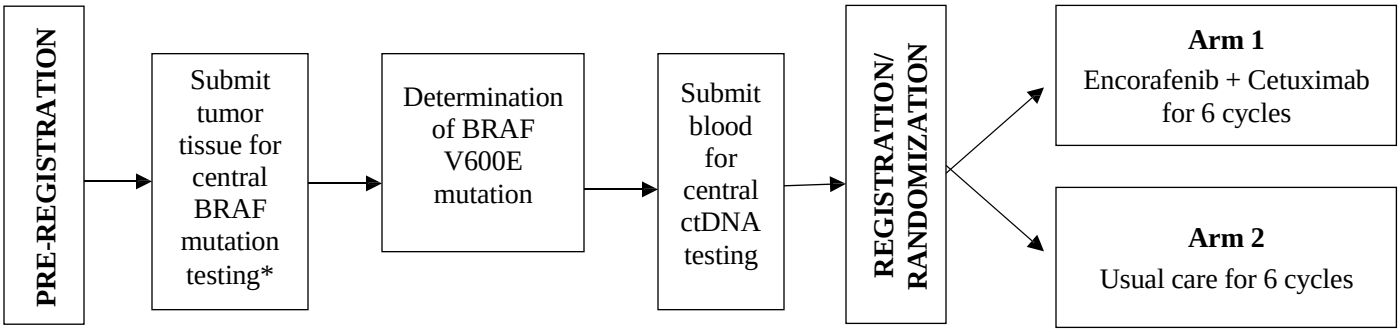
Schema

1 Cycle = 28 Days



*If BRAF V600E mutation already determined locally, then submission of tissue for central testing is still required. Documentation from either local or central laboratory required to be submitted per Section 3.3.1.

About 236 patients will be enrolled to the Phase II portion of the trial. Enrollment will continue without pause to the Phase III portion of the trial.

Treatment is to continue for 6 cycles or until disease recurrence, unacceptable adverse event, or withdrawal of consent. Patients will be followed every 6 months for 6 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Treatment must be administered at the registering institution. Imaging and CEA measurement may be conducted at a non-registering institution. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, double barrier method (diaphragm plus condom).
- Females of reproductive potential should agree to use an effective, non-hormonal method of contraception since encorafenib can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the final dose of encorafenib.
- The risk of anaphylactic reactions to cetuximab may be increased in patients with a history of tick bites or red meat allergy.

3.3 Pre-Registration (Step 0) Eligibility Criteria

Pre-registration for central tumor testing will occur after colon resection. Pre-registration can occur at any time after surgery through a five week period after completion of standard adjuvant therapy.

3.2.1 BRAF Mutation Testing

BRAF V600 mutational status may be determined either locally or by central testing. This testing is mandatory prior to registration to determine eligibility. Tissue submission should be initiated as soon after surgery as possible. For tumors evaluated at local laboratories, formalin-fixed paraffin-embedded (FFPE) tumor tissue must still be submitted for central confirmation of BRAF status.

3.4 Registration (Step 1) Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

There is an 8-week window from completion of standard adjuvant therapy and study registration.

3.3.1 Documentation of Disease

Histologically-proven stage III (any T [Tx, T1, T2, T3, or T4], N1-2M0; includes N1C) or

high-risk (pT4) stage II colon adenocarcinoma. Tumors must be deemed to originate in the colon including tumors that extend into/involve the small bowel (e.g. those at the ileocecal valve) and must have been completely resected.

BRAF V600E mutation.

MMR proficient (pMMR) or microsatellite stable (MSS) tumor.

Histologic Documentation: adenocarcinoma

Stage: III (any T [Tx, T1, T2, T3, or T4], N1-2M0; includes N1C) or high-risk II (pT4)

Tumor Site: colon

___ **3.3.2 Prior Treatment**

Patients must have received at least 3 months of adjuvant chemotherapy with either FOLFOX (minimum of 5 cycles) or CAPOX (minimum of 3 cycles).

Adjuvant therapy must be completed at most 8 weeks prior to registration.

No other prior medical therapy (chemotherapy, immunotherapy, biologic, or targeted therapy) or radiation therapy for the current colon cancer is permitted.

___ **3.3.3 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.3.4 Age ≥ 18 years**

___ **3.3.5 ECOG Performance Status: 0-2**

___ **3.3.6 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1.0 x 10^9/L
Platelet Count	≥ 75 x 10^9/L
Hemoglobin	> 9.0 g/dL
Total Bilirubin	≤ 2.0 x upper limit of normal (ULN)*
AST / ALT	≤ 3.0 x ULN
QTc Interval	≤ 480 msec
Creatinine	≤ 1.5 x upper limit of normal (ULN)
OR	
Calc. Creatinine Clearance	≥ 40 mL/min

3.3.7 Comorbid Conditions

HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

No medical condition such as uncontrolled infection, uncontrolled diabetes mellitus, or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

Patients with known history or current symptoms of cardiac disease or history of treatment with cardiotoxic agents in the last 12 months, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

No uncontrolled or poorly-controlled hypertension (>180 mmHg systolic or > 130 mmHg diastolic).

No history of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab

No "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

- Patients are not considered to have a "currently active" malignancy if they had a gastric or bowel carcinoid < 1 cm, DCIS/LCIS of the breast without invasive cancer, or endometrial dysplasia/carcinoma in situ.
- Patients are not considered to have a "currently active" malignancy if they had a sebaceous neoplasm (sebaceous adenoma, sebaceous epithelioma, sebaceous adenocarcinoma, keratoacanthoma, and squamous cell carcinoma) that was noninvasive.

No known medical condition causing an inability to swallow oral formulations of agents.

No residual CTCAE v5.0 grade ≥ 2 toxicity from prior chemotherapy, with the exception of grade 2 alopecia or neuropathy.

3.3.8 Concomitant Medications

Drugs that prolong the QTc interval should be avoided if possible, as encorafenib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix IV) should be discontinued or replaced with drugs that do not carry this risk if at all possible. Patients who receive potential QTc-prolonging medications (see Appendix IV) should be monitored closely.

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during treatment on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1.9 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed during treatment on this study. Patients must discontinue the drug 14 days prior to registration on the study. See Section 8.1.10 for more information.