Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online March 27, 2014

DOI: 10.1634/theoncologist.2014-0028

Title: An Open-Label Phase II Study Evaluating the Safety and Efficacy of Ramucirumab Combined With mFOLFOX-6 as First-Line Therapy for Metastatic Colorectal Cancer

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ClinicalTrials.gov Identifier: NCT00862784

Sponsor(s): Eli Lilly and Company

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IRB Approved: Yes

Disclosures

Fernando Rivera: Roche, Amgen, Celgene, Sanofi, Bayer (C/A); Roche, Amgen, Sanofi, Imclon, Bayer (RF); **Malcolm J. Moore:** Imclone (RF); **Timothy R. Asmis:** Sanofi, Lilly (C/A, RF); **Jonathan D. Schwartz:** Imclon/Lilly (E, OI); **Federico Nasroulah:** Eli Lilly and Company (E); **Shaila Ballal:** ImClone, Lilly (E, OI); **Josep Tabernero:** Lilly, Imclone (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) are believed to mediate angiogenesis in colorectal cancer (CRC). Ramucirumab (RAM; IMC-1121B) is a human IgG1 monoclonal antibody that inhibits VEGF ligand binding to VEGFR-2, inhibiting VEGFR-2 activation and signaling.

Methods

Patients with metastatic CRC, Eastern Cooperative Oncology Group performance status 0–1, and adequate organ function who had not received chemotherapy for metastatic disease received RAM and the modified FOLFOX-6 regimen every 2 weeks. Endpoints included progression-free survival (PFS), objective response rate, overall survival, and safety. The sample size was based on a potentially improved median PFS from 8 months to 11 months.

Results

Forty-eight patients received therapy. Median PFS was 11.5 months (95% confidence interval [CI]: 8.6–13.1 months). The objective response rate was 58.3% (95% CI: 43.21–72.39). The disease control rate (complete or partial response plus stable disease) was 93.8% (95% CI: 82.8–98.7). Median overall survival was 20.4 months (95% CI: 18.5–25.1 months). The most frequent grade 3–4 adverse events included neutropenia (grade 3: 33.3%; grade 4: 8.3%), hypertension (grade 3: 16.7%), and neuropathy (grade 3: 12.5%). Two patients died during the study due to myocardial infarction and cardiopulmonary arrest.

Conclusion

RAM may enhance the efficacy of modified FOLFOX-6 chemotherapy with an acceptable safety profile in metastatic CRC.

Discussion

The combination of ramucirumab (RAM) and the modified FOLFOX-6 regimen (mFOLFOX-6) appears efficacious in the first-line treatment of patients with metastatic colorectal cancer (mCRC). The median progression-free survival (PFS) of 11.5 months (Fig. 1), an objective response rate of 58.3%, a disease control rate of 93.8% (stable disease defined as neither shrinkage sufficient to qualify for partial response nor increase sufficient to qualify for progressive disease, taking as a reference the smallest sum longest diameter since the start of treatment), and median overall survival (OS) of 20.4 months are encouraging and suggest that RAM may enhance the efficacy of mFOLFOX-6 in mCRC. Figure 2 shows that the majority of the study population experienced some tumor burden reduction, including patients with liver-only disease and those with more extensive patterns of metastases. Although many patients discontinued oxaliplatin after 5–8 months of therapy, 23% continued to receive RAM and 5-fluorouracil with ongoing disease control for more than 5 months after discontinuation of oxaliplatin. The median OS was 20.4 months.

The incidence of most adverse events in patients receiving RAM and mFOLFOX-6 was consistent with the known adverse event profile of mFOLFOX-6 in mCRC [1–6]. Hypertension (including 16.7% at grade 3 and no grade 4) and proteinuria (12.5% at grade 2 and one grade 4 nephrotic syndrome) were observed. Two patients experienced grade 5 potential arterial thromboembolic events (myocardial infarction and cardiopulmonary arrest), and three patients had grade 3–4 venous thromboembolic events (pulmonary embolism, deep vein thrombosis, jugular vein thrombosis).

Exploratory pharmacokinetic, pharmacodynamic, and correlative analyses were conducted in samples collected from nine patients. Mean trough levels after repeated dosing of 8 mg/kg of RAM every 2 weeks exceeded concentrations associated with antitumor activity in preclinical models. Higher baseline levels of soluble Flt-1 (soluble VEGFR-1) and VEGF-A and lower baseline levels of VEGF-D appeared to be associated with longer PFS and OS. Because this was a single-arm trial, no conclusions can be drawn regarding whether these potential associations are prognostic or predictive. Conclusions are also limited by the sample size and should be considered hypothesis generating.

In conclusion, RAM may enhance the efficacy of mFOLFOX-6 in mCRC. The overall adverse event profile of the combination appears to be largely consistent with the toxicity profile of the constituent chemotherapeutic agents and the known safety profile of RAM to date. However, the modest sample size and the single-arm design of the study preclude definitive assessment regarding these conclusions.

Trial Information

Disease:	Colorectal cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Single Arm
Primary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Response Rate
Secondary Endpoint:	Overall Survival
Secondary Endpoint:	Correlative Endpoint
Additional Details of Endpoints or Study Design:	Additional secondary endpoints: Safety, duration of response, pharmacokinetics, immunogenicity
Investigator's Analysis:	Active and should be pursued further.

Drug Information

Drug 1: **Generic/Working name:**	Ramucirumab
Company name:	Eli Lilly and Company
Drug type:	Antibody
Drug class:	VEGFR
Dose:	8 mg (mg) per kilogram (kg)
Route:	IV
Schedule of Administration:	Ramucirumab + mFOLFOX-6 every 2 weeks Ramucirumab 8 mg/kg iv Oxaliplatin 85 mg/m^2 iv d1 Folinic acid 400 mg/m^2 iv d1 (2 hour infusion) 5-Fluorouracil 400 mg/m^2 iv d1 (2-4 minutes bolus infusion) 5-Fluorouracil 2,400 mg/m^2 iv 46 h immediately following bolus d1 and d2

Patient Characteristics

Number of patients, male:	25
Number of patients, female:	23
Stage:	Not Collected
Age:	Median (range): 60.5 (28–81)
Number of prior systemic therapies:	Median (range): Not Collected
Performance Status:	ECOG 0 — 30 1 — 18 2 — 3 — unknown —
Other:	Not Collected

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients enrolled:	48
Number of patients evaluable for toxicity:	48
Number of patients evaluated for efficacy:	48
Evaluation method:	RECIST 1.0
Response assessment CR:	2.1%
Response assessment PR:	56.3%
Response assessment SD:	35.4%
Response assessment PD:	2.1%
Response assessment other:	4.2%
(Median) duration assessments PFS	11.5 months, CI: 8.6–13.1
(Median) duration assessments OS	20.4 months, CI: 18.5–25.1
(Median) duration assessments response duration	11.0 months

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not collected
Investigator's Assessment:	Active and should be pursued further

Discussion

Colorectal cancer is the third most common cancer worldwide [7]. Approximately 25% of patients with CRC have metastatic disease at the time of diagnosis; metastases may develop in up to 50% of patients with less advanced disease following potentially curative resection [8]. FOLFOX regimens (a combination of oxaliplatin, 5-fluorouracil, and leucovorin) are one of the standards of care in mCRC and are frequently utilized in first-line treatment with or without the addition of the anti-VEGF-A antibody bevacizumab. Median PFS for first-line FOLFOX is approximately 8 months, as recently reported in phase III evaluations [9, 10]. We hypothesized that the addition of RAM to mFOLFOX-6 would prolong PFS and other efficacy parameters when administered as a first-line regimen in patients with mCRC.

In this open-label, multicenter, multinational phase II trial, previously untreated patients with mCRC received RAM once every 2 weeks in combination with mFOLFOX-6. The primary objective was to evaluate PFS; secondary objectives included evaluation of objective response rate; OS; duration of response; safety; and pharmacokinetic, pharmacodynamic, and immunogenicity profiles of RAM. The sample size was based upon the assumption of uniform accrual over an 8-month period, with a follow-up of 20 months, no loss to follow-up, and a negative exponential distribution for the time to events. A sample size of 45 patients allowed differentiation of an expected increase in median PFS from 8 months (historical control; mFOLFOX-6) to 11 months with the addition of RAM.

All patients had metastatic disease. The liver was the most common site of metastasis (79.2%); 13 patients (27.1%) had liver-only metastases. The majority of patients (68.8%) had undergone previous surgery for colorectal cancer. At the time of enrollment, 45.8% of patients had a medical history of hypertension (Table 1).

The median PFS was 11.5 months (95% confidence interval [CI]: 8.6–13.1) (Fig. 1). The objective response rate was 58.3% (95% CI: 43.21–72.39) (Table 2). The duration of response was measured from the time measurement criteria were first met for complete response or partial response (whichever was first recorded) until the first date that the criteria for progressive disease were met, initiation of other or additional antitumor therapy was first reported, or death was objectively documented. Median duration of response was 11.0 months (95% CI: 6.9–12.6), and the median OS was 20.4 months (95% CI: 18.5–25.1) (Fig. 3).

Although many patients discontinued oxaliplatin treatment after the initial 5–8 months of therapy, a substantial subset continued to receive RAM and 5-fluorouracil with ongoing disease control, including 11 patients (22.9% of the overall population) who received this combination for 5 months or longer before discontinuing therapy due to disease progression or adverse events.

The adverse event profile was largely consistent with what has been reported for FOLFOX and an antiangiogenic antibody targeting VEGF [3, 5, 11]. All 48 patients (100%) experienced at least one treatment-emergent adverse event (TEAE), and 45 patients (93.8%) experienced a TEAE related to RAM. The most common ($\geq$5%) grade 3 TEAE related to RAM was hypertension ($n = 7$, 14.6%). No grade 4 hypertension was reported. Other potential RAM-related TEAEs were grade 2 proteinuria (12.5%), with one case of grade 4 nephrotic syndrome, and eight epistaxis events (14.6% grade 1, 2.1% grade 2). Nine patients (18.8%) experienced infusion-related hypersensitivity reactions either during or immediately following the initial RAM infusions (all grade 1–2); eight of these nine patients were able to receive subsequent RAM without symptom recurrence with the use of premedication and/or reduced infusion rate. No grade 3 or higher infusion-related reactions were reported (Table 3).

Two patients died within 30 days of receiving a dose of the study treatment. One died due to an acute myocardial infarction after 111 days on the study, and the other had a cardiorespiratory arrest after 3 days on the study treatment. Both events were considered by the investigators as possibly related to RAM, whereas the death due to acute myocardial infarction was also considered possibly related to mFOLFOX-6 chemotherapy. Cardiotoxicity has been associated with fluoropyrimidine-containing regimens [12, 13]. Three patients had grade 3–4 venous thromboembolic events, including one patient who had grade 3 pulmonary embolism and deep vein thrombosis, one who had grade 4 pulmonary embolism, and one who had grade

3 jugular vein thrombosis in proximity to a central venous access catheter. Hematologic adverse events reported in ≥10% of patients are listed in Table 4.

Thirty-eight patients (79.2%) received systemic anticancer treatment after study discontinuation. The most frequently used medication was irinotecan-based therapy (66.7%); 33% of patients received subsequent bevacizumab; EGFR inhibitors (cetuximab or panitumumab) were administered to 29.2% of patients (Table 5). Two patients who did not receive systemic anticancer treatment received radiotherapy and surgery, respectively.

Pharmacokinetic, pharmacodynamic, and correlative analyses were conducted on an exploratory basis in samples collected from a subset of nine patients. Mean trough levels after repeated dosing of 8 mg/kg of RAM every 2 weeks exceeded the target concentrations associated with antitumor activity in preclinical models. Higher baseline levels of soluble Flt-1 (soluble VEGFR-1) and VEGF-A and lower baseline levels of VEGF-D appeared to be associated with longer PFS and OS. Given that this was a single-arm trial, no conclusions can be made regarding whether these potential associations may be prognostic or predictive. Conclusions are also limited by the small sample size and should be considered hypothesis generating only.

In conclusion, first-line RAM with mFOLFOX-6 was associated with a median PFS of 11.5 months in patients with mCRC. The study met the primary objective of an increase in median PFS to 11 months or longer (relative to a historical median of 8 months with FOLFOX). Secondary objectives of objective response rate (58.3%), disease control rate (93.8%), and median OS (20.4 months) suggest that RAM may enhance the efficacy of mFOLFOX-6 in mCRC. These results support ongoing randomized phase II and III investigations with RAM in mCRC. A randomized global phase III trial is under way, evaluating RAM in combination with the FOLFIRI regimen following disease progression on first-line oxaliplatin and bevacizumab therapy [14].

Acknowledgments

We thank Ashwini Dhume and Anastasia Perkowski of ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, for their medical writing and editorial assistance with the manuscript.

References

1. McLeod HL, Sargent DJ, Marsh S et al. Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: Results from North American Gastrointestinal Intergroup Trial N9741. J Clin Oncol 2010;28:3227–3233.
2. Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004;22:229–237.
3. Hochster HS, Hart LL, Ramanathan RK et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the TREE study. J Clin Oncol 2008;26:3523–3529.
4. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25: 1539–1544.
5. Cassidy J, Clarke S, Díaz-Rubio E et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011;105:58–64.
6. Saltz LB, Clarke S, Díaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 2008;26:2013–2019.
7. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–2917.
8. Schmoll HJ, Van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23:2479–2516.
9. Hecht JR, Trarbach T, Hainsworth JD et al. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol 2011;29:1997–2003.
10. Saltz L, Clarke S, Diaz-Rubio E et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/ NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. J Clin Oncol 2007;25(suppl):4028a.
11. Takahari D, Yamada Y, Matsumoto H et al. A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/l-LV/oxaliplatin (mFOLFOX6) plus bevacizumab in patients with metastatic colorectal cancer: The SOFT study. J Clin Oncol 2013;31(suppl):3519a.
12. Wacker A, Lersch C, Scherpinski U et al. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. Oncology 2003;65:108–112.
13. Keefe DL, Roistacher N, Pierri MK. Clinical cardiotoxicity of 5-fluorouracil. J Clin Pharmacol 1993;33:1060–1070.
14. A study in second line metastatic colorectal cancer. Available at http://clinicaltrials.gov/ct2/show/NCT01183780?term=NCT01183780&rank=1. Accessed September 20, 2013.

Figures and Tables

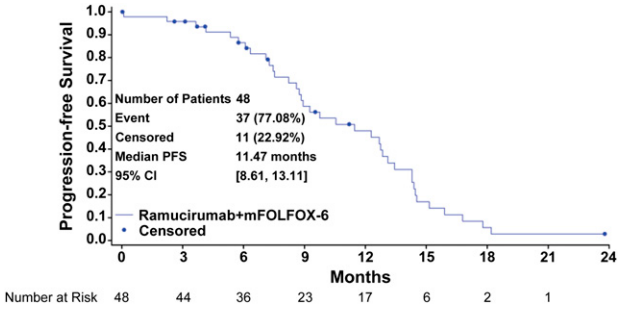

Figure 1. Progression-free survival curve: Kaplan-Meier plot for progression-free survival for all patients.
Abbreviations: CI, confidence interval; mFOLFOX-6, modified FOLFOX-6 regimen; PFS, progression-free survival.

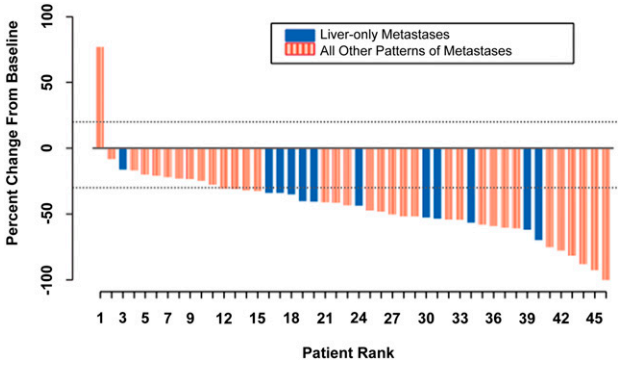

Figure 2. Waterfall plot of best percentage change from baseline in size of target tumor lesions. Best change in target-lesion size is maximum reduction from baseline or minimum increase in absence of reduction.

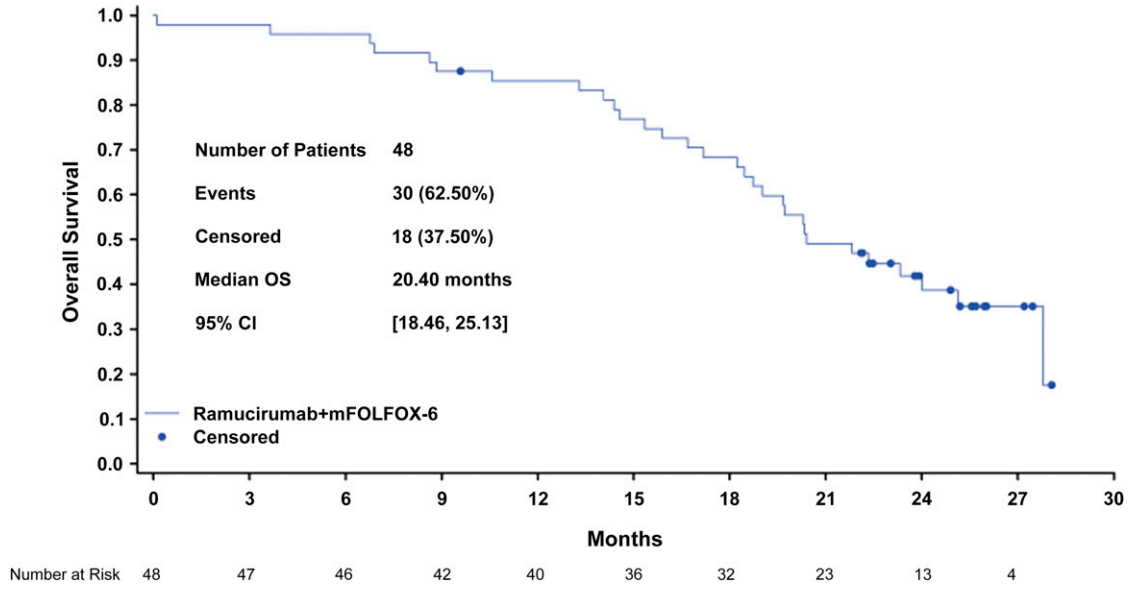

Figure 3. Overall survival curve: Kaplan-Meier plot for overall survival for all patients.
Abbreviations: CI, confidence interval; mFOLFOX-6, modified FOLFOX-6 regimen; OS, overall survival.

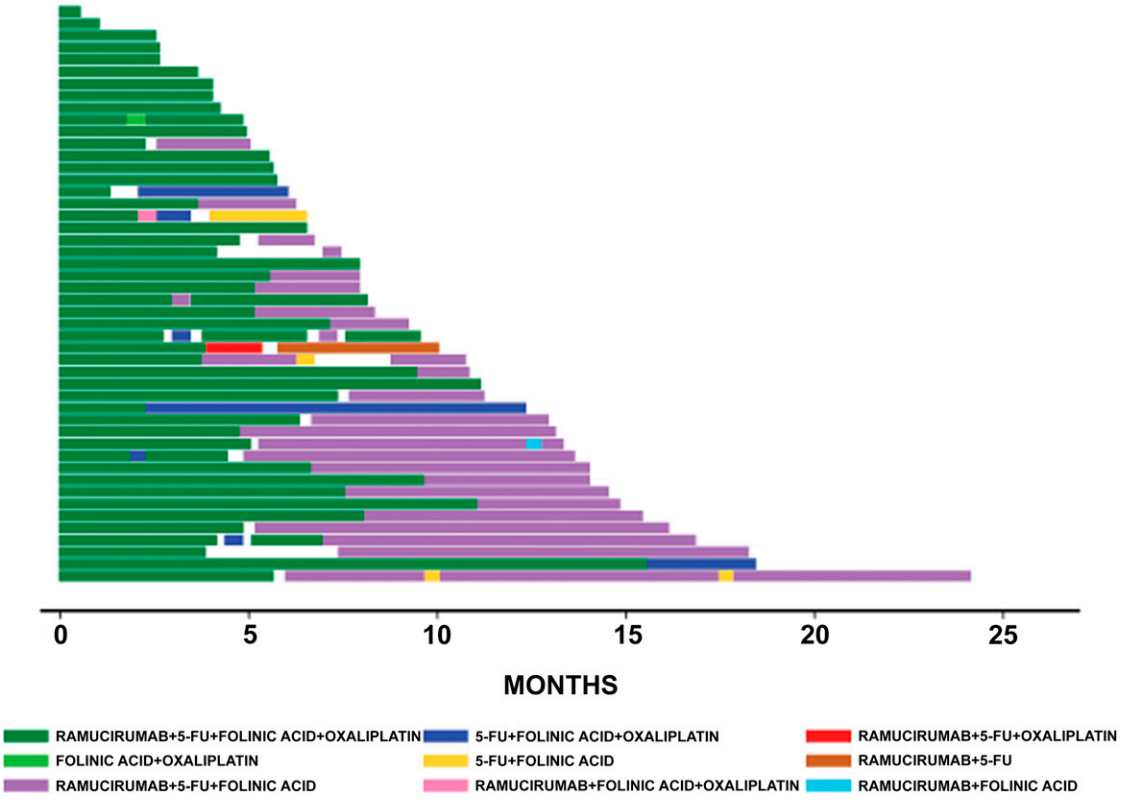

Figure 4. Treatment exposure.
Abbreviation: 5-FU, 5-fluorouracil.

Table 1. Baseline patient characteristics

Characteristic	*n*		%
Number of patients			
Enrolled	48		
Treated, ITT population	48		100.0
On study therapy as of August 2011	0		
Off study therapy as of August 2011	48		100.0
Gender			
Male	25		52.1
Female	23		47.9
Age (years)			
18 to $<$65	31		64.6
$\geq$65	17		35.4
Median age (range)		60.5 (28–81)	
ECOG PS			
0	30		62.5
1	18		37.5
Type of cancer			
Colon	32		66.7
Colorectal	7		14.6
Rectal	9		18.8
Metastases			
Patients with metastases	48		100.0
Patients with liver-only metastases	13		27.1
Patients with lung-only metastases	1		2.1
Site of metastatic disease ($>$5%)			
Liver	38		79.2
Lung	17		35.4
Lymph nodes (abdomen)	14		29.2
Peritoneal	11		22.9
Lymph nodes (thoracic)	9		18.8
Gastrointestinal tract	3		6.3
Other[a]	7		14.6
Number of metastatic sites (involved organs)			
1	17		35.4
$\geq$2	31		64.6
Previous surgery			
Yes	33		68.8
No	15		31.3
Prior adjuvant therapy			
Chemotherapy	5		10.4
Radiotherapy	2		4.2
Comorbidities			
Patients with prior hypertension	22		45.8

All percentages may not add up to 100% due to rounding.
[a]Other sites of metastatic disease included soft tissue, spleen, pleura, lymph nodes (cervical and other), and pelvis.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat.

Table 2. Best overall response, disease control rate, objective response rate, and progression-free survival

	Ramucirumab + mFOLFOX-6 (N = 48)	
Result	***n***	**%**
Best overall response		
CR	1	2.1
PR	27	56.3
SD	17	35.4
PD	1	2.1
Not evaluable	2	4.2
Disease control rate (CR + PR + SD)	45	93.8
95% CI	(82.8–98.7)	
Objective response rate (CR + PR)	28	58.3
95% CI	(43.2–72.4)	
Progression-free survival		
Median, months (95% CI)	11.5 (8.6–13.1)	
1-year rate, % (95% CI)	48.0 (31.9–62.5)	

Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Incidence and severity of treatment-emergent adverse events (reported in at least 10% of patients)

	Ramucirumab + mFOLFOX-6 (N = 48)		
Preferred term	**All grades, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
Fatigue	38 (79.2)	6 (12.5)	0
Asthenia	35 (72.9)	6 (12.5)	0
Fatigue	4 (8.3)	0	0
Neuropathy	31 (64.6)	6 (12.5)	0
Dysesthesia	23 (47.9)	4 (8.3)	0
Paresthesia	7 (14.6)	1 (2.1)	0
Peripheral neuropathy	5 (10.4)	1 (2.1)	0
Peripheral sensory neuropathy	5 (10.4)	0	0
Hypoesthesia	3 (6.3)	0	0
Abdominal pain	16 (33.3)	0	0
Abdominal pain	14 (29.2)	0	0
Abdominal pain upper	2 (4.2)	0	0

Grade 5 events were progressive disease, acute myocardial infarction, and cardiorespiratory arrest, each reported in one treated patient (detailed below). Fatigue, neuropathy, and abdominal pain are presented as consolidated adverse events terms in addition to the specific MedDRA terms based on investigator reporting; both consolidated and MedDRA terms are indicated.

Table 4. Incidence and severity of hematologic adverse events (reported in at least 10% of patients)

	Ramucirumab + mFOLFOX-6 (N = 48)				
Preferred term	**All grades, *n* (%)**	**Grade 1, *n* (%)**	**Grade 2, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, N (%)**
Neutropenia	27 (56.3)	1 (2.1)	6 (12.5)	16 (33.3)	4 (8.3)
Thrombocytopenia	17 (35.4)	6 (12.5)	10 (20.8)	1 (2.1)	0
Anemia	8 (16.7)	5 (10.4)	1 (2.1)	2 (4.2)	0
Leukopenia	8 (16.7)	1 (2.1)	6 (12.5)	1 (2.1)	0

Note: One patient (2.1%) experienced a grade 4 febrile neutropenia.

Table 5. Summary of poststudy anticancer systemic therapy: all treated patients

	Ramucirumab + mFOLFOX-6 (N = 48)	
Poststudy therapy	***n***	**%**
Any treatment[a]	38	79.2
Irinotecan-based therapy	32	66.7
Bevacizumab	16	33.3
EGFR inhibitors[b]	14	29.2
Other agents[c]	10	20.8
Oxaliplatin-based therapy	5	10.4
Fluoropyrimidines without subsequent irinotecan/oxaliplatin (5-fluorouracil, capecitabine, UFT)	3	6.3

[a]Excludes two patients who received only radiotherapy and surgery.
[b]Cetuximab and panitumumab.
[c]Raltitrexed, mitomycin, investigational drugs.