First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group

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Summary

Background Patients with initially unresectable colorectal cancer liver metastases might qualify for local treatment with curative intent after reducing the tumour size by induction systemic treatment. We aimed to compare the currently most active induction regimens.

Methods In this open-label, multicentre, randomised, phase 3 study (CAIRO5), patients aged 18 years or older with histologically confirmed colorectal cancer, known *RAS*/*BRAF*^{V600E} mutation status, WHO performance status of 0–1, and initially unresectable colorectal cancer liver metastases were enrolled at 46 Dutch and one Belgian secondary and tertiary centres. Resectability or unresectability of colorectal cancer liver metastases was assessed centrally by an expert panel of liver surgeons and radiologists, at baseline and every 2 months thereafter by predefined criteria. Randomisation was done centrally with the minimisation technique via a masked web-based allocation procedure. Patients with right-sided primary tumour site or *RAS* or *BRAF*^{V600E} mutated tumours were randomly assigned (1:1) to receive FOLFOX or FOLFIRI plus bevacizumab (group A) or FOLFOXIRI plus bevacizumab (group B). Patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type tumours were randomly assigned (1:1) to receive FOLFOX or FOLFIRI plus bevacizumab (group C) or FOLFOX or FOLFIRI plus panitumumab (group D), every 14 days for up to 12 cycles. Patients were stratified by resectability of colorectal cancer liver metastases, serum lactate dehydrogenase concentration, choice of irinotecan versus oxaliplatin, and *BRAF*^{V600E} mutation status (for groups A and B). Bevacizumab was administered intravenously at 5 mg/kg. Panitumumab was administered intravenously at 6 mg/kg. FOLFIRI consisted of intravenous infusion of irinotecan at 180 mg/m² with folinic acid at 400 mg/m², followed by bolus fluorouracil at 400 mg/m² intravenously, followed by continuous infusion of fluorouracil at 2400 mg/m². FOLFOX consisted of oxaliplatin at 85 mg/m² intravenously together with the same schedule of folinic acid and fluorouracil as in FOLFIRI. FOLFOXIRI consisted of irinotecan at 165 mg/m² intravenously, followed by intravenous infusion of oxaliplatin at 85 mg/m² with folinic acid at 400 mg/m², followed by continuous infusion of fluorouracil at 3200 mg/m². Patients and investigators were not masked to treatment allocation. The primary outcome was progression-free survival, analysed on a modified intention-to-treat basis, excluding patients who withdrew consent before starting study treatment or violated major entry criteria (no metastatic colorectal cancer, or previous liver surgery for colorectal cancer liver metastases). The study is registered with ClinicalTrials.gov, NCT02162563, and accrual is complete.

Findings Between Nov 13, 2014, and Jan 31, 2022, 530 patients (327 [62%] male and 203 [38%] female; median age 62 years [IQR 54–69]) were randomly assigned: 148 (28%) patients to group A, 146 (28%) patients to group B, 118 (22%) patients to group C, and 118 (22%) patients to group D. Groups C and D were prematurely closed for futility. 521 patients were included in the modified intention-to-treat population (147 in group A, 144 in group B, 114 in group C, and 116 in group D). The median follow-up at the time of this analysis was 51·1 months (95% CI 47·7–53·1) in groups A and B and 49·9 months (44·5–52·5) in in groups C and D. Median progression-free survival was 9·0 months (95% CI 7·7–10·5) in group A versus 10·6 months (9·9–12·1) in group B (stratified hazard ratio [HR] 0·76 [95% CI 0·60–0·98]; p=0·032), and 10·8 months (95% CI 9·9–12·6) in group C versus 10·4 months (9·8–13·0) in group D (stratified HR 1·11 [95% CI 0·84–1·48]; p=0·46). The most frequent grade 3–4 events in groups A and B were neutropenia (19 [13%] patients in group A *vs* 57 [40%] in group B; p<0·0001), hypertension (21 [14%] *vs* 20 [14%]; p=1·00), and diarrhoea (five [3%] *vs* 28 [19%]; p<0·0001), and in groups C and D were neutropenia (29 [25%] *vs* 24 [21%]; p=0·44), skin toxicity (one [1%] *vs* 29 [25%]; p<0·0001), hypertension (20 [18%] *vs* eight [7%]; p=0·016), and diarrhoea (five [4%] *vs* 18 [16%]; p=0·0072).

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Serious adverse events occurred in 46 (31%) patients in group A, 75 (52%) patients in group B, 41 (36%) patients in group C, and 49 (42%) patients in group D. Seven treatment-related deaths were reported in group B (two due to multiorgan failure, and one each due to sepsis, pneumonia, portal vein thrombosis, septic shock and liver failure, and sudden death), one in group C (multiorgan failure), and three in group D (cardiac arrest, pulmonary embolism, and abdominal sepsis).

Interpretation **In patients with initially unresectable colorectal cancer liver metastases, FOLFOXIRI-bevacizumab was the preferred treatment in patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated primary tumour. In patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour, the addition of panitumumab to FOLFOX or FOLFIRI showed no clinical benefit over bevacizumab, but was associated with more toxicity.**

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Introduction

Patients with initially unresectable colorectal cancer liver metastases might qualify for curative-intent local treatment (surgery or local ablative treatment, or both) after reducing the tumour size by induction systemic treatment. Liver metastases can be considered unresectable if too many liver segments are involved or if liver vessels or biliary structures are affected. However, there is no consensus on criteria for unresectability. Results of subgroup analysis of patients with colorectal cancer liver metastases have been difficult to interpret because of absent or varying criteria for unresectability, absence of long-term outcome of liver resections, and heterogeneity in study populations, trial design, and patient selection by *RAS*/*BRAF*^{V600E} mutation status.[1] Since anti-EGFR treatment is only beneficial for patients with *RAS*/*BRAF*^{V600E} wild-type and left-sided primary tumours, these factors should be considered for selecting targeted therapy.[2,3] A small number of prospective studies of patients with initially unresectable colorectal cancer liver metastases have shown that 11–57% of patients might convert to resectable disease on induction systemic

Research in context

Evidence before this study

There is no consensus on the optimal induction systemic regimen for patients with initially unresectable colorectal cancer liver metastases. Moreover, published data in this patient population are difficult to interpret due to absent or varying criteria for resectability or unresectability, scarcity of long-term follow-up of patients who received local treatment, and heterogeneity in study populations, trial design, and use of *RAS*/*BRAF*^{V600E} mutation status. We searched PubMed for relevant published studies from database inception until Nov 24, 2022. Search terms were "colorectal cancer or carcinoma", "rectal cancer or carcinoma", "colon cancer or carcinoma", and "liver" or "hepatic", combined with "FOLFOXIRI" and "triplet" to identify studies comparing FOLFOXIRI versus FOLFOX or FOLFIRI and with "panitumumab" and "EGFR" to identify studies comparing panitumumab with bevacizumab. We identified 96 reports in the first search and 411 in the second search and have confined our discussion to the randomised controlled trials that compared the treatments of interest.

Added value of this study

To our knowledge, the CAIRO5 trial is the first randomised phase 3 study to prospectively compare the currently most active systemic regimens in patients with initially unresectable colorectal cancer liver metastases in which CT scans were evaluated at baseline and during follow-up by a liver expert panel using predefined unresectability criteria at baseline. Moreover, to our knowledge, this is the first study comparing bevacizumab with an anti-EGFR antibody, both with a chemotherapy backbone, in which both *RAS* and *BRAF*^{V600} mutation status and sidedness of the primary tumour are prospectively considered. Our findings show that in patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour, or both, FOLFOXIRI plus bevacizumab significantly increases progression-free survival, response rate, and R0–1 resection or ablation rate compared with FOLFOX or FOLFIRI plus bevacizumab. In patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour no benefit was observed in median progression-free survival and R0–1 local treatment rate by the addition of panitumumab to FOLFOX or FOLFIRI compared to the addition of bevacizumab, despite the fact that the addition of panitumumab resulted in a significantly higher response rate. Chemotherapy plus panitumumab was associated with a significantly higher incidence of adverse events.

Implications of all the available evidence

Our results show that FOLFOXIRI plus bevacizumab should be considered as the currently optimal systemic induction regimen for patients with initially unresectable colorectal cancer liver metastases and a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour, or both. For patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour, the addition of panitumumab offered no advantage over bevacizumab in combination with FOLFOX or FOLFIRI. Results on overall survival should be awaited for final conclusions.

treatment, but do not allow for selecting an optimal systemic regimen and are subject to the same issues regarding the interpretation of results.[1] We aimed to find the optimal induction regimen for patients with initially unresectable colorectal cancer liver metastases.

Methods

Study design and participants

In this open-label, multicentre, randomised, phase 3 study (CAIRO5) of the Dutch Colorectal Cancer Group patients were enrolled at 46 secondary and tertiary centres in The Netherlands and one tertiary centre in Belgium (appendix p 2).

Eligible patients were 18 years or older, had histologically proven colorectal cancer with known *RAS*/*BRAF*^{V600E} mutation status, previously untreated and unresectable liver-only metastases (as centrally assessed by an expert panel of liver surgeons and radiologists) that were measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[4] on a CT scan obtained within 3 weeks of registration, WHO performance status of 0–1, a life expectancy of more than 12 weeks, no contraindications for liver surgery or ablation, resectable primary tumour if still in situ, and adequate organ function as determined by normal bone marrow function (haemoglobin ≥6·0 mmol/L, absolute neutrophil count ≥1·5×10^9/L, and platelets ≥100×10^9/L), renal function (serum creatinine ≤1·5×upper limit of normal [ULN] and creatinine clearance ≥30 mL/min), liver function (serum bilirubin ≤2×ULN and serum transaminases ≤5×ULN).

Exclusion criteria were extrahepatic metastases, serious comorbidity or any other condition preventing the safe administration of study treatments (both systemic and local treatment), major cardiovascular event (myocardial infarction, severe or unstable angina, congestive heart failure, or cerebrovascular accident) within 12 months before randomisation, uncontrolled hypertension or unsatisfactory blood pressure control with three or more antihypertensive drugs, previous systemic or local treatment for metastases, previous adjuvant chemotherapy unless completed 6 months or more before randomisation, previous intolerance to study drugs in the adjuvant setting, pregnant or lactating women, and a second primary malignancy within the past 5 years with the exception of adequately treated in situ carcinoma of any organ, basal cell carcinoma of the skin, or a second primary colorectal cancer.

The study was done in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The study was approved by the medical ethical committee of the Amsterdam University Medical Centre, Amsterdam, The Netherlands. Data monitoring was done by The Netherlands Comprehensive Cancer Organisation. A data and safety monitoring board assessed all serious adverse events and data. All patients provided written informed consent to study procedures before enrolment. The study protocol has been published previously,[5] and is in the appendix. Except for administrative issues, the protocol was amended only once, in relation to randomisation (detailed in later section).

Randomisation and masking

Patients with right-sided or *RAS* or *BRAF*^{V600E} mutated tumours were randomly assigned (1:1) to receive FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, and irinotecan) plus bevacizumab (group A) or FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan) plus bevacizumab (group B). Patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type tumours were randomly assigned (1:1) to receive FOLFOX or FOLFIRI plus bevacizumab (group C) or FOLFOX or FOLFIRI plus panitumumab (group D). The choice between FOLFOX or FOLFIRI was at the discretion of the local investigator based on patient preference. Randomisation was stratified by resectability of colorectal cancer liver metastases (potentially resectable *vs* permanently unresectable according to the panel), serum lactate dehydrogenase concentration (normal *vs* abnormal according to the cutoff value of the local laboratory), and treatment centre choice of irinotecan versus oxaliplatin, and *BRAF*^{V600E} mutation status (wild-type *vs* mutated, only for groups A and B). Randomisation was done centrally by The Netherlands Comprehensive Cancer Organisation according to Pocock's minimisation technique via a masked web-based allocation procedure (ALEA software version 17.1, FormsVision, Abcoude, Netherlands). Patients were enrolled by their treating physician. Investigators, physicians, and participants were not masked to treatment group allocation. The panel surgeons and radiologists were masked to treatment allocation.

Initially, randomisation was based on *RAS* mutation status only.[6] After the start of the trial, data emerged that patients with right-sided or *BRAF*^{V600E} mutated tumours did not derive benefit from anti-EGFR treatment; these data led to a protocol amendment (version 7.0; appendix), which was approved by the medical ethical committee.[2,3] As of February, 2017, patients with right-sided or *RAS* or *BRAF*^{V600E} mutated tumours were randomly assigned between groups A and B and not allocated to groups C or D, and patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type tumours were randomly assigned between groups C and D.

Procedures

Bevacizumab was administered intravenously at 5 mg/kg for 15–30 min. Panitumumab was administered intravenously at 6 mg/kg (first dose over 60 min, and if well tolerated subsequent doses were given over 30 min). FOLFIRI consisted of irinotecan at 180 mg/m² intravenously for 60 min together with folinic acid at 400 mg/m² intravenously for 120 min, followed by bolus fluorouracil at 400 mg/m² intravenously within 4 min,

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See **Online** for appendix

followed by continuous infusion of fluorouracil at 2400 mg/m² over 46 h. FOLFOX consisted of oxaliplatin at 85 mg/m² intravenously together with the same schedule of folinic acid and fluorouracil as in FOLFIRI. FOLFOXIRI consisted of irinotecan at 165 mg/m² intravenously for 60 min, followed by oxaliplatin at 85 mg/m² intravenously together with folinic acid at 400 mg/m² intravenously for 120 min, followed by continuous infusion of fluorouracil at 3200 mg/m² for 46 h. Treatment cycles were repeated every 14 days for a maximum of 12 cycles or until disease progression, unacceptable toxicity, or patient refusal. If local treatment was planned, bevacizumab was discontinued at least 5 weeks before surgery. Patients were allowed to receive an additional cycle of chemotherapy without bevacizumab during this period. Adjuvant systemic treatment without the targeted drug (bevacizumab or panitumumab) was recommended to be continued within 12 weeks of (final) local liver treatment to complete the planned 12 cycles. For patients who received no local treatment, maintenance treatment with fluorouracil and folinic acid plus targeted drug was recommended after 12 cycles of treatment. Dose modifications and dose delays were applied according to standard practice at the discretion of the local investigator. *RAS* and $BRAF^{V600E}$ mutation status were determined at the local laboratories using next generation sequencing, MassARRAY, high resolution melt analysis, Sanger sequencing, pyrosequencing, or PCR, which were accredited by external quality assurance programmes. Response evaluation via CT imaging was based on RECIST version 1.1 according to a masked central review by one of the panel radiologists from Amsterdam University Medical Centres and Radboud University Medical Centre. If progression occurred after completion of panel evaluations, it was assessed by the local radiologist without central review because the objective of the panel was to assess resectability or unresectability of colorectal cancer liver metastases and not disease progression. A CT scan of thorax and abdomen was done every 8 weeks until disease progression or death. Patients who had received local treatment of colorectal cancer liver metastases were followed up according to the national guidelines with an ultrasound or CT scan of the liver every 6 months for 2 years, then every 12 months up to 5 years after surgery. Before each cycle, adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, WHO performance status, results of physical examination, and blood pressure (in patients who received bevacizumab) were evaluated. No data on grade 1–2 adverse events were collected because these treatments are standard of care treatments. Sex was self-reported, and race and ethnicity information were not collected. Patients were followed up after discontinuation or completion of study treatment and data on subsequent treatments were collected. Local treatment was done in specialised liver surgery centres. These centres needed to fulfil key requirements, including availability of an interventional radiologist at all hours every day and two hepatobiliary surgeons, at least 20 resections per year, and mandatory participation in an annual audit, as defined by the Dutch Federation of Oncologic Societies.[7] Patients receiving systemic treatment outside these centres were referred to these specialised centres if necessary.

For the central liver expert panel, 15 liver surgeons and three abdominal radiologists from 13 Dutch centres and one Belgian centre that perform liver surgery were invited to participate. The panel evaluated resectability at baseline on the basis of predefined criteria to fulfil the inclusion criteria and again every 2 months during follow-up. Colorectal cancer liver metastases were considered unresectable at baseline if an R0 resection could not be done with surgical resection only in one stage based on a liver CT or MRI scan. Resectability during follow-up was assessed at first evaluation (after 8–9 weeks), and, if deemed appropriate, at the second (after 16–18 weeks) and the third (after 24–27 weeks) evaluations, and was based on less stringent resection criteria that allowed all established local treatments to reach an R0 resection with a sufficient future liver remnant (ie, surgery combined with ablation, two-stage hepatectomies, and portal vein embolisation). The design of the panel and its feasibility has previously been described.[8] Briefly, after evaluation by one radiologist, each CT scan with panel radiology report (including patient's age, location, resection [yes *vs* no] of primary tumour, and number of treatment cycles at follow-up) was evaluated by three randomly selected panel surgeons who independently categorised the patient (considering the different criteria for resectability at baseline versus follow-up) as having (1) resectable, (2) potentially resectable (which could either be technically resectable but systemic treatment was preferred to allow a more parenchymal-sparing approach or technically unresectable), or (3) permanently unresectable colorectal cancer liver metastases. Permanently unresectable was selected in case of expected failure of having a complete R0 resection or ablation of all colorectal cancer liver metastases at any time during systemic therapy. If no consensus (ie, same category selected by all three surgeons) was obtained, two additional surgeons were consulted, and the majority vote was accepted as the final vote. If there was no majority vote (eg, two for resectable, two for potentially resectable, and one for permanently unresectable), the panel chair determined the vote. If the final vote was permanently unresectable during follow-up, patients were not re-evaluated. If panel surgeons evaluated the liver metastases of a patient as resectable, they were asked to provide a detailed technical plan for the local treatment approach. The following items were included in the technical plan: modality (wedge resection, segmental resection, ablation, or [extended] hemihepatectomy) specified per segment, one-stage or two-stage approach, portal vein embolisation (no *vs* yes

and left *vs* right). The panel chair decided on one final technical plan based on the plans of the other panel surgeons. The panel conclusion was forwarded to the referring hospital, and, in case of resectable colorectal cancer liver metastases, the proposed local treatment advice was also sent to the referring hospital.

Outcomes

The primary outcome was progression-free survival, defined as the time from randomisation to disease progression according to RECIST version 1.1 or death from any cause, whichever occurred first. Patients without disease progression or death were censored on their last clinical visit date. Secondary outcomes were R0–1 resection rate (R1 defined as microscopic tumour involvement in the resection margin; hereafter referred to as complete local treatment because ablation was also allowed to achieve clearance of all colorectal cancer liver metastases), secondary progression-free survival, overall survival, objective response rate, toxicity (according to CTCAE version 4.0), postoperative morbidity (according to the Clavien Dindo grading system[9]), pathological complete response rate of resected lesions, and correlation of evaluation by the panel with outcome. We defined secondary progression-free survival as progression after interruption of first-line systemic treatment for more than 3 months due to planned local therapies of liver metastases or primary tumour, and the initial systemic treatment was resumed after progression-free survival. Secondary progression-free survival was calculated from the randomisation date to progression upon resumption of first-line systemic treatment. If a different systemic treatment was initiated after interruption, secondary progression-free survival was not applicable. Overall survival was defined as time from randomisation to death from any cause, and was censored if a patient was still alive on their last clinical visit date. Objective response rate was defined as the proportion of patients who had partial or complete response according to RECIST version 1.1. Masked panel evaluations were used for the assessment of resectability or unresectability and tumour response. However, for the evaluations of CT scans that

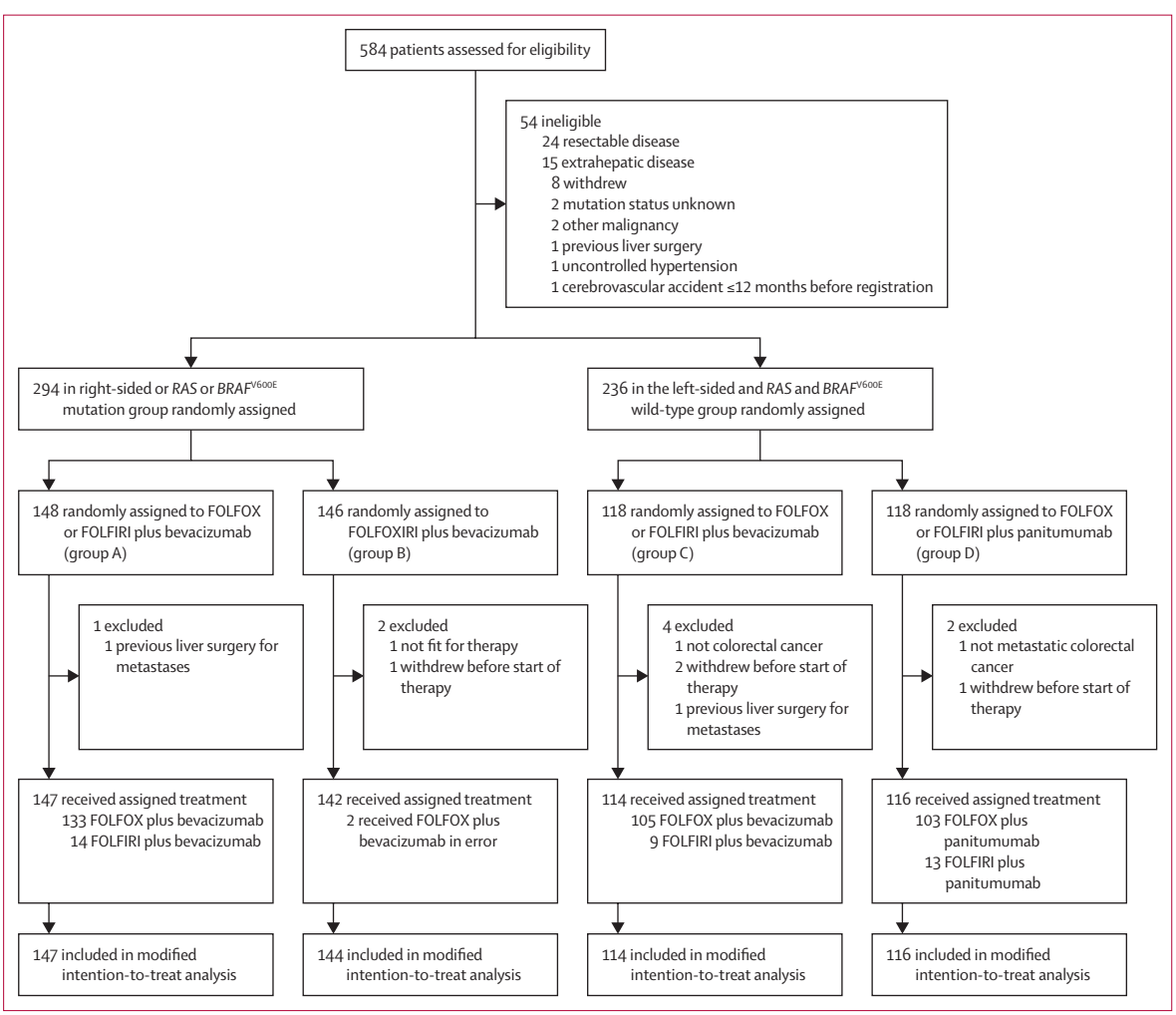

Figure 1: **Trial profile**

	Patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour or both		Patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour	
	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)	FOLFOXIRI plus bevacizumab (group B; n=144)	FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)	FOLFOX or FOLFIRI plus panitumumab (group D; n=116)
Age (years)	61 (54–70)	65 (57–70)	59 (53–67)	60 (52–69)
Sex				
Male	94 (64%)	87 (60%)	70 (61%)	73 (63%)
Female	53 (36%)	57 (40%)	44 (39%)	43 (37%)
WHO performance status				
0	94 (64%)	100 (69%)	74 (65%)	68 (59%)
1	51 (35%)	44 (31%)	40 (35%)	47 (41%)
2	1 (1%)	0	0	1 (1%)
Unknown	1 (1%)	0	0	0
Primary tumour site				
Right	60 (41%)	62 (43%)	5 (4%)	6 (5%)
Left	87 (59%)	82 (57%)	109 (96%)	110 (95%)
Time to metastases				
Synchronous*	127 (86%)	129 (90%)	100 (88%)	107 (92%)
Metachronous	20 (14%)	15 (10%)	14 (12%)	9 (8%)
Resection of primary tumour at baseline				
Yes	48 (33%)	40 (28%)	39 (34%)	35 (30%)
No	99 (67%)	104 (72%)	75 (66%)	81 (70%)
Previous adjuvant treatment				
Yes	7 (5%)	7 (5%)	5 (4%)	4 (3%)
No	140 (95%)	137 (95%)	109 (96%)	112 (97%)
Previous radiotherapy				
Yes	15 (10%)	20 (14%)	19 (16%)	14 (12%)
No	132 (90%)	124 (86%)	95 (83%)	102 (88%)
RAS mutation status				
RAS mutated	126 (86%)	124 (86%)	0	0
KRAS mutation	115/126 (91%)	114/124 (92%)	0	0
NRAS mutation	11/126 (9%)	9/124 (7%)	0	0
KRAS and *NRAS* mutation	0	1/124 (1%)	0	0
RAS wild-type	21 (14%)	20 (14%)	114 (100%)	116 (100%)
BRAF^{V600E} mutation status				
BRAF^{V600E} mutated	10 (7%)	12 (8%)	4 (3·5%)	3 (3%)
BRAF^{V600E} wild-type	137 (93%)	132 (92%)	110 (96·5%)	113 (97%)
RAS/*BRAF*^{V600E} mutation status and primary tumour site				
RAS mutated and right-sided	45 (31%)	46 (32%)	0	0
RAS mutated and left-sided	81 (55%)	78 (54%)	0	0
BRAF^{V600E} mutated and right-sided	4 (3%)	8 (6%)	2 (2%)	2 (2%)
BRAF^{V600E} mutated and left-sided	6 (4%)	4 (3%)	2 (2%)	1 (1%)
Wild-type and right-sided	11 (7%)	8 (6%)	3 (3%)	4 (3%)
Wild-type and left-sided	0	0	107 (94%)	109 (94%)
Lactate dehydrogenase				
More than ULN	71 (48%)	69 (48%)	61 (54%)	64 (55%)
Less than ULN	76 (52%)	75 (52%)	53 (46%)	52 (45%)
Number of liver metastases	12 (7–24)	12 (7–22)	12 (8–19)	12 (8–22)

(Table 1 continues on next page)

were done outside the scheduled panel evaluations (ie, in case of clinical suspicion of disease progression or when panel evaluations were discontinued when local treatment of colorectal cancer liver metastases was administered or colorectal cancer liver metastases were considered by the panel as permanently unresectable during systemic treatment), the assessment of the local investigator was used. Translational research as specified in the protocol and analysis of pathological response is ongoing and will be published separately.

Statistical analysis

To detect a hazard ratio (HR) of 0·70 for progression-free survival (in groups A *vs* B, and groups C *vs* D) with 80% power at a two-sided 5% significance level, including an interim analysis, 257 events were required for groups A and B and 256 for groups C and D. These calculations assumed a median progression-free survival of 8·7 months for group A and 11·6 months for group C. An interim analysis, monitored by the data and safety monitoring board, was planned to assess efficacy when approximately 50% of the total number of progression-free survival events were observed. Efficacy and non-binding futility boundaries were specified using Hwang-Shih-DeCani α-spending and β-spending functions.[10] The choice of parameters for the spending function used to control the overall (two-sided) type I error rate of 5% produced boundaries similar to the O'Brien–Fleming method.[11] p values of 0·006 or less were considered statistically significant in the interim analysis for efficacy.

Efficacy and safety analyses were based on a modified intention-to-treat analysis, excluding patients who withdrew consent before starting study treatment or who violated major entry criteria (no metastatic colorectal cancer, or previous liver surgery for colorectal cancer liver metastases). Progression-free survival curves by treatment group were estimated with the Kaplan-Meier method and were compared using the two-sided stratified log-rank test. A prespecified per-protocol analysis of patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type tumours, excluding patients with right-sided or *BRAF*^{V600E} mutated tumours, or both, was done for groups C and D. HRs and 95% CIs were calculated with a stratified Cox proportional hazards analysis. The proportional hazards assumption was met according to a test for independence between scaled Schoenfeld residuals and time (groups A and B p=0·074; group C and D p=0·99).[12] Visual inspection confirmed this (data not shown). Progression-free survival for patients with and without local treatment were analysed per group in a post-hoc analysis. Prespecified subgroup analyses and Cox regression models with treatment-by-subgroup interaction terms were done for potentially resectable versus permanently unresectable metastases (panel decision), and in groups A and B *RAS* versus *BRAF*^{V600E} mutation status. Prespecified subgroup analyses were planned to evaluate the outcome of

FOLFIRI versus FOLFOX-treated patients, and R0 versus R1 resected patients. Prespecified analyses to evaluate the prognostic value of *RAS* and *BRAF*^{V600E} mutations for progression-free survival were done in groups A and B. Subgroup analyses with mutation status were not done for groups C and D because patients with *RAS* or *BRAF*^{V600E} mutations were no longer randomly assigned in these arms after protocol amendment 7.0. Secondary outcomes were compared with Fisher's exact test. Overall survival will be analysed when the data is considered mature by the statistical team. Toxicities were compared between the different randomised groups with a Fisher's exact test. Median depth of response, defined as the relative change in the sum of longest diameters of RECIST target lesions at the nadir compared with baseline, was determined for groups C and D as a post-hoc exploratory outcome. Median depth of response has been shown to be of additional value only when evaluating anti-EGFR therapy, so was not analysed in groups A and B. For outcomes of response, patients without post-baseline measurements were classified as not evaluable and were not included in the depth of response analysis. Statistical analyses were done using SAS (version 9.4) and R (version 4.0.3). This trial is registered with ClinicalTrials.gov, NCT02162563, and European Clinical Trials Database, 2013-005435-24.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 13, 2014, and Jan 31, 2022, 584 patients were assessed for eligibility, of whom 530 (327 [62%] male and 203 [38%] female; median age 62 years [IQR 54–69]) were randomly assigned: 148 (28%) patients to group A, 146 (28%) patients to group B, 118 (22%) patients to group C, and 118 (22%) patients to group D (figure 1). Due to entry criteria or withdrawal of consent before starting study treatment, nine patients were excluded, resulting in 147 patients in group A, 144 in group B, 114 in group C, and 116 in group D being included in the modified intention-to-treat analyses. Baseline characteristics are in table 1. Most patients in all treatment groups had synchronous disease, had their primary tumour in situ, and had colorectal cancer liver metastases that were considered to be potentially resectable by the liver expert panel provided that sufficient downsizing by systemic induction treatment would occur. The median number of colorectal cancer liver metastases in all treatment groups was 12 (table 1). Before protocol amendment 7.0, 14 patients with a right-sided or *BRAF*^{V600E} mutated tumour or both were randomly assigned to groups C or D. In March, 2022, the steering group of the study followed the advice of the data and safety monitoring board to discontinue accrual in groups C and D due to futility.

	Patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour or both		Patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour	
	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)	FOLFOXIRI plus bevacizumab (group B; n=144)	FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)	FOLFOX or FOLFIRI plus panitumumab (group D; n=116)
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Size of largest liver metastasis (mm)	42 (27–66)	39 (25–60)	40 (27–75)	47 (32–67)
Number of liver segments involved	6 (5–7)	6 (5–8)	6 (5–7)	6 (5–8)
Distribution of liver metastases				
Unilobar	137 (93%)	138 (96%)	110 (96%)	110 (95%)
Bilobar	10 (7%)	6 (4%)	4 (4%)	6 (5%)
Fong risk score				
Low	6 (4%)	3 (2%)	0	3 (3%)
Medium	114 (78%)	106 (74%)	83 (73%)	87 (75%)
High	27 (18%)	35 (24%)	31 (27%)	26 (22%)
Resectability according to panel				
Permanently unresectable	18 (12%)	21 (15%)	20 (18%)	20 (17%)
Potentially resectable	129 (88%)	123 (85%)	94 (82%)	96 (83%)

Data are n (%) or median (IQR). Before protocol amendment 7.0, 14 patients with a right-sided or *BRAF*^{V600E} mutated tumour or both were randomly assigned to groups C or D. ULN=upper limit of normal. *Synchronous is defined as metastases diagnosed within 6 months after diagnosis of the primary tumour.

Table 1: **Baseline characteristics**

All patients in groups A, C, and D received their originally assigned treatment regimens; two patients in group B received FOLFOX-bevacizumab instead of their originally assigned treatment (figure 1). The median number of systemic treatment cycles (excluding postoperative and maintenance treatment) was eight cycles (IQR 5–11) in group A, eight (5–10) in group B, seven (5–10) in group C, and six (5–9) in group D. Maintenance treatment, consisting of a fluoropyrimidine with or without a targeted drug, was given in 22 (28%) of 79 patients in group A versus 28 (45%) of 62 patients in group B who received no local treatment, and 18 (50%) of 36 patients in group C versus eight (22%) of 36 patients in group D receiving no local treatment.

The median follow-up at the time of this analysis was 51·1 months (95% CI 47·7–53·1) in groups A and B and 49·9 months (44·5–52·5) in group C and D. With 271 observed events, median progression-free survival was 9·0 months (95% CI 7·7–10·5) in group A versus 10·6 months (9·9–12·1) in group B (stratified HR 0·76 [95% CI 0·60–0·98]; p=0·032; figure 2A). With 205 events, median progression free survival was 10·8 months (95% CI 9·9–12·6) in group C versus 10·4 months (9·8–13·0) in group D (stratified HR 1·11 [95% CI 0·84–1·48]; p=0·46; figure 2B). Progression-free survival events were reported in 140 (95%; 136 progressions and four deaths) patients in group A, 131 (91%; 118 progressions and 13 deaths) in group B,

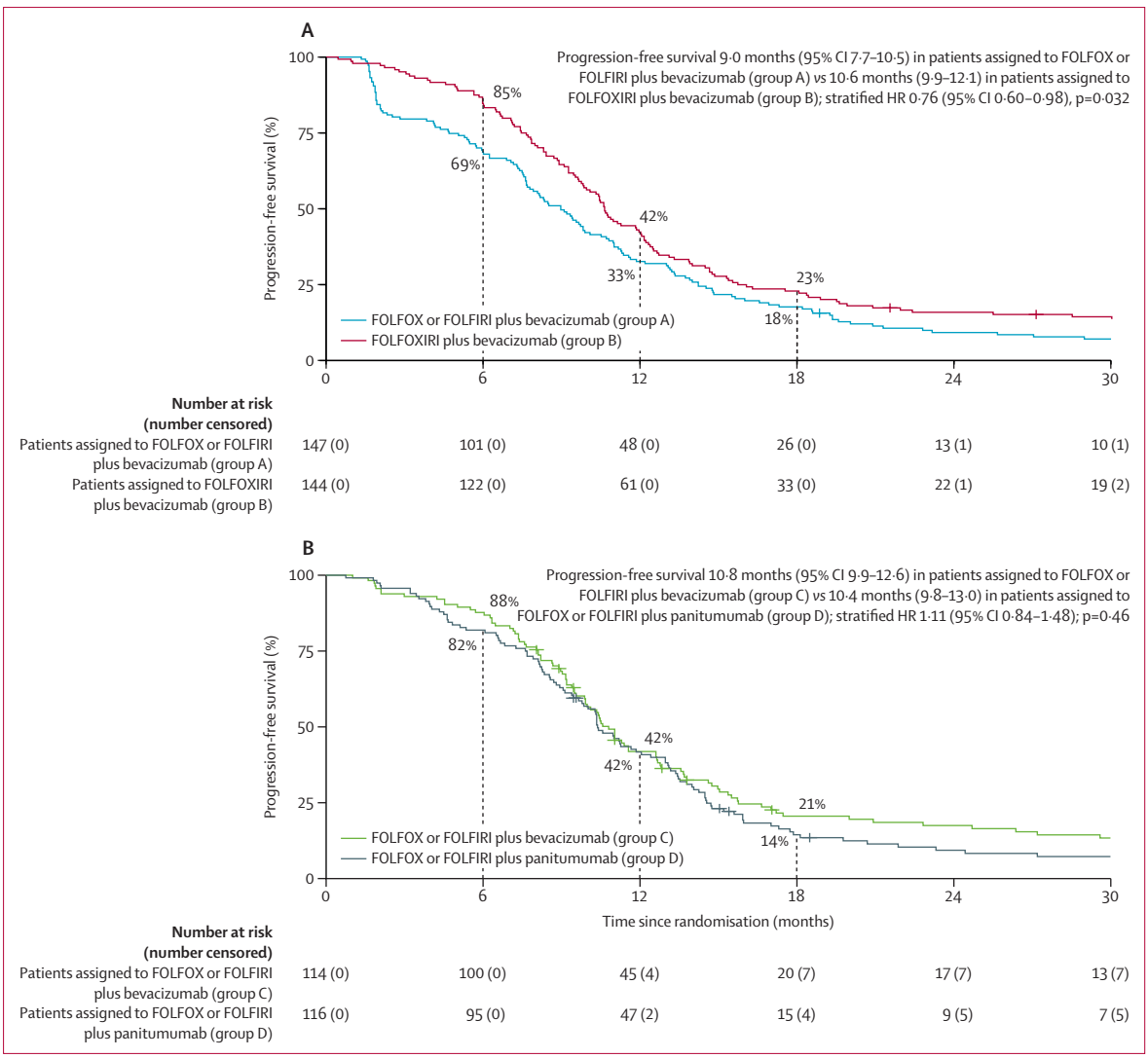

Figure 2: **Progression-free survival in the intention-to-treat analysis**
(A) Progression-free survival in patients with right-sided or *RAS* or *BRAF*^{V600E} mutated primary tumour randomly assigned to receive FOLFOX or FOLFIRI plus bevacizumab (group A) and FOLFOXIRI plus bevacizumab (group B). (B) Progression-free survival in patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type primary tumour randomly assigned to receive FOLFOX or FOLFIRI plus bevacizumab (group C) and FOLFOX or FOLFIRI plus panitumumab (group D). HR=hazard ratio.

99 (87%; 98 progressions and one death) in group C, and 106 (91%; 100 progressions and six deaths) in group D.

In the per-protocol analysis of patients with left-sided and *RAS* and *BRAF*^{V600E} wild-type primary tumours, median progression-free survival was 11·0 months (95% CI 10·0–12·8) in group C versus 10·6 months (9·7–13·0) in group D (stratified HR 1·12 [95% CI 0·83–1·50]; p=0·46) with 191 events; 92 (86%; 91 progressions and one death) events in group C and 99 (91%; 93 progressions and six deaths) in group D. Median progression-free survival in patients receiving local treatment was significantly longer than in patients not receiving local treatment in all treatment arms (group A HR 0·55 [95% CI 0·40–0·78]; p=0·0005; group B 0·48 [0·34–0·68]; p<0·0001; group C 0·52 [0·34–0·80]; p=0·0023; group D 0·49 [0·32–0·74]; p=0·0005; appendix p 3). Progression-free survival was not significantly different in patients with R0 versus R1 resections (HR 1·37 [95% CI 0·97–1·92]; p=0·083; appendix p 4). The prespecified subgroup analyses showed no significant interaction between baseline resectability or *RAS* and *BRAF*^{V600E} mutation status (for groups A and B) and progression-free survival (appendix p 5). The subgroup analysis comparing patients who received FOLFOX versus those who received FOLFIRI was not done because the subgroups were too small (figure 1). Progression-free survival was not significantly different between patients with *RAS* mutated, *BRAF*^{V600E} mutated, and right-sided wild-type tumours in groups A and B (p=0·44; appendix p 6). None of the patients met

the criteria for analysing secondary progression-free survival. Best overall response is shown in table 2. In a post-hoc analysis, the median depth of response was 33% (IQR 21–44) in group C versus 49% (34–61) in group D (p<0·0001; appendix p 7). Data on overall survival were not yet mature at the time of analysis and will be published separately along with subsequent treatments. The total number of patients who died was 219 (75%) in groups A and B and 125 (54%) in groups C and D.

Consensus among panel surgeons was present in 345 (66%) of 521 patients at baseline, and in 286 (42%) of 689 follow-up evaluations. The panel conclusion was forwarded to the local centres within a median of 6 days (IQR 3–9) after uploading. According to the liver expert panel, the number of patients who were considered to have resectable colorectal cancer liver metastases during follow-up was 84 (57%) of 147 patients in group A, 92 (64%) of 144 in group B, 83 (73%) of 114 in group C, and 87 (75%) of 116 in group D. After a median of seven induction cycles (IQR 6–9) and 136 days (IQR 112–176), 68 (46%) of 147 patients in group A received local treatment versus 82 (57%) of 144 patients in group B who received local treatment after six induction cycles (IQR 5–9) and a median of 141 (IQR 108–176) days, (p=0·079); complete local treatment was done in 54 (37%) patients in group A versus 74 (51%) patients in group B (p=0·013). 78 (68%) patients in group C versus 80 (69%) patients in group D received local treatment (p=1·00), and 66 (58%) patients in group C versus 67 (58%) patients in group D (p=1·00) received complete local treatment after a median of six induction cycles (IQR 5–8) and 134 days (IQR 111–166) in group C versus six induction cycles (IQR 5–9) and 150 days (IQR 115–179) in group D. Conversion to local treatment according to systemic treatment response is reported in the appendix (p 8). Complete local treatment was done in seven (9%) of 79 patients who were considered to have permanently unresectable colorectal cancer liver metastases at baseline: one in group B, three in group C, and three in group D. In patients receiving liver-first complete local treatment of colorectal cancer liver metastases, the primary tumour was subsequently resected in 23 (70%) of 33 patients in group A, 39 (76%) of 51 patients in group B,

	Patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour, or both			Patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour		
	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)	FOLFOXIRI plus bevacizumab (group B; n=144)	p value	FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)	FOLFOX or FOLFIRI plus panitumumab (group D; n=116)	p value
Objective response	49 (33%)	78 (54%)	0·0004	60 (53%)	93 (80%)	<0·0001
Disease control	119 (81%)	134 (93%)	0·0028	105 (92%)	109 (94%)	0·61
Complete response	0	1 (1%)	..	0	1 (1%)	..
Partial response	49 (33%)	77 (53%)	..	60 (53%)	92 (79%)	..
Stable disease	70 (48%)	56 (39%)	..	45 (39%)	16 (14%)	..
Progressive disease	27 (18%)	6 (4%)	..	7 (6%)	4 (3%)	..
Not evaluable	1 (1%)	4 (3%)	..	2 (2%)	3 (3%)	..

Objective response was defined as a partial or complete response. Disease control was defined as a partial or complete response and stable disease.

Table 2: **Best overall response**

	Patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour, or both			Patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour		
	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)	FOLFOXIRI plus bevacizumab (group B; n=144)	p value	FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)	FOLFOX or FOLFIRI plus panitumumab (group D; n=116)	p value
Local treatment (resection or ablation)	68 (46%)	82 (57%)	0·079	78 (68%)	80 (69%)	1·00
Complete local treatment*	54 (37%)	74 (51%)	0·013	66 (58%)	67 (58%)	1·00
Details of patients who received complete local treatment						
Two-stage surgery	6 (11%)	21 (28%)	0·0027	14 (21%)	18 (27%)	0·54
Major resection*	25 (46%)	39 (53%)	0·59	34 (52%)	29 (43%)	0·39
Type of procedure						
Surgical resection only	26 (48%)	38 (51%)	..	31 (47%)	28 (42%)	..
Ablation only	4 (7%)	1 (1%)	..	4 (6%)	3 (4%)	..
Combination of resection and ablation	24 (44%)	35 (47%)	..	31 (47%)	36 (54%)	..

*All liver metastases treated with an R0–1 resection or ablation, or both. †Resection of at least three segments or an (extended) hemihepatectomy.

Table 3: **Details of local treatment**

	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)			FOLFOXIRI plus bevacizumab (group B; n=144)			FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)			FOLFOX or FOLFIRI plus panitumumab (group D; n=116)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Neutropenia	11 (7%)	8 (5%)	0	25 (17%)	32 (22%)	0	20 (18%)	9 (8%)	0	16 (14%)	8 (7%)	0
Hypertension	21 (14%)	0	0	20 (14%)	0	0	20 (18%)	0	0	8 (7%)	0	0
Diarrhoea	5 (3%)	0	0	27 (19%)	1 (1%)	0	5 (4%)	0	0	17 (15%)	1 (1%)	0
Leukopenia	5 (3%)	0	0	14 (10%)	2 (1%)	0	8 (7%)	1 (1%)	0	4 (3%)	2 (2%)	0
Mucositis or stomatitis	6 (4%)	1 (1%)	0	11 (8%)	1 (1%)	0	4 (4%)	0	0	11 (9%)	0	0
Thromboembolic event	15 (10%)	0	0	8 (6%)	1 (1%)	0	6 (5%)	0	0	2 (2%)	0	1 (1%)
Skin toxicity	0	0	0	0	0	0	1 (1%)	0	0	27 (23%)	2 (2%)	0
Peripheral sensory neuropathy	7 (5%)	0	0	6 (4%)	0	0	10 (9%)	1 (1%)	0	5 (4%)	0	0
Fatigue	8 (5%)	0	0	8 (6%)	0	0	3 (3%)	0	0	7 (6%)	0	0
Hypokalaemia	3 (2%)	0	0	6 (4%)	1 (1%)	0	4 (4%)	0	0	6 (5%)	0	0
Infection	6 (4%)	1 (1%)	0	5 (3%)	0	0	6 (5%)	1 (1%)	0	1 (1%)	0	0
Febrile neutropenia	3 (2%)	1 (1%)	0	10 (7%)	0	0	3 (3%)	1 (1%)	0	1 (1%)	0	0
Gamma glutamyl transferase increased	6 (4%)	0	0	1 (1%)	0	0	2 (2%)	0	0	5 (4%)	0	0
Nausea	4 (3%)	0	0	7 (5%)	0	0	0	0	0	2 (2%)	0	0
Fever	4 (3%)	0	0	6 (4%)	0	0	1 (1%)	0	0	0	0	0
Dehydration	1 (1%)	0	0	6 (4%)	0	0	1 (1%)	0	0	2 (2%)	0	0
Ileus	1 (1%)	1 (1%)	0	3 (2%)	0	0	2 (2%)	0	0	2 (2%)	1 (1%)	0
Vomiting	1 (1%)	0	0	5 (3%)	0	0	0	0	0	4 (3%)	0	0
Anaemia	0	0	0	4 (3%)	0	0	2 (2%)	0	0	3 (3%)	0	0
Anorexia	0	0	0	5 (3%)	0	0	0	0	0	4 (3%)	0	0
Hyperglycaemia	2 (1%)	0	0	1 (1%)	0	0	1 (1%)	2 (2%)	0	1 (1%)	0	0
Abdominal pain	1 (1%)	0	0	3 (2%)	0	0	2 (2%)	0	0	0	0	0
Hand-foot syndrome	0	0	0	0	0	0	2 (2%)	0	0	4 (3%)	0	0
Hyponatraemia	0	0	0	4 (3%)	0	0	0	0	0	2 (2%)	0	0
Urinary tract infection	2 (1%)	0	0	3 (2%)	0	0	0	0	0	1 (1%)	0	0
Weight loss	0	0	0	5 (3%)	0	0	0	0	0	1 (1%)	0	0
Colonic perforation	1 (1%)	2 (1%)	0	1 (1%)	0	0	0	0	0	0	1 (1%)	0
Anal fistula	1 (1%)	0	0	4 (3%)	0	0	0	0	0	0	0	0
Dyspnoea	2 (1%)	0	0	2 (1%)	0	0	1 (1%)	0	0	0	0	0
Hypomagnesaemia	0	0	0	0	1 (1%)	0	0	0	0	4 (3%)	0	0
Sepsis	0	2 (1%)	0	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0
Syncope	2 (1%)	0	0	1 (1%)	0	0	2 (2%)	0	0	0	0	0
Alkaline phosphatase increased	2 (1%)	0	0	1 (1%)	0	0	0	0	0	1 (1%)	0	0
Alanine aminotransferase increased	1 (1%)	0	0	2 (1%)	0	0	1 (1%)	0	0	0	0	0
Anal pain	1 (1%)	0	0	3 (2%)	0	0	0	0	0	0	0	0
Chest pain	0	0	0	1 (1%)	0	0	3 (3%)	0	0	0	0	0
Gastroenteritis	2 (1%)	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Malaise	1 (1%)	0	0	1 (1%)	0	0	2 (2%)	0	0	0	0	0
Acute kidney injury	0	0	0	1 (1%)	1 (1%)	0	0	0	0	1 (1%)	0	0
Aspartate aminotransferase increased	1 (1%)	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Catheter-related infection	2 (1%)	0	0	1 (1%)	0	0	0	0	0	0	0	0
Headache	1 (1%)	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Hypophosphataemia	2 (1%)	0	0	1 (1%)	0	0	0	0	0	0	0	0
Myocardial infarction	0	0	0	1 (1%)	0	0	1 (1%)	0	0	1 (1%)	0	0
Pain	0	0	0	2 (1%)	0	0	1 (1%)	0	0	0	0	0
Paronychia	0	0	0	0	0	0	0	0	0	3 (3%)	0	0
Thrombocytopenia	0	0	0	1 (1%)	0	0	1 (1%)	0	0	1 (1%)	0	0
Colonic obstruction	0	0	0	1 (1%)	0	0	0	0	0	0	1 (1%)	0
Colonic fistula	0	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Creatinine increased	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0	0	0

(Table 4 continues on next page)

	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)			FOLFOXIRI plus bevacizumab (group B; n=144)			FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)			FOLFOX or FOLFIRI plus panitumumab (group D; n=116)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
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Duodenal ulcer	0	0	0	2 (1%)	0	0	0	0	0	0	0	0
Hypotension	1 (1%)	0	0	1 (1%)	0	0	0	0	0	0	0	0
Infusion related reaction	0	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Lung infection	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0	0	0
Multiorgan failure	0	0	0	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Neurological disorders, other	0	0	0	0	0	0	1 (1%)	0	0	1 (1%)	0	0
Obesity	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0	0	0
Pain in extremity	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0	0	0
Upper respiratory infection	2 (1%)	0	0	0	0	0	0	0	0	0	0	0
Acute coronary syndrome	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Ankle fracture	0	0	0	0	0	0	1 (1%)	0	0	0	0	0
Arthralgia	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Aspiration	0	0	0	0	1 (1%)	0	0	0	0	0	0	0
Colitis	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Atrial fibrillation	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Cardiac arrest	0	0	0	0	0	0	0	0	0	0	0	1 (1%)
Constrictive pericarditis	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Confusion	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Constipation	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Coronary artery spasm	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Cough	0	0	0	0	1 (1%)	0	0	0	0	0	0	0
Delirium	0	0	0	0	0	0	1 (1%)	0	0	0	0	0
Depression	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Dizziness	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Dysarthria	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Dyspepsia	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Dysphagia	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Electrocardiogram QT corrected interval prolonged	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Enterocolitis	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Oesophagitis	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Generalised muscle weakness	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
General disorders, malaise	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Glucose intolerance	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Granulocytopenia	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Haematuria	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Hearing impaired	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Hepatic failure	0	1 (1%)	0	0	0	0	0	0	0	0	0	0
Hiccups	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Hypercalcaemia	0	1 (1%)	0	0	0	0	0	0	0	0	0	0
Hypernatraemia	0	0	0	0	1 (1%)	0	0	0	0	0	0	0
Hypoalbuminaemia	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Port-A-Cath broke through	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Vascular access complication	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Insomnia	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Lung embolism	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Meningitis	0	0	0	1 (1%)	0	0	0	0	0	0	0	0
Myalgia	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Periodontal disease	1 (1%)	0	0	0	0	0	0	0	0	0	0	0

(Table 4 continues on next page)

	FOLFOX or FOLFIRI plus bevacizumab (group A; n=147)			FOLFOXIRI plus bevacizumab (group B; n=144)			FOLFOX or FOLFIRI plus bevacizumab (group C; n=114)			FOLFOX or FOLFIRI plus panitumumab (group D; n=116)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
(Continued from previous page)												
Premature menopause	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Pneumothorax	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Proximal muscle weakness	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Renal insufficiency	0	0	0	0	0	0	1 (1%)	0	0	0	0	0
Rectal pain	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Stevens-Johnson syndrome	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Small bowel ischaemia	0	0	0	0	1 (1%)	0	0	0	0	0	0	0
Stomach pain	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Treatment-related secondary malignancy	0	0	0	0	0	0	0	0	0	0	0	1 (1%)
Tooth infection	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Weight gain	0	0	0	0	0	0	1 (1%)	0	0	0	0	0
Xerosis	0	0	0	0	0	0	0	0	0	1 (1%)	0	0

Data are n (%). No data on grade 1–2 adverse events were collected.

Table 4: **All-cause grade 3–5 adverse events during induction and maintenance treatment**

27 (73%) of 37 patients in group C, and 31 (67%) of 46 patients in group D. Local liver treatment was performed against panel advice in three (2%) patients in group A and five patients each in group B (3%), C (4%), and D (4%). Details of complete local treatment are in table 3. One patient in groups A, C, and D and two patients in group B who had complete local treatment also received radiotherapy for a lesion which could not be treated with surgery nor ablation. Adjuvant chemotherapy was administered in 26 (38%) of 68 patients in group A versus 39 (48%) of 82 patients in group B who received local treatment, and 28 (36%) of 78 patients in group C versus 33 (41%) of 80 patients in group D who received local treatment.

Any grade 3 or worse adverse events occurred in 87 (59%) of 147 patients in group A versus 109 (76%) of 144 patients in group B (p=0·0027), and 61 (54%) of 114 patients in group C versus 80 (69%) of 116 patients in group D (p=0·021) (table 4). The most frequent grade 3–4 events in groups A and B were neutropenia (19 [13%] patients *vs* 57 [40%] patients; p<0·0001), hypertension (21 [14%] *vs* 20 [14%]; p=1·00), and diarrhoea (five [3%] *vs* 28 [19%] patients; p<0·0001). The most frequent grade 3–4 events in groups C and D were neutropenia (29 [25%] patients *vs* 24 [21%] patients; p=0·44), skin toxicity (one [1%] *vs* 29 [25%]; p<0·0001), hypertension (20 [18%] *vs* eight [7%]; p=0·016), and diarrhoea (five [4%] *vs* 18 [16%]; p=0·0072). Dose reductions due to toxicity were required in 45 (31%) patients in group A and 79 (55%) patients in group B, and 50 (44%) patients in group C and 62 (53%) patients in group D. Discontinuation of treatment for treatment-related toxicity occurred in five (3%) patients in group A, ten (7%) in group B, three (3%) in group C, and five (4%) in group D (appendix p 9). Patients could discontinue treatment for more than one reason, and the most common was fatigue in group A (two [40%] patients), and peripheral neuropathy in groups B (three [30%] patients), C (two [67%] patients), and D (two [40%] patients). Postoperative complications occurred in 27 (40%) patients in group A versus 42 (51%) patients in group B (p=0·19), and Clavien Dindo grade 3 or worse in ten (15%) patients in group A versus 22 (27%) patients in group B (p=0·076). 33 (42%) patients in group C versus 34 (43%) patients in group D (p=1·00) had postoperative complications, and 17 (22%) patients in group C versus 12 (15%) patients in group D (p=0·31) had Clavien Dindo grade 3 or worse complications. Serious adverse events occurred in 46 (31%) patients in group A, 75 (52%) patients in group B, 41 (36%) patients in group C, and 49 (42%) patients in group D (appendix p 10). Four (1%) deaths, two in group B and two in group D, were reported to be related to adverse events: sepsis (group B), multiorgan failure (group B), cardiac arrest (group D), and pulmonary embolism (group D). One death due to pneumonia occurred during maintenance treatment in group B, which might have been related to treatment. Five (1%) deaths were considered related to local liver treatment: portal vein thrombosis (group B), septic shock and liver failure (group B), multiorgan failure (group B and C), and abdominal sepsis (group D). One treatment-related sudden death in group B occurred after the primary tumour resection.

Discussion

To our knowledge, this is the first study in which systemic induction regimens have been prospectively compared in patients with initially unresectable colorectal cancer liver metastases with the use of a central expert panel and

predefined criteria for unresectability at baseline. Moreover, to our knowledge, the CAIRO5 trial is the first randomised study in patients with metastatic colorectal cancer comparing bevacizumab with an anti-EGFR antibody, both with a chemotherapy backbone, in which both *RAS* and *BRAF*^{V600E} mutation status and sidedness of the primary tumour are prospectively considered. Our results show that in initially unresectable colorectal cancer liver metastases, patients with a right-sided or *RAS* or *BRAF*^{V600E} mutated tumour, or both, FOLFOXIRI plus bevacizumab is associated with a significantly longer progression-free survival, higher response rate, and higher complete local treatment rate than is FOLFOX or FOLFIRI plus bevacizumab. Although the benefit in median progression-free survival was small, the increase in the proportion of patients who had complete local treatment could be considered of greater clinical significance. In patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour, there was no difference in median progression-free survival between the addition of either bevacizumab or panitumumab to FOLFOX or FOLFIRI. The addition of panitumumab significantly increased objective response rate and depth of response (post hoc), but this did not translate into an increased local treatment rate of colorectal cancer liver metastases, whereas it was associated with increased toxicity.

Comparing our results on conversion rates with other prospective studies in patients with unresectable colorectal cancer liver metastases or with retrospective subgroup analyses from studies of patients with metastatic colorectal cancer is challenging due to the absence of consensus on resectability or unresectability criteria, and differences in trial design and study populations. This results in a varying a priori probability of local treatment rates across studies. For instance, the rate of secondary local treatments depends to a large extent on the proportion of patients with permanently unresectable colorectal cancer liver metastases at baseline, which is unknown in most, if not all, studies. Obviously, the absence of a transparent internationally accepted definition for this subgroup plays an important role. However, the absence of consensus on criteria for resectability or unresectability implies that studies of patients with initially unresectable colorectal cancer liver metastases might have included patients who were retrospectively considered as having upfront resectable colorectal cancer liver metastases.[13,14] Furthermore, previous studies have not incorporated *RAS* and *BRAF*^{V600E} mutation status and sidedness of the primary tumour as a prospective parameter in their design, mostly because these studies were done before the relevance of these parameters became known. Concerns regarding potential selection biases associated with unplanned retrospective subset analyses of these parameters have been expressed.[15] Therefore, direct comparisons between our results and those of previous prospective studies in patients with unresectable colorectal cancer liver metastases do not appear to be appropriate.[13,16–18] Also, the options for local treatment of colorectal cancer liver metastases have expanded over the past decade, resulting in a larger number of patients with colorectal cancer liver metastases being eligible for local treatment, and thus hampering comparisons with older studies.[19] Providing the proportion of patients in whom conversion to local treatment was reported without data of its long-term outcome, as is especially the case in retrospective subgroup analyses, might be misleading.[1] A trend towards a lower overall survival in patients with locally treated colorectal cancer liver metastases who had more serious postoperative complications has been observed.[19] However, overall survival for our analysis population was not mature at the time of reporting and will be reported elsewhere.

A strength of our study was the inclusion of all patients with initially unresectable colorectal cancer liver metastases based on transparent and uniform entry criteria established by general consensus between Dutch Belgian liver surgeons, allowing a homogeneous study population, which was stratified by the currently most relevant prognostic and predictive parameters. Our baseline unresectability criterion (unresectable if an R0 resection could not be achieved with surgical resection only in one stage) implies that some patients could have been treated locally upfront by adding ablation or by performing a two-stage resection with or without portal vein embolisation. However, perioperative systemic treatment is often administered to these patients as well,[20] and since patients were stratified by resectability status (permanently unresectable versus potentially resectable colorectal cancer liver metastases) this was unlikely to have caused an imbalance between the treatment groups. An additional strength of our study is that resectability was also assessed by the liver expert panel during follow-up. The observed variability between liver surgeons in assessing resectability or unresectability, in our opinion, supports the evaluation by a panel, since our data suggest that a substantial number of patients might have been denied the option of local treatment when evaluated by a single liver surgeon.

Several issues deserve attention. In patients with a *RAS* or *BRAF*^{V600E} mutated or right-sided primary tumour, or both, progressive disease as best response was more often observed in the FOLFOX or FOLFIRI group than in the FOLFOXIRI group, 18% versus 4%. This might have resulted in missing out on local treatment due to early progression, and supports the benefit of FOLFOXIRI plus bevacizumab.

Our finding that anti-EGFR-based treatment was not superior to anti-VEGF-based treatment in terms of progression-free survival in patients with a *RAS* and *BRAF*^{V600E} wild-type and left-sided primary tumour is in line with previous results in patients with metastatic colorectal cancer not selected for metastatic site.[21–24] However, notably, the relevance of progression-free

survival as a surrogate outcome for overall survival has been questioned.[25,26] Consequently, alternative outcomes, such as early tumour shrinkage and depth of response have been suggested.[27] The significantly higher objective response rate and depth of response (post hoc) with the addition of panitumumab versus bevacizumab in our study, which is also reported in other studies,[23,24] did not translate into a higher conversion rate of colorectal cancer liver metastases. A possible explanation might be that in this group of patients with a poor prognosis, as indicated by the high number of colorectal cancer liver metastases or an increase in objective response rate or depth of response beyond a specific cutoff, does not increase the conversion rate to locally treatable colorectal cancer liver metastases due to limiting surgical-technical factors, such as colorectal cancer liver metastases involving liver vessels and biliary structures or too many liver segments. This will be analysed in the future, and data on overall survival should be awaited before drawing final conclusions.

The significantly higher incidence of grade 3 or worse adverse events with the use of FOLFOXIRI versus FOLFOX or FOLFIRI plus bevacizumab is consistent with previous studies,[28] and was mainly caused by a higher incidence of diarrhoea and non-febrile neutropenia. Grade 3 or worse adverse events were also more common in patients treated with FOLFOX or FOLFIRI plus panitumumab than FOLFOX or FOLFIRI plus bevacizumab, which is in line with previous studies.[23,24] This difference was mainly caused by a higher incidence of skin toxicity and diarrhoea in patients treated with panitumumab, whereas bevacizumab was associated with a higher incidence of hypertension.

Adjuvant chemotherapy after local treatment was delivered to only a small number of patients. This might have been due to a delayed patient recovery after surgery, but is more likely because Dutch guidelines do not recommend treatment with adjuvant chemotherapy because a benefit in overall survival has not been clearly shown for adjuvant treatment in patients with upfront resectable colorectal cancer liver metastases,[29] and data on its value in patients who converted to resectable colorectal cancer liver metastases after downsizing are not available.

A limitation of this study might be that the use of FOLFOXIRI was not investigated in patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour. However, in this population a propensity score-based analysis showed no benefit of FOLFOXIRI plus bevacizumab compared with FOLFOX plus panitumumab,[30] and a phase 3 study showed no benefit of FOLFOXIRI plus panitumumab compared with FOLFOX plus panitumumab.[31] Our results show that FOLFOXIRI plus bevacizumab should be preferred as a systemic induction regimen for patients with initially unresectable colorectal cancer liver metastases and a right-side or *RAS* or *BRAF*^{V600E} mutated tumour, or both. For patients with a left-sided and *RAS* and *BRAF*^{V600E} wild-type tumour, the addition of panitumumab offered no advantage over bevacizumab in combination with FOLFOX or FOLFIRI. However, data on overall survival should be awaited before drawing definitive conclusions.

Contributors

CJAP designed the study. KB and MJGB coordinated the study. MJGB, KB, ML-Y, R-JS, and CJAP analysed and interpreted the data and wrote the report. ML-Y designed the methods and did the statistical analysis. AMR, CV, GK, IQM, JHWdW, JMK, KPdJ, KPvL, MFG, MJvA, MRWE, MSLL, and R-JS did the panel evaluations. JMK and R-JS were panel chairs. OJLL, JWBdG, HD, HHH, MPH, BdV, BCMH, EDK, FE, RJvA, DM-vS, and CJAP recruited patients. MJGB, AK, and ML-Y verified the raw data. All authors had access to the data in the study and approved the final version of the manuscript. All authors take responsibility for decision to submit for publication.

Declaration of interests

CJAP reports fees for an advisory role for Nordic Pharma, paid to their institution. KB reports fees for an advisory role for Amgen, paid to their institution. JWBdG reports personal fees from Bristol Myers Squibb. All other authors declare no competing interests.

Data sharing

Individual patient-level data can be requested from the corresponding author after publication. Data will be provided with an accompanying dictionary defining each field in the set. The study protocol is provided in the appendix. The informed consent form will be shared upon request. Study data will be shared after approval of a proposal, and with a signed data access agreement.

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