

# BMJ Open Protocol of a randomised phase III clinical trial of sequential capecitabine or 5-fluorouracil plus bevacizumab (Cape/5-FU-Bmab) to capecitabine or 5-fluorouracil plus oxaliplatin plus bevacizumab (CapeOX/mFOLFOX6-Bmab) versus combination CapeOX/mFOLFOX6-Bmab in advanced colorectal cancer: the C-cubed (C<sup>3</sup>) study

**To cite:** Nagasaka T, Mishima H, Sawaki A, *et al*. Protocol of a randomised phase III clinical trial of sequential capecitabine or 5-fluorouracil plus bevacizumab (Cape/5-FU-Bmab) to capecitabine or 5-fluorouracil plus oxaliplatin plus bevacizumab (CapeOX/mFOLFOX6-Bmab) versus combination CapeOX/mFOLFOX6-Bmab in advanced colorectal cancer: the C-cubed (C<sup>3</sup>) study. *BMJ Open* 2016;**6**:e011454. doi:10.1136/bmjopen-2016-011454

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2016-011454>).

Received 9 February 2016  
Revised 2 May 2016  
Accepted 13 May 2016



CrossMark

For numbered affiliations see end of article.

## Correspondence to

Dr Takeshi Nagasaka;  
takeshin@cc.okayama-u.ac.jp

Takeshi Nagasaka,<sup>1</sup> Hideyuki Mishima,<sup>2</sup> Akira Sawaki,<sup>3</sup> Mototsugu Shimokawa,<sup>4</sup> Michio Inukai,<sup>5</sup> Katsunori Shinozaki,<sup>6</sup> Hiroaki Tanioka,<sup>7</sup> Junichiro Nasu,<sup>8</sup> Tomohiro Nishina,<sup>9</sup> Shoichi Hazama,<sup>10</sup> Masazumi Okajima,<sup>11</sup> Yoshiyuki Yamaguchi<sup>3</sup>

## ABSTRACT

**Introduction:** Results from several randomised trials suggest that the sequential use of cytotoxic agents in patients with metastatic colorectal cancer (mCRC) has the potential to improve overall survival compared with combination chemotherapy. This study is designed to investigate whether sequential treatment with bevacizumab-based first-line treatment with oxaliplatin is superior to combination treatment of mCRC.

**Methods and analysis:** The C-cubed (C<sup>3</sup>) study is a two-arm, multicentre, open-label, randomised phase III trial in Japan comparing the efficacy and safety of sequential capecitabine or 5-fluorouracil plus bevacizumab (Cape/5-FU-Bmab) with escalation to capecitabine or 5-fluorouracil plus oxaliplatin plus bevacizumab (CapeOX/mFOLFOX6-Bmab) versus combination CapeOX/mFOLFOX6-Bmab as the first-line treatment of mCRC. In the sequential arm (Arm A: oxaliplatin 'wait-and-go'), treatment escalation from Cape/5-FU-Bmab to CapeOX/mFOLFOX6-Bmab is recommended in the case of progressive disease. In the combination arm (Arm B: oxaliplatin 'stop-and-go'), de-escalation from CapeOX/mFOLFOX6-Bmab to Cape/5-FU-Bmab is possible after 12 weeks of treatment. Re-escalation to CapeOX/mFOLFOX6-Bmab after progressive disease is considered only for patients who received de-escalation of oxaliplatin after 12 weeks of treatment not caused by oxaliplatin-associated toxicity. A target sample size of 304 evaluable patients is considered sufficient to validate an expected HR for time to failure of strategy of the

## Strengths and limitations of this study

- This study is the first phase III trial to determine whether a sequential bevacizumab-based first-line treatment with oxaliplatin is superior to conventional bevacizumab-based treatment regimens.
- A particular strength of this study design is the time to failure of a strategy that allows for a wide range of approaches to manage patients with metastatic colorectal cancer while retaining them on the study, thus providing a more complete assessment of a given strategy's benefit.
- This innovative design allows for the analysis of therapeutic strategies and associated toxicities.
- Although a limitation of this study is that treatment assignment is stratified on the basis of only the clinical criteria, we believe that the results will provide immediate implications for current and future clinical trials, as well as for the patients and their physicians.

sequential approach 'wait-and-go' compared to the combination approach 'stop-and-go' with 80% power and 2-sided 5%  $\alpha$  in case of a true HR<0.69.

**Ethics and dissemination:** This study is conducted according to the standards of Good Clinical Practice and in compliance with the Declaration of Helsinki 2013 and local regulations, and has been submitted and approved by the Ethical Committee of the Non-Profit Organization MINS Institutional Review Board.

The protocol and the trial results, even inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

**Trial registration number:** UMIN000015405, Pre-results.

## INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths and the most common cancer type, with more than one million new cases annually diagnosed worldwide.<sup>1 2</sup> In ~25% of patients with CRC, synchronous metastasis is apparent at initial diagnosis.<sup>3</sup> Additionally, 20–25% of patients with CRC who undergo curative resection for the primary lesion develop metachronous metastases. Of these patients with CRC with synchronous or metachronous metastases, unfortunately, only 10–20% are resectable at the time of diagnosis.<sup>4 5</sup> Patients with metastatic CRC (mCRC) can be classified into four groups. Group 0 includes patients with primarily technically R0 (cancerous cells that are not observed microscopically in surgical margins)-resectable liver or lung metastases with no biological relative contraindications. Group 1 patients have potentially resectable metastatic disease with curative intention; active induction chemotherapy is required in this group. Group 2 patients are those with disseminated disease that is technically never or unlikely resectable; intermediate intensive treatment for these patients is intended to be palliative. Group 3 patients have unresectable metastatic disease; in these patients, the maximal shrinkage of metastases is not the primary treatment aim and non-intensive and/or sequential treatment is considered in the absence of imminent symptoms and limited risk for rapid deterioration to prevent tumour progression and to achieve prolongation of life with minimal treatment burden.<sup>3</sup> Therefore, less intensive regimens focusing on survival and disease control may be a better choice for first-line treatment in Group 3 patients with mCRC. Grothey *et al* analysed the AVF2107g and N9741 trials that demonstrated survival benefits of bevacizumab in first-line mCRC and identified that tumour response was not a required factor to provide benefit as a first-line therapy for patients with mCRC. Although patients achieving response had a better prognosis, response was not predictive of the benefit derived from the superior treatment in either trial.<sup>6</sup>

Several randomised trials have indicated that combination chemotherapy in mCRC did not significantly improve overall survival (OS) compared with the sequential use of cytotoxic agents (FOCUS, FOCUS2, CAIRO, FFCD 2000–2005).<sup>7–10</sup> The present study investigated whether these conclusions also hold true for bevacizumab-based first-line treatment with oxaliplatin. The combination of a fluoropyrimidine plus bevacizumab was previously shown to be effective as a first-line treatment for mCRC with progression-free survival (PFS) times of 8.5–10.8 months and disease

control rates of 71–92.5%.<sup>11–13</sup> In addition, relatively low rates of progressive disease (PD) at 2.7–19% have been reported with this treatment regimen.

This trial is designed to investigate the efficacy and safety of a sequential capecitabine or 5-fluorouracil (5-FU) plus bevacizumab (Cape/5-FU-Bmab) with escalation to capecitabine or 5-FU plus oxaliplatin plus bevacizumab (CapeOX/mFOLFOX6-Bmab) compared with a conventional combination CapeOX/mFOLFOX6-Bmab for the first-line treatment of unresectable mCRC with the goal of long-term disease stabilisation and moderate toxicity. In the case of first occurrence of PD (PFS-1) in the sequential arm (Arm A: oxaliplatin ‘wait-and-go’), treatment is escalated by adding oxaliplatin. PFS-2 can be investigated in patients developing stable disease or partial remission/complete remission after treatment intensification (figure 1).

In the combination arm (Arm B: oxaliplatin ‘stop-and-go’), patients received CapeOX/mFOLFOX6-Bmab as the first-line therapy. De-escalation to Cape/5-FU-Bmab is allowed either after 12 weeks (3 months) of treatment or if oxaliplatin-induced toxicity develops. The primary end point is the time to failure of strategy (TFS). The quality of life assessment by several questionnaires is performed in both treatment arms to investigate the impact of sequential chemotherapy and combination chemotherapy as first-line therapy options.

## METHODS AND ANALYSIS

### Primary objective

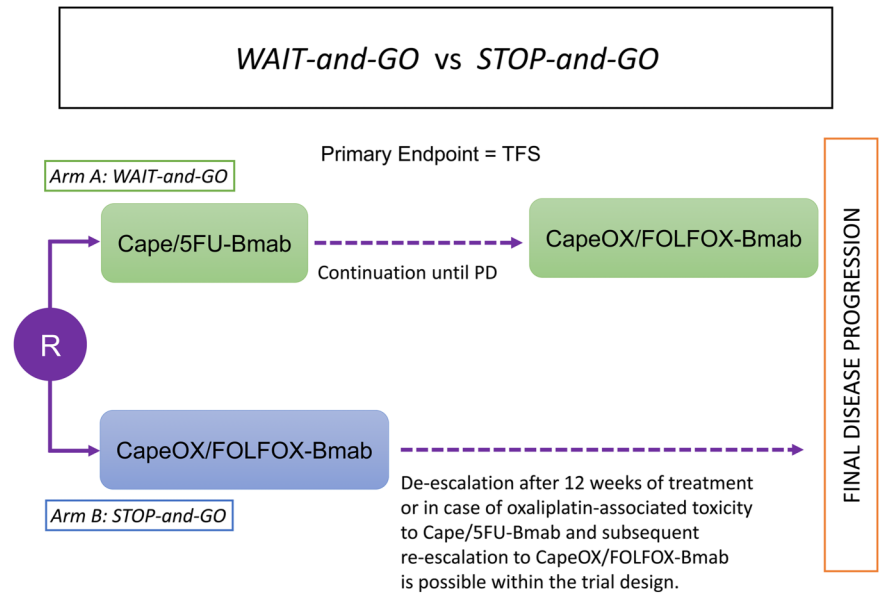
The primary objective is to examine the efficacy of the sequential arm as the first-line treatment in patients with unresectable mCRC. Since the sequential administration of treatment regimens is evaluated, TFS is selected as the primary end point (figure 1).<sup>14</sup>

In the sequential arm, Cape/5-FU-Bmab treatment will be escalated after disease progression (PFS-1) by the addition of oxaliplatin (CapeOX/mFOLFOX6-Bmab); in those patients, PFS-2 will then be assessed after treatment intensification. In the sequential arm, TFS is defined as PFS-1+PFS-2, where PFS-1 is the time between randomisation and the first failure of Cape/5-FU-Bmab and PFS-2 is the time between PFS-1 and PD after treatment intensification to CapeOX/mFOLFOX6-Bmab.

In the combination arm, treatment will be de-escalated to Cape/5-FU-Bmab and re-escalated to CapeOX/mFOLFOX6-Bmab according to a predefined algorithm. TFS is defined as the time between randomisation and progression on the combination arm treatment strategy.

In this study, PD is defined as a <20% increase in the sum of the longest dimensions of target lesions from baseline.<sup>15</sup> The exacerbation of the underlying disease and appearance of new lesions (a clinical diagnosis of distinct disease progression) was included in the

**Figure 1** The flow chart for the C<sup>3</sup> study. Patients are randomised to receive either single-agent chemotherapy (Cape/5-FU-Bmab) and escalation to CapeOX/FOLFOX-Bmab at progressive disease (Arm A, 'wait-and-go') or combination chemotherapy (CapeOX/FOLFOX-Bmab) with a de-escalation option to Cape/5-FU-Bmab and subsequent re-escalation if required (Arm B, 'stop-and-go'). CapeOX/FOLFOX-Bmab, 5-fluorouracil plus oxaliplatin plus bevacizumab; Cape/5-FU-Bmab, 5-fluorouracil plus bevacizumab; PD, progressive disease; TFS, time to failure of strategy.



assessment of PD for new non-target lesions. Additionally, PFS was calculated on the basis of PD assessed according to the Response Evaluation Criteria in Solid Tumors V.1.1.

### Secondary objective

Secondary objectives are to compare the overall response rate (ORR), PFS-1, PFS-2 (Arm A only), OS, time to treatment failure, the duration of disease control (DDC), safety, toxicity and the quality of life. Survival is defined as the interval between randomisation and death from any cause. The grade of toxicity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.4.0. The quality of life will be studied by the following: the EuroQol questionnaire (EQ-5D), patient neurotoxicity questionnaire (PNQ), European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C-3 and Japanese health assessment questionnaire (J-HAQ).<sup>16</sup>

### Design

The C<sup>3</sup> study is a two-arm, multicentre, open label, randomised phase III trial comparing the efficacy and safety of a sequential Cape/5-FU-Bmab with escalation to CapeOX/mFOLFOX6-Bmab compared with a conventional combination CapeOX/mFOLFOX6-Bmab for the first-line treatment of unresectable mCRC.

### Enrolment

A total of 304 patients will be enrolled in a 1:1 randomisation into the two treatment arms. Patients will be enrolled at one of the 80–100 study centres in Japan. The study started on 1 December 2014. The estimated primary completion date, which is the final data collection date for primary outcome measure, is November 2016, and the estimated study completion date is May 2018.

### Stratification

Treatment assignment will be stratified on the basis of the following criteria:

1. Köhne Index (low/intermediate/high);<sup>17</sup>
  - ▶ Eastern Cooperative Oncology Group (ECOG) performance status
  - ▶ Number of metastatic sites
  - ▶ Alkaline phosphatase (AP) level
  - ▶ White cell (WCC) count
2. Institution;
3. Prior adjuvant chemotherapy (with or without oxaliplatin).

### Eligibility criteria

#### Inclusion criteria

1. Histologically confirmed adenocarcinoma of the colon or rectum;
2. Advanced or recurrent CRC that is not a candidate for curative resection;
  - ▶ Patients with advanced colorectal cancer who received no intervention expect for surgical procedure (R0 surgery is not included)
  - ▶ Patients with recurrent CRC who did not receive any therapy to the site of recurrence.
3. Age of 20 years or older;
4. ECOG performance status of 0–2;
5. Presence of evaluable lesions as confirmed using CT or MRI and no previous chemotherapy or radiotherapy;
6. Life expectancy of longer than 90 days;
7. No limitation of oral administration;
8. Adequate organ function according to the following laboratory values obtained within 14 days prior to enrolment in the study (Data recorded nearest to the entry should be referred, and patients who received blood transfusions or haematopoietic growth factors within 14 days prior to the laboratory tests are excluded);

9. Neutrophils  $\geq 1500/\text{mm}^3$ ;
10. Platelets  $\geq 10.0 \times 10^4/\text{mm}^3$ ;
11. Haemoglobin  $\geq 8.0 \text{ g/dL}$ ;
12. Total bilirubin  $\leq 2.0 \text{ mg/dL}$ ;
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 100 \text{ IU/L}$  (for patients with liver metastasis,  $\leq 200 \text{ IU/L}$ );
14. Serum creatinine  $\leq 1.5 \times$  institution standard value;
15. Creatinine clearance rate  $\geq 30 \text{ mL/min}$  by the Cockcroft-Gault formula;
16. Proteinuria  $\leq 1+$ ;
17. Prothrombin time (PT)-international normalised ratio (INR)  $< 3.0$ ;
18. Written informed consent after receiving an explanation of the planned treatments in the study.

### Exclusion criteria

1. History of active double cancer within 5 years prior to enrolment in the study;
2. History of serious drug hypersensitivity or drug allergy;
3. Severe renal failure, haematological toxicities, diarrhoea, infections, massive pleural effusion and peritoneal fluid;
4. Severe or uncontrolled complications (diabetes mellitus, high-blood pressure, diarrhoea, electrolyte abnormalities);
5. Complication due to cerebrovascular disease or symptoms within 1 year prior to enrolment in the study;
6. Bleeding tendency, coagulopathy (PT-INR  $\geq 3.0$  within 1 week prior to enrolment in the study);
7. Thrombosis, thromboembolism or receiving anti-coagulant drugs (except aspirin  $\leq 325 \text{ mg/day}$ );
8. Unhealed wound or major surgical procedure within 28 days prior to enrolment in the study;
9. Invasive procedure within 7 days prior to enrolment in the study, excluding regular blood sampling, drip infusion, endoscopic examination and central port;
10. Aortic aneurysm or aortic dissection;
11. Uncontrollable peptic ulcer;
12. Concurrent or history of gastrointestinal perforation (within 1 year prior to enrolment in the study);
13. Untreated traumatic bone fracture;
14. Uncontrolled hypertension;
15. Peripheral neuropathy  $\geq$  grade 1;
16. Patients who are pregnant, lactating, with child-bearing potential or those who refuse contraceptive measures;
17. History of adverse events related to dihydropyrimidine dehydrogenase deficiency;
18. Psychological disorders or central nervous system disease that can hinder study treatments;
19. Participants who are judged by the investigator to be unsuitable for study participation for any reason.

### Randomisation

Patients are registered to the study after confirming the eligibility criteria and obtaining written informed

consent. They are randomised to either treatment group at the data centre (EPS Corporation, Osaka, Japan) using the minimisation method.<sup>18</sup>

### Safety

All serious adverse events (SAEs) must be entered into the electronic data capturing system and reported to the principal investigator and the study office (Japan South West Oncology Group, Hiroshima, Japan) within 24 hours using the completed SAE report and case report form. The principal investigator is responsible for the management of safety reporting requirements according to the local regulations and guidelines. Copies of all report submissions by the principal investigator to regulatory authorities and to the EC that has approved the study will be provided to the pharmacovigilance department of the license holders of the study drugs. If necessary, additional information and clarifications on cases will be forwarded to the license holders by the principal investigator.

### Data quality assurance

All patient data are collected in the central database of the data centre at Osaka, and the patient identifiers are kept confidential. Computerised and visual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies.

### Monitoring and source data verification

The sponsor will perform on-site monitoring with clinical research associates.

The monitoring visits will cover  $\sim 10\%$  of the study centres enrolled in this study.

The aim of on-site visits will be as follows:

- ▶ Adherence to recruitment rate;
- ▶ Adherence to eligibility criteria;
- ▶ To evaluate the local facilities available to the responsible investigator for performing clinical trials and to comply with all requirements of the present protocol;
- ▶ Adherence to scheduled examination and evaluation appointments;
- ▶ Existence of written informed consent;
- ▶ Integrity of study documentation;
- ▶ Source data verification: to assess the consistency of the data reported on CRF with the source data.

### Statistical analysis

Statistical analyses will be performed according to the intention-to-treat principle, that is, all eligible patients will be included in the analysis in the arm to which they were randomised independently of whether they received the assigned treatment or not. Toxicity analysis will be conducted in all patients receiving at least one dose of study medication. Demographic and prognostic baseline measures will be analysed for heterogeneity between the two treatment arms.

The primary objective of the study is to determine if TFS is superior in the experimental arm. The primary

end points will be estimated by the Kaplan-Meier method and compared between groups with a stratified log-rank test.

The secondary end points in the study are ORR, safety, quality of life measurements and time-to-event data. Clinical and laboratory toxicity graded according to NCI CTCAE (V.4.0) will be collected for all patients. The quality of life will be measured using EQ-5D, PNQ, EORTC QLQ C-3 and J-HAQ. Categorical data comparisons between treatment arms will be performed using Fisher's exact,  $\chi^2$  and Mantel-Haenszel tests, where appropriate. Continuous data comparisons between treatment arms will be performed using generalised estimating equations or generalised linear mixed models. Time-to-event data (PFS, OS) will be reported according to the Kaplan-Meier method and compared using the log-rank test. In case of non-conformity with proportional hazard assumptions, the generalised Wilcoxon signed-rank test, modified by Peto *et al*,<sup>19</sup> can be used. All p values will be estimated without adjustment of the level of significance, using two-sided test procedures.

### Sample size

This trial hypothesises that TFS with the sequential approach 'wait-and-go' will be superior to the combination approach 'stop-and-go.' On the basis of published data on mFOLFOX6, CapeOX or SOX (S-1 plus oxaliplatin) plus bevacizumab and with regard to a marginally decreased prognosis due to the exclusion of resectable patients, a median TFS of 11 months will be expected in Arm B.<sup>15</sup> Median PFS (PFS-1 of Arm A) with Cape/5-FU-Bmab for the first-line treatment of unresectable mCRC ranged from 8.5 to 10.8 months.<sup>11-13</sup> Median PFS of second-line CapeOX/FOLFOX6-Bmab, PFS-2, was 5.7 months when bevacizumab was continuously administered from first-line to second-line treatment.<sup>20</sup> Therefore, we estimate TFS of Arm A as 16 months (10 months for PFS-1 plus 6 months for PFS-2). With these estimations, a total of 223 events are required to achieve a power of 80% with a two-sided type 1 error of 0.05. Under the assumption of a recruitment period of 2 years and a minimum follow-up period of 1.5 years,<sup>21</sup> when taking prematurely withdrawn or censored cases into account, the sample size is set at 304 patients for the study.

### Baseline assessment

Baseline assessment will be performed within 14 days before the first application of study medication and will include the following items:

1. CT scan of the thorax and abdomen within 4 weeks prior to randomisation (definition of target lesions);
2. Haematology and differential blood count;
3. Serum chemistry, including creatinine, lactate-dehydrogenase, C reactive protein, bilirubin, AP, AST, ALT, serum iron, total iron binding capacity and ferritin;
4. Urine analysis by dipstick;

5. Vital signs, for example, blood pressure and heart rate;
6. Tumour markers (carcinoembryonic antigen, carbohydrate antigen 19-9);
7. Quality of life questionnaires (EQ-5D, PNQ, EORTC QLQ C-3 and J-HAQ).

### Study medication

#### 5-fluorouracil

5-FU is a pyrimidine analogue used in the treatment of a wide variety of cancers, including CRC. While 5-FU has been shown to exert its antitumour effect through several mechanisms, its principal mechanism of action is through the inhibition of thymidylate synthase (TS) enzyme. TS methylates deoxyuridine monophosphate to form thymidine monophosphate (dTMP), and its inhibition blocks the synthesis of the pyrimidine thymidine required for DNA replication. 5-FU causes a scarcity in dTMP; thus, rapidly dividing cancerous cells undergo cell death via thymineless death.<sup>22</sup>

#### Leucovorin

Leucovorin, a form of folic acid, is generally administered as calcium or sodium folinate (leucovorin calcium/sodium). Leucovorin is used as an adjuvant in methotrexate-containing cancer chemotherapy regimens;<sup>23</sup> it provides an exogenous source of reduced folinates and stabilises the 5-FU-TS complex, enhancing 5-FU cytotoxicity. First discovered in 1948 as a citrovorum factor, it is occasionally called by that name.<sup>24</sup>

#### Capecitabine

Capecitabine is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour tissue through the exploitation of high-intratatumoral concentrations of thymidine phosphorylase (TP). TP is found in significantly increased concentrations in a wide range of cancers, including colorectal, breast and gastric cancers, compared with normal tissues.<sup>25</sup> Previous pharmacokinetic studies in humans have shown almost complete absorption of capecitabine through the gastrointestinal wall after oral administration; direct intestinal exposure to 5-FU is thereby avoided. Capecitabine is metabolised to 5-FU via a three-step enzymatic cascade, with the final conversion to 5-FU mediated by TP.<sup>26</sup>

#### Oxaliplatin

Oxaliplatin is a platinum derivative in which the platinum (Pt) atom is complexed with a 1, 2 diaminocyclohexane and an oxalate ligand. It was synthesised with the goal of overcoming resistance to first and second-generation Pt compounds by Sanofi-Synthelabo in 2001. The mechanism of action of oxaliplatin is similar to that of cisplatin as well as other Pt compounds. Studies conducted until now indicate that the types and percentages of Pt-DNA adducts formed by oxaliplatin are qualitatively similar to those formed by cisplatin; however, preclinical

data suggest several unique attributes of the cytotoxic/antitumour activity of oxaliplatin. Oxaliplatin demonstrated a broad spectrum of *in vitro* cytotoxicity and *in vivo* antitumour activity distinct from those achieved by either cisplatin or carboplatin.<sup>27</sup> Oxaliplatin was active against several cell lines, CRC and other solid tumours that were not responsive to cisplatin.<sup>27</sup> In addition, oxaliplatin in combination with 5-FU led to the synergistic antiproliferative activity in several *in vivo* models.<sup>27 28</sup>

### Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody targeting a vascular endothelial growth factor (VEGF or VEGF-A) that plays a central role in signalling pathways that control tumour angiogenesis and survival. The disruption of this signalling pathway prevents tumour angiogenesis and controls proliferation of abnormally existing tumour blood vessels and vessel permeability allowing cytotoxic drug access into the tumour.<sup>29 30</sup>

### Treatment programme

This study does not allow crossover between capecitabine and 5-FU throughout the study. The experimental arm (Arm A, 'wait-and-go' arm) of the trial consists of two regimens: Cape-Bmab or 5-FU-Bmab. Cape-Bmab consists of capecitabine (1000 mg/m<sup>2</sup> two times day 1–14) plus bevacizumab 7.5 mg/kg over 90 min on day 1 every 3 weeks. Treatment continuation is intended until disease progression or development of toxicity. In case of progression, escalation to combined chemotherapy with CapeOX-Bmab is provided. CapeOX-Bmab consists of capecitabine (1000 mg/m<sup>2</sup> two times day 1–14), oxaliplatin 130 mg/m<sup>2</sup> as a 2-hour infusion on day 1 and bevacizumab 7.5 mg/kg over 90 min on day 1 every 3 weeks.

5-FU-Bmab consists of bevacizumab at 5 mg/kg as a 30-min infusion and leucovorin 200 mg/m<sup>2</sup> as a 2-hour infusion, followed by a bolus of 5-FU 400 mg/m<sup>2</sup> within 15 min and 46-hour infusion of 5-FU 2400 mg/m<sup>2</sup> on day one every 2 weeks. Treatment continuation is intended until disease progression or development of toxicity. In case of progression, escalation to combined chemotherapy with mFOLFOX6-Bmab is provided, which consists of bevacizumab at 5 mg/kg as a 30 min infusion and leucovorin 200 mg/m<sup>2</sup> as a 2-hour infusion, and the concurrent administration of oxaliplatin 100 mg/m<sup>2</sup> as a 2-hour infusion, followed by a bolus of 5-FU 400 mg/m<sup>2</sup> within 15 min and 46-hour infusion of 5-FU 2400 mg/m<sup>2</sup> on day 1 every 2 weeks.

The control arm (Arm B: 'stop-and-go') of the trial starts with either CapeOX-Bmab or mFOLFOX6-Bmab regimen selected by the doctor who treated the enrolled patient. Treatment continuation is intended until disease progression or development of toxicity. After 12 weeks of treatment or in the case of oxaliplatin-associated toxicity, de-escalation to Cape-Bmab or 5-FU-Bmab is recommended. In case of disease progression after treatment de-escalation, re-escalation to the combination chemotherapy is possible.

## ETHICS AND DISSEMINATION

### Ethics

This study is conducted according to the standards of Good Clinical Practice and in compliance with the Declaration of Helsinki 2013 and local regulations. The independent medical ECs of all participating hospitals have approved the study protocol. Oral and written informed consent forms are obtained from all patients prior to randomisation.

### Dissemination

The protocol and the trial results, even inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

## DISCUSSION

Currently, four clinically distinct groups of patients with mCRC are recognised. Group 0 patients are those with technically R0-resectable liver or lung metastases, while group 1 patients have potentially resectable metastatic disease with curative intention. Group 2 patients have disseminated disease that is technically never or unlikely resectable and requires intermediate intensive treatment. Group 3 patients, on the other hand, are those with never-resectable metastatic disease needing non-intensive or sequential treatment.<sup>3</sup> With respect to the sequential approach, only the AIO KRK 0110 trial, which contains a sequential strategy with bevacizumab as a starting single-agent chemotherapy (capecitabine-Bmab) and allows for escalation to combination chemotherapy with capecitabine with irinotecan-Bmab, examined the efficacy of a single cytotoxic agent with bevacizumab.<sup>31</sup> However, the AIO KRK 0110 trial is designed for patients with disseminated, albeit asymptomatic, mCRC who are not potential candidates for the surgical resection of metastases. Previous studies that examined the efficacies of sequential use of cytotoxic agents, namely FOCUS, FOCUS2, CAIRO and FFCD 2000–2005, were performed in patients with mCRC without stratification according to clinical presentation.<sup>7–10</sup> Therefore, the C<sup>3</sup> study is designed to examine the efficacy of sequential use of cytotoxic agents combined with bevacizumab in subgroups of patients with mCRC.

An escalation strategy in the preantibody era has been investigated in the CApecitabine, IRinotecan and Oxaliplatin in advanced CRC (CAIRO) study. Koopman *et al*<sup>9</sup> reported a trial arm where treatment was escalated in sequential steps from capecitabine (first-line) and irinotecan (second-line) to third-line capecitabine plus oxaliplatin (CAPOX). Comparison with a combination application of capecitabine with irinotecan as first-line and CAPOX as second-line led to the interpretation that the combination treatment did not significantly improve OS compared with the sequential use of cytotoxic drugs.<sup>9</sup> Another study of the preantibody era was the FOCUS trial,<sup>7</sup> which compared 5-FU/leucovorin followed by irinotecan at progression (Arm A), 5-FU/leucovorin

followed by combination chemotherapy (both FOLFIRI and FOLFOX) (Arm B), and combination chemotherapy (both FOLFIRI and FOLFOX) (Arm C) from the onset. This large-scale study also challenged the assumption that in a non-curative setting, maximum tolerable treatment must necessarily be used as a first-line therapy.<sup>7</sup> Another study, the FOCUS2 trial,<sup>8</sup> compared 5-FU/leucovorin followed by FOLFOX at progression (Arm A), FOLFOX from the onset (Arm B), capecitabine followed by CAPOX (Arm C) at progression and CAPOX from the onset (Arm D). This study also confirmed that initially intensive regimens do not induce a superior outcome compared with single-agent first-line strategies.<sup>8</sup> The FFCD 2000–2005 trial compared the sequential 5-FU/leucovorin, FOLFOX (second-line) and FOLFIRI (third-line) treatment strategy to the more conventional sequential FOLFOX and FOLFIRI (second-line) strategy.<sup>10</sup> Again, this trial confirmed that initially intensive regimens do not induce a superior outcome compared with the well-tolerated single-agent first-line strategies.

The C<sup>3</sup> study does not simply investigate two treatment regimens but rather compares two strategies of treatment; for this reason, TFS is selected as the primary end point. TFS, as well as DDC, showed better correlation with OS than conventional PFS as shown previously by Chibaudel B *et al* who analysed three trials with ‘stop-and-go’ strategies. In this study protocol, TFS is defined as the time between randomisation and final failure of CapeOX/mFOLFX6-Bmab treatment in both treatment arms. This end point allows for a wide range of options to manage patients with mCRC while retaining them on the study, thus providing a more complete assessment of a given strategy’s benefit.<sup>29</sup> In the case of comparable TFS times, toxicity will be evaluated according to the NCI CTCAE criteria with a predefined score system using symptomatic grade 2–4 toxicities per cycle. This innovative design allows for the analysis of both the therapeutic strategies and associated toxicities.

The C<sup>3</sup> study is designed for patients with unresectable mCRC. Two bevacizumab-based strategies are compared: one starting as a single-agent chemotherapy (Cape/5-FU-Bmab) allowing escalation to CapeOX/mFOLFOX6-Bmab and another starting with combination chemotherapy (CapeOX/mFOLFOX6-Bmab) and allowing de-escalation to Cape/5-FU-Bmab with the option of subsequent re-escalation if required.

#### Author affiliations

<sup>1</sup>Department of Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

<sup>2</sup>Cancer Center, Aichi Medical University, Yazakokarimata, Japan

<sup>3</sup>Department of Clinical Oncology, Kawasaki Medical School, Okayama, Japan

<sup>4</sup>Cancer Biostatistics Lab, Clinical Research Institute, National Hospital Organization Kyusyu Cancer Center, Fukuoka, Japan

<sup>5</sup>Department of Integrated Medicine, Kagawa University Hospital, Kagawa, Japan

<sup>6</sup>Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan

<sup>7</sup>Department of Medical Oncology, Okayama Rosai Hospital, Okayama, Japan

<sup>8</sup>Department of Internal Medicine, Okayama Saiseikai General Hospital, Okayama, Japan

<sup>9</sup>Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama City, Japan

<sup>10</sup> Department of Digestive Surgery and Surgical Oncology, Yamaguchi University Graduate School of Medicine, Ube, Japan

<sup>11</sup>Department of Surgery, Hiroshima City Hospital, Hiroshima City, Japan

**Contributors** TaN, HM, MO and YY designed and wrote the original protocol for the study, and drafted the manuscript. MS designed the statistical analyses for the study. AS, MI, KS, HT, JN, ToN and SH participated in drafting the original protocol for the study. All authors read and approved the final manuscript.

**Funding** The trial is funded by Chugai Pharmaceutical Co, Ltd.

**Competing interests** TaN received lecture fees from Chugai Pharmaceutical Co Ltd, Takeda Pharmaceutical Company Limited, Merck Serono Co Ltd. and Taiho Pharmaceutical Co Ltd. HM received lecture fees from Chugai Pharmaceutical Co Ltd. and Takeda Pharmaceutical Company Limited. AS received lecture fees from Pfizer Japan Inc and Novartis Pharma K.K. MS received lecture fees from Chugai Pharmaceutical Co Ltd. and Taiho Pharmaceutical Co Ltd. KS received lecture fees from Chugai Pharmaceutical Co Ltd, Merck Serono Co Ltd, Taiho Pharmaceutical Co Ltd, Shionogi & Co Ltd and Yakult Co Ltd. HT received lecture fees from Chugai Pharmaceutical Co Ltd. and Merck Serono Co Ltd. JN received lecture fees from Chugai Pharmaceutical Co Ltd, Merck Serono Co Ltd. Taiho Pharmaceutical Co Ltd, Takeda Pharmaceutical Company Limited. and Eli Lilly Japan K.K. ToN received lecture fees from Chugai Pharmaceutical Co Ltd, Merck Serono Co Ltd. Taiho Pharmaceutical Co Ltd, Takeda Pharmaceutical Company Limited. and Eli Lilly Japan K.K. MI, SH, MO and YY received lecture fees from Chugai Pharmaceutical Co Ltd.

**Patient consent** Obtained.

**Ethics approval** The Ethical Committee of the Non-Profit Organization MINS Institutional Review Board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Patient level data and full dataset are available from NPO Japan Southwest Oncology Research Support Organization Mitsuhiro Ayukawa 14-19-602 noboricho naka-ku Hiroshima city, Hiroshima 730-0016, Japan Phone/ FAX: +8-82-222-1350 E-mail: office@jswog.org. Participants gave informed consent for data sharing.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

#### REFERENCES

1. Soerjomataram I, Lortet-Tieulent J, Parkin DM, *et al*. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012;380:1840–50.
2. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
3. Van Cutsem E, Cervantes A, Nordlinger B, *et al*. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3):iii1–9.
4. Adam R, Haller DG, Poston G, *et al*. Toward optimized front-line therapeutic strategies in patients with metastatic colorectal cancer—an expert review from the International Congress on Anti-Cancer Treatment (ICACT) 2009. *Ann Oncol* 2010;21:1579–84.
5. Petrelli NJ, Abbuzzese J, Mansfield P, *et al*. Hepatic resection: the last surgical frontier for colorectal cancer. *J Clin Oncol* 2005;23:4475–7.
6. Grothey A, Hedrick EE, Mass RD, *et al*. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. *J Clin Oncol* 2008;26:183–9.
7. Seymour MT, Maughan TS, Ledermann JA, *et al*. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;370:143–52.

8. Seymour MT, Thompson LC, Wasan HS, *et al.* Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet* 2011;377:1749–59.
9. Koopman M, Antonini NF, Douma J, *et al.* Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007;370:135–42.
10. Ducreux M, Malka D, Mendiboure J, *et al.* Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011;12:1032–44.
11. Tebbutt NC, Wilson K, GebSKI VJ, *et al.* Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol* 2010;28:3191–8.
12. Cunningham D, Lang I, Marcuello E, *et al.* Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1077–85.
13. Feliu J, Salud A, Safont MJ, *et al.* First-line bevacizumab and capecitabine-oxaliplatin in elderly patients with mCRC: GEMCAD phase II BECOX study. *Br J Cancer* 2014;111:241–8.
14. Chibaudel B, Bonnetain F, Shi Q, *et al.* Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy—an Aide et Recherche en Cancerologie Digestive Group Study. *J Clin Oncol* 2011;29:4199–204.
15. Yamada Y, Takahari D, Matsumoto H, *et al.* Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial. *Lancet Oncol* 2013;14:1278–86.
16. Matsuda Y, Singh G, Yamanaka H, *et al.* Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. *Arthritis Rheum* 2003;49:784–8.
17. Kohne CH, Cunningham D, Di Costanzo F, *et al.* Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002;13:308–17.
18. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103–15.
19. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1–39.
20. Bennouna J, Sastre J, Arnold D, *et al.* Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29–37.
21. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982;38:163–70.
22. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer* 2003;3:330–8.
23. Keshava C, Keshava N, Whong WZ, *et al.* Inhibition of methotrexate-induced chromosomal damage by folinic acid in V79 cells. *Mutat Res* 1998;397:221–8.
24. Doctor VM, Couch JR. Occurrence and properties of a conjugated form of Leuconostoc citrovorum factor. *J Biol Chem* 1953;200:223–31.
25. Miwa M, Ura M, Nishida M, *et al.* Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998;34:1274–81.
26. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet* 2001;40:85–104.
27. Graham J, Mushin M, Kirkpatrick P. Oxaliplatin. *Nat Rev Drug Discov* 2004;3:11–12.
28. Raymond E, Chaney SG, Taamma A, *et al.* Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998;9:1053–71.
29. Ferrara N, Hillan KJ, Gerber HP, *et al.* Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov* 2004;3:391–400.
30. Shibuya M. Angiogenesis regulated by VEGF and its receptors and its clinical application. *Rinsho Ketsueki* 2009;50:404–12.
31. Giessen C, von Weikersthal LF, Hinke A, *et al.* A randomized, phase III trial of capecitabine plus bevacizumab (Cape-Bev) versus capecitabine plus irinotecan plus bevacizumab (CAPIRI-Bev) in first-line treatment of metastatic colorectal cancer: the AIO KRK 0110 trial/ML22011 trial. *BMC Cancer* 2011;11:367.