original reports abstract

Phase III Study to Evaluate Efficacy and Safety of Andecaliximab With mFOLFOX6 as First-Line Treatment in Patients With Advanced Gastric or GEJ Adenocarcinoma (GAMMA-1)

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PURPOSE Andecaliximab (ADX) is a monoclonal antibody that inhibits matrix metalloproteinase 9, an extracellular enzyme involved in matrix remodeling, tumor growth, and metastases. A phase I and Ib study of modified oxaliplatin, leucovorin, and fluorouracil (mFOLFOX6) with ADX revealed encouraging antitumor activity in patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma.

MATERIALS AND METHODS This phase III, randomized, double-blinded, placebo (PBO)-controlled multicenter study investigated the efficacy and safety of mFOLFOX6 with and without ADX in patients with untreated human epidermal growth factor receptor 2–negative gastric or GEJ adenocarcinoma. Random assignment was 1:1 to mFOLFOX6 + ADX or mFOLFOX6 + PBO. ADX/PBO 800 mg was infused on days 1 and 15 of each 28-day cycle. Protocol therapy was given until disease progression or intolerance. The primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS), objective response rate (RECIST 1.1), and safety.

RESULTS Between September 2015 and May 2017, 432 patients were randomly assigned, 218 to ADX and 214 to PBO. The median OS was 12.5 versus 11.8 months in the ADX and PBO groups, respectively. The median PFS was 7.5 versus 7.1 months in the ADX and PBO groups, respectively. The objective response rate was 51% in the ADX group and 41% in the PBO group. Among the subgroup analyses, patients of age ≥ 65 years had an improved OS and PFS with ADX versus PBO; the *P* values and CIs were not adjusted for multiplicity. There were no meaningful differences in the safety profile of the ADX versus PBO groups.

CONCLUSION The addition of ADX to mFOLFOX6 did not improve OS in unselected patients with untreated human epidermal growth factor receptor 2–negative gastric or GEJ adenocarcinoma.

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INTRODUCTION

More than 27,000 US residents were estimated to have gastric adenocarcinoma in 2019, leading to more than 11,000 deaths.[1] Advanced gastric adenocarcinoma continues to be a deadly disease with a 5-year survival rate of only 5%.[1]

Patients with advanced gastric adenocarcinoma have multiple chemotherapy options that have marginal efficacy.[2] Traditional cytotoxic chemotherapy regimens in the second-line or later setting have shown poor median overall survival (OS) rates, ranging from 3 to 5 months (comparable with the median 2-4 months with best supportive care).[3-6] In 2010, the approval of trastuzumab for human epidermal growth factor receptor 2 (HER2)–positive gastric adenocarcinoma increased median OS rates to 11-25 months,[7-14] and the approvals of ramucirumab,[15] pembrolizumab,[16] and trifluridine/tipiracil[17] for gastric adenocarcinoma added three additional options to the treatment armamentarium. Although these new treatment options represent significant advances for the treatment of gastric adenocarcinoma, the disease remains incurable for the majority of patients, and there remains an unmet need for more effective treatments.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases that play an important role in the remodeling of extracellular matrix (ECM) and basement membranes and in the regulation of growth factors, cytokines, and chemokines.[18,19] One member, MMP9, is an inducible protease expressed by tumor epithelia, associated with macrophage and neutrophil infiltration, and can regulate ECM remodeling, neovascularization, and inflammatory signaling.[20-22] In gastric tumors, MMP9 expression is frequently observed in both tumor epithelia and stromal compartments. Elevated expression of MMP9 is associated with shorter overall and disease-free survival in gastric adenocarcinoma.[23-25] Transforming growth factor β

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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and other immune-suppressive factors are activated via MMP9, which may foster a protumorigenic tumor microenvironment.[26-29] Based on these observations, MMP9 was evaluated as a target for the treatment of gastric adenocarcinoma.

Andecaliximab (ADX, formerly GS-5745) is a recombinant chimeric immunoglobulin G_4 monoclonal antibody that demonstrates high affinity and selectivity for MMP9.[30,31] In a phase I and Ib study, ADX (800 mg every 2 weeks) plus modified oxaliplatin, leucovorin, and fluorouracil (mFOLFOX6) was well-tolerated and showed encouraging antitumor activity in patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma.[18] The median progression-free survival (PFS) was 7.8 months in all patients and 9.9 months in first-line patients, with overall response rates of 48% and 50% in the respective populations.[18] Based on these encouraging results, we examined the efficacy of ADX plus mFOLFOX6 compared with placebo (PBO) plus mFOLFOX6 in patients with HER2-negative gastric or GEJ adenocarcinoma.

MATERIALS AND METHODS

Study Design

This was a phase III, random assignment, double-blinded, PBO-controlled, multicenter study (ClinicalTrials.gov identifier: NCT02545504, GS-US-296-1080) conducted from October 13, 2015, to May 15, 2019 (last patient last observation for the primary end point), at 132 study sites worldwide.

Patients with advanced gastric and GEJ adenocarcinoma were randomly assigned via interactive web-response system 1:1 to ADX + mFOLFOX6 or PBO + mFOLFOX6. Treatment assignment was stratified by Eastern Cooperative Oncology Group (ECOG) status (0 or 1), geographic region (Latin America or other participating countries), and primary tumor site (gastric or GEJ).

Computed tomography or magnetic resonance imaging scans were performed every 8 weeks to evaluate response to treatment by RECIST v1.1.[32] Patients received ADX/PBO 800 mg intravenously once every 2 weeks on days 1 and 15 of each 28-day cycle (Data Supplement, online only); mFOLFOX6 was given on days 1 and 15 of each 28-day treatment cycle for a total of six cycles followed thereafter by leucovorin (LV) and fluorouracil (5-FU) dosing on days 1 and 15 of each 28-day treatment cycle. The mFOLFOX6 dosing regimen consisted of l-LV 200 mg/m^2 or dl-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus FU 400 mg/m^2 and a 46-hour infusion of FU 2400 mg/m^2. Treatment cycles continued until disease progression, unacceptable toxicity, withdrawal of consent, or patient's refusal of treatment.

Eligibility

Patients eligible for participation in this study were adults with histologically confirmed adenocarcinoma of the stomach or GEJ that was locally advanced or metastatic and not amenable to curative therapy. Disease was required to be evaluable per RECIST v1.1.[32] Eligible patients had adequate hematologic, liver, coagulation, and kidney function as defined by neutrophils $\geq 2.0 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; hemoglobin 9 g/dL; direct or total bilirubin $\leq 1.5 \times$ ULN; alanine transaminase and aspartate transaminase $\leq 2.5 \times$ ULN (or in the case of liver metastases $\leq 5 \times$ ULN); and creatinine clearance (CrCl) ≥ 30 mL/min based on the Cockroft-Gault formula (patients with a CrCl just below 30 mL/min may be eligible if a measured CrCl [based on 24-hour urine collection or other reliable method] is ≥ 30 mL/min). All patients had ECOG statuses of 0 to 1.

Patients were excluded for the following: HER2-positive gastric adenocarcinoma, known or suspected CNS metastases, grade ≥ 2 peripheral neuropathy, any requirement for chronic daily oral corticosteroids, or previous chemotherapy for locally advanced or metastatic gastric or GEJ adenocarcinoma. Also, patients with viral infections such as HIV and hepatitis B or C virus infection and women who were pregnant or breastfeeding were also ineligible. The Protocol was approved by Institutional Review Boards at each site. The study was conducted in accordance with principles of the Declaration of Helsinki and International Good Clinical Practice Guidelines. All patients provided written informed consent.

Outcomes

The primary outcome was OS, measured as the time from random assignment to death from any cause. Secondary outcomes included PFS, objective response rate (ORR), and safety. PFS was defined as the interval of time from random assignment to the earlier of first documentation of definitive disease progression or death from any cause. Patients who discontinued the study drug before disease progression were followed up until they had documented disease progression. Objective response was assessed according to RECIST v1.1. ORR was defined as the proportion of patients who achieved a complete response or partial response. The overall safety profile of ADX was evaluated by the incidence of adverse events (AEs) and clinically relevant changes in laboratory values and vital signs.

Data Monitoring Committee

An independent data monitoring committee (DMC) reviewed the progress of the study and performed interim reviews of safety data. Safety review by the DMC was performed after the first 60 patients completed four treatment cycles (16 weeks). Thereafter, review of safety data was performed every 6 months. In addition, the DMC met after approximately 33.3% and approximately 66.7% of the expected number of events occurred to review the results from the futility and efficacy interim analysis, respectively.

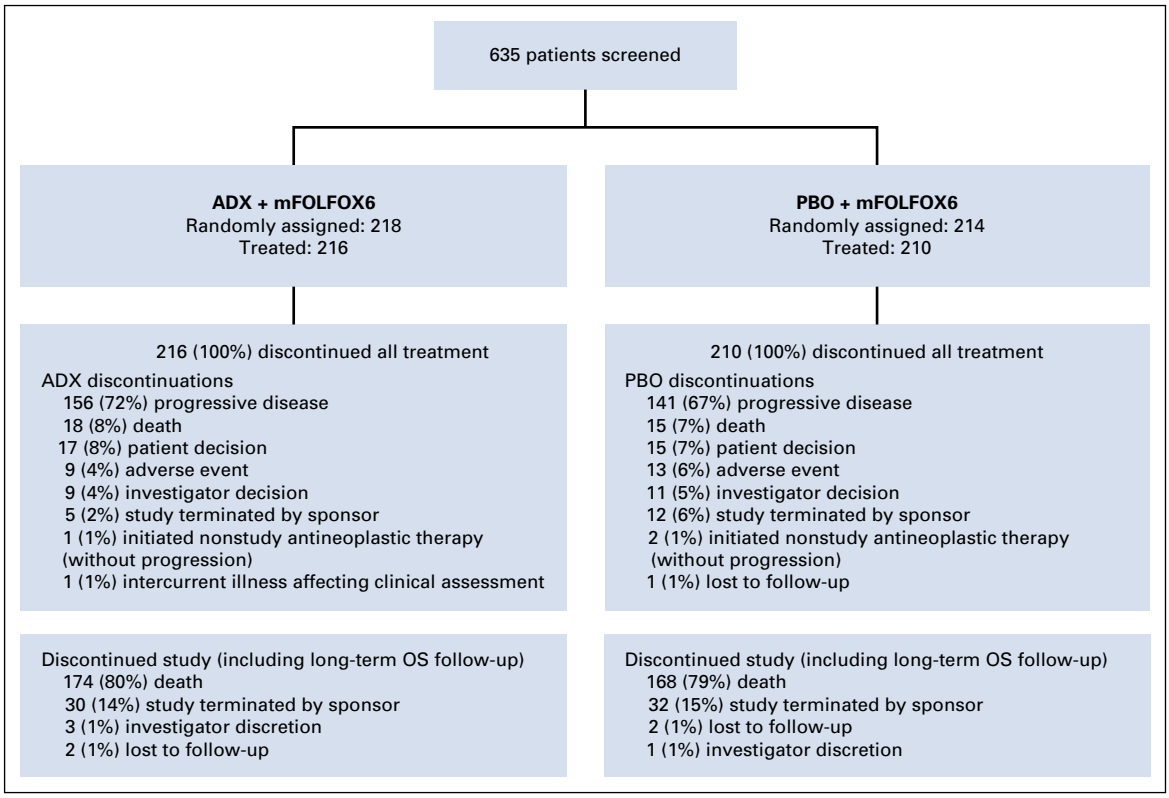

FIG 1. Patient disposition. ADX, andecaliximab; mFOLFOX6, modified oxaliplatin, leucovorin, and fluorouracil; OS, overall survival; PBO, placebo.

Statistical Analysis

To detect a hazard ratio (HR) of 0.70 with 85% power at a one-sided significance level of 0.025, given one efficacy interim after 66.7% of expected events, 286 events were needed. Assuming a median OS time for the mFOLFOX6 plus PBO group of 11.5 months, with an accrual period of 18 months, a minimum follow-up of 18 months, and a 10% annual dropout rate, a total sample size of 430 patients (215 patients per treatment group) was needed to observe the required 286 events within the 36-month time frame.

Two interim analyses were conducted when approximately 33% (futility interim analysis) and approximately 67% (efficacy interim analysis) of expected 286 OS events had occurred. The final analysis was conducted after approximately 286 OS events had occurred. In the efficacy interim and final analysis, the primary and secondary end points were tested sequentially in the following gatekeeping order: the primary OS end point, then the secondary PFS end point, and finally the secondary ORR end point. The testing strategy employs the O'Brian-Fleming type boundary for the primary OS end point and the Pocock type boundary for the secondary PFS and/or ORR end points. The testing strategy controls the overall one-sided family-wise type 1 error to be at 0.025, equivalent to two-sided error of 0.05 by appropriately adjusting for multiplicity in the efficacy interim and final analyses.

After adjusting for the actual number of OS events observed, the significance level for OS was one-sided (0.006) at the efficacy interim and one-sided (0.023) at the final analysis. If the OS end point is rejected at the efficacy interim or final analysis, the PFS end point will be tested at a one-sided alpha level of 0.016. If the PFS end point is also rejected, the ORR end point will be tested at a one-sided alpha level of 0.016.

After the final analysis, the follow-up analysis was performed when all patients discontinued the study to satisfy regulatory requirements and to perform long-term efficacy (eg, OS) and follow-up safety assessments.

Herein, we report efficacy results based on the final analysis and safety results based on the follow-up analysis. The primary efficacy analysis set was the intent-to-treat analysis set, which included all randomly assigned patients and was analyzed according to treatment assigned. The OS primary end point was analyzed using the Kaplan-Meier (KM) method; log-rank test was used to compare the OS distribution between the two treatment groups and stratified by ECOG status (0 or 1), geographic region (Latin America or other participating countries), and primary tumor site (gastric or GEJ). A Cox proportional hazard model with the

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	ADX (n = 218)	PBO (n = 214)
Median age (range), years	61 (25-85)	63 (24-82)
Male, n (%)	168 (77)	153 (72)
ECOG PS, n (%)		
0	92 (42)	93 (44)
1	125 (57)	121 (57)
Missing[a]	1 (0.5)	0
Primary tumor site, n (%)		
Gastric	142 (65)	143 (67)
Diffuse	78 (55)	83 (58)
Intestinal	52 (37)	54 (38)
Missing	12 (9)	6 (4)
GEJ	76 (35)	71 (33)
Disease stage at screening, n (%)		
III	10 (5)	15 (7)
IV (metastatic)	208 (95)	199 (93)
Differentiation, n (%)		
Well differentiated	9 (4)	11 (5)
Moderately differentiated	58 (27)	56 (26)
Poorly differentiated	107 (49)	100 (47)
Undifferentiated	4 (2)	4 (2)
Others	1 (0.5)	1 (0.5)
Unknown	37 (17)	42 (20)
Missing	2 (1)	0

Abbreviations: ADX, andecaliximab; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; PBO, placebo.
[a]Patient ECOG at screening was missing; the ECOG at the time of random assignment was one. For the stratified overall survival, progression-free survival, and objective response rate analyses, patients were considered to have ECOG = 1.

same stratification factors was used to estimate the HR and corresponding 95% CI. The secondary end point of PFS was analyzed and compared similarly with the primary end point of OS.

ORR was summarized by count and percent of patients with each response category. Patients who did not have sufficient baseline or on-study tumor assessment to characterize response were counted as nonresponders and were included in the denominator. A Cochran-Mantel-Haenszel chi-square test, after adjusting for stratification factors, was performed to compare the two treatment groups. Odds ratios adjusting for stratification factors and the corresponding 95% CIs are presented.

Sixteen subgroups based on patient characteristics were examined for each of the three efficacy outcomes, and multiplicity was not adjusted.

Safety results are summarized by treatment group received for data collected on or after the date that ADX/PBO was first administered, up to the date of last dose of ADX/PBO plus 55 days or the last dose of all study treatment (ADX/PBO and chemotherapy), plus 30 days (whichever was later).

RESULTS

A total of 635 patients were screened; 432 were randomly assigned, and 426 were treated (Fig 1). As of May 15, 2019, all patients had discontinued study, including long-term OS follow-up. Baseline characteristics are shown in Table 1. Patient and disease characteristics were well-balanced between ADX and PBO treatment groups. Most patients (77% and 72%) were male, and 57% in each group had ECOG Performance Status Grade 1. The primary tumor type was gastric in 65% and 67% of patients, with 55% and 58% being of diffuse histology (≥ 93% stage IV metastatic), respectively.

The median number of ADX/PBO doses administered was 14 doses in the ADX group and 12 doses in the PBO group. Median exposure to ADX/PBO was 32.1 (range, 2.0-161.7) weeks in the ADX group and 26.0 (range, 2.0-112.3) weeks in the PBO group.

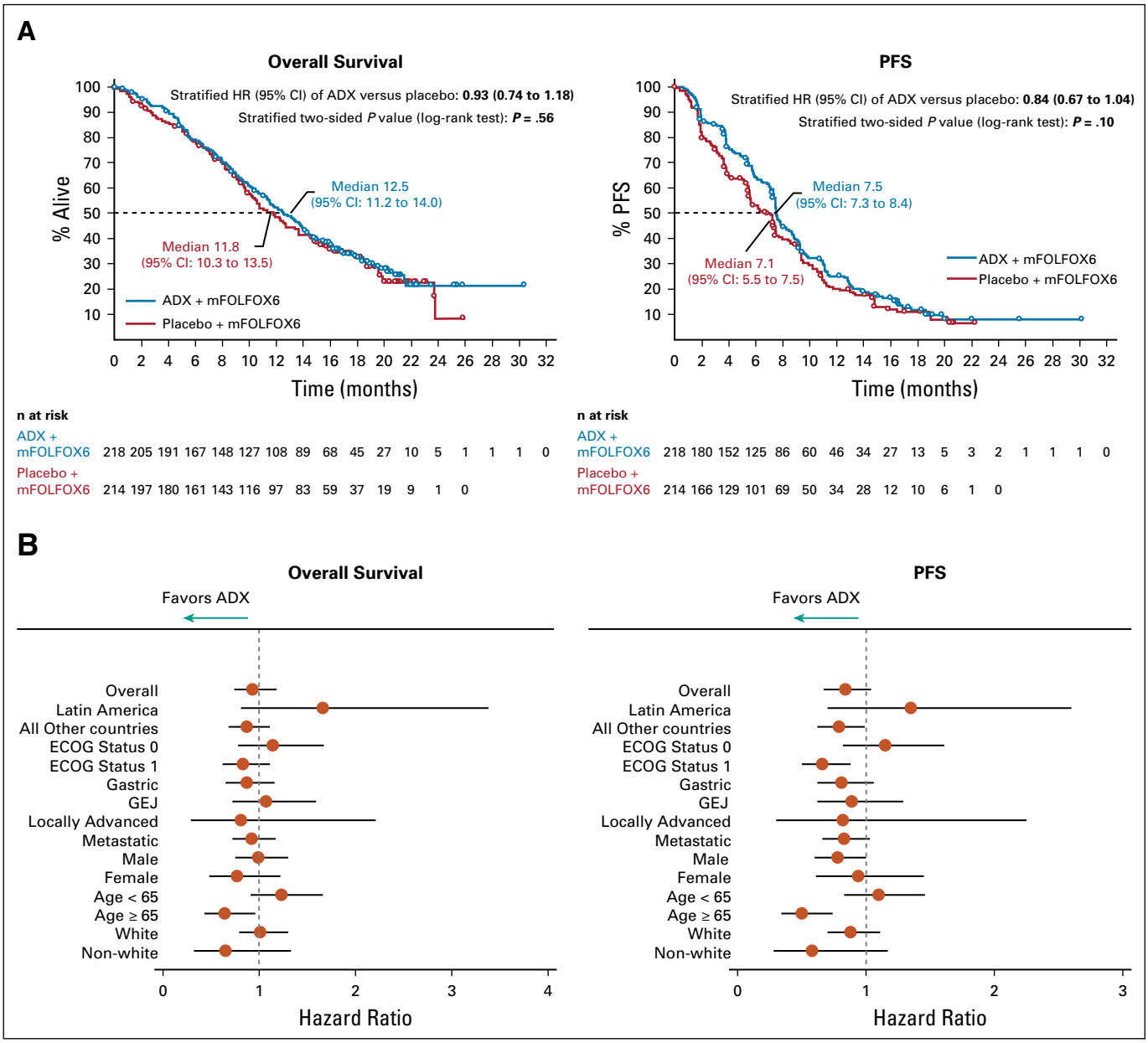

FIG 2. Overall survival and PFS by (A) treatment group and (B) subgroups of interest. ADX, andecaliximab; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; mFOLFOX6, modified oxaliplatin, leucovorin, and fluorouracil; PFS, progression-free survival.

Efficacy

At the time of the final analysis, 293 OS events had occurred. The KM estimate of the median (95% CI) OS was 12.5 (11.2 to 14.0) months in the ADX group and 11.8 (10.3 to 13.5) months in the PBO group (Fig 2A). The stratified HR (95% CI) for OS on ADX treatment versus PBO was 0.93 (0.74 to 1.18; $P = .56$).

The KM estimate of median (95% CI) PFS was 7.5 (7.3 to 8.4) months in the ADX group and 7.1 (5.5 to 7.5) months in the PBO group. The stratified HR (95% CI) for PFS on ADX treatment versus PBO was 0.84 (0.67 to 1.04; $P = .10$). The ORR was 51% (44%-77%) in the ADX group and 41% (35%-48%) in the PBO group (Table 2 and Fig 3). The stratified odds ratio was 1.47 (95% CI, 1.0 to 2.2, and $P = .049$).

OS was analyzed by subgroups (Fig 2B). Patients of age ≥ 65 years had a decreased risk of an OS event with ADX versus PBO (HR 0.64, 95% CI, 0.43 to 0.96, and $P = .03$) and a decreased risk of a PFS event with ADX versus PBO (HR 0.50, 95% CI, 0.34 to 0.74, and $P < .001$). In the post hoc analysis of Cox proportional hazards regression that includes treatment, age group (≥ 65 or < 65 years), and treatment by age group interaction as predictors and is stratified by ECOG status at screening, geographic region,

TABLE 2. Best Overall Response

Variable	ADX (n = 218)	PBO (n = 214)
Objective response rate,[a] % (95% CI)	50.5 (43.6-57.3)	41.1 (34.5-48.0)
Responders[b]	110	88
Nonresponders	108	126
Best overall response, n (%)		
CR	18 (8)	10 (5)
PR	92 (42)	78 (36)
SD	50 (23)	50 (23)
PD	22 (10)	28 (13)
NN	21 (10)	24 (11)
NE	1 (1)	2 (1)
Discontinued tumor assessment before first assessment (NA)[c]	14 (6)	22 (10)

Abbreviations: ADX, andecaliximab; CR, complete response; NE, not evaluable; NN, non-CR, non-PD; PBO, placebo; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Objective response rate = (CR + PR) ÷ (SD + PD + NN + NE + NA).

[b]Responder = CR or PR.

[c]Discontinued study or started new anticancer therapy before first assessment.

and primary tumor site, the *P* value for the interaction term was .0063 for OS and .0003 for PFS (Data Supplement). The *P* values were not adjusted for multiplicity in the subgroup analyses. In the post hoc analysis of OS by additional age intervals, a trend emerged (Fig 4A), with a lower HR in each successively older age bracket in patients receiving ADX versus PBO. A trend for improved OS emerged in patients ≥ 65 years of age (Fig 4B). The median PFS in patients ≥ 65 versus < 65 years is shown in the Data Supplement.

The median (range) percent change from baseline in sum of lesion diameters was –37% (–100% to 100%) in the ADX group and −42% (−100% to 65%) in the PBO group (Data Supplement).

Safety

A total of 214 patients (99.1%) in the ADX group and 209 patients (99.5%) in the PBO group who received study treatment reported AEs. Nine patients (4.2%) in the ADX group and 13 patients (6.2%) in the PBO group discontinued because of AEs. In the ADX and PBO groups, 103 (47.7%) and 108 (51.4%) experienced serious AEs, respectively. The rate of grade 3 or higher musculoskeletal AEs was similar between treatment groups (Data Supplement).

The most common grade ≥ 3 treatment-emergent AEs were decreased absolute neutrophil count (30% with ADX *v* 29% with PBO), neutropenia (22% with ADX and 27% with PBO), decreased white blood cells (13% with ADX and 12% with PBO), and decreased lymphocyte count (11% with ADX and 12% with PBO) (Table 3). Neutropenia was the most common grade ≥ 3 treatment-emergent AE related to ADX/PBO. Serious AEs occurred in 103 (48%) of patients in the ADX group and 108 (51%) in the PBO group. Serum chemistry laboratory abnormalities occurred in 198 (92%) patients in the ADX group and 195 (93%) in the PBO group. Patients of age ≥ 65 years who received ADX experienced less grade 2-4 nausea and vomiting compared with those receiving PBO. This was not observed in the age group of < 65 years (Data Supplement).

Overall, there were 339 deaths on study (80% of patients): 173 in the ADX group and 166 in the PBO group. Disease progression was the most common cause of death, with 30 and 21 deaths in the ADX and PBO groups occurring within the interval of 30 days from the last dose of any study drug (or within 55 days from the last dose of ADX or PBO). Subsequent to this interval, deaths because of disease progression occurred in 112 and 113 patients who had completed treatment in the ADX and PBO groups, respectively. Deaths because of AEs were similar between the ADX and PBO groups, occurring in 13 and 17 patients, respectively, within the interval of 30 days from the last dose of any study drug (or within 55 days from the last dose of ADX or PBO). No deaths because of AEs occurred beyond this interval.

DISCUSSION

In gastric adenocarcinoma, the role of the ECM in each step of carcinogenesis, from initiation to metastasis, has been well-documented.[33] MMPs are important enzymes that degrade ECM proteins and are secreted and activated by malignant cells, tumor-associated macrophages, and cancer-associated fibroblasts.[24] Gastric adenocarcinoma cells infected by *Helicobacter pylori* increased the activity of MMP proteins, such as MMP2, MMP9, and MMP10, shaping the tumor microenvironment and affecting cell invasion.[34,35] MMP9 expression is associated with more

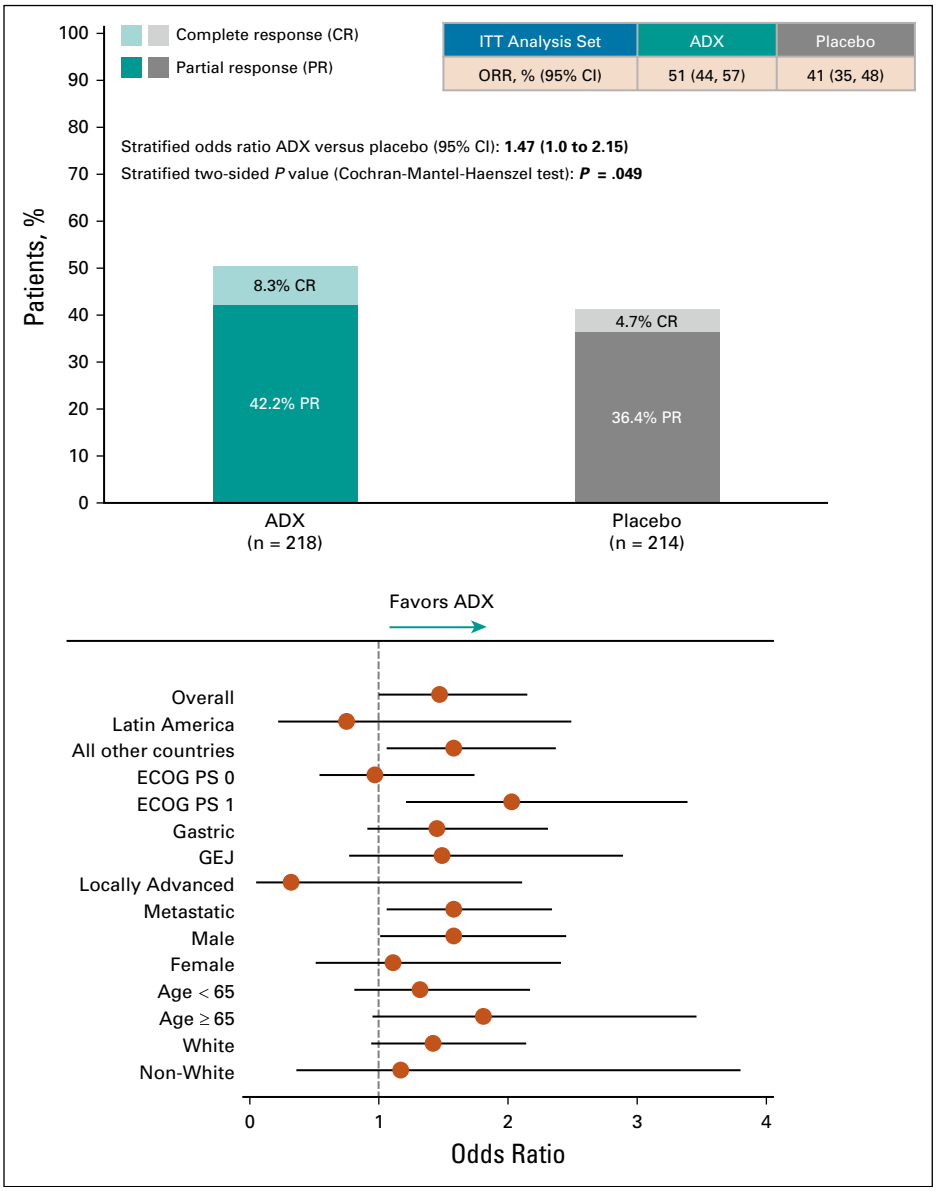

FIG 3. ORR by treatment group and subgroups of interest. ADX, andecaliximab; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; ITT, intent to treat; ORR, overall response rate.

aggressive disease.[24,36] Therefore, targeting ECM-related enzymes and receptors in gastric and other solid tumors is a promising therapeutic strategy. Antibodies and small molecules targeting the ECM currently in development include the antibody Fab 3369 that targets MMP14[37] and abituzumab that targets αvβ6[38] and JNJ0966, an MMP9 inhibitor.[39]

A phase I dose-finding study previously demonstrated the initial efficacy of ADX in combination with mFOLFOX6 in patients with advanced metastatic gastric or GEJ adenocarcinomas. We performed this phase III study to further evaluate the efficacy of ADX in combination with mFOLFOX6 in this patient population. In the overall study population, although ADX in combination with mFOLFOX6 was well-tolerated, the addition of ADX did not provide an added survival benefit versus mFOLFOX6 alone. Higher ORR was observed in the ADX versus PBO group (51% *v* 41%; stratified odds ratio 1.47; 95% CI, 1.0 to 2.2, $P = .049$); however, this did not translate into a prolongation of PFS or OS. The median OS was 12.5 months with ADX plus mFOLFOX6, compared with 11.8 months in the PBO plus mFOLFOX6 group (HR 0.93; $P = .56$).

Previous pan-MMP inhibitors have demonstrated marginal activity but limiting musculoskeletal toxicity.[40] ADX notably was not associated with the increased musculoskeletal toxicity seen with early pan-MMP inhibitors.[40,41] In this study, treatment with ADX in combination with mFOLFOX6

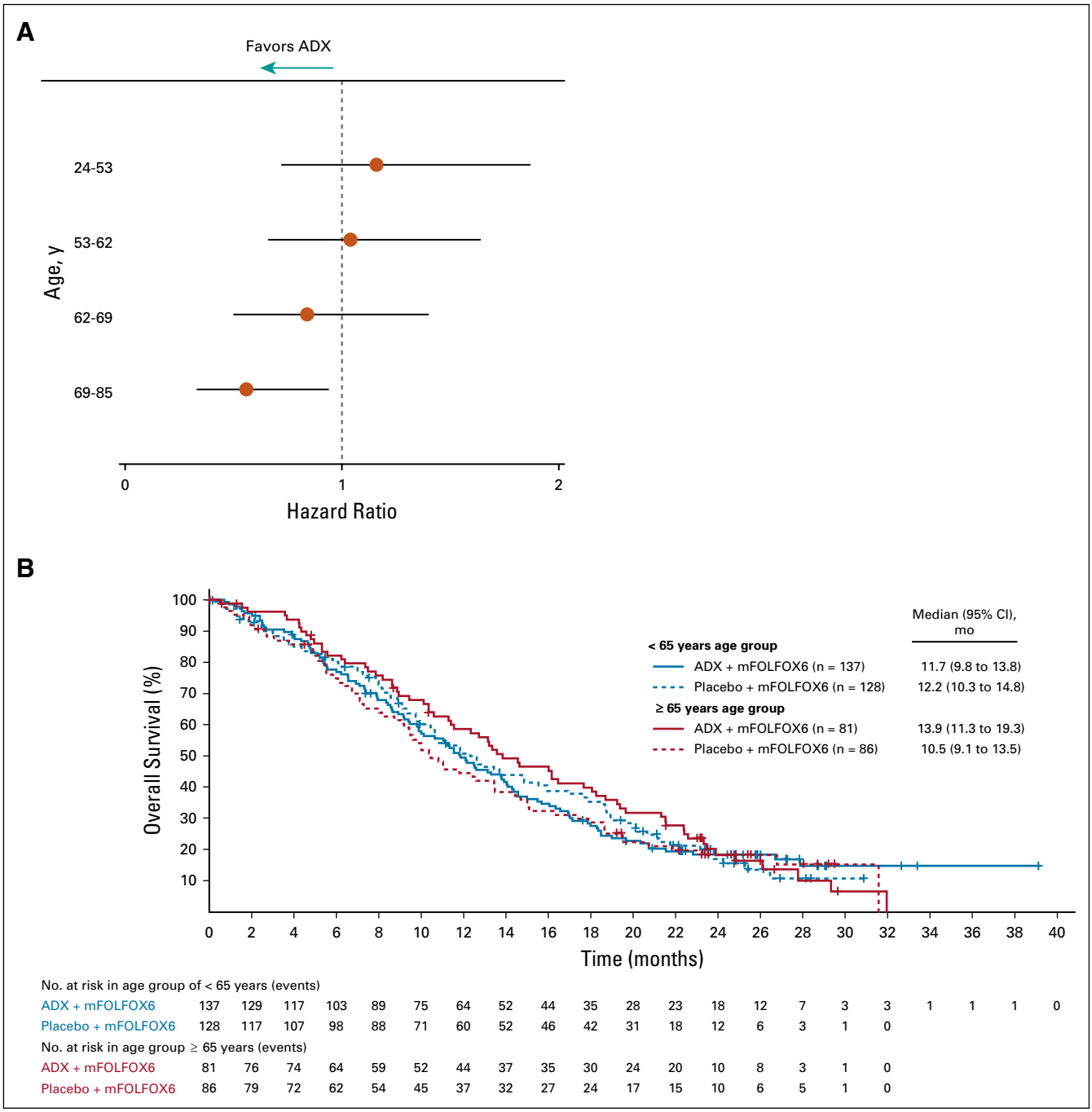

FIG 4. Overall survival by age. (A) Hazard ratio for overall survival by age subgroups. (B) OS in patients of age ≥ 65 years and < 65 years. The analysis is exploratory and for hypothesis generation. The result is not adjusted for multiplicity because of subgroup analyses. ADX, andecaliximab; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; mFOLFOX6, modified oxaliplatin, leucovorin, and fluorouracil.

was well-tolerated, with no meaningful differences in the rates of AEs or laboratory abnormalities between treatment groups and no differences in deaths within 30 days of treatment. In the subgroup analyses, it appears that ADX provided a survival benefit when added to mFOLFOX6 in patients of age ≥ 65 years. In this subgroup, the median OS was 13.9 versus 10.5 months in the ADX and PBO groups, respectively. Similarly, PFS in patients of age ≥ 65 years who received ADX with mFOLFOX6 was 8.7 months versus 5.6 months in patients receiving PBO. The effect of ADX on OS and PFS was found to be different for different age groups (Data Supplement). However, *P* values were not adjusted for multiplicity. The potential mechanism for this observation is not entirely clear but may be associated with better tolerance of chemotherapy in patients of age ≥ 65 years who received ADX (Data Supplement). There were no clear differences in ADX serum levels following treatment in patients above or below the age of 65 years (data not

TABLE 3. Incidence of Treatment-Emergent Adverse Events and Laboratory Abnormalities[a]

	ADX (n = 216)		PBO (n = 210)	
Event	**Grade 1-4**	**Grade ≥ 3**	**Grade 1-4**	**Grade ≥ 3**
Number of patients (%)				
Decreased absolute neutrophil count	151 (70)	65 (30)	142 (68)	61 (29)
Decreased white blood cells	147 (68)	28 (13)	138 (66)	25 (12)
Decreased platelet count	132 (61)	3 (1)	117 (56)	6 (3)
Hemoglobin (anemia)	136 (63)	19 (9)	126 (60)	14 (7)
Nausea	107 (50)	6 (3)	119 (57)	7 (3)
Increased AST	98 (45)	3 (1)	82 (39)	2 (1)
Hyperglycemia	97 (45)	17 (8)	81 (39)	6 (3)
Decreased lymphocyte count	88 (41)	23 (11)	84 (40)	26 (12)
Diarrhea	88 (41)	9 (4)	90 (43)	8 (4)
Increased ALT	80 (37)	3 (1)	65 (31)	4 (2)
Fatigue	79 (37)	12 (6)	73 (35)	18 (9)
Increased alkaline phosphatase	77 (36)	8 (4)	72 (34)	4 (2)
Neutropenia	76 (35)	48 (22)	76 (36)	56 (27)
Peripheral sensory neuropathy	73 (34)	12 (6)	72 (34)	5 (2)
Decreased creatinine clearance	74 (34)	2 (1)	73 (35)	1 (1)
Vomiting	68 (32)	13 (6)	67 (32)	9 (4)
Anemia	63 (29)	18 (8)	64 (31)	23 (11)
Decreased appetite	63 (29)	8 (4)	73 (35)	5 (2)

NOTE. Treatment-emergent adverse events are adverse events with onset dates on or after the first dose of ADX/PBO and up to 30 days after permanent withdrawal of any study drug or up to 55 days after permanent withdrawal of ADX/PBO. A treatment-emergent laboratory abnormality was defined as an increase of at least one toxicity grade from baseline at any time up to 30 days after the last dose of all study treatment or 55 days after the last dose of ADX/PBO.

Abbreviations: ADX, andecaliximab; PBO, placebo.

[a]With adverse events and laboratory abnormalities of any grade occurring in ≥ 30% of patient in any treatment group.

shown), suggesting that any difference in efficacy is not related to drug exposure.

This was an international phase III study examining the addition of ADX to mFOLFOX6 in first-line therapy for metastatic gastric adenocarcinoma. Despite compelling early-phase data, the addition of ADX did not improve outcomes in an unselected patient population. Tissue or blood samples were not available for correlative analyses to understand why ADX was less active than expected or to identify any gastric cancer subset that may derive greater benefit with ADX. Currently, we do not have an explanation for the improved efficacy of ADX with mFOLFOX6 in patients of age ≥ 65, but these results are intriguing and warrant further examination.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02755.

DATA SHARING STATEMENT

Anonymized individual patient data will be available upon request to qualified external researchers 6 months after FDA and European Medicines Agency approval per Gilead's Clinical Trial Disclosure & Data Transparency Policy as posted at https://www.gilead.com/research/disclosure-and-transparency.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: All authors
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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REFERENCES

1. National Cancer Institute. Surveillance, epidemiology, and end results (SEER) program. Cancer stat facts: Stomach cancer. 5-year relative survival. https://seer.cancer.gov/statfacts/html/stomach.html
2. Shah MA: Update on metastatic gastric and esophageal cancers. J Clin Oncol 33:1760-1769, 2015
3. Ford HE, Marshall A, Bridgewater JA, et al: Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. Lancet Oncol 15:78-86, 2014
4. Kang JH, Lee SI, Lim DH, et al: Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 30:1513-1518, 2012
5. Thuss-Patience PC, Kretzschmar A, Bichev D, et al: Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 47:2306-2314, 2011
6. Shitara K, Doi T, Dvorkin M, et al: Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 19:1437-1448, 2018
7. Rivera F, Romero C, Jimenez-Fonseca P, et al: Phase II study to evaluate the efficacy of trastuzumab in combination with capecitabine and oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. Cancer Chemother Pharmacol 83:1175-1181, 2019
8. Mondaca S, Margolis M, Sanchez-Vega F, et al: Phase II study of trastuzumab with modified docetaxel, cisplatin, and 5 fluorouracil in metastatic HER2-positive gastric cancer. Gastric Cancer 22:355-362, 2019
9. Roviello G, Petrioli R, Nardone V, et al: Docetaxel, oxaliplatin, 5FU, and trastuzumab as first-line therapy in patients with human epidermal receptor 2-positive advanced gastric or gastroesophageal junction cancer: Preliminary results of a phase II study. Medicine (Baltimore) 97:e10745, 2018
10. Kagawa S, Muraoka A, Kambara T, et al: A multi-institution phase II study of docetaxel and S-1 in combination with trastuzumab for HER2-positive advanced gastric cancer (DASH study). Cancer Chemother Pharmacol 81:387-392, 2018
11. Kimura Y, Fujii M, Masuishi T, et al: Multicenter phase II study of trastuzumab plus S-1 alone in elderly patients with HER2-positive advanced gastric cancer (JACCRO GC-06). Gastric Cancer 21:421-427, 2018
12. Kurokawa Y, Sugimoto N, Miwa H, et al: Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). Br J Cancer 110:1163-1168, 2014
13. Shah MA, Xu RH, Bang YJ, et al: HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 35:2558-2567, 2017
14. Kataoka H, Mori Y, Shimura T, et al: A phase II prospective study of the trastuzumab combined with 5-weekly S-1 and CDDP therapy for HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol 77:957-962, 2016
15. Cyramza (Ramucirumab). Prescribing Information. Eli Lilly and Company, 2020. http://uspl.lilly.com/cyramza/cyramza.html
16. Keytruda (Pembrolizumab). Prescribing Information. Merck, 2020. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
17. Lonsurf (Trifluridine and Tipiracil) Tablets. Prescribing Information. Taiho Oncology, 2019. https://www.lonsurfhcp.com/us/prescribing-information.pdf
18. Shah MA, Starodub A, Sharma S, et al: Andecaliximab/GS-5745 alone and combined with mFOLFOX6 in advanced gastric and gastroesophageal junction adenocarcinoma: Results from a phase I study. Clin Cancer Res 24:3829-3837, 2018
19. Visse R, Nagase H: Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. Circ Res 92:827-839, 2003
20. Farina AR, Mackay AR: Gelatinase B/MMP-9 in tumour pathogenesis and progression. Cancers (Basel) 6:240-296, 2014
21. Hijova E: Matrix metalloproteinases: Their biological functions and clinical implications. Bratisl Lek Listy 106:127-132, 2005
22. Vandooren J, Van den Steen PE, Opdenakker G: Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): The next decade. Crit Rev Biochem Mol Biol 48:222-272, 2013
23. Chen J, Chen LJ, Zhou HC, et al: Prognostic value of matrix metalloproteinase-9 in gastric cancer: A meta-analysis. Hepatogastroenterology 61:518-524, 2014
24. Yang Q, Ye ZY, Zhang JX, et al: Expression of matrix metalloproteinase-9 mRNA and vascular endothelial growth factor protein in gastric carcinoma and its relationship to its pathological features and prognosis. Anat Rec (Hoboken) 293:2012-2019, 2010
25. Jia X, Lu M, Rui C, et al: Consensus-expressed CXCL8 and MMP9 identified by meta-analyzed perineural invasion gene signature in gastric cancer microarray data. Front Genet 10:851, 2019
26. Melani C, Sangaletti S, Barazzetta FM, et al: Amino-biphosphonate-mediated MMP-9 inhibition breaks the tumor-bone marrow axis responsible for myeloid-derived suppressor cell expansion and macrophage infiltration in tumor stroma. Cancer Res 67:11438-11446, 2007
27. Condeelis J, Pollard JW: Macrophages: Obligate partners for tumor cell migration, invasion, and metastasis. Cell 124:263-266, 2006
28. Kessenbrock K, Plaks V, Werb Z: Matrix metalloproteinases: Regulators of the tumor microenvironment. Cell 141:52-67, 2010
29. Baragano Raneros A, Suarez-Alvarez B, Lopez-Larrea C: Secretory pathways generating immunosuppressive NKG2D ligands: New targets for therapeutic intervention. Oncoimmunology 3:e28497, 2014
30. Appleby TC, Greenstein AE, Hung M, et al: Biochemical characterization and structure determination of a potent, selective antibody inhibitor of human MMP9. J Biol Chem 292:6810-6820, 2017
31. Marshall DC, Lyman SK, McCauley S, et al: Selective allosteric inhibition of MMP9 is efficacious in preclinical models of ulcerative colitis and colorectal cancer. PLoS One 10:e0127063, 2015

32. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
33. Moreira AM, Pereira J, Melo S, et al: The extracellular matrix: An accomplice in gastric cancer development and progression. Cells 9:394, 2020
34. Costa AM, Ferreira RM, Pinto-Ribeiro I, et al: Helicobacter pylori activates matrix metalloproteinase 10 in gastric epithelial cells via EGFR and ERK-mediated pathways. J Infect Dis 213:1767-1776, 2016
35. Oliveira MJ, Costa AC, Costa AM, et al: Helicobacter pylori induces gastric epithelial cell invasion in a c-Met and type IV secretion system-dependent manner. J Biol Chem 281:34888-34896, 2006
36. Gao H, Lan X, Li S, et al: Relationships of MMP-9, E-cadherin, and VEGF expression with clinicopathological features and response to chemosensitivity in gastric cancer. Tumour Biol 39:1010428317698368, 2017
37. Ling B, Watt K, Banerjee S, et al: A novel immunotherapy targeting MMP-14 limits hypoxia, immune suppression and metastasis in triple-negative breast cancer models. Oncotarget 8:58372-58385, 2017
38. Elez E, Kocakova I, Hohler T, et al: Abituzumab combined with cetuximab plus irinotecan versus cetuximab plus irinotecan alone for patients with KRAS wild-type metastatic colorectal cancer: The randomised phase I/II POSEIDON trial. Ann Oncol 26:132-140, 2015
39. Scannevin RH, Alexander R, Haarlander TM, et al: Discovery of a highly selective chemical inhibitor of matrix metalloproteinase-9 (MMP-9) that allosterically inhibits zymogen activation. J Biol Chem 292:17963-17974, 2017
40. Sparano JA, Bernardo P, Stephenson P, et al: Randomized phase III trial of marimastat versus placebo in patients with metastatic breast cancer who have responding or stable disease after first-line chemotherapy: Eastern Cooperative Oncology Group trial E2196. J Clin Oncol 22:4683-4690, 2004
41. Bramhall SR, Hallissey MT, Whiting J, et al: Marimastat as maintenance therapy for patients with advanced gastric cancer: A randomised trial. Br J Cancer 86: 1864-1870, 2002

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase III Study to Evaluate Efficacy and Safety of Andecaliximab With mFOLFOX6 as First-Line Treatment in Patients With Advanced Gastric or GEJ Adenocarcinoma (GAMMA-1)

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