S-1 and CPT-11 Plus Ramucirumab (IRIS+Rmab) as Second-Line Chemotherapy for Patients with Oxaliplatin-Refractory Metastatic Colorectal Cancer (mCRC): A Multicenter Phase II Study in Japan (N-DOCC-F-C-1701)

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Summary: This multicenter phase II N-DOCC-F-C-1701 trial is being planned in order to investigate the efficacy and safety of CPT-11+S-1+Ramucirumab (IRIS+Rmab), which is anticipated to have a stronger anti-tumor effect than IRIS+Bmab in patients with metastatic colorectal cancer (mCRC) previously treated with oxaliplatin (L-OHP) containing regimen, in consideration of the result of RAISE, FIRIS and some phase II trials of IRIS+Bevacizumab (Bmab). The number of patients is set at 38 for the statistical analysis, assuming an expected median PFS of 5.0 months (threshold: 3.0 months). The primary endpoint of the study is the progression free sur-

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Abbreviations: AE, adverse event; ANC, Absolute neutrophil count; Bmab, Bevacizumab; Ccr, Creatine clearance; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; hGFs, hematopoietic growth factors; L-OHP, oxaliplatin; mCRC, metastatic colorectal cancer; NSCLC, non-small lung cell carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QOL, quality of life; RECIST, response evaluated criteria for solid tumor; Rmab, Ramucirumab; RR, Response rate; VEGFR-2, vascular endothelial growth factor receptor-2.

This trial has been registered in the UMIN Clinical Trials Registry as UMIN000028170.
 INTRODUCTION

Bevacizumab (Bmab; an anti-angiogenesis agent) + oxaliplatin (L-OHP)-containing regimens are frequently chosen as the first-line treatment for metastatic colorectal cancer (mCRC) [1]. However, until the development of next-generation anti-angiogenesis agents such as ziv-aflibercept (AFL) [2] or ramucirumab (Rmab) [3], no candidate anti-angiogenesis agents were deemed appropriate for the second-line treatment of patients in whom the first-line progression-free survival (PFS) was <3 months. Ramucirumab (Rmab) is a fully human immunoglobulin gamma G-1 (IgG-1) monoclonal antibody that binds with high affinity (KD 50 pmol/L) to the vascular endothelial growth factor receptor-2 (VEGFR-2) extracellular domain, thereby preventing the binding of all VEGF ligands and receptor activation and blocking not only VEGF-A but also VEGF-C and VEGF-D [3], leading to stronger anti-angiogenetic effects than Bmab, which can only inhibit VEGF-A.

Based on the results of the RAISE trial, The Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for the Treatment of Colorectal Cancer (JSCCR guidelines) [4] regard FOLFIRI+Rmab as a standard second-line regimen for mCRC [3]. This trial also showed that Rmab was effective, even in cases in which the first-line anti-tumor effect of Bmab was insufficient [3].

In contrast, the FIRIS trial showed that S-1+CPT-11 (IRIS) had a non-inferior effect to FOLFIRI, with regard to PFS and overall survival (OS), in second-line chemotherapy for mCRC [5]. IRIS+Bmab is also considered to have almost the same anti-tumor effect as FOLFIRI+Bmab, based on the results of several phase II trials [6-8]; thus, IRIS+Bmab was regarded as a standard regimen in the JSCCR guidelines 2016 [4].

The median PFS of IRIS+Bmab in the second-line setting is 5.6 months [6].

These results suggest that IRIS+Rmab may have more powerful anti-tumor effects than IRIS+Bmab.

Under these circumstances, a multicenter phase II N-DOCC-F-C-1701 trial was planned to investigate the efficacy and safety of Rmab+IRIS. The name of this trial originates from the Nagasaki Digestive Organ Cancer Chemotherapy Forum. This forum is a biannual meeting held by the Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences and affiliated hospitals to review state of the art chemotherapy.

PATIENTS AND METHODS

Study outline

Figure 1.

Eligibility

Inclusion criteria

For inclusion in this trial, patients must fulfill all of the following criteria:

1) Ability to understand this trial and provide written informed consent
2) Recognized by investigators as appropriate to join this trial
3) Histologically confirmed advanced or metastatic colorectal cancer
4) Withdrawal from first-line oxaliplatin-based chemotherapy because of intolerable toxicity or progressive disease or relapse within 180 days after the last session of oxaliplatin-based adjuvant chemotherapy
5) No history of radiotherapy for target lesion except for palliative use such as for bone metastasis
6) Age ≥ 20 years
7) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
8) Measurable lesions on the basis of the response evaluated criteria for solid tumor (RECIST) criteria ver. 1.1
9) Oral intake tolerable
10) Patients must have adequate organ functions, as demonstrated within 7 days from enrollment (the latest data within a specified period of time should
be used). Patients who received any blood transfusion or hematopoietic growth factors (hGFs) such as granulocyte colony-stimulating factor (G-CSF) within 14 days before enrollment will be excluded. The bone marrow, hepatic, and renal functions must be within the ranges shown below:

- White blood cell count $>3,000/mm^3$ and $<12,000/mm^3$
- Absolute neutrophil count (ANC) $>1,500/mm^3$
- Platelet cell count $>100,000/mm^3$
- Hemoglobin $>9.0$ g/dL
- Serum total bilirubin $<1.5$ UNL
- AST and ALT $<2.5$ UNL (in case of liver metastasis $<5.0$ UNL)
- Serum creatinine $<1.5$ UNL
- Urinary protein: 0, +/−, 1+ or 2+ and Up/Uc $<2.0$
- Creatinine clearance (Ccr) $\geq 30$ mL/min (calculated by Cockroft formula)
- UGT1A1 polymorphism: *6, *28 (except for double homozygous cases)
- Estimated life expectancy $>3$ months

**Exclusion criteria**

A patient will not be eligible for inclusion in this study if any of the following criteria apply:
1) Severe complications, such as intestinal pneumonia, lung fibrosis, renal dysfunction, hepatic dysfunction, uncontrolled hypertension, and severe diabetes mellitus that cannot be controlled by the administration of high-dose insulin
2) Markedly abnormal electrocardiogram findings or symptomatic heart disease (heart failure, myocardial infarction, or angina)
3) Symptomatic infectious disease, undertreated, or untreated HCV
4) Symptomatic pleural effusion or ascites requiring frequent puncture
5) History of severe drug allergy
6) Active double cancer
7) Psychopathy, central nervous system abnormality, or cerebrovascular disease
8) Radiological evidence of brain tumor, or brain metastasis
9) Gastrointestinal ulcer, bleeding, obstruction, paralysis, or perforation
10) Obstructive bowel disease
11) Watery or grade $>2$ diarrhea
12) History of thrombosis or cerebral infarction other than asymptomatic lacunar infarction
13) Congenital bleeding tendency
14) The need for anti-coagulant drugs (other than those equivalent to low-dose aspirin $<325$ mg/day)

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**Fig. 1.** This figure shows the study outflow and the method of drug administration.
15) Requiring steroids  
16) Requiring flucytosine or Atazanavir sulfuric acid  
17) Pregnant or breastfeeding  
18) Female patients hoping to become pregnant  
19) History of treatment with irinotecan-hydrochloride  
20) History of hemoptysis grade 2 (radiological)  
21) Contraindications for S-1, CPT-11, or ramucirumab  
22) Recognized by investigators as inappropriate for joining this trial  

**FOLLOW-UP**  
All registered patients are to be followed-up for at least 3 years after the completion of patient accrual. Enhanced chest and upper abdominal computed tomography (CT) are to be performed every 6 weeks (±2 weeks is acceptable) or every two courses of treatment during the treatment protocol. After the termination of the treatment protocol, enhanced chest and upper abdominal CT are to be performed every 2 months.

**RESULTS**  
This is the first trial of IRIS+Rmab in human patients with mCRC. The trial was started on September 1, 2017. A total of 38 patients will be accrued from 7 Japanese institutions over a period of 3 years.

**DISCUSSION**  

**Trial design**  
This trial has been designed as an open-label, single-arm interventional prospective exploratory phase II trial.

**Aims**  
We will review the efficacy and safety of Rmab+IRIS in mCRC patients who had previously been treated with L-OHP-containing regimens.

**Endpoints**  
Primary endpoint: Progression free survival (PFS).  
Secondary endpoints: Response rate (RR), overall survival (OS), safety (CTCAE ver. 4.0), quality of life (QOL) (1 course, 2 courses, and at the end of the trial), and status of nausea and vomiting for 1 to 3 courses.

**Treatment**  
Rmab (10 mg/kg) and CPT-11 (150 mg/m²) with adjustment by UGT1A1 will be administered every 3 weeks [6]. S-1 will be administered orally, twice daily for 14 consecutive days at a dose 40 mg/m², based on the patient’s body surface area adjusted for creatine clearance (Ccr), as calculated by the Cockcroft-Gault formula. In Japan, the effects of the tri-weekly administration of Rmab (10 mg/kg) with docetaxel have only been investigated in patients with non-small lung cell carcinoma (NSCLC) [9]. Based on the typical tri-weekly Rmab regimens [1], tri-weekly Rmab is expected to be administered at a dose of 12 mg/kg. However, the administration of Rmab at this dose has not been attempted. A phase I trial should be performed to determine the recommended dose of ramucirumab; however, this will take some time. The dose of Rmab that we selected for this trial was 10 mg/kg. This was selected out of concern for patient safety, and to facilitate the completion of the trial.

**Statistical Analyses**  
The PFS of patients receiving FOLFIRI was reported to be 2.5-3.9 months [6]. The null hypothesis median threshold PFS was 3.0 months, and the expected median PFS was 5.0 months. Assuming that the PFS shows exponential distribution, with a one-sided α error of 0.05 and a β-error of 0.1, 34 patients are required for the study. The number of patients was therefore set at 38, considering the possible ineligibility or exclusion of patients from the analysis.

**CONCLUSION**  
If this trial meets the endpoints, and based on the adoption of IRIS+Bmab as a standard second-line regimen in the JSCCR guidelines 2016, Rmab+IRIS without the use of infuser pumps might be supported as a future standard second-line regimen for mCRC.

The essence of this manuscript was presented at ESMO ASIA 2017, Singapore 2017/11/18.

**CONFLICT OF INTEREST:** The authors declare no conflicts of interest in association with the present study. The findings of this study were obtained from ordinary clinical practice covered by national medical insurance, thus we do not receive any funds or any financial support.

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