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Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial

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Background: For patients with initially unresectable liver metastases from colorectal cancer, chemotherapy can downsize metastases and facilitate secondary resection. We assessed the efficacy of bevacizumab plus modified FOLFOX-6 (5-fluorouracil/folinic acid, oxaliplatin) or FOLFOXIRI (5-fluorouracil/folinic acid, oxaliplatin, irinotecan) in this setting.

Patients and methods: OLIVIA was a multinational open-label phase II study conducted at 16 centres in Austria, France, Spain, and the UK. Patients with unresectable liver metastases were randomised to bevacizumab (5 mg/kg) plus mFOLFOX-6 [oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, 5-fluorouracil 400 mg/m^2 (bolus) then 2400 mg/m^2 (46-h infusion)] or FOLFOXIRI [oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2, folinic acid 200 mg/m^2, 5-fluorouracil 3200 mg/m^2 (46-h infusion)] every 2 weeks. Unresectability was defined as ≥1 of the following criteria: no possibility of upfront R0/R1 resection of all lesions; <30% residual liver volume after resection; metastases in contact with major vessels of the remnant liver. Resectability was evaluated by multidisciplinary review. The primary end point was overall resection rate (R0/R1/R2). Efficacy end points were analysed by intention-to-treat analysis.

Results: In patients assigned to bevacizumab–FOLFOXIRI ($n = 41$) or bevacizumab–mFOLFOX-6 ($n = 39$), the overall resection rate was 61% [95% confidence interval (CI) 45% to 76%] and 49% (95% CI 32% to 65%), respectively (difference 12%; 95% CI −11% to 36%). R0 resection rates were 49% and 23%, respectively. Overall tumour response rates were 81% (95% CI 65% to 91%) with bevacizumab–FOLFOXIRI and 62% (95% CI 45% to 77%) with bevacizumab–mFOLFOX-6. Median progression-free survival (PFS) was 18·6 (95% CI 12.9–22.3) months and 11·5 (95% CI 9.6–13.6) months, respectively. The most common grade 3–5 adverse events were neutropenia (bevacizumab–FOLFOXIRI, 50%; bevacizumab–mFOLFOX-6, 35%) and diarrhoea (30% and 14%, respectively).

Conclusions: Bevacizumab–FOLFOXIRI was associated with higher response and resection rates and prolonged PFS versus bevacizumab–mFOLFOX-6 in patients with initially unresectable liver metastases from colorectal cancer. Toxicity was increased but manageable with bevacizumab–FOLFOXIRI.

ClinicalTrials.gov: NCT00778102.

Key words: bevacizumab, liver metastases, secondary resection, chemotherapy, colorectal cancer

introduction

The liver is the most common site of metastasis in patients with colorectal cancer. Treatment strategies that allow hepatic resection as part of an interdisciplinary consensus offer better 5-year survival rates than palliative treatment alone [1, 2]. Patients with liver-only metastases [colorectal liver metastases (CLM)] seem to be an exceptional group with regard to the possible benefits of potentially curative multidisciplinary strategies [3]. Clarification of resectability status, i.e. upfront or potentially resectable as opposed to clearly unresectable disease, before any

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treatment decision is of utmost importance. Categorisation of CLM has been previously described, and we know that for selected patients with borderline resectable CLM, chemotherapy can downsize metastases and facilitate secondary resection [4, 5].

Currently, there is no standard of care for patients with borderline resectable CLM, and treatment guidelines permit several combinations [6–8]. Conducting trials in this area is hampered by the lack of a standard regimen and variable definitions for unresectability [4, 6]. Despite clear eligibility criteria [9, 10], the patient population that is recruited is often variable with respect to anatomical and potentially biological demographics.

Standard chemotherapy regimens, i.e. infused 5-fluorouracil/folinic acid plus irinotecan (FOLFIRI) or oxaliplatin (FOLFOX), facilitate secondary resection and are accepted treatment options in patients with initially unresectable CLM [5]. NCCN and ESMO guidelines [6, 7] suggest treatment with the most active combination regimen upfront, which often comprises doublet chemotherapy plus a targeted agent (e.g. bevacizumab or cetuximab for *KRAS* wild-type tumours), although few studies of these regimens have been done specifically in patients with initially unresectable CLM.

This randomised multicentre phase II study evaluated resection rates and safety of bevacizumab plus modified FOLFOX-6 (mFOLFOX-6) or bevacizumab plus FOLFOXIRI in patients with initially clearly defined unresectable CLM. 'Unresectability' was determined by a multidisciplinary team to permit a pragmatically defined patient population.

patients and methods

study design

OLIVIA was a multicentre, open-label, randomised phase II study. The primary end point was the overall resection rate (R0/R1/R2). Secondary end points included overall response rate, time to response, histopathological response, progression-free survival (PFS), relapse-free survival (RFS), overall survival, and surgical safety. The study was carried out in accordance with the Declaration of Helsinki and all patients provided written informed consent before enrolment. The protocol was approved by institutional or regional ethics committees.

patients

Patients with previously untreated, upfront unresectable, histologically confirmed colorectal cancer with metastases confined to the liver were eligible. Patients had to meet ≥1 of the following criteria for unresectability of hepatic metastases as assessed by a local multidisciplinary team: no upfront R0/R1 resection of all hepatic lesions possible; <30% estimated residual liver volume after resection; and metastases in contact with major vessels of the remnant liver. Hepatic lesions were assessed using three-phase computed tomography (CT) or magnetic resonance imaging (MRI) including liver-specific contrast. Fluorodeoxyglucose–positron emission tomography (FDG–PET) was carried out to exclude extrahepatic metastases. The patient's general condition had to be such that major abdominal surgery was feasible.

Other inclusion criteria were: age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Exclusion criteria included prior (neo)adjuvant chemotherapy completed <6 months before randomisation and any extrahepatic disease.

randomisation and masking

Randomisation (block size 10) was stratified according to centre ($n = 16$), ECOG performance status (0 or 1), and number of baseline metastatic lesions (<3 or ≥3). No masking was employed for patients or investigators giving interventions and assessing outcomes.

treatment

preoperative chemotherapy. Patients were randomly assigned (1 : 1) to receive bevacizumab plus mFOLFOX-6 or bevacizumab plus FOLFOXIRI. Bevacizumab 5 mg/kg was given by i.v. infusion on day 1 every 2 weeks. mFOLFOX-6 consisted of oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, and bolus 5-fluorouracil 400 mg/m^2 followed by 2400 mg/m^2 as a 46-h continuous infusion on day 1 every 2 weeks. FOLFOXIRI consisted of oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2, folinic acid 200 mg/m^2, and 5-fluorouracil 3200 mg/m^2 as a 46-h continuous infusion on day 1 every 2 weeks. The chemotherapy cycle before resection was given without bevacizumab.

post-operative chemotherapy. Patients rendered tumour free (R0/R1 resection) resumed study treatment of eight additional cycles starting 4–6 weeks after surgery (following confirmation of complete resection by CT 4 weeks after surgery and after complete wound healing). Patients with residual disease after surgery (R2 resection) and unresected patients continued study treatment until disease progression, unacceptable toxicity, or patient refusal. After 12 cycles of study treatment, oxaliplatin could be discontinued in the bevacizumab–mFOLFOX-6 arm, and ≥1 cytotoxic agent had to be discontinued in the bevacizumab–FOLFOXIRI arm.

tumour assessments and surgery

Tumour status was assessed every 6 weeks and preoperatively (within 4 weeks of surgery) using CT or MRI. The technique used (CT or MRI) was left to the discretion of the assessor. Surgery was carried out without further cycles as soon as the appropriate tumour reduction for potential curative resection was evident. Resectability was evaluated by a multidisciplinary review team, including at least a liver surgeon, radiologist, and medical oncologist. Patients deemed resectable were offered surgery 5–7 weeks after their last bevacizumab dose and 3–5 weeks after their last chemotherapy cycle. As per the protocol, radiofrequency ablation was allowed only for lesions with an unfavourable location (noted in the electronic case report form accordingly as a suboptimal surgical approach). A two-stage approach to achieve tumour clearance was permitted.

Resection status (R0/R1/R2) was evaluated by histopathological assessment of excised metastases together with the operation notes. Follow-up tumour assessments were carried out 4 weeks after surgery; clinical assessments of surgical outcomes and safety were carried out at the time of surgery, and 48 h, 1 and 3 months post-surgery. Follow-up assessments were carried out at the end of postoperative therapy, every 3 or 6 months (in patients with progressive disease) for the first 12 months, and annually thereafter.

End points are defined in the supplementary Material, available at *Annals of Oncology* online.

statistical analysis

The sample size (40 patients/treatment group) was based on feasibility and allowed a reasonably precise estimate of resection rates in each treatment arm. The study was not powered for confirmatory hypothesis testing of treatment comparisons; therefore, all statistical analyses were exploratory only.

The final study analysis, the cut-off date for which was 22 November 2013, is presented. Efficacy end points were analysed according to the intention-to-treat (ITT) principle. Overall resection rate was presented by treatment arm with exact two-sided 95% Pearson–Clopper confidence intervals (CIs). Time-to-event end points were analysed using Kaplan–Meier methods; estimates for median values were presented with 95% CIs.

This trial is registered with ClinicalTrials.gov, number NCT00778102.

results

patients

From October 2008 to December 2011, 80 patients were enrolled at 16 sites in Austria, France, Spain, and the UK and were included in the ITT population (bevacizumab–FOLFOXIRI, $n = 41$; bevacizumab–mFOLFOX-6; $n = 39$) (supplementary Figure S1, available at *Annals of Oncology* online). Treatment groups were generally well balanced, although patients in the bevacizumab–FOLFOXIRI group were slightly older, and included more men at baseline than the bevacizumab–mFOLFOX-6 group (Table 1). Although ECOG performance status was a stratification factor, an imbalance developed between arms in the 28 days between randomisation and first drug intake resulting in an unfavourable distribution for the bevacizumab–FOLFOXIRI arm.

Seventy-seven patients (bevacizumab–FOLFOXIRI, $n = 40$; bevacizumab–mFOLFOX-6, $n = 37$) received treatment and were included in the safety population. Treatment exposure is described in the supplementary Material and Table S1, available at *Annals of Oncology* online.

surgery

Median time to resection in the ITT population was similar in both treatment groups (bevacizumab–FOLFOXIRI, 4.3 months; bevacizumab–mFOLFOX-6, 4.4 months). Surgery (segmentectomy,

Table 1. Baseline characteristics (intention-to-treat population)

Variable	Bevacizumab plus FOLFOXIRI ($N = 41$)		Bevacizumab plus mFOLFOX-6 ($N = 39$)	
	n	%	*n*	%
Sex				
Male	29	71	18	46
Female	12	29	21	54
Age, years				
Median	63	57		
Range	32–77	28–80		
ECOG performance status at baseline				
0	23	56	31	80
1	16	39	8	21
2[a]	2	5	0	0
Criteria for unresectability[b]				
No upfront R0/R1 resection of hepatic lesions possible	33	80	31	80
Less than 30% estimated residual liver after resection	26	63	23	59
Disease in contact with major vessels of remnant liver	15	37	17	44
Primary tumour site				
Colon	29	71	27	69
Rectum	8	20	9	23
Colorectal	4	10	3	8
Tumour differentiation				
Well differentiated	8	20	8	21
Moderately differentiated	21	51	24	62
Poorly differentiated	3	7	2	5
Undetermined/unknown	9	22	5	13
No. of metastatic lesions at baseline				
<3	2	5	3	8
≥3	39	95	36	92
Disease stage at diagnosis				
Locoregional	11	27	7	18
Metastatic	30	73	32	82
Primary tumour *in situ*				
Yes	25	61	27	69
No	16	39	12	31

Percentages may not add up to 100% due to rounding or patients meeting ≥1 unresectability criterion.

[a]Two patients had an ECOG score of 1 at randomisation, but had an ECOG score of 2 before study drug administration (baseline).

[b]Based on manual medical science review of the case report forms.

ECOG, Eastern Cooperative Oncology Group; FOLFOXIRI, infused 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan; mFOLFOX-6, modified infused 5-fluorouracil, folinic acid, and oxaliplatin.

sectorectomy or hemihepatectomy) was carried out in 44 patients (bevacizumab–FOLFOXIRI, $n = 25$; bevacizumab–mFOLFOX-6; $n = 19$). Nine of 52 patients (bevacizumab–FOLFOXIRI, $n = 5$; bevacizumab–mFOLFOX-6; $n = 4$), with primary tumours *in situ* had primary resection surgery during the study. Eleven patients had preoperative portal vein embolisation (bevacizumab–FOLFOXIRI, $n = 5$; bevacizumab–mFOLFOX-6; $n = 6$). Ten patients had adjunctive radiofrequency ablation (bevacizumab–FOLFOXIRI, $n = 5$; bevacizumab–mFOLFOX-6; $n = 5$). Median duration of hospitalisation after first surgery was 11 (range, 5–39) days in the bevacizumab–FOLFOXIRI group and 9 (range, 5–39) days in the bevacizumab–mFOLFOX-6 group.

efficacy

The overall resection rate for first resections—the primary end point—was 61% (95% CI 45% to 76%) in the bevacizumab–FOLFOXIRI group and 49% (95% CI 32% to 65%) in the bevacizumab–mFOLFOX-6 group (difference 12%; 95% CI −11% to +36%; Table 2). The R0 resection rate was numerically higher

Table 2. Efficacy outcomes[a]

Variable	Bevacizumab plus FOLFOXIRI ($N = 41$)	Bevacizumab plus mFOLFOX-6 ($N = 39$)	Difference or hazard ratio (95% CI)
Resection rate (first resection)			
Overall (R0/R1/R2), *n* (%)	25 (61)	19 (49)	12 (−11 to 36)
95% CI	45–76	32–65	
R0/R1, *n* (%)	21 (51)	13 (33)	18 (−5 to 41)
95% CI	35–67	19–50	
R0, *n* (%)	20 (49)	9 (23)	26 (4 to 48)
95% CI	33–65	11–39	
R1, *n* (%)	1 (2)	4 (10)	
R2, *n* (%)[b]	4 (10)	6 (15)	
Not resected, *n* (%)	16 (39)	20 (51)	
Histopathological response[c]			
Patients in analysis, *n*	21	14	
Histopathological response rate, *n* (%)[d]	11 (52)	8 (57)	−5 (−43 to 34)
95% CI	30–74	29–82	
Complete response, *n* (%)	1 (5)	0	
Major response, *n* (%)	10 (48)	8 (57)	
Minor response, *n* (%)	7 (33)	4 (29)	
Unknown, *n* (%)	3 (14)	2 (14)	
Overall response rate (confirmed), *n* (%)[e]	33 (81)	24 (62)	
95% CI	65–91	45–77	19 (−2 to 40)
Complete response, *n* (%)[f]	22 (54)	9 (23)	
Partial response, *n* (%)	11 (27)	15 (39)	
Stable disease, *n* (%)	5 (12)	13 (33)	
Progressive disease, *n* (%)	0	1 (3)	
Unknown, *n* (%)	3 (7)	1 (3)	
Time to response			
Median (95% CI), months	3.1 (1.9–3.9)	3.1 (2.7–8.6)	
Relapse-free survival[g]			
Patients in analysis, *n*	21	13	
Median (95% CI), months	17.1 (12.3–NR)	8.1 (3.8–11.7)	0.31 (0.12–0.75)
Progression-free survival			
Median (95% CI), months	18.6 (12.9–22.3)	11.5 (9.6–13.6)	0.43 (0.26–0.72)

[a]Intention-to-treat population unless otherwise stated.
[b]Two patients in each treatment group went on to have a second surgery with an R0 outcome in all cases.
[c]Complete response, 0% viable tumour cells within resected specimen; major response, 1%–49% viable tumour cells; minor response, 50%–99% viable tumour cells. Histopathological assessment was carried out after first resection but was not mandatory.
[d]Complete plus major response.
[e]According to Response Evaluation Criteria In Solid Tumours (RECIST), version 1. In patients who underwent liver resection, radiological confirmation of complete response was performed after surgery and thus would include treatment effects from both chemotherapy and surgery.
[f]Of the patients with a complete response, one patient in each treatment group had >5 target lesions and all remaining patients had 1–5 target lesions.
[g]Assessed in patients with a R0/R1 outcome after first resection.
CI, confidence interval; FOLFOXIRI, infused 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan; mFOLFOX-6, modified infused 5-fluorouracil, folinic acid, and oxaliplatin; NR, not reached.

with bevacizumab–FOLFOXIRI (49%; 95% CI 33% to 65%) compared with bevacizumab–mFOLFOX-6 (23%; 95% CI 11% to 39%). Two patients in each group with residual disease following initial surgery (R2 resections) had pre-planned two-stage hepatectomies; all four patients had an R0 outcome after the second surgery. The final R0 resection rates were 54% (95% CI 37% to 69%) with bevacizumab–FOLFOXIRI and 31% (95% CI 17% to 48%) with bevacizumab–mFOLFOX-6.

Overall tumour response rate was 81% (95% CI 65% to 91%) with bevacizumab–FOLFOXIRI and 62% (95% CI 45% to 77%) with bevacizumab–mFOLFOX-6. Median time to response was similar in both treatment groups (3.1 months). The histopathological response rate (complete/major) was 52% with bevacizumab–FOLFOXIRI (11 of 21 patients) and 57% with bevacizumab–mFOLFOX-6 (8 of 14 patients).

Median PFS in the ITT population was numerically longer with bevacizumab–FOLFOXIRI (18.6 months; 95% CI 12.9–22.3 months) than with bevacizumab–mFOLFOX-6 (11.5 months; 95% CI 9.6–13.6 months) (hazard ratio 0.43; 95% CI 0.26–0.72; supplementary Figure S2, available at *Annals of Oncology* online). PFS according to outcome of first surgery is presented in supplementary Figure S2, available at *Annals of Oncology* online.

Median RFS, which was assessed in patients with an R0/R1 status after first resection, was 17.1 months (95% CI 12.3 months to not reached) with bevacizumab–FOLFOXIRI ($n = 21$) and 8.1 (95% CI 3.8–11.7) months with bevacizumab–mFOLFOX-6 ($n = 13$) (hazard ratio 0.31; 95% CI 0.12–0.75).

Eight patients in the bevacizumab–FOLFOXIRI group and 19 in the bevacizumab–mFOLFOX-6 group died. Median time to overall survival was not reached (range 0–56.0 months) in the bevacizumab–FOLFOXIRI group and was 32·2 (range 0.7–59.6) months in the bevacizumab–mFOLFOX-6 group (hazard ratio 0.35; 95% CI 0.15–0.80).

safety

Toxicity events (all grades) occurred in 100% of patients in both groups, and a grade ≥3 event occurred in 38 bevacizumab–FOLFOXIRI patients (95%) and 31 bevacizumab–mFOLFOX-6 patients (84%; supplementary Table S2, available at *Annals of Oncology* online). The most frequently occurring grade ≥3 adverse events were neutropenia (bevacizumab–FOLFOXIRI, 50%; bevacizumab–mFOLFOX-6, 35%), diarrhoea (bevacizumab–FOLFOXIRI, 30%; bevacizumab–mFOLFOX-6, 14%), and febrile neutropenia (bevacizumab–FOLFOXIRI, 13%; bevacizumab–mFOLFOX-6, 8%). Grade ≥3 peripheral neuropathy was rare (bevacizumab–FOLFOXIRI, $n = 1$). With the exception of grade 3–5 venous thromboembolic events and diarrhoea, all other grade 3–5 bevacizumab-associated events occurred infrequently (<8%).

Adverse events causing discontinuation of bevacizumab occurred in 8 patients (20%) in the bevacizumab–FOLFOXIRI group and 13 patients (35%) in the bevacizumab–mFOLFOX-6 group. One patient in the bevacizumab–FOLFOXIRI group died of disseminated intravascular coagulation related to sepsis that occurred after emergency surgery due to perforation during an intestinal stenting procedure. This was considered by the investigator to be causally related to pre-existing disease. Two patients in the bevacizumab–mFOLFOX-6 group died of hepatic failure. One of these patients received 13 cycles of bevacizumab–mFOLFOX-6 and died 37 days after surgery (64 days after chemotherapy) after developing hepatic and renal failure. The other patient received 12 cycles of bevacizumab–mFOLFOX-6 and died 20 days after surgery (136 days after chemotherapy) after developing multiple organ failure. Both events were judged to be related to surgery after extended systemic treatment.

In the surgical safety population (bevacizumab–FOLFOXIRI, $n = 25$; bevacizumab–mFOLFOX-6; $n = 19$), all-grade surgery-related events were reported in 15 patients (60%) in the bevacizumab–FOLFOXIRI group and 15 (79%) in the bevacizumab–mFOLFOX-6 group; grade 5 events were reported in 0 (0%) and 2 (11%) patients, respectively (supplementary Table S3, available at *Annals of Oncology* online). No anastomotic leaks were observed after resection of the primary tumour.

discussion

There are currently limited data to define the optimal treatment approach for patients with unresectable liver-only metastases, especially as resectability is determined—through necessity—by a multidisciplinary team on a patient-by-patient basis. Accepting these limitations, results from the OLIVIA study suggest that bevacizumab plus FOLFOXIRI improves tumour response rates, resection rates, and PFS in patients with upfront defined unresectable CLM compared with bevacizumab plus mFOLFOX-6. Although the findings can be viewed as exploratory only, the trends in favour of the bevacizumab–FOLFOXIRI combination are consistent for all end points. Although toxicity was clearly greater in the four-agent arm, no new safety concerns were identified. Our findings support the feasibility of the addition of irinotecan to FOLFOX in combination with bevacizumab, which offers an effective treatment option in patients with initially unresectable CLM and may allow them to progress to surgery. They also compliment phase II and III studies which support the efficacy of bevacizumab–FOLFOXIRI in patients with unresectable metastatic disease [11, 12].

Although combination regimens have been tested in patients with initially unresectable liver-limited disease in a few studies, data in this patient group remain limited (supplementary Table S4, available at *Annals of Oncology* online) [9, 10, 13–15]. Ye et al. [15] showed that cetuximab plus chemotherapy (mFOLFOX6 or FOLFIRI) improved both resectability and overall survival compared with chemotherapy alone supporting the use of this regimen in patients with *KRAS* wild-type CLM. The OLIVIA study provides an estimate of the efficacy of bevacizumab-containing regimens in patients with initially unresectable liver-limited disease. While OLIVIA did not include a chemotherapy-only arm, the activity demonstrated by bevacizumab–FOLFOXIRI compares favourably with other regimens tested in this patient group (supplementary Table S4, available at *Annals of Oncology* online). We suggest further testing of bevacizumab–FOLFOXIRI in clinical trials of patients with initially unresectable CLM.

Our results concur with the findings from two phase III trials in patients with inoperable disease, which also showed that the addition of a third chemotherapeutic agent to a chemotherapy doublet (with or without a targeted agent) offered improved

efficacy [11, 16]. The response rate achieved with bevacizumab–FOLFOXIRI in OLIVIA (81%) is higher than that reported in TRIBE with the same regimen (65%) [11], supporting the hypothesis that patients with liver-limited disease respond better.

In the absence of a standardised definition for resectability, a key issue for any study involving patients with unresectable or borderline resectable CLM is how to identify the target population. To date, four other studies have been carried out in this patient group, all of whom were deemed unresectable by a multidisciplinary team (supplementary Table S4, available at *Annals of Oncology* online) [9, 10, 13, 15]. The OLIVIA study included three a priori criteria for unresectability specified by a multidisciplinary team. FDG–PET scanning was also mandatory at baseline to exclude patients with extrahepatic disease. We suggest that OLIVIA included a homogeneous patient population with initially unresectable CLM, and recommend our definition of unresectabilty for further evaluation, especially if technical unresectabilty defines the target population.

No new or unexpected safety signals were observed in the OLIVIA trial. The incidence of grade ≥3 neutropenia in both the bevacizumab–FOLFOXIRI and bevacizumab–mFOLFOX-6 groups was consistent with other recent phase II/III trials of these regimens [11, 12, 17, 18], although the rate of febrile neutropenia with bevacizumab–FOLFOXIRI was slightly higher than expected [11, 12]. Grade ≥3 diarrhoea was also slightly more common than previously documented with both regimens [11, 12, 17, 18]. These data are consistent with the expected but manageable toxicities associated with four-agent systemic therapy. One patient in the bevacizumab–FOLFOXIRI group died of disseminated intravascular coagulation during conversion therapy, and two patients in the bevacizumab–mFOLFOX-6 group died of hepatic failure during the post-operative period after ≥12 courses of preoperative treatment. This outcome concurs with Cauchy et al. [19] who reported an increased rate of mortality and major morbidities in patients with initially unresectable CLM who received ≥12 cycles of preoperative chemotherapy.

Bleeding and wound-healing complications are potential adverse events of bevacizumab that can interfere with peri-operative continuation of therapy. However, liver surgery can be carried out safely without a marked increase in post-operative complications if bevacizumab is discontinued 4–5 weeks before surgery [20, 21]. The incidences of grade ≥3 bleeding, wound-healing complications, and gastrointestinal perforation in our study are in line with the large observational First BEAT study [22] and a comparative study [23].

In OLIVIA, treatment was continued after surgery as recommended by current treatment guidelines [6–8], even though supporting data are limited. Of interest are the findings from the HEPATICA trial, which compared bevacizumab plus capecitabine and oxaliplatin (CAPOX) with CAPOX alone given after radical resection of CLM [24]. Even though the study was closed before completion, a higher 2-year disease-free survival rate of 70% was reported with bevacizumab–CAPOX compared with CAPOX (52%; $P = 0.074$), providing support for this approach.

The OLIVIA trial was conducted in specialised centres that allowed a precise assessment of surgery and peri-operative safety parameters. Study limitations included the exploratory nature of the findings, limited sample size, and the primary study end point (resection rate), which is a surrogate for long-term outcomes.

In conclusion, bevacizumab in combination with FOLFOXIRI was associated with higher response and resection rates and prolonged PFS compared with bevacizumab–mFOLFOX6 in patients with initially unresectable metastases from colorectal cancer confined to the liver. Bevacizumab plus FOLFOXIRI should be evaluated further in this setting.

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disclosure

TG has performed consultancy/advisory roles for F. Hoffmann-La Roche, Merck Serono, Sanofi-Aventis and Bayer, and received honoraria from F. Hoffmann-La Roche, Merck Serono, Sanofi-Aventis, Pfizer, Bayer and Amgen. JB has performed consultancy/advisory roles for F. Hoffmann-La Roche and Merck, and received honoraria from Merck. IC has received honoraria from F. Hoffmann-La Roche. SM has performed consultancy/advisory roles for F. Hoffmann-La Roche. SL, ML, and DW are employees of F. Hoffmann-La Roche, and DW has received F. Hoffmann-La Roche stock. RA has performed consultancy/advisory roles for F. Hoffmann-La Roche, and received honoraria from F. Hoffmann-La Roche, Sanofi, and Merck Serono. All remaining authors have declared no conflicts of interest.

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