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Randomized phase II study of modified FOLFOX-6 in combination with ramucirumab or icrucumab as second-line therapy in patients with metastatic colorectal cancer after disease progression on first-line irinotecan-based therapy

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Background: Icrucumab and ramucirumab are recombinant human IgG1 monoclonal antibodies that bind VEGF receptors 1 and 2 (VEGFR-1 and -2), respectively. This randomized phase II study evaluated the antitumor activity and safety of icrucumab and ramucirumab each in combination with mFOLFOX-6 in patients with metastatic colorectal cancer after disease progression on first-line therapy with a fluoropyrimidine and irinotecan.

Patients and methods: Eligible patients were randomly assigned to receive mFOLFOX-6 alone (mFOLFOX-6) or in combination with ramucirumab 8 mg/kg IV (RAM+mFOLFOX-6) or icrucumab 15 mg/kg IV (ICR+mFOLFOX-6) every 2 weeks. Randomization was stratified by prior bevacizumab therapy. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), tumor response, safety, and PK.

Results: In total, 158 patients were randomized, but only 153 received treatment (49 on mFOLFOX-6, 52 on RAM+mFOLFOX-6, and 52 on ICR+mFOLFOX-6). Median PFS was 18.4 weeks on mFOLFOX-6, 21.4 weeks on RAM+mFOLFOX-6, and 15.9 weeks on ICR+mFOLFOX-6 (RAM+mFOLFOX-6 versus mFOLFOX-6, stratified hazard ratio [HR] 1.116 [95% CI 0.713–1.745], $P = 0.623$; ICR+mFOLFOX-6 versus mFOLFOX-6, stratified HR 1.603 [95% CI 1.011–2.543], $P = 0.044$). Median survival was 53.6 weeks on mFOLFOX-6, 41.7 weeks on RAM+mFOLFOX-6, and 42.0 weeks on ICR+mFOLFOX-6. The most frequent adverse events reported on the ramucirumab arm (RAM+mFOLFOX-6) were fatigue, nausea, and peripheral sensory neuropathy; those on the icrucumab arm (ICR+mFOLFOX-6) were fatigue, diarrhea, and peripheral sensory neuropathy. Grade $\geq$3 serious adverse events occurred at comparable frequency across arms.

Conclusions: In this study population, combining ramucirumab or icrucumab with mFOLFOX-6 did not achieve the predetermined improvement in PFS.

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Key words: ramucirumab, icrucumab, VEGF, colorectal cancer, modified FOLFOX-6, irinotecan

introduction

Colorectal cancer is the fourth leading cause of cancer-related deaths worldwide [1]. Approximately 25% of patients present with metastases, and 50% develop metastatic disease [2]. Despite improved prognosis for patients with metastatic colorectal cancer (mCRC), unresectable metastatic disease remains incurable and warrants new therapies.

Vascular endothelial growth factor A (VEGF) and VEGF receptors 1 and 2 (VEGFR-1 and -2) are involved in tumor angiogenesis, growth, and metastasis [3]. Disabling the VEGF receptor signaling pathway via anti-VEGF antibodies, anti-VEGFR antibodies, and small molecule tyrosine kinase inhibitors can inhibit or reduce vascularization and tumor growth [3]. VEGF- and VEGFR-interfering agents have demonstrated antitumor activity.

Current standard of care for unresectable mCRC is oxaliplatin- or irinotecan-based therapy combined with fluoropyrimidines [2]. In phase II and III studies, combinations of oxaliplatin- or irinotecan-based chemotherapies with bevacizumab, a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets circulating VEGF, improved survival [4–6] in patients with metastatic disease. A number of other anti-VEGF therapies are undergoing study in mCRC [7].

Ramucirumab is a recombinant human IgG1 mAb that binds VEGFR-2, blocks VEGF ligands, and inhibits VEGF-stimulated proliferation and migration of endothelial cells [8]. In a phase II study, combining ramucirumab with modified FOLFOX-6 (mFOLFOX-6; oxaliplatin + folinic acid + 5-fluorouracil) as first-line therapy for mCRC enhanced mFOLFOX-6 efficacy in terms of PFS, OS, objective response rate, and disease control rate (DCR) when compared with historical controls [9]. In the phase III RAISE study, patients whose mCRC progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine were randomized to receive ramucirumab plus folinic acid, fluorouracil, and irinotecan (FOLFIRI) or placebo plus FOLFIRI. Adding ramucirumab to FOLFIRI significantly improved survival and was well tolerated [8].

Icrucumab (IMC-18F1) is a recombinant human IgG1 mAb that binds VEGFR-1, blocks ligand binding, and inhibits receptor phosphorylation and downstream signaling. In a phase I study, icrucumab was well tolerated when infused every 1–3 weeks in patients with advanced solid tumors. Six patients achieved stable disease, for a DCR of 23.1% [10].

This open-label, randomized, multicenter, phase II trial evaluated the antitumor activity and safety of mFOLFOX-6 alone or in combination with ramucirumab or icrucumab in patients with mCRC after disease progression on first-line irinotecan-based therapy.

patients and methods

study design and patients

Patients were randomized to mFOLFOX-6 alone (mFOLFOX-6), ramucirumab + mFOLFOX-6 (RAM+mFOLFOX-6), or icrucumab + mFOLFOX-6 (ICR+mFOLFOX-6) (Figure 1), stratified by prior bevacizumab therapy. Study treatment continued until disease progression, unacceptable toxicity, patient noncompliance or consent withdrawal, or investigator decision. See Supplementary Materials, available at *Annals of Oncology* online, for study enrollment criteria. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and with local ethics committee approval. All participants provided written informed consent.

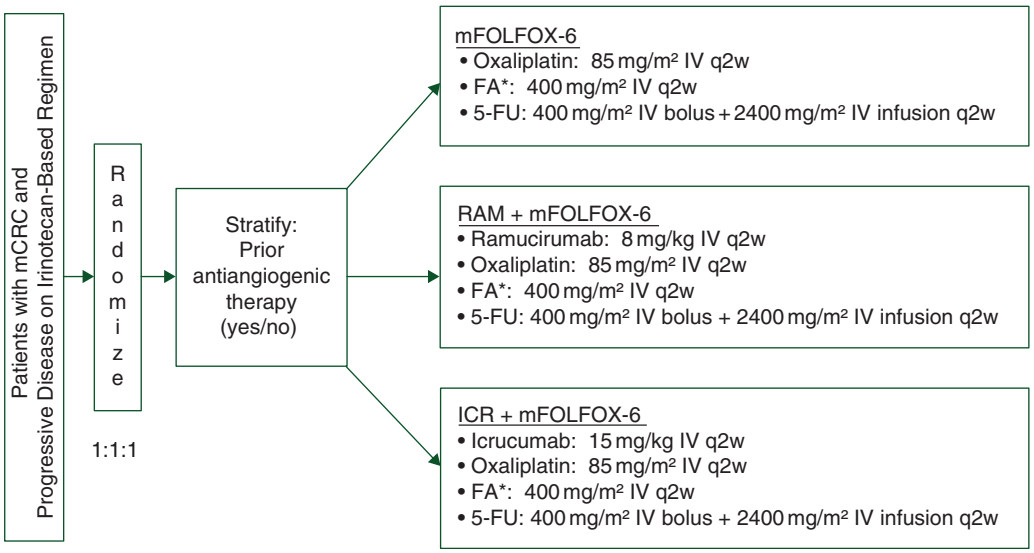

Figure 1. Study design. The asterisk (*) indicates that, when folinic acid (FA) was unavailable, levofolinic acid (LFA) (200 mg/m^2 every 2 weeks [q2w]) could be administered instead. 5-FU, 5-fluorouracil; ICR, icrucumab; IV, intravenous(ly); mCRC, metastatic colorectal cancer; mFOLFOX-6, modified FOLFOX-6 (oxaliplatin + folinic acid + 5-fluorouracil); RAM, ramucirumab.

study procedures

On all three arms, mFOLFOX-6 was started on Day 1 of each 2-week treatment cycle. On the RAM+mFOLFOX-6 and ICR+mFOLFOX-6 arms, ramucirumab 8 mg/kg and icrucumab 15 mg/kg, respectively, were infused intravenously (IV) over 1 h on Day 1 of each cycle immediately before mFOLFOX-6. Treatment assessment and pharmacokinetic (PK) sampling methods are described in Supplementary Materials, available at *Annals of Oncology* online.

study end points

The primary end point was PFS using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1. Secondary end points included objective response rate (ORR), OS, safety, and PK of ramucirumab and icrucumab. Safety assessments included adverse events (AEs) collected through 30-day follow-up, AEs of special interest (AESIs) for ramucirumab and icrucumab, concomitant medications, laboratory data, vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and electrocardiograms (ECGs).

statistical analysis

Enrollment of 150 patients (50 patients/arm) was planned to provide the 126 PFS events necessary for 72% power at one-sided alpha of 7.5% in detecting a hazard ratio (HR) of 0.64 (i.e. increase in median PFS from 4.5 months on the mFOLFOX-6 arm to 7 months on either combination arm) using the log-rank test.

Efficacy was analyzed in all randomized patients who received any study drug (i.e. modified intent-to-treat [mITT] population). PFS and OS were analyzed by Kaplan–Meier method and log-rank test, stratified by prior bevacizumab therapy. The HR of each combination therapy (RAM+mFOLFOX-6 or ICR+mFOLFOX-6) to mFOLFOX-6 alone was estimated by stratified Cox proportional hazards model. ORR (complete response [CR] + partial response [PR]) with 2-sided 95% CI was compared for the RAM+mFOLFOX-6 and ICR+mFOLFOX-6 arms versus mFOLFOX-6, using the Cochran–Mantel–Haenszel test adjusted for stratification variable.

Safety was analyzed for all patients receiving any dose of study drug, according to actual treatment received. Cumulative dose, relative dose intensity (based on planned total dose), dose reduction/delay, infusion rate modification, and infusion interruption were evaluated for each study drug. AEs were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). AESIs for ramucirumab and icrucumab were summarized, using consolidated terms comprising one or more MedDRA preferred terms (see Supplementary Materials, available at *Annals of Oncology* online, for details). Clinical laboratory abnormalities were graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Predose blood samples were analyzed for serum trough concentrations of ramucirumab and icrucumab (Supplementary Materials, available at *Annals of Oncology* online). Statistical analyses were conducted using the Statistical Analysis Software® (SAS®), version 8.2 or later (SAS Institute, Cary, NC, USA).

results

patient demographics, characteristics, and treatment

Of 178 patients enrolled from August 2010 through October 2013 at study sites in North America, 158 patients were randomized to treatment. Five randomized patients (all on the mFOLFOX-6 arm) were discontinued before receiving treatment. Hence, 153 patients received treatment: 49 on mFOLFOX-6, 52 on RAM+mFOLFOX-6, and 52 on ICR+mFOLFOX-6. Patient disposition is shown in Figure 2. Patient demographics and baseline characteristics are given in

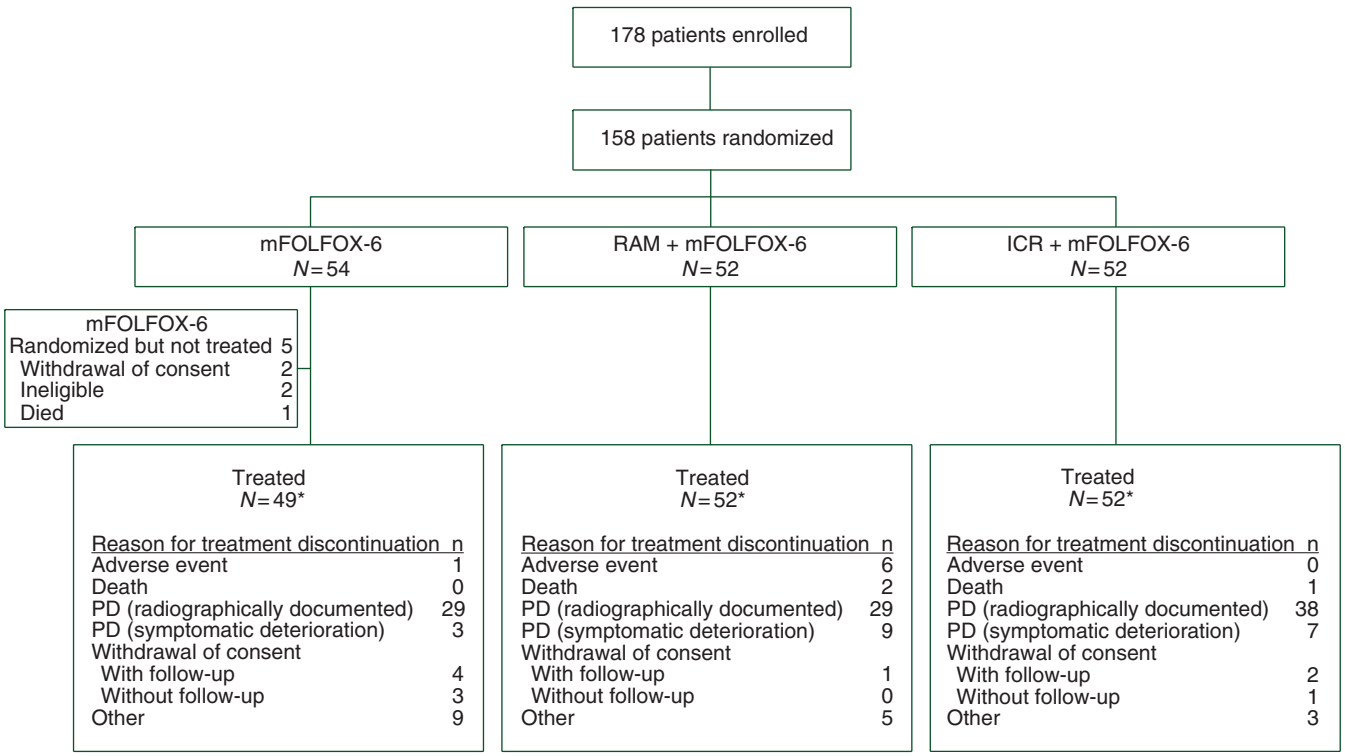

Figure 2. Patient disposition. The asterisk (*) indicates the mITT population (i.e. all randomly assigned patients who received any amount of any study drug, regardless of eligibility or protocol compliance). ICR, icrucumab; mFOLFOX-6, modified FOLFOX-6 (oxaliplatin + folinic acid + 5-fluorouracil); mITT, modified intent-to-treat; PD, progressive disease; RAM, ramucirumab.

Table 1. Patient demographics and baseline characteristics

Characteristic, *n* (%)	mFOLFOX-6 (*N* = 49)	RAM+mFOLFOX-6 (*N* = 52)	ICR+mFOLFOX-6 (*N* = 52)	All patients (*N* = 153)
Sex				
Male	28 (57.1)	31 (59.6)	23 (44.2)	82 (53.6)
Female	21 (42.9)	21 (40.4)	29 (55.8)	71 (46.4)
ECOG PS				
0	21 (42.9)	20 (38.5)	13 (25.0)	54 (35.3)
1	27 (55.1)	31 (59.6)	39 (75.0)	97 (63.4)
2	1 (2.0)	1 (1.9)	0	2 (1.3)
KRAS status				
Wild type	9 (18.4)	7 (13.5)	9 (17.3)	25 (16.3)
Mutant	14 (28.6)	17 (32.7)	9 (17.3)	40 (26.1)
Unknown	26 (53.1)	28 (53.8)	34 (65.4)	88 (57.5)
Mean serum CEA, mg/l[a]	220 (716.77)	229 (727.88)	202 (463.16)	217 (639.08)
Bevacizumab in first-line regimen				
Yes	46 (93.9)	50 (96.2)	49 (94.2)	145 (94.8)
No	3 (6.1)	2 (3.8)	3 (5.8)	8 (5.2)
Oxaliplatin as prior (neo)adjuvant therapy[b]				
Yes	5 (10.2)	7 (13.5)	4 (7.7)	16 (10.5)
No	44 (89.8)	45 (86.5)	48 (92.3)	137 (89.5)
Cancer type				
Colon	29 (59.2)	33 (63.5)	33 (63.5)	95 (62.1)
Colorectal	7 (14.3)	11 (21.2)	9 (17.3)	27 (17.6)
Rectum	13 (26.5)	8 (15.4)	10 (19.2)	31 (20.3)
Metastatic disease site				
Bone	7 (14.3)	6 (11.5)	4 (7.7)	17 (11.1)
Liver	41 (83.7)	46 (88.5)	40 (76.9)	127 (83.0)
Lung	27 (55.1)	35 (67.3)	27 (51.9)	89 (58.2)
Lymph nodes	25 (51.0)	23 (44.2)	23 (44.2)	71 (46.4)
Peritoneal	12 (24.5)	12 (23.1)	15 (28.8)	39 (25.5)

CEA, carcinoembryonic antigen; ECOG, European Cooperative Oncology Group; ICR, icrucumab; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; PS, performance status; RAM, ramucirumab.

[a]Data shown are mean (SD).

[b]Prior (neo)adjuvant oxaliplatin-based therapy was allowed if administered >12 months before randomization.

Table 1. Some imbalances between treatment arms were noted (Table 1). Patients with mutant *KRAS* tumors were less frequent on the ICR+mFOLFOX-6 arm (17.3%) than on mFOLFOX-6 (28.6%) or RAM+mFOLFOX-6 (32.7%); however, *KRAS* status was unknown for more than half of patients. The ICR+mFOLFOX-6 arm had fewer patients with a baseline ECOG PS of 0 (25%) than did mFOLFOX-6 (43%) or RAM+mFOLFOX-6 (39%).

progression-free survival

Median PFS (95% CI) was 18.4 (15.7–24.4) weeks on the mFOLFOX-6 arm, 21.4 (16.1–25.0) weeks on RAM+mFOLFOX-6, and 15.9 (14.1–16.4) weeks on ICR+mFOLFOX-6 (Figure 3). PFS was comparable between the mFOLFOX-6 and RAM+mFOLFOX-6 arms (stratified HR, 1.116 [95% CI 0.713–1.745], $P = 0.6228$), but significantly longer on mFOLFOX-6 than on ICR+mFOLFOX-6 (stratified HR, 1.603 [95% CI 1.011–2.543], $P = 0.044$).

overall survival

Median OS (95% CI) was 53.6 (36.1–68.4) weeks on the mFOLFOX-6 arm, 41.7 (28.4–60.3) weeks on RAM+mFOLFOX-6, and 42.0 (32.0–50.4) weeks on ICR+mFOLFOX-6 (Table 2 and supplementary Figure S1, available at *Annals of Oncology* online). OS on both combination arms was not significantly different than on the mFOLFOX-6 arm. The stratified HR (95% CI) was 1.183 (0.754–1.854) for RAM+mFOLFOX-6 versus mFOLFOX-6 and 1.228 (0.783–1.925) for ICR+mFOLFOX-6 versus mFOLFOX-6.

tumor response

Eleven patients had a CR or PR (Table 2). The ORR (95% CI) was not significantly higher for the mFOLFOX-6 arm (14.3% [5.94%–27.24%]) than for either RAM+mFOLFOX-6 (3.8% [0.47%–13.21%]) or ICR+mFOLFOX-6 (3.8% [0.47%–13.21%]) (Table 2). The DCR (95% CI) was similar across arms: 73.5% (58.92%–85.05%) for mFOLFOX-6, 73.1% (58.98%–84.43%) for RAM+mFOLFOX-6, and 65.4% (50.91%–78.03%) for

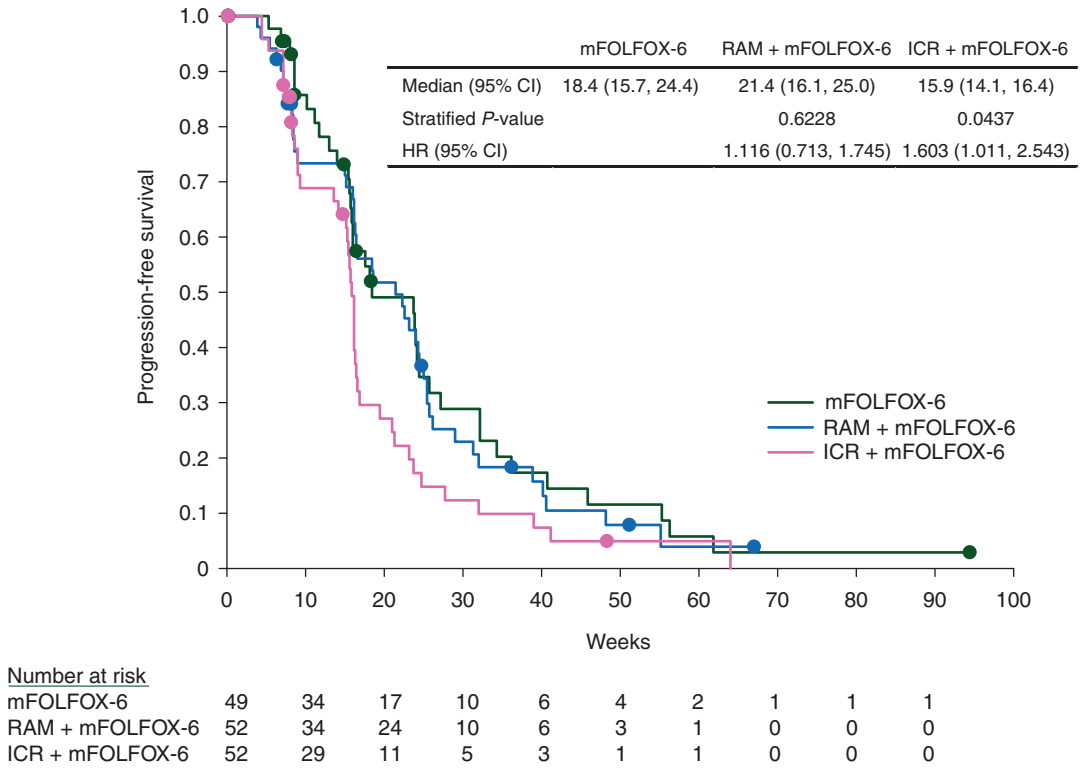

Figure 3. Kaplan–Meier curve for progression-free survival (mITT population).

Table 2. Overall survival and tumor response

	mFOLFOX-6 ($N = 49$)	RAM+mFOLFOX-6 ($N = 52$)	ICR+mFOLFOX-6 ($N = 52$)
Overall survival			
Deaths, *n* (%)	37 (75.5)	41 (78.8)	40 (76.9)
Median, weeks (95% CI)[a]	53.6 (36.1, 68.4)	41.7 (28.4, 60.3)	42.0 (32.0, 50.4)
Stratified log-rank *P*-value[b] (2-sided)		0.463	0.369
Stratified hazard ratio[c] (95% CI)		1.18 (0.75, 1.85)	1.23 (0.78, 1.93)
Overall tumor response			
Best overall response, *n* (%)			
Complete response	1 (2.0)	0	0
Partial response	6 (12.2)	2 (3.8)	2 (3.8)
Stable disease	29 (59.2)	36 (69.2)	32 (61.5)
Progressive disease	6 (12.2)	12 (23.1)	13 (25.0)
Not evaluable	7 (14.3)	2 (3.8)	5 (9.6)
Disease control,[d] *n* (%)	36 (73.5)	38 (73.1)	34 (65.4)
95% CI[e]	58.92, 85.05	58.98, 84.43	50.91, 78.03
Objective response, *n* (%)	7 (14.3)	2 (3.8)	2 (3.8)
95% CI[e]	5.94, 27.24	0.47, 13.21	0.47, 13.21
P-value[b] (2-sided Fisher's exact test)		0.086	0.086
P-value[b] (2-sided, stratified Cochran–Mantel–Haenszel test)		0.105	0.085

CI, confidence interval; ICR, icrucumab; RAM, ramucirumab.
[a]Estimated by Kaplan–Meier method.
[b]Between combination therapy arm and mFOLFOX-6 arm.
[c]Hazard ratio for combination therapy/mFOLFOX-6 and estimated from Cox model.
[d]Complete response + partial response + stable disease.
[e]Estimated using binomial distribution.

ICR+mFOLFOX-6 (Table 2). The greatest change from baseline in target lesion measurements and best overall response for each patient, by treatment arm, are presented in supplementary Figure S2, available at *Annals of Oncology* online (mITT Population).

safety

Median cycle number ranged from 6 to 8 (see supplementary Table S1, available at *Annals of Oncology* online, for all treatment exposure details). Table 3 summarizes AEs, including commonly reported treatment-emergent AEs (TEAEs). No TEAEs were grade 4. Diarrhea, constipation, stomatitis, toothache, fatigue, peripheral edema, weight decreased, headache, dyspnea, cough, epistaxis, rash, and hypertension occurred more frequently on RAM+mFOLFOX-6 than on mFOLFOX-6. Vomiting, diarrhea, abdominal pain, constipation, abdominal distension, ascites, peripheral edema, face edema, anorexia, dysgeusia, dyspnea, and periorbital edema occurred more frequently on ICR+mFOLFOX-6 than on mFOLFOX-6.

The most common grade ≥3 TEAEs that occurred in ≥5% of patients and more frequently on RAM+mFOLFOX-6 than on mFOLFOX-6 were fatigue (23.1% versus 12.2%), hypertension (13.5% versus 2.0%), and diarrhea (7.7% versus 0%) (all grade 3). Those more frequent on ICR+mFOLFOX-6 than on mFOLFOX-6 were fatigue (26.9% versus 12.2%; all grade 3) and hypokalemia (9.6% versus 0%; 7.7% grade 3% and 1.9% grade 4). Grade ≥3 SAEs were comparable on all treatment arms (22.4% [mFOLFOX-6]; 28.8% [RAM+mFOLFOX-6]; 21.2% [ICR+mFOLFOX-6]).

TEAEs led to discontinuation of any study drug more frequently on RAM+mFOLFOX-6 than on mFOLFOX-6 (34.6% versus 12.2%) and more frequently, though to a lesser degree, on ICR+mFOLFOX-6 than on mFOLFOX-6 (21.2% versus 12.2%).

Ramucirumab AESIs (any grade), as categorized by consolidated terms, that were notably more frequent (by ≥10%) on RAM+mFOLFOX-6 than on mFOLFOX-6 included bleeding and hemorrhagic events (48.1% versus 18.4%), dyspnea (25.0% versus 10.2%), edema (44.2% versus 18.4%), hypertension (28.8% versus 2.0%), and proteinuria (13.5% versus 2.0%). Most AESIs were of low grade. Icrucumab AESIs notably more frequent (by ≥10%) on ICR+mFOLFOX-6 than on mFOLFOX-6 included dyspnea (34.6% versus 10.2%), edema (65.4% versus 18.4%), and vomiting (55.8% versus 36.7%).

Deaths were similarly frequent across arms (Table 2), with most due to disease progression (75.5% on mFOLFOX-6, 69.2% on RAM+mFOLFOX-6, and 67.3% on ICR+mFOLFOX-6). Five deaths were reported as being due to TEAEs, including one each due to hepatic failure, cerebrovascular accident, and neoplasm progression on RAM+mFOLFOX-6 and one each due to intestinal perforation and neoplasm progression on ICR+mFOLFOX-6 (see Table 3 and Supplementary Materials, available at *Annals of Oncology* online, for details).

pharmacokinetics

Pharmacokinetic trough concentrations are shown in supplementary Figures S3 (ramucirumab) and S4 (icrucumab), available at *Annals of Oncology* online.

discussion

In this phase II study, the median PFS for patients treated with mFOLFOX-6 alone was 18.4 weeks versus 21.4 weeks and 15.9 weeks for those treated with mFOLFOX-6 in combination with ramucirumab (RAM+mFOLFOX-6) and icrucumab (ICR+mFOLFOX-6), respectively. The difference in PFS was statistically significant between the mFOLFOX-6 and ICR+mFOLFOX-6 arms in favor of mFOLFOX-6 ($P = 0.044$, stratified log-rank test) but not between the mFOLFOX-6 and RAM+mFOLFOX-6 arms.

There were some minor imbalances in known or potential prognostic factors between treatment arms that could confound interpretation of the results. The mFOLFOX-6 alone arm had fewer patients with an ECOG PS of 0, which may have contributed to the poorer outcome on this arm. Tumor *KRAS* mutation status was unevenly distributed among arms. Since *KRAS* mutation is a predictive factor for EGFR inhibitor use in mCRC [11], the patients with known *KRAS* wild-type tumors may have benefitted from additional therapy, and this may have skewed overall survival results. The prognostic significance of *KRAS* mutations in advanced CRC is less clear. We did see differing EGFR inhibitor use after on-study progression (32.7% [mFOLFOX-6], 25.0% [RAM+mFOLFOX-6], and 36.5% [ICR+mFOLFOX-6]). Rates of study discontinuation due to an AE differed between arms. Six patients on the RAM+mFOLFOX-6 arm discontinued therapy due to AEs versus 1 patient on the mFOLFOX-6 arm and none on the ICR+mFOLFOX-6 arm (Figure 2). Finally, 5 randomized patients (all on the mFOLFOX-6 arm) were discontinued from the study before ever receiving treatment: 2 withdrew consent, 2 were deemed ineligible, and 1 died. Ramucirumab or icrucumab plus mFOLFOX-6 safety profiles were consistent with the safety profiles of the individual therapy components. Overall, AEs for ramucirumab-treated patients were consistent with those reported in other ramucirumab trials.

Icrucumab therapy was associated with increased incidence of toxicities related to alterations in vascular permeability and the gastrointestinal system. Fluid shifts resulting in peripheral edema, face edema, and ascites were more frequent on the ICR+mFOLFOX-6 arm than on the mFOLFOX-6 arm (Table 3). Rates of certain gastrointestinal AEs (nausea, diarrhea, dysgeusia, and anorexia) were also higher in the icrucumab-containing arm.

Discontinuation of any study drug due to TEAEs occurred more often on RAM+mFOLFOX-6 (34.6%) than on either mFOLFOX-6 (12.2%) or ICR+mFOLFOX-6 (21.2%). The overall AE profile in this study suggests that, even though there is an increase in certain toxicities typically associated with the antiangiogenic therapy, adding ramucirumab or icrucumab to mFOLFOX-6 is safe. Trough concentrations of ramucirumab and icrucumab observed in this study were similar to those observed in other studies using similar dosing regimens [10, 12; unpublished observations].

conclusions

This study did not meet its primary predetermined end point of improving PFS by 2.5 months in patients with unresectable locally advanced or metastatic colorectal cancer. The study size and imbalances in baseline characteristics mean that a smaller improvement in PFS cannot be definitively ruled out. At the time of publication, the study sponsor plans no further research in mCRC with icrucumab. For ramucirumab, the findings from the

Table 3. Overview of adverse events

Patient events[a], *n* (%)	mFOLFOX-6 (*N* = 49) *n* (%)		RAM+mFOLFOX-6 (*N* = 52) *n* (%)		ICR+mFOLFOX-6 (*N* = 52) *n* (%)	
AE with outcome of death	0		3 (5.8)[b]		2 (3.8)[b]	
SAE	11 (22.4)		17 (32.7)		12 (23.1)	
AE leading to discontinuation of any study drug	6 (12.2)		18 (34.6)		11 (21.2)	
mFOLFOX-6	6 (12.2)		11 (21.2)		10 (19.2)	
Ramucirumab	NA		16 (30.8)		NA	
Icrucumab	NA		NA		7 (13.5)	
Grade ≥3 AE	30 (61.2)		37 (71.2)		31 (59.6)	
TEAE	49 (100.0)		52 (100.0)		52 (100.0)	
TEAE related to any study drug[c]	48 (98.0)		52 (100.0)		52 (100.0)	
TEAE reported in ≥10% of patients in any arm[d]	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Blood and lymphatic system disorders						
Neutropenia[e]	17 (34.7)	10 (20.4)	17 (32.7)	10 (19.2)	12 (23.1)	9 (17.3)
Anemia	9 (18.4)	1 (2.0)	7 (13.5)	1 (1.9)	12 (23.1)	3 (5.8)
Thrombocytopenia	12 (24.5)	0	9 (17.3)	3 (5.8)	3 (5.8)	0
Eye disorders						
Lacrimation increased	3 (6.1)	0	2 (3.8)	0	8 (15.4)	0
Gastrointestinal disorders						
Nausea	31 (63.3)	2 (4.1)	24 (46.2)	0	36 (69.2)	1 (1.9)
Vomiting	18 (36.7)	3 (6.1)	13 (25.0)	0	28 (53.8)	2 (3.8)
Diarrhea	19 (38.8)	0	30 (57.7)	4 (7.7)	27 (51.9)	2 (3.8)
Abdominal pain	14 (28.6)	3 (6.1)	16 (30.8)	1 (1.9)	24 (46.2)	4 (7.7)
Constipation	12 (24.5)	0	18 (34.6)	0	19 (36.5)	1 (1.9)
Stomatitis	12 (24.5)	0	19 (36.5)	0	12 (23.1)	0
Abdominal distension	3 (6.1)	0	6 (11.5)	0	9 (17.3)	0
Ascites	2 (4.1)	1 (2.0)	6 (11.5)	3 (5.8)	8 (15.4)	3 (5.8)
Flatulence	2 (4.1)	0	0	0	6 (11.5)	0
Dyspepsia	7 (14.3)	0	2 (3.8)	0	1 (1.9)	0
Proctalgia	5 (10.2)	0	2 (3.8)	0	1 (1.9)	1 (1.9)
Toothache	0	0	6 (11.5)	0	1 (1.9)	0
General disorders and administration site conditions						
Fatigue	35 (71.4)	6 (12.2)	45 (86.5)	12 (23.1)	36 (69.2)	14 (26.9)
Edema peripheral	5 (10.2)	0	15 (28.8)	1 (1.9)	29 (55.8)	0
Temperature intolerance	21 (42.9)	0	13 (25.0)	0	18 (34.6)	0
Face edema	0	0	2 (3.8)	0	13 (25.0)	0
Pyrexia	11 (22.4)	0	9 (17.3)	0	10 (19.2)	1 (1.9)
Infusion-related reaction	5 (10.2)	2 (4.1)	7 (13.5)	1 (1.9)	3 (5.8)	0
Investigations						
Neutrophil count decreased	7 (14.3)	4 (8.2)	5 (9.6)	3 (5.8)	5 (9.6)	4 (7.7)
Platelet count decreased	3 (6.1)	0	8 (15.4)	3 (5.8)	4 (7.7)	0
Weight decreased	7 (14.3)	0	14 (26.9)	0	4 (7.7)	0
Aspartate aminotransferase increased	6 (12.2)	1 (2.0)	3 (5.8)	1 (1.9)	4 (7.7)	0
Blood alkaline phosphatase increased	6 (12.2)	1 (2.0)	5 (9.6)	0	2 (3.8)	0
Metabolism and nutrition disorders						
Anorexia	16 (32.7)	2 (4.1)	20 (38.5)	0	27 (51.9)	2 (3.8)
Hypokalemia	4 (8.2)	0	3 (5.8)	0	9 (17.3)	5 (9.6)
Hypoalbuminemia	3 (6.1)	0	4 (7.7)	2 (3.8)	7 (13.5)	0
Dehydration	3 (6.1)	0	6 (11.5)	1 (1.9)	7 (13.5)	2 (3.8)
Hypomagnesemia	3 (6.1)	0	2 (3.8)	0	6 (11.5)	0
Musculoskeletal and connective tissue disorders						
Back pain	7 (14.3)	1 (2.0)	8 (15.4)	0	7 (13.5)	0
Arthralgia	3 (6.1)	0	3 (5.8)	0	6 (11.5)	0
Pain in jaw	5 (10.2)	0	0	0	3 (5.8)	0
Pain in extremity	5 (10.2)	1 (2.0)	1 (1.9)	0	1 (1.9)	0

Continued

Table 3. *Continued*

Patient events[a], *n* (%)	mFOLFOX-6 (*N* = 49) *n* (%)		RAM+mFOLFOX-6 (*N* = 52) *n* (%)		ICR+mFOLFOX-6 (*N* = 52) *n* (%)	
Nervous system disorders						
Peripheral sensory neuropathy	27 (55.1)	3 (6.1)	25 (48.1)	4 (7.7)	32 (61.5)	0
Dysgeusia	5 (10.2)	0	6 (11.5)	0	17 (32.7)	0
Neuropathy peripheral	12 (24.5)	1 (2.0)	12 (23.1)	2 (3.8)	10 (19.2)	2 (3.8)
Headache	8 (16.3)	0	16 (30.8)	0	9 (17.3)	0
Dizziness	2 (4.1)	0	7 (13.5)	0	6 (11.5)	1 (1.9)
Dysesthesia	3 (6.1)	0	7 (13.5)	0	4 (7.7)	0
Psychiatric disorders						
Insomnia	7 (14.3)	0	7 (13.5)	0	10 (19.2)	1 (1.9)
Renal and urinary disorders						
Proteinuria	1 (2.0)	0	6 (11.5)	1 (1.9)	1 (1.9)	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	4 (8.2)	0	11 (21.2)	2 (3.8)	16 (30.8)	1 (1.9)
Cough	9 (18.4)	0	16 (30.8)	0	10 (19.2)	0
Oropharyngeal pain	1 (2.0)	0	2 (3.8)	0	6 (11.5)	0
Epistaxis	5 (10.2)	0	14 (26.9)	0	3 (5.8)	0
Skin and subcutaneous tissue disorders						
Rash	3 (6.1)	0	15 (28.8)	0	8 (15.4)	0
Periorbital edema	0	0	0	0	6 (11.5)	0
Palmar–plantar erythrodysesthesia syndrome	3 (6.1)	1 (2.0)	6 (11.5)	1 (1.9)	1 (1.9)	0
Alopecia	5 (10.2)	0	0	0	1 (1.9)	0
Vascular disorders						
Hypertension	1 (2.0)	1 (2.0)	15 (28.8)	7 (13.5)	5 (9.6)	1 (1.9)

AE, adverse event; ICR, icrucumab; mFOLFOX-6, oxaliplatin + folinic acid + 5-fluorouracil; NA, not applicable; SAE, serious adverse event; RAM, ramucirumab; TEAE, treatment-emergent adverse event.

[a]Patients could be counted in more than one category.

[b]Two deaths (1 each on the RAM+mFOLFOX-6 and ICR+mFOLFOX-6 arms) were reported as being due to adverse event of 'neoplasm progression' (i.e. disease progression).

[c]Adverse events that were considered possibly, probably, or definitely related to study drug, as judged by the investigator.

[d]Adverse events summarized by system organ class (bold text) and preferred term per MedDRA (version 12.0).

[e]Consolidated term including neutropenia and febrile neutropenia. Febrile neutropenia was reported in only 2 patients (1 each on the mFOLFOX-6 and RAM+mFOLFOX-6 arms, both grade 3).

recent global phase III RAISE trial showing a significant survival benefit for ramucirumab combined with FOLFIRI in mCRC [8] have stimulated further studies of ramucirumab in mCRC.

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The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy†

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Background: Cancer may cause financial difficulties, but its impact in countries with public health systems is unknown. We evaluated the association of financial difficulties with clinical outcomes of cancer patients enrolled in academic clinical trials performed within the Italian public health system.

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