Exclusion Criteria (cont’d)

- 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).
- History of organ allograft
- Evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ Grade 4 within 4 weeks of start of FOLFIRI
- Non-healing wound, ulcer, or bone fracture
- Renal failure requiring hemo- or peritoneal dialysis
- Dehydration according to NCI-CTC v 4.0 Grade ≥1
- Substance abuse, medical, psychological, or social conditions that may interfere with the patient’s participation in the study or evaluation of the study results
- Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation
- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent
- Inability to swallow oral medications
- Any malabsorption condition
- 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)
- Patients unable or unwilling to discontinue (and substitute if necessary) use of prohibited drugs for at least 2 weeks prior to Day 1 of FOLFIRI initiation (see Appendix B for list of prohibited drugs)
- Unwilling to provide consent for genetic studies of tumor, whole blood, or plasma specimens

LCCC 1029 Contacts

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Inclusion Criteria

Subject Inclusion Criteria

Age ≥18 years of age (no upper age limit)

Histological or cytological documentation of adenocarcinoma of the colon or rectum.

Archived, paraffin-embedded tissue block (primary or metastatic) available for genomic studies required.

Metastatic disease not amenable to surgical resection with curative intent.

Progression during or within 3 months following administration of a standard regimen for treatment of metastatic disease that included oxaliplatin with any of the following agents with or without bevacizumab: 5-fluorouracil (F-U) 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 (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 6 months of adjuvant FOLFOX for stage II or III colon cancer.

Measurable disease, defined as at least 1 unidimensionally measurable lesion on a CT scan as defined by RECIST 1.1.

Eastern Cooperative Oncology Group (ECOG) performance status ≤1.

Life expectancy of at least 3 months

Adequate bone marrow, renal, and hepatic function, as evidenced by the following within 7 days of study treatment initiation.

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.

The subject is capable of understanding and complying with parameters as outlined in the protocol.

LCCC 1029

Regorafenib

- Orally available multi-kinase inhibitor targeting both receptor tyrosine kinases (RTKs) and tumor cell proliferations signaling pathways kinases (RAS/RAF/MEK/ERK).

Inhibition of these pathways may be of clinical benefit in CRC.

- Regorafenib targets mutant KRAS/BRAF (69 nM)

- Demonstrates inhibition of a number of RTKs involved in tumor progression including VEGFR 2/3, TIE-2*, c-KIT and PDGFR-β

- Significant tumor growth inhibition in CRC xenografts

- Potential interaction with SN-38 via UGT1A1

Exclusion Criteria

Subject Exclusion Criteria

Prior treatment with regorafenib.

More than 1 prior chemotherapy regimen for mCRC. Previous adjuvant FOLFOX based chemotherapy is allowed. Prior FOLFIRI is prohibited.

Known history of or concomitant malignancy likely to affect life expectancy in the judgment of the investigator.

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.

History of Gilbert’s syndrome

Known DPD deficiency

Pernicious anemia or other anemias due to vitamin B12 deficiency (due to potential masking of deficiency with leucovorin)

Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of Day 1 of treatment with FOLFIRI.

Radiotherapy within 4 weeks prior to first dose of FOLFIRI.

Active cardiac disease (see protocol)

Patients with pheochromocytoma

Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 6 months before start of FOLFIRI.

Ongoing infection >Grade 2 according to NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0)

Known history of human immunodeficiency virus (HIV) infection

Known history of chronic hepatitis B or C

Patients with seizure disorder requiring medication

Continued...