Recurrence monitoring using ctDNA in patients with metastasis of colorectal cancer: COSMOS- oligo study

Eiji Oki (oku.eiji.857@m.kyushu-u.ac.jp)  
Kyushu University

Ryota Nakanishi  
Kyushu University

Koji Ando  
Kyushu University

Sho Nambara  
Kyushu University

Ichiro Takemasa  
Sapporo Medical University

Jun Watanabe  
Yokohama City University Medical Center

Nobuhisa Matsuhashi  
Gifu University Hospital

Takeshi Kato  
National Hospital Organization Osaka National Hospital

Yoshinori Kagawa  
Osaka General Medical Center

Masahito Kotaka  
Sano Hospital

Keiji Hirata  
University of Occupational and Environmental Health

Masahiko Sugiyama  
National Hospital Organization Kyushu Cancer Center

Tetsuya Kusumoto  
National Hospital Organization Kyushu Medical Center

Yuji Miyamoto  
Kumamoto University

Kayo Toyosaki  
Kyushu University Hospital

Junji Kishimoto
Study protocol

**Keywords:** adjuvant chemotherapy, colorectal cancer, ctDNA, FOLOFOXI plus bevacizumab, liver metastasis, oligo metastasis

**Posted Date:** May 3rd, 2023

**DOI:** [https://doi.org/10.21203/rs.3.rs-2844259/v1](https://doi.org/10.21203/rs.3.rs-2844259/v1)

**License:** ☕️ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](https://creativecommons.org/licenses/by/4.0/)
Abstract

The best treatment strategy for resectable metastatic colorectal cancer is surgical resection of the metastatic site. However, approximately 60% of patients show recurrence after the resection of metastatic lesions, and some patients require aggressive perioperative chemotherapy. We initiated new trials to evaluate the clinical benefits of circulating tumor DNA analysis and refine precision adjuvant therapy for resectable metastatic colorectal cancer, named COSMOS-oligo trials, including two studies. The COSMOS-CRC03 study is a prospective observational study to monitor circulating tumor DNA in patients with metastatic colorectal cancer who can undergo complete surgical resection. The AURORA trial is a randomized Phase II study designed to test whether postoperative mFOLFOXIRI plus bevacizumab is superior to the standard therapy with FOLFOX6 for 6 months in patients with metastatic colorectal cancer if the circulating tumor DNA status is positive at week 4 after curative surgery in the COSMOS-CRC03 study.

In these studies, only patients with resectable distant metastases of colorectal cancer will be included. The study will examine the negative predictive value of circulating tumor DNA for recurrence, whether stratification using 28-day postoperative circulating tumor DNA results can select a population with a good prognosis, and whether circulating tumor DNA testing every 12 weeks will detect recurrence earlier than diagnostic imaging. Further, the Phase II trial will determine whether intensive treatment of circulating tumor DNA-positive cases can reduce recurrence. Stage IV colorectal cancer has no standard perioperative treatment. We designed this study to stratify patients using circulating tumor DNA and determine the optimal treatment. COSMOS-CRC03(jRCT2072220055); AURORA trial(jRCT1071220087)

Introduction

Many clinical trials of adjuvant chemotherapy for colorectal cancer have been conducted worldwide, and surgery and appropriate adjuvant chemotherapy can successfully manage Stage I-III colorectal cancer. Resection is currently considered the best approach for Stage IV disease with distant metastases. However, even with complete resection of distant metastases, > 60% of patients experience recurrence. Furthermore, treatment strategies for perioperative chemotherapy after resection of metastases are not as well established as those for Stage II-III cases.

Multi-gene assays and cDNA microarray analysis have been used worldwide to stratify the prognosis of postoperative patients and to optimize chemotherapy. 12-Gene recurrence score assay is a test that evaluates the risk of recurrence of colon cancer using seven genes and five reference genes and is used in medical practice in the United States and some European countries [1–3]. Attempts to evaluate this assay in Asia have also demonstrated that the 12-Gene recurrence score assay is a prognostic factor independent of pathologic stage classification and can change the actual chemotherapy prescription status after surgery [4, 5]. Other assays that classify colon cancer into several subtypes based on RNA expression have shown that the mesenchymal subtype responds less effectively to adjuvant therapy, including oxaliplatin, whereas the microsatellite instability subtype responds more effectively [6].
addition to multi-gene analysis, various diagnostic and therapeutic tools for predicting the response to therapy and prognosis have been developed. Recently, the use of circulating tumor DNA (ctDNA), which is released from cancer cells into the bloodstream, has been reported to be particularly useful as a prognostic factor [1, 7, 8]. Using these genetic tests, the prognosis of patients with colorectal cancer can be improved by implementing therapeutic strategies based on the risk of recurrence. However, most of these tests are designed for Stage I-III cases and do not target metastatic colorectal cancer.

This study aims to determine the utility of ctDNA as a potential tool for risk stratification of colorectal cancer with resectable distant metastases and the early detection of recurrence. A randomized Phase II trial will be conducted simultaneously as an exploratory study to further explore the selection of the optimal adjuvant chemotherapy.

**Material and Methods**

**PROTOCOL DESIGN**

The COSMOS-oligo trial consists of two trials: COSMOS-CRC03 and AURORA. AURORA is a trial of ctDNA-positive cases of COSMOS-CRC03 (Fig. 1).

**COSMOS-CRC03**

In this clinical trial, we will investigate the clinical significance of ctDNA under the following hypothesis: ctDNA at postoperative 28 days can be used to select a population with a good prognosis after resection of distant metastases of colorectal cancer, and ctDNA testing every 12 weeks can detect recurrence earlier than imaging tests. Detailed Inclusion and Exclusion criteria are listed in Table 1. This trial is exploratory in design and will be conducted on a single-arm, open-label basis. The results of this trial will provide the basis for a validation trial to establish the clinical significance of stratifying the patient population with respect to the risk of recurrence using ctDNA. Postoperative 28-day ctDNA-negative patients will not receive adjuvant therapy until ctDNA positivity is confirmed and will be followed by ctDNA testing and imaging evaluation every 12 weeks for two years.
### Table 1
COSMOS-CRC03 criteria

**Inclusion criteria**

1. The patient was diagnosed with colorectal cancer based on histological diagnosis of the primary lesion.

2. The following metastatic lesions have been clinically diagnosed as colorectal cancer (regardless of whether they are synchronous or metachronous):
   1) lung metastasis (< 5 in preoperative diagnosis)
   2) liver metastasis (any number)
   3) peritoneal metastasis (< 5 in preoperative diagnosis)
   4) extra-regional lymph node metastasis (< 3 in preoperative diagnosis)
   5) ovarian metastasis
   6) other metastases such as adrenal or splenic metastases (confirm with coordinating physician prior to enrollment)

Metastases involving multiple organs are also eligible.

3. The distant metastases are diagnosed by one of following tests:
   1) Chest computed tomography (CT) (5 mm slices) (both plain and contrast-enhanced CT are acceptable)
   2) Upper abdominal contrast-enhanced CT (5 mm slices) * or upper abdominal magnetic resonance imaging (MRI) (5 mm slices)
   3) Pelvic contrast-enhanced CT (5 mm slices) * or pelvic MRI (5 mm slices)

*If the patient is allergic to contrast agent, plain CT is acceptable.

4. Surgical resection is planned for the primary and metastatic lesions. One-stage surgery should be performed for distant metastases. However, two-stage surgery within 28 days is acceptable in cases of metastasis in the right or left lung. Either of the following cases are eligible:
   1) R0 resection is planned for the primary lesion and distant metastases. (Resection of the primary and metastatic lesions as a two-step surgery within 28 days is permitted. Resection of the primary tumor is performed first in the cases.)
   2) R0 resection has been performed for the primary lesion, and the first R0 resection for a distant lesion is scheduled.
   3) R0 resection has been performed for the primary and metastatic lesion, and the R0 resection for a distant lesion is scheduled.

5. Patients will be eligible only if the history of chemotherapy or radiotherapy meets either of the conditions 1) or 2) below.
   1) At the time of enrollment, 28 days have passed since the final infusion of chemotherapy.
   2) Preoperative radiotherapy was administered for the primary or previous metastatic lesion.
### Inclusion criteria

6. If metastases to the liver or lungs are present, the patient has no history of cryotherapy or thermocoagulation therapy such as radiofrequency cauterization (including concomitant administration at the time of resection of metastases to the liver).

7. Being aged $\geq 18$ years at the time of obtaining written consent.

8. Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1. For patients aged $\geq 75$ years, only a PS 0 is acceptable.

9. The patient is able to have blood collected according to the protocol for this study after enrollment.

10. The patient has fulfilled all of the following test findings: (The latest test results within the period of 14 days before enrollment should be used. The day 1 week before the enrollment is acceptable)

1) Neutrophil count $\geq 1,500 / \text{mm}^3$

2) Platelet count $\geq 10 \times 10^4 / \text{mm}^3$

3) GOT $\leq 100$ IU/L

4) GPT $\leq 100$ IU/L

5) T. Bil $\leq 1.5$ mg/dL

6) Cr $\leq 1.4$ mg/dL

11. Written consent to participate in the study has been provided by the patient himself/herself.

### Exclusion criteria

1. The patient has active multiple cancers (synchronous multiple cancers and metachronous multiple cancers with a disease-free period of $\leq 5$ years.) However, patients with intraepithelial or intramucosal cancer in any organ that is determined to have been cured with localized therapy can be enrolled.

2. In the case of female patients, the patient is possibly pregnant or is breastfeeding.

3. The patient has concurrent interstitial pneumonia, pulmonary fibrosis, or severe emphysema.

4. The patient has concurrent psychiatric disease or psychiatric symptoms determined to make it difficult for the patient to participate in the clinical trial.

5. The patient is receiving continuous systemic steroid therapy (oral or intravenous).

6. The patient has concurrent diabetes mellitus that is being treated with continuous insulin administration or is poorly controlled.

7. The patient has concurrent poorly controlled hypertension.

8. The patient has a history of one or more of the following: serious heart disease, cardiac failure, myocardial infarction within the past 6 months, or angina attacks within the past 6 months.

9. Patients whom the PI or investigators decided as inappropriate for the clinical trial.
The primary endpoint will be the 2-year recurrence-free survival (RFS) rate based on Kaplan–Meier curves in ctDNA-negative patients at 28 days postoperatively, defined as the negative predictive value (NPV). Based on previous reports [9], the 2-year RFS rate of surgery alone for colorectal cancer patients with resectable distant metastases is 45%-60%. Assuming an expected value of 70% and a threshold value of 50%, with an alpha of 5% bilaterally and 1-beta = 80%, the number of cases required is 47. Assuming a dropout rate of 20%, the target number of ctDNA-negative patients is 60. If the ctDNA-negative rate 28 days postoperatively is assumed to be 40%, the actual planned number of patients for this trial is 150. However, based on past experience, it is anticipated that the ctDNA assay to be used will become unmeasurable at 5.5%. Therefore, approximately 5.5% of the cases will be added to the final number of patients, resulting in an enrollment of 160 patients. In this study, the positive predictive value of ctDNA for recurrence during the postoperative observation period is set as another primary endpoint. If we assume that the expected value is 70%, the threshold is 50%, α is 5% (two-sided), and 1-β = 80%, the required number of patients would be 47, assuming that LUNAR-1 will be used for the accurate and early detection of recurrence. In contrast, in the case of NPV, in which the primary endpoint is the predictive accuracy of RFS in ctDNA-negative patients at 28 days after surgery, the planned number of enrolled patients is set at 150 (postoperative ctDNA-negative patients: 60 and postoperative ctDNA-positive patients: 90). If we assume that the percentage of positive ctDNA results after adjuvant therapy is 50% in the 90 ctDNA-positive patients at 28 days after surgery, the number of eligible patients is 45. For the 60 ctDNA-negative patients at 28 days after surgery, if we assume that the positive conversion rate within 2 years is 30% and the percentage of positive results after postoperative adjuvant chemotherapy is 50%, there will be 9 ctDNA-positive patients after postoperative adjuvant therapy. Thus, the number of ctDNA-positive patients during the postoperative observation period is expected to be 54; therefore, even if there are dropouts, 47 patients can be included.

Secondary endpoints will be the 2-year RFS rate in ctDNA-positive patients at 28 days postoperatively, the time from ctDNA detection to imaging recurrence (lead time for recurrence) during the postoperative observation period, the sensitivity of ctDNA for recurrence during the postoperative observation period, the percentage of patients positive for ctDNA at each ctDNA collection point, and overall survival (OS). The planned enrollment period for this study is through March 2025 and the follow-up period is through March 2027. This study was registered with the Japan Registry of Clinical Trials (jRCT2072220055).

**AURORA trial**

This is a randomized controlled trial to evaluate the superiority of mFOLFOXIRI plus bevacizumab over mFOLFOX6 therapy in ctDNA-positive patients in the COSMOS-CRC03 trial, that is, ctDNA-positive patients after curative resection of distant colorectal cancer metastases (Fig. 1). Participating institutions will be expanded to 11 hospitals. Detailed Inclusion and Exclusion criteria are listed in Table 2. After confirming eligibility, a dynamic allocation using the minimization method will be performed through the registration allocation system. The allocation factors will be the metastatic site (liver only metastasis or other than liver metastasis), primary site (present or absent), primary site location (right or left), and history of drug therapy for the primary site (with or without). After randomization, the patients receive
mFOLFOX6 or FOLFOXIRI + BEV. The dose schedule of mFOLFOX6 is as follows: 2-h infusion of oxaliplatin 85 mg/m², l-LV 200 mg/m² on day 1, and 48-h continuous infusion of 5-FU 2400 /m² every 2 weeks. Up to 12 courses of this treatment will be performed. The dose schedule of FOLFOXIRI + BEV is as follows: 30–90-min infusion of BEV 5 mg/kg, 1-h infusion of IRI 150g/m², 2-h infusion of oxaliplatin 85 mg/m², l-LV 200 mg/m² on day 1, and 48-h continuous infusion of 5-FU 2400 /m² every 2 weeks. This treatment should be given as mFOLFOXIRI + BV for up to 8 courses and 5-FU / l-LV + BV maintenance therapy for a total of up to 12 courses.

Table 2 AURORA criteria
Inclusion criteria

1. The patient is diagnosed with colorectal cancer based on histological diagnosis of the primary lesion.

2. The patient has participated in COSMOS-CRC03 study and has undergone surgical resection of the metastatic lesion.

3. The surgical resection is pathologically diagnosed as R0.

4. ctDNA is positive at 28 days postoperatively or positive during 1-year follow-up period without recurrence during computed tomography/magnetic resonance imaging.

5. Inclusion within 6 weeks after positive ctDNA

6. Patients will be eligible only if the history of chemotherapy or radiotherapy meets either of the conditions 1) or 2) below.

1) At the time of enrollment, 28 days have passed since the final infusion of chemotherapy.

2) Preoperative radiotherapy was administered for the primary or previous metastatic lesion.

7. If metastases to the liver or lungs are present, the patient has no history of cryotherapy or thermocoagulation therapy such as radiofrequency cauterization (including concomitant administration at the time of resection of metastases to the liver).

8. Being aged ≥ 18 years at the time of obtaining written consent.

9. Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1. For patients aged ≥ 75 years, only a PS 0 is acceptable.

10. The patient has fulfilled all of the following test findings: (The latest test results within the period of 14 days before enrollment should be used. The day 1 week before the enrollment is acceptable)

1) Neutrophil count ≥ 1,500 / mm³

2) Platelet count ≥ 10 x 10⁴ / mm³

3) GOT ≤ 100 IU/L

4) GPT ≤ 100 IU/L

5) T. Bil ≤ 1.5 mg/dL

6) Cr ≤ 1.4 mg/dL

7) Urine protein ≤ 2+

8) Wild type or single heterozygous (i.e., *1/*6 or *1/*28) UGT 1A1 genotype

11. Written consent to participate in the study has been provided by the patient himself/herself.
Exclusion criteria

1. The patient has active multiple cancers (synchronous multiple cancers and metachronous multiple cancers with a disease-free period of $\leq 5$ years.) However, patients with intraepithelial or intramucosal cancer in any organ that is determined to have been cured with localized therapy can be enrolled.

2. In the case of female patients, the patient is possibly pregnant or is breastfeeding.

3. The patient has concurrent interstitial pneumonia, pulmonary fibrosis, or severe emphysema.

4. The patient has concurrent psychiatric disease or psychiatric symptoms determined to make it difficult for the patient to participate in the clinical trial.

5. The patient is receiving continuous systemic steroid therapy (oral or intravenous).

6. The patient has undergone uncontrolled anticoagulant therapy.

7. The patient with non-healing wound (except for central venous port)

8. Surgery, biopsy with skin incision and suture procedure for traumatic injury within 28 days prior to enrollment (except for central venous port)

9. Requiring the continuous treatment of flucytosine, phenytoin, or warfarin potassium.

10. The patient has concurrent diabetes mellitus that is being treated with continuous insulin administration or is poorly controlled.

11. Grade 2 or higher diarrhea or sensory neuropathy.

12. The patient has concurrent poorly controlled hypertension.

13. The patient has a history of one or more of the following: serious heart disease, cardiac failure, myocardial infarction within the past 6 months, or angina attacks within the past 6 months.

14. Patients whom the PI or investigators decided as inappropriate for the clinical trial.

The primary endpoint is the proportion of ctDNA-negative patients in the eligible population at any time point 12 months after the start of adjuvant chemotherapy. In short, this is the percentage of ctDNA-negative conversion. The patients will be followed by ctDNA testing and imaging evaluation 28 days after surgery and every 12 weeks for 12 month.

It is expected that 50% of cDNA-positive patients will become ctDNA-negative after postoperative adjuvant chemotherapy including oxaliplatin (unpublished data). Considering that mFOLFOXIRI plus bevacizumab has a 30% higher response rate in first-line therapy than mFOLFOX, we predict a 30% higher ctDNA-negative conversion rate. Based on this prediction, a chi-square test with a one-sided significance level of 5% and a power of 80% yields a target number of 62 patients in both arms. Seventy-four patients (37 per arm) are assigned as the target number, considering the patients who would be ineligible after enrollment because of the timing of ctDNA results and the start of adjuvant therapy. The secondary endpoints will be RFS, OS, and the time to ctDNA-negative changes. The planned enrollment period for
this study is through March 2026 and the follow-up period is through September 2027. This study was registered with the Japan Registry of Clinical Trials (jRCT1071220087).

**Discussion**

Evidence of the benefits of adjuvant chemotherapy after resection of metastases of colorectal cancer has been reported. In a combined analysis of the FFCD09002 (n = 173) and ENG (n = 129) trials comparing postoperative adjuvant chemotherapy with 5-fluorouracil plus l-leucovorin versus surgery alone, Mitry et al. found that postoperative chemotherapy improved RFS and OS, and multivariate analysis identified the use of postoperative chemotherapy as a favorable prognostic factor (RFS, hazard ratio [HR]: 1.39, 95% confidence interval [CI]: 1.04–1.85; OS, HR: 1.39, 95% CI: 1.00–1.93) [10]. In a randomized controlled trial by Hasegawa et al. comparing postoperative adjuvant chemotherapy with uracil-tegafur plus leucovorin (UFT + LV) versus surgery alone for curative resection of colorectal liver metastases (CRLM), the 3-year RFS was significantly better in the UFT + LV group (p = 0.003) than in the surgery group; however, the OS did not differ between the two groups (p = 0.41) [11]. Trials have also been conducted to evaluate the efficacy of perioperative chemotherapy for CRLM. The European Organization for Research and Treatment of Cancer 40983 conducted a randomized controlled study comparing surgical resection alone versus preoperative and postoperative chemotherapy with FOLFOX4 plus surgical resection in 330 patients with curatively resectable CRLM. A secondary analysis of eligible patients showed a statistically significant difference in the 3-year RFS (29.9% [23.2–36.9] vs. 39.0% [31.7–46.3], p = 0.035), but no significant difference in RFS for the primary endpoint of all enrolled patients was observed; moreover, no significant difference was found for OS [12]. In addition, the New EPOC trial, which evaluated cetuximab in addition to perioperative cytotoxic drugs in patients with wild-type KRAS resectable CRLM, found no additional benefit of cetuximab on survival (RFS, HR: 1.48, 95% CI: 1.04–2.12; OS, HR: 1.49, 95% CI: 0.86–2.60) [13]. Recently, a randomized Phase II/III trial (JCOG0603) of mFOLFOX6 versus surgery alone in patients with CRLM was reported from Japan. The 5-year RFS was 38.7% (95% CI: 30.4–46.8) in the surgery alone group and 49.8% (95% CI: 41.0–58.0) in the mFOLFOX6 group, a statistically significant improvement (HR: 0.67, 95% CI: 0.50–0.92 p = 0.006). However, the 5-year OS was 83.1% (95% CI: 74.9–88.9) in the surgery alone group and 71.2% (95% CI: 61.7–78.8) in the mFOLFOX6 group, indicating no improvement [9]. Thus, adjuvant therapy for patients after resection of distant metastases has not been proven to improve the OS.

Based on these results, it is important to establish evidence of treatment that contributes to improved survival, even though systemic chemotherapy is often used in daily practice after the resection of metastases such as liver and lung metastases. The results of trials to date indicate that a uniform approach to chemotherapy for all postoperative patients is unlikely to improve survival, even if drug intensity is increased. In addition to increasing drug intensity, we believe that patient stratification is important.

Recently, many reports have shown that patients with minimal residual disease (MRD) detected using ctDNA have a high recurrence rate and poor prognosis after surgical resection or adjuvant chemotherapy,
and the clinical usefulness of ctDNA in predicting prognosis has been recognized [1, 7, 8, 14].

In a study of 130 patients with Stage I-III colorectal cancer, Reinert et al. reported that the risk of recurrence was seven times higher in patients with positive ctDNA 30 days after surgical resection than in those with negative ctDNA (HR: 7.2, 95% CI: 2.7–19.0, p < 0.001) [1]. In a prospective clinical trial of 155 patients with localized colorectal cancer, patients with ctDNA detected in several postoperative ctDNA follow-up analyses had poorer disease-free survival than patients without ctDNA detection in any period [14]. A randomized Phase II study was conducted to prove the usefulness of ctDNA, and it showed that ctDNA can eliminate unnecessary postoperative adjuvant therapy.

In accordance with these findings, several prospective clinical trials are currently being conducted to evaluate adjuvant chemotherapy and treatment regimens using ctDNA as a biomarker [15–17]. In our project, CIRCULATE-JAPAN, we showed that ctDNA-indexed treatment strategies can contribute to improving the prognosis of patients with Stage II-III colon cancer.

As described above, the relationship between MRD detection using ctDNA and the risk of postoperative recurrence and prognosis in patients with various stages of colorectal cancer who have undergone curative surgical resection has been reported. However, no trials have demonstrated the usefulness of ctDNA, specifically in colorectal cancer with resectable distant metastases. Moreover, no trials have stratified positive patients for more aggressive drug therapy. This trial includes a unique randomized Phase II trial in which patients after resection of ctDNA-positive metastases are considered residual tumor cases and are treated with more aggressive drug therapy. Based on the results of this trial, a Phase III trial is expected to be planned in the future.

**Abbreviations**

RFS, recurrence-free survival; OS, overall survival; CRLM, colorectal liver metastases; MRD, minimal residual disease; CI, confidence interval; HR, hazard ratio, ctDNA, circulating tumor DNA; NPV, negative predictive value; UFT + LV, uracil-tegafur plus leucovorin

**Declarations**

**Ethics approval and consent to participate**

The COSMOS-CRC03 and AURORA trials were conducted in accordance with the Declaration of Helsinki, the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the Clinical Trial Acts in Japan. Each trial was approved by the Kyushu University Hospital Certified Review Board. Written informed consent was obtained from all patients before their enrollment.

**Consent for publication**

Not applicable.
Availability of data and materials

EO has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The datasets generated during the current study will be available from the corresponding author upon a reasonable request. The data will not be reposed in the Gene Expression Omnibus (GEO) database due to concerns related to the Japanese Act of the Protection of Personal Information.

Competing interests

EO reports research funding from Guardant Health, Inc. and reports honoraria from Ono Pharm., Takeda Pharm., Bayer, Chugai Pharm, Taiho Pharm., Eli Lilly Japan, and Bristol-Myers Squibb.

Funding

COSMOS CRC03 trial is funded by Guardant Health Co. Ltd.

Author Contributions

Authors making substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data: EO, RN, UT, JW, YK, TK, JK, YN; authors participating in drafting the article or revising it critically for important intellectual content: EO, RN, KA, SN, IT, JW, NM, TK, YK, MK, KH, MS, TK, YM, KT, JK, YK, TY, YN; authors giving final approval of the version to be published: EO, RN, KA, SN, IT, JW, NM, TK, YK, MK, KH, MS, TK, YM, KT, JK, YK, TY, YN.

Acknowledgments: The authors thank Ms. Junko Eguchi for her assistance with the experiment and manuscript preparation. We would like to thank Editage (www.editage.com) for English language editing.

References


15. BESPOKE study of ctDNA guided therapy in colorectal cancer. ([https://clinicaltrials.gov/ct2/show/NCT04264702](https://clinicaltrials.gov/ct2/show/NCT04264702)).


**Figures**

**Figure 1**

COSMOS-oligometastasis overview.

ctDNA, circulating tumor DNA; F/U, follow up; POD, postoperative days; BV, bevacizumab