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ORIGINAL REPORT

SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose
SIRFLOX was a randomized, multicenter trial designed to assess the efficacy and safety of adding selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy in patients with previously untreated metastatic colorectal cancer.

Patients and Methods
Chemotherapy-naïve patients with liver metastases plus or minus limited extrahepatic metastases were randomly assigned to receive either modified FOLFOX (mFOLFOX6; control) or mFOLFOX6 plus SIRT (SIRT) plus or minus bevacizumab. The primary end point was progression-free survival (PFS) at any site as assessed by independent centralized radiology review blinded to study arm.

Results
Between October 2006 and April 2013, 530 patients were randomly assigned to treatment (control, 263; SIRT, 267). Median PFS at any site was 10.2 *v* 10.7 months in control versus SIRT (hazard ratio, 0.93; 95% CI, 0.77 to 1.12; $P = .43$). Median PFS in the liver by competing risk analysis was 12.6 *v* 20.5 months in control versus SIRT (hazard ratio, 0.69; 95% CI, 0.55 to 0.90; $P = .002$). Objective response rates (ORRs) at any site were similar (68.1% *v* 76.4% in control *v* SIRT; $P = .113$). ORR in the liver was improved with the addition of SIRT (68.8% *v* 78.7% in control *v* SIRT; $P = .042$). Grade ≥ 3 adverse events, including recognized SIRT-related effects, were reported in 73.4% and 85.4% of patients in control versus SIRT.

Conclusion
The addition of SIRT to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver-only metastatic colorectal cancer did not improve PFS at any site but significantly delayed disease progression in the liver. The safety profile was as expected and was consistent with previous studies.

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INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in males and the second most frequent in females, with an estimated 1.4 million cases and 693,900 deaths occurring in 2012.[1] The liver is the dominant site of metastatic disease in CRC, and an increasingly aggressive surgical approach to this patient population is leading to more long-term survivors. However, 80% to 90% of patients with liver metastases are not amenable to surgery at diagnosis,[2-5] and liver metastases remain the dominant cause of death for patients with CRC.[6-9]

Many liver-directed therapies have been developed to control liver metastases or primary liver cancer, but no large phase III trials have been undertaken to fully assess the clinical usefulness of such therapies. Selective internal radiation

therapy (SIRT), also known as radioembolization (SIR-Spheres®, Sirtex Medical Limited, Sydney, Australia),[10] delivers a single, measured, targeted radiation dose to liver tumors via injection into the hepatic artery. Yttrium-90 (^{90}Y)–labeled resin microspheres have a median diameter of 32.5 μm, considerably smaller than the particles of other liver-directed therapies such as transarterial chemoembolization, which enables the microspheres to lodge distally within the microvascular plexus of tumors.[11] Indeed, several authors have described SIRT as a form of liver-directed brachytherapy.[10,12,13]

Previous small studies have demonstrated that combining SIRT with first-line fluoropyrimidine-based chemotherapy increased objective response rates (ORRs) and extended time to progression and overall survival (OS) in patients with metastatic CRC (mCRC).[14] A phase I study demonstrated that SIRT could be added safely to oxaliplatin-based chemotherapy, with promising outcome data.[15] Given these data, the SIRFLOX study, a large randomized controlled trial of fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy with or without ^{90}Y-labeled resin microspheres as first-line treatment of patients with liver-only or liver-dominant mCRC, was undertaken.[16]

PATIENTS AND METHODS

The SIRFLOX study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the relevant institutional review boards for each participating center. The study protocol has been described previously.[16]

Patients

Patients 18 years or older with histologically confirmed adenocarcinoma of the colon or rectum (with or without the primary tumor in situ) with proven liver metastases were enrolled. Patients had to be chemotherapy naïve for mCRC (previous adjuvant systemic chemotherapy for primary CRC or neoadjuvant chemoradiotherapy to the pelvis completed > 6 months before recruitment was permitted), have a WHO performance status of 0 to 1, and have a life expectancy of ≥ 3 months. Patient inclusion and exclusion criteria are described in Appendix Table A1 (online only).

Study Design and Interventions

SIRFLOX was a randomized, multicenter trial of systemic chemotherapy with modified FOLFOX (mFOLFOX6) plus or minus SIRT as first-line treatment of patients with nonresectable liver-only or liver-dominant mCRC. Liver-dominant mCRC was defined as the presence of liver metastases and limited lung (fewer than five nodules of ≤ 1 cm diameter or a single nodule of ≤ 1.7 cm diameter), and/or lymph node involvement (a single anatomic area of < 2 cm diameter). Bevacizumab was allowed, combined with mFOLFOX6, at the investigator's discretion (Fig 1A).[16] The treatment schedules are described in Figure 1B.

Predefined stratification parameters included liver-only versus liver plus extrahepatic metastases (the aim was for at least 60% of recruited patients to have liver-only metastases), the extent of tumor involvement of the liver (classified as ≤ 25% or > 25% determined objectively on baseline computed tomography scan), intent to use bevacizumab with chemotherapy, and investigational center.[16] All patients were monitored until death or for a maximum of 5 years.

Outcome Measures

The primary study end point was progression-free survival (PFS) at any site as assessed by independent centralized imaging review blinded to study arm. Secondary end points included PFS in the liver; tumor response rate in the liver; tumor response rate at any site; liver resection rate; hepatic and extrahepatic recurrence rate; health-related quality of life (analysis ongoing, not reported in this publication); toxicity and safety (adverse events [AEs] graded according to National Cancer Institute Common Toxicity Criteria version 3.0; serious AEs defined as any event resulting in death, that is life-threatening, resulting in congenital anomaly, requiring or prolonging inpatient hospitalization, resulting in persistent or significant disability; or another medically important event); and OS, to be evaluated as a preplanned combined analysis of data from SIRFLOX and two other studies, FOXFIRE[17] and FOXFIRE Global (clinicaltrials.gov identifier: NCT01721954).

The screening assessment was conducted ≤ 28 days before random assignment. Patients were assessed subsequently on day 1, day 3 or 4, and every 2 weeks (plus or minus 1 week) during each chemotherapy cycle, and every 12 weeks after progression.[16] Follow-up assessments included clinical assessment and physical examination, review of performance status, hematologic and biochemical assessments, serum carcinoembryonic antigen measurement, contrast-enhanced computed tomography of chest/abdomen/pelvis, assessment of suitability for liver resection, assessment of concurrent medications, and health-related quality of life assessment.

Independent Blinded Evaluation of Radiologic Imaging

The imaging response evaluation used response evaluation criteria in solid tumors (RECIST) version 1.0[18] modified a priori as follows: (1) The documentation of tumor progression required an increase in the sum of the longest diameters of ≥ 20% and an absolute increase in the sum of the longest diameters of ≥ 5 mm, or the appearance of a new lesion (analogous to the criteria from RECIST version 1.1).[19] (2) Lymph nodes were assessed per RECIST version 1.1 (ie, a lymph node qualified as a potential target lesion when its short axis diameter was ≥ 15 mm at baseline).

All radiologic images were assessed in two separate and independent reading sessions by radiologists blinded to the study arm. In the event of discordance, a third independent radiologist adjudicated the image assessment to determine the final outcome.

The assessment of the pattern of progression included the site of progression; whether it was intra- or extrahepatic; and whether this occurred as a result of the growth of existing lesions, the appearance of new lesions, or both.

Statistical Methods

Using previously reported data on PFS with FOLFOX plus bevacizumab[20] and on SIRT added to first-line fluoropyrimidine-based chemotherapy,[14,21] a sample size of at least 450 patients for the SIRFLOX study was estimated to be needed to detect an increase in the median PFS at any site from 9.4 months to 12.5 months with 80% power and 95% confidence. Taking into account the number of patients who might receive the alternative treatment or lack imaging data, the sample size was increased to 530.

All efficacy measures were assessed in the intent-to-treat (ITT) population. Response rates were compared between treatment arms using a test of proportions, and time-to-event end points were compared using the log-rank test. A predefined competing risk analysis[22] was used to assess PFS in the liver, to account for the competing risk of death or progression outside the liver. For unplanned exploratory analyses, $P < .01$ was used to define statistical significance.

RESULTS

Between October 2006 and April 2013, patients were recruited from 87 centers in Australia, Europe, Israel, New Zealand, and the United States. Of the 530 patients randomly assigned to treatment (ITT population), 263 were assigned to control and 267 were assigned to SIRT (Fig 2). There were no statistically significant differences between treatment arms in any characteristic at baseline (Table 1).

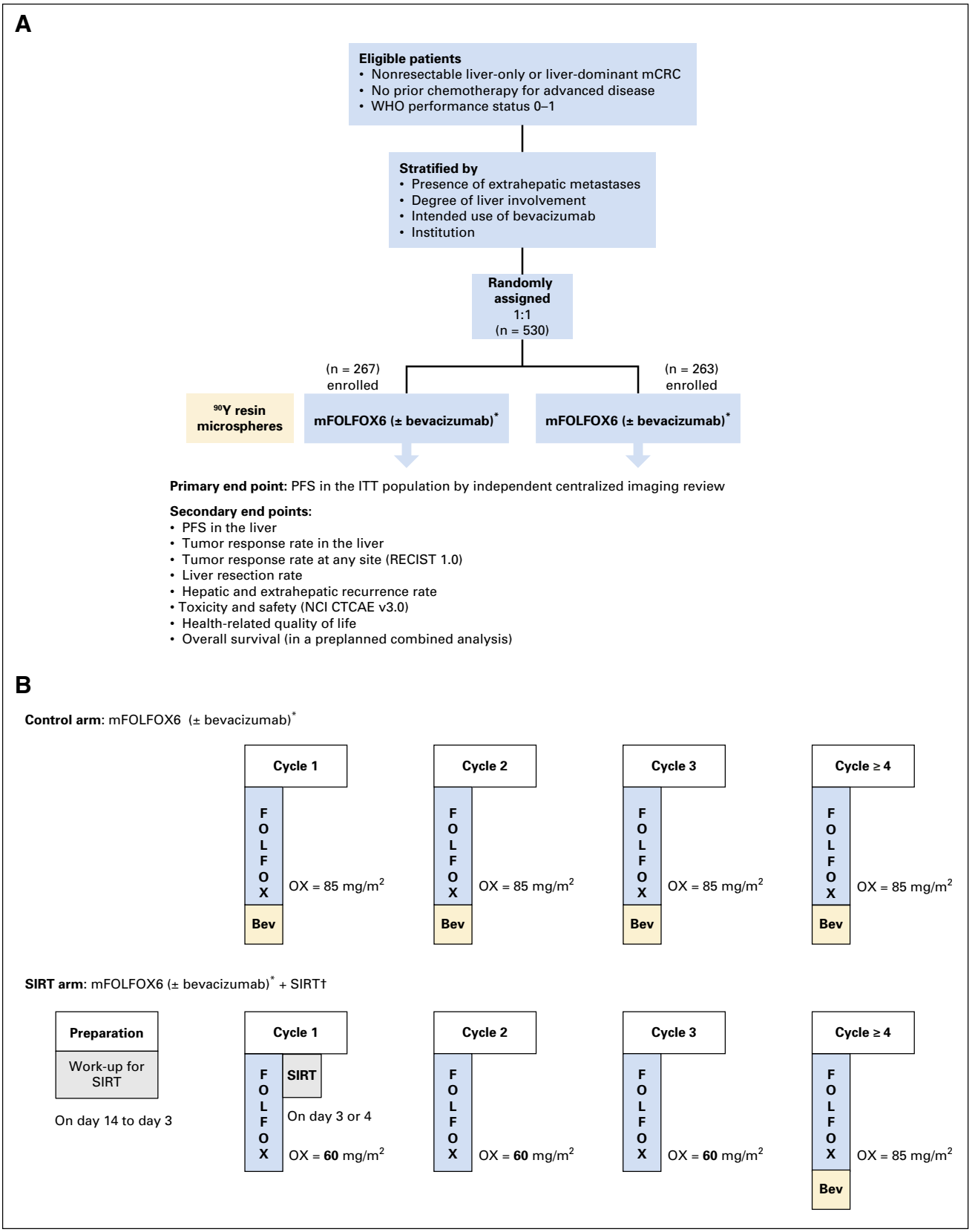

Fig 1. (A) Study design and end points. (B) Treatment schedules. *Bevacizumab allowed at investigator's discretion, per institutional practice; †Work-up procedure at day 14 to day 3 before SIRT; SIR-Spheres ^{90}Y resin microspheres administered on either day 3 or day 4, of either cycle 1 or cycle 2. Bev, bevacizumab; ITT, intent to treat; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; mCRC, metastatic colorectal cancer; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; NCI-CTCv3, National Cancer Institute Common Toxicity Criteria version 3; OX, oxaliplatin; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; SIRT, selective internal radiation therapy; ^{90}Y, yttrium-90.

Treatment

The median (interquartile range [IQR]) number of cycles of fluorouracil administered was 12.0 (9.0) and 12.0 (9.0) in control and SIRT, respectively, and the median (IQR) number of cycles of oxaliplatin administered was 10.0 (4.0) and 10.0 (5.0) in control and SIRT, respectively. The median (IQR) number of cycles of bevacizumab administered was 13.0 (11.0) and 8.0 (8.0) in the 144 of 263 patients (54.8%) and 125 of 267 patients (46.8%) planned for bevacizumab treatment at study entry in control and SIRT, respectively, with bevacizumab administration in SIRT not to commence before cycle 4.

In SIRT, ^{90}Y resin microspheres were implanted a median of 20 days after random assignment (range, 8 to 76 days), and the median implanted activity was 1.4 (range 0.4 to 3.1) GBq. Of the 21 patients in the SIRT arm who did not receive SIRT, 18 of 267 (7%) were not able to receive SIRT and three of 267 (1%) did not receive any study treatment as a consequence of compromised performance status, serious AEs, or disease progression before study treatment (Fig 2). Of the 246 patients who received SIRT, both liver lobes were treated in 227 patients (92.3%) and a single lobe was treated in 19 (7.7%). Of the 11 control patients (4.2%) who did not receive any study treatment, 10 withdrew consent after randomization.

Efficacy

PFS at any site and PFS in the liver. Median PFS at any site was similar for control and SIRT (10.2 versus 10.7 months, respectively; hazard ratio [HR], 0.93; 95% CI, 0.77 to 1.12; $P = .43$; Fig 3 and Appendix Fig A1, online only). By competing risk analysis, the addition of SIRT improved median PFS in the liver from 12.6 (control) to 20.5 months (SIRT; HR, 0.69; 95% CI, 0.55 to 0.90; $P = .002$; Fig 4). This finding was consistent irrespective of tumor burden, bevacizumab therapy, or performance status (Appendix Fig A1).

Site of first disease progression. The numbers of patients with disease progression as their first study event in control and SIRT were 178 and 166, respectively (Table 2). First progression only in the liver occurred in a higher proportion of control versus SIRT patients (77% versus 52.4%; $P < .001$). There was a corresponding increase in first progression occurring outside the liver, particularly in the lung, for SIRT patients ($P < .001$), but there was no significant difference in timing of lung progression compared with control patients (median time to lung-only progression events, 8.9 *v* 12.5 months; $P = .049$ exploratory analysis). A higher proportion of first progression events occurred in existing lesions within the liver (plus or minus other sites) in control versus SIRT patients ($P < .001$; Appendix Table A2, online only).

ORR. The ORR at any site according to RECIST version 1.0 was not significantly different between control and SIRT (68.1% *v* 76.4%; $P = .113$). In the liver, the ORR (68.8% *v* 78.7%; $P = .042$) and the complete response rate (1.9% *v* 6.0%; $P = .020$) were significantly improved with the addition of SIRT (Appendix Table A3, online only).

There was no significant difference between study arms in the rate of liver resection, with 36 patients (13.7%) undergoing liver resection in control compared with 38 patients (14.2%) in SIRT

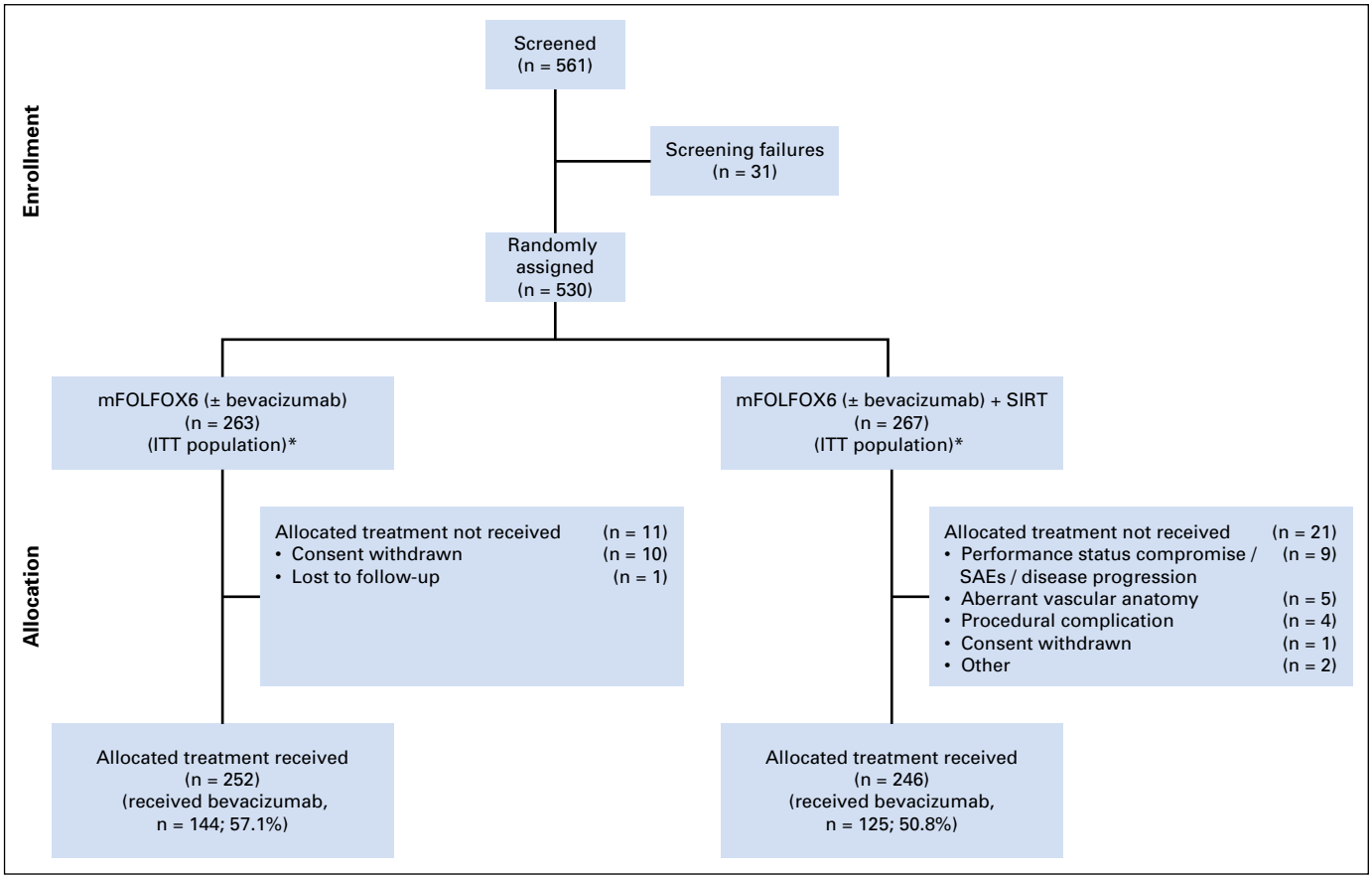

Fig 2. Patient disposition. *Included in primary outcome analysis. ITT, intent to treat; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SAE, serious adverse event; SIRT, selective internal radiation therapy.

Table 1. Baseline Patient and Disease Characteristics (ITT Population)

Variable	Control Arm (mFOLFOX6 [± bev]) n = 263	Treatment Arm (SIRT + mFOLFOX6 [± bev]) n = 267
Age, years, median (range)	63 (23-89)	63 (28-81)
Sex		
Male	174 (66.2)*	182 (68.2)
Female	88 (33.5)	85 (31.8)
Race		
White	243 (92.4)	248 (92.9)
Black	8 (3.0)	2 (0.7)
Other	7 (2.7)	11 (4.1)
Unknown	5 (1.9)	6 (2.2)
WHO performance status		
0	175 (66.5)	176 (65.9)
1	87 (33.1)*	90 (33.7)*
Extrahepatic metastases at randomization	104 (39.5)	108 (40.4)
Lungs alone	36 (34.6)	41 (38.0)
Lungs and lymph nodes	18 (17.3)	14 (13.0)
Lymph nodes alone	48 (46.2)	47 (43.5)
Unspecified	2 (1.9)	6 (5.6)
Primary tumor in situ	121 (46.0)*	119 (44.6)
Primary tumor location		
Left	137 (52.1)	141 (52.8)
Right	55 (20.1)	72 (27.0)
Rectal	59 (22.4)	45 (16.9)
Left + right	4 (1.5)	5 (1.9)
Left + rectal	4 (1.5)	2 (0.7)
Left + right + rectal	2 (0.8)	0 (0.0)
Unknown	2 (0.8)	2 (0.7)
Synchronous metastases	233 (88.6)	241 (90.3)
Tumor liver involvement, %		
≤ 25	192 (73.0)	185 (69.3)
> 25	70 (26.6)*	81 (30.3)*
Prior adjuvant chemotherapy	16 (6.1)	13 (4.9)
Prior radiotherapy to nonliver sites	14 (5.3)	11 (4.1)
Reasons for unresectability of liver metastases		
Extrahepatic disease	28 (10.6)	33 (12.4)
Insufficient liver reserve	19 (7.2)	21 (7.9)
Proximity to major vessels	14 (5.3)	13 (4.9)
Medically inoperable	32 (12.2)	46 (17.2)
Patient age	7 (2.7)	3 (1.1)
Tumor too large	43 (16.3)	49 (18.4)
Too many tumors	199 (75.7)	197 (73.8)
Attachment to another major structure	1 (0.4)	1 (0.4)
Other	9 (3.4)	10 (3.7)

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: bev, bevacizumab; ITT, intent to treat; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.
*Unknown for one patient: patient withdrew consent and records.

(P = .857); all patients had been considered unresectable at study entry by a multidisciplinary team.

Safety

Treatment-emergent grade ≥ 3 AEs were reported in 73.3% of control and 85.4% of SIRT patients (Table 3). Hematologic toxicities were reported at a higher rate in SIRT compared with control (P < .05). Known SIRT-associated AEs were reported in SIRT patients only (Table 3). Eight of the nine grade ≥ 3 gastric or duodenal ulcers were considered SIRT related, and one patient (0.4%) developed a grade 4 ulcer. Two patients with ulcers required surgical management.

Grade 5 AEs of any causality were reported in five patients (1.9%) in control and nine patients (3.7%) in SIRT (P = .279). Four treatment-related grade 5 AEs were attributed to chemotherapy (two cardiac-related events in control, and one respiratory failure and one febrile neutropenia in SIRT), two were attributed to SIRT (hepatic failure and radiation hepatitis), and one was attributed to both chemotherapy and SIRT (hepatic failure in SIRT).

Serious AEs were reported less frequently in control patients (41.6%) than in SIRT patients (54.1%; P = .005). AEs that led to reduction, delay, or discontinuation of protocol therapy occurred in 9.3%, 33.1%, and 15.6% of control and 4.1%, 41.5%, and 17.5% of SIRT patients, respectively.

Five patients with SIRT-related hepatotoxicity (radiation hepatitis or hepatic failure) were managed with supportive treatment. Both cases of radiation hepatitis, one of which was fatal, occurred 2 to 3 months after SIRT and were treated with low–molecular-weight heparin, diuretics, and corticosteroids. Two patients experienced fatal hepatic failure, one case occurring 5 days after SIRT and the

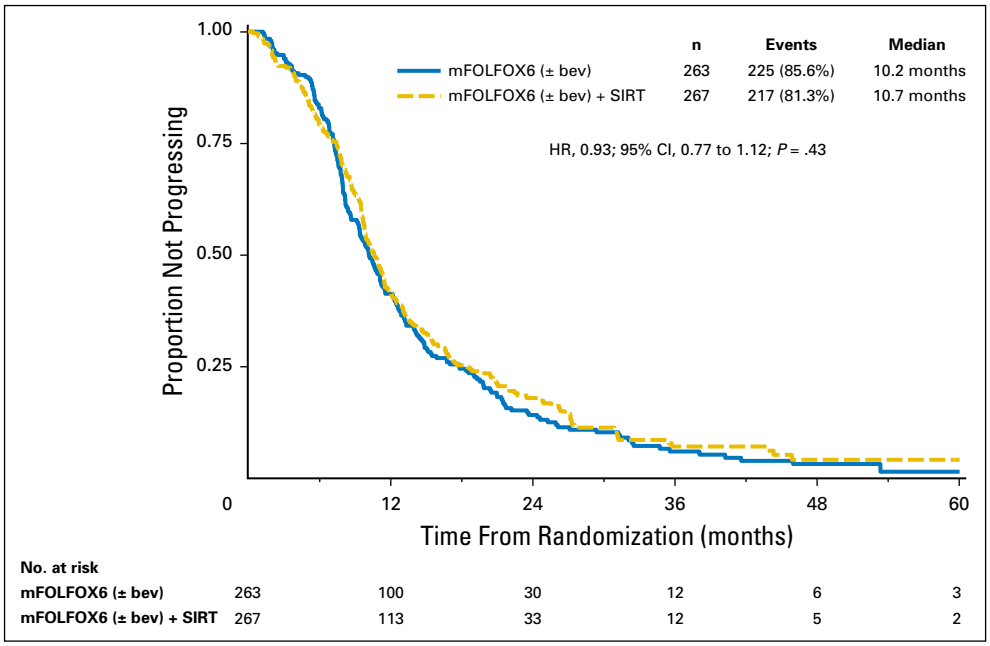

Fig 3. Kaplan-Meier analysis of progression-free survival at any site (intent-to-treat population) determined by independent centralized imaging review. bev, bevacizumab; HR, hazard ratio; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.

other case > 2 years after SIRT. The latter case presented with portal hypertension (splenomegaly and thrombocytopenia) and subsequently developed hepatic insufficiency consistent with prior subclinical radiation hepatitis.[23] A third (nonfatal) case of hepatic failure in a SIRT patient occurred 1 day after resection of liver metastases.

DISCUSSION

SIRFLOX is the first large phase III randomized controlled trial to assess the efficacy and safety of a liver-directed therapy in patients with mCRC. Unlike previous studies combining SIRT with first-line fluoropyrimidine-based chemotherapy in patients with mCRC, the SIRFLOX study failed to show an improvement in median PFS at any site with the addition of SIRT. The addition of SIRT significantly improved median PFS in the liver by 7.9 months, corresponding to a 31% risk reduction. OS data from a combined analysis of SIRFLOX and two other first-line studies are awaited to determine whether this substantial gain in control of existing liver metastases translates into a significant gain in survival.

The site and pattern of first disease progression in control and SIRT patients offer insight into the apparent discordance between

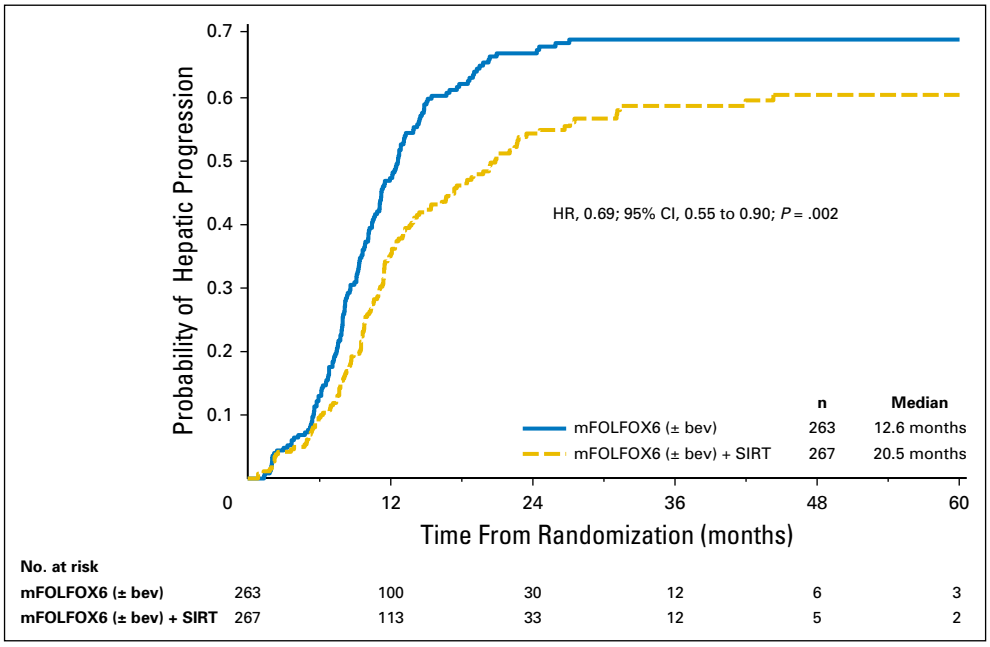

Fig 4. Cumulative incidence of liver progression (intent-to-treat population) determined by independent central image reading, accounting for the risk of death or progression outside the liver. bev, bevacizumab; HR, hazard ratio; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.

Table 2. Site of First Disease Progression

Number of First Disease Progression and Site(s)	Control Arm (mFOLFOX6 [± bev])	Treatment Arm (SIRT + mFOLFOX6 [± bev])	*P*
Number of first progressions	178	166	
Site(s) of first disease progression			
Liver only	137 (77.0)	87 (52.4)	< .001
Liver + nonliver sites	27 (15.2)	33 (19.9)	.251
Liver + lung	21 (11.8)	29 (17.5)	.136
Liver + lymph nodes	6 (3.4)	2 (1.2)	.184
Liver + lung + lymph nodes	0 (0.0)	1 (0.6)	.300
Liver + abdominal wall	0 (0.0)	1 (0.6)	.300
Nonliver sites only	14 (7.9)	46 (27.7)	< .001
Lung only	13 (7.3)	39 (23.5)	< .001
Lymph nodes only	1 (0.6)	5 (3.0)	.083
Lung + lymph nodes	0 (0.0)	2 (1.2)	.142

NOTE. Data are presented as No. (%) unless indicated otherwise.
Abbreviations: bev, bevacizumab; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.

PFS at any site and PFS in the liver. Whereas control of intra- and extrahepatic disease is required to achieve a benefit in PFS at any site, the analysis of first progression site suggests that progressive disease in nonliver sites (7.9% *v* 27.7%) may mitigate the benefit of controlling liver disease with SIRT. Furthermore, the appearance of new lesions accounted for a substantially greater proportion of first progressions in the liver in SIRT (Appendix Table A2). Collectively, these data suggest that although SIRT used in conjunction with systemic chemotherapy provides prolonged control of evident liver disease, this is insufficient to influence PFS at any site. The increased incidence of progression within the lungs for SIRT patients would seem to reflect lung progression destined to occur in patients receiving a liver-directed intervention.

Other factors that may have compromised the ability of SIRT to significantly affect PFS at any site and the gains achieved in control of liver metastases include the 21 patients (7.9%) randomly assigned to SIRT but not receiving SIRT and the 19 patients (7.7%) with bilobar disease who received SIRT in only one liver lobe. Ultimately, only 84% of patients allocated to SIRT received SIRT as per protocol. This is explained partly by the random assignment of patients before consideration of their suitability for SIRT, but, on the basis of previous experience, the proportion of patients not receiving SIRT as per protocol was unexpectedly high.[14,15,24] Also unanticipated was the large proportion of patients (approximately 45%) with an intact primary tumor; this had an uncertain impact on the primary study end point of PFS at any site and was reported to be associated with inferior survival outcomes.[25] There are also uncertainties regarding the 10 patients (3.8%) who withdrew consent after being randomly assigned to control (and may have received SIRT off protocol as part

Table 3. Summary of AEs of Grade ≥ 3

Adverse Event	Control Arm (mFOLFOX6 [± bev])	Treatment Arm (SIRT + mFOLFOX6 [± bev])	*P*
Safety population	270 (100)	246 (100)	
Total ≥ grade 3 AEs	198 (73.3)	210 (85.4)	.516
Any*			
Neutropenia	77 (28.5)	100 (40.7)†	.004
Febrile neutropenia	5 (1.9)	15 (6.1)†	.020
Thrombocytopenia	7 (2.6)	24 (9.8)†	< .001
Diarrhea	24 (8.9)	18 (7.3)	.535
Peripheral neuropathy	23 (8.5)	14 (5.7)	.235
Pulmonary embolism	15 (5.6)	17 (6.9)	.586
Fatigue	13 (4.8)	26 (10.6)†	.019
Nausea/vomiting	11 (4.1)	20 (8.1)	.064
Abdominal pain	7 (2.6)	19 (7.7)†	.009
SIRT-associated events‡			
Gastric/duodenal ulcer	0 (0.0)	9 (3.7)†	.001
Ascites	0 (0.0)	7 (2.8)†	.005
Hepatic failure	0 (0.0)	3 (1.2)	.108
Radiation hepatitis	0 (0.0)	2 (0.8)	.227
Total grade 5 AEs§	5 (1.9)	9 (3.7)	.279
Treatment-related grade 5 AEs‖	2 (0.7)	5 (2.0)	.266

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; bev, bevacizumab; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.
*All grade ≥ 3 adverse events occurring with an incidence of ≥ 5% in either study arm, irrespective of attribution to treatment.
†Statistically significant difference in incidence ($P < .05$).
‡AEs typically associated with SIRT.
§Occurring with an incidence of > 0% in either study arm, irrespective of attribution to treatment.
‖Attributed to either or both treatments.

of first-line therapy) but were included in the ITT population PFS analyses for control.

The median 20.5-month liver PFS for patients treated with chemotherapy plus SIRT represents a substantial prolongation of local disease control compared with systemic chemotherapy alone (median, 12.6 months). Because, to the best of our knowledge, this is the first study to evaluate PFS in the liver, there are no other studies that provide context for this result. However, recently reported data from the Chemotherapy + Local Ablation Versus Chemotherapy (CLOCC) study, which combined radiofrequency ablation with FOLFOX-based systemic chemotherapy in patients with unresectable mCRC confined to the liver, demonstrated that improved control of hepatic metastases can translate to a substantial impact on OS.[26] In contrast to those in SIRFLOX, all patients randomly assigned in the CLOCC study, which also demonstrated an improvement in PFS at any site (HR, 0.57; 95% CI 0.38 to 0.85; $P = .005$), had a low burden of liver disease and no extrahepatic disease, and all had had their primary CRC resected.

OS is a secondary outcome for the SIRFLOX study. During the 7-year recruitment period of the study, when it became evident that improved patient care and new chemotherapy regimens were extending survival for patients with mCRC receiving first-line chemotherapy treatment,[20,27-32] a decision was made to preplan a combined OS analysis including data from SIRFLOX and two additional randomized studies (Sharma et al[17] and NCT NCT01721954). In all three studies, SIRT has been added to oxaliplatin-based chemotherapy in an almost identical patient population. The FOXFIRE and FOXFIRE Global studies have completed accrual and, combined with SIRFLOX, have a total recruitment of $>$ 1,100 patients; this provides adequate power to detect a survival advantage. The result of the combined OS analysis is anticipated in 2017.

Despite the addition of SIRT improving ORR in the liver, there was no difference in liver resection rates in the two study arms, in contrast to previous studies in which increasing response rates have typically translated into increased liver resection rates.[33] At study entry, the dominant reason for metastases not being resectable as recorded in the case report form was the number of liver metastases, suggesting that liver disease would not become resectable irrespective of response. For the 40% of patients with extrahepatic disease, an improvement in liver response rates is also unlikely to affect resection rates because liver resection is generally pursued only when all sites of disease can be resected completely. Of uncertain significance is the potential reluctance of liver surgeons to operate after SIRT even though there are no reliable data to suggest that surgical outcomes or complications are worse after SIRT.

The combination of SIRT with mFOLFOX6 resulted in a predictable increase in grade $\geq$ 3 AEs attributable to both chemotherapy and SIRT. Common grade $\geq$ 3 AEs associated with chemotherapy such as neutropenia, febrile neutropenia, and thrombocytopenia occurred more frequently with the addition of SIRT (28.5% *v* 40.7%, 1.9% *v* 6.1%, and 2.6% *v* 9.7%, respectively). The frequency of events reported in this study is consistent with reports of other studies with mFOLFOX6 plus or minus bevacizumab–based regimens (grade $\geq$ 3 neutropenia, 44%–53%; grade $\geq$ 3 thrombocytopenia ,5%–6%).[34,35] There was an increase in grade $\geq$ 3 toxicities known to be associated with SIRT caused by the acute effects of radiation (eg, nausea, vomiting, abdominal pain, and fatigue), nontarget implantation (gastric or duodenal ulcers), and hepatotoxicity (ascites, radiation hepatitis, and hepatic failure). SIRT-related toxicities were predictable and were predominantly medically manageable (but two patients required surgical intervention for duodenal or gastric ulcers). No previously unreported toxicities emerged.

In conclusion, the addition of SIRT, using ^{90}Y resin microspheres, to standard FOLFOX-based first-line systemic chemotherapy in patients with liver-dominant mCRC did not improve PFS at any site but significantly delayed progression in the liver. The addition of SIRT did not adversely affect the delivery of chemotherapy, and the AE profile was anticipated and manageable. No unexpected toxicities were observed. The potential long-term impact on survival from integrating SIRT into the first-line treatment of mCRC will be evident when the results of the preplanned combined analysis of SIRFLOX, FOXFIRE, and FOXFIRE Global are available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients with Metastatic Colorectal Cancer

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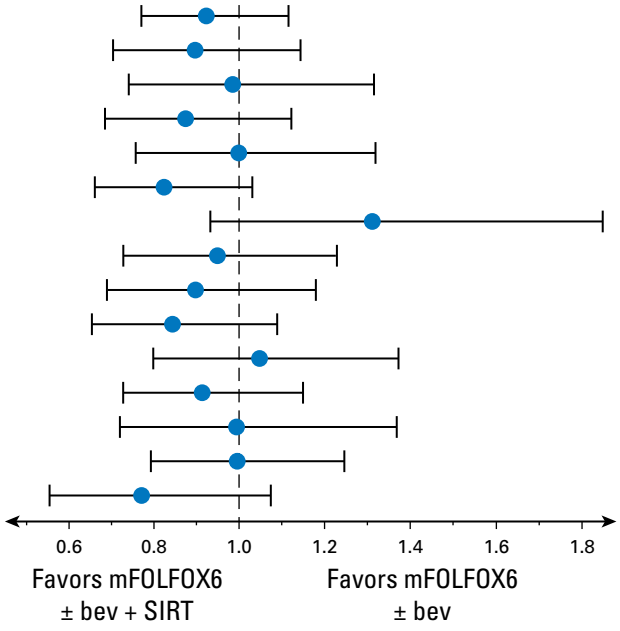
A

Strata	n	Events	HR (95% CI)
All patients	530	304	0.93 (0.77 to 1.12)
Liver only	318	179	0.90 (0.70 to 1.15)
Liver + EHD	212	125	0.98 (0.74 to 1.32)
No primary tumor in situ	289	180	0.88 (0.68 to 1.12)
Primary tumor in situ	240	124	1.00 (0.76 to 1.33)
Liver tumor burden ≤ 25%	377	218	0.82 (0.66 to 1.03)
Liver tumor burden > 25%	151	85	1.32 (0.93 to 1.86)
ITT with bevacizumab	292	159	0.95 (0.73 to 1.23)
ITT no bevacizumab	238	145	0.90 (0.69 to 1.18)
Age < 65 years	292	163	0.84 (0.65 to 1.09)
Age ≥ 65 years	238	141	1.05 (0.80 to 1.38)
WHO performance status 0	351	207	0.91 (0.73 to 1.15)
WHO performance status 1	177	96	0.99 (0.72 to 1.37)
Male	356	212	0.99 (0.79 to 1.25)
Female	173	92	0.77 (0.55 to 1.08)



B

Strata	n	Events	HR (95% CI)
All patients	530	304	0.69 (0.55 to 0.90)
Liver only	318	179	0.64 (0.48 to 0.86)
Liver + EHD	212	125	0.77 (0.54 to 1.09)
No primary tumor in situ	289	180	0.68 (0.51 to 0.90)
Primary tumor in situ	240	124	0.70 (0.49 to 1.01)
Liver tumor burden ≤ 25%	377	218	0.73 (0.58 to 0.95)
Liver tumor burden > 25%	151	85	0.61 (0.40 to 0.91)
ITT with bevacizumab	292	159	0.69 (0.50 to 0.94)
ITT no bevacizumab	238	145	0.69 (0.50 to 0.96)
Age < 65 years	292	163	0.62 (0.46 to 0.84)
Age ≥ 65 years	238	141	0.74 (0.54 to 1.08)
WHO performance status 0	351	207	0.73 (0.58 to 0.96)
WHO performance status 1	177	96	0.61 (0.41 to 0.91)
Male	356	212	0.65 (0.50 to 0.86)
Female	173	92	0.77 (0.51 to 1.15)

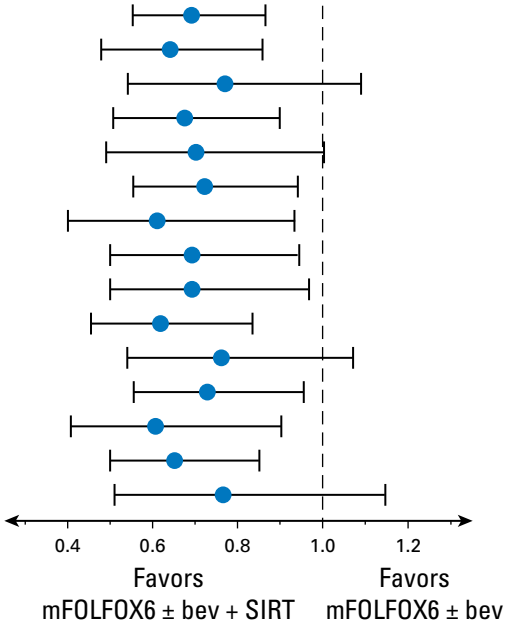


Fig A1. (A) Forest plot of planned subgroup analyses of progression-free survival at any site (ITT population). (B) Forest plot of planned subgroup analyses of progression in the liver. Determined by independent centralized imaging review. bev, bevacizumab; EHD, extrahepatic disease; HR, hazard ratio; ITT, intent to treat; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.

Table A1. Patient Eligibility Criteria for SIRFLOX Study

Inclusion Criteria	Exclusion Criteria
Written informed consent provided	Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumor involvement, or main portal venous thrombosis
≥ 18 years old with histologically confirmed adenocarcinoma of the colon or rectum (with or without the primary tumor in situ)	Previous radiation therapy to the upper abdomen
Proven liver metastases	Nonmalignant disease that renders patients unsuitable for the study treatment
WHO performance status of 0 to 1	Grade > 1 peripheral neuropathy (NCI-CTCv3)
Life expectancy of ≥ 3 months	Previous dose-limiting toxicity associated with adjuvant FU or oxaliplatin chemotherapy
Patients with additional limited extrahepatic metastases in the lung (fewer than five nodules of ≤ 1 cm diameter or a single nodule of ≤ 1.7 cm diameter) and/or lymph node involvement in a single anatomic area of < 2 cm diameter) with the aim of these patients being < 40% of the total number of patients recruited (but not being excluded even if they account for more than this proportion).	Pregnancy or breast-feeding
Chemotherapy naïve for mCRC, but previous adjuvant systemic chemotherapy for primary CRC or neoadjuvant chemoradiotherapy to the pelvis > 6 months before recruitment are permitted	Current or history of cancer other than adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix
Deemed suitable for either treatment regimen by the investigator	Allergy to nonionic contrast agents.
Adequate hematologic, renal, and hepatic function	
Using an acceptable method of contraception	

Abbreviations: CRC, colorectal cancer; FU, fluorouracil; mCRC, metastatic colorectal cancer; NCI-CTCv3, National Cancer Institute Common Toxicity Criteria version 3.

Table A2. Pattern of First Disease Progression

Number of First Progressions and Pattern of First Disease Progression	Control Arm (mFOLFOX6 [± bev])	Treatment Arm (SIRT + mFOLFOX6 [± bev])	*P*
Number of first progressions	178	166	
Pattern of first disease progression			
Any site			< .001
Existing lesions	118 (66.3)	68 (41.0)	
New lesions	22 (12.4)	57 (34.3)	
Existing + new lesions	38 (21.3)	41 (24.7)	
Liver (± other sites)			< .001
Existing lesions	129 (72.5)	80 (48.2)	
New lesions	10 (5.6)	24 (14.5)	
Existing + new lesions	25 (14.0)	16 (9.6)	
Lung (± other sites)			.273
Existing lesions	5 (2.8)	8 (4.8)	
New lesions	28 (15.7)	54 (32.5)	
Existing + new lesions	1 (0.6)	9 (5.4)	
Lymph nodes (± other sites)			.596
Existing lesions	3 (1.7)	3 (1.8)	
New lesions	4 (2.2)	7 (4.2)	
Existing + new lesions	0 (0.0)	0 (0.0)	
Abdominal wall (± other sites)			
Existing lesions	0 (0.0)	0 (0.0)	
New lesions	0 (0.0)	1 (0.6)	
Existing + new lesions	0 (0.0)	0 (0.0)	

NOTE. Data are presented as No. (%).
Abbreviations: bev, bevacizumab; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; SIRT, selective internal radiation therapy.

Table A3. Objective Response According to RECIST v1.0 at Any Site and in the Liver (ITT Population) as Assessed by Independent Readers

Responses	Control Arm (mFOLFOX6 [± bev])	Treatment Arm (SIRT + mFOLFOX6 [± bev])	*P*
ITT Population	263	267	
Response at any site			
Objective response (CR + PR)	179 (68.1)	204 (76.4)	.113
Complete response (CR)	4 (1.5)	12 (4.5)	.054
Partial response (PR)	175 (66.5)	192 (71.9)	
Stable disease	48 (18.3)	28 (10.5)	
Progressive disease	17 (6.5)	25 (9.4)	
Not evaluable	19 (7.2)	10 (3.7)	
Response in the liver			
Objective response (CR + PR)	181 (68.8)	210 (78.7)	.042
Complete response (CR)	5 (1.9)	16 (6.0)	.020
Partial response (PR)	176 (66.9)	194 (72.7)	
Stable disease	47 (17.9)	29 (10.9)	
Progressive disease	16 (6.1)	18 (6.7)	
Not evaluable	19 (7.2)	10 (3.7)	

NOTE. Data are presented as No. (%).
Abbreviations: bev, bevacizumab; ITT, intent to treat; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; RECIST, Response Evaluation Criteria In Solid Tumors; SIRT, selective internal radiation therapy.