N0147: A Randomized Phase III Trial of Oxaliplatin plus 5-Fluorouracil, and Leucovorin (modified FOLFOX6) with or without Cetuximab after Curative Resection for Patients with Stage III Colon Cancer

by Steven R. Alberts, MD, and Frank Sinicrope, MD

Until recently adjuvant therapy for resected Stage III colon cancer consisted of 5-fluorouracil (5FU) and leucovorin (LV). More recently the drug oxaliplatin was introduced into the treatment of patients with colorectal cancer. Building on the benefits of oxaliplatin combined with 5-FU and LV in the metastatic setting, several adjuvant trials for resected colon cancer have now been reported.[1,2] In the pivotal MOSAIC trial, patients received either a regimen of bolus 5FU and LV followed by infusional 5FU (LV5FU2) on day 1 and day 2 or that same regimen with the addition of oxaliplatin on day 1 (FOLFOX4).[1] At the time of the most recent report of this trial, both 3- and 5-year disease-free survival (DFS) were significantly better in patients receiving FOLFOX4. In addition, overall survival with FOLFOX4 was better in patients with Stage III colon cancer. A separate trial performed in North America by the NSABP (C-07) showed similar benefits with the regimen FLOX.[2] Recognizing that further significant gains in DFS for resected Stage III colon cancer with chemotherapy alone are unlikely to occur, the focus of current national and international trials is to evaluate the potential added benefit of biological agents to chemotherapy.

Recently, several monoclonal antibodies targeting specific molecular targets of malignant tumors have been approved for use in metastatic colorectal cancer. Of these antibodies, cetuximab exerts a direct anti-tumor effect by binding to the transmembranous epidermal-growth-factor receptor (EGFR) on the surface of tumor cells with documented single agent activity. Report of this activity led to the approval of cetuximab in the salvage setting.[3] Since these initial reports, a variety of other reports have been published on the potential added benefit of cetuximab combined with chemotherapy, including FOLFOX.[4,5,6] Cetuximab is now being evaluated in the adjuvant setting based on the belief that the use of cetuximab in the adjuvant setting permits a monoclonal antibody to directly target tumor cells and thus micrometastatic disease prior to the onset of angiogenesis.

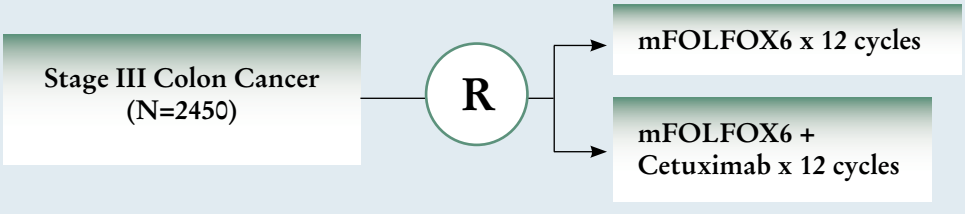
About N0147

The North American Phase III Intergroup Trial N0147 is currently evaluating the potential benefit of adding cetuximab to a modified FOLFOX6 regimen as adjuvant therapy for patients with completely resected Stage III colon cancer (Figure 1). A total of 2,450 patients will be randomized in this Phase III trial to one of two arms: modified FOLFOX6 or modified FOLFOX6 plus cetuximab.

Patient Characteristics. Patients must have histologically documented adenocarcinoma of the colon. The gross inferior (caudal) margin of the primary tumor must be ≥12 cm from the anal verge by rigid proctoscopy (i.e., patients with rectal cancer are not eligible). Tumor must have been completely resected. In patients with tumor adherence to adjacent structures en bloc resection must be documented in the operative report. Patients with tumor-related obstruction or colonic perforation are eligible for enrollment.

Inclusion and Exclusion Criteria. Inclusion criteria include: 1) identi-

Figure 1. Intergroup/ NCCTG Trial N0147 Schema



- **mFOLFOX6:** Oxaliplatin 85 mg/m² (2 hrs), LV 400 mg/m² (2 hrs), 5-FU bolus 400 mg/m² followed by 46 hour-infusion 2400 mg/m²; every 2 weeks
- **Cetuximab:**
  Week 1: 400 mg/m² (2 hrs), subsequently weekly 250 mg/m² (1 hr)
- Total treatment duration: 12 cycles

fication of at least one pathologically confirmed positive lymph node; 2) reasonable performance status (ECOG 0, 1); and 3) adequate hematologic values and organ function.

Exclusion criteria include: 1) evidence of metastatic disease, 2) prior chemotherapy and/or radiation for this disease, and 3) pregnant and lactating women. Additional criteria are outlined in the protocol. Of particular importance, patients *do not* need to have tumors that express EGFR to be eligible.

Potential Toxicities. Toxicities that would be expected to occur with FOLFOX include a risk of neutropenia, increased risk of infection, peripheral dysesthesias, nausea, vomiting, and diarrhea. Toxicities associated with cetuximab include acneform-like rash, potential for allergic reaction, hypomagnesemia, and fatigue.

Planned Statistical Analysis. Patients will be randomized equally to the two arms. The trial is designed to assess 3-year DFS as the primary endpoint. The trial will enroll 1,225 patients into each arm, giving a 90 percent power to detect a hazard ratio of 1.3. Secondary endpoints include overall survival, toxicity, quality of life, and translational markers.

Information about the trial, contact information, and participating institutions can be found through the NCI Cancer Trials Support Unit at *http://www.ctsu.org/.*

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