A randomized clinical trial to test whether the use of bevacizumab as part of second-line therapy improves colorectal cancer survival

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GROUP 1

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Abbreviation:

CRC: Colorectal cancer
FOLFIRI: Irinotecan, bolus fluorouracil, and leucovorin (IFL), leucovorin calcium, fluorouracil, and irinotecan
FOLFOX (folinic acid, fluorouracil, oxaliplatin)
5-FU: 5- fluorouracil
LV: Leucovorin
HR: Hazard Ratio

Note for Prof. Trivedi: Red colored font refers to changes made to the previous version of this document (deliverable 4). For each of the sections of this protocol (sections 1, 2 and 3), work was divided evenly among individual members. All members made intellectual edits to all sections and approved the final submission.

1.1 Background

Colorectal cancer (CRC), also known as colon cancer, is a condition characterized by the abnormal growth of cells in the colon and or the rectum (the final parts of the gastrointestinal tract). CRC is one of the top 3 most common cancers and it is the 4th leading cause of mortality among cancers worldwide [1]. In 2022, an estimated 104,610 new cases of colon cancer and 43,340 new cases of rectal cancer were be diagnosed in the United States [2]. CRC is almost always proceeded by noncancerous growth from the mucosal layer, polyps. Factors such as advanced age, inflammatory bowel diseases, alcohol and tobacco consumption, family history, and genetic syndromes like Lynch syndrome contribute to the risk of developing CRC. CRC commonly presents with bleeding from the rectum, blood in stool, dark stools, cramping, constipation, and an urge to pass stool although the bowel is empty. CRC stage is determined clinically but the later stage is characterized by the involvement of other organs, commonly the liver [3]. Earlier stages of CRC can be effectively treated with surgery with relatively good survival, however, for the later stages (stage IV), chemotherapy has become the main treatment modality. This is so because most patients have

metastases that render surgical intervention ineffective. Metastatic CRC patients have a poor prognosis where the median survival time is 5-6 months [4].

Angiogenesis, the process of forming new blood vessels, plays a crucial role in tumor growth and is a complex, multi-step process. Vascular Endothelial Growth Factor (VEGF) is a glycoprotein that is produced by both healthy and cancer cells and is a key factor in promoting angiogenesis in both normal physiological conditions and pathological conditions such as tumor progression. VEGF-A, also known as VEGF, is recognized as the primary mediator of tumor angiogenesis. Studies have shown that higher levels of VEGF are associated with increased micro vessel density, higher incidence of metastasis, poor overall survival (OS) in patients with CRC [5] and decreased apoptotic index (apoptosis is programmed cell death). The apoptotic index is often used as a marker to evaluate the success of the treatment. It is measured by the number of apoptotic cells divided by the total number of carcinoma cells multiplied by a hundred. Bevacizumab, a recombinant humanized monoclonal antibody, targets VEGF-A and binds to all isoforms of VEGF-A with high affinity.

The cure rate of CRC is directly correlated with the stage of the illness with later stages having the worst prognosis. Traditionally, chemotherapeutic agents such as fluorouracil and leucovorin are used together for treatment of stage IV colorectal cancer improving survival times between 8.5-18 months [6]. Currently, several other chemotherapies, including irinotecan, oxaliplatin and capecitabine, are being used to treat advanced CRC. The standard treatment for stage IV CRC is known as FOLFIRI which is a combination of fluorouracil, leucovorin calcium (folinic acid) and irinotecan hydrochloride administered as a slow intravenously infusion of folinic acid and

irinotecan and bolus of fluorouracil [7]. Another common chemotherapy regimen is irinotecan, 5-fluorouracil bolus and leucovorin [8].

A 2008 observational study (BRiTE: Bevacizumab Regimens: Investigation of Treatment Effects) of 1445 patients compared overall survival and progression free survival depending on whether patients received therapy including bevacizumab or not [9]. The study compared patients who received no post disease progression (PD) therapy to those who received therapy but no bevacizumab post PD (no BBP) to those who received therapy containing bevacizumab (BBP). The Median OS was 25.1 months (95% CI, 23.4 to 27.5 months), and median progression-free survival was 10.0 months in the overall study. Median OS rates were 12.6, 19.9, and 31.8 months in the no post-PD treatment, no-BBP, and BBP groups, respectively. When no-BBP was compared to BBP, BBP was independently associated with improved survival (HR, 0.48; $p<0.001$). The addition of bevacizumab to these therapy regimens in the management of colon cancer has been shown to improve patient survival. The topic of bevacizumab beyond initial progression is a topic of hot debate with some RCTs showing no benefit in progression-free survival (PFS). In a study by Carmen *et. al.*[10], 2672 patients with stage II and III CRC were randomized to receive either bevacizumab administered at a dose equivalent to 5 mg/kg in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356), the hazard ratio for PFS was 0.89 (95% CI, 0.76 to 1.04; $p = .15$) [10]. A recent systematic review of 11 RCTs with totalling 3178 patients with advanced colorectal cancer demonstrated that the objective response rate (odds ratio [OR]=3.15, 95% confidence intervals [CI]: 2.25–4.40, $P<.001$) and cancer control rate (OR=2.73, 95% CI: 1.91–3.90, $P<.001$) of the bevacizumab group were higher than that of no bevacizumab group [11].

1.2 Rationale

The use of bevacizumab–based treatment is an important part of first-line therapy for metastatic colorectal cancer. In addition to its success in improving survival rates for patients with advanced colorectal cancer as a first-line treatment, one study showed that median overall survival increased from 19.9 months (95% CI: 18-22) among those who did not receive bevacizumab to 31.8 months (95% CI: 27.9-NA) among those who received bevacizumab [12]. All participants between these two groups used bevacizumab as a first-line therapy and continued using the drug after the first investigator assessment of disease progression.

Kohne *et al.* [13] is one of several groups that demonstrated that using irinotecan along with the fluorouracil and leucovorin regimen (FOLFIRI) for metastatic CRC meant the median progression-free survival time (PFS) increased to 8.5 months (95% CI: 7.6 - 9.9 months) compared to 6.4 months (95% CI: 5.3 - 7.2 months) for the control group who received FU and LV only ($p<.0001$; HR = 0.65; 95% CI: 0.53 - 0.79)[13]. Although this statistically significant difference observed for PFS was not observed for overall survival ($p=.2779$; HR: 0.88; 95% CI: 0.70-1.11), several studies have shown that when bevacizumab is combined with different fluorouracil-based regimen (FOLFIRI, IFL or simply fluorouracil and leucovorin), there is an increase in survival metrics across the board (progression free survival, response rates, overall survival and duration of response) [14-16]. In a retrospective observational study performed by Lopez *et al.* the median progression-free survival time for patients who were administered bevacizumab with FOLFIRI was 10.6 months (95% CI: 9.8-11.3) while an overall response was observed in 50.5% (95% CI: 40.1 - 60.9) (complete response (CR) + partial response (PR)) of patients with CR occurring in 8.4% (95% CI: 3.7 - 15.9) of those cases. Taken together, these results demonstrate that

bevacizumab combined with any of the fluorouracil-based regimens is effective at improving survival among metastatic CRC patients and is a suitable therapeutic candidate for second –line therapy.

The objective of this study is to investigate whether incorporating bevacizumab into second-line therapy along with FOLFIRI can improve progression-free survival (PFS) in patients suffering from metastatic colorectal cancer. The choice of only including patients 50 years of age and older is justified given that most CRC cases are usually 50 years and older with the median age at onset being 67 years old. In fact, only about 12% of cases in the United States are expected to occur among individuals under 50 years old [2]. Both FOLFIRI and IFL when combined with bevacizumab have similar high efficacy and are considered relatively safe for CRC treatment [8], therefore the choice to use FOLFIRI in this trial is due to the desire to investigate any change in PFS and OR when bevacizumab is added to this standard of care treatment.

1.3 Risks and Benefits

Benefits

A randomized controlled trial demonstrated that the addition of bevacizumab to the IFL regimen for previously untreated metastatic colorectal cancer patients resulted in a significant improvement in both progression-free survival (PFS) and overall survival (OS). Specifically, patients who received IFL/bevacizumab had a median PFS of 10.6 months, which was significantly longer than the 6.2 months observed in the IFL/placebo arm (HR disease progression, 0.54; $P < .001$). The IFL/bevacizumab arm also had a median OS of 20.3 months, which was significantly longer than the 15.6 months observed in the IFL/placebo arm (HR death , 0.66; $P < .001$) [17]

Bevacizumab in combination with 5-FU and irinotecan, is well tolerated by patients. Hence, we anticipate that it will improve the overall survival of patients and produce a consistent result.

Risks

Possible serious side effects of bevacizumab [18]:

- **GI perforation.** Symptoms include pain in your abdomen, nausea, vomiting, constipation, or fever
- **Abnormal passage in the body.** A fistula—an irregular connection from one part of the body to another and can sometimes be fatal
- **Wounds that don't heal.**
- **Serious bleeding.** Includes vomiting or coughing up blood; bleeding in the stomach, brain, or spinal cord; nosebleeds; and vaginal bleeding. If you recently coughed up blood or had serious bleeding.
- **Severe high blood pressure.** Blood pressure that severely spikes or shows signs of affecting the brain. Blood pressure should be monitored every 2 to 3 weeks while on Avastin and after stopping treatment
- **Kidney problems.** These may be caused by too much protein in the urine and can sometimes be fatal
- **Infusion-related reactions.** These were uncommon with the first dose (less than 3% of patients). 0.4% of patients had severe reactions. Infusion-related reactions include high blood pressure or severe high blood pressure that may lead to stroke, trouble breathing, decreased oxygen in red blood cells, serious allergic reactions, chest pain, headache, tremors, and excessive sweating. Your doctor or nurse will monitor you for signs of infusion-related reactions

- **Severe stroke or heart problems.** Includes blood clots, mini-stroke, heart attack, chest pain, and your heart may become too weak to pump blood to other parts of your body (congestive heart failure). These can sometimes be fatal
- **Nervous system and vision problems.** Signs include headache, seizure, high blood pressure, sluggishness, confusion, and blindness.

Contraindications:

- **Undergoing surgery.** Avastin should not be used for 28 days before or after surgery and until surgical wounds are fully healed
- **Pregnant or think you are pregnant.** Data have shown that Avastin may harm your unborn baby. Use birth control while on Avastin. If you stop Avastin, you should keep using birth control for 6 months before trying to become pregnant
- **Planning to become pregnant.** Taking Avastin could cause a woman's ovaries to stop working and may impair her ability to have children
- **Breastfeeding.** Breastfeeding while on Avastin may harm your baby, therefore, women should not breastfeed during and for 6 months after taking Avastin

Efficiency and safety data *:*

Grothey et. al. [9] in his study evaluated the safety and effectiveness of bevacizumab along with chemotherapy on patients who have untreated mCRC. His evaluations were based on Earlier reports from Investigation of Treatment Effects and Safety (BRiTE) that domostrated a median PFS of 10.0 months (95% CI, 9.7 to 10.4 months) and a median OS of 25.1 months (95% CI, 23.4 to 27.5 months).

Thus, we can say that use of bevacizumab in end-stage colorectal cancer is intended to improve patient survival, it is crucial to evaluate the potential risks and adverse effects of this treatment when used in combination with other drugs for first- and second-line treatments [12].

2.1: Study Design

This is a large, US-based randomized controlled unblinded clinical trial that is planned to be conducted in 22 months. The study will be conducted at 10 sites (hospitals) specializing in the treatment of colorectal cancer. These centers should have the necessary infrastructure needed for patient follow-up, out and in patient care services. Experienced healthcare professionals and storage and logistics operations are also required to carry out the trial effectively. To identify the information needed to achieve the objectives of the trial the oncologists from the 10 sites will review the clinical records of the patients with at least 10 cycles of the first line of treatment previous stage.

Participants will be randomly assigned to receive either FOLFIRI or FOLFIRI + bevacizumab in a 1:1 ratio. Folinic acid and Irinotecan will be given intravenously at a dose of 20mg/m^2 and 125mg/m^2, Fluorouracil will be given in a divided dose of 250mg/m^2 intravenously and 250mg/m^2 as a slow bolus. For the treatment arm, Bevacizumab will be given as a bolus in addition to the Fluorouracil at a dose of 5mg/kg.

After screening, participants will be randomized with equal allocation to treatment and control arms. This will be followed by collection of baseline information and clinical assessment of tumor size and location. Treatment in the control arm will be given once weekly for 6 weeks every 8 weeks while bevacizumab will be given once every 3 weeks to those in the treatment arm in addition to FOLFIRI. We will administer up to 10 cycles of chemotherapy.

Post baseline, participants will be evaluated every 6 weeks from the start of each cycle of FOLFIRI till the end of the study at 22 months.

Furthermore, patients will be recruited independent of the primary tumour location.

Assessment of efficacy: The assessment of the efficacy of FOLFIRI + bevacizumab combination will be done by the investigators according to the RECIST version 1.1 (see Appendix A) criteria. All the patients should have one computed tomography (CT) at baseline and at each follow up visit to assess progression of the disease.

Assessment of safety: The safety of FOLFIRI and bevacizumab combination will be assessed based on the data collected from the medical charts about the number and kind of toxicities experienced by the patients in the study. The severity of toxicities will be evaluated according to the toxicity criteria at the National Care Institute (NCI-CTC).

The study protocol will be reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the respective study sites before initiation. Informed consent will be obtained from all the study participants. The trial will be conducted following the principles of Good Clinical Practice (GCP) in accordance with the local regulations.

2.2: Objectives

The primary objective of this randomized controlled trial is to demonstrate the superiority of the addition of bevacizumab along with FOLFIRI, into second-line therapy for CRC among Bevacizumab naïve patients aged 50 years or above. The primary outcome is to improve the progression-free survival (PFS) of the subjects who have experienced the progression of disease after failure of the first line of therapy by delaying the event of progression of colorectal tumor size or death. The study is conducted over a period of 96 weeks (22 months).

The secondary objective of the study is to compare the overall response rate (ORR) between FOLFIRI + Bevacizumab and FOLFIRI groups in patients with metastatic colorectal cancer aged 50 years and above which will be measured by the proportion of patients who have complete or partial response based on the imaging techniques and Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 guidelines (see Appendix A).

The study will enroll patients with metastatic colorectal cancer who have received the first-line treatment of chemotherapy. The patients will be randomized to receive the second-line chemotherapy regimen of FOLFIRI with Bevacizumab in one arm and compared with FOLFIRI in the other arm in metastatic colorectal cancer.

2.3: Endpoints

2.3.1 Primary Endpoint

The primary endpoint will be progression free survival (PFS) which will be measured from the date of initiation of second-line treatment (date of randomization) to the first observation of disease progression as determined by the investigator using radiographic assessment methods or death from any cause. The Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1 (see Appendix A) are the guidelines used when assessing patients for disease progression [19]. PFS has a lead time advantage (treatment effect can be observed quicker) over overall survival, therefore making it a suitable clinical endpoint for metastatic CRC.

Patients will be censored if they are lost to follow-up, alive at the end of the study or if the disease has not progressed as observed at the last visual assessment of the tumor status.

The Null hypothesis (H0) is that there is no statistically significant difference in progression free survival between standard treatment FOLFIRI group and FOLFIRI + bevacizumab group.

The Alternate Hypothesis (HA) is that there is a difference in PFS between FOLFIRI and FOLFIRI+ bevacizumab group indicating that the addition of Bevacizumab to FOLFIRI provides a superior outcome compared to the FOLFIRI alone.

2.3.2 Secondary Endpoint

The secondary endpoint will be overall response rates (ORR). ORR is divided into complete response (CR) and partial response (PR). According to the RECIST version 1.1 (see Appendix A) CR requires a complete disappearance of the disease after 4 weeks while PR requires at least a 30% decrease in tumor size from baseline also confirmed after 4 weeks [20]. However, for our study, we will evaluate the end points using CT scans done at 6 weeks follow up interval till the end of the study at 22 months. Tumor size will be assessed by the investigator using computed tomography as per the RECIST version 1.1guidelines (see Appendix A) [21]. The best overall response (BOR) is defined as the best response recorded from the beginning of treatment to the end of the study including the requirement for confirmation. A response is only considered genuine if it is confirmed after repeat measurements conducted every 6 weeks. BOR will be summarized by response category in tabular form as shown in table 3 of section 4.4.3 of the RECIST version 1.1 guidelines and will be assessed by the investigator (see Appendix A).

The Null hypothesis (H0) is there is no difference in overall response rates between the standard treatment FOLFIRI group and FOLFIRI + bevacizumab group.

The Alternate Hypothesis (HA) is that there is a difference in overall response rates between the FOLFIRI and FOLFIRI+ bevacizumab group indicating that the addition of Bevacizumab to FOLFIRI provides a superior outcome compared to the FOLFIRI alone.

2.4: Allocation of Intervention

		Dose	Schedule
Arm 1	Folinic acid (Leucovorin)	20 mg/m^2 IV	Given once weekly for 6 weeks every 8 weeks
	Fluorouracil	500 mg/m^2 IV	
	Irinotecan	125 mg/m^2 IV	
Arm 2	FOLFIRI		
	+ Bevacizumab	5 mg/kg IV	Every 3 weeks

Patients in the comparison group (Arm 1) will be administered FOLFIRI, which is a combination of Folinic acid, Fluorouracil, and Irinotecan. The dosage for the patients in this group will be as follows: Folinic acid will be given intravenously at a dose of 20mg/m^2, Fluorouracil will be given intravenously at a dose of 500mg/m^2, and Irinotecan will be given intravenously at a dose of 125mg/m^2. Leucovorin and fluorouracil will be administered as bolus, followed by fluorouracil and Irinotecan infusion based on patient's weight. [22] We are planning to administer drugs through a take-home infusion pump. The patient can leave the center with the pump and return after two days to have it removed. This method of drug delivery is considered the most comfortable and helps to reduce the hospital stay, making it more convenient for the patient. However, if the patient is too ill to receive treatment on an outpatient basis, then the medication will be administered in a hospital setting.[23]

In the treatment arm (Arm 2), patients will receive the same treatment as in the first group, but with the addition of bevacizumab. Bevacizumab will be administered at 5 mg/kg every 3 weeks in combination with fluorouracil and Irinotecan as infusion followed by leucovorin and fluorouracil bolus. The bevacizumab treatment will be given every once every 3 weeks until the study endpoints are reached. Folinic acid, Fluorouracil and bevacizumab have similar packaging and all the drugs are colourless fluids.

The allocation ratio for both treatment arms will be 1:1, which means that participants will be randomly assigned to either the FOLFIRI group or the FOLFIRI + Bevacizumab group, with an equal number of participants in each group. After written informed consent has been obtained, the study site will register/randomize the participant via an interactive voice and/or web-based response system (IxRS), which will allocate a unique subject identifier and the subject's unblinded treatment group. Subjects screened but not randomized for any reason have to be registered as Screening Failure in IxRS.

2.5: Inclusion and Exclusion Criteria

To be eligible for this study an individual must satisfy all the following criteria:

- Willing to provide a signed and dated informed consent form
- Participants must be willing to comply with all study procedures and be available for the duration of the study or until death/lost to follow-up (whichever comes first)
- Participants must be at least 50 years of age
- Participants must have a histological diagnosis of metastatic colorectal cancer (stages 3 or 4) according to RECIST version 1.1 (see Appendix A)
- Disease must have progressed after at least 10 cycles of the first line chemotherapy
- Participants must have an Eastern Cooperative Oncology Group (ECOG) Performance status ≤ 2 (see Appendix B)
- Ability to accept medication intravenously and be willing to adhere to the medication regimen

Participants will be excluded from the study if any of the following criteria are satisfied:

- Those who received bevacizumab as a first line therapy
- Active bacterial or viral infections in 2 weeks prior to starting the dosing regimen

- Symptomatic brain metastases

2.6: Sample Size

The sample size calculated based on primary endpoint (progression free survival):

Index	Two-sided alpha	hazard ratio (λc/λi)	Nominal Power	Total N	Total N Adjusted for 20% drop out rate
1	0.05	0.48	0.9	40	50
2	0.05	0.54	0.9	55	69
3	0.05	0.48	0.95	69	86
4	0.05	0.54	0.95	49	61
5	0.05	0.48	0.8	44	55
6	0.05	0.89	0.8	1716	2145
7	0.05	0.48	0.8	30	38
8	0.05	0.54	0.8	42	53
9	0.05	0.75	0.98	388	485
10	0.05	0.89	0.98	2368	2960

The hazard ratio (HR) values of 0.48 was selected in accordance with study by Grothey, A., et al.[9]. The hazard ratio (HR) of 0.54 was selected in accordance with study by Hurwitz et al. [24] and the hazard ratio (HR) of 0.89 and 0.75 was selected based on a study and analysis by Leonard B. Saltz et al. [25].

The total sample size required to observe a hazard ratio of 0.75 for the Bevacizumab + FOLFIRI arm at the α=0.05 significance level and power=98%, is 388 in total, i.e 194 patients for each intervention arm accounting for 20% dropout rate as depicted in the table above.

The formula used for sample size calculation: (Total) $N = 2(Z_a + Z_b)^{\wedge 2} / [\ln(\lambda c/\lambda i)]^{\wedge 2}$

The calculation for sample size measurements were calculated on excel sheet and a table was generated.

2.7: Statistical Analysis

This study will utilize a parallel arm design to assess the impact of the treatment arms: FOLFIRI alone and the FOLFIRI + bevacizumab arm.

Demographic characteristics (age, sex, race/ethnicity etc.) and baseline disease characteristics (ECOG Performance Status, years since diagnosis, location of metastatic sites) will be compared between the treatment and control group in a table using descriptive statistics.

2.7.1 Primary Endpoint

The Null hypothesis (H0) is there is no statistically difference in progression free survival between standard treatment FOLFIRI group and FOLFIRI + Bevacizumab group.

H_0: $\lambda_{FOLFIRI} = \lambda_{FOLFIRI+Bevacizumab}$

The Alternate Hypothesis (HA) is that there is a difference in PFS between FOLFIRI and FOLFIRI+ Bevacizumab group indicating that the addition of Bevacizumab to FOLFIRI provides a superior outcome compared to the FOLFIRI alone.

H_A: $\lambda_{FOLFIRI} \neq \lambda_{FOLFIRI+Bevacizumab}$

Kaplan Meier (KM) curves will be plotted to estimate the median PFS along with two-sided 95% CIs. Stratified Log-rank tests (α=0.05, two-sided) will be the objective test of difference in PFS between the two intervention groups where we will test the null hypothesis that all survival curves are the same. KM methodology would be conducted under the assumption that censoring is non-informative. This means that study participants who are censored have the same risk of an

event as those who continued to be followed [26]. Individuals are censored if they are lost to follow-up or have not experienced disease progression at the end of study (22 months).

A stratified Cox Proportional Hazards (PH) model will be used to compare the hazards ratio between the bevacizumab + FOLFIRI group and the FOLFIRI only group. The proportional hazards assumption states that the ratio of hazards between two individuals is constant. For variables in violation of this assumption, a stratified Cox PH model is suitable for analysis. Stratification analysis will include the following variables: number of metastatic sites, ECOG performance status and site of primary disease (colon, rectum). The stratified Cox model is shown below:

$$h_{og}(t,X) = h_{0g}(t)\exp[\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4]$$

Where g denotes the stratum number, β represents the regression coefficient and X represents the predictor variables: randomization group, ECOG performance status, number of metastatic sites and site of primary disease.

2.7.2 Secondary Endpoint

The Null hypothesis (H0) is there is no difference in overall response rates between the standard treatment FOLFIRI group and FOLFIRI + bevacizumab group.

The Alternate Hypothesis (HA) is that there is a difference in overall response rates between the FOLFIRI and FOLFIRI+ bevacizumab group indicating that the addition of Bevacizumab to FOLFIRI provides a superior outcome compared to the FOLFIRI alone.

Let p1 be the overall response rate in the standard treatment FOLFIRI group, and p2 be the overall response rate in the FOLFIRI + Bevacizumab group.

H_0: p1 - p2 = 0 (There is no difference in overall response rates between the two groups)

H_A: p1 - p2 ≠ 0 (There is a difference in overall response rates between the two groups)

The endpoint of interest will be the difference in overall response rate (ORR=CR+PR) between FOLFIRI and FOLFIRI +bevacizumab treated groups in patients with metastatic colorectal cancer (mCRC). The Chi-square test will be used to compare different response categories between the two groups at an $\alpha = 0.05$ significance level. Baseline characteristics included age, gender, tumor size, and stage. Response rate will be assessed using RECIST version 1.1 guidelines (see Appendix A).

Descriptive statistics would also be documented for patients whose achieve a BOR of PR or CR as assessed by the investigator. This determination (patient achieves PR of CR) will be made at the end of the study based on the assessments at the first time point and subsequent assessments every 6 weeks from the start of each cycle.

3.1: Schedule of Participant Visits

Trial Duration

All patients will receive trial treatment for 22 months post randomization depending on the study arm assigned. After 22 months, they will be able to continue treatment with Bevacuzimab if there is clinical benefit, at the discretion of the treating Investigator, and their response will be reassessed after 8 week intervals till 130 weeks post randomization (34 weeks post trial end). The last patient visit will be 14 days after the last administration of trial treatment. Recruitment will be carried out over 6 months at 10 trial centers.

3.1.1 Baseline

Informed Consent

Informed consent form (ICF) may be obtained before randomization and prior to any protocol required procedure (i.e., Baseline), which is not performed as part of local site standard of care. Signed ICF to be obtained within 30 days of randomization. Signed and dated ICFs for all

screened participants, even for those who are not subsequently randomized, must be maintained at the study site. All eligibility criteria must be confirmed prior to randomization.

Medical History

Demographic and Medical history includes clinically significant diseases that are currently active or that were active within the previous 5 years and previous rounds of chemotherapy, (major) surgeries with special emphasis gastroenterology and urinary and reproductive surgeries, and fracture history. Demographic data will include age at time of randomization, marital status, level of education, smoking status, alcohol use, and self-reported race/ethnicity.

Physical Examination

All physical examinations should be performed by a physician or registered nurse or other qualified health care provider according to site regulations and standard of care. Each physical examination will include assessment of vital signs (temperature, heart rate, blood pressure, O2 saturations and respiratory rate), oral status, height (during baseline only), weight, ECOG performance status. Clinically significant findings should be captured in the participant's medical history.

CT scan and blood samples [27]

CT scans will be performed at baseline and or before randomization to ascertain the stage of CRC. Baseline samples of blood will be drawn to get hematological investigations including hemoglobin levels, white and red cell counts, liver, renal and thyroid function tests. The blood work will be performed as part of the standard of care at the different sites per site schedule.

3.1.2 Treatment visits

Participants will be administered treatment at the primary cancer care center. The treatment will be shipped to the care centers with the unique participant identifier. The drugs will be shipped to the center in monthly batches. For participants who are ably ambulatory with home care nurses, they will be allowed to go home with drug infusions. The participants who are unable to go home with infusions, they will be administered the drugs at the treatment site under monitoring of study personnel. After baseline and randomization, patients will be scheduled to receive the allocated treatment within a 2 week window.

Control arm: FOLFIRI will be administered once weekly for 6 weeks every 8 weeks. The cycle will repeat for a total of 12 cycles (22 months).

Treatment arm: In addition to FOLFIRI, bevacizumab will be administered once every 3 weeks for the same duration as participants in the control arm. A cycle for the treatment arm arm will be FOLFIRI will be administered once weekly for 6 weeks every 8 weeks and bevacizumab given at week 3 and week 6 of this 8 week cycle.

3.1.3 Follow-up visits

Participants' follow-up visits will be scheduled for 6 weeks from initiation of treatment during the 22 months of the study. The rationale behind scheduling follow-up visits every six weeks is that the administration of FLOFIRI occurs once a week for a duration of six weeks. By the end of these six weeks, one complete cycle of FLOFIRI and two cycles of FLOFIRI + BEV will have been completed. Conducting follow-up scans at the conclusion of the treatment cycles will aid in assessing the efficacy of the therapy. At each follow-up visit, participant updates will be collected. For the control arm, this corresponds to completion of a treatment cycle which aligns

with the RECIST version 1.1 guidelines. However, for the treatment arm, this corresponds to 1 cycle of FOLFIRI and 2 doses of bevacizumab.

Update on Medical History and Demographic data

At the 30, 54 and 78 weeks' visit, participants will be asked for updates on medical illness and drugs being taken. Any other changes from the previous visit will be captured. Updates to demographic data will include physical activity, smoking habits and alcohol use.

Physical Examination

During each follow up visit, a physical examination will be performed before administration of due chemotherapy. All physical examinations should be performed by a physician or registered nurse or other qualified health care provider according to local regulations. Each physical examination will include assessment of vital signs (temperature, heart rate, blood pressure, O2 saturations and respiratory rate), oral status, height (during baseline only) ,weight, ECOG performance status.

CT scan and blood samples will be performed at each follow up visit.

Visit (Week) **Procedures**	Enrolment/ Baseline (visit1)*	6 weeks	14 weeks	22 weeks	30 weeks	38 weeks	46 weeks	54 weeks	62 weeks	70 weeks	78 weeks	86 weeks	94 weeks	Weeks***
Informed Consent	x													
Demographics	x				x			x			x			
Medical history	x				x			x			x			
Randomization	x	x												
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood work	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CT scan	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Treatment **	x	x	x	x	x	x	x	x	x	x	x	x	x	x

* Screening, randomization and filling the ICF will occur before any study procedure
** Treatment is given weekly for 6 weeks then 2 weeks rest before starting another cycle for both arms.
*** assessment after trial completion if bev is found to be effective. Check ups 8 week intervals till 130 weeks post randomization (34 weeks post trial end).

3.1.4 Treatment Compliance.

The local trial pharmacist will be responsible for maintaining and updating the drug accountability log in the pharmacy file. All unused bottles of any of the trial drugs at the end of treatment visit will be returned to the trial pharmacist who will document any unused medication.

3.1.5 End of trial:

The end of trial will be the last patient's last visit (2 weeks from the last treatment). The Trials Office will notify the main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

3.2: Evaluation Plan for the Primary Endpoint

The primary end point, PFS, will be assessed using CT scans at baseline as a reference. PFS will be measured from the date of initiation of second-line treatment (date of randomization) to the first observation of disease progression as determined by the investigator using radiographic assessment methods or death from any cause. According to RECIST criteria version 1.1 (see appendix A), disease progression is identified as at least a 20% increase in the sum of the longest diameter of the target lesions and an absolute increase of 5mm or the appearance of new lesions. Site study radiologists will be responsible for radiographical staging and monitoring of disease progress. For sensitivity analysis, the study will randomly assign de-identified CT scans of 20% of the participants to non-study radiologists and compare the reading with those of the study radiologists. In case of disagreement, a third independent radiologist will be used as a tie breaker.

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Appendix A

See the summary of RECIST version 1.1 criteria below relevant to this protocol. For additional information see the full criteria list here:
https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

- Measurability of tumor at baseline: see sections on Measurable (section 3.1.1) and No-measurable tumors (section 3.1.2)
- Specification by methods of measurements (section 3.2) with special attention paid to guidelines for CT scan measurements
- Baseline documents of ‘target’ and ‘non-target' lesions (section 4.2)
- Response criteria (section 4.3) including the definitions of complete response, partial response, progressive disease and stable disease for both target and non-target lesions
- Evaluation of best overall response (section 4.4)

Appendix B

Table 1: Table showing the descriptions of each of the ECOG Performance Status grades

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead