

# CLINICAL TRIALS Broadcast

In Focus: Colorectal Cancer

## CALGB/SWOG C80405:

A Phase III Trial of FOLFIRI or FOLFOX With Bevacizumab or Cetuximab or Both for Untreated Metastatic Adenocarcinoma of the Colon or Rectum

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### Rationale

Advances in the chemotherapeutic treatment of colorectal cancer over the past 5 years have led to the establishment of two basic regimens, both building on the combination of 5-fluorouracil (5-FU) and leucovorin (LV). The addition of irinotecan to 5-FU/LV has been shown to confer a significant survival advantage compared to 5-FU/LV alone.<sup>1,2</sup> As a result of these findings, irinotecan plus bolus 5-FU/LV (IFL) and irinotecan plus continuous infusion 5-FU/LV (FOLFIRI) have become standard frontline regimens. Because IFL appears to be associated with a higher degree of toxicity than FOLFIRI, the latter regimen has been generally deemed to warrant further testing.

The platinum agent oxaliplatin has also been studied in combination with 5-FU/LV. Referred to generally as FOLFOX, several variations of this combination have been explored, all of which employ continuous infusion oxaliplatin over 120 minutes with various bolus and infusional 5-FU regimens. FOLFOX is approved as both first- and second-line therapy, with studies suggesting that FOLFOX offers an advantage over IFL in treatment-naïve patients.<sup>3</sup> A European study found no significant difference between the use of FOLFOX followed by FOLFIRI and vice versa,<sup>4</sup> although the two regimens have not been directly compared in the United States.

Recent years have seen the development of two monoclonal antibodies that have been found to be effective in the treatment of colorectal cancer: bevacizumab and cetuximab. A recombinant humanized version of a murine anti-human vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab in combination with 5-FU-based chemotherapy is approved for the first-line treatment of patients with colorectal cancer. This approval is based on several studies showing the efficacy of this agent, the most dramatic of which was a study of

bevacizumab in combination with IFL versus IFL alone, in which a 4-month survival advantage was observed with the experimental arm.<sup>5</sup> In addition, it appears that bevacizumab plus FOLFOX improves survival among patients who have progressed after treatment with IFL.<sup>6</sup>

Cetuximab is a chimerized monoclonal antibody to the epidermal growth factor receptor (EGFR), which is expressed in approximately 70% of patients with colorectal cancer. Studies have found that cetuximab plus irinotecan is associated with tumor regression in approximately 20% of EGFR-positive colorectal cancer patients.<sup>7</sup>

Saltz and colleagues<sup>8</sup> conducted a pilot trial of cetuximab plus bevacizumab to explore the safety and efficacy of these agents with or without irinotecan. The enrolled patients had all progressed on irinotecan but had not received either of the monoclonal antibodies. The combination was well tolerated, with no unexpected increases in toxicity. The response rates were 38% among patients receiving the antibodies plus irinotecan and 23% among patients receiving the antibodies alone. Time to tumor progression appeared to be longer than in historical controls.

With the evidence garnered thus far about the benefit of combining monoclonal antibodies with chemotherapeutic regimens in the treatment of patients with colorectal cancer, the prospect of developing a regimen in which multiple antibodies are used is appealing. In Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) C80405, the treating physician will choose FOLFOX or FOLFIRI as the chemotherapeutic regimen. FOLFIRI or FOLFOX plus bevacizumab will serve as the control arm. The study will evaluate whether the addition of cetuximab to either FOLFIRI or FOLFOX with or without bevacizumab leads to a superior outcome compared to chemotherapy plus bevacizumab alone. Correlative studies will aim to assess predictors or response to these various approaches and to confirm the previously reported 70% incidence of EGFR positivity mentioned above.

### References

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2. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet.* 2000;355:1041-1047.

3. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2004;22:23-30.

4. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol.* 2004;22:229-237.

5. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335-2342.

6. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group study E3200. *Proc Am Soc Clin Oncol.* 2005;23. Abstract 2.

7. Saltz LB, Meropol NJ, Loehrer PJ. Single agent IMC-C225 has activity in CPT-11-refractory colorectal cancer that expresses epidermal growth factor receptor. *Proc Am Soc Clin Oncol.* 2002;21. Abstract 504.

8. Saltz LB, Lenz H, Hochster H, et al. Randomized phase II trial of cetuximab/bevacizumab/irinotecan versus cetuximab/bevacizumab in irinotecan-refractory colorectal cancer. *Proc Am Soc Clin Oncol.* 2005;23. Abstract 3508.

## Objectives

- Primary: To determine if the addition of cetuximab to FOLFIRI or FOLFOX chemotherapy with and without bevacizumab prolongs survival compared to FOLFIRI or FOLFOX with bevacizumab in patients with untreated, advanced or metastatic colorectal cancer.
- Secondary:
  1. To evaluate response, progression-free survival, time to treatment failure, and duration of response among patients with unresectable advanced metastatic colorectal cancer treated with bevacizumab, cetuximab or the combination in addition to chemotherapy with FOLFIRI or FOLFOX.
  2. To evaluate toxicity and, in particular, 60-day mortality among patients with unresectable advanced metastatic colon cancer treated with bevacizumab, cetuximab, or the combination in addition to chemotherapy with FOLFIRI or FOLFOX.
  3. To describe patients with unresectable locally advanced or metastatic colorectal cancer that has been rendered resectable with chemotherapy.

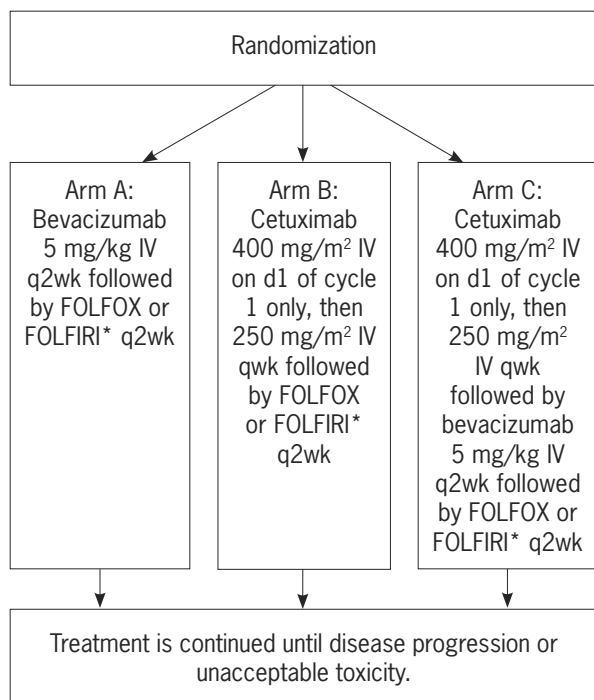
## Eligibility Criteria

- Histologically or cytologically documented locally advanced or metastatic cancer
- No prior treatment for advanced or metastatic colorectal cancer; no prior radiotherapy to >25% of bone marrow and ≥4 weeks since major surgery

- No evidence of Gilbert syndrome for FOLFIRI patients
- No grade ≥2 sensory peripheral neuropathy for FOLFOX patients
- Eastern Cooperative Oncology Group performance status of 0–1
- Age ≥18 years
- Required initial laboratory values: granulocytes ≥1,500/μL; hemoglobin ≥9 g/dL (patient may be transfused to meet this criterion); platelet count ≥100,000/μL; creatinine ≤1.5 × upper limits of normal; bilirubin ≤1.5 μg/dL; albumin ≥2.5 g/dL; urinalysis ≤1+ protein (see protocol for more information)

## Schema

1 cycle = 8 weeks



\* The decision to use either FOLFOX or FOLFIRI is at the patient/treating physician's discretion, but must be declared prior to registration and must not be changed during the course of the patient's treatment.