

**NSABP FC-6 - A Phase II Study to Determine the Surgical Conversion Rate in Patients Receiving  
Neoadjuvant mFOLFOX7 Plus Cetuximab for Unresectable Wild-Type K-RAS Colorectal Cancer with  
Metastases Confined to the Liver**

*Fast Facts*

Cetuximab provided

CTC v3; RECIST n/a; Staging Criteria n/a

**Patient eligibility**

1. Patients must consent to be in the study and must have signed and dated an IRB-approved consent form conforming to federal and institutional guidelines.
2. Patients must be 18 years of age or older.
3. Patients must have an ECOG performance status of 0 or 1 and must be considered a potential candidate for a major hepatic surgical procedure.
4. The patient must have histologic or cytologic confirmation of a diagnosis of colorectal adenocarcinoma.
5. There must be documentation by PET/CT scan, CT scan, MRI, or intraoperative palpation (at the time of resection of the primary colorectal tumor, if applicable) that the patient has evidence of hepatic metastasis. (Histologic confirmation of hepatic metastasis is not required.)
6. Patients are eligible with any of the following:
  - primary tumor and regional nodes resected with clear surgical margins and no evidence of extrahepatic disease or
  - unresected primary tumor with plans to resect the primary tumor prior to study entry or
  - unresected primary tumor with plans to resect the primary tumor and the liver
  - metastases in a single surgical procedure performed within 2–7 weeks after the last preoperative dose of chemotherapy/cetuximab or
  - unresected primary with plans to resect the primary tumor and the liver metastases in staged procedures performed within 2–7 weeks after the last preoperative dose of chemotherapy/cetuximab
7. The colorectal primary tumor or metastatic tumor must be determined to be *wild-type* K-RAS. The K-RAS test may have been performed through the local hospital, or a tumor sample may be submitted to the FC-6 central lab for K-RAS testing. If local K-RAS test results are reported as indeterminate, submission of a tumor sample for central testing is required.  
Note: Needle biopsy of liver metastasis is not recommended for the express purpose of obtaining tissue for K-RAS testing because of the risk of needle track dissemination of malignant cells.
8. There must be documentation that the liver metastases have been determined by a hepatic surgeon approved to participate in FC-6 to be **unresectable based on at least one of the following criteria**:
  - All of the liver metastases cannot be resected (and/or ablated) with negative margins, ie., lesion(s) located in an area that would result in the resection of all of the hepatic veins *or* the main portal vein *or* the right and left hepatic arteries *or* the common bile duct.
  - Complete resection and/or ablation would require > 60% of the liver parenchyma to be removed.  
Note: At the discretion of the hepatic surgeon, portal vein embolization (PVE) may be utilized preoperatively following neoadjuvant therapy to enhance the volume of the hepatic remnant. However, the determination of unresectability will be based on the estimate, at the time of study entry, of the percentage of liver parenchyma that would need to be removed. PVE may be employed preoperatively to enhance the overall safety, but not specifically the resectability of the liver metastasis(es).
9. There must be documentation that;
  - At least 3 of the 8 hepatic segments free of metastases or
  - Based on imaging studies, it is anticipated that the patient will have at least 40% of the liver remaining intact after surgery
10. If an adjuvant therapy regimen of 5-FU given alone or in combination with leucovorin, irinotecan, capecitabine, oxaliplatin, cetuximab, or bevacizumab was administered, the adjuvant therapy must have been discontinued more than 6 months prior to study entry.
11. The patient must have had the following tests and exams **within 4 weeks** prior to study entry:
  - Medical history and physical exam;
  - Consultation with a hepatic surgeon approved for FC-6 participation (see Section 13.1); and

- PET/CT scan **or** both a PET scan **and** a CT scan of the chest, abdomen, and pelvis must be performed. (MRI scan can be substituted for the CT scan.)
12. There must be evidence of adequate bone marrow function.
    - ANC  $\geq 1500/\text{mm}^3$
    - Hemoglobin  $\geq 10$  g/dL
    - Platelet  $\geq 100,000/\text{mm}^3$
  13. There must be evidence of adequate hepatic function.
    - Total bilirubin  $\leq$  ULN for the lab  
*Note: Patients with Gilbert's syndrome or similar syndromes involving slow conjugation of bilirubin are eligible for FC-6, but total bilirubin must be  $\leq$  ULN for the lab.*
    - AST  $\leq 5.0 \times$  ULN for the lab
  14. Serum creatinine must be  $\leq 1.5$  mg/dL.

### Patient ineligibility

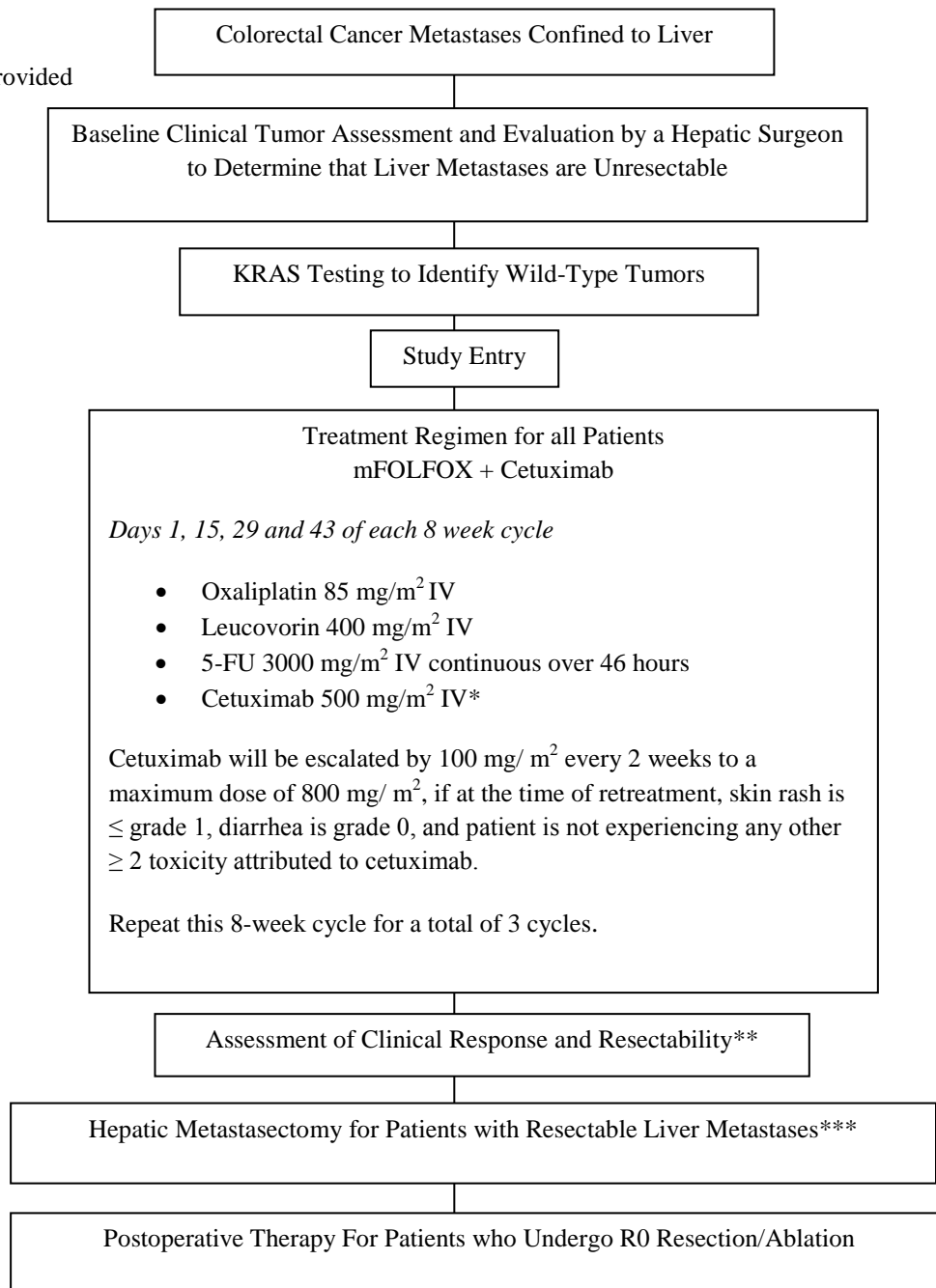
1. Diagnosis of anal or small bowel carcinoma.
2. Colorectal cancers other than adenocarcinoma, e.g., sarcoma, lymphoma, carcinoid.
3. Unresected primary tumor in the colon or rectum with significant symptoms related to obstruction of that will require radiation therapy.
4. Evidence of extrahepatic metastases or non-contiguous extension of intra-hepatic metastases to non-hepatic tissues.
5. Radiographic evidence of metastases to portal lymph nodes (node  $> 1$  cm in diameter) unless the node(s) are proven by biopsy to be negative.
6. Previous hepatic resection and/or ablation, hepatic arterial infusion therapy, or any systemic therapy for metastatic disease. (Patients who have only had an excisional biopsy are eligible.)
7. Radiation therapy to the liver.
8. Pre-existing chronic hepatic disease (e.g. chronic active hepatitis, cirrhosis) that, in the opinion of the investigator and hepatic surgeon, would limit the patient's ability to undergo hepatic metastasectomy.
9. CTCAE v3.0 grade 3 or 4 anorexia or nausea related to metastatic disease.
10. CTCAE v3.0  $\geq$  grade 2 vomiting related to metastatic disease
11. CTCAE v3.0  $\geq$  grade 2 sensory/motor neuropathy
12. Any of the following cardiac conditions:
  - Documented congestive heart failure
  - Myocardial infarction within 6 months prior to study entry
  - Unstable angina within 6 months prior to study entry
  - Symptomatic arrhythmia
13. Serious or non-healing wound, skin ulcers or bone fractures.
14. History of bleeding diathesis or coagulopathy. (Patients on stable anticoagulant therapy are eligible.)
15. Symptomatic interstitial lung disease *or* definitive evidence of interstitial lung disease described in CT scan, MRI or chest x-ray in asymptomatic patients.
16. Any evidence of active infection.
17. Other malignancies unless the patient is considered to be disease-free and has completed therapy for the malignancy  $\geq 12$  months prior to study entry. Patients with the following cancers are eligible if diagnosed and treated within the past 12 months: carcinoma in situ of the cervix, colorectal carcinoma in situ, melanoma in situ, and basal cell and squamous cell carcinoma of the skin.
18. Previous serious hypersensitivity reaction to monoclonal antibodies. (Determination of "serious" hypersensitivity reaction is at the investigator's discretion.)
19. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
20. Pregnancy or lactation at the time of study entry. (WOCBP must have a negative pregnancy test **within 2 weeks prior to study entry**. Male and female patients of reproductive potential must agree to use adequate contraceptive methods during and for 2 months after study entry.)
21. Any other serious concomitant medical condition that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to participate in the study.
22. Use of any investigational product within 30 days prior to study entry.

### Pre-Study Parameters

1. KRAS testing (can be completed at local hospital)
2. Assessment by FC-6 hepatic surgeon and determination that the liver lesions are not resectable
3. History and physical including performance status, height, weight
4. Labs including CBC with differential and platelets, CMP, Mg, pregnancy test if applicable
5. PET/CT or PET scan and CT chest, abdomen, pelvis (MRI can be substituted for CT)

**Treatment**

Cetuximab provided



\*Initiate an emollient and prophylactic doxycycline 100 mg PO BID with the first dose of cetuximab.

\*\*Patients will be assessed for objective clinical response and resectability after Cycle 1 (before cycle 2). Patients who have stable disease or a partial response, but whose liver metastases are not deemed resectable, will continue therapy and will be re-assessed after Cycle 2 (before cycle 3) and if necessary after cycle 3.

\*\*\*If liver metastases meet criteria for respectability after a minimum of 1 cycle and a maximum of 3 cycles of neoadjuvant therapy, liver resection will be undertaken as soon as judged technically feasible by the hepatic surgeon to minimize cytotoxic damage to the liver and related surgical morbidity. **At the investigator's discretion, chemotherapy/cetuximab may be continued for 1 additional treatment given at least 2 weeks before the planned date of surgery.** This additional treatment, if given, will not be considered to be part of the 3 study therapy cycles.