METGastric: Phase III Study of mFOLFOX6 +/- Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma

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ABSTRACT

Purpose The *mesenchymal-epithelial transition* (*MET*) oncogene plays an important role in gastroesophageal adenocarcinoma (GEC). We report results of a phase III trial of the MET inhibitor, onartuzumab, plus standard first-line chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative, MET-positive, advanced GEC.

Methods METGastric (YO28322; NCT01662869) was a randomized, double-blind, multicenter trial. Patients were randomized 1:1 to receive mFOLFOX6 with or without onartuzumab (10 mg/kg). Tumor samples were centrally tested for MET expression using Ventana® anti-Total c-MET (SP44) rabbit monoclonal antibody, HER2 status, and Lauren histologic subtype. MET-positive tumors were defined as ≥ 50% of tumor cells showing weak, moderate, and/or strong staining intensity (MET 1+/2+/3+, respectively) by immunohistochemistry. Co-primary endpoints were overall survival (OS) in the intent-to-treat (ITT) population and in patients with MET 2+/3+ GEC. Secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety.

Results Enrollment was stopped early due to sponsor decision. At the data cut-off (April 25, 2014) there were 562 patients in the ITT population (n = 283 placebo plus mFOLFOX6; n = 279 onartuzumab plus mFOLFOX6); 109 (38.5%) and 105 (37.6%) of the ITT population were MET 2+/3+, respectively. Addition of onartuzumab to mFOLFOX6 did not result in significant improvement in OS, PFS, or ORR *v* placebo plus mFOLFOX6 in the ITT (OS hazard ratio [HR], 0.82, *P* = .24; PFS HR, 0.90, *P* = .429; ORR, *P* = .253) or MET 2+/3+ populations (OS HR, 0.64, *P* = .062; PFS HR, 0.79, *P* = .223; ORR, *P* = .228). Safety was as expected for onartuzumab.

Conclusion Addition of onartuzumab to first-line mFOLFOX6 did not significantly improve clinical benefits in the ITT or MET 2+/3+ populations.

INTRODUCTION

Gastroesophageal adenocarcinoma (GEC), which comprises tumors of the gastroesophageal junction and the stomach, is the fifth most frequently diagnosed cancer worldwide, and is the third highest cause of cancer mortality.[1] The median overall survival (OS) for patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic GEC treated with chemotherapy is approximately 8–11 months in Europe and 10–16 months in Asia.[2] For patients with unresectable, metastatic GEC, the main therapeutic option is doublet or triplet combination chemotherapy ~~with~~ containing a platinum-fluoropyrimidine combination, such as the mFOLFOX6 regimen (5-fluorouracil [5-FU], leucovorin [LV], and oxaliplatin).[3] Chemotherapy plus trastuzumab is standard of care for patients with HER2-positive metastatic GEC.[4] Other effective therapeutics for the treatment of gastric cancer in the refractory setting include chemotherapy such as taxanes and irinotecan,[5-8] and the vascular endothelial growth factor (VEGF) receptor 2 inhibitor ramucirumab (in the second-line setting).[9,10] Despite all efforts, prognosis for patients with HER2-negative GEC is poor, with a 5-year OS rate of less than 10%.[11]

The hepatocyte growth factor (HGF) receptor that activates key oncogenic pathways through RAS, PI3K and STAT3, plays an important role in tumorigenesis, and is encoded by the *mesenchymal-epithelial transition* (*MET*) oncogene.[12] Signaling through the HGF/MET pathway stimulates tissue repair and regeneration in normal tissue but can promote proliferation, survival, and metastasis in tumor cells.[13,14] In GEC, dysregulation of the MET/HGF pathway is associated with poor prognosis and more aggressive disease, with *MET* activation stimulating tumor invasiveness.[15-17] In a randomized phase II study in patients with advanced gastric or gastroesophageal junction cancer, a trend for improved survival was observed with

the anti-HGF monoclonal antibody, rilotumumab, plus epirubicin, cisplatin, and capecitabine (ECX) *v* placebo plus ECX in patients with MET-positive (MET+) tumors.[18]

Onartuzumab is a recombinant, fully humanized, monovalent monoclonal antibody that binds with the extracellular domain of MET. By binding with MET, onartuzumab prevents MET from binding with HGF and restricts cellular signaling via the MET pathway.[19] Results of a phase II study demonstrated that second-/third-line onartuzumab in combination with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib, improved progression-free survival (PFS) and OS *v* placebo plus erlotinib in patients with MET+ (50% of tumor cells staining with an immunohistochemistry [IHC] intensity of 2+/3+) non-small-cell lung cancer (NSCLC).[20]

To investigate whether onartuzumab has clinical efficacy in patients with HER2-negative, MET+ GEC, METGastric was designed to determine if the addition of onartuzumab to first-line mFOLFOX6 improves efficacy outcomes when compared with mFOLFOX6 plus placebo.

METHODS

Study Design

METGastric (YO28322; NCT01662869) was a randomized, double-blind, multicenter, placebo-controlled, phase III study designed to evaluate the efficacy and safety of onartuzumab plus mFOLFOX6 *v* placebo plus mFOLFOX6 in patients with metastatic HER2-negative and MET+ GEC. Patients were enrolled between November 19, 2012 and March 7, 2014. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was

approved by the local institutional review board/ethics committee at each participating site. All patients provided written informed consent.

Inclusion and Exclusion Criteria

Eligible patients were aged ≥ 18 years with an adenocarcinoma of the stomach or gastroesophageal junction with metastatic disease not amenable for curative therapy. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease or non-measurable but evaluable disease, adequate organ function, and no previous treatment for metastatic disease. Only patients with HER2-negative, MET+ (as assessed by IHC; score of 1+, 2+ or 3+) GEC were enrolled. Key exclusion criteria included a history of HER2+ tumors, previous chemotherapy for locally advanced or metastatic gastric carcinoma (adjuvant or neoadjuvant chemotherapy must have been completed at least 6 months prior to randomization), a significant history of cardiac disease, peripheral neuropathy, and/or active (significant or uncontrolled) gastrointestinal bleeding.

Procedures

Patients were randomized in a 1:1 ratio to receive placebo plus mFOLFOX6 (oxaliplatin 85 mg/m^2 intravenous (IV), day 1, 5-FU 400 mg/m^2 IV bolus followed by 2,400 mg/m^2 over 48 hours starting on day 1, LV 400 mg/m^2 IV, day 1) or onartuzumab (10 mg/kg IV on day 1, every 14 days) plus mFOLFOX6 for a maximum of 12 cycles (Supplementary Fig 1). Patients whose disease has not progressed after 12 cycles could continue treatment with either onartuzumab or placebo until disease progression (PD), unacceptable toxicity, or death. Patients were randomized using a permutated block randomization method and stratification

was performed by MET expression by IHC status score (1+ *v* 2+/3+), region (Asia-Pacific *v* other), and prior gastrectomy (yes *v* no). The first dose of study drug had to be administrated within 3 days of randomization. No modifications of the onartuzumab/placebo dose were allowed. If onartuzumab/placebo were discontinued due to tolerability, patients could continue on mFOLFOX6 treatment (if onartuzumab/placebo was stopped during the first 12 cycles of study treatment) or 5-FU/folinic acid if agreed upon by the investigator and patient.

HER2 and MET Status

The provision of tumor samples (archival tissue block or 15 serial cut unstained slides) was mandatory. Tumor samples were tested centrally (Targos, Germany) to determine MET expression status (using the Ventana® anti-Total c-MET [SP44] rabbit monoclonal antibody IHC assay), HER2 status (using the Ventana® anti-HER2 [4B5] rabbit monoclonal antibody IHC assay), and the Lauren histologic subtype status. To be eligible for the study, patients were considered positive if their tumor samples demonstrated at least 50% of cells staining positive with an intensity of 1+ or above using the Ventana® IUO assay system guidelines. A MET IHC positive subgroup, for the purpose of testing the MET hypothesis, was defined as those patients with ≥ 50% of tumor cells showing moderate and/or strong staining intensity (MET 2+/3+).

Study Endpoints

The co-primary endpoints were OS in the intent-to-treat (ITT) population and in the subgroup of patients with MET 2+/3+ GEC. Secondary endpoints included PFS,

overall response rate (ORR), disease control rate (DCR), duration of response (DOR), patient-reported outcomes, and safety.

Assessments

Tumor response and progression were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Evaluation of tumor response was documented every 6 weeks for the first 12 months. For patients who remained on study treatment and were followed-up for more than 12 months, repeat chest, abdomen, and pelvis computed tomography or magnetic resonance imaging scans were taken every 12 weeks. OS was defined as the time from randomization to death from any cause. PFS was defined as the time from randomization to the first occurrence of PD, as determined by investigator-assessed RECIST v1.1, or death from any cause, whichever occurred first. DOR was defined as the time from first occurrence of a documented objective response to PD as determined by investigator-assessed RECIST v1.1, or death from any cause during the study. DCR comprised complete response (CR), partial response, and stable disease according to RECIST. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, v4.0. An Independent Data Monitoring Committee monitored patient safety data approximately every 6 months during the course of the study.

Statistical Analysis

The study was designed to enroll approximately 800 patients and was powered to demonstrate an improvement of median OS from 9 to 12.3 months in the ITT

population (hazard ratio [HR], 0.73) and 9 to 18 months in the MET 2+/3+ population (HR, 0.49).

The ITT population included all randomized patients and the safety population included all randomized patients who received at least one dose of study treatment. Kaplan–Meier methodology was used to estimate median PFS and median OS for each treatment arm. A stratified Cox regression model was used to estimate HR and 95% confidence intervals (CIs) of PFS and OS; a log-rank test was used to calculate the p-value.

RESULTS

Patients

Enrollment was stopped early due to a lack of efficacy in a phase II trial also assessing mFOLFOX6 plus onartuzumab (YO28252; NCT01590719).[21] Patients were given the option of continuing treatment with onartuzumab after enrollment was stopped. At the data cut-off (April 25, 2014), the ITT population comprised 562 patients, of whom 283 received placebo plus mFOLFOX6 and 279 were allocated to onartuzumab plus mFOLFOX6 (Fig 1). Baseline characteristics between treatment arms were balanced (Table 1). In total, there were 109 (38.5%) and 105 (37.6%) patients with MET 2+/3+ GEC in the placebo plus mFOLFOX6 and onartuzumab plus mFOLFOX6 groups, respectively.

Efficacy: ITT Population

At the data cut-off, in the ITT population, 26.1% of patients in the placebo plus mFOLFOX6 group and 25.8% of patients in the onartuzumab plus mFOLFOX6 group had OS events (defined as death from any cause); 49.8% and 47.3% of

patients had PFS events in the placebo plus mFOLFOX6 and onartuzumab plus mFOLFOX6 groups, respectively. The addition of onartuzumab to mFOLFOX6 did not result in significant differences in OS or PFS compared with placebo plus mFOLFOX6 (Fig 2A and 2B). Median OS was 11.3 months for placebo plus mFOLFOX6 *v* 11.0 months for onartuzumab plus mFOLFOX6 (HR, 0.82; 95% CI, 0.59 to 1.15, stratified *P* = .24), and median PFS was 6.8 *v* 6.7 months (HR, 0.90; 95% CI, 0.71 to 1.16, stratified *P* = .429), respectively.

Subgroup analyses of OS in the ITT population showed no difference between onartuzumab and placebo in any subgroup (Fig 2C). There was no difference in ORR between treatment arms in the ITT population for onartuzumab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (46.1% *v* 40.6%, *P* = .253; Table 2). Four patients in each group achieved a CR.

Efficacy: MET 2+/3+ Subgroup

MET IHC comprised both staining intensity and the percentage of MET-expressing tumor cells (Supplementary Fig 2). MET IHC positive tumors were defined as those with ≥ 50% of tumor cells showing moderate and/or strong staining intensity (MET 2+/3+). Overall agreement between central laboratory pathologists was > 95% (Supplementary Table 1).

In the MET 2+/3+ subgroup, 37.6% of patients in the placebo plus mFOLFOX6 group and 33.3% of patients in the onartuzumab plus mFOLFOX6 group had OS events at the data cut-off. In the MET 2+/3+ subgroup, the addition of onartuzumab to mFOLFOX6 did not significantly improve efficacy outcomes compared with placebo (Fig 3). Median OS was 9.7 months for placebo plus mFOLFOX6 *v* 11.0 months for onartuzumab plus mFOLFOX6 (HR, 0.64; 95% CI,

0.40 to 1.03, stratified *P* = .062); median PFS was 5.7 months *v* 6.9 months (HR, 0.79; 95% CI, 0.54 to 1.15, stratified *P* = .223), respectively.

Efficacy: Exploratory Subgroup Analyses

Exploratory subgroup analyses of OS by region and prior gastrectomy are shown in Supplementary Fig 3. In the MET 2+/3+ subgroup, non-Asian patients without prior gastrectomy (n = 125) appeared to derive a clinical benefit from onartuzumab plus mFOLFOX6 (HR, 0.51; 95% CI, 0.29 to 0.89). There was no difference in ORR between the treatment arms in the MET 2+/3+ subgroup for onartuzumab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (53.8% *v* 44.6%, *P* = .228; Table 2). Three patients in the MET 2+/3+ subgroup achieved a CR in the onartuzumab plus mFOLFOX6 group compared with none in the placebo plus mFOLFOX6 group.

Safety

Overall, 97.5% of patients in the placebo plus mFOLFOX6 group and 98.2% of patients in the onartuzumab plus mFOLFOX6 group experienced at least one AE. Serious AEs were more frequent with onartuzumab than with placebo (35.8% *v* 32.5%, respectively) (Table 3). All grade AEs and grade ≥ 3 AEs are summarized in Table 4. Grade ≥ 3 AEs more commonly observed with onartuzumab included neutropenia (35.1% *v* 29.3%), hypoalbuminemia (5.7% *v* 0.4%), peripheral edema (4.7% *v* 0.4%), thrombocytopenia (4.3% *v* 1.1%), pulmonary embolism (6.1% *v* 3.6%), and gastric perforation (0.7% *v* 0%).

DISCUSSION

The addition of onartuzumab to first-line mFOLFOX6 did not improve OS, PFS, or ORR compared with mFOLFOX6 alone in patients with HER2-negative GEC, irrespective of MET expression status. These negative results are in line with other phase II/III trials that have reported similarly disappointing results with onartuzumab, including in triple-negative breast cancer,[22] recurrent glioblastoma,[23] and NSCLC[24] after initial phase II data in second-line/third-line NSCLC were promising.[20]

Several hypotheses have been advanced to explain the failure of onartuzumab, as well as other MET-directed drugs, in GEC and other solid tumors.[25,26] One explanation is that MET overexpression might not be an appropriate target for onartuzumab in the majority of GEC patients. Dysregulation of the MET pathway in GEC can arise from *MET* amplification, or rare *MET* mutations affecting the extracellular domain (involving the HGF binding domain), the tyrosine kinase domain (leading to a constitutive MET activation), or the juxtamembrane domain (causing a disruption in negative regulation of MET signaling).[25,26] Alternatively, overexpression of HGF in the tumor cells or stroma may lead to autocrine or paracrine loop formation.[26] In contrast to the situation of oncogene addiction, this inappropriate MET signaling is a consequence, rather than the cause, of the cell transformation, and targeting MET signaling in these tumors will not fundamentally affect tumor behavior or cancer outcomes.[25] However, this does leave open the possibility that some tumors may still be dependent on sustained MET signaling for their growth and survival, and may therefore be sensitive to MET blockade. Identification of these tumors would require an alternate biomarker to identify tumors that are driven by MET signaling. Another possible explanation for why MET

inhibition alone may not yield an improvement in survival in GEC is the potential redundancy of signaling via the MET pathway.[27,28]

Trials of a number of other targeted therapeutics combined with front-line chemotherapy regimens in advanced gastric cancer have also failed to meet their primary endpoints in phase III trials, including rilotumumab,[29] anti-EGFR antibodies (cetuximab[30] or panitumumab[31]), and bevacizumab.[32] These negative studies suggest that targeting single transduction pathways may not be sufficient , necessitating a combination approach.

Unexpectedly, unplanned post-hoc exploratory analyses in this study identified a possible clinical benefit with onartuzumab plus mFOLFOX6 in non-Asian patients with MET 2+/3+ tumors without prior gastrectomy. Although this may be a chance finding, it may also reflect a difference in biology in this subpopulation of patients making the tumor more susceptible to MET inhibition.

In conclusion, although METGastric failed to meet its co-primary endpoints, further research is required to better understand which patient populations can derive clinical benefits from onartuzumab.

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Tables

Table 1. Baseline Characteristics of the ITT Population

Characteristics	Placebo + mFOLFOX6 (n = 283)	Onartuzumab + mFOLFOX6 (n = 279)
Median age, years (range)	58.0 (23–84)	60.0 (24–82)
Gender, n (%)		
Male	183 (64.7)	188 (67.4)
Female	100 (35.3)	91 (32.6)
Race, n (%)		
Caucasian	180 (63.6)	172 (61.6)
Black or African American	2 (0.7)	3 (1.1)
Asian	89 (31.4)	94 (33.7)
Other	12 (4.3)	10 (3.7)
ECOG PS, n (%)		
0	118 (41.7)	112 (40.1)
1*	158 (55.8)	162 (58.1)
Primary tumor site, n (%)		
Stomach	218 (77.0)	214 (76.7)
Gastroesophageal junction	65 (23.0)	65 (23.3)
Gastric cancer histologic subtype, n (%)	(n = 283)	(n = 277)

Intestinal	133 (47.0)	136 (49.1)
Diffuse	98 (34.6)	83 (30.0)
Mixed	42 (14.8)	39 (14.1)
Not evaluable	10 (3.5)	19 (6.9)
Prior gastrectomy, n (%)		
Yes	101 (35.7)	98 (35.1)
No	182 (64.3)	181 (64.9)
MET score, n (%)		
1+	173 (61.1)	171 (61.3)
2+	94 (33.2)	85 (30.5)
3+	15 (5.3)	20 (7.2)
Not done	1 (0.4)	3 (1.1)
Region, n (%)		
Asia-Pacific	88 (31.1)	88 (31.5)
Other	195 (68.9)	191 (68.5)

*Includes patients who were considered ECOG PS 2 after enrollment.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; MET, mesenchymal-epithelial transition; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

Table 2. Response Rates in the ITT and MET 2+/3+ Populations With Measurable Disease at Baseline

	ITT Population		MET 2+/3+	
Response	Placebo + mFOLFOX6 (n = 207)	Onartuzumab + mFOLFOX6 (n = 217)	Placebo + mFOLFOX6 (n = 92)	Onartuzumab + mFOLFOX6 (n = 78)
ORR, %	40.6	46.1	44.6	53.8
P-value	.253		.228	
Complete response, n (%)	4 (1.9)	4 (1.8)	0 (0.0)	3 (3.8)
Partial response, n (%)	80 (38.6)	96 (44.2)	41 (44.6)	39 (50.0)
Stable disease, n (%)	69 (33.3)	70 (32.3)	25 (27.2)	20 (25.6)
Progressive disease, n (%)	27 (13.0)	26 (12.0)	13 (14.1)	9 (11.5)
Disease control rate, %	73.9	78.3	71.7	79.5

Abbreviations: ITT, intent-to-treat; MET, mesenchymal-epithelial transition; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, overall response rate.

Table 3. Overall AE Profile in the Safety Population

n (%)	Placebo + mFOLFOX6 (n = 280)	Onartuzumab + mFOLFOX6 (n = 279)
Total number of patients with at least one AE	273 (97.5)	274 (98.2)
Total number of deaths*	73 (26.1)	70 (25.1)
Serious AEs	91 (32.5)	100 (35.8)
AE leading to treatment withdrawal	61 (21.8)	87 (31.2)
Grade 3–5 AE at greatest intensity	187 (66.8)	192 (68.8)

*Including death from PD. Multiple occurrences of the same AE in one individual are counted only once. Note, one patient randomized to the placebo arm received onartuzumab during the first treatment cycle; data for this patient were included in the onartuzumab arm for analysis of safety.

Abbreviations: AE, adverse event; mFOLFOX6, 5-fluorouracil, leucovorin and oxaliplatin.

Table 4. All Grade* and Grade ≥3 AEs

AE, n (%)	Placebo + mFOLFOX6 (n = 280)		Onartuzumab + mFOLFOX6 (n = 279)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea	141 (50.4)	13 (4.6)	133 (47.7)	7 (2.5)
Neutropenia	112 (40.0)	82 (29.3)	126 (45.2)	98 (35.1)
Fatigue	87 (31.1)	11 (3.9)	77 (27.6)	13 (4.7)
Diarrhea	78 (27.9)	5 (1.8)	85 (30.5)	8 (2.9)
Vomiting	79 (28.2)	12 (4.3)	72 (25.8)	8 (2.9)
Decreased appetite	78 (27.9)	8 (2.9)	75 (26.9)	6 (2.2)
Peripheral edema	22 (7.9)	1 (0.4)	110 (39.4)	13 (4.7)
Constipation	62 (22.1)	1 (0.4)	46 (16.5)	1 (0.4)
Asthenia	54 (19.3)	10 (3.6)	55 (19.7)	13 (4.7)
Peripheral neuropathy	51 (18.2)	5 (1.8)	52 (18.6)	7 (2.5)
Anemia	48 (17.1)	15 (5.4)	48 (17.2)	14 (5.0)
Paresthesia	50 (17.9)	1 (0.4)	40 (14.3)	6 (2.2)
Abdominal pain	40 (14.3)	7 (2.5)	38 (13.6)	3 (1.1)
Thrombocytopenia	29 (10.4)	3 (1.1)	47 (16.8)	12 (4.3)
Alopecia	40 (14.3)	-	33 (11.8)	-
Stomatitis	37 (13.2)	0 (0.0)	35 (12.5)	2 (0.7)

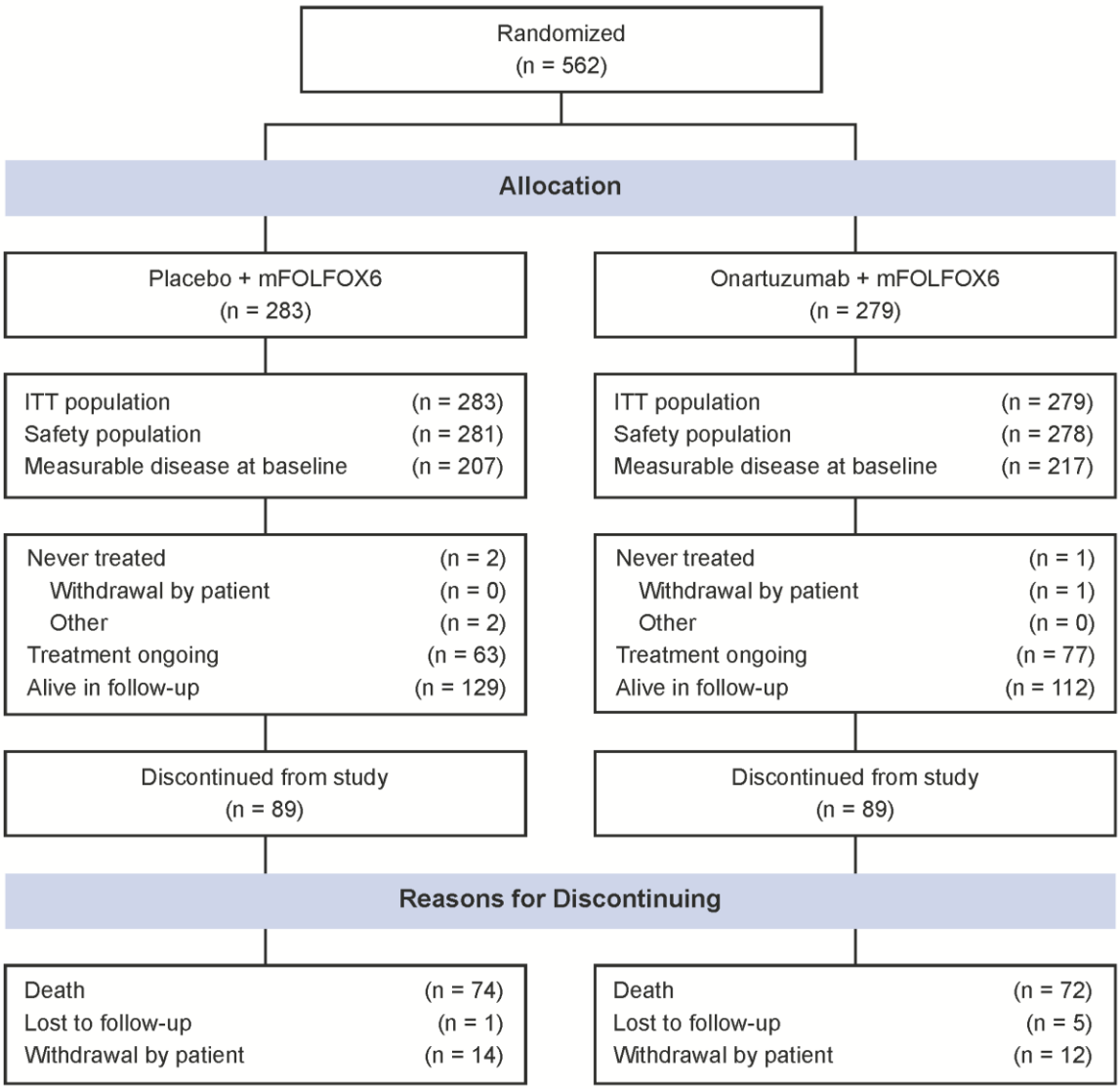
Dysgeusia	34 (12.1)	-	34 (12.2)	-
Hypoalbuminemia	10 (3.6)	1 (0.4)	56 (20.1)	16 (5.7)
Pyrexia	35 (12.5)	1 (0.4)	29 (10.4)	0 (0.0)
Peripheral sensory neuropathy	29 (10.4)	4 (1.4)	18 (6.5)	1 (0.4)
Insomnia	29 (10.4)	-	13 (4.7)	-

*Includes all grade AEs occurring at an incidence of >10% in either treatment arm. Multiple occurrences of the same AE in one individual are counted only once. Note, one patient randomized to the placebo arm received onartuzumab during the first treatment cycle; data for this patient were included in the onartuzumab arm for analysis of safety.

Abbreviations: AE, adverse event; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

FIGURES

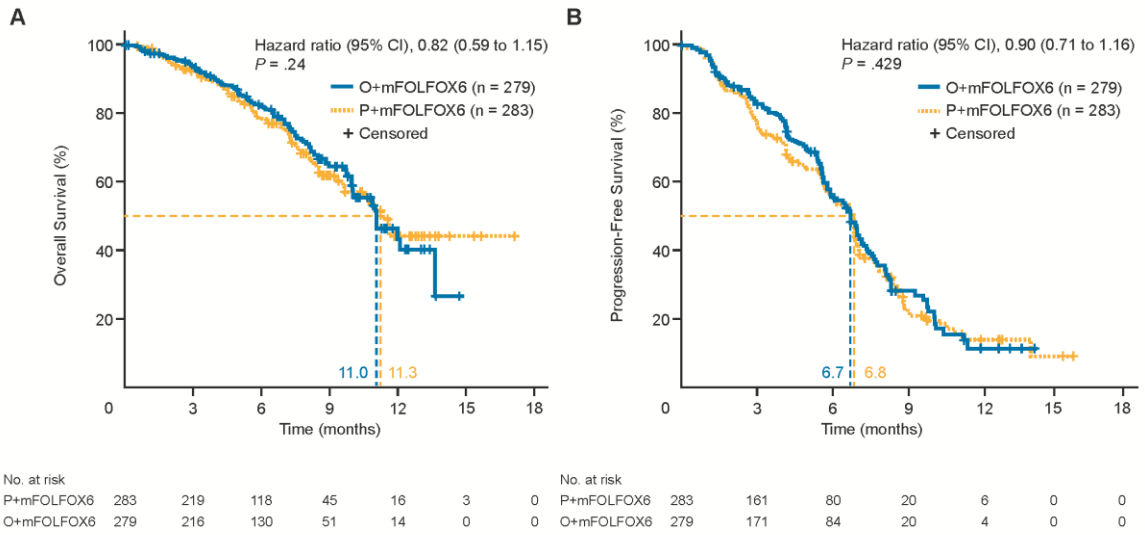
Fig 1. CONSORT diagram.



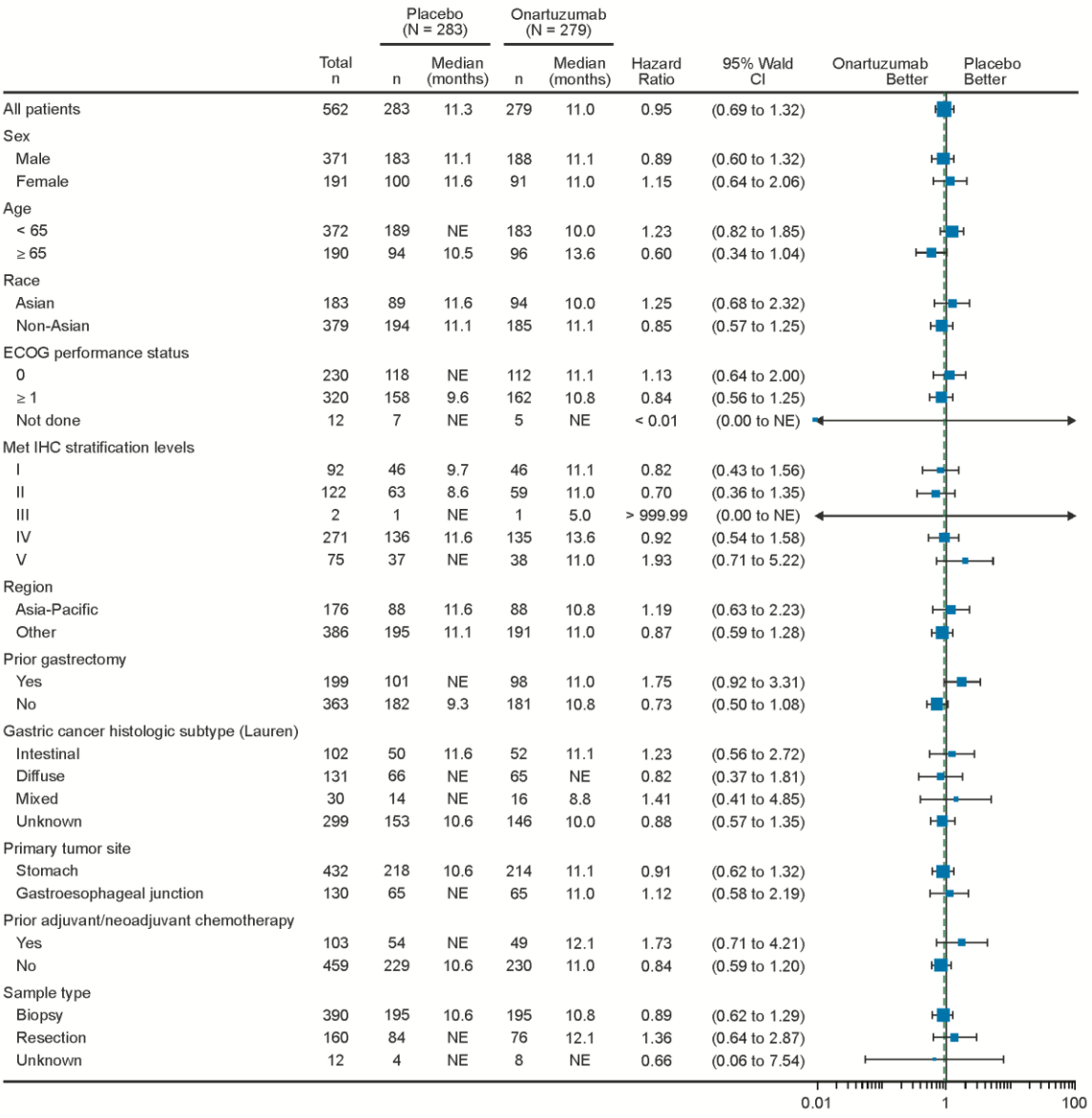
Safety population = all randomized patients who received at least one dose of study treatment; ITT population = all randomized patients.

Abbreviations: ITT, intent-to-treat population; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

Fig 2. OS (A), PFS (B), and subgroup analysis of OS (C) in the ITT population.

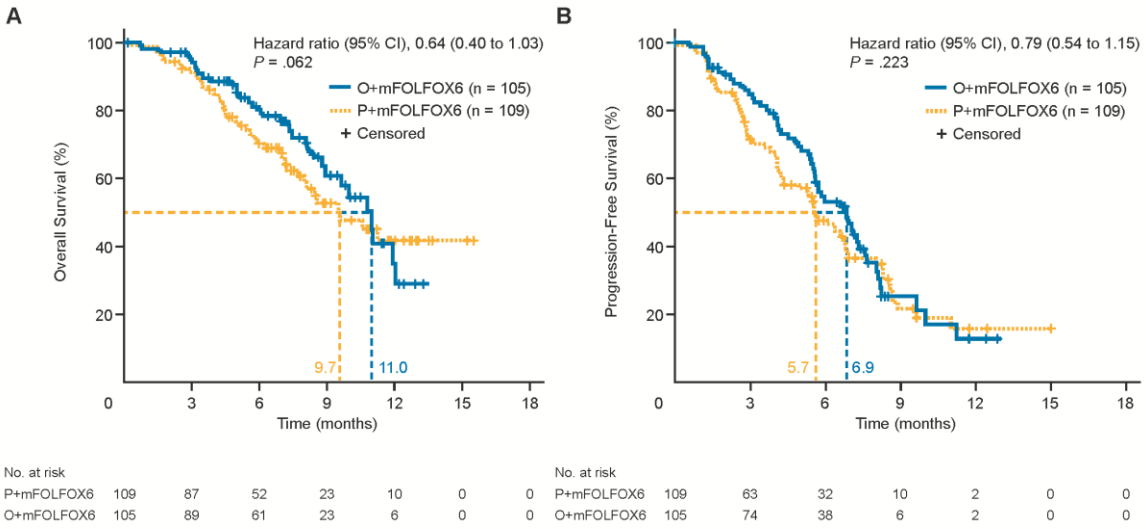


C



	Total n	Placebo (N = 283) n	Placebo (N = 283) Median (months)	Onartuzumab (N = 279) n	Onartuzumab (N = 279) Median (months)	Hazard Ratio	95% Wald CI
All patients	562	283	11.3	279	11.0	0.95	(0.69 to 1.32)
Sex							
Male	371	183	11.1	188	11.1	0.89	(0.60 to 1.32)
Female	191	100	11.6	91	11.0	1.15	(0.64 to 2.06)
Age							
< 65	372	189	NE	183	10.0	1.23	(0.82 to 1.85)
≥ 65	190	94	10.5	96	13.6	0.60	(0.34 to 1.04)
Race							
Asian	183	89	11.6	94	10.0	1.25	(0.68 to 2.32)
Non-Asian	379	194	11.1	185	11.1	0.85	(0.57 to 1.25)
ECOG performance status							
0	230	118	NE	112	11.1	1.13	(0.64 to 2.00)
≥ 1	320	158	9.6	162	10.8	0.84	(0.56 to 1.25)
Not done	12	7	NE	5	NE	< 0.01	(0.00 to NE)
Met IHC stratification levels							
I	92	46	9.7	46	11.1	0.82	(0.43 to 1.56)
II	122	63	8.6	59	11.0	0.70	(0.36 to 1.35)
III	2	1	NE	1	5.0	> 999.99	(0.00 to NE)
IV	271	136	11.6	135	13.6	0.92	(0.54 to 1.58)
V	75	37	NE	38	11.0	1.93	(0.71 to 5.22)
Region							
Asia-Pacific	176	88	11.6	88	10.8	1.19	(0.63 to 2.23)
Other	386	195	11.1	191	11.0	0.87	(0.59 to 1.28)
Prior gastrectomy							
Yes	199	101	NE	98	11.0	1.75	(0.92 to 3.31)
No	363	182	9.3	181	10.8	0.73	(0.50 to 1.08)
Gastric cancer histologic subtype (Lauren)							
Intestinal	102	50	11.6	52	11.1	1.23	(0.56 to 2.72)
Diffuse	131	66	NE	65	NE	0.82	(0.37 to 1.81)
Mixed	30	14	NE	16	8.8	1.41	(0.41 to 4.85)
Unknown	299	153	10.6	146	10.0	0.88	(0.57 to 1.35)
Primary tumor site							
Stomach	432	218	10.6	214	11.1	0.91	(0.62 to 1.32)
Gastroesophageal junction	130	65	NE	65	11.0	1.12	(0.58 to 2.19)
Prior adjuvant/neoadjuvant chemotherapy							
Yes	103	54	NE	49	12.1	1.73	(0.71 to 4.21)
No	459	229	10.6	230	11.0	0.84	(0.59 to 1.20)
Sample type							
Biopsy	390	195	10.6	195	10.8	0.89	(0.62 to 1.29)
Resection	160	84	NE	76	12.1	1.36	(0.64 to 2.87)
Unknown	12	4	NE	8	NE	0.66	(0.06 to 7.54)

Fig 3. OS (A) and PFS (B) in the MET 2+/3+ subpopulation.

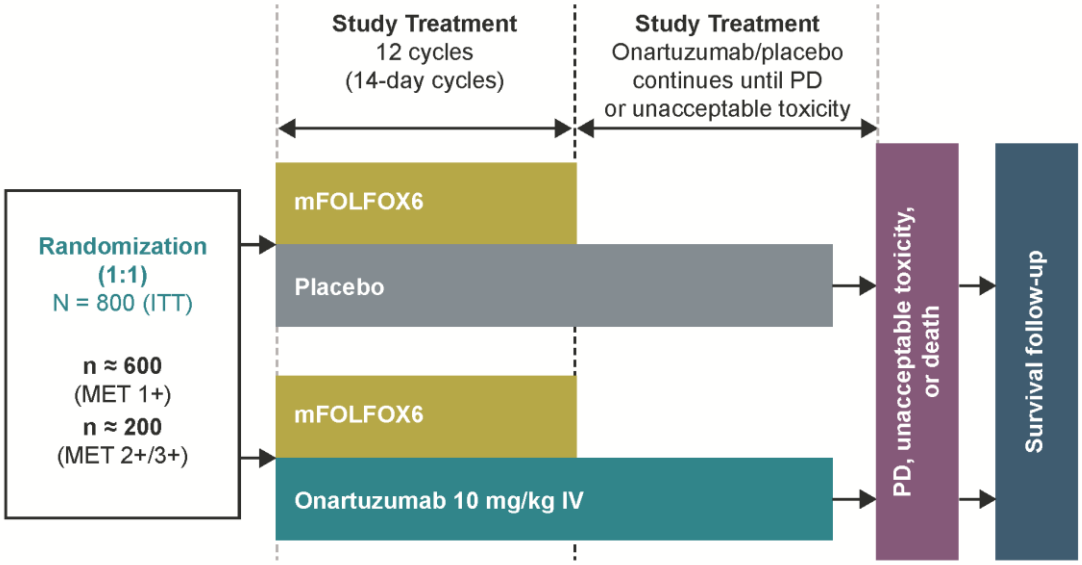


SUPPLEMENTARY MATERIAL

Supplementary Table 1. MET IHC Scoring Qualification of Central Laboratory Pathologists

Agreement Rate	n (%)
Overall percent agreement	247/250 (98.8)
Average positive agreement	210/210 (100)
Average negative agreement	37/40 (92.5)

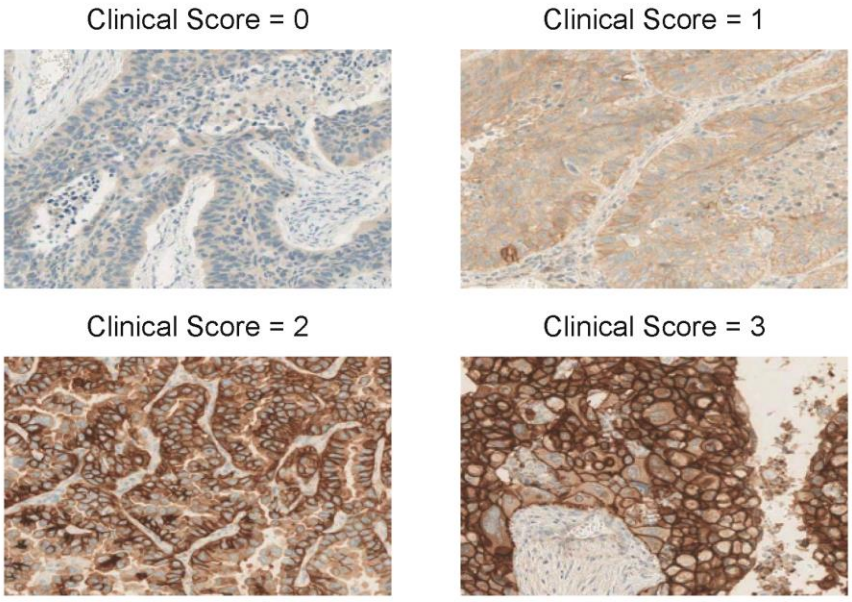
Supplementary Fig 1. Study design.



Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intent-to-treat; MET, mesenchymal-epithelial transition; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; PD, disease progression.

Supplementary Fig 2. Met IHC scoring criteria and representative staining.

Clinical Diagnosis	Clinical Score	Staining Criteria
Negative	0	No or equivocal staining in tumor cells or < 50% tumor cells with membrane and/or cytoplasmic staining
Negative	1+	≥ 50% tumor cells with WEAK or higher membrane and/or cytoplasmic staining but < 50% tumor cells with moderate or higher staining intensity
Positive	2+	≥ 50% tumor cells with MODERATE or higher membrane and/or cytoplasmic staining but < 50% tumor cells with strong staining intensity
Positive	3+	≥ 50% tumor cells with STRONG or higher membrane and/or cytoplasmic staining intensity



Supplementary Fig 3. OS by MET status, region, and prior gastrectomy.