ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: June 28, 2019

ClinicalTrials.gov ID: NCT01298570

Study Identification

Unique Protocol ID:	LCCC 1029
Brief Title:	Regorafenib+FOLFIRI Versus Placebo+FOLFIRI as 2nd Line Tx in Metastatic Colorectal Cancer
Official Title:	Multi-Center, Randomized, Placebo-Controlled Phase II Study of Regorafenib in Combination With FOLFIRI Versus Placebo With FOLFIRI as Second-Line Therapy in Patients With Metastatic Colorectal Cancer
Secondary IDs:	10-2176 [UNC IRB]

Study Status

Record Verification:	June 2019
Overall Status:	Active, not recruiting
Study Start:	April 7, 2011 [Actual]
Primary Completion:	November 15, 2016 [Actual]
Study Completion:	July 2, 2020 [Anticipated]

Sponsor/Collaborators

Sponsor:	UNC Lineberger Comprehensive Cancer Center
Responsible Party:	Sponsor
Collaborators:	Bayer

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	

Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	Yes
IND/IDE Information:	FDA Center: CDER IND/IDE Number: 110556 Serial Number: 000 Has Expanded Access: No
Human Subjects Review:	Board Status: Approved Approval Number: 10-2176 Board Name: Office of Human Research Ethics Board Affiliation: University of North Carolina, Chapel Hill Phone: 919-966-3113 Email: IRB_subjects@unc.edu Address: Medical School Building 52 105 Mason Farm Road Chapel Hill, NC 27599-7097
Data Monitoring:	Yes
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	This randomized (2:1), multi-center, placebo-controlled, phase II efficacy study is designed to compare PFS between regorafenib + FOLFIRI chemotherapy (ARM A) versus placebo + FOLFIRI (ARM B) in patients with mCRC previously treated with a FOLFOX regimen.
Detailed Description:	This randomized (2:1 ratio), multi-center, placebo-controlled, phase II efficacy study is designed to compare progression-free survival (PFS) between regorafenib + FOLFIRI (5-fluorouracil + leucovorin + irinotecan [ARM A] versus placebo + FOLFIRI [ARM B]) in patients with metastatic colorectal carcinoma (mCRC) previously treated with a FOLFOX (5-fluorouracil + leucovorin + oxaliplatin) regimen. Secondary objectives include objective response (OR) rates, disease control (DC) rates, and overall survival (OS). A pharmacokinetic (PK) evaluation of irinotecan will be conducted in a subset of patients at selected sites. This trial also incorporates a number of exploratory analyses designed to evaluate potential correlations between blood and tissue biomarkers and clinical benefit.

Conditions

Conditions:	Colorectal Cancer Metastatic
Keywords:	Metastatic Colorectal Cancer

K-RAS mutation
BRAF mutation
Regorafenib
BAY 73-4506
FOLFIRI
Irinotecan
5-FU
Leucovorin
Placebo
Phase II
Multi-Center
Randomized
Lineberger
North Carolina Cancer Hospital
UNC

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized
Enrollment:	181 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Regorafenib + FOLFIRI regorafenib 160 mg + FOLFIRI	Drug: Regorafenib (BAY 73-4506) Regorafenib, 160 mg, PO, Days 4-10 and Days 18-24 of 28 day cycle Other Names: • Regorafenib (BAY 73-4506) Drug: FOLFIRI FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Arms	Assigned Interventions
	Other Names: • FOLFIRI (Irinotecan + 5-Fluorouracil + Leucovorin)
Placebo Comparator: Placebo + FOLFIRI Placebo + FOLFIRI	Drug: Placebo Placebo, 160 mg, PO, Days 4-10 and Days 18-24 of 28 day cycle Other Names: • Placebo Drug: FOLFIRI FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle. Other Names: • FOLFIRI (Irinotecan + 5-Fluorouracil + Leucovorin)

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study:

1. Age ≥18 years of age (no upper age limit)
2. Histological or cytological documentation of adenocarcinoma of the colon or rectum
3. Archived, paraffin-embedded tissue block (primary or metastatic) available for genomic studies required
4. Metastatic disease not amenable to surgical resection with curative intent
5. Progression during or within 6 months following administration of a standard regimen[2] for treatment of metastatic disease that included oxaliplatin with any of the following agents with or without bevacizumab:
   - 5-fluorouracil (F-FU) with or without leucovorin or levoleucovorin
   - Capecitabine

Note: In patients receiving FOLFOX, oxaliplatin is sometimes discontinued due to toxicity or as part of maintenance therapy strategy. If such patients progress while on 5-FU alone, they are eligible for this trial. As an example, a patient who is begun on FOLFOX or CapeOx (capecitabine with oxaliplatin, with or without bevacizumab), whose oxaliplatin is held for neurotoxicity and who is switched to capecitabine monotherapy or capecitabine with bevacizumab, would be considered to have had one prior therapy.

OR

Patients who develop metastatic disease within 9 months of adjuvant FOLFOX for stage II or III colon cancer

6. Measurable disease, defined as at least 1 unidimensionally measurable lesion on a CT scan as defined by RECIST 1.1.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (see Appendix C)
8. Life expectancy of at least 3 months
9. Adequate bone marrow, renal, and hepatic function, as evidenced by the following:

    - absolute neutrophil count (ANC) ≥1,500/mm3
    - platelets ≥100,000/mm3
    - hemoglobin ≥9.0 g/dL
    - serum creatinine ≤1.5 x upper limit of normal (ULN)
    - Glomerular filtration rate (GFR) ≥30 ml/min/1.73m2 (see Appendix A)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3x ULN (≤5.0 × ULN for patients with liver involvement of their cancer
    - Bilirubin ≤1.5 X ULN
    - Alkaline phosphatase ≤3 x ULN (≤5 x ULN with liver involvement of their cancer)
    - Amylase and lipase ≤1.5 x ULN
    - Spot urine must not show 1+ or more protein in urine or the patient will require a repeat urine analysis.If repeat urinalysis shows 1+ protein or more, a 24-hour urine collection will be required and must show total protein excretion <1000 mg/24 hours
    - International normalized ratio (INR)/Partial thromboplastin time (PTT) ≤1.5 x ULN

    Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
10. Women of childbearing potential and male subjects must agree to use adequate contraception for the duration of study participation and up to 3 months following completion of therapy. Adequate contraception is defined as any medically recommended method (or combination of methods) as per standard of care.
11. The subject is capable of understanding and complying with parameters as outlined in the protocol
12. Signed, Institutional Review Board (IRB)-approved written informed consent

Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be ineligible for study participation:

1. Prior treatment with regorafenib
2. More than 1 prior chemotherapy regimen for mCRC (see section 3.1.5) Previous adjuvant FOLFOX based chemotherapy is allowed. Prior FOLFIRI or single agent irinotecan is prohibited.
3. Known history of or concomitant malignancy likely to affect life expectancy in the judgment of the investigator

4. Pregnant or breastfeeding patients. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of FOLFIRI treatment, and a negative result must be documented before start of treatment.
5. History of Gilbert's syndrome
6. Known Dihydropyrimidine dehydrogenase (DPD) deficiency
7. Pernicious anemia or other anemias due to vitamin B12 deficiency (due to potential masking of deficiency with leucovorin)
8. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of Day 1 of treatment with FOLFIRI
9. Radiotherapy within 4 weeks prior to first dose of FOLFIRI
10. Active cardiac disease including any of the following:
    - Congestive heart failure (New York Heart Association (NYHA)) ≥Class 2 (see Appendix D)
    - Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of Day 1 of FOLFIRI
    - Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
    - Uncontrolled hypertension. (Systolic blood pressure >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management)
11. Patients with pheochromocytoma
12. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), or pulmonary embolism within the 6 months before start of FOLFIRI
13. Ongoing infection >Grade 2 according to NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0)
14. Known history of human immunodeficiency virus (HIV) infection
15. Known history of chronic hepatitis B or C
16. Patients with seizure disorder requiring medication
17. Symptomatic metastatic brain or meningeal tumors unless the patient is >6 months from definitive therapy, has a negative imaging study within 4 weeks of FOLFIRI initiation, and is clinically stable with respect to the tumor at the time of study entry. Also, the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies)
18. History of organ allograft
19. Evidence or history of bleeding diathesis. Any hemorrhage or bleeding event > Grade 4 within 4 weeks of start of FOLFIRI
20. Non-healing wound, ulcer, or bone fracture
21. Renal failure requiring hemo- or peritoneal dialysis
22. Dehydration according to NCI-CTC v 4.0 Grade >1
23. Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
24. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation
25. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent
26. Inability to swallow oral medications
27. Any malabsorption condition
28. Unresolved toxicity higher than CTCAE v. 4.0 Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin-induced neurotoxicity (which must be ≤Grade 2)
29. Patients unable or unwilling to discontinue (and substitute if necessary) use of prohibited drugs for at least 30 days prior to Day 1 of FOLFIRI initiation (see Appendix B for list of prohibited drugs)

30. Unwilling to provide consent for genetic studies of tumor, whole blood, or plasma specimens

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IPDSharing

Plan to Share IPD:

References

Citations:

Links: URL: http://unclineberger.org
Description Lineberger Comprehensive Cancer Center website

Available IPD/Information:

Study Results

Participant Flow

Recruitment Details	224 participants were consented to the study from 39 institutions from 4/7/11 - 8/10/15.
Pre-assignment Details	30 participants were ineligible, 7 withdrew prior to beginning protocol therapy, 3 could not participate due to study closure, 2 were unable to participate for financial reasons, 1 did not provide a reason for non-participation; 181 patients were enrolled and went on treatment.

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Overall Study

	Arm A	Arm B
Started	120	61
Completed [1]	0	0
Not Completed	120	61
Disease progression, relapse during acti	64	40
Adverse Event	20	2

	Arm A	Arm B
Withdrawal by Subject	21	6
Treatment delay > 4 weeks	4	5
Physician Decision	4	2
Other complicating disease	2	1
Surgery	2	1
Symptomatic progression/ deterioration	3	2
Death	0	1
Ineligibility	0	1

[1] Patients treated until progression

Baseline Characteristics

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Baseline Measures

		Arm A	Arm B	Total
Overall Number of Participants		120	61	181
Age, Continuous Median (Full Range) Unit of measure: years	Number Analyzed	120 participants	61 participants	181 participants
		62 (30 to 94)	62 (30 to 82)	62 (30 to 94)
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	Female	52 43.33%	29 47.54%	81 44.75%
	Male	68 56.67%	32 52.46%	100 55.25%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	American Indian or Alaska Native	0 0%	0 0%	0 0%
	Asian	0 0%	0 0%	0 0%
	Native Hawaiian or Other Pacific Islander	0 0%	0 0%	0 0%
	Black or African American	20 16.67%	11 18.03%	31 17.13%
	White	99 82.5%	48 78.69%	147 81.22%
	More than one race	0 0%	0 0%	0 0%
	Unknown or Not Reported	1 0.83%	2 3.28%	3 1.66%

		Arm A	Arm B	Total
Region of Enrollment Measure Type: Number Unit of measure: count of participants	Number Analyzed	120 participants	61 participants	181 participants
United States		84	43	127
Ireland		36	18	54
ECOG Performance Status [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	0	52 43.33%	23 37.7%	75 41.44%
	1	68 56.67%	38 62.3%	106 58.56%
		[1] Measure Description: A scale by the Eastern Cooperative Oncology Group (ECOG) from 0-5 to describe patient's selfcare ability and activity level. 0, Fully active 1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 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		
Stage at diagnosis [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	I	3 2.5%	0 0%	3 1.66%
	II	4 3.33%	4 6.56%	8 4.42%
	III	24 20%	11 18.03%	35 19.34%
	IV	86 71.67%	46 75.41%	132 72.93%

		Arm A	Arm B	Total
	Unknown	3 2.5%	0 0%	3 1.66%
		[1] Measure Description: Stages I, II, III indicate that cancer is present, and the higher the number the larger the cancer tumor and the more it has spread into nearby tissues. Stage IV indicates that cancer has spread to distant parts of the body.		
Prior Biologic Agent Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	None	33 27.5%	16 26.23%	49 27.07%
	Bevacizumab	76 63.33%	41 67.21%	117 64.64%
	EGFR inhibitor	11 9.17%	4 6.56%	15 8.29%
Locally Reported RAS [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	Wildtype	49 40.83%	18 29.51%	67 37.02%
	Mutated	54 45%	37 60.66%	91 50.28%
	Unknown	17 14.17%	6 9.84%	23 12.71%
		[1] Measure Description: The 3 Ras genes in humans (HRas, KRas, and NRas) are the most common oncogenes in human cancer; some therapies are more effective with nonmutated wildtype genes.		
Locally Reported BRAF [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	120 participants	61 participants	181 participants
	Wildtype	22 18.33%	12 19.67%	34 18.78%
	Mutated	10 8.33%	2 3.28%	12 6.63%
	Unknown	88 73.33%	47 77.05%	135 74.59%
		[1] Measure Description: Many mutations of the BRAF gene are associated with cancer. Some drugs are designed to work with mutated forms of the gene.		

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression Free Survival (PFS)
Measure Description	To compare PFS between regorafenib + FOLFIRI chemotherapy (ARM A) versus placebo + FOLFIRI (ARM B) in patients failing one prior oxaliplatin-containing regimen for metastatic colorectal cancer. PFS is defined as the time from randomization until metastatic colorectal cancer (mCRC) progression or death as a result of any cause. Radiographic response will be measured by RECIST, Response Evaluation Criteria In Solid Tumors Criteria, indicating if subject experienced a Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Stable Disease (SD), no response or less response than Partial or Progressive; or Progressive Disease (PD), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.
Time Frame	5.5 years

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

	Arm A	Arm B
Overall Number of Participants Analyzed	120	61
Progression Free Survival (PFS) Median (95% Confidence Interval) Unit of measure: Months	6.1 (5.5 to 7.3)	5.3 (4.1 to 6.0)

2. Secondary Outcome Measure:

Measure Title	Overall Response(OR)Rate
Measure Description	To compare overall response (OR) rates (OR= CR + PR) between ARM A and ARM B as defined via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.
Time Frame	3 years

Analysis Population Description

Only evaluable participants (those who had RECIST measurements after baseline) were included in this analysis

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

		Arm A	Arm B
Overall Number of Participants Analyzed		102	58
Overall Response(OR)Rate Measure Type: Count of Participants Unit of measure: participants	Complete Response (CR)	0 0%	0 0%
	Partial Response (PR)	35 34.31%	12 20.69%
	Other	67 65.69%	46 79.31%

3. Secondary Outcome Measure:

Measure Title	Disease Control (DC) Rate
Measure Description	To compare Disease Control (DC) Rate (DC= CR + PR + SD) between ARM A and ARM B as defined via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions and Stable Disease (SD)), no response or less response than Partial or Progressive; or Progressive Disease (PD), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.
Time Frame	3 years

Analysis Population Description

Only evaluable participants (those who had RECIST measurements after baseline) were included in this analysis

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

		Arm A	Arm B
Overall Number of Participants Analyzed		102	58
Disease Control (DC) Rate Measure Type: Count of Participants Unit of measure: participants	Disease Control Total (CR+PR+SD)	84 82.35%	43 74.14%
	Progression	18 17.65%	15 25.86%

4. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	To compare overall survival (OS) between ARM A and ARM B. OS is defined as the time from randomization until death as a result of any cause.
Time Frame	5.5 years

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

	Arm A	Arm B
Overall Number of Participants Analyzed	120	61
Overall Survival (OS) Median (Full Range) Unit of measure: Months	13.8 (10.5 to 14.8)	11.7 (9.0 to 15.9)

5. Secondary Outcome Measure:

Measure Title	Drug Metabolism

Measure Description	To compare the pharmacokinetic (PK) profile of FOLFIRI between a subset of patients receiving regorafenib (ARM A) and patients receiving placebo (Arm B). The Area Under the Curve (AUC) levels of the irinotecan metabolite SN-38 were compared.
Time Frame	28 days

Analysis Population Description

This objective was designed to only look at a small subset of participants (11 on each arm)

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

	Arm A	Arm B
Overall Number of Participants Analyzed	11	11
Drug Metabolism Median (Inter-Quartile Range) Unit of measure: AUC/dose=(ng/mL*h)/(mg/m^2)		
Cycle 1	0.68 (0.49 to 0.89)	0.63 (0.47 to 0.91)
Cycle 2	0.59 (0.24 to 0.85)	0.72 (0.47 to 0.91)

6. Secondary Outcome Measure:

Measure Title	Percentage of Patients With Severe Adverse Events

Measure Description	Toxicity Assessments were made according to NCI CTCAE v. 4.0 . Severe events (grades 3-4) that occurred in a higher percentage of regorafenib treated participants as compared to placebo are reported below.
Time Frame	3 years

Analysis Population Description

All patients who received treatment

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

Measured Values

	Arm A	Arm B
Overall Number of Participants Analyzed	120	61
Percentage of Patients With Severe Adverse Events Measure Type: Number Unit of measure: percentage of participants		
neutropenia	41	30
diarrhea	15	5
hypophosphatemia	14	0
hypertension	8	2
elevated lipase	8	3

Reported Adverse Events

Time Frame	[Not specified]
Adverse Event Reporting Description	[Not specified]

Reporting Groups

	Description
Arm A	regorafenib 160 mg + FOLFIRI Regorafenib (BAY 73-4506): Regorafenib, 160 mg, PO, daily, per 7 day cycle FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.
Arm B	Placebo + FOLFIRI Placebo: Placebo, oral administration, Days 4-10 and Days 18-24 of 28 day cycle + FOLFIRI: FOLFIRI (Irinotecan,180 mg/m2 IV over 90 minutes; 5-Fluorouracil l400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours; Leucovorin 200-400c mg/m2 IV over 2 hours) Day 1 and Day 15 of each 28 day cycle.

All-Cause Mortality

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Total All-Cause Mortality	112/120 (93.33%)	59/61 (96.72%)

Serious Adverse Events

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Total	60/120 (50%)	20/61 (32.79%)
Blood and lymphatic system disorders		
Anemia [A] *	2/120 (1.67%)	3/61 (4.92%)
Febrile neutropenia [A] *	7/120 (5.83%)	3/61 (4.92%)
Cardiac disorders		
Atrial fibrillation [A] *	1/120 (0.83%)	0/61 (0%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Chest pain - cardiac [A] *	2/120 (1.67%)	1/61 (1.64%)
Left ventricular systolic dysfunction [A] *	1/120 (0.83%)	0/61 (0%)
Palpitations [A] *	1/120 (0.83%)	0/61 (0%)
Sinus bradicardia [A] *	1/120 (0.83%)	0/61 (0%)
Ventricular tachycardia [A] *	1/120 (0.83%)	0/61 (0%)
Endocrine disorders		
Hypothyroidism [A] *	0/120 (0%)	1/61 (1.64%)
Gastrointestinal disorders		
Abdominal pain [A] *	9/120 (7.5%)	2/61 (3.28%)
Ascites [A] *	0/120 (0%)	1/61 (1.64%)
Colitis [A] *	1/120 (0.83%)	0/61 (0%)
Colonic hemorrhage [A] *	1/120 (0.83%)	0/61 (0%)
Colonic obstruction [A] *	1/120 (0.83%)	0/61 (0%)
Colonic perforation [A] *	1/120 (0.83%)	0/61 (0%)
Constipation [A] *	1/120 (0.83%)	2/61 (3.28%)
Diarrhea [A] *	10/120 (8.33%)	1/61 (1.64%)
Esophageal varices hemorrhage [A] *	0/120 (0%)	1/61 (1.64%)
Ileus [A] *	3/120 (2.5%)	0/61 (0%)
Mucositis oral [A] *	3/120 (2.5%)	1/61 (1.64%)
Nausea [A] *	2/120 (1.67%)	1/61 (1.64%)
Rectal hemorrhage [A] *	4/120 (3.33%)	0/61 (0%)
Small intestinal perforation [A] *	1/120 (0.83%)	0/61 (0%)
Vomiting [A] *	0/120 (0%)	2/61 (3.28%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
General disorders		
Chills [A] *	0/120 (0%)	1/61 (1.64%)
Death NOS [A] *	2/120 (1.67%)	2/61 (3.28%)
Fatigue [A] *	2/120 (1.67%)	1/61 (1.64%)
Fever [A] *	9/120 (7.5%)	3/61 (4.92%)
Generalized muscle weakness [A] *	1/120 (0.83%)	0/61 (0%)
Infusion related reaction [A] *	1/120 (0.83%)	0/61 (0%)
Non-cardiac chest pain [A] *	1/120 (0.83%)	0/61 (0%)
Pain [A] *	1/120 (0.83%)	1/61 (1.64%)
Pressure in Head [A] *	1/120 (0.83%)	0/61 (0%)
Rigors [A] *	1/120 (0.83%)	0/61 (0%)
flu like symptoms [A] *	1/120 (0.83%)	0/61 (0%)
Hepatobiliary disorders		
Cholangitis [A] *	1/120 (0.83%)	0/61 (0%)
Cholecystitis [A] *	3/120 (2.5%)	1/61 (1.64%)
Hepatic failure [A] *	1/120 (0.83%)	0/61 (0%)
Infections and infestations		
Abdominal infection [A] *	1/120 (0.83%)	0/61 (0%)
Anorectal infection [A] *	0/120 (0%)	1/61 (1.64%)
Catheter related infection [A] *	1/120 (0.83%)	0/61 (0%)
Cecal infection [A] *	1/120 (0.83%)	0/61 (0%)
Enterocolitis infectious [A] *	0/120 (0%)	1/61 (1.64%)
Infection of unknown source [A] *	1/120 (0.83%)	0/61 (0%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Infections and infestations - Other, specify [A] *	0/120 (0%)	1/61 (1.64%)
Lung infection [A] *	0/120 (0%)	1/61 (1.64%)
Lung infection [A] *	2/120 (1.67%)	0/61 (0%)
Sepsis [A] *	2/120 (1.67%)	0/61 (0%)
Skin infection [A] *	0/120 (0%)	1/61 (1.64%)
Soft tissue infection [A] *	2/120 (1.67%)	0/61 (0%)
Upper respiratory infection [A] *	1/120 (0.83%)	0/61 (0%)
Urinary tract infection [A] *	0/120 (0%)	1/61 (1.64%)
Injury, poisoning and procedural complications		
Fall [A] *	2/120 (1.67%)	0/61 (0%)
Intestinal stoma site bleeding [A] *	1/120 (0.83%)	0/61 (0%)
Stomal ulcer [A] *	1/120 (0.83%)	0/61 (0%)
Investigations		
Alanine aminotransferase increased [A] *	1/120 (0.83%)	0/61 (0%)
Alkaline phosphatase increased [A] *	1/120 (0.83%)	0/61 (0%)
Aspartate aminotransferase increased [A] *	1/120 (0.83%)	0/61 (0%)
Blood bilirubin increased [A] *	1/120 (0.83%)	0/61 (0%)
Deteriorating LFT's [A] *	1/120 (0.83%)	0/61 (0%)
Elevated INR [A] *	1/120 (0.83%)	0/61 (0%)
GGT increased [A] *	1/120 (0.83%)	0/61 (0%)
Neutrophil count decreased [A] *	6/120 (5%)	0/61 (0%)
Obstructive Jaundice [A] *	1/120 (0.83%)	0/61 (0%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Platelet count decreased [A] *	2/120 (1.67%)	0/61 (0%)
Metabolism and nutrition disorders		
Anorexia [A] *	3/120 (2.5%)	1/61 (1.64%)
Dehydration [A] *	5/120 (4.17%)	3/61 (4.92%)
Hypoalbuminemia [A] *	1/120 (0.83%)	0/61 (0%)
Malnutrician [A] *	1/120 (0.83%)	0/61 (0%)
severely elevated lipase level [A] *	1/120 (0.83%)	0/61 (0%)
Musculoskeletal and connective tissue disorders		
Back pain [A] *	1/120 (0.83%)	0/61 (0%)
Muscle weakness lower limb [A] *	0/120 (0%)	1/61 (1.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumor pain [A] *	1/120 (0.83%)	0/61 (0%)
Nervous system disorders		
Headache [A] *	1/120 (0.83%)	0/61 (0%)
Movements involuntary [A] *	0/120 (0%)	1/61 (1.64%)
Syncope [A] *	1/120 (0.83%)	0/61 (0%)
Psychiatric disorders		
Insomnia [A] *	1/120 (0.83%)	0/61 (0%)
Psychosis [A] *	1/120 (0.83%)	0/61 (0%)
Renal and urinary disorders		
Acute kidney injury [A] *	1/120 (0.83%)	0/61 (0%)
Reproductive system and breast disorders		
Pelvic pain [A] *	0/120 (0%)	1/61 (1.64%)
Respiratory, thoracic and mediastinal disorders		

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Aspiration [A] *	0/120 (0%)	1/61 (1.64%)
Cough [A] *	1/120 (0.83%)	0/61 (0%)
Dyspnea [A] *	3/120 (2.5%)	1/61 (1.64%)
Pleural effusion [A] *	1/120 (0.83%)	0/61 (0%)
Pneumonitis [A] *	0/120 (0%)	1/61 (1.64%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis [A] *	1/120 (0.83%)	0/61 (0%)
Palmar-plantar erythrodysesthesia syndrome [A] *	1/120 (0.83%)	0/61 (0%)
right hip abscess [A] *	1/120 (0.83%)	0/61 (0%)
Surgical and medical procedures		
Surgical and medical procedures - Other, specify [A] *	0/120 (0%)	1/61 (1.64%)
Vascular disorders		
Hypertension [A] *	1/120 (0.83%)	0/61 (0%)
Thromboembolic event [A] *	3/120 (2.5%)	2/61 (3.28%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, CTCAE (4.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Total	118/120 (98.33%)	61/61 (100%)
Blood and lymphatic system disorders		
Anemia [A] *	67/120 (55.83%)	38/61 (62.3%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Febrile neutropenia [A] *	7/120 (5.83%)	1/61 (1.64%)
Cardiac disorders		
Sinus tachycardia [A] *	6/120 (5%)	2/61 (3.28%)
Endocrine disorders		
Hypothyroidism [A] *	8/120 (6.67%)	1/61 (1.64%)
Gastrointestinal disorders		
Abdominal pain [A] *	41/120 (34.17%)	9/61 (14.75%)
Constipation [A] *	41/120 (34.17%)	17/61 (27.87%)
Diarrhea [A] *	63/120 (52.5%)	28/61 (45.9%)
Dysgeusia [A] *	6/120 (5%)	2/61 (3.28%)
Dyspepsia [A] *	9/120 (7.5%)	1/61 (1.64%)
Dysphagia [A] *	6/120 (5%)	1/61 (1.64%)
Hemorrhoids [A] *	10/120 (8.33%)	2/61 (3.28%)
Mucositis oral [A] *	65/120 (54.17%)	20/61 (32.79%)
Nausea [A] *	60/120 (50%)	34/61 (55.74%)
Oral pain [A] *	8/120 (6.67%)	0/61 (0%)
Rectal pain [A] *	10/120 (8.33%)	1/61 (1.64%)
Vomiting [A] *	40/120 (33.33%)	10/61 (16.39%)
General disorders		
Edema limbs [A] *	5/120 (4.17%)	4/61 (6.56%)
Fatigue [A] *	76/120 (63.33%)	33/61 (54.1%)
Fever [A] *	18/120 (15%)	3/61 (4.92%)
Flu like symptoms [A] *	7/120 (5.83%)	1/61 (1.64%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Pain [A] *	26/120 (21.67%)	4/61 (6.56%)
Infections and infestations		
Urinary tract infection [A] *	11/120 (9.17%)	3/61 (4.92%)
Investigations		
Activated partial thromboplastin time prolonged [A] *	7/120 (5.83%)	3/61 (4.92%)
Alanine aminotransferase increased [A] *	30/120 (25%)	9/61 (14.75%)
Alkaline phosphatase increased [A] *	35/120 (29.17%)	14/61 (22.95%)
Aspartate aminotransferase increased [A] *	28/120 (23.33%)	10/61 (16.39%)
Blood bilirubin increased [A] *	22/120 (18.33%)	4/61 (6.56%)
Creatinine increased [A] *	6/120 (5%)	5/61 (8.2%)
INR increased [A] *	6/120 (5%)	5/61 (8.2%)
Lipase increased [A] *	21/120 (17.5%)	13/61 (21.31%)
Lymphocyte count decreased [A] *	15/120 (12.5%)	11/61 (18.03%)
Neutrophil count decreased [A] *	69/120 (57.5%)	36/61 (59.02%)
Platelet count decreased [A] *	34/120 (28.33%)	9/61 (14.75%)
Serum amylase increased [A] *	16/120 (13.33%)	8/61 (13.11%)
Weight loss [A] *	27/120 (22.5%)	5/61 (8.2%)
White blood cell decreased [A] *	35/120 (29.17%)	23/61 (37.7%)
Metabolism and nutrition disorders		
Anorexia [A] *	43/120 (35.83%)	7/61 (11.48%)
Dehydration [A] *	15/120 (12.5%)	5/61 (8.2%)
Hyperglycemia [A] *	17/120 (14.17%)	16/61 (26.23%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Hypertriglyceridemia [A] *	25/120 (20.83%)	19/61 (31.15%)
Hyperuricemia [A] *	5/120 (4.17%)	7/61 (11.48%)
Hypoalbuminemia [A] *	37/120 (30.83%)	14/61 (22.95%)
Hypocalcemia [A] *	29/120 (24.17%)	10/61 (16.39%)
Hypokalemia [A] *	40/120 (33.33%)	19/61 (31.15%)
Hypomagnesemia [A] *	16/120 (13.33%)	9/61 (14.75%)
Hyponatremia [A] *	20/120 (16.67%)	13/61 (21.31%)
Hypophosphatemia [A] *	38/120 (31.67%)	6/61 (9.84%)
Musculoskeletal and connective tissue disorders		
Back pain [A] *	12/120 (10%)	4/61 (6.56%)
Bone pain [A] *	6/120 (5%)	0/61 (0%)
Pain in extremity [A] *	8/120 (6.67%)	3/61 (4.92%)
Nervous system disorders		
Dizziness [A] *	9/120 (7.5%)	1/61 (1.64%)
Headache [A] *	24/120 (20%)	6/61 (9.84%)
Peripheral sensory neuropathy [A] *	28/120 (23.33%)	8/61 (13.11%)
Psychiatric disorders		
Anxiety [A] *	6/120 (5%)	1/61 (1.64%)
Depression [A] *	9/120 (7.5%)	5/61 (8.2%)
Insomnia [A] *	13/120 (10.83%)	3/61 (4.92%)
Renal and urinary disorders		
Hematuria [A] *	9/120 (7.5%)	3/61 (4.92%)
Proteinuria [A] *	18/120 (15%)	14/61 (22.95%)

	Arm A	Arm B
	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	15/120 (12.5%)	4/61 (6.56%)
Dyspnea [A] *	22/120 (18.33%)	7/61 (11.48%)
Epistaxis [A] *	9/120 (7.5%)	2/61 (3.28%)
Hoarseness [A] *	15/120 (12.5%)	0/61 (0%)
Sore throat [A] *	11/120 (9.17%)	1/61 (1.64%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	30/120 (25%)	15/61 (24.59%)
Dry skin [A] *	15/120 (12.5%)	5/61 (8.2%)
Palmar-plantar erythrodysesthesia syndrome [A] *	35/120 (29.17%)	6/61 (9.84%)
Rash acneiform [A] *	12/120 (10%)	2/61 (3.28%)
Rash maculo-papular [A] *	18/120 (15%)	5/61 (8.2%)
Vascular disorders		
Hypertension [A] *	23/120 (19.17%)	9/61 (14.75%)
Hypotension [A] *	10/120 (8.33%)	3/61 (4.92%)
Thromboembolic event [A] *	10/120 (8.33%)	1/61 (1.64%)

***** Indicates events were collected by non-systematic methods.
A Term from vocabulary, CTCAE (4.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:
All Principal Investigators ARE employed by the organization sponsoring the study.

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