Regorafenib plus FOLFIRI with irinotecan dose escalated according to uridine diphosphate glucuronosyltransferase 1A1 genotyping in previous treated metastatic colorectal cancer patients: study protocol for a randomized controlled trial

CURRENT STATUS: ACCEPTED

Cheng-Jen Ma
Kaohsiung Medical University

Tsung-Kun Chang
Kaohsiung Medical University

Hsiang-Lin Tsai
Kaohsiung Medical University

Wei-Chih Su
Kaohsiung Medical University

Ching-Wen Huang
Kaohsiung Medical University

Yung-Sung Yeh
Kaohsiung Medical University

Yu-Tang Chang
Kaohsiung Medical University

Jaw Yuan Wang
Kaohsiung Medical University Chung Ho Memorial Hospital

cy614112@ms14.hinet.net Corresponding Author

DOI:
10.21203/rs.2.11809/v1

SUBJECT AREAS
Integrative & Complementary Medicine

KEYWORDS
Regorafenib, UGT1A1, FOLFIRI, Dose escalation, Metastatic colorectal cancer
Abstract

Background

Regorafenib is an oral multi-kinase inhibitor for metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidines, irinotecan, oxaliplatin, monoclonal antibodies targeting vascular endothelial growth factor (VEGF), and monoclonal antibodies targeting epidermal growth factor receptor (EGFR). A dose reduction from 160 mg to 120 mg regorafenib reduces regorafenib-associated adverse events (AEs). Dose adjustment of irinotecan in FOLFIRI regimen on basis of individual uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype provides optimal oncological outcomes with acceptable AEs. This study is trying to address the efficacy and safety of dose adjusted combination of regorafenib and FOLFIRI for patients with mCRC.

Methods

A prospective, multicenter, randomized in a 2:1 ratio, controlled, clinical trial with two parallel arms will be conducted to compare irinotecan dose escalated FOLFIRI according to UGT1A1 genotyping plus 120 mg regorafenib with 120 mg regorafenib alone in previously treated patients with mCRC. The primary endpoint is progression-free survival (PFS) and the secondary endpoints are overall survival (OS), disease control rate (DCR), time to progression (TTP), and duration of treatment (DoT). Safety assessments are recorded as well.

Discussion

Dose adjustment for regorafenib and irinotecan makes treatment-related AEs tolerable and makes the concomitant treatment practicable. This study will provide initial evidences regarding the efficacy and safety of a new combination of chemotherapy and a targeted agent for mCRC.

Background

Regorafenib monotherapy is currently the standard of care for 3rd or 4th line metastatic colorectal cancer (mCRC) patients who are previously treated with fluoropyrimidines, irinotecan, oxaliplatin, and monoclonal antibodies targeting vascular endothelial growth factor (VEGF); and monoclonal antibodies targeting epidermal growth factor receptor (EGFR) for those with KRAS wild-type cancers. Regorafenib targets and inhibits membrane-bound and intracellular receptor tyrosine kinases (RTKs)
that involve in signaling for oncogenesis, angiogenesis and proliferation of cancer [1]. The global CORRECT trial demonstrated that regorafenib monotherapy had significantly better progression-free survival (PFS), overall survival (OS), and disease control rate (DCR) in previously treated mCRC (1.9 versus 1.7 months, \( P < 0.001 \); 6.4 versus 5.0 months; \( P = 0.0052 \); 41% versus 15%, \( P < 0.0001 \), respectively) [2]. Similarly, the CONCUR study, which was conducted for Asians, also yielded significant differences in PFS, OS, and DRC (3.2 versus 1.7 months, \( P < 0.0001 \); 8.8 versus 6.3 months; \( P = 0.00016 \); 51.5% versus 7.4%, \( P < 0.0001 \), respectively) [3]. The most frequently encountered adverse event (AE) of regorafenib is hand-foot skin reaction (HFSR), which leads to dose reduction or interruption of treatment in response to the AE. Dose reduction of regorafenib at 120 mg reduces the severity of AEs and allows better patient tolerance and compliance with comparable oncological results [4].

Irinotecan is a prodrug that is converted to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which acts on topoisomerase I in vivo to interrupt DNA replication in cancer cells and then makes cell death. SN-38 is metabolized and detoxified by glucuronidation of uridine diphosphate glucuronosyl transferase (UGT), mainly the \( UGT1A1 \) isoenzyme in the liver, to SN-38G [5]. The differences of capacity of glucuronidation of \( UGT1A1 \) is determined by the number of repeats in the TATA box on \( UGT1A1 \) promoter, with the most common \( UGT1A1 \) allele, 6 TA repeats (\( UGT1A1^*1 \), wild type) and a variant allele, 7 TA repeats (\( UGT1A1^*28 \), mutant type). Individuals with \( UGT1A1^*28 \) exhibit reduced \( UGT1A1 \) transcription and expression and consequently reduced SN-38 glucuronidation and increased toxicities of irinotecan [6]. Polymorphisms of \( UGT1A1 \) therefore decide the rate of SN-38 glucuronidation and the following effects on the pharmacokinetics and toxicities of irinotecan [7]. Accordingly, dose adjustment of irinotecan based on individual \( UGT1A1 \) genotyping along with 5-fluorouracil (5-FU) and leucovorin (LV) (FOLFIRI regimen) obtains acceptable AEs along with optimal oncological outcomes [8].

Based on the current literature, concomitant use of chemotherapy and targeted agents in treating mCRC shows potentially add-on benefits on tumor control in the front line setting. In our previous preliminary observational study, in which regorafenib plus FOLFIRI with dose escalation according to
UGT1A1 genotype were administered to previously treated patients with mCRC, revealed superior oncological effects over regorafenib monotherapy [9]. As the result, the current study aims to explore the efficacy and safety of regorafenib and FOLFIRI concomitant treatment with irinotecan dose adjusted based on UGT1A1 genotype in previously treated mCRC patients compared to those who receive regorafenib alone in prospective, randomized, two-arm, controlled setting.

Methods/design

Trial design

This is a multicenter, randomized in a 2:1 ratio, controlled clinical trial with two parallel arms summarized in Fig 1. Neither the investigators nor the patients are masked to treatment allocation. In order to compare the efficacy and safety of regorafenib plus FOLFIRI with irinotecan dose adjusted based on UGT1A1 genotype (study group) and regorafenib monotherapy (control group), a total of 153 mCRCs that were previously treated with fluoropyrimidines, irinotecan, oxaliplatin, and monoclonal antibodies targeting VEGF; and monoclonal antibodies targeting EGFR for those with KRAS wild-type tumors will be recruited, of which 102 participants will be assigned to the study group and 51 participants will be assigned to the control group in a 2:1 ratio.

Study setting

The study will be conducted in 4 hospital centers in Taiwan.

Study participants

Participants will be recruited from Kaohsiung medical university hospital, Cathay General Hospital, Taichung Veterans General Hospital and Taipei Veterans General Hospital by the colorectal surgeons. The planned recruitment period is 24 months and informed consent will be obtained from all participants before randomization.

Eligibility criteria

Inclusion criteria

Cyto-/histological confirmed mCRC

Patients who have been previously treated, or are not considered candidates for, other locally approved standard treatment(s) and for whom the decision has been made per investigator’s routine treatment practice to prescribe regorafenib as 3rd line (RAS mutant) or 4th line (RAS wildtype) therapy

Aged no less than 20 years, at the time of acquisition of informed consent

Eastern Cooperative Oncology Group (ECOG) performance score of 0–1
Patients with measurable or non-measurable disease in the colon or rectum, according to RECIST criteria version 1.1
Life expectancy more than 12 weeks
Women with childbearing potential must agree to perform adequate contraception measures since informed consent till a least 12 weeks after the last study drug administration. The investigators or designee are requested to advise the patient to achieve adequate birth control.
Adequate organ and bone marrow function as defined below:
- Total bilirubin 1.5 x upper limit of normal (ULN)
- Alanine amino-transferase (ALT) and aspartate amino-transferase (AST) 2.5x ULN (5x ULN for patients with liver metastases)
- Alkaline phosphatase (ALP) 2.5x ULN (5x ULN for patients with liver metastases)
- Amylase and lipase 1.5 x ULN
- Serum creatinine 1.5 x ULN
- Glomerular filtration rate (GFR) 30 ml/min/1.73 m2, according to the modified diet in renal disease (MDRD) abbreviated formula
- International normalized ratio (INR)/partial thromboplastin time (PTT) 1.5 x ULN
- Platelet count 100000/mm3
- Hemoglobin level 9 g/dL
- Absolute neutrophil count 1500/mm3

9. Ability to understand and willingness to sign written Informed Consent Form

Exclusion criteria

Prior treatment with regorafenib within 28 days
Other concurrent cancer or prior treatment for other carcinomas within the last five years, except curatively treated non-melanoma skin cancer, superficial bladder tumors, and cervical cancer in-situ
Extended field radiotherapy within 28 days or limited radiotherapy within 14 days prior to randomization
Major surgery within 28 days prior to start of study treatment (diagnostic biopsy, laparotomy, line placement is not considered as major surgery)
Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, myocardial infarction in the past 12 months, active gastrointestinal bleeding, central nervous system disorders or psychiatric illness/social situation that would limit compliance with study requirements or judged to be ineligible for the study by the investigator
History of myocardial infarction, deep venous or arterial thrombosis, CVA during the last 6 months
Uncontrolled cardiac arrhythmias, unstable angina, or newly-onset angina within 3 months prior to study entry
Uncontrolled hypertension despite optimal management (systolic blood pressure >150 mmHg or diastolic pressure >90 mmHg)
Patients with known CNS metastases
Having received any investigational agents or participated in any investigational drug study within 4 weeks prior to study enrollment
Pregnant or breast-feeding female (a pregnancy test must be performed on all female patients who are of child-bearing potential within 7 days of treatment initiation, and the result must be negative)
Inability to take oral medication

13. Poor compliance as judged by the investigator.
Genotyping

DNA is extracted from 4 mL of patients’ peripheral blood with a PUREGENE® DNA isolation kit (Gentra Systems, Inc., Minneapolis, MN, USA). Then the genomic DNA extracted is analyzed using direct sequencing to determine the UGT1A1 promoter genotype. The primers are designed by primer 3 free software (http://primer3.wi.mit.edu), and the sequence of the forward is 5-AGT-CACGTGACACAGTCAAACA-3 and the reverse primer is 5-CTTTGCTCCTGCCAGAGGTT-3. The polymerase chain reaction (PCR) volume is 40 µL and the PCR conditions for the UGT1A1 are as follows: 94.0 °C for 5 minutes; annealing for 20 seconds at 67.5 °C; primer extension for 20 seconds at 72.0 °C; and final extension for 10 minutes at 72.0 °C. A fragment analysis of the PCR products is conducted to verify the genotypes by using the automated capillary electrophoresis on the ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA), and the genotypes are analyzed using GeneScan and Genotyper software (Applied Biosystems, Foster City, CA, USA) [10].

Interventions

Control group

The treatment for the control group will be oral regorafenib monotherapy in the dosing schedule of 120 mg once daily for the first 3 weeks of each 4 week cycle, without UGT1A1 genotyping.

Study group

The treatment for the study group will be composed of oral regorafenib 120 mg once daily for the first 3 weeks of each 4 week cycle as described above and additional infusion of FOLFIRI regimen.

According to the UGT1A1 genotypes, the study group is further divided into three subgroups:

Subgroup 1: UGT1A1*1/*1 genotype

Oral regorafenib will be administered in a dose of 120 mg once daily for the first 3 weeks of each 4 week cycle. FOLFIRI regimen will be initiated at a dose of 180 mg/m² irinotecan and 200 mg/m² LV intravenously (IV) infused over 2 hours followed by 5-FU (2800 mg/m² as an IV infusion over a 46-hour period). If no greater than grade 3 FOLFIRI related AEs is observed after two cycles of each dose of irinotecan, the dose of irinotecan will be escalated in steps of 30 mg/m². If any FOLFIRI related AEs
greater than grade 3 are encountered, the dose of irinotecan will be reduced by 30 mg/ m² or back to the previous dose and be withheld at that dose at the next cycle. The maximal dose of irinotecan for subgroup 1 is 260 mg/ m².

**Subgroup 2: UGT1A1*1/*28 genotype**

Oral regorafenib will be administered in a dose of 120 mg once daily for the first 3 weeks of each 4 week cycle. FOLFIRI regimen will be initiated at a dose of 180 mg/m² irinotecan and 200 mg/ m² LV intravenously (IV) infused over 2 hours followed by 5-FU (2800 mg/ m² as an IV infusion over a 46-hour period). If no greater than grade 3 FOLFIRI related AEs is observed after two cycles of each dose of irinotecan, the dose of irinotecan will be escalated in steps of 30 mg/ m². If any FOLFIRI related AEs greater than grade 3 are encountered, the dose of irinotecan will be reduced by 30 mg/ m² or back to the previous dose and be withheld at that dose at the next cycle. The maximal dose of irinotecan for subgroup 2 is 240 mg/ m².

**Subgroup 3: UGT1A1*28/*28 genotype**

Oral regorafenib will be administered in a dose of 120 mg once daily for the first 3 weeks of each 4 week cycle. FOLFIRI regimen will be initiated at a dose of 120 mg/m² irinotecan and 200 mg/ m² LV intravenously (IV) infused over 2 hours followed by 5-FU (2800 mg/ m² as an IV infusion over a 46-hour period). If no greater than grade 3 FOLFIRI related AEs is observed after two cycles of each dose of irinotecan, the dose of irinotecan will be escalated in steps of 30 mg/ m². If any FOLFIRI related AEs greater than grade 3 are encountered, the dose of irinotecan will be reduced by 30 mg/ m² or back to the previous dose and be withheld at that dose at the next cycle. The maximal dose of irinotecan for subgroup 3 is 180 mg/ m².

All the treatment will be stopped in the event of patient withdrawal, disease progression, or unacceptable AEs, which are defined as non-hematological grade 4 AEs, no recovery from grade 3 AEs after two consecutive dose reductions or no recovery after a 2-week treatment delay.

Throughout the study period, participants should not receive other cytotoxic or biological treatments...
for mCRC. If concomitant treatments are considered necessary based on investigators’ discretion, product package insert should be referenced for contraindication and all concomitant treatments should be recorded on the relevant case report form (CRF) page.

**Outcome measurements**

**Primary outcome**

The treatment response will be radiologically assessed every 2 months through computed tomography, magnetic resonance imaging, or positron emission tomography. Objective responses were classified according to RECIST and optimal treatment responses will be recorded. The primary endpoint is PFS, which is defined as the time from initiation of study treatment to first radiological progression or tumor-related death, whichever comes first.

**Secondary outcome**

Secondary outcome will be as follows:

- **OS** is defined as the time from initiation of study treatment to death, due to any cause
- **DCR** is defined as percentage of patients, whose best response was not progressive disease [i.e. complete response (CR), partial response (PR) or stable disease (SD)]
- **Time to progression (TTP)** is defined as the time (days) from the start of study treatment to the first documented disease progression
- **Duration of treatment (DoT)** is defined as the time interval from the start of study treatment to the day of permanent discontinuation (including death); mean dose and reasons for treatment discontinuation or dose modification will be recorded

**Safety assessment**

The treatment-associated AEs will be assessed and recorded in each cycle using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

**Participant timeline**

Study is planned to start in May 2018 and is expected to end in May 2020, last for 2 years including recruitment, follow-up, data collection and data analysis. The schedule of study visits and assessments is summarized in Table 1.

**Sample size estimation**

Using a per-protocol two-sided α of 0.025, a 2:1 randomization between regorafenib plus FOLFIRI dose escalation and regorafenib, and a median progression free survival of 3.2 months in the regorafenib
group [9], the study would have 90% power to detect assumed median progression free survival 7.0 months with Regorafenib plus FOLFIRI [3]. The assumption of overall probability of events: 0.77 (10 progressions at the end of the study/ 13 in total) [9]. The calculated sample size is 121 patients. Considering 20% of drop rate, total of 153 patients would be enrolled into the study, assigned 102 in the study group (FOLFIRI plus regorafenib group) and 51 in the control group (regorafenib monotherapy group).

Recruitment

Participants will be enrolled from patients with mCRC, whose diseases are refractory to fluoropyrimidines, irinotecan, oxaliplatin, and monoclonal antibodies targeting vascular endothelial growth factor (VEGF); and monoclonal antibodies targeting epidermal growth factor receptor (EGFR) for those with KRAS wild-type cancers.

Assignment of interventions

Randomization and allocation

Before study initiation, a randomization sequence is computer generated (GraphPad statistical software, GraphPad, USA) and participants are allocated to either the study or the control group in 2:1 ratio in blocks of size 6 by an independent investigator.

Data collection, management, and analysis

Data collection methods

Table 1 shows details of data collection throughout the study period

Data management

An electronic CRF will be made available and for the assurance of the data accuracy, completeness, and reliability, the following procedures will be enforced:

Monitored if the data on CRF is accurate
Audited the clinical data regularly
Evaluated CRFs by visual review and standard computer editing to detect errors in data collection

To protect the safety of the subjects and to ensure the data accuracy, completeness and reliability, the research staff will preserve documented data from all sources on CRF, including laboratory test results, chart records, treatment conditions, physical examination, concomitant medication and any
Statistical methods

Results would be compared using Mann-Whitney U test or Kruskal-Wallis test for categorical unpaired data. The Wilcoxon rank-sum test or the Friedman test was used to analyze paired data. The Fisher’s exact test was used to compare dichotomous variables. The Pearson chi-square test was used to analyze nominal variables. The McNemar test was used to analyze paired categorical data. The means were compared using the 2-sample test and using analysis of variance (ANOVA) or linear regression, as appropriate. However, for all aforementioned inferential analysis methods, the center effect was not considered when comparing one treatment with another. Therefore, ANOVA incorporating the center effect and Cochran–Mantel–Haenszel test stratified by the center effect were applied to replace the 2-sample t-test and the Fisher’s exact test. For efficacy analyses and part of the safety analyses (including laboratory data and vital sign data), considering the effect of baseline data on the endpoints, analysis of covariance (ANCOVA) was applied when comparing one treatment mean with another, with their respective baseline as covariates. Baseline data were defined as the data obtained before the first administration of treatment before surgery. Endpoints were defined as the net change of post-treatment data from baseline data. Statistical analyses were conducted using SPSS 20.0 (SPSS, Chicago, IL, USA). P values less than 0.05 were statistically significant.

Data monitoring

All aspect of the study will be conducted under international conference on harmonization (ICH), good clinical practice (GCP) guidelines, and government regulations. Monitoring (by phone, fax, or on site) will be done by a representative of the study monitor designated by the investigators. The monitor will check CRFs for completeness and clarify, and crosscheck them with source documents. In addition to monitoring visits, frequent communications (letter, telephone, and fax), by the study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements. The investigators agree to all these monitors access to the clinical supplies, dispensing, and storage area, and to the clinical files of the study subjects, and if requested, agree to assist the monitor.

Interim analysis
No interim analysis will be performed.

**Adverse events**

All AEs including local and systemic reactions will be captured on the appropriate AE page of CRF. Information to be collected includes the event description, time of onset, clinicians’ assessment of severity, relation to study drugs (assessed only by those with the training and authority to make a diagnosis) and time of resolution or stabilization of the event. All AEs occurring while on study will be documented regardless of relationship to the study treatment. All AEs will be followed up until adequate resolution.

Pre-existing conditions will be recorded as medical histories. If the pre-existing condition does not change, it will not be recorded as an AE. Instead, if it deteriorates at any time during the study, it will be recorded as an AE.

All AEs will be graded for severity and documented the relationship to study treatment.

**Auditing**

In accordance with the principles of GCP, the study is subjected to internal audits. Domestic authorities and the institutional reviewing board may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents is guaranteed by the investigators, who provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection. Subject names are obliterated on the copies to ensure confidentiality. The purpose of the audits is to evaluate study conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements. The observations and findings will be documented.

**Consent**

Patients will be completely and openly informed, in terms that are understandable to them, of the objectives and constraints of the study, of the possible risks incurred, of the required measures of supervision and safety, of their right to refuse to participate in the study, and of the possibility of withdrawing their consent at any time.

All this information is contained in an information and consent form given to the patient. The patients’
free, informed and written consent will be collected by the investigator, or a doctor representing them prior to final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient; the investigator will keep the original.

Confidentiality

Only the patient number will be recorded in the CRF. The investigators maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

The blood samples collected for laboratory evaluation and genetic analysis will not be stored for future use.

Discussion

RTKs, such as VEGF receptor, EGFR, fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), RET and KIT, are responsible for several biological signaling pathways involve in regulation of angiogenesis, oncogenesis and tumor microenvironment [1]. Regorafenib is a small molecule that binds to and inhibits RTKs and therefore has antineoplastic activities. It is for this reason that regorafenib also has various AEs, including HFSR, hypertension, thrombocytopenia, proteinuria, diarrhea, mucositis, hepatotoxicity and so on. The most frequent grade 3 or higher AE related to regorafenib is HFSR, which results in dose reduction or interruption of treatment [2] and may limit the oncological efficacy of regorafenib. The occurrence of HFSR is even higher in Asian population [11]. Modification the dosing schedule (change from 160 mg dose given once daily, 21 days on, 7 days off to 120 mg daily, 28 days on with the same accumulated dose of 3360 mg in a cycle) still has high rates of grade 3 HFSR although it recovers sooner than the standard dosing schedule [9]. A Japanese study in which a dose reduction from 160 mg to 120 mg for 3 weeks in a 4 week cycle largely decreased the occurrence of grade 3 HFSR (75.0% in the 160 mg group and 16.7% in the 120 mg group) with comparable DCR (60.0% in the 160 mg group and 58.3% in the 120 mg group [4]. As the result, the dose of regorafenib administered in the present study will be 120 mg once daily for the first 3 weeks in each 4 week cycle.

*UGT1A1* activity is the main factor determines cytotoxicities and AEs of irinotecan and Food and Drug
Administration of the United States has approved *UGT1A1* genotyping to predict irinotecan induced severe diarrhea and neutropenia [12]. According to *UGT1A1* genotype, optimal dose of irinotecan can be achieved with balanced efficacy and toxicities for individuals. Lu *et al.*, which is an observational study demonstrated prognostic advantage of irinotecan dose escalation on basis of *UGT1A1* genotyping for mCRC treated with FOLFIRI plus bevacizumab [8] and an ongoing prospective randomized controlled clinical trial is conducted to examine the efficacy and safety of aforementioned treatment [10].

In our preliminary, retrospective and observational study, which 41 mCRC patients treated with regorafenib plus irinotecan dose escalated FOLFIRI as a third- or fourth-line setting were analyzed, median PFS was 6.0 months, median OS was 12.0 months and DCR was 58.5% [13]. Compared to CORRECT and CONCUR studies, the oncological outcomes were satisfactory and treatment-related adverse events were acceptable. To the best of our knowledge, there is no prospective study concerning reintroduction of irinotecan for patients with mCRC though, reintroduction of dose-escalated irinotecan for those previously treated with no irinotecan escalation may have the similar results.

This trial combines regorafenib, a targeted agent with irinotecan dose escalated FOLFIRI may provide an alternative salvage treatment for previously treated mCRC.

**Trial Status**

The trial is currently recruiting and the first patient was recruited on 1 April 2019. Recruitment will be completed approximately before 31 March 2021 and the trial is estimated to be ended in October 2021. The current protocol is version 1.0, created on 1 February 2019. Any noncompliance with the trial protocol, GCP or manual of procedures requirements will be addressed in study subject source documents and correction actions and/or protocol modifications will be developed and implemented promptly. All protocol modifications will be approved by institutional reviewing board and communicated to investigators and trial registries.

**Abbreviations**

*mCRC*: metastatic colorectal cancer; *VEGF*: vascular endothelial growth factor; *EGFR*: epidermal
growth factor receptor; RTK: receptor tyrosine kinase; PFS: progression-free survival; OS: overall survival; DCR: disease control rate; AE: adverse event; HFSR: hand-foot skin reaction; SN–38: 7-ethyl-10-hydroxycamptothecin; UGT: uridine diphosphate glucuronosyl transferase; 5-FU: 5-fluorouracil; LV: leucovorin; RECIST: Response Evaluation Criteria in Solid Tumors; ECOG: Eastern Cooperative Oncology Group; ULN: upper limit of normal; AST: Aspartate transaminase; ALT: alanine aminotransferase; PCR: polymerase chain reaction; GSTP1: glutathione S-transferase pi 1; IV: intravenous; CRF: case report form; CR: complete response; PR: partial response; SD: stable disease; TTP: time to progression; DoT: duration of treatment; ANOVA: analysis of variance; ANCOVA: analysis of covariance; ICH: international conference on harmonization; GCP: good clinical practice; FGFR: fibroblast growth factor receptor; PDGFR: platelet-derived growth factor receptor

Declarations

Acknowledgments

This manuscript was edited by Wallace Academic Editing.

Funding

This work was supported by grants through funding from the Ministry of Science and Technology (MOST107–2314-B–037–023-MY2), and the Kaohsiung Medical University Hospital (KMUH107–7R28, KMUH107–7R30, KMUH107–7M23). In addition, this study was supported by the Grant of Biosignature in Colorectal Cancers, Academia Sinica, Taiwan, R. O. C. No industrial support is involved.

Availability of data and materials

The anonymized participant data will be available for other researchers to apply to use one year after publication on request. Written proposals will be assessed by members of the trial steering committee and a decision will be made about the appropriateness of the use of data. A data sharing agreement will be put in place before any data will be shared.

Author contributions

All of the authors participated in the trial design. CJM wrote the study protocol and helped to draft the manuscript. CJM and TKC contributed to the statistical methods and the analysis. HLT carried out the molecular genetic studies. WCH participated in the design and coordination of the study. WCS and
YSY conceived of the study and participated in its design. YSY and YTC participated in the sequence alignment. JYW critically revised the manuscript. All of the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

In compliance with the Helsinki Declaration, central ethical approval has been confirmed from the Institutional Review Board of Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan (ref approval no. KMUHIRB-F(II)-20190032) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained. Written informed consent will be obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1.Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schutz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. International journal of cancer. 2011;129(1):245-55.

2.Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

3.Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2015;16(6):619-29.

4.Osawa H. Response to regorafenib at an initial dose of 120 mg as salvage therapy for metastatic colorectal cancer. Molecular and clinical oncology. 2017;6(3):365-72.
5. Mathijssen RH, van Alphen RJ, Verweij J, Loos WJ, Nooter K, Stoter G, et al. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). Clinical cancer research: an official journal of the American Association for Cancer Research. 2001;7(8):2182–94.

6. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet. 1996;347(9001):578–81.

7. Iyer L, King CD, Whittington PF, Green MD, Roy SK, Tephly TR, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. The Journal of clinical investigation. 1998;101(4):847–54.

8. Lu CY, Huang CW, Hu HM, Tsai HL, Huang CM, Yu FJ, et al. Prognostic advantage of irinotecan dose escalation according to uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotyping in patients with metastatic colorectal cancer treated with bevacizumab combined with 5-fluorouracil/leucovorin with irinotecan in a first-line setting. Translational research: the journal of laboratory and clinical medicine. 2014;164(2):169–76.

9. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.

10. Yeh YS, Tsai HL, Huang CW, Wang JH, Lin YW, Tang HC, et al. Prospective analysis of UGT1A1 promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab plus FOLFIRI as the first-line setting: study protocol for a randomized controlled trial. Trials. 2016;17:46.

11. Yoshino T, Komatsu Y, Yamada Y, Yamazaki K, Tsuji A, Ura T, et al. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Investigational new drugs. 2015;33(3):740–50.

12. Cecchin E, Innocenti F, D’Andrea M, Corona G, De Mattia E, Biasoin P, et al. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009;27(15):2457–65.
13. Ma CJ, Huang CW, Chang TK, Tsai HL, Su WC, Yeh YS, et al. Oncologic Outcomes in Metastatic Colorectal Cancer with Regorafenib with FOLFIRI as a Third- or Fourth-Line Setting. Translational oncology. 2019;12(3):502-12.

Table 1. Schedule of visits and assessments

| Assessment/Procedure | Enrollment | Allocation | Clinical regimen |
|----------------------|------------|------------|------------------|
| Eligibility screen   | X          |            |                  |
| Informed Consent     |            | X          |                  |
| Randomization        |            | X          |                  |
| Demographic and medical history | X |            |                  |
| Cancer treatment history |             | X          |                  |
| Tumor assessment: carcinoembryonic antigen (CEA), and computed tomography (CT) or magnetic resonance imaging (MRI) | X |            | X                |
| ECOG performance status | X          |            | X                |
| Urinalysis           | X          |            | X                |
| Hematology           | X          |            | X                |
| Clinical chemistry   | X          |            | X                |
| Creatinine clearance (calculated) | X |            | X                |
| Physical examination and vital signs | X |            | X                |
| Weight and height    | X          |            | X                |
| Concomitant medications | X          |            | X                |
| Adverse Events       | X          |            | X                |
| Study drug administration |            | X          |                  |
| Survival and tumor status/other anticancer treatment | | |                  |
Figure 1

Flow diagram of this study. Iri, irinotecan; AE, adverse event; Gr, grade

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
SPIRIT-Checklist-download-8Jan13.docx