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PARAGON II – A single arm multicentre phase II study of neoadjuvant therapy using irinotecan bead in patients with resectable liver metastases from colorectal cancer☆

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Abstract

Purpose: Perioperative chemotherapy confers a 3-year progression free survival advantage following resection of colorectal liver metastases (CRLM), but is associated with significant toxicity. Chemoembolisation using drug eluting PVA microspheres loaded with irinotecan (DEBIRI) allows sustained delivery of drug directly to tumour, maximising response whilst minimising systemic exposure. This phase II single arm study examined the safety and feasibility of DEBIRI before resection of CRLM.

Methods: Patients with resectable CRLM received lobar DEBIRI 1 month prior to surgery, with a radiological endpoint of near stasis. The trial had a primary end-point of tumour resectability (R0 resection). Secondary end-points included safety, pathologic tumour response and overall survival.

Results: 40 patients received DEBIRI, with a median dose of 103 mg irinotecan (range 64–175 mg). Morbidity was low (2.5%, CTCAE grade 2) with no evidence of systemic chemotoxicity. All patients proceeded to surgery, with 38 undergoing resection (95%, R0 resection rate 74%). 30-day post-operative mortality was 5% (n = 2), with neither death TACE related. 66 lesions were resected, with histologic major or complete pathologic response seen in 77.3% of targeted lesions. At median follow up of 40.6 months, 12 patients (34.3%) had died of recurrent disease with a median overall survival of 50.9 months. Nominal 1, 3 and 5-year OS was 93, 78 & 49% respectively.

Conclusions: Resection after neoadjuvant DEBIRI for CRLM is feasible and safe. Single treatment with DEBIRI resulted in tumour pathologic response and median overall survival comparable to that seen after systemic neoadjuvant chemotherapy.

Registered at clinicaltrials.gov (NCT00844233).

Keywords: Liver; TACE; DEBIRI; Colorectal; Metastases

Introduction

For patients with irresectable colorectal liver metastases (CRLM), standard of care remains first line systemic chemotherapy with the aim of shrinking tumour and bringing patients to resection. Response to chemotherapy is known to correlate with resection rate[1] and so it is vital that patients are treated with the most effective chemotherapeutic

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regimen possible. Patients who exhibit good pathological response to chemotherapy on post-operative assessment also have better overall survival[2] with tumour replacement by fibrosis associated with good long term outcome.[3]

The benefit of perioperative therapy for initially resectable disease is less clear. A large multicentre study compared long term outcomes following 12 cycles of perioperative FOLFOX (6 before surgery, 6 after) against surgery alone for initially resectable disease.[4] Three year progression free survival (PFS) was 36.2% in the perioperative chemotherapy arm compared with 28.1% in the surgery alone group but this did not translate into an improvement in overall survival.[5] The follow-on New EPOC study aimed to evaluate the possible benefit of the addition of monoclonal antibody therapy to epidermal growth factor receptor (EGFR) in KRAS wild-type disease by adding Cetuximab to FOLFOX in the neoadjuvant setting. However, the authors reported a significantly shorter PFS for combination therapy (14.1 vs. 20.5 months).[6] The reasons behind this different result to some palliative studies remain unclear.[7] Both studies demonstrated an increase in surgical morbidity associated with neoadjuvant chemotherapy, suggesting that perioperative chemotherapy is not without risk. Growing evidence also suggests that preoperative therapy is associated with agent-specific patterns of chemotherapy-associated liver injury (CALI),[8–10] with a clear association between CALI and 90-day post-operative mortality.[11] The decision to treat resectable disease with neoadjuvant therapy is therefore a delicate balance between risk and benefit, with little way of predicting which patients are likely to gain a survival advantage.

The liver dominant pattern of metastatic colorectal cancer has led to the development of liver-directed therapy in an effort to increase tumour exposure whilst reducing off-target side effects. Drug eluting beads (DEBs) composed of polyvinyl alcohol (PVA) microspheres loaded with irinotecan (DEBIRI, BTG, Farnham, United Kingdom) have been used in heavily pre-treated irresectable patients. These patients had received multiple lines of systemic therapy prior to DEBIRI, with 2/3rds having radiological disease control 6 months after treatment.[12]

There is no prospective evidence that it is safe to perform hepatic surgery on patients who have been treated with DEBIRI. The demonstration of safety in this setting is vital before further trials assess the use of DEBIRI in a neoadjuvant or downsizing/induction protocol. The objective of this study was therefore to assess the safety and efficacy of neoadjuvant DEBIRI prior to resection of colorectal liver metastases.

Methods

Patients

This was a pan-European multicentre single arm phase II study. The trial had full ethical approval (South West Regional Ethics Committee reference 08/H0206/51) and was registered at clinicaltrials.gov (NCT00844233). Patients were identified as eligible for recruitment by a specialist hepatobiliary multidisciplinary team meeting (MDT). The trial had a recruitment target of 40 patients successfully treated with DEBIRI. To be eligible for recruitment, patients had to be aged between 18 and 80 years with an ECOG status $\leq$2. All had undergone an R0 primary colorectal resection and had liver-only metastatic disease with a maximum of 4 potentially resectable colorectal liver metastases. Patients were not allowed any previous exposure to irinotecan-based chemotherapy and did not receive any other neoadjuvant chemotherapy. Resectability was defined by the local hepatobiliary MDT after full staging with triple-phase CT chest/abdomen/pelvis, MRI with liver-specific contrast and PET-CT.

Procedures

After obtaining written informed consent to trial participation, patients underwent baseline assessment. Transarterial chemoembolization with DEBIRI (DEBIRI-TACE) was performed within 4 weeks of baseline screening visit and 4 weeks prior to the planned resection (see Fig. 1). Treatment consisted of a nominal dose of 2 ml of 100–300 μM diameter beads preloaded with 200 mg of irinotecan supplied in sterile lyophilized vials. The beads were hydrated with water for injection, and mixed with a non-ionic contrast media in the vial immediately prior to use according to the manufacturers instructions.

Using a unilateral femoral approach, selective catheterisation of the hepatic artery was performed and an angiogram performed to identify any aberrant arterial anatomy and verify portal patency. Initially, very selective

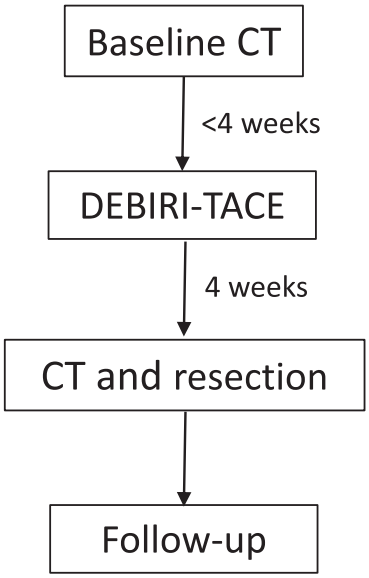

Figure 1. Trial schema for PARAGON study.

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embolization was performed and beads were delivered directly to the subsegment containing the tumour. As experience accumulated, a more proximal catheter placement into the right or left hepatic artery was used. Once catheter placement was confirmed, the embolic mixture was injected slowly into the artery supplying the lobe where the lesion was located until the blood flow became sluggish i.e. embolization did not proceed to full stasis. If the embolization endpoint was achieved before the delivery of 2 ml irinotecan bead, the injection was stopped and the volume of beads (and therefore drug) administered was recorded. No patients received systemic neoadjuvant chemotherapy.

Four weeks after embolization patients underwent repeat CT chest/abdomen/pelvis to assess radiological response, followed by surgical resection. All patients underwent resection during open surgery by an experienced hepatobiliary surgeon.

Follow-up visits took place at 3, 6, 9 and 12 months post-resection, followed by routine 6-monthly review. These follow-up visits included clinical examination, measurement of tumour markers (CEA) and triple-phase CT chest/abdomen/pelvis. Irresectable recurrence was treated with 5-FU based systemic chemotherapy according to local protocol.

The trial had a primary endpoint of R0 tumour resectability (defined as a negative margin of $\geq$1 mm on histopathological assessment). Safety and toxicity after DEBIRI was assessed according to NCI CTCAE v 3.0.[13] Post-operative morbidity was measured using the Clavien-Dindo classification.[14] Radiological response was assessed by triple-phase contrast enhanced CT performed 4 weeks after DEBIRI. Two independent reviewers performed assessment of radiological response, and response was agreed by consensus using RECIST criteria v 1.1.[15] Pathological tumour response was assessed using a minimum of 4 blocks stained with haematoxylin-eosin and reviewed by a specialised gastrointestinal pathologist. This was performed using a validated method described by Blazer et al.,[16] whereby a estimation of the proportion of lesion consisting of viable tumour cells, proportion consisting of fibrotic tissue and proportion consisting of necrosis within the whole tumour assessed across all 4 blocks was made. Complete pathological response was defined as no viable tumour cells, major response as 1%–49% of viable tumour cells and minor response as >50% viable tumour cells. Patients with no response (100% viable tumour) were included in the minor response group. Where more than one lesion was present, a mean % response across all targeted lesions was calculated.

Statistical analysis

Quantitative and qualitative variables were expressed as medians (with range) and frequencies. Comparisons between groups were analysed with the chi-square test or Fisher exact test for proportions and the Mann–Whitney U test for continuous variables. Overall and disease free survival (OS, DFS) were calculated using the Kaplan–Meier method. To identify factors associated with OS and DFS in the entire cohort, univariate analysis was performed. Factors for analysis were selected based on previous evidence of prognostic value.[17] For comparison of pathological response rates in patients with more than one lesion, the mean response score for all targeted lesions was used for stratification. This was calculated by the sum of % viable tumour in all lesions, divided by the number of resected lesions. Comparisons were made using log-rank test. All variables associated with $p < 0.05$ in the univariate proportional hazards model were entered into a Cox proportional hazards multivariate model using a forward step wise procedure. $p < 0.05$ was considered significant. All statistical analyses were performed using IBM SPSS Statistics (v.20).

Results

Forty-nine patients were screened for recruitment, of which 9 were not treated with DEBIRI. Reasons for non-treatment were withdrawal of consent (n = 2), did not meet inclusion criteria (n = 5), physician decision to offer alternative therapy (n = 1) and failure to gain peripheral access for treatment with DEBIRI (n = 1). Forty patients were successfully treated with DEBIRI-TACE (see Fig. 2) and patient demographics are outlined in Table 1. Median patient age was 63, with nearly half of patients having a primary tumour located in the rectum (18/40, 45%). Twenty-six (65%) had node positive primary disease, with 22 (55%) receiving adjuvant 5-FU based chemotherapy after primary resection. Median time from resection of primary tumour to time of diagnosis of liver metastases was 26.2 months, with 11 patients (27.5%) developing liver

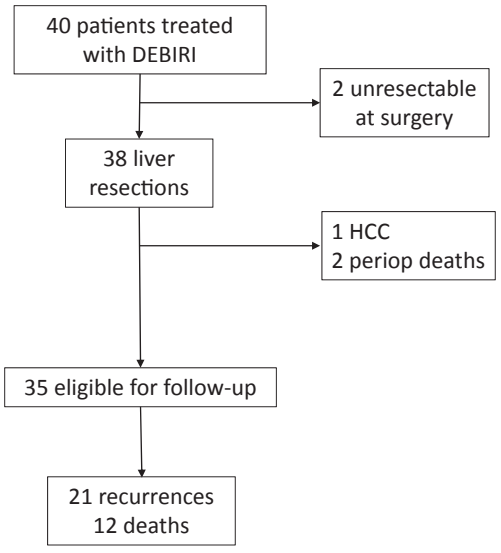

Figure 2. CONSORT diagram of PARAGON study.

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Table 1
Patient demographics.

		n	%
Age	Median, years	63	–
Sex	Male	31	77.5
	Female	9	22.5
Site of primary tumour	Colon	22	55
	Rectum	18	45
Primary tumour nodal status	Positive	26	65
	Negative	14	35
Adjuvant therapy for primary tumour	Yes	22	55
	No	18	45
Time from resection of primary tumour	Median, months	26.2	–
Number of colorectal liver metastases	1	28	70
	2	9	22.5
	3	3	7.5
Longest diameter of CRLM	>30 mm	22	45
	<30 mm	18	55
KRAS status	Mutant	7	22.6
	Wild type	24	77.4

metastases within 12 months of primary resection. 28 patients (70%) had only 1 liver metastasis. Primary tumour tissue for *KRAS* status was evaluable in 31 patients.

Chemoembolisation procedure

All 40 patients underwent treatment with DEBIRI. A single consultant interventional radiologist at each centre, each with >5 years experience, performed the procedure. Sixty-six discrete lesions were targeted, and patients received a median dose of 119 mg irinotecan (range 25–200 mg). IV paracetamol, IV lignocaine and fentanyl was used for peri-procedural pain control. No patients required sedation, and 39 patients were discharged home within 24 h. One patient was discharged after 48 h for social reasons. One patient developed post-DEBIRI pancreatitis (CTCAE grade 2, treated with supportive care) and was readmitted after 48 h (2.5% morbidity). After an uneventful 3-day inpatient stay they were discharged home, and underwent liver resection 95 days after TACE. No patients developed any systemic toxicity to irinotecan, or required any post-discharge pain medication.

Surgery

All forty patients proceeded to surgery. Median interval from DEBIRI-TACE to surgery was 30 days (IQR 27-35). At laparotomy, 2 patients were found to have unresectable disseminated peritoneal disease neither of which was identified on preoperative imaging. Thirty-eight patients therefore underwent liver resection (95% resection rate). Twelve patients (32%) underwent anatomical resection (7 left hemihepatectomy, 4 left lateral sectionectomy, 1 right hemihepatectomy), with the remainder undergoing non-anatomical metastectomies. Four previously undetected intrahepatic lesions were found in three patients. A total of sixty-eight lesions were therefore resected.

Two patients died within 30 days of surgery (30-day mortality 5%), neither of which was TACE related. One patient died from haemo-pneumo-mediastinum following false route insertion of a central line on the critical care unit on the day of surgery. The second patient died 8 days after surgery, having developed aspiration pneumonia followed by multi-organ dysfunction syndrome (MODS). Eleven patients (27.5%) developed complications (Dindo-Clavien grade 1–3), with 1 (2.5%) developing ≥grade 3 complication (bile leak requiring percutaneous drainage).

Tumour response

One patient was found to have hepatocellular carcinoma on histopathology and so was excluded from further pathological and long-term analysis. Four intraoperatively detected untreated lesions were also excluded from analysis. The remaining 63 treated lesions from 37 resected patients were assessed for pathological response. 74% of lesions were resected with an R0 margin, with 26% undergoing an R1 resection. Median tumour diameter was 21 mm (range 4–150 mm). Median viable tumour was 20% (range 0–100), necrosis 50% (range 0–100) and fibrosis 17% (range 0–70). Tumour response was defined as complete in 11 lesions (17%), major in 37 lesions (59%), minor in 14 lesions (22%) and no response in 1 lesion (2%) (See Fig. 3). Tumour response assessed by RECIST criteria demonstrated stable disease (22 patients, 55%), partial response (1 patient, 2.5%) or progressive disease (11 patients, 27.5%). There was no correlation between radiological response rates and pathological tumour response. As previously reported, there was no difference in pathological response between subsegmental and lobar embolisation.[18]

Long-term outcome

Survival analysis was performed on 35 of 38 patients who underwent hepatectomy for CRLM (2 early post-operative deaths were excluded from analysis, as was one patient found to have hepatocellular carcinoma on histopathology). No patients received systemic adjuvant therapy after liver resection. At a median follow up of 40.6 months, 12 patients (34.3%) had died of recurrent disease giving a median overall survival of 50.9 months. Nominal 1, 3 and 5-year OS was 93, 78 & 49% respectively (see Fig. 4). There were 21 recurrences at median follow-up, of whom 11 (52.3%) had liver-only recurrence. Median disease free survival was 19.7 months, with a 1, 3 and 5-year actuarial disease free survival of 68, 44 and 38% respectively. Results of univariate and multivariate predictors of overall survival are detailed in Table 2. Gender was the only factor associated with OS on univariate analysis, but was not significant on multivariate analysis. No statistically significant predictors of disease free survival were identified.

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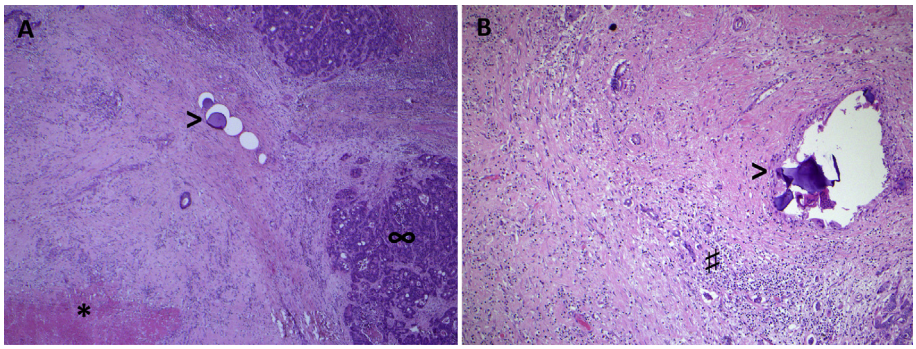
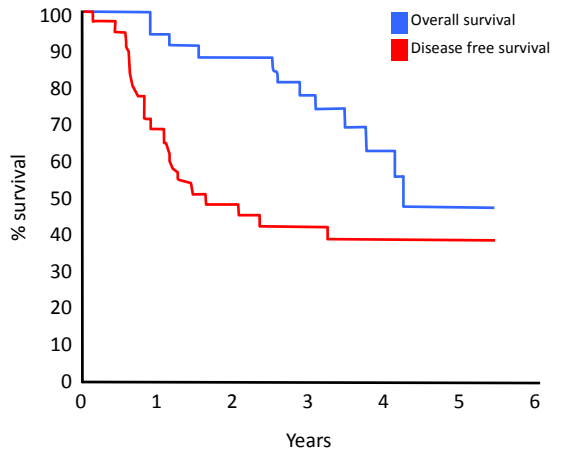


Figure 3. Representative photomicrographs of pathological tumour response after treatment with DEBIRI. (A) Major response – between 1 and 49% viable tumour. Magnification × 10 (B) Complete response – no viable tumour within lesion. Magnification × 20. > = DEBIRI microsphere in tissue vasculature, * = tissue fibrosis, ♯ = tumour necrosis, ∞ = tumour.

Discussion

The decision to treat resectable CRLM with neoadjuvant therapy is complex, with clinicians required to balance the potential long-term benefits with the risk of toxic side effects. The global model of cancer-drug development aims to shift this balance through novel agents targeting a narrow selection of molecular changes that occur in only a minority of tumours. This approach leads to rising cancer care costs, often without proportional gains in outcome.[19] By contrast, DEBIRI offers the potential to maximize tumour targeting whilst minimizing off-target side effects by physically localizing a commonly used cytotoxic agent directly to the tumour. The overall cost per treatment therefore remains an order of magnitude lower than for existing first-line biologic based systemic therapy.

This trial clearly demonstrated that administration of DEBIRI was safe, with no technical complications associated with the embolization procedure. These results compare favourably with reports describing alternative methods of liver directed therapy, such as hepatic arterial infusion pumps.[20,21] Contemporary trials assessing irinotecan based therapies for systemic disease report dose-limiting side effects (diarrhea and neutropenia) in 10–15% of cases[22] and the use of neoadjuvant systemic therapy for initially resectable disease remains controversial.[5,6,24] Preliminary pharmacokinetic modelling from this study suggests that systemic exposure to irinotecan after DEBIRI is low[25] and the absence of systemic toxicity reported in this trial suggest that DEBIRI would be a rational approach in such cases where the risk: benefit balance in favour of treatment may be marginal. These results also imply that DEBIRI may be used in combination with existing systemic therapies without a significant increase in treatment-related toxicity, although this would need confirmation in a prospective setting.



OS	35	32	28	22	8	2
DFS	35	23	16	14	6	2

Figure 4. Kaplan Meier curve demonstrating overall and disease free survival following liver resection after neoadjuvant DEBIRI. Table shows number at risk.

Surgical safety was not compromised by neoadjuvant treatment with DEBIRI. Hepatic resection was performed in thirty-eight of forty cases (resectability rate 95%), with two patients having widespread intraperitoneal carcinomatosis discovered at laparotomy. This pattern of disease is difficult to detect on preoperative imaging, and the delay of 4 weeks between DEBIRI-TACE and surgery would seem unlikely to be sufficient interval for the development of micrometastases. 74% of lesions treated with DEBIRI were resected with an R0 margin, with 26% R1 resection. This resection rate is comparable with other series reporting resection of CRLM without neoadjuvant therapy,[26] and likely reflects the easily resectable nature of patients recruited to this trial. Post-operative surgical mortality (5%) was higher than other reports which commonly cite 30-day mortality for hepatectomy after neoadjuvant chemotherapy consistently lower than 2%.[4,11,27] However, it seems unlikely that either of the deaths seen in this study were directly related to the neoadjuvant administration of DEBIRI. One patient died from anesthetic misadventure, whilst a second died from a recognized postoperative complication. Post-operative morbidity was in keeping with other published series.[28]

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Table 2
Univariate analysis of clinicopathological variables associated with overall survival after liver resection following neoadjuvant DEBIRI.

		n = 35 (%)	Median OS (months)	Number of deaths	P
Sex	Male	26 (74%)	55.1	6	0.04
	Female	9 (26%)	41.0	6	
Age	<65	18 (51%)	51.7	5	0.88
	>65	17 (49%)	49.5	7	
Interval from primary to secondary	<12 months	11 (31%)	58.1	2	0.11
	>12 months	24 (69%)	46.7	10	
Nodal status of primary	Positive	17 (49%)	48.3	6	0.60
	Negative	18 (51%)	52.8	6	
Size of largest lesion, mm	<30	18 (51%)	54.5	5	0.34
	>30	17 (49%)	45.7	7	
Margin	R0	19 (54%)	53.9	4	0.40
	R1	16 (46%)	49.5	8	
Pathological response	Minor	5 (14%)	52.0	2	0.23
	Major	22 (86%)	42.5	9	
	Complete	8 (23%)	60.0	1	
Ras status	Mutant	7 (77%)	45.8	2	0.58
	Wild-type	24 (69%)	53.0	7	
Number of lesions	1	18 (51%)	45.9	8	0.24
	>1	17 (49%)	55.9	4	
RECIST response	Partial response	1 (3%)	55.0	0	0.34
	Stable disease	22 (63%)	48.7	8	
	Progressive disease	11 (31%)	53.7	6	

Pathological response rates were impressive, with 76% of lesions showing a major or complete pathological response - comparable to that seen after six cycles of systemic FOLFOX/FOLFIRI.[16] By contrast, radiological response rates were very low with only 2.5% of patients demonstrating response by RECIST criteria. RECIST remains the gold standard for assessing response of solid tumours but there is growing evidence that traditional size-based criteria (such as RECIST and mRECIST) do not optimally reflect tumour response to novel therapies such as DEBIRI.[29–31] The trial protocol allowed only 4 weeks between treatment and resection, and it may also be that inadequate time had passed to allow maximal tumour response (as measured by reduction in tumour size). It has also been suggested that peritumoral edema in the immediate post-DEBIRI phase may lead to a transient increase in tumour size on scanning.[31] This may have an impact on potential future roles for DEBIRI in the down-staging or initially irresectable disease.

The mechanism of action of DEBIRI has not yet been fully elucidated. Although pathological response rates are impressive, it is unclear whether this is predominantly due to the embolisation effect, local cytotoxic drug effect or a combination of the two. Preliminary animal modelling suggests that bland bead embolisation is ineffective compared to treatment with drug-loaded bead,[32] whilst early clinical studies have suggested that drug activation in normal liver surrounding tumour (i.e. off-target delivery) is a predictor of treatment response.[25] It therefore seems likely that targeted drug delivery is a significant contributor to the efficacy of DEBIRI. Stage IV colorectal cancer is a systemic disease, and it would appear logical that the eventual role for DEBIRI will be alongside a systemic therapy in an effort to maximize treatment of liver dominant disease. In this setting, addition of DEBIRI to FOLFOX may increase response and therefore resection rates without a significant increase in toxicity.[33] However, the optimal systemic therapy backbone requires clarification. If embolisation is an important factor in the mechanism of action, systemic anti-angiogenic agents (such as Bevacizumab and Aflibercept) are likely to have a synergistic effect by preventing revascularization of tumour after treatment.

Although we have not directly addressed the subsequent multi-modal therapies offered to these patients following disease recurrence, the 5-year survival of 49% reported in this trial reinforces the excellent long-term outcomes associated with liver resection for CRLM in this group of patients. At median follow-up of 40 months, 53% patients had developed recurrent disease, of which approximately half had liver-only recurrence. Given that the aim of the study was to assess the feasibility of resecting treated liver, rather than reducing occult disease burden, these figures are unsurprising and in keeping with other contemporary series.

In conclusion, this trial clearly demonstrates the safety and efficacy of neoadjuvant DEBIRI in patients with easily resectable colorectal liver metastases. This treatment can be delivered prior to surgery, with minimal morbidity and without any delay in primary treatment. DEBIRI has no impact on resectability of tumour or on surgical outcomes and the impressive pathological response rates after a single treatment with DEBIRI are comparable with that seen after multiple cycles of systemic chemotherapy, with no evidence of systemic toxicity. The results of this preliminary study will be used to guide further prospective studies on the precise role of DEBIRI in the management of CRLM. This seems likely to be alongside systemic therapies, either in a true neoadjuvant model or as an adjunct to induction chemotherapy for initially irresectable disease, where conversion to resectability is the primary aim of therapy. A better understanding of the interactions between DEBIRI and other agents is therefore crucial. With treatment value becoming an increasingly important cancer metric, formal health economic assessment of the efficacy of treatments like DEBIRI is also likely to be critical in defining its role in the multi-modality management of colorectal cancer.

Conflicts of interest

RJ, HZM, SWF & GJP have received research support from BTG.

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