)	4 (2–6)	
Patients with previous radiation treatment, *n* (%)	1 (25)	2 (67)	3 (50)	11 (28)

[a]Two patients with colon cancer.
[b]One patient with rectal cancer and one patient with mesothelioma.
[c]One patient with ovarian cancer and one patient with nasopharyngeal cancer.
[d]Carboplatin+paclitaxel ($n = 8$), 5-fluorouracil containing regimen ($n = 3$).

for localized gastric/GEJ adenocarcinoma. Patients were not followed for overall survival.

Safety assessments

Safety assessments were performed prior to each andecaliximab infusion, following the CTCAE version 4.03 criteria (21). Paresthesias/dysesthesias were graded according to the following scale: grade 1, of short duration that resolved and did not interfere with function; grade 2, interfered with function, but not with activities of daily living (ADL); grade 3, presented with pain or with functional impairment that also interfered with ADL; grade 4, persistent and disabling or life-threatening.

Results

Part A: monotherapy cohorts

Patient characteristics. Between April and August 2013, 13 patients with advanced solid tumors were enrolled into part A of the study from three sites in the Unites States. All 13 patients were treated and evaluable for the safety analysis (Table 1).

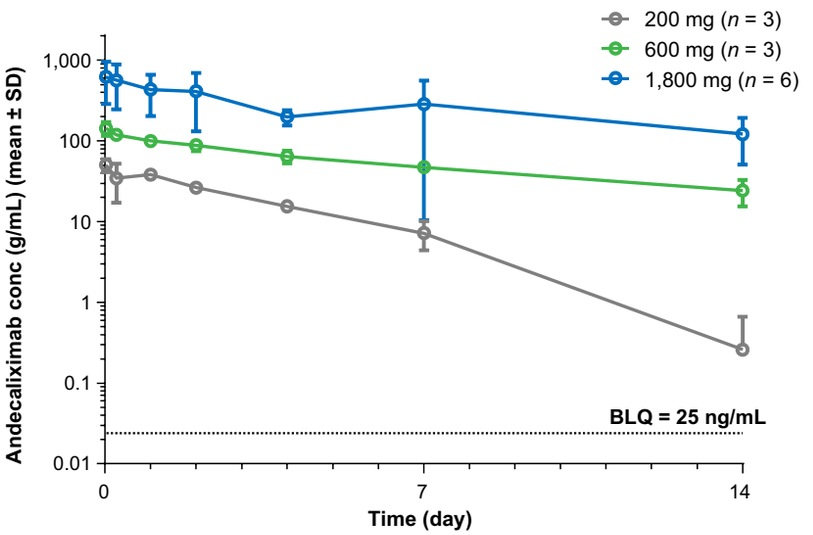
Safety. Across the three monotherapy cohorts in part A, the median duration of exposure to andecaliximab was 6.1 (range, 0.1–31.7) weeks with a median of 4 (range, 1–16) doses received. No dose reductions of andecaliximab were required. No DLTs were reported. No patients discontinued monotherapy because of AEs. AEs attributed to andecaliximab (all grades 1–2) were observed in 7 of 13 (53.8%) patients; and the most common AEs were nausea (31%), vomiting, and fatigue (23% each), and diarrhea, asthenia, arthralgia, joint stiffness, and dyspnea (8% each). Grade 3–4 AEs were observed in four patients: aspartate transaminase increase [cohort 1, one patient (8%)]; and acute kidney injury, duodenal obstruction, and pleural effusion [cohort 3, one patient (8%) each]. No grade 3–4 AEs were attributed to andecaliximab (Table 2). No grade 5 AEs were reported. All patients discontinued study treatment due to progression.

Pharmacokinetics. The mean plasma concentration versus time profile and the calculated PK parameters of andecaliximab following doses of 200, 600, and 1,800 mg are shown in Fig. 1. At each dose level, maximum plasma concentrations were observed at the end of infusion and increased approximately dose-proportionally, whereas the area under the curve increased more than dose-proportionally. The terminal phase of elimination was faster at the lowest dose and approached parallel elimination at the higher doses. The clearance decreased from 1,172 mL/day in the 200 mg cohort to 377 mL/day in the 1,800 mg cohort. The terminal half-life increased with dose from approximately 2.4 days to 8.3 days. These data are consistent with target-mediated drug disposition having a significant effect on the clearance of andecaliximab at the lower doses.

Table 2. Most common all-cause treatment-emergent AEs; only those occurring in ≥15% of patients in the gastric/GEJ adenocarcinoma combination cohort (part B) are shown

	Part A All monotherapy cohorts $N = 13$[a]		Part B Gastric/GEJ cohort (andecaliximab + mFOLFOX6) $N = 40$[b]	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Any AE	12 (92)	4 (31)	40 (100)	29 (73)
Nausea	5 (39)	0	26 (65)	4 (10)
Fatigue	4 (31)	0	24 (60)	3 (8)
Diarrhea	2 (15)	0	19 (48)	2 (5)
Neuropathy, peripheral	1 (8)	0	19 (48)	1 (3)
Neutropenia	0	0	16 (40)	10 (25)
Constipation	1 (8)	0	13 (33)	0
Anemia	0	0	12 (30)	3 (8)
Decreased appetite	1 (8)	0	12 (30)	0
Temperature intolerance	0	0	12 (30)	0
Vomiting	0	0	12 (30)	0
Dysgeusia	0	0	10 (25)	0
Insomnia	1 (8)	0	10 (25)	0
Edema, peripheral	0	0	10 (25)	0
Paresthesia	0	0	9 (23)	0
Dehydration	0	0	8 (20)	2 (5)
Rash	0	0	8 (20)	0
Thrombocytopenia	0	0	8 (20)	1 (3)
Dyspnea	4 (31)	0	7 (18)	2 (5)
Neutrophil count decreased	0	0	7 (18)	4 (10)
Platelet count decreased	0	0	7 (18)	0
Pyrexia	0	0	7 (18)	1 (3)
Stomatitis	0	0	7 (18)	1 (3)
Abdominal pain	1 (8)	0	6 (15)	2 (5)
Arthralgia	2 (15)	0	6 (15)	0
Back pain	0	0	6 (15)	0
Cough	3 (23)	0	6 (15)	0
Dizziness	3 (23)	0	6 (15)	0
Dry mouth	0	0	6 (15)	0
Dysphagia	0	0	6 (15)	1 (3)
Headache	0	0	6 (15)	0

[a]No grade 5 events were observed.
[b]Four grade 5 events were observed: ascites, gastrointestinal hemorrhage, septic shock, and pneumothorax in one patient each (3%).



	200 mg	600 mg	1,800 mg
C_{max}, μg/mL*	50.2 (18.4)	148.4 (13.0)	619.5 (54.1)
$AUC_{0\text{-last}}$, day·μg/mL*	154.2 (2.0)	781.4 (10.2)	4,197.7 (71.3)
$AUC_{0\text{-}\infty}$, day·μg/mL*	172.5 (12.8)	1,046.6 (17.2)	5,910.0 (59.4)
CL (mL/days)*	1,171.8 (12.0)	585.5 (18.3)	377.4 (40.7)
V_z (mL)†	4,324.9 (339.5, 4,441.9)	5,509.2 (4,418.9, 7,365.0)	5,656.8 (1,222.2, 7,340.8)
T_{max}, day†	0.02 (0.02, 0.02)	0.02 (0.02, 0.26)	0.02 (0.02, 0.03)
$t_{1/2}$, day†	2.37 (1.88, 3.05)	7.66 (4.34, 9.23)	8.25 (6.01, 11.16)

Figure 1.
The plasma concentration versus time profile (top) and PK profile (bottom) of andecaliximab monotherapy. *Mean [% coefficient of variation (CV)]; †Median [quartile (Q)1, Q3]. Abbreviations: $AUC_{0\text{-}\infty}$, area under curve from time 0 to infinity; $AUC_{0\text{-last}}$, AUC from time 0 to last measurable concentration time point; BLQ, below the limit of quantification; C_{max}, maximal concentration; $t_{1/2}$, terminal half-life; T_{max}, time to C_{max}; V_z, volume of distribution at terminal phase.

Part B: Gastric/GEJ adenocarcinoma combination cohort

Patient characteristics. Between November 2013 and July 2015, 41 patients with gastric/GEJ adenocarcinoma were enrolled into part B of the study from 10 sites in the United States; one patient did not receive study treatment, so 40 patients were treated and followed for safety and efficacy (Table 1).

Safety. In the gastric/GEJ adenocarcinoma cohort, the median duration of exposure to andecaliximab was 21.0 (range, 0.1–121) weeks with a median of 10.5 (range, 1–57) doses received. The median duration of exposure and median number of doses of mFOLFOX6 were as follows: 5-fluorouracil 21.3 (range, 0.4–121.4) weeks, 10.5 (range, 1–57) doses; leucovorin 19.4 (range, 0.4–121.4) weeks, 10 (range, 1–57) doses; and oxaliplatin 16.4 (range, 0.4–121.4) weeks, 8 (range, 1–20) doses.

AEs of any grade related to andecaliximab observed in ≥10% of all patients included fatigue (35%), nausea (28%), neutropenia (18%), dysgeusia (15%), decreased platelet count (15%), decreased appetite (13%), diarrhea (13%), thrombocytopenia (10%), and decreased neutrophil count (10%; Table 2). Four grade 5 AEs were observed (all considered unrelated to andecaliximab or mFOLFOX6 by the investigator): abdominal ascites (in the setting of disease progression in the peritoneum), gastrointestinal hemorrhage (classified as disease-related in a patient with stage IV disease at diagnosis who had not undergone resection), septic shock, and pneumothorax (classified as intercurrent illnesses in the setting of pneumonia and bronchopleural fistula following a thoracentesis) in 1 patient each (3%). As of August 31, 2016, 6 patients with gastric/GEJ adenocarcinoma continued to receive study treatment. As of September 22, 2017, one patient remains on study treatment.

Efficacy. Exposure and response data for the gastric/GEJ adenocarcinoma cohort are shown in Supplementary Fig. S2. The ORR for all patients was 47.5% (90% CI, 33.8–61.5) with 3 (7.5%) CRs and 16 (40%) PRs observed, and 50% for first-line patients (Table 3). Although the ORR was approximately 50%, the percent change in tumor size for all patients (Fig. 2A, waterfall plot) demonstrates that all but five patients with measurable disease had a reduction in tumor size. The duration of response was 8.4 months for all patients and 9.3 months for first-line patients. PFS was 7.8 (90% CI, 5.5–13.9) months in all patients and 9.9 (90% CI, 5–13.9) months in first-line patients (Fig. 2B).

Table 3. Investigator-assessed efficacy data in the gastric/GEJ adenocarcinoma cohort

Response[a], *n* (%)	All patients, *n* = 40[b]	First-line patients, *n* = 36
CR	3 (8)	3 (8)
PR	16 (40)	15 (42)
SD	6 (15)	5 (14)
Non-CR/non-PD	6 (15)	5 (14)
PD	3 (8)	3 (8)
ORR, % (90% CI)	48 (34–62)	50 (35–65)
DOR, (90% CI) months	8.4 (5.4–24.9)[c]	9.3 (5.8–24.9)[d]
PFS, (90% CI) months	7.8 (5.5–13.9)	9.9 (5–13.9)

Abbreviations: PD, progressive disease; SD, stable disease.
[a]Five patients (two treatment-naïve) discontinued study prior to the first response assessment, and one patient was not evaluated.
[b]Among the four patients with <190 days since their previous treatment for gastric/GEJ adenocarcinoma, one had a response to treatment with andecaliximab+mFOLFOX6.
[c]Based on investigator assessment in patients with CR or PR (*n* = 19).
[d]Based on investigator assessment in patients with CR or PR (*n* = 18).

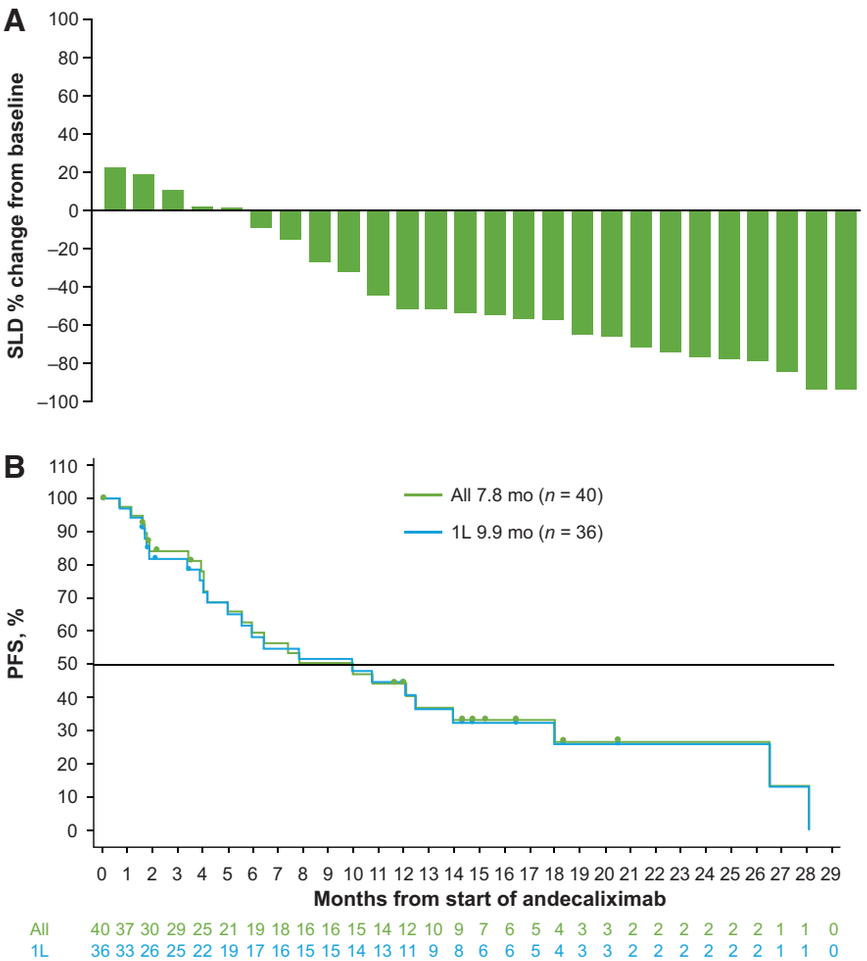


Figure 2.
Efficacy summary for patients with gastric/GEJ adenocarcinoma (part B). **A,** Best percent change from baseline in sum of longest diameter in patients with target lesions ($n = 26$) at screening **B,** PFS in all patients and first-line patients (patients who were treatment-naïve or >190 days since previous therapy for localized gastric/GEJ adenocarcinoma). SLD, sum of longest diameter; 1L, first-line patients.

Biomarker assessments in monotherapy and combination therapy cohorts. Total MMP9 (andecaliximab-bound plus -free) and andecaliximab-free MMP9 in circulation were measured in plasma. The total and free MMP9 concentrations at baseline (prior to andecaliximab infusion) were within 5% (Supplementary Material). In the monotherapy cohorts, free MMP9 was undetectable in all treated subjects except for two subjects in the 200-mg cohort (1 at days 15 and 43 and 1 at day 43), indicating that all circulating MMP9 was bound to andecaliximab at the 600- and 1,800-mg dose levels (Fig. 3A; Supplementary Fig. S3). In the gastric/GEJ adenocarcinoma cohort, free MMP9 was detectable at baseline in all patients, and undetectable in 91% to 100% of patients at postbaseline time points, with little change in total MMP9 (Fig. 3B).

MMP9 cleaves extracellular matrix proteins including collagens; therefore, fragments of collagen, such as C1M, detectable in blood may serve as a marker of MMP activity. Serum C1M was not dose-dependently modulated at day 15 or 43 in the monotherapy cohorts of mixed tumor types (Fig. 3C). However, a significant decrease in C1M was observed at week 4 [median % baseline, 79.0 (Q1 46.5, Q3 112.1), $P = 0.001$] and maintained over time for the gastric/GEJ adenocarcinoma cohort (Fig. 3D). Patients with the highest concentration of circulating C1M at baseline had the largest decrease in C1M upon treatment (Fig. 3E).

Discussion

Andecaliximab is a novel, highly selective antibody inhibitor of MMP9. The purpose of this study was to determine the MTD of andecaliximab monotherapy and to assess its efficacy and safety in combination with chemotherapy in patients with advanced solid tumors. In the monotherapy cohort, the plasma concentration versus time profile of andecaliximab displayed typical nonlinear PK at the low dose, 200 mg, and was linear in the higher-dose cohorts, 600 and 1,800 mg. The clearance of andecaliximab decreased as the dose increased. Combined, these data suggest a contribution of target-mediated drug disposition to andecaliximab plasma elimination. As is typical for monoclonal antibodies, the steady-state volume of distribution was low, suggesting limited extravascular distribution. Based on known clearance mechanisms, no drug–drug interaction between andecaliximab and mFOLFOX is expected when andecaliximab is combined with mFOLFOX in the gastric/GEJ adenocarcinoma cohort.

The MTD of andecaliximab was not determined in this study. Andecaliximab monotherapy appeared well tolerated when administered at 200, 600, and 1,800 mg i.v. q2w, and no DLTs were observed at any dose. A dose of 800 mg q2w (or 1,200 mg q3w) was selected for further development as it was expected to achieve plasma concentrations that are in the linear range of the

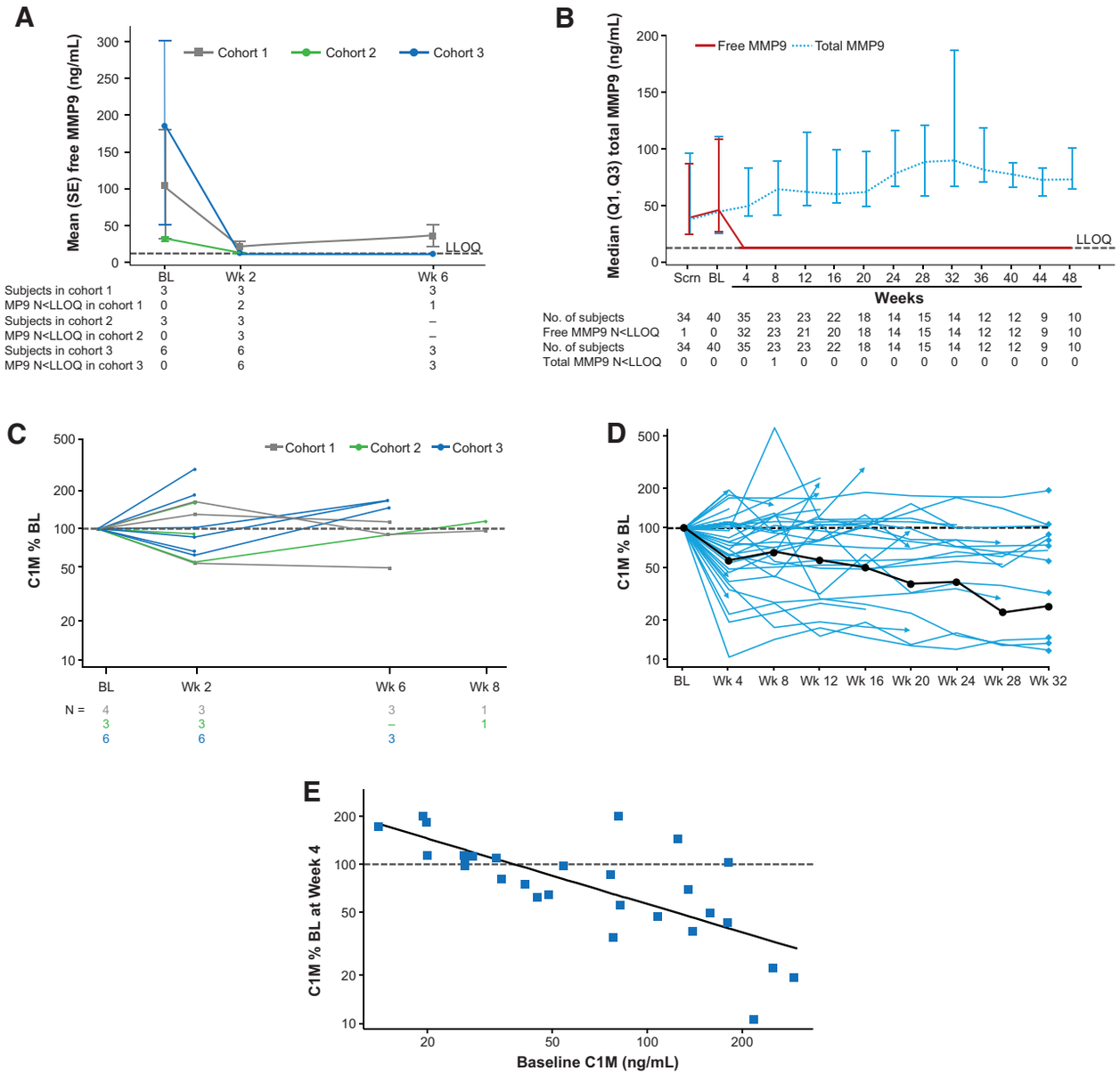


Figure 3.

Pharmacodynamic measures of andecaliximab activity. Andecaliximab-free MMP9 is undetectable at weeks 2 and 6 for 600 and 1,800 mg doses (cohorts 2 and 3) in the monotherapy cohorts (**A**) and in the gastric/GEJ cohort dosed at 800 mg q2w (**B**). **C,** Individual patient changes from baseline in collagen neoepitope C1M over time in the monotherapy cohorts. **D,** Individual patient changes from baseline through week 32 in C1M in the gastric/GEJ cohort (arrowheads indicate subjects still on-study as of biomarker data cut-off; black line indicates the population mean). **E,** Correlation of percent change from baseline in C1M at week 4 versus baseline levels. BL, baseline; LLOQ, lower limit of quantitation.

PK profile and to achieve adequate steady trough concentrations (i.e., saturate target-mediated drug disposition). A population PK model for andecaliximab, incorporating nonlinear elimination processes and relevant covariates, was developed and supports evaluation of the 800 mg q2w i.v. regimen (22).

Reduction in the level of circulating andecaliximab-free MMP9 after treatment demonstrated on-target binding of andecaliximab. In the monotherapy cohorts, all circulating MMP9 was bound to andecaliximab after single doses of 600 or 1,800 mg. Maximal binding of MMP9 by andecaliximab was achieved in all patients in the gastric/GEJ adenocarcinoma cohort, supporting further development of the 800 mg q2w dose.

Treating patients who have advanced gastric/GEJ adenocarcinoma with andecaliximab 800 mg + mFOLFOX6 q2w resulted in a median PFS of 7.8 (90% CI, 5.5–13.9) months with ORR of 48%. Among first-line patients (defined as patients who were treatment-naïve or >190 days since previous therapy for localized gastric/GEJ adenocarcinoma), PFS was 9.9 (90% CI, 5–13.9)

months, suggesting a potential improvement over conventional chemotherapy in first-line metastatic or unresectable advanced gastric/GEJ adenocarcinoma (23–25).

The most frequently reported toxicities in the monotherapy cohorts were nausea, fatigue, and dyspnea, whereas the most common toxicities of andecaliximab + mFOLFOX6 were nausea, fatigue, diarrhea, and peripheral neuropathy. In contrast to the pan-MMP inhibitor marimastat (14), andecaliximab was not associated with treatment-emergent musculoskeletal syndrome. Andecaliximab + mFOLFOX6 appears well tolerated without new or unexpected safety signals. The safety profile of andecaliximab + mFOLFOX6 appears similar to the previously characterized toxicity profile of mFOLFOX6 in advanced gastric adenocarcinoma, with nausea, vomiting, diarrhea, neuropathy, and neutropenia being commonly observed in previous reports (23–25). Of note, the four on-study deaths were not attributed to study treatment, but to either disease progression or intercurrent illness.

Generation of the collagen cleavage fragment C1M was investigated as a marker of MMP9 activity. C1M did not decrease in the monotherapy cohorts; however, a significant decrease in C1M was sustained from week 4 onward in the gastric/GEJ adenocarcinoma cohort treated with andecaliximab + mFOLFOX6. Patients with the highest baseline level of C1M had the greatest decrease. The discrepancy in C1M reduction between the monotherapy and gastric/GEJ adenocarcinoma cohorts could be due to the impact of mFOLFOX6 on C1M. In addition, because other MMPs cleave collagens (26), the difference could be related to the distribution of MMPs in particular diseases as patients with eight different solid tumor diseases were treated in the monotherapy cohorts.

Based on the safety and efficacy profile in the gastric/GEJ adenocarcinoma combination cohort, a randomized phase III study (27) comparing mFOLFOX6 with and without andecaliximab 800 mg q2w as first-line treatment for HER2-negative advanced gastric/GEJ adenocarcinoma has been initiated (28).

Disclosure of Potential Conflicts of Interest

A. Starodub reports receiving speakers bureau honoraria from Bristol-Myers Squibb and Lexicon, and is a consultant/advisory board member for AstraZeneca. Z.A. Wainberg is a consultant/advisory board member for Array, Gilead, and Merck. No potential conflicts of interest were disclosed by the other authors.

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