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Adjuvant mFOLFOXIRI after curative-intent resection of oligometastatic colorectal cancer: phase II FANTASTIC trial

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Abstract

Background **Patients with oligometastatic colorectal cancer (mCRC) remain at high risk of recurrence after curative surgery, yet the benefit of adjuvant chemotherapy remains inconclusive. This study evaluated the feasibility and efficacy of adjuvant modified (m)FOLFOXIRI (irinotecan, oxaliplatin, L-leucovorin (L-LV), 5-fluorouracil (5-FU)), as well as the utility of circulating tumour DNA (ctDNA) as a prognostic and predictive biomarker in mCRC.**

Methods **Between October 2020 and January 2024, patients with histologically confirmed mCRC undergoing complete metastasectomy were enrolled in this multicentre non-randomized phase II study. Eligible and consenting patients received eight cycles of mFOLFOXIRI followed by four cycles of 5-FU/L-LV; ineligible/non-consenting patients received standard of care (SOC; CAPOX (capecitabine and oxaliplatin), 5-FU, or observation). ctDNA was assessed using the tumour-informed personalized Signatera™ assay (Natera, Austin, TX, USA) at 28 days and 7 months after surgery. The primary endpoint was completion of eight cycles of mFOLFOXIRI in a target sample of 36 patients.**

Results **Of the 83 registered patients, 73 were enrolled (39 mFOLFOXIRI, 34 SOC). The mFOLFOXIRI completion rate was 74% (80% confidence interval 63% to 83%; $P < 0.001$). ctDNA positivity predicted significantly inferior recurrence-free survival across both the mFOLFOXIRI and SOC treatment groups at 28 days (hazard ratios (HR) 7.27 and 7.17, respectively) and 7 months (HR 3.96 and 4.38, respectively) after surgery. Multivariate analysis identified ctDNA positivity, *RAS* mutation, metachronous metastases, and mFOLFOXIRI as significant prognostic factors. mFOLFOXIRI improved recurrence-free survival compared with SOC in the overall population (HR 0.44; $P = 0.012$), with a trend towards benefit in ctDNA-positive but not ctDNA-negative patients. ctDNA clearance rates were 33% (mFOLFOXIRI) and 20% (SOC).**

Conclusions **This study indicates the feasibility of adjuvant mFOLFOXIRI in patients with mCRC, with an acceptable safety profile and potential clinical benefit among those with ctDNA positivity 28 days after surgery.**

Keywords oligometastatic disease, circulating tumour DNA, minimal residual disease

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Introduction

Colorectal cancer (CRC) is one of the most common and lethal malignancies globally, with nearly half of patients eventually developing metastatic disease. Metastatic dissemination represents the principal cause of CRC-related mortality, occurring synchronously at diagnosis in approximately 14.5–19% of patients and metachronously in 8.1–12.8% of patients during follow-up[1]. Five-year survival declines sharply with advancing stage, from over 90% in stage I disease to < 15% in stage IV disease, reflecting the prognostic impact of distant spread[2,3]. For patients with limited, resectable metastases, metastasectomy is a potential curative strategy for select patients, with reported 5-year survival rates ranging from 20% to 50%[4–6]. However, many of these patients experience disease recurrence. For example, approximately 60–75% of patients who undergo complete (R0) resection of colorectal liver metastases (CLM) will develop a secondary metastatic recurrence[7]. These factors underscore the need for effective postoperative systemic therapy to eradicate micrometastatic or molecular residual disease (MRD).

Clinical data around the benefit of adjuvant therapy following curative-intent resection of oligometastases is limited. Several studies have evaluated the benefit of adjuvant chemotherapy in CLM[4,6,8–11], yet none has demonstrated a clear overall survival advantage. The JCOG0603 trial investigated postoperative mFOLFOX6 (fluorouracil, leucovorin, oxaliplatin) *versus* observation after hepatectomy for resected CLM, showing improved disease-free survival but no overall survival (OS) benefit[9]. For lung metastases, no prospective or randomized trial has been conducted[12].

Persistent uncertainty regarding the benefit of adjuvant chemotherapy after curative-intent resection of colorectal metastases has been highlighted in multiple reviews. A recent meta-analysis[13] of patients undergoing liver or lung metastasectomy reported that adjuvant chemotherapy significantly reduced recurrence risk and suggested a possible improvement in OS, although interpretation is limited by the small number of studies and the heterogeneity of patient populations and treatment protocols. Similarly, other analyses[6,9,11] have emphasized that even after complete resection, recurrence remains frequent, and the survival advantage conferred by standard adjuvant regimens is modest and inconsistent. To achieve meaningful improvements in survival after curative-intent metastasectomy, more precise selection of patients for adjuvant therapy is required, ideally through biomarkers that can detect residual disease and refine recurrence risk, allowing treatment intensification for those at highest risk while minimizing unnecessary toxicity in patients unlikely to benefit.

Circulating tumour DNA (ctDNA) has emerged as a particularly promising tool for detecting MRD, refining prognostic assessment, and guiding postoperative therapeutic strategies[14–16]. The prognostic value of ctDNA has been demonstrated in CRC and other solid tumours[17–22].

In the GALAXY study, the largest ctDNA platform in CRC, ctDNA positivity after resection of stage IV disease was strongly associated with inferior disease-free survival and OS[14,15]. Patients with stage II/III disease who were ctDNA positive benefited from adjuvant chemotherapy, whereas ctDNA-negative patients did not. Similar trends were observed in a subgroup of patients with resected CLM[15,16]. However, the optimal chemotherapy regimen for ctDNA-positive patients after metastasectomy remains unclear.

FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan) is one of the most effective regimens in metastatic CRC, but due to its toxicity it has limited use[23]. A modified regimen (mFOLFOXIRI; irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, and 46-hour continuous infusion of 5-fluorouracil (5-FU) 2400 mg/m^2 every 2 weeks) was developed to retain efficacy with improved tolerability[24]. Its role as adjuvant therapy in resected oligometastatic CRC (mCRC), particularly in ctDNA-positive patients, has not been evaluated.

A multicentre phase II study was conducted to assess the feasibility of adjuvant mFOLFOXIRI and to explore the utility of ctDNA as a predictive biomarker in patients with mCRC following metastasectomy.

Methods

Study design and patient selection

This was a multicentre non-randomized phase II trial designed to evaluate the feasibility of mFOLFOXIRI and the utility of ctDNA as a predictive biomarker in CRC patients following resection of oligometastases (*Fig. S1*). Oligometastatic disease was defined as metastatic lesions deemed to be resectable with curative intent without the need for chemotherapy. Details of the trial design, endpoints, and expanded eligibility criteria have been published previously[25]. Patients aged ≤ 75 years with mCRC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who were candidates for upfront metastasectomy were eligible for inclusion. Patients with a previous history of surgery for metastatic disease were excluded. At the time of registration, the primary tumour had been resected or was scheduled for simultaneous resection with metastatic disease. Key eligibility criteria for inclusion in the treatment (mFOLFOXIRI) arm included R0 resection, registration 28–70 days after surgery, no extrahepatic metastasis or recurrence on recent imaging, acceptable *UGT1A1* status, sufficient organ function, and written informed consent. After curative-intent surgery, patients in the mFOLFOXIRI group were treated with eight cycles of mFOLFOXIRI followed by four cycles of 5-FU/L-LV (L-leucovorin 200 mg/m^2 and 46-hour continuous infusion of 5-FU 2400 mg/m^2 every 2 weeks), administered at the same dose as in the JACCRO CC-11 phase II study[26]. Patients who did not meet eligibility criteria (for example, patients homozygous for *UGT1A1*

variants or with inadequate organ function for mFOLFOXIRI) or who declined mFOLFOXIRI received standard-of-care treatment (SOC; CAPOX (capecitabine and oxaliplatin), 5-FU, or observation). ctDNA analysis was planned before and after adjuvant chemotherapy, corresponding to 28 days and 7 months after surgery, respectively.

This study was approved by a certified review board in Hyogo Medical University (Certification no. C0016) and was conducted in accordance with the *Clinical Trials Act* (Act No. 16 of April 14, 2017) in Japan and ethical guidelines for medical and health research involving human subjects. This trial was registered with the Japan Registry of Clinical Trials (jRCTs051200026). All patients provided written informed consent to participate in the study.

ctDNA analysis

At each collection time point, 30 ml blood was drawn into Streck tubes, centrifuged, and plasma aliquoted into 15-ml tubes for storage at −80°C. Formalin-fixed, paraffin-embedded (FFPE) tumour tissue samples from surgical resection or biopsy were also collected. Plasma (6 ml) and FFPE tissue samples were shipped to Natera and analysed retrospectively using a clinically validated, personalized, tumour-informed 16-plex polymerase chain reaction next-generation sequencing assay (Signatera™; Natera, Austin, TX, USA) after the completion of the study.

Briefly, FFPE tumour tissue from surgical resection or biopsy samples and matched normal DNA extracted from peripheral blood samples were processed for whole-exome sequencing to identify and track up to 16 patient- and tumour-specific somatic single nucleotide variants in the associated patient's plasma using a multiplex polymerase chain reaction-based next-generation sequencing approach[19]. Cell-free DNA was extracted from patient plasma (median 9.6 ml; range 3.0–12.2 ml) at a given time point and was used to detect ctDNA. Plasma samples with at least two tumour-specific variants detected above a predefined threshold were defined as ctDNA positive. The ctDNA concentration was reported as mean tumour molecules per millilitre (MTM/ml) of plasma.

Endpoints and statistical analysis

All statistical analyses were performed by the Shizuoka Cancer Center and Natera, as described in the previously published trial protocol[25]. Patients enrolled into this phase II study were divided into two groups, the mFOLFOXIRI group and the SOC group, as defined in the eligibility criteria and per patient preference. The primary endpoint was treatment compliance with eight cycles of mFOLFOXIRI. The completion rate for eight cycles of treatment was determined by the percentage of patients who received both oxaliplatin and irinotecan for at least eight cycles, as outlined in the protocol. The key secondary endpoints were the ctDNA-positivity rate and recurrence-free survival (RFS) stratified by ctDNA status and treatment group at 28 days and 7 months after surgery.

The sample size in the mFOLFOXIRI group was estimated to be 36 patients to achieve 70% power, assuming the primary endpoint's expected value was 50% and threshold was 35%, based on the JCOG0603 study[9] with one-sided testing at a 10% significance level. Considering the ratio of patients in the observational arm to the treatment arm, the total sample size was expected to be 85. The patient accrual and follow-up periods were 4 and 3 years, respectively.

Survival analyses were performed using R v4.4.1 (RRID: SCR_001905) using the survival v.3.7.0 (RRID:SCR_021137) and survminer v.0.4.9 (RRID:SCR_021094) packages (R Foundation for Statistical Computing, Vienna, Austria). Landmark analyses were performed to mitigate immortal time bias. Analyses based on ctDNA measured at 28 days and 7 months after surgery were landmarked at 1 month and 7 months, respectively. Comparisons of mFOLFOXIRI to SOC were landmarked at 1 month, except for the 7-month landmark applied in analyses within ctDNA-positive and ctDNA-negative subgroups at 7 months after surgery. The landmark approach was applied to both Kaplan–Meier and Cox regression analyses.

To address potential confounding due to the non-randomized study design, inverse probability of treatment weighting was applied in the 1-month landmark cohort using the WeightIt (v.1.2.0) and cobalt (v.4.5.5) packages. Propensity scores were estimated to calculate the average treatment effect based on the following baseline covariates: age, sex, tumour location, pathological (p) T category, pN category, *RAS* and *BRAF* status, ECOG performance status, surgical margins, site of metastases, and metastasis type. Covariate balance was assessed using absolute standardized mean differences, with a threshold of < 0.1 indicating adequate balance. These weights were subsequently incorporated into weighted Kaplan–Meier estimators and weighted Cox proportional hazards models.

Results

Patient characteristics

Between October 2020 and January 2024, 83 patients with mCRC were initially registered. After exclusions, 73 patients were subsequently enrolled in the study with 53% (39 of 73) of patients assigned to the mFOLFOXIRI group and 47% (34 of 73) receiving SOC. ctDNA results were available for 72 patients. A flow chart of patient inclusion is presented in *Fig. 1*. The median follow up time was 37.1 months.

Patient characteristics are detailed in *Table 1* and *Table S1*. The median age was 61 (range 34–75) years, with 62% (45 of 73) of patients aged < 65 years. Complete (R0) resection was achieved in 96% (70 of 73) of patients. The liver represented the predominant site of metastases, observed in 73% (53 of 73) of patients, followed by the lung (15%; 11 of 73). Peritoneal and ovarian metastases were less frequent, occurring in 11% (8 of 73) and 1% (1 of 73) of patients, respectively. The distribution and number of metastases are summarized in *Table S2*. The median number of lesions was 1 across all major metastatic sites. Surgically complete resection was performed in all patients with lung or peritoneal metastases. Among patients with liver metastases, minor hepatectomy was performed in 92% (49 of 53). Ablation was not performed in any patients. The reasons for allocation to the SOC group included ineligibility for second registration (8 patients), patient refusal (24; patients preferred adjuvant management other than mFOLFOXIRI), and physician

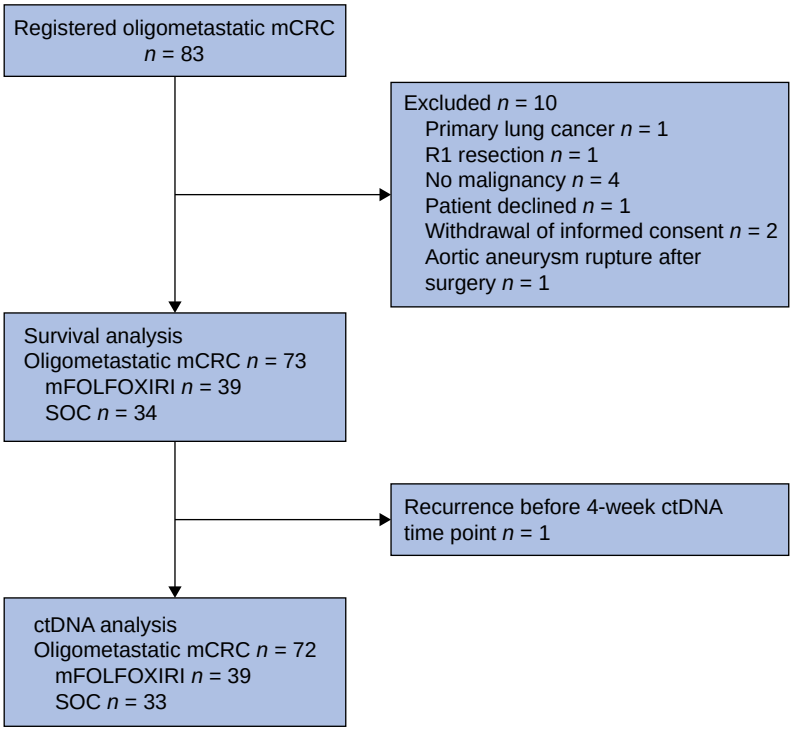


Figure 1 Flow chart showing patient inclusion in this study

mCRC, oligometastatic colorectal cancer; mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; SOC, standard of care; ctDNA, circulating tumour DNA.

decision (2). A detailed breakdown of patients in the SOC group and the types of treatment are provided in *Table S2*.

Baseline characteristics were generally well balanced between the mFOLFOXIRI and SOC groups, with comparable distributions in age, sex, resectability, and sites of metastases. Minor differences included a higher proportion of patients with *BRAF* mutations in the SOC *versus* mFOLFOXIRI group (12% *versus* 0%, respectively, $P = 0.043$), however the differences were not statistically significant after Bonferroni correction ($q = 0.5$). Among the patients in the SOC group, 18% (6 of 34) received CAPOX and 15% (5 of 34) received 5-FU. The remaining patients (67%; 23 of 34) chose to receive no adjuvant chemotherapy (that is, they underwent observation).

Safety and completion rate of mFOLFOXIRI

Treatment with mFOLFOXIRI was generally well tolerated. The most frequent grade 3 or higher adverse events were diarrhoea (8%), febrile neutropenia (3%), neuropathy (3%), infusion reaction (3%), and bowel obstruction (3%; *Table S3*). Grade 2 toxicities, such as neuropathy (18%), nausea (15%), and alopecia (13%), were more common but manageable with standard supportive measures. No new or unexpected safety signals were observed in the mFOLFOXIRI group, and the overall toxicity profile was consistent with previous reports of this regimen in the mCRC setting.

The treatment completion rate in the mFOLFOXIRI group was 74% (80% confidence interval (c.i.) 63 to 83%; $P < 0.001$), exceeding the prespecified threshold (35% as described in the trial design). Among patients completing mFOLFOXIRI treatment, treatment completion rates differed across metastatic sites (*Fig. S2*). Completion was achieved in the single patient with ovarian metastases (100%), as well as in 85% (23 of 27) of those with liver metastases and 80% (4 of 5) of those with lung metastases. In contrast, only 17% (1 of 6) of patients with peritoneal metastases completed the planned treatment.

RFS analysis by ctDNA status

Overall, ctDNA positivity was detected in 35% (25 of 72) of patients at the 4-week postoperative MRD time point and in 28% (19 of 69) of patients at 7 months after surgery. RFS rates stratified by ctDNA status at two defined time points, namely 28 days (MRD) and 7 months after complete metastasectomy, were calculated using Kaplan–Meier analyses. RFS was determined across the overall population and by treatment subgroup (mFOLFOXIRI *versus* SOC) to assess the prognostic value of ctDNA detection for early recurrence risk.

At both 28 days and 7 months after surgery, ctDNA status was strongly associated with RFS across all cohorts (*Fig. 2*). In the overall population, ctDNA-positive patients showed significantly inferior RFS compared with ctDNA-negative patients (hazard ratio (HR) 8.25; 95% c.i. 4.08 to 16.67; $P < 0.001$; *Fig. 2a*), with a median RFS of 7.83 months for ctDNA-positive patients and median RFS not reached for ctDNA-negative patients. Among those treated with mFOLFOXIRI, ctDNA positivity similarly correlated with worse outcomes (HR 7.27; 95% c.i. 2.59 to 20.39; $P < 0.001$; *Fig. 2b*).

Recurrence patterns varied by ctDNA status at 4 weeks after surgery. Among the 23 ctDNA-positive patients who developed recurrence, 78% (18 patients) experienced liver recurrence; lung (1 patient, 4%) and peritoneal (3, 13%) recurrences were less frequent. In contrast, lung recurrence was the most common

Table 1 Patient characteristics

	All patients ($n = 73$)	mFOLFOXIRI group ($n = 39$)	SOC group ($n = 34$)
Sex			
Female	30 (41%)	17 (44%)	13 (38%)
Male	43 (59%)	22 (56%)	21 (62%)
Age group			
< 65 years	45 (62%)	24 (62%)	21 (62%)
≥65 years	28 (38%)	15 (38%)	13 (38%)
Tumour location			
Colon	46 (63%)	25 (64%)	21 (62%)
Rectum	27 (37%)	14 (36%)	13 (38%)
Pathological T stage			
T1	4 (6%)	4 (10%)	0 (0%)
T2	7 (10%)	4 (10%)	3 (8.8%)
T3	42 (58%)	20 (51%)	22 (65%)
T4	20 (27%)	11 (28%)	9 (26%)
Pathological N stage			
N0	30 (41%)	15 (38%)	15 (44%)
N1a	14 (19%)	7 (18%)	7 (21%)
N1b	9 (12%)	4 (10%)	5 (15%)
N2a	10 (14%)	8 (21%)	2 (5.9%)
N2b	10 (14%)	5 (13%)	5 (15%)
Microsatellite instability			
MSS	73 (100%)	39 (100%)	34 (100%)
RAS			
Mutant	36 (49%)	20 (51%)	16 (47%)
Wild type	37 (51%)	19 (49%)	18 (53%)
BRAF			
Mutant	4 (5%)	0 (0%)	4 (12%)
Wild type	69 (95%)	39 (100%)	30 (88%)
ECOG performance status			
0	71 (97%)	38 (97%)	33 (97%)
1	2 (3%)	1 (2.6%)	1 (2.9%)
Resectability			
R0	70 (96%)	37 (95%)	33 (97%)
R1	2 (2.7%)	2 (5%)	0 (0%)
R2	1 (1%)	0 (0%)	1 (2.9%)
Site of metastases			
Liver	53 (73%)	27 (69%)	26 (76%)
Lung	11 (15%)	5 (13%)	6 (18%)
Ovary	1 (1%)	1 (3%)	0 (0%)
Peritoneum	8 (11%)	6 (15%)	2 (6%)
Synchronicity			
Metachronous	40 (55%)	19 (49%)	21 (62%)
Synchronous	33 (45%)	20 (51%)	13 (38%)

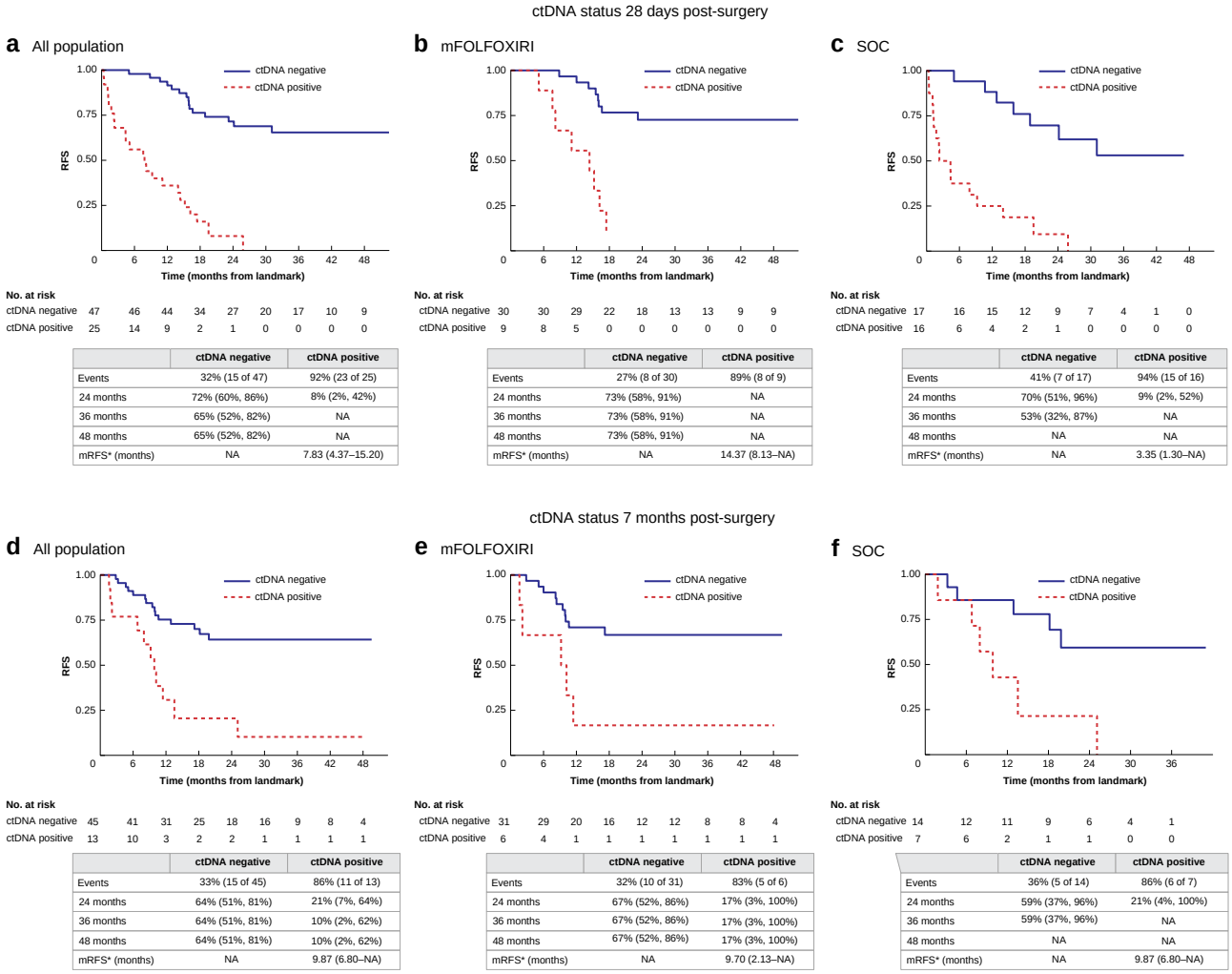
Values are *n* (%). mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; SOC, standard of care; ECOG, Eastern Cooperative Oncology Group.

pattern among the 15 ctDNA-negative patients (9, 60%) and liver recurrence was less frequent (5, 33%).

Consistent findings were observed at 7 months after surgery, where ctDNA positivity remained prognostic for inferior RFS (overall HR 4.16; 95% c.i. 1.89 to 9.18; $P < 0.0001$; *Fig. 2d*). ctDNA-positive patients in both the mFOLFOXIRI (HR 3.96; 95% c.i. 1.34 to 11.69; $P = 0.013$) and SOC (4.38; 95% c.i. 1.28 to 14.98; $P = 0.019$) groups showed inferior RFS compared with ctDNA-negative patients. The median RFS for ctDNA-positive patients was 9.87 months in the overall cohort, whereas ctDNA-negative patients in all cohorts had not reached median RFS at the time of analysis.

RFS analysis by treatment group

Next, whether adjuvant mFOLFOXIRI provided RFS benefit over SOC was evaluated in the overall population and in exploratory



	ctDNA negative	ctDNA positive
Events	32% (15 of 47)	92% (23 of 25)
24 months	72% (60%, 86%)	8% (2%, 42%)
36 months	65% (52%, 82%)	NA
48 months	65% (52%, 82%)	NA
mRFS* (months)	NA	7.83 (4.37–15.20)

	ctDNA negative	ctDNA positive
Events	27% (8 of 30)	89% (8 of 9)
24 months	73% (58%, 91%)	NA
36 months	73% (58%, 91%)	NA
48 months	73% (58%, 91%)	NA
mRFS* (months)	NA	14.37 (8.13–NA)

	ctDNA negative	ctDNA positive
Events	41% (7 of 17)	94% (15 of 16)
24 months	70% (51%, 96%)	9% (2%, 52%)
36 months	53% (32%, 87%)	NA
48 months	NA	NA
mRFS* (months)	NA	3.35 (1.30–NA)

	ctDNA negative	ctDNA positive
Events	33% (15 of 45)	86% (11 of 13)
24 months	64% (51%, 81%)	21% (7%, 64%)
36 months	64% (51%, 81%)	10% (2%, 62%)
48 months	64% (51%, 81%)	10% (2%, 62%)
mRFS* (months)	NA	9.87 (6.80–NA)

	ctDNA negative	ctDNA positive
Events	32% (10 of 31)	83% (5 of 6)
24 months	67% (52%, 86%)	17% (3%, 100%)
36 months	67% (52%, 86%)	17% (3%, 100%)
48 months	67% (52%, 86%)	17% (3%, 100%)
mRFS* (months)	NA	9.70 (2.13–NA)

	ctDNA negative	ctDNA positive
Events	36% (5 of 14)	86% (6 of 7)
24 months	59% (37%, 96%)	21% (4%, 100%)
36 months	59% (37%, 96%)	NA
48 months	NA	NA
mRFS* (months)	NA	9.87 (6.80–NA)

Figure 2 RFS according to ctDNA status at 28 days and 7 months after surgery

Values in parentheses are 95% confidence intervals, except *interquartile range. **a–c** RFS at 28 days after surgery. RFS was significantly worse among ctDNA-positive patients in **a** the entire population (HR 8.25; 95% c.i. 4.80 to 16.67; $P < 0.001$), **b** mFOLFOXIRI-treated patients (HR 7.27; 95% c.i. 2.59 to 20.39; $P < 0.001$), and **c** patients receiving SOC (HR 7.17; 95% c.i. 2.68 to 19.17; $P < 0.0001$). **d–f** RFS 7 months after surgery. RFS was worse among ctDNA-positive patients in **d** the entire population (HR 4.16; 95% c.i. 1.89 to 9.18; $P < 0.001$), **e** mFOLFOXIRI-treated patients (HR 3.96; 95% c.i. 1.34 to 11.69; $P = 0.013$), and **f** patients receiving SOC (HR 4.38; 95% c.i. 1.28 to 14.98; $P = 0.019$). RFS, recurrence-free survival; ctDNA, circulating tumour DNA; HR, hazard ratio; c.i., confidence interval; mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; SOC, standard of care; NA, not achieved; mRFS, median recurrence-free survival.

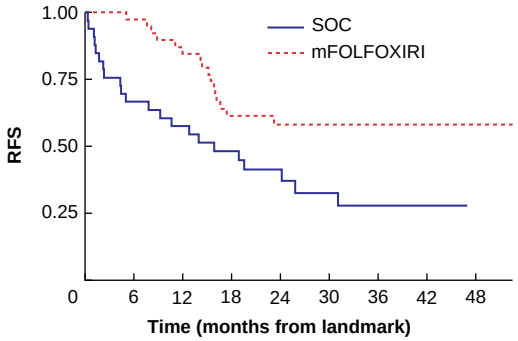
analyses across ctDNA-defined risk groups. In the overall cohort, patients treated with mFOLFOXIRI showed improved RFS compared with those receiving SOC (HR 0.44; 95% c.i. 0.23 to 0.83; $P = 0.012$), with the median RFS not reached in the mFOLFOXIRI arm *versus* 15.87 months in the SOC group (*Fig. 3a*). After applying inverse probability of treatment weighting, baseline covariates were well balanced between treatment cohorts, with all adjusted absolute mean differences < 0.1, indicating comparable clinical and molecular factors between groups in the 1-month landmark cohort (*Fig. S3a*). Patients treated with mFOLFOXIRI showed improved RFS compared with those receiving SOC (log-rank $P = 0.001$; *Fig. S3b*). The risk assessment confirmed this significance, with an HR of 0.33 (95% c.i. 0.17 to 0.66; Cox $P = 0.002$).

Among patients who were ctDNA positive at 28 days after surgery, mFOLFOXIRI was associated with longer RFS (median RFS 14.37 *versus* 3.35 months in the mFOLFOXIRI and SOC groups, respectively), although this difference did not reach statistical significance (HR 0.60; 95% c.i. 0.25 to 1.46; $P = 0.260$; *Fig. 3b*). Patients who were ctDNA-positive at 7 months after surgery had poor outcomes (median RFS 9.7 and 9.87 months in the mFOLFOXIRI and SOC groups, respectively), regardless of treatment group (HR 1.06; 95% c.i. 0.32 to 3.50; $P = 0.922$; *Fig. 3c*).

In the ctDNA-negative subgroup, RFS remained high across both treatment groups, with no significant differences observed between the mFOLFOXIRI and SOC groups when assessing ctDNA at either 28 days (HR 0.59; 95% c.i. 0.21 to 1.62; $P = 0.300$; *Fig. 3d*) or 7 months (HR 0.92; 95% c.i. 0.32 to 2.70; $P = 0.880$; *Fig. 3e*).

To further explore the interaction between ctDNA dynamics and treatment efficacy, multivariate analyses were performed incorporating clinical and molecular covariates, including age, sex, *RAS* status, synchronicity, and receipt of mFOLFOXIRI (*Fig. 4*).

a All patients

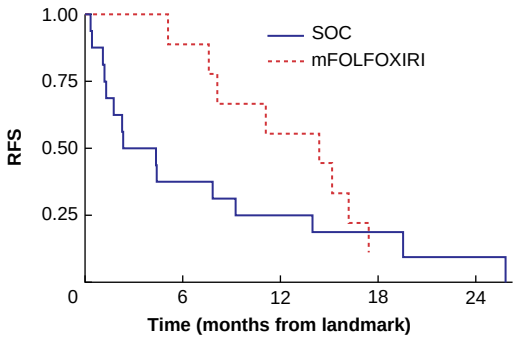


No. at risk

SOC	33	22	19	14	10	7	4	1	0
mFOLFOXIRI	39	38	34	22	18	13	13	9	9

Median RFS (months): SOC: 15.87 (7.83–NA)□ mFOLFOXIRI: NA

b ctDNA positive 28 days after surgery

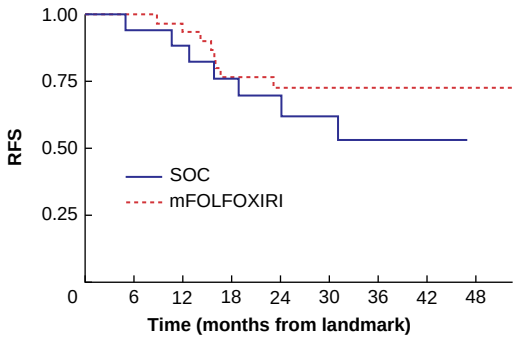


No. at risk

SOC	16	6	4	2	1
mFOLFOXIRI	9	8	5	0	0

Median RFS (months): SOC: 3.35 (1.30–NA)□ mFOLFOXIRI: 14.37 (8.13–NA)

d ctDNA negative 28 days after surgery

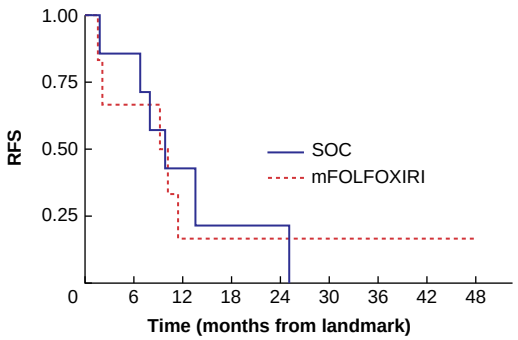


No. at risk

SOC	17	16	15	12	9	7	4	1	0
mFOLFOXIRI	30	30	29	22	18	13	13	9	9

Median RFS (months): SOC: NA□ mFOLFOXIRI: NA

c ctDNA positive 7 months after surgery

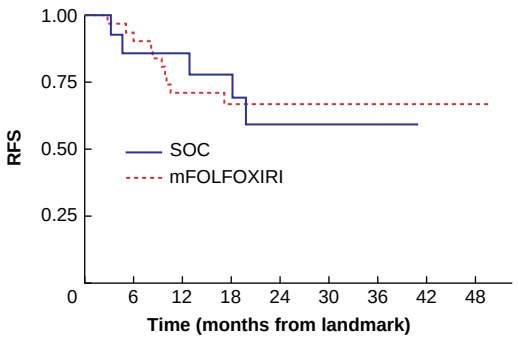


No. at risk

SOC	7	6	2	1	1	0	0	0	0
mFOLFOXIRI	6	4	1	1	1	1	1	1	1

Median RFS (months): SOC: 9.87 (6.80–NA)□ mFOLFOXIRI: 9.70 (2.13–NA)

e ctDNA negative 7 months after surgery



No. at risk

SOC	14	12	11	9	6	4	1	0	0
mFOLFOXIRI	31	29	20	16	12	12	8	8	4

Median RFS (months): SOC: NA□ mFOLFOXIRI: NA

Figure 3 Kaplan–Meier curves showing RFS in all patients and according to ctDNA status

a RFS in the entire study population. mFOLFOXIRI treatment significantly improved RFS compared with SOC in the entire population (HR 0.44; 95% c.i. 0.23 to 0.83; $P = 0.012$). **b, c** RFS in patients who were ctDNA positive at 28 days (**b**) and 7 months (**c**) after surgery. mFOLFOXIRI was associated with longer RFS at 28 days (HR 0.60; 95% c.i. 0.25 to 1.46; $P = 0.260$), although the difference *versus* SOC was not statistically significant. At 7 months, post-surgery outcomes were poor in both the mFOLFOXIRI and SOC groups (HR 1.06; 95% c.i. 0.32 to 3.50; $P = 0.922$). **d, e** RFS in patients who were ctDNA negative at 28 days (**d**) and 7 months (**e**) after surgery. RFS remained high across both treatment groups, with no significant differences between the mFOLFOXIRI and SOC groups at either 28 days (HR 0.59; 95% c.i. 0.21 to 1.62; $P = 0.300$) or 7 months (HR 0.92; 95% c.i. 0.32 to 2.70; $P = 0.880$). RFS, recurrence-free survival; ctDNA, circulating tumour DNA; mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; SOC, standard of care; HR, hazard ratio; c.i., confidence interval; NA, not achieved.

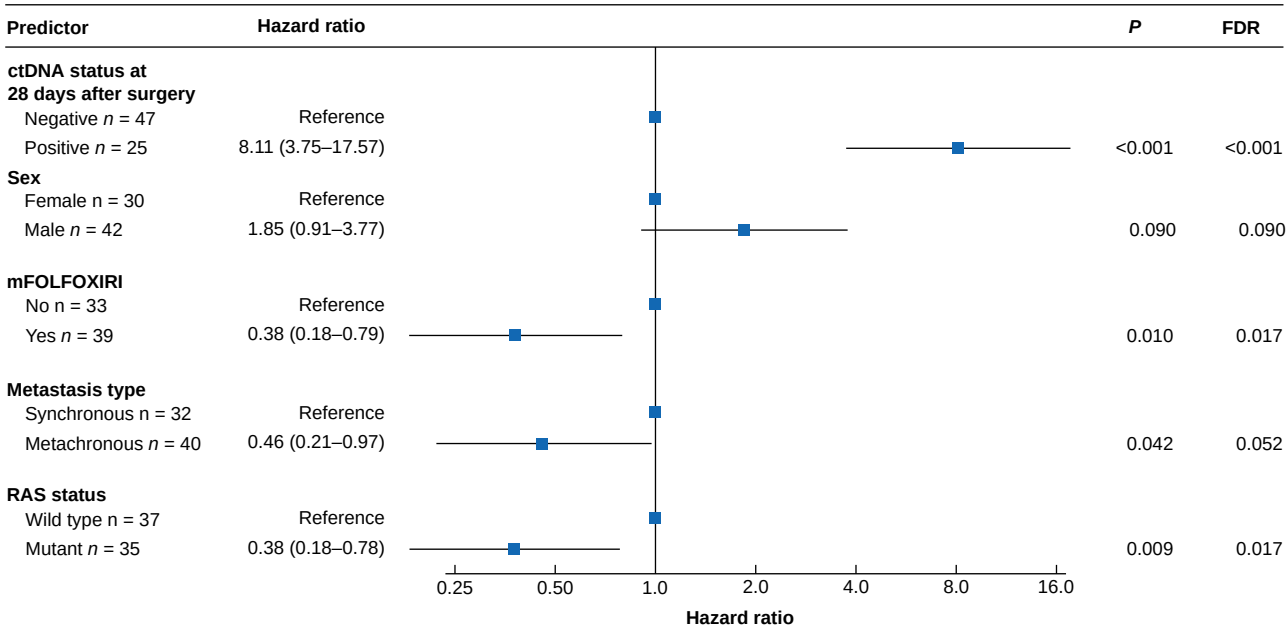


Figure 4 Multivariate analysis of recurrence-free survival incorporating clinical and molecular predictors

Forest plots showing hazard ratios for recurrence-free survival according to ctDNA status at 28 days after surgery (molecular residual disease time point), sex, adjuvant mFOLFOXIRI treatment, metastasis type, and *RAS* mutation status. Values in parentheses and error bars are 95% confidence intervals. ctDNA, circulating tumour DNA; mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; FDR, false discovery rate.

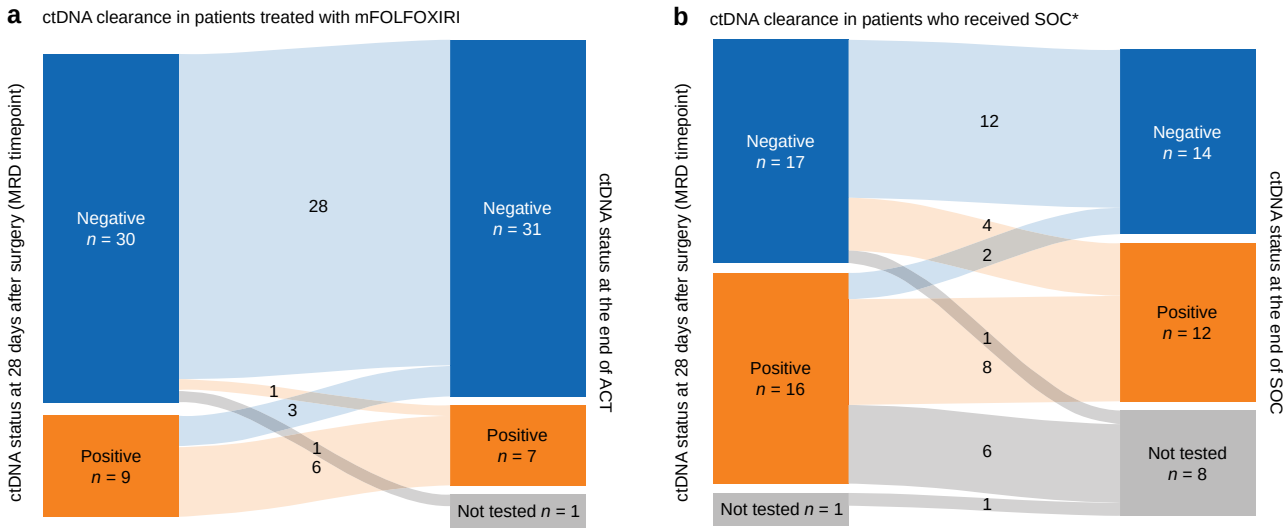


Figure 5 Sankey diagrams showing ctDNA clearance from 28 days after surgery (MRD time point) to the end of adjuvant therapy

a Patients receiving mFOLFOXIRI. **b** Patients receiving SOC. ctDNA clearance occurred in 33% (3/9) of ctDNA-positive patients treated with mFOLFOXIRI, compared with 20% (2/10) of patients receiving SOC. *Eleven of 34 patients in the SOC group received ACT. ctDNA, circulating tumour DNA; MRD, molecular residual disease; mFOLFOXIRI, irinotecan, oxaliplatin, L-leucovorin, 5-fluorouracil; ACT, adjuvant chemotherapy.

ctDNA positivity at 28 days after surgery emerged as the strongest independent prognostic factor for recurrence, with an eight-fold higher risk of relapse compared with ctDNA-negative patients (HR 8.11; 95% c.i. 3.75 to 17.57; $P < 0.0001$; false discovery rate (FDR) P adjustment < 0.0001). Treatment with mFOLFOXIRI was independently associated with improved RFS (HR 0.38; 95% c.i. 0.18 to 0.79; $P = 0.010$; FDR = 0.017), whereas metachronous disease (HR 0.46; 95% c.i. 0.21 to 0.97; $P = 0.042$; FDR = 0.052) and *RAS* mutation (HR 0.38; 95% c.i. 0.18 to 0.78; $P = 0.009$; FDR = 0.017) were also associated with lower recurrence risk.

ctDNA clearance

In the mFOLFOXIRI group, ctDNA clearance occurred in 33% (3 of 9) of patients who were ctDNA positive at 28 days after surgery (median ctDNA at 4 weeks 0.50 (range 0.05–2.96) MTM/ml; *Fig. 5a*). One patient who was ctDNA negative at 28 days became ctDNA positive at 7 months.

In the SOC group, 16 patients were ctDNA positive at 28 days after surgery; of these patients, only three received chemotherapy (one receiving CAPOX and two receiving 5-FU). Among 10

patients with ctDNA data available at subsequent time points (median ctDNA at 28 days 2.13 (range 0.11–67.77) MTM/ml), ctDNA clearance was observed in two patients (20%; (*Fig. 5b*). One of the patients achieving ctDNA clearance had received CAPOX treatment, whereas the other patient experienced spontaneous clearance. Neither of the two patients treated with 5-FU achieved ctDNA clearance. Of the 16 ctDNA-negative patients at the MRD time point, 75% (12) remained ctDNA negative, whereas 25% (4) converted to a ctDNA-positive status during follow-up.

Discussion

The emergence of ctDNA as a biomarker to detect MRD provides a new approach to improve postoperative risk assessment and personalize management in patients with mCRC. Unlike conventional clinicopathological factors, ctDNA offers a direct, tumour-derived measure of residual disease burden and provides dynamic insight into recurrence risk following curative-intent surgery. Many prospective studies[15,19] have demonstrated that ctDNA detection after resection identifies patients at markedly higher risk of relapse and who derive benefit from adjuvant chemotherapy, whereas ctDNA negativity correlates with durable remission, positioning ctDNA as a powerful prognostic tool in oncology. Such a biomarker-driven approach is particularly relevant in mCRC, where recurrence rates remain substantial despite curative resection and data supporting the benefit of adjuvant chemotherapy remain limited.

This study evaluated the safety and efficacy of adjuvant mFOLFOXIRI compared with SOC treatment (primarily observation) after metastatectomy in patients with mCRC in association with longitudinal ctDNA dynamics. The findings indicate that mFOLFOXIRI was feasible as adjuvant therapy, with a favourable completion rate and an acceptable safety profile. The TRIBE[23] and JACCRO CC-11[24] studies reported the efficacy of FOLFOXIRI and modified FOLFOXIRI (dose-reduced triplet regimen; lower irinotecan and 5-FU doses), respectively, in treating patients with mCRC, albeit with some adverse events. In the present study, the incidence of febrile neutropenia was 3%, which was lower than that reported in both the JACCRO CC-11[24] (5%) and TRIBE[23] (8.8%) studies. Other toxicities were comparable across these studies, supporting the tolerability of mFOLFOXIRI even in the postoperative setting for 'fit' patients after hepatectomy. The FANTASTIC study appears to be the first study to explore the feasibility of mFOLFOXIRI in resected mCRC patients who test positive for ctDNA after metastatectomy[25].

Consistent with previous reports, ctDNA positivity was strongly associated with recurrence in the present cohort, with similar HRs. This reaffirms the role of ctDNA as one of the most robust prognostic biomarkers in patients with mCRC.

In the present study, mFOLFOXIRI treatment significantly improved RFS compared with SOC in all patients, and mFOLFOXIRI treatment showed a trend for improved RFS among patients who were ctDNA positive 28 days after surgery. However, no difference in RFS was observed between mFOLFOXIRI and SOC in ctDNA-negative patients. These findings indicate a potential benefit of mFOLFOXIRI in the MRD-positive but not MRD-negative population. This may explain the results of previous trials in resected mCRC patients unselected for ctDNA status after surgery, where systemic chemotherapy variably improved RFS but not OS[4,9]. However, this interpretation should be made cautiously given the limited sample size, lack of randomization, lack of adjustment for clinicopathological factors, heterogeneity of treatment in the SOC group (with most patients undergoing observation and not receiving adjuvant chemotherapy), and limited follow-up duration. In the present study, ctDNA clearance was higher in the mFOLFOXIRI than SOC group (33% *versus* 20%). However, these clearance rates are lower than those observed in patients with CRC with liver metastases in the GALAXY cohort[16] (50%), one of the largest cohorts with patients undergoing ctDNA testing. Additional larger prospective studies using mFOLFOXIRI may explain the apparent discrepancy in these results and the intensity of MRD eradication achievable with this regimen.

Although ctDNA has emerged as a promising biomarker for postoperative risk stratification, there is no established standard for adjuvant therapy in patients with mCRC following metastatectomy due to lack of demonstrated OS benefit. Recent interventional studies have yielded mixed results. In the ALTAIR study[26], treatment with trifluridine/tipiracil did not improve survival compared with placebo, although exploratory analyses suggested potential activity in patients with stage IV disease. Similarly, the phase 2 escalation portion of the DYNAMIC-III trial[27] found comparable outcomes between mFOLFOXIRI and mFOLFOX6 in ctDNA-positive patients with stage III CRC, highlighting that increasing chemotherapy intensity alone may not translate into improved outcomes without more precise patient selection. Several large ongoing studies, including CIRCULATE-North America, AFFORD, SAGITTARIUS, and CLAUDIA, will provide additional evidence, investigating whether biomarker-guided escalation using doublet chemotherapy, triplet chemotherapy, and/or biologics (for example anti-vascular endothelial growth factor or anti-epidermal growth factor antibodies) can improve outcomes in ctDNA-positive patients[14,15]. However, data in the oligometastatic setting remain sparse. A randomized phase II study comparing mFOLFOXIRI + bevacizumab *versus* mFOLFOX6 in resected oligometastatic disease is currently ongoing[28]. The findings of the present study contribute to this evolving landscape by suggesting that adjuvant mFOLFOXIRI may provide clinical benefit in ctDNA-positive mCRC following metastatectomy, although this study is limited by the factors noted above. Further validation in larger studies is warranted.

Interestingly, recurrence patterns differed by postoperative ctDNA status. Among ctDNA-negative patients, lung recurrence was more frequent, whereas among ctDNA-positive patients liver recurrence was more common. This distribution suggests potential differences in ctDNA shedding based on the site of recurrence. A subgroup analysis of patients with CLM in the GALAXY study[14,15] similarly demonstrated lower ctDNA sensitivity for lung and peritoneal metastases compared with hepatic or nodal recurrences, particularly when the metastatic burden was small. These findings are consistent with previous reports suggesting[29,30] that ctDNA detectability is influenced by both anatomical site and tumour burden, likely reflecting differences in vascularization, tumour biology, and DNA shedding into the circulation. Importantly, these limitations have direct clinical implications. ctDNA negativity should not be interpreted as the absence of residual disease, especially in patients with low-volume disease or metastases in sites associated with limited ctDNA shedding, such

as the lung or peritoneum. Therefore, ctDNA testing should be interpreted in conjunction with conventional imaging, and continued radiological surveillance remains essential even in ctDNA-negative patients. Serial ctDNA monitoring may also help identify patients who are initially ctDNA negative but subsequently convert to a ctDNA-positive status during surveillance. Such molecular recurrence may represent an opportunity for earlier therapeutic intervention before radiological relapse, although whether delayed adjuvant chemotherapy or other systemic treatment improves outcomes in this setting remains investigational and requires prospective validation.

This study provides prospective evidence showing an RFS benefit with adjuvant mFOLFOXIRI *versus* SOC (mostly observation) in patients with mCRC who test positive for ctDNA following curative-intent metastatectomy, whereas ctDNA-negative patients do not benefit. The data confirm the feasibility and tolerability of this intensive regimen in the postoperative setting. These findings may provide preliminary data supporting ctDNA-guided treatment intensification and deintensification strategies in this post-metastatectomy, high-risk population.

Several study limitations should be acknowledged. The modest sample size, lack of randomization, and relatively short follow-up preclude definitive conclusions regarding long-term survival outcomes. In addition, heterogeneity within the SOC arm complicates direct comparisons with mFOLFOXIRI. Patient assignment to treatment *versus* SOC arms and choice of treatment may have been influenced by unmeasured differences in postoperative recovery, organ reserve, and co-morbidity between patients, even though the recorded baseline ECOG performance status appeared similar. Because most patients in the SOC arm did not receive adjuvant chemotherapy, this trial cannot evaluate the relative benefit of escalating adjuvant chemotherapy from a doublet to a triplet regimen. Overall, the survival analyses presented here should be interpreted as exploratory and hypothesis generating rather than definitive evidence of treatment efficacy. Larger randomized studies would be needed for definitive assessment. Collectively, the results of this study lay the groundwork for larger, randomized studies to validate the role of mFOLFOXIRI and to refine ctDNA-guided postoperative treatment strategies in mCRC.

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Author contributions

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Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The fully documented code to generate raw outputs from the R statistical computing environment for analyses related to this manuscript have been deposited at the GitHub repository and can be accessed at https://github.com/Natera-TMED/Kataoka-et-al_FANTASTIC_analysis. Patient characteristics and demographic information are available in *Table 1* and *Table S1*. To ensure compliance with the ethics committee and to protect the privacy and confidentiality of the patients in this study, the sequencing data and source data supporting the findings are not publicly available. However, they can be requested from the corresponding author for academic use only, within the limitations of the provided informed consent. Data will not be made available for commercial use. Any requests will be reviewed within a time frame of 2–4 weeks to verify whether the request is subject to any intellectual property or confidentiality obligations. All data shared will be deidentified and provided to researchers with access limited for scientific verification purposes, subject to strict prohibitions on secondary use. Applying researchers will be required to sign a data usage agreement.

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