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A Phase II Randomized Trial (GO27827) of First-Line FOLFOX Plus Bevacizumab with or Without the MET Inhibitor Onartuzumab in Patients with Metastatic Colorectal Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Bevacizumb • FOLFOX • Metastatic colorectal cancer • Onartuzumab • Phase II • Randomized

Abstract

Background. Dysregulated hepatocyte growth factor/mesenchymal-epithelial transition (MET) signaling is associated with poor prognosis and resistance to vascular endothelial growth factor inhibition in metastatic colorectal cancer (mCRC). We report outcomes from a double-blind, multicenter phase II trial of the MET inhibitor onartuzumab in combination with mFOLFOX-6 and bevacizumab for mCRC (GO27827; NCT01418222).

Materials and Methods. Patients were randomized 1:1 to receive onartuzumab (10 mg/kg intravenously [IV]) or placebo plus mFOLFOX-6 and bevacizumab (5 mg/kg IV). Oxaliplatin was given for 8–12 cycles; other agents were continued until disease progression, unacceptable toxicity, or death. The primary endpoint was progression-free survival (PFS) in the intent-to-treat (ITT) and MET immunohistochemistry (IHC) expression-positive populations.

Results. Between September 2011 and November 2012, 194 patients were enrolled. In September 2013, an interim analysis recommended stopping onartuzumab treatment due to lack of efficacy. At the time of the final analysis in February 2014, no significant improvement in PFS was seen with onartuzumab versus placebo in either the ITT or MET IHC-positive populations. An improvement in PFS was noted in the MET IHC-negative population. Neither overall survival nor response rate was improved with onartuzumab. The incidence of fatigue, peripheral edema, and deep vein thrombosis was increased with onartuzumab relative to placebo.

Conclusion. Onartuzumab combined with mFOLFOX-6 and bevacizumab did not significantly improve efficacy outcomes in either the ITT or MET IHC-positive populations. MET expression by IHC was not a predictive biomarker in this setting. ***The Oncologist*** 2017;22:264–271

Implications for Practice: The addition of onartuzumab to mFOLFOX-6 plus bevacizumab did not improve outcomes in patients with previously untreated metastatic colorectal cancer in this randomized, phase II study. Although initial results with onartuzumab were promising, a number of phase II/III clinical trials have reported a lack of improvement in efficacy with onartuzumab combined with standard-of-care therapies in several tumor types. Furthermore, negative study data have been published for rilotumumab and ficlatuzumab, both of which block hepatocyte growth factor binding to the mesenchymal-epithelial transition (MET) receptor. MET immunohistochemistry was not a predictive biomarker. It remains to be seen if other biomarkers or small molecule inhibitors may be more appropriate for inhibiting this oncogenic pathway.

Introduction

Metastatic colorectal cancer (mCRC) is a common and highly morbid malignancy, representing the second leading cause of cancer-related deaths worldwide [1]. Treatment for advanced mCRC has improved considerably over the past decade with the addition of biologic agents to standard chemotherapy regimens, leading to increases in median overall survival (OS),

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which has increased from about 12 months in the mid-1990s to more than 30 months in recent studies [2, 3]. Reflecting this, 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX), plus the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, is a widely accepted standard first-line treatment [4]. Despite improved clinical outcomes, the five-year survival rate of patients with mCRC remains less than 10% [5], necessitating new treatment options.

Mesenchymal-epithelial transition (MET) is a cell membrane receptor that binds hepatocyte growth factor (HGF) [6]. Signaling through HGF/MET stimulates tissue repair and regeneration in normal tissue but can be co-opted by tumors to promote proliferation, survival, metastasis, and resistance to VEGF inhibition in tumor cells [7, 8]. In addition, oncogenic crosstalk between the HGF/MET pathway and the VEGF angiogenic pathway has been reported, suggesting a synergistic role between the two [9]. In mCRC, MET overexpression has a proposed role in both tumorigenesis and metastasis, with dysregulation of the HGF/MET pathway being associated with poor prognosis and aggressive biologic tumor characteristics [10, 11]. Furthermore, elevated levels of HGF have been observed in the plasma of patients with mCRC undergoing treatment with bevacizumab prior to disease progression (PD) [12].

Onartuzumab is a recombinant, fully humanized, monovalent monoclonal antibody that binds to the extracellular domain of MET, thereby preventing it from binding with HGF and restricting cellular signaling via the MET pathway [13]. Results of a phase II study demonstrated that second-/third-line treatment with onartuzumab in combination with erlotinib improved progression-free survival (PFS) and OS versus placebo plus erlotinib in patients with MET-positive non-small cell lung cancer (NSCLC) [14]. To determine whether onartuzumab has a beneficial role in either unselected or MET-selected populations with mCRC, the GO27827 randomized, phase II study was initiated to evaluate the combination of bevacizumab and mFOLFOX-6 with or without onartuzumab.

Materials and Methods

Study Design

GO27827 (ClinicalTrials.gov identifier: NCT01418222) was a randomized, double-blind, placebo-controlled, phase II trial conducted at 22 sites in the U.S. and designed to compare mFOLFOX-6/bevacizumab plus onartuzumab versus mFOLFOX-6/bevacizumab plus placebo in stage IV mCRC.

Patients, investigators, study team members (except for the unblinded mixing pharmacist/nurse), and any other persons involved with the conduct of the study from the time of randomization until the interim analysis were blinded to the identity of the treatment assignment. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent as approved by local institutional review boards.

Patients

Eligible patients were aged $\geq$18 years with histologically or cytologically confirmed stage IV adenocarcinoma of the colon or rectum in the first-line setting for metastatic disease. Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of $\geq$3 months, adequate organ system function, and confirmed availability of archival tissue (either a paraffin-embedded tissue block or 20 unstained slides) for evaluation of MET expression and pathway-related biomarkers.

Patients were excluded if they had received prior systemic or radiation therapy for mCRC (including chemotherapy and bevacizumab), had received chemotherapy for colorectal carcinoma within 12 months prior to the date of diagnosis of metastatic disease, and had previously untreated brain metastases and grade $\geq$1 peripheral neuropathy.

Treatment

Patients were randomized in a 1:1 ratio according to an interactive voice/web response system to receive onartuzumab (10 mg/kg intravenously [IV]) or placebo, plus mFOLFOX-6 (oxaliplatin [85 mg/m^2 IV], 5-FU [400 mg/m^2 IV bolus], and LV [400 mg/m^2 IV]) and bevacizumab (5 mg/kg IV) every 2 weeks. Patients were stratified by prior administration of adjuvant chemotherapy (yes versus no).

All treatments were given on days 1–3 of a 2-week cycle. Oxaliplatin was given for 8–12 cycles (at the discretion of the treating physician), following which patients received maintenance 5-FU 400 mg/m^2 IV bolus (after the administration of LV) and then 2,400 mg/m^2 5-FU in a continuous IV infusion over 46 hours, LV 400 mg/m^2 IV, bevacizumab 5 mg/kg IV, and study agent (onartuzumab or placebo) 10 mg/kg IV on day 1 of each 14-day cycle. Both treatment regimens were repeated at 14-day intervals (defined as one treatment cycle). Treatment was continued until PD, unacceptable toxicity, or death.

Biomarker Methods

MET status was determined centrally by immunohistochemistry (IHC) using the CONFIRM SP44 anti-MET monoclonal antibody (Ventana Medical Systems, Inc., Tucson, AZ, USA; http://www.ventana.com), with scores of 2+/3+ ($\geq$50% moderate or strong intensity staining in tumor cells) considered MET IHC-positive and scores of 1+/0 considered MET IHC-negative. Provision of fresh or archival tissue to determine MET expression and evaluation of other biomarkers was mandatory. HGF expression in tissue samples was assessed using IHC. An enzyme-linked immunosorbent assay was utilized for HGF expression in plasma samples.

Study Endpoints

The primary endpoint was to compare PFS between the two treatment arms in both the intent-to-treat (ITT) and the MET IHC-positive populations. Secondary endpoints included OS and overall response rate (ORR) in the ITT and MET IHC-positive populations as well as safety.

Assessments

Tumor response and progression were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with scans repeated every 8 weeks. PFS was calculated from the date of randomization until the date of first PD or death, whichever occurred first. OS was calculated from the date of randomization until death from any cause. ORR was defined as the percentage of patients with a complete or partial response, according to RECIST.

The ITT population comprised all randomized patients, and the safety population comprised all patients who received at

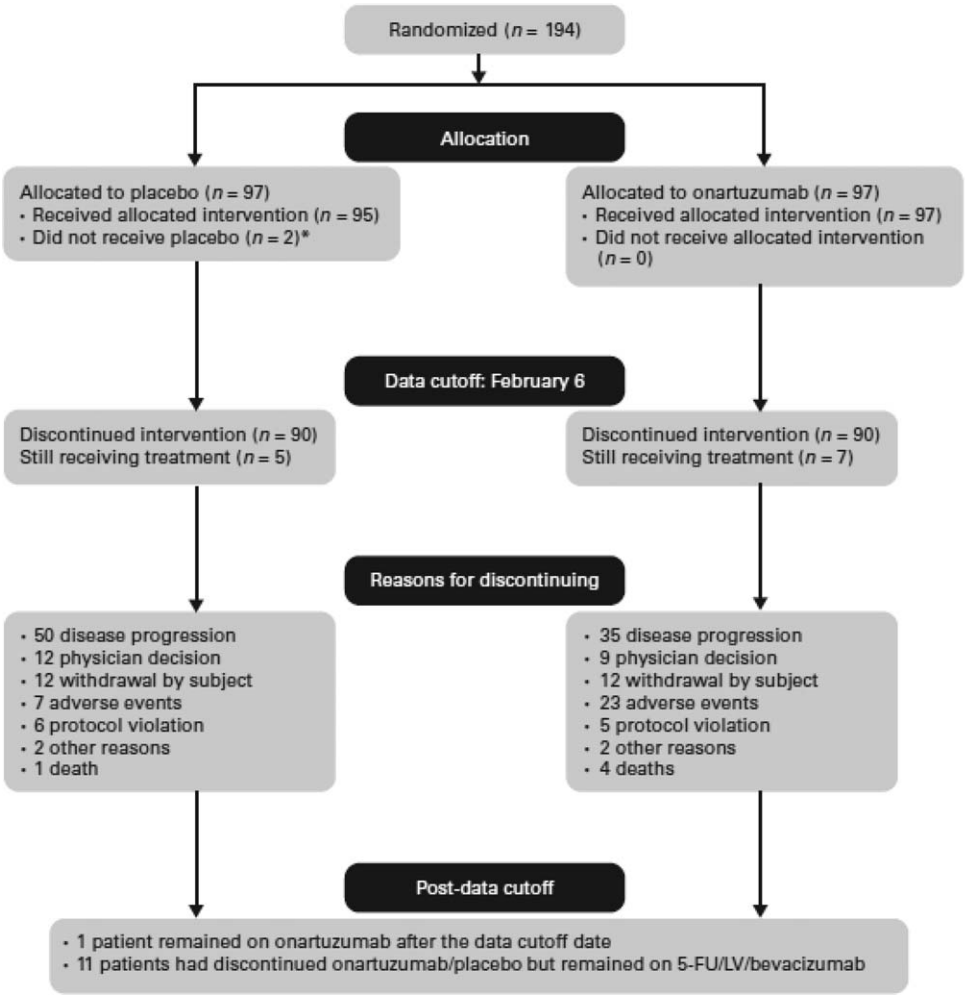

Figure 1. CONSORT diagram. *, One patient due to serious adverse event; one patient due to medical costs.
Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

least one dose of any study drug. The MET IHC-positive population comprised all patients who had tissue with ≥50% of tumor cells with strong staining (3+ score) or ≥50% of tumor cells with either moderate or strong staining, but <50% of cells with strong staining (2+ score) for MET expression.

Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and classified according to the Medical Dictionary for Regulatory Activities version 16.1.

Statistical Analysis

A total of 178 evaluable patients were planned (89 in each arm) to achieve a target of 90% power at a significance level of 10% in order to detect a hazard ratio (HR) of 0.625 given a median PFS of 10.0 months in the placebo arm. 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. The nonparametric subpopulation treatment effect pattern plot (STEPP) methodology was used to assess treatment effect differences according to the IHC assay.

An interim analysis of PFS and safety was planned to be performed when 50% of all patients in the ITT population experienced a PFS event or 6 months after the final patient was enrolled in the study, whichever occurred later. The final analysis was conducted on February 6, 2014.

Results

Patients

Between September 2011 and November 2012, 194 patients were randomized to treatment, with 97 patients allocated to each of the onartuzumab and placebo arms (ITT population). A number of patients were in screening at the time that the target of 178 evaluable patients was met, thus all 194 patients were enrolled onto the study. Two patients in the placebo arm did not receive treatment, and another two patients inadvertently received onartuzumab, leaving 192 patients in the safety population (Fig. 1). Overall, 79 patients (41%) were included in the MET IHC-positive population (42 received onartuzumab and 37 received placebo), and 108 patients (56%) were included in the MET-negative population (51 received onartuzumab and 57 received placebo). Five patients had inadequate tissue available for IHC assessment and were therefore not evaluable for MET determination.

Patient characteristics were generally balanced between treatment arms for the ITT population (Table 1). For the MET

Table 1. Baseline characteristics of the ITT, MET IHC-positive, and MET IHC-negative populations

Characteristic	ITT population ($n = 194$)		MET IHC-positive population ($n = 79$)		MET IHC-negative population ($n = 108$)	
	Onartuzumab ($n = 97$)	Placebo ($n = 97$)	Onartuzumab ($n = 37$)	Placebo ($n = 42$)	Onartuzumab ($n = 57$)	Placebo ($n = 51$)
Median age, years (range)	60 (31–84)	62 (32–86)	60 (40–78)	58 (37–86)	61 (31–84)	63 (32–85)
Gender, *n* (%)						
Male	57 (58.8)	55 (56.7)	22 (59.5)	22 (52.4)	34 (59.6)	31 (60.8)
Female	40 (41.2)	42 (43.3)	15 (40.5)	20 (47.6)	23 (40.4)	20 (39.2)
Race, *n* (%)						
White	86 (88.7)	76 (78.4)	32 (86.5)	30 (71.4)	51 (89.5)	44 (86.3)
Baseline ECOG PS, *n* (%)						
0	65 (67.0)	55 (56.7)	20 (54.1)	23 (54.8)	43 (44.3)	30 (30.9)
1	32 (33.0)	41 (42.3)	17 (45.9)	19 (45.2)	14 (14.4)	20 (20.6)
2	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Prior adjuvant therapy, *n* (%)						
Yes	10 (10.3)	11 (11.3)	5 (13.5)	6 (14.3)	5 (8.8)	5 (9.8)
No	87 (89.7)	86 (88.7)	32 (86.5)	36 (85.7)	52 (91.2)	46 (90.2)
Primary tumor site, n (%)						
Colon	79 (81.4)	85 (87.6)	31 (83.8)	37 (88.1)	45 (78.9)	45 (88.2)
Rectum	18 (18.6)	12 (12.4)	6 (16.2)	5 (11.9)	12 (21.1)	6 (11.8)
Number of metastatic sites, *n* (%)						
1	24 (24.7)	24 (24.7)	7 (18.9)	13 (31.0)	16 (28.1)	10 (19.6)
≥2	73 (75.3)	73 (75.3)	30 (81.1)	29 (69.0)	41 (71.9)	41 (80.4)
Metastatic disease, *n* (%)						
Liver only	13 (13.4)	18 (18.6)	1 (2.7)	11 (26.2)	12 (21.1)	6 (11.8)
Liver and other site	62 (63.9)	57 (58.8)	25 (67.6)	24 (57.1)	35 (61.4)	30 (58.8)
Non-liver only	22 (22.7)	22 (22.7)	11 (29.7)	7 (16.7)	10 (17.5)	15 (29.4)
Stage at initial diagnosis, *n* (%)	$n = 97$	$n = 97$	$n = 37$	$n = 42$	$n = 57$	$n = 50$
I	3 (3.1)	1 (1.0)	1 (2.7)	0 (0.0)	2 (3.5)	1 (2.0)
II	13 (13.4)	14 (14.6)	5 (13.5)	4 (9.5)	8 (14.0)	10 (20.0)
III	8 (8.2)	10 (10.4)	3 (8.1)	4 (9.5)	5 (8.8)	6 (12.0)
IV	73 (75.3)	71 (74.0)	28 (75.7)	34 (81.0)	42 (73.7)	33 (66.0)
MET IHC score, *n* (%)	$n = 94$	$n = 93$	$n = 37$	$n = 42$	$n = 57$	$n = 51$
0	1 (1.0)	1 (1.0)	—	—	1 (1.0)	1 (1.0)
1	56 (57.7)	50 (51.5)	—	—	56 (57.7)	50 (51.5)
2	34 (35.1)	40 (41.2)	34 (91.9)	40 (95.2)	0 (0.0)	0 (0.0)
3	3 (3.1)	2 (2.1)	3 (8.1)	2 (4.8)	0 (0.0)	0 (0.0)
KRAS mutation status, *n* (%)	$n = 73$	$n = 74$	$n = 27$	$n = 34$	$n = 46$	$n = 40$
Mutant*	41 (56.2)	38 (51.4)	15 (55.6)	18 (52.9)	26 (56.5)	20 (50.0)
Wild type	32 (43.8)	36 (48.6)	12 (44.4)	16 (47.1)	20 (43.5)	20 (50.0)
BRAF mutation status, *n* (%)	$n = 73$	$n = 74$	$n = 27$	$n = 34$	$n = 46$	$n = 40$
Mutant	8 (11.0)	7 (9.5)	3 (11.1)	4 (11.8)	5 (10.9)	3 (7.5)
Wild type	65 (89.0)	67 (90.5)	24 (88.9)	30 (88.2)	41 (89.1)	37 (92.5)

**KRAS* mutations included: G12A, G12C, G12D, G12S, G12R, G12V, G13D, G12F, G13A, G13C, G13R, G13S, and G13V.

Abbreviations: —, no data; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ITT, intent-to-treat; MET, mesenchymal-epithelial transition; Onartuzumab, onartuzumab plus bevacizumab plus mFOLFOX-6; Placebo, placebo plus bevacizumab plus mFOLFOX-6.

IHC-positive population, the onartuzumab arm had a higher proportion of males compared with the placebo arm (59.5% versus 52.4%).

Dose intensity of onartuzumab/placebo was 98.3% (50–116) and 99.6% (66–112) for onartuzumab versus placebo, respectively; median treatment duration was 6.4 and 7.1 months for onartuzumab ($n = 99$) and placebo ($n = 93$), respectively. Reasons for patient withdrawal are listed in Figure 1.

Efficacy

On September 19, 2013, after the planned interim analysis, investigators were recommended to discontinue onartuzumab due to lack of efficacy and the observed increased incidence of venous thromboembolism.

ITT Population

At the final data analysis of February 6, 2014, with a median follow-up of 19.2 months, there was no significant improvement in PFS with onartuzumab versus placebo in the ITT population (HR, 0.75; 95% CI, 0.52–1.08; $p = .12$; median PFS, 11.0 versus 10.3 months, respectively, Fig. 2A). Onartuzumab also did not demonstrate an improvement in OS compared with placebo (HR, 0.96; 95% CI, 0.61–1.50; $p = .85$; median OS, 22.2 months versus not reached, respectively, Fig. 3A). There was no significant difference in ORR between the treatment arms ($p = 1.00$, Table 2).

MET IHC-Positive Population

At the final data analysis, there was no significant difference in PFS between the onartuzumab and placebo arms in the MET IHC-positive population (HR, 1.03; 95% CI, 0.56–1.89; $p = .93$;

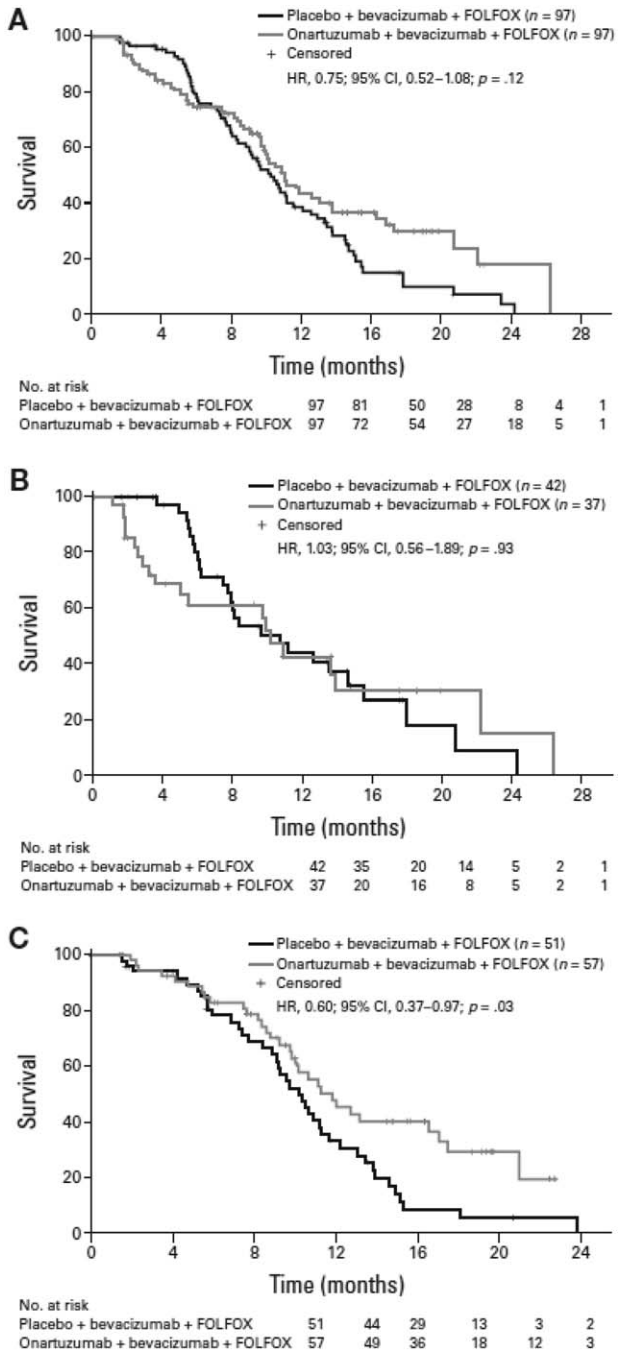

Figure 2. Progression-free survival. **(A)**: Intent-to-treat population. **(B)**: mesenchymal-epithelial transition (MET) immunohistochemistry (IHC)-positive population. **(C)**: MET IHC-negative population.
Abbreviations: CI, confidence interval; HR, hazard ratio.

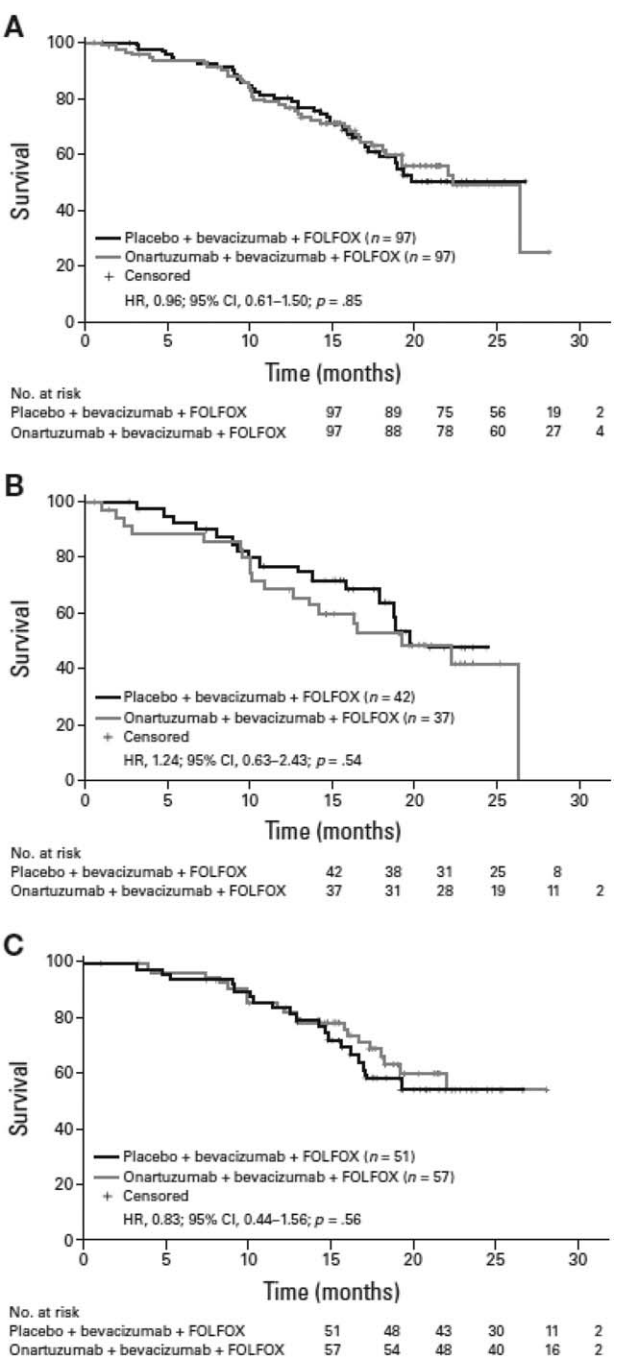

Figure 3. Overall survival. **(A)**: Intent-to-treat population. **(B)**: mesenchymal-epithelial transition (MET) immunohistochemistry (IHC)-positive population. **(C)**: MET IHC-negative population.
Abbreviations: CI, confidence interval; HR, hazard ratio.

median PFS, 10.2 versus 10.7 months, respectively, Fig. 2B). Median OS was also not improved with onartuzumab versus placebo (HR, 1.24; 95% CI, 0.63–2.43; $p = .54$; median OS, 19.2 versus 19.7 months, respectively, Fig. 3B). Furthermore, there was no significant difference in ORR between the treatment arms ($p = .26$, Table 2).

MET IHC-Negative Population

Onartuzumab prolonged PFS compared with placebo in the MET-negative population (HR, 0.60; 95% CI, 0.37–0.97; $p = .03$; median PFS, 11.7 versus 10.2 months, respectively, Fig. 2C). However, there was no significant difference in OS between the treatment arms (HR, 0.83; 95% CI, 0.44–1.56; $p = .56$; median OS not reached in either arm, Fig. 3C) and no statistical difference in ORR ($p = .69$, Table 2).

Exploratory Biomarker Data

STEPPs for HGF and MET showed no association between MET IHC or HGF expression at any level (supplemental online Figs. 1 and 2). Exploratory PFS and OS analyses revealed no significant differences between the treatment arms in patient subgroups defined by *KRAS* or *BRAF* mutation status (supplemental online Fig. 3).

Table 2. Overall response rates in patients with tumor assessment at baseline

	ITT population		MET IHC-positive population		MET IHC-negative population	
n **(%)**	**Onartuzumab (*n* = 96)**	**Placebo (*n* = 97)**	**Onartuzumab (*n* = 37)**	**Placebo (*n* = 42)**	**Onartuzumab (*n* = 56)**	**Placebo (*n* = 51)**
ORR	55 (57.3)	56 (57.7)	16 (43.2)	24 (57.1)	37 (66.1)	31 (60.8)
Complete response	3 (3.1)	3 (3.1)	1 (2.7)	1 (2.4)	2 (3.6)	2 (3.9)

Abbreviations: IHC, immunohistochemistry; ITT, intent-to-treat; MET, mesenchymal-epithelial transition; Onartuzumab, onartuzumab plus bevacizumab plus mFOLFOX-6; ORR, overall response rate; Placebo, placebo plus bevacizumab plus mFOLFOX-6.

Table 3. Summary of AEs in the safety and MET subgroup populations

	Safety population		MET IHC-positive safety population		MET IHC-negative safety population	
AE, *n* (%)	**Onartuzumab (*n* = 99)**	**Placebo (*n* = 93)**	**Onartuzumab (*n* = 38)**	**Placebo (*n* = 41)**	**Onartuzumab (*n* = 58)**	**Placebo (*n* = 50)**
AE (any grade)	98 (99.0)	93 (100.0)	37 (97.4)	41 (100.0)	58 (100.0)	50 (100.0)
Grade ≥3 AE	86 (86.9)	79 (84.9)	33 (86.8)	36 (87.8)	50 (86.2)	41 (82.0)
Grade 5 AE*	3 (3.0)	0 (0.0)	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	46 (46.5)	37 (39.8)	20 (52.6)	17 (41.5)	24 (41.4)	18 (36.0)
AE leading to discontinuation of any study drug	48 (48.5)	35 (37.6)	18 (47.4)	15 (36.6)	28 (48.3)	19 (38.0)

*Grade 5 AEs were cerebrovascular accident, respiratory failure, and sepsis.
Abbreviations: AE, adverse event; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition; Onartuzumab, onartuzumab plus bevacizumab plus mFOLFOX-6; Placebo, placebo plus bevacizumab plus mFOLFOX-6.

Table 4. Grade ≥3 AEs with an incidence of >5% in either arm (safety population)

AE, *n* (%)	**Onartuzumab (*n* = 99)**	**Placebo (*n* = 93)**
Neutropenia	28 (28.3)	24 (25.8)
Fatigue	23 (23.2)	8 (8.6)
Pulmonary embolism	12 (12.1)	8 (8.6)
Peripheral edema	11 (11.1)	0 (0.0)
Hypertension	9 (9.1)	14 (15.1)
Neutrophil count decreased	8 (8.1)	6 (6.5)
Hypokalemia	7 (7.1)	9 (9.7)
Hyponatremia	6 (6.1)	0 (0.0)
Deep vein thrombosis	5 (5.1)	0 (0.0)
White blood cell count decreased	5 (5.1)	0 (0.0)
Dehydration	4 (4.0)	5 (5.4)
Nausea	4 (4.0)	5 (5.4)
Diarrhea	3 (3.0)	9 (9.7)
Abdominal pain	3 (3.0)	6 (6.5)
Hyperglycemia	2 (2.0)	6 (6.5)

Abbreviations: AE, adverse event; Onartuzumab, onartuzumab plus bevacizumab plus mFOLFOX-6; Placebo, placebo plus bevacizumab plus mFOLFOX-6.

Safety

Overall, the frequency of AEs was similar between the two treatment arms in the ITT and MET populations (Table 3). Serious AEs (SAEs; safety population: 46.5% versus 39.8%; MET IHC-positive: 52.6% versus 41.5%; MET IHC-negative: 41.4% versus 36.0%) and AEs leading to discontinuation of any study drug (ITT: 48.5% versus 37.6%; MET IHC-positive: 47.4% versus 36.6%; MET IHC-negative: 48.3% versus 38.0%) were numerically higher with onartuzumab than with placebo. Median duration of treatment was comparable between the onartuzumab and placebo arms, respectively, for bolus 5-FU (5.5 versus 6.7 months), bevacizumab (5.1 versus 6.9 months), LV (6.0 versus 7.1 months), onartuzumab/placebo (6.4 versus 7.1 months), and oxaliplatin (3.2 versus 3.3 months).

Grade ≥3 AEs with an incidence of >5% in either arm in the safety population are shown in Table 4. In general, fatigue (23.2% versus 8.6%), peripheral edema (11.1% versus 0%), and deep vein thrombosis (5.1% versus 0%) occurred at a higher frequency in the onartuzumab arm compared with the placebo arm.

Discussion

In the present study, the addition of onartuzumab to mFOLFOX-6 plus bevacizumab in patients with previously untreated mCRC did not improve PFS, OS, or ORR in either the ITT population or the MET IHC-positive population. Somewhat surprisingly, a significant prolongation of PFS with onartuzumab was noted in the MET IHC-negative population, although this is of uncertain significance. Exploratory biomarker analyses revealed no association between MET IHC or HGF expression at any level and no significant survival differences between the treatment arms in patient subgroups defined by *KRAS* or *BRAF* mutation status.

Although initial preclinical and early clinical results with onartuzumab showed promising efficacy data [15], a number of phase II/III clinical trials have since reported a lack of improvement in efficacy with onartuzumab combined with standard-of-care therapies in several tumor types. For example, METLung, a randomized phase III study of erlotinib with or without onartuzumab in patients with NSCLC and MET IHC-positive tumors, was halted for futility following a planned interim analysis because the combination did not confirm the efficacy results observed in the phase II NSCLC trial [16]. In other tumors,

including gastroesophageal adenocarcinoma [17], triple-negative breast cancer [18], and recurrent glioblastoma [19], the addition of onartuzumab to standard treatment regimens reported similarly disappointing results.

These results, coupled with the lack of efficacy with onartuzumab reported in the present study and other negative studies of the MET antibodies rilotumumab [20] and ficlatuzumab [21] (both of which are fully humanized monoclonal antibodies that block HGF binding to the MET receptor [15]), suggest that monoclonal antibodies that compete with or interfere with HGF binding to the MET receptor may not be suitable for targeting HGF/MET dysregulation. Alternative means of inhibiting the MET pathway may be more successful in controlling oncogenic MET/HGF signaling, which can occur through several mechanisms, including gene amplification or mutation, protein overexpression, or abnormal gene splicing [22]. The anaplastic lymphoma kinase (ALK) inhibitor crizotinib, which also targets MET tyrosine kinase (TK), has shown promising efficacy in patients with lung cancer and de novo genomic *MET* amplification but who have no *ALK* gene rearrangements [23]. Alternatively, targeting the MET pathway for control of signal transduction in cancer may require multiple points of blockade.

An unexpected finding of this study was a trend toward improved PFS benefit in patients with MET IHC-negative mCRC, which is contrary to the detrimental outcomes seen with MET inhibitors in previous phase II studies of patients with MET IHC-negative tumors [14, 24, 25]. Although this finding could be due to chance, it is in line with an exploratory analysis of the monoclonal antibody ficlatuzumab in NSCLC, which demonstrated that the addition of ficlatuzumab to gefitinib appeared to benefit patients with low tumoral MET expression [15]. In addition, a subgroup analysis of a phase Ib study in colorectal cancer showed that patients with low MET expression tumors derived a statistically significant improvement in PFS with the possible anti-MET TK inhibitor tivantinib [26, 27]. These results indicate a complex and as yet not understood relationship between MET expression and tumor response to anti-MET agents. However, it should be noted that because secondary endpoints were similar between arms in the MET IHC-negative subgroup, the PFS finding could represent type 1 error.

Onartuzumab combined with mFOLFOX-6 plus bevacizumab was generally well tolerated in patients with mCRC. The incidence of grade $\geq$3 deep vein thrombosis, fatigue, and peripheral edema was higher with onartuzumab than with placebo, which was expected [14]. Peripheral edema has also been frequently reported as a common toxicity associated with anti-HGF/MET antibodies across multiple tumor types and combination regimens [28, 29]. In addition, higher rates of SAEs and AEs leading to study withdrawal were recorded in the onartuzumab arm compared with placebo, although these are in line with previous studies of onartuzumab [14, 18]. Overall, the safety profile was as expected, with no new safety signals for onartuzumab.

Conclusion

In this randomized phase II study, onartuzumab combined with mFOLFOX-6/bevacizumab failed to improve PFS, OS, or ORR in patients with mCRC. Collective experience across multiple trials with onartuzumab suggests that MET IHC was not an appropriate biomarker for this agent. It remains to be seen if other biomarkers might have worked better, or, alternatively, small molecule inhibitors might be a more appropriate approach to inhibiting this important oncogenic pathway.

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Disclosures

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