


BMJ Open Multicentre single-arm phase II trial evaluating the safety and efficacy of Panitumumab and irinotecan in NeoRAS Wild-type metastatic colorectal cancer patients (C-PROWESS trial): study protocol

Hiroki Osumi ¹, Naoki Ishizuka,² Atsuo Takashima,³ Yosuke Kumekawa,⁴ Daisuke Nakano,⁵ Manabu Shiozawa,⁶ Tadamichi Denda,⁷ Ryoichi Sawada,⁸ Kota Ouchi,⁹ Takeru Wakatsuki,¹ Boku Narikazu,¹⁰ Ken Kato,³ Kensei Yamaguchi,¹ Eiji Shinozaki¹

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For numbered affiliations see end of article.

Correspondence to

Eiji Shinozaki;
eiji.shinozaki@jfc.or.jp

ABSTRACT

Introduction A new concept of 'NeoRAS wild-type (WT)', which means conversion of RAS status from RAS mutant to RAS WT after treatment, has been reported. Previous observational and proof-of-concept studies have demonstrated the efficacy of epidermal growth factor receptor inhibitors in patients with NeoRAS WT metastatic colorectal cancer (mCRC). Moreover, posthoc biomarker analyses of these studies have suggested that not only the RAS status in the circulating tumour DNA (ctDNA) but also other gene mutational status may be useful as biomarkers of epidermal growth factor receptor inhibitors for NeoRAS WT mCRC.

Methods and analysis This trial is a multicentre, single-arm, phase II trial to assess the efficacy and safety of panitumumab plus irinotecan therapy for patients with NeoRAS mCRC. The key eligibility criteria include RAS mutant mCRC initially proven in tumour tissue refractory or intolerant to fluoropyrimidine, oxaliplatin and irinotecan; RAS WT in ctDNA (defined as plasma mutant allele frequencies of all RAS $\leq 0.1\%$) within 28 days before enrolment and Eastern Cooperative Oncology Group performance status ≤ 2 . The primary endpoint is the response rate. The target sample size is 30 patients. Biomarker analyses are planned to be performed using next-generation sequencing-based ctDNA analysis.

Ethics and dissemination This study was approved by the certified review board of National Cancer Center Hospital. The main results of the trial will be presented in international meetings and in medical journals.

Trial registration number s031210565.

INTRODUCTION

RAS mutations (MTs) induce the activation of the protein kinase pathway and promote carcinogenesis and cancer growth.¹ Patients with RAS MT metastatic colorectal cancer (mCRC) have a poorer prognosis than those

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The C-PROWESS trial is a prospective multicentre, single-arm, phase II trial.
- ⇒ The trial is designed to assess the efficacy and safety of panitumumab plus irinotecan therapy in patients with NeoRAS.
- ⇒ However, no comparator is a limitation.
- ⇒ Translational research of biomarkers using liquid biopsies at baseline and after discontinuation of the treatment is planned to be performed.

with RAS wild-type (WT) mCRC.^{2,3} Epidermal growth factor receptor (EGFR) inhibitors (such as cetuximab and panitumumab), which are key drugs for mCRC, are ineffective for patients with RAS MT mCRC (KRAS/NRAS exons 2, 3 and 4).⁴⁻¹⁰

International guidelines recommend RAS genetic testing prior to the administration of an EGFR inhibitor in patients with mCRC.¹¹⁻¹³ Repeat biopsies are not performed in routine clinical practice to monitor the RAS MT status;¹¹⁻¹³ the consistency of the RAS MT status before and after chemotherapy remains unclear.

Recent advances in diagnostic technology for the detection of genetic MTs by liquid biopsy, especially circulating tumour DNA (ctDNA), have made minimally invasive, simple and repeatable testing possible.¹⁴⁻¹⁶ It is well known that RAS status can change before and after treatment. First reported was the identification of RAS MTs in ctDNA in EGFR inhibitor-resistant RAS WT mCRC patients.^{17,18} This involved acquired

resistance to EGFR inhibitors, and several clinical trials have reported that remeasuring the RAS status before treatment is an important predictor of treatment efficacy when considering EGFR inhibitor rechallenge.^{19–21}

On the other hand, there have been some reports that RAS MT observed at the initial diagnosis converted to RAS WT after treatment.²² These cases have been called ‘NeoRAS WT’ mCRC.²² The incidence of NeoRAS WT mCRC has been reported to range from 10.7% to 40% when assessed in tumour tissue samples,^{23 24} and from 18.8% to 83.3% in the ctDNA.^{25–31}

There have been several reports of the use of EGFR inhibitors in patients with NeoRAS WT. Mohamed *et al*, in a proof-of-concept study of EGFR inhibitors in patients with NeoRAS WT,³¹ reported that the objective response rate (RR) was 55.6% and progression-free survival (PFS) was 9 months in patients with NeoRAS WT mCRC treated with fluorouracil, folinic acid, irinotecan and cetuximab.³¹ This result suggested that EGFR inhibitors may be effective in patients with NeoRAS WT mCRC.

Although retrospective analyses and proof-of-concept studies have indicated the potential efficacy of EGFR inhibitors in NeoRAS WT mCRC,^{22 31} the safety and efficacy have not been validated prospectively. Furthermore, the definition of NeoRAS WT mCRC has not been established.

Therefore, this trial will evaluate the efficacy of panitumumab and irinotecan in patients with NeoRAS WT mCRC confirmed in ctDNA after prior treatment.

METHODS AND ANALYSIS

Trial design

This trial is a multicentre, single-arm, phase II trial to investigate the safety and efficacy of Panitumumab and irinotecan in NeoRAS Wild-type metastatic colorectal cancer patients (C-PROWESS trial). The overall trial scheme is illustrated in figure 1.

Patients

The key eligibility criteria are as follows: (1) RAS MT (KRAS/NRAS exons 2, 3 and 4) and BRAF V600E WT mCRC initially diagnosed in the tumour tissue; (2)

refractory or intolerant to fluoropyrimidine, oxaliplatin and irinotecan; (3) RAS WT in ctDNA (mutant allele frequencies of all RAS $\leq 0.1\%$) within 28 days prior to enrolment; (4) an Eastern Cooperative Oncology Group performance status ≤ 2 and (5) preserved organ function. The details of the eligibility criteria are presented in box 1.

Treatment

Patients will receive panitumumab at 6 mg/kg and irinotecan at 150 mg/m² biweekly until progressive disease, unacceptable toxicity, withdrawal of informed consent or death. The starting dose of irinotecan can be reduced to 120 mg/m² according to UGT1A1 status (homozygosity/double heterozygosity).

Outcomes and statistical considerations

The primary endpoint of the C-PROWESS trial is RR, defined as the proportion of patients who achieve complete or partial response by the investigator’s assessment. The secondary endpoints include PFS, overall survival (OS), disease control rate, incidences of adverse events and the ratio of NeoRAS WT mCRC after failure of fluoropyrimidines, oxaliplatin and irinotecan. The response is evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, using CT at 6 and 12 weeks after the start of the protocol treatment and repeated every 8 weeks thereafter. The RR threshold is set at 4%, according to the results of previous clinical trials with tipiracil/trifluridine (+bevacizumab)^{32–34} or regorafenib.³⁵ The required sample size is 30, whereas an RR of 15% is deemed to be promising (one-sided $\alpha=0.10$; $\beta=0.2$). The primary endpoint is planned to be analysed in all the patients who receive at least one dose of the protocol treatment and who satisfy all the inclusion and exclusion criteria. Participant enrolment started on 1 February 2022 and will end on 31 January 2023.

Biomarker analysis

Samples for liquid biopsies are planned to be collected at baseline and after discontinuation of the protocol treatment (figure 1). The ctDNA will be analysed using a highly sensitive digital PCR method, the OncoBEAM RAS CRC kit and targeted next-generation sequencing, Guardant360. The OncoBEAM RAS CRC kit, which has been approved in Japan to detect RAS MTs in the ctDNA derived from mCRC, detects 34 MTs in KRAS/NRAS codons 12, 13, 59, 61, 117 and 146 in plasma.³⁶ Guardant360, a hybrid capture-based next-generation sequencing panel of the ctDNA developed by Guardant Health, detects other gene alterations.³⁷ Exploratory analyses will be performed to identify the proportion of patients without RAS and other MTs related to resistance to anti-EGFR inhibitors (defined as ‘True NeoRAS WT’). The clinical outcomes (RR, PFS, OS and disease control rate) of patients with true NeoRAS WT receiving panitumumab and irinotecan combination therapy will be compared with those of patients without true NeoRAS WT and the

Overall Trial Scheme

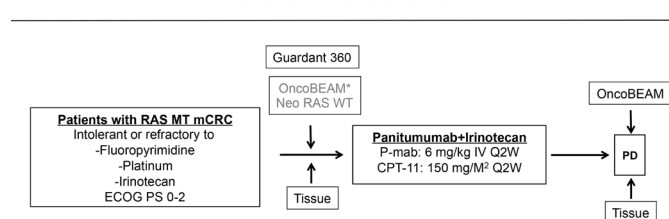


Figure 1 Overall trial scheme. Liquid biopsies for the OncoBEAM RAS CRC kit and Guardant360 will be performed at baseline, and the OncoBEAM RAS CRC kit will be used after the discontinuation of the protocol treatment. OncoBEAM: OncoBEAM RAS CRC kit; *Substitution of results immediately before enrolment. CRC, colorectal cancer.

Box 1 Eligibility criteria for the C-PROWESS trial
Inclusion criteria

1. Histologically proven diagnosis of colorectal adenocarcinoma.
2. Advanced or recurrent colorectal cancer (excluding appendix and anal canal cancer).
3. RAS mutation (MT) (KRAS/NRAS exons 2, 3 or 4 MT) confirmed by tumour histology prior to first-line chemotherapy.
4. Confirmation of refractoriness or intolerance to previous treatments with chemotherapy, including fluoropyrimidines, oxaliplatin or irinotecan (irinotecan is applied to refractory disease only), regardless of prior treatment with trifluridine tipiracil hydrochloride, regorafenib or angiogenesis inhibitors.
5. Confirmation of the RAS WT within 28 days from the test result date by ctDNA analysis using the OncoBEAM RAS CRC KIT.
6. At least one measurable lesion according to the RECIST V.1.1 criteria evaluated by CT or MRI within 28 days before registration.
7. Eastern Cooperative Oncology Group performance status ≤ 2 .
8. Age ≥ 20 years.
9. Adequate organ function (bone marrow, liver and renal function) as defined by the following laboratory values obtained within 15 days prior to enrolment in the study:
 - a. Absolute neutrophil count $\geq 1500/\text{mm}^3$.
 - b. Platelets $\geq 75\,000/\text{mm}^3$.
 - c. Serum total bilirubin ≤ 1.5 mg/dL; serum AST (GOT) and ALT (GPT) ≤ 100 U/L (except for patients with tumour involvement of the liver who must have AST and ALT ≤ 200 U/L).
10. A life expectancy of at least 60 days.
11. Written informed consent.

Exclusion criteria

1. Evidence of BRAF V600E MT by tumour histology.
2. Treated with blood transfusion, blood products or haematopoietic factor products such as Granulocyte Colony Stimulating Factor within 7 days prior to enrolment in this study.
3. A history of severe drug hypersensitivity or severe drug allergy.
4. Active infection (fever of 38°C or higher due to infection).
5. Ascites, pleural effusion or pericardial effusion requiring continuous drainage.
6. Uncontrolled diabetes mellitus.
7. Uncontrolled hypertension.
8. Patients who have been treated with any of the following treatments prior to starting the study drug:
 - a. Extensive surgery ≤ 4 weeks prior to starting the study drug (eg, surgical treatment with organ resection, excluding colostomy).
 - b. Proctocolectomy ≤ 2 weeks prior to starting the study drug.
 - c. Any chemotherapy ≤ 2 weeks prior to starting the study drug.
 - d. Radiotherapy ≤ 2 weeks prior to starting the study drug.
9. Clinically significant electrocardiographic abnormality or clinically significant cardiovascular accidents within 6 months prior to study enrolment, including myocardial infarction, severe unstable angina or New York Heart Association functional classification class III or IV congestive heart failure.
10. Patients with severe lung disease (interstitial pneumonia, pulmonary fibrosis or severe emphysema).
11. History of clinically significant mental disorder or central nervous system disorder.
12. Symptomatic brain metastasis or clinically suspected brain metastasis on symptoms.
13. Diarrhoea that interferes with daily life.
14. Intestinal paralysis, intestinal obstruction.

Continued

Box 1 Continued

15. Coexisting active malignancies.
16. Pregnant or lactating women; women of childbearing potential or men with female partners of childbearing potential who are unwilling to use a highly effective method of contraception or avoid intercourse during and on completion of the study.
17. Patients who have been assessed by the site physician as inappropriate for this study.
18. Patients who have been treated with EGFR inhibitors prior to starting the study drug.
CRC, colorectal cancer; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; WT, wild-type.

overall study population. Moreover, the clinical outcomes will be compared according to the presence or absence of each genetic and epigenetic abnormality using exome sequencing and immunohistochemical staining in tissue samples and in ctDNA analysis before and after treatment with the protocol treatment using NGS, to explore the relationship with clinical outcomes and the mechanism of resistance.

Trial organisation

Eight core high-volume centres in Japan will participate in this trial.

ETHICS AND DISSEMINATION

This study was approved by the certified review board of the national cancer centre hospital (jRCT, s031210565; registration date, 20 January 2022.). The main results of the trial will be presented in international meetings and in medical journals.

Clinical questions

The clinical questions to be addressed in this study will be the definition of NeoRAS WT mCRC and the therapeutic effect of EGFR inhibitors on NeoRAS WT mCRC.

First, when 'NeoRAS WT' mCRC is defined by RAS MT status only, it is not possible to determine whether the RAS MT has completely disappeared or has not been measured due to a low volume of ctDNA. Therefore, we will perform NGS analysis using ctDNA before administering the protocol treatment to confirm the incidence of 'True NeoRAS WT' mCRC patients. 'True NeoRAS WT' mCRC is defined as the disappearance of RAS and the detection of other genetic MTs after treatment. If the proportion of 'True NeoRAS WT' mCRC patients is clarified, it may be even more useful in the enrichment of the population that will respond to treatment with EGFR inhibitors.

Second, our trial will evaluate the relationship between gene MTs other than RAS in ctDNA and the efficacy of EGFR inhibitors in NeoRAS WT mCRC. The ORR, PFS and OS may differ according to the presence or absence of some genetic abnormality that may lead to primary resistance to EGFR inhibitors, such as EGFR

extracellular domain, Erb-B2 Receptor Tyrosine kinase 2, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit alpha, among others, in the ctDNA (NGS) prior to protocol treatment.

In addition, we plan to measure the ctDNA RAS again after the administration of the protocol treatment. This will allow us to understand how frequently RAS MT reappears after treatment and whether the same RAS MT reappears or different variants of RAS MT newly appear. If the same RAS variant allele frequency increases after the administration of treatment, it may be due to tissue heterogeneity in which dominant clones with/out RAS mutation in tumours are changed by an EGFR inhibitor. Furthermore, the mechanism of resistance to EGFR inhibitors will be clarified.

Limitations

The limitations of this study are the small sample size and lack of a control arm.

Summary

Our trial will evaluate the efficacy of panitumumab and irinotecan in patients with NeoRAS WT mCRC to develop personalised therapeutic regimens based on the ctDNA results.

Author affiliations

¹Department of Gastroenterology, Cancer Institute Hospital Gastroenterology Center, Koto-ku, Tokyo, Japan

²Department of Clinical Trial Planning and Management, Cancer Institute Hospital Gastroenterology Center, Koto-ku, Tokyo, Japan

³Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

⁴Division of Gastrointestinal Oncology, Saitama Cancer Center, Saitama, Japan

⁵Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

⁶Department of Surgery, Kanagawa Cancer Center, Kanagawa, Japan

⁷Division of Gastroenterology, Chiba Cancer Center, Chiba, Japan

⁸Division of Gastroenterology and Hepatology, Jikei University Hospital, Tokyo, Japan

⁹Department of Medical Oncology, Tohoku University Hospital, Miyagi, Japan

¹⁰Department of Medical Oncology and General Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

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Contributors HO, AT, KK, NB, KY and ES, as task managers, participated in the coordination of this trial, the design and the writing of the protocol, data collection, data analysis, data interpretation and writing of the manuscript. AT, YK, DN, MS, TD, KO, RS, KO and TW, as the protocol preparation committee, participated in this trial, including design and writing of the protocol, data collection, data analysis, data interpretation and preparation of the manuscript. NI, as the chief of statistical analysis, participated in the statistical setting of the trial, design and data analysis. All the authors have reviewed and approved the final manuscript.

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ORCID iD

Hiroki Osumi <http://orcid.org/0000-0002-4742-0446>

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