JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2024-025
http://journal-arc.jp

Trial Protocol

Trial Protocol of a Phase II Study of mFOLFOXIRI after Metastasectomy in Patients with Oligometastatic Colorectal Cancer (FANTASTIC Study)

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Abstract

Background: The survival benefit of adjuvant chemotherapy after surgical resection of oligometastases from colorectal cancer (CRC) remains unclear. The prognostic role of circulating-tumor DNA (ctDNA) was reported recently and a risk stratification strategy based on monitoring minimal/molecular residual disease (MRD) has been proposed, however, which drug regimen is most effective for ctDNA-positive patients is unknown.

Methods/Design: Oligometastatic CRC patients planning to undergo surgery were registered in this study. After metastasectomy, the registered patients were enrolled in the treatment arm, in which 8 courses of modified-FOLFOXIRI (mFOLFOXIRI; irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, l-leucovorin (l-LV) 200 mg/m^2, and 46-h continuous infusion of 5-fluorouracil (5-FU) 2400 mg/m^2 every 2 weeks) followed by 4 courses of 5-FU/l-LV are administered. The patients who did not meet the eligibility criteria for the treatment arm or did not consent to mFOLFOXIRI enrolled in the observation arm in which standard of care treatment is provided. Prospective blood collections for retrospective ctDNA analysis are scheduled pre-surgery, and at 28 days, 4 and 7 months after surgery. The primary endpoint is treatment compliance at 8 courses of mFOLFOXIRI and the key secondary endpoints are the ctDNA-positivity rate and survival outcomes in ctDNA-positive and -negative groups. A total of 85 patients will be enrolled from 11 institutions. First patient-in was on July 2020. Accrual completed in February 2024.

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Received: March 21, 2024, Accepted: April 23, 2024

Discussion: This study will potentially identify a better treatment strategy for patients with resectable oligometastatic CRC having postsurgical ctDNA positivity, compared to the current standard of care approaches.

Keywords
colorectal cancer, oligometastases mFOLFOXIRI, circulating tumor DNA

J Anus Rectum Colon 2024; 8(3): 246-252

Background

Metastsectomy is one of the promising treatment options for oligometastatic colorectal cancer (CRC) patients[1,2]. The benefit of adjuvant therapy for CRC patients who underwent curative-intent resection of oligometastases, such as liver metastases, remains controversial. Several studies have evaluated the efficacy of adjuvant chemotherapy for patients with colorectal liver metastases (CLM)[3-6]. The preliminary results of the phase III JCOG0603 trial, which aimed to confirm the superiority of mFOLFOX6 after hepatectomy to observation in resected CLM, demonstrated that postoperative mFOLFOX6 conferred a disease-free survival (DFS) benefit but did not affect the overall survival (OS)[7]. For lung metastases from CRC no randomized controlled trial (RCT) has been performed. Imanishi et al. retrospectively analyzed 1273 patients who underwent surgical resection of lung metastases from CRC using propensity score matching, but no survival benefit of adjuvant chemotherapy, which mostly consisted of 5-FU monotherapy, was noted[8]. Currently, there is no established standard treatment for resected oligometastatic CRC; and the prognosis remains poor for the majority of patients. Therefore, new treatment strategies using more effective chemotherapy regimens and biomarkers to determine subgroups that may benefit from chemotherapy are needed.

The TRIBE study reported FOLFOXIRI (irinotecan (IRI): 165 mg/m^2, oxaliplatin (OX) 85 mg/m^2, levofolinate calcium (l-LV 200) mg/m^2, and 46-h continuous infusion of 5-fluorouracil (5-FU) 3200 mg/m^2 every 2 weeks) to be one of the most promising regimens with high efficacy among patients with metastatic CRC[9]. However, there are concerns about the high incidence of adverse events, such as hematological toxicity. The modified-FOLFOXIRI (mFOLFOXIRI) regimen, which consists of IRI 150 mg/m^2, OX 85 mg/m^2, l-LV 200 mg/m^2, and 46-h continuous infusion of 5-FU 2400 mg/m^2 every 2 weeks, demonstrated manageable toxicity and sustained efficacy in a Japanese population[10]. The efficacy of mFOLFOXIRI has not been evaluated as adjuvant chemotherapy in oligometastatic CRC patients who underwent metastasectomy.

Circulating tumor DNA (ctDNA) for detection of minimal/molecular residual disease (MRD) has emerged as a novel, sensitive and specific method to predictpatients' risk of recurrence. The prognostic role of ctDNA has been reported in CRC and several other types of solid tumors[11-17]. In the GALAXY trial, the largest ctDNA platform study in CRC, the 18-month DFS in ctDNA-positive patients with resected oligometastatic CRC was reported to be 49.0%, while in those with ctDNA negativity was 92.4%[18]. Several other studies have also reported a marked difference in survival of ctDNA-positive vs -negative patients in this setting[13,19-22]. Furthermore, the GALAXY study reported that high-risk stage II and stage III CRC patients with postsurgical ctDNA positivity derived benefit from adjuvant chemotherapy, whereas ctDNA-negative patients did not. Although ctDNA-driven strategy seems promising in identifying the patient subpopulation who may benefit from adjuvant chemotherapy, little is known about which chemotherapy regimen would be the most effective in patients with surgically resected CRC with ctDNA positivity and negativity, respectively.

Therefore, we designed a phase II study to evaluate the utility of ctDNA as a prognostic and predictive biomarker and the feasibility of mFOLFOXIRI among patients with CRC undergoing curative resection of oligometastases, including liver, lung, ovary and peritoneum metastases.

Method/Design

Objectives

The aim of this trial is to investigate the feasibility of mFOLFOXIRI and the utility of ctDNA as a predictive biomarker in patients with CRC after resection of oligometastases.

Study setting

A multi-institutional, non-randomized phase II trial.

Endpoints

The primary endpoint is treatment compliance at 8 courses of mFOLFOXIRI. Treatment compliance at 8 courses is defined as the proportion of patients to whom

both OX and IRI are administered for at least 8 courses according to the protocol. The key secondary endpoints are the ctDNA-positivity rate, and DFS and OS in ctDNA-positive and -negative patients. The other secondary endpoints are overall DFS, OS, and ctDNA clearance rate. OS is defined as days from the date of surgery to death from any cause, and it will be censored at the last day when the patient is alive. DFS is defined as days from the date of surgery to recurrence or death from any cause, and it will be censored at the last day when the patient is alive without any evidence of recurrence.

Key eligibility criteria for first registration

1) Histologically confirmed primary adenocarcinoma of the colorectum
2) Potential R0 resection is planned for either of the following;
   1. Liver and/or ovary and/or peritoneal metastases with or without primary tumor
   2. Lung metastases with or without primary tumor
3) No past history of chemotherapy. Chemotherapy for the primary tumor is allowed only when more than 1 year after the last use of oxaliplatin or more than 6 months after the last use of 5-FU has passed
4) Age 20 to 75 years old
5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (PS 0 for patients aged 71 or older)
6) Sufficient organ function
7) Written informed consent from the patient (including for collecting blood samples)

Key eligibility criteria for the treatment arm

1) R0 resection has been performed for either of the following;
   1. Liver and/or ovary and/or peritoneal metastases with or without primary tumor
   2. Lung metastases with or without primary tumor
2) Oligometastases were histologically confirmed as adenocarcinoma of the colorectum
3) Time since surgery is between 28 and 70 days
4) No extrahepatic metastasis or recurrence on chest-abdominal pelvic CT or MRI within 4 weeks before enrollment
5) UGT1A1 polymorphism is wild-type or single heterozygous type
6) Sufficient organ function
7) Written informed consent from the patient

Exclusion criteria

1) Synchronous or metachronous (within 5 years) malignancies except for carcinoma in situ or mucosal tumors curatively treated by local therapy
2) Active infection requiring systemic therapy
3) Pregnancy, possible pregnancy or breastfeeding
4) Psychiatric disease
5) Patients requiring systemic steroid medication
6) Current treatment with flucytosine, phenytoin or warfarin
7) Poorly controlled diabetes mellitus or routine administration of insulin
8) Severe pulmonary fibrosis or emphysema
9) Poorly controlled hypertension
10) Unstable angina within 6 months, or with a history of myocardial infarction within 6 months

Treatment methods

The design of FANTASTIC study is shown in Figure 1. Patients with oligometastatic CRC who plan to undergo metastasectomy can be registered in this study. When the patients meet the eligibility criteria for the treatment arm after curative surgery, they can be enrolled, and 8 courses of mFOLFOXIRI (IRI 150 mg/m^2, OX 85 mg/m^2, l-LV 200 mg/m^2, and 46-h continuous infusion of 5-FU 2400 mg/m^2 every 2 weeks) followed by 4 courses of 5-FU/LV (l-LV 200 mg/m^2, and 46-h continuous infusion of 5-FU 2400 mg/m^2 every 2 weeks; the same dose as JACCRO CC11 phase II study [23]) will be administered. When the patients do not meet the eligibility criteria for the treatment arm or do not consent to mFOLFOXIRI, they will be enrolled in the observation arm, in which standard care will be provided at each participating site. ctDNA analysis is planned at the following four time points; before surgery, and 28 days, 4 months and 7 months after surgery. This study is being conducted in accordance with the Clinical Trials Act (Act No. 16 of April 14, 2017) in Japan, and with the ethical guidelines for medical and health research involving human subjects. This trial is registered in the Japan Registry of Clinical Trials (jRCTs051200026).

ctDNA analysis

At each collection time-point, 30 mL of blood will be drawn into Streck tubes, centrifuged, and plasma will be aliquoted into 15-mL tubes for storage at −80°C. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from surgical resection or biopsy were also collected. Six mL of plasma as well as FFPE tissue samples will be shipped to Natera, Inc. and analyzed retrospectively using a clinically-validated, personalized, tumor-informed, 16-plex PCR-NGS assay (Signatera™, Natera, Inc.) after the completion of the study.

cfDNA analysis

We have previously reported the utility of the long cfDNA fragment/β-globin-ratio as a tool to predict MRD in patients with CLM after hepatectomy[31]. As planned ancillary analysis, the remaining plasma will be used for cfDNA analysis. cfDNA will be extracted from 1-mL of plasma,

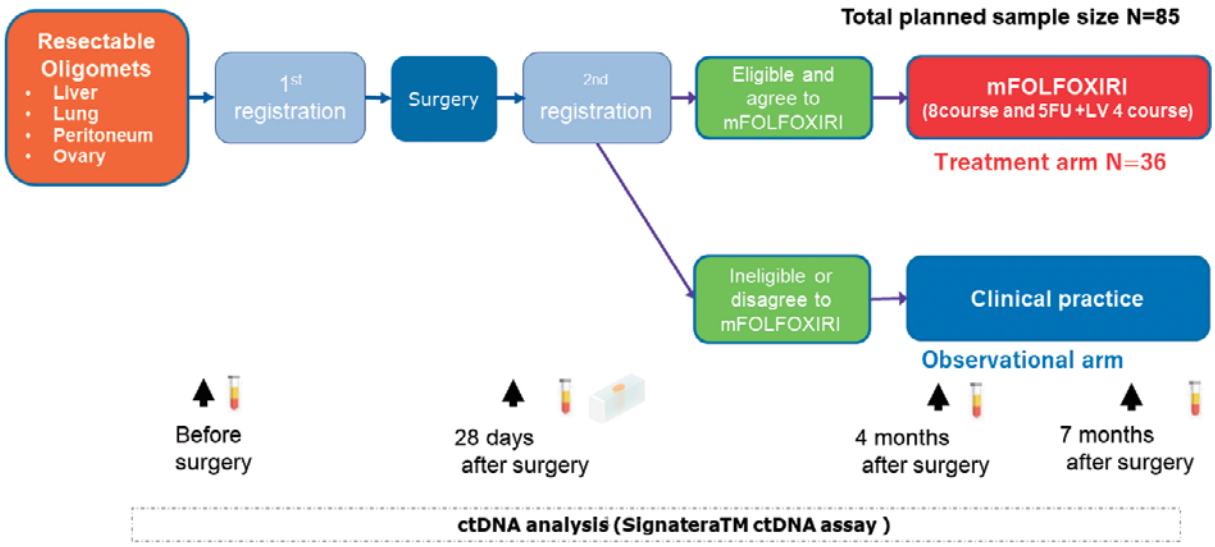

Figure 1. Trial Schema of FANTASTIC study (jRCTs051200026). Oligomets, Oligometastases; mFOLFOXIRI, modified-FOLFOXIRI

and the long fragment/β-globin ratio will be measured by real-time polymerase chain reaction.

Follow-up

All registered patients will be followed-up for at least 3 years after patient accrual is completed. Contrast-enhanced CT of chest and abdominal will be performed every 8 weeks after surgery.

Study design and statistical analysis

This phase II single-arm trial is separated into two cohorts, the observational arm and the treatment arm. The sample size was amended in 2023 after accounting for the accrual pace. The sample size in the treatment arm was estimated to be 49 patients in order to provide 80% power, with the hypothesis that the primary endpoint has an expected value of 50% and threshold value of 35%, based on the JCOG0603 study using one-sided testing at a significance level of 10%. The total sample size in the treatment arm was set at 50 patients assuming some patients would be lost to follow-up. The sample size of the observational arm was set as 50 patients assuming that half of the patients at the first registration will proceed to the observational arm. In total, the initial planned sample size was 100 patients. In Oct 2023, the sample size was recalculated. The amended sample size in the treatment arm is calculated to be 36 patients in order to provide 70% power. Considering the ratio of patients in the observational arm to the treatment arm, the amended total sample size is 85. All statistical analyses will be conducted at the Shizuoka Cancer Center. In-house monitoring will be performed every year by the Shizuoka Cancer Center to improve study progress, data integrity and patient safety. This study was approved by a certified review board in Hyogo Medical University (Certification No. C0016).

Discussion

The risk-based treatment strategy using strong biomarkers such as ctDNA is being investigated in several clinical trials. Clinical trials to compare less-intensive treatment such as observation to standard care are under recruitment for CRC patients with ctDNA-negativity after curative surgery[24,25]. On the other hand, clinical trials to compare more intensive adjuvant therapy such as FOLFOXIRI are currently ongoing for ctDNA-positive patients after curative surgery (CIRCULAE-US, NCT05174169; AFFORD, NCT05427669; DYNAMIC-III, ACTRN126170015, and CLAUDIA, NCT 05534087)[26]. Among these, FANTASTIC study is expected to be the first study to provide us with the results regarding the efficacy of mFOLFOXIRI in patients with resected oligometastatic CRC who are ctDNA positive. Accrual to the study completed in February 2024. Protocol defined treatment and follow-up are ongoing.

Among CRC patients, ctDNA clearance is shown to be prognostic of better outcomes[18,27]. Thus, the “first strike” using intensive chemotherapy may be effective to eradicate MRD[27]. As mentioned previously, which chemotherapy regimen is most effective to eradicate MRD remains unknown. Since the addition of anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) therapy to CRC patients after curative surgery does not result in improved prognosis[5,28], FOLFOXIRI is considered to be one of the most effective regimens for surgically resected metastatic CRC. However, FOLFOXIRI is associated with adverse events such as hematological toxicity, which can be difficult to manage. In the QUATTRO study,

which evaluated the efficacy of FOLFOXIRI+bevacizumab in Japanese patients with metastatic CRC, grade 3/4 neutropenia was observed in 72.5% of all registered patients[29]. Thus, further improvement of the FOLFOXIRI regimen is needed to reduce the toxicity while maintaining efficacy. The JACCRO CC11 study, which evaluated the safety and efficacy of mFOLFOXIRI in patients with metastatic CRC, reported an overall response rate of 75.8%, which was comparable with that reported by the TRIBE study using FOLFOXIRI (IRI 150 mg/m^2) +bevacizumab regimen[9]. The frequency of febrile neutropenia in the JACCRO CC11 was 5%, lower than that in the TRIBE study (8.8%)[9]. Therefore, we adopted mFOLFOXIRI as the adjuvant chemotherapy regimen and planned a phase II study to evaluate its feasibility in patients with oligometastatic CRC who are ctDNA-positive after surgery. The observational arm was designed to compare the efficacy of mFOLFOXIRI with other regimens such as CAPOX/mFOLFOX.

Although ctDNA is considered to be a powerful prognostic biomarker, not all ctDNA tests have similar performance. Bando et al. reported the discordance between tissue and plasma-based analyses mainly due to lung and peritoneal metastases[30]. We have previously reported the utility of the long cfDNA fragment/β-globin-ratio as a tool to predict MRD in patients with CLM after hepatectomy[31]. In this study, the sensitivity of a tumor-informed ctDNA assay for lung and peritoneal metastasis should be carefully interpreted.

In conclusion, the safety and efficacy of mFOLFOXIRI and ctDNA-guided treatment strategy will be evaluated in this study. When the potential efficacy of mFOLFOXIRI for ctDNA positive patients is verified, a phase III RCT is planned to evaluate the efficacy of mFOLFOXIRI compared with mFOLFOX6 among CRC patients who are ctDNA-positive after resection of oligometastases in the Japan Clinical Oncology Group (JCOG).

Acknowledgements

We would like to thank all the members of the Center for Clinical Research and Education in Hyogo Medical Univeristy and Mai Fujimori for data management.

Conflicts of Interest

Kozo Kataoka receives honoraria from Merck, Takeda, and Eli Lilly, and research grant from Japanese Society of Clinical Oncology. Kentaro Yamazaki receives lecture fees from Merck Biopharma, Takeda, Chugai, Taiho, Yakult, Ono, Eli Lily, MSD and Bristol. Keita Mori receives lecture fees from Chugai, Ono, Daiichi Sankyo and Eli Lilly. Nobuhisa Matsuhashi receives honoraria from Abbott, AMCO, Asahi Kasei Pharma, AstraZeneca, Bayer Yakuhin, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, EA Pharma, Eisai, Eli Lilly, Gunze Medical Limited, Kaken Pharm., Kyowa Kirin, MC Medical, Merck Biopharma, Miyarisan Pharm., MSD, Novartis, Ono, Taiho, Takeda Pharm., TERUMO, Tsumura, Viatris, Yakult Honsha; research funding from Daiichi Sankyo, EP-CRSU, EPS Corporation, MSD, Ono Pharm., ShiftZero K.K., Taiho Pharm. Masahiro Goto receives honoraria from Daiichi Sankyo, MSD, Taiho, and Ono Pharm and research funding from Taiho, Chugai Pharma and Nippon Kayaku. Manabu Shiozawa received lecture fees from Merck Biopharma, Takeda, Yakult Honsha, Ono Pharmaceutical, and Eli Lilly. Shruti Sharma, Joe Ensor, Adham Jurdi and Minetta C. Liu are employees at Natera, Inc. with stock or option to own stock. Minetta C. Liu received grants (funding to Mayo Clinic) from Eisai, Exact Sciences, Genentech, Genomic Health, GRAIL, Menarini Silicon Biosystems, Merck, Novartis, Seattle Genetics, and Tesaro; travel support from AstraZeneca, Genomic Health, and Ionis; and Ad hoc advisory board meetings (all funds to Mayo Clinic): AstraZeneca, Celgene, Roche/Genentech, Genomic Health, GRAIL, Ionis, Merck, Pfizer, Seattle Genetics, Syndax. Masataka Ikeda receives honoraria from Taiho, Bayer, Pfizer, and consulting fee from Daiichi Sankyo. The remaining authors have declared no conflict of interest.

Source of Funding

This study was supported by a research grant from the Japanese Society of Clinical Oncology.

Author Contributions

We have nineteen authors, and all authors have reviewed the manuscript critically, have contributed significantly, and are in agreement with the content of the manuscript. KK, TY, KY and YK are the principal investigators; they are responsible for the trial design and study procedures. KM is responsible for statistical analysis. The rest of the coauthors except for SS, JE, AJ, and ML are responsible for patient accrual. SS, JE, AJ, and ML are staff of Natera and responsible for ctDNA analysis. KK and TY drafted the manuscript, which was reviewed by all coauthors.

Approval by Institutional Review Board (IRB)

FANTASTIC was approved by a certified review board in Hyogo Medical University (Certification No. C0016).

Disclaimer

Takeshi Yamada is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Trial registration information

jRCTs051200026.

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