fact, as in the EVEREST trial, these patients did worse on the combination. PFS for the combination versus FOLFOX alone was 7.7 versus 7.2 (p=0.016). The adverse events outcomes were as expected; the incidence of neutropenia and rash was higher in the combination arm but not considered significant.

Commenting on this study, Dr. Rothenberg expressed several concerns. Regarding the outcome for KRAS-mt patients on the combination, "Here we see the opposite, and possibly detrimental, effect on patient outcomes as compared with KRAS wild-type." Further, he took issue with the higher rates of grade 3/4 hematological and GI toxicities for the combination as compared with FOLFOX alone. "There's a difference in patterns of toxicity that are based on KRAS status – why?" He wondered if these observations would carry over to CTX combination with the FOLFIRI regimen and if the effect was limited to CTX or also would be seen with panitumumab. Dr. Rothenberg concluded, "Monoclonal antibodies against EGFR clearly are useful drugs in CRC, but we must learn how to use these drugs in a fashion that maximizes benefit and minimizes risk."

Initial Safety Data of Bevacizumab as Adjuvant Therapy for Colorectal Cancer

The results of a National Surgical Adjuvant Breast and Bowel Project (NSABP) (NCT00096278) trial indicate that bevacizumab is safe when it is given as postoperative adjuvant therapy (in conjunction with conventional chemotherapy) to patients with stage II or stage III colorectal cancer. The efficacy data from the study are not yet available, but the safety data were reported first because of the potential effect on ongoing or planned investigations that involve bevacizumab and other antiangiogenic agents.

Carmen J. Allegra, MD, University of Florida, Gainesville, FL, reported the initial safety data from NSABP C-08. This randomized phase 3 trial was designed to compare modified FOLFOX6 (5-FU/leucovorin plus oxaliplatin) with and without bevacizumab. The primary endpoint was disease-free survival. One of the most important findings of the safety analysis, said Dr. Allegra, is that bevacizumab is safe in the postoperative period in the patient population that is eligible for C-08. It is not clear how far the data can or should be extrapolated beyond the eligible population. "The fear has been that, as an antiangiogenic agent, bevacizumab could have serious toxicity for postoperative patients. This was not borne out in the study," he said.

The trial enrolled 2710 patients who were randomly assigned to either FOLFOX6 every 2 weeks for 12 doses or the same chemotherapy regimen with bevacizumab given every 2 weeks for 26 doses. Patients were assigned to a treatment group after Day 29 and before Day 50 postoperatively. The data that were presented by Dr. Allegra represented findings for 1321 patients who were treated with FOLFOX6 alone and 1326 who were treated with FOLFOX6 plus bevacizumab. The mean duration of follow-up was 28.5 months.

The addition of bevacizumab did not adversely affect the dose intensity of FOLFOX6. Dr. Allegra noted that the median dose intensity was 40.6 mg/m2/wk for FOLFOX6 alone and 41.6 mg/m2/wk for FOLFOX6 plus bevacizumab (p=0.13). A significantly greater percentage of patients who were treated with FOLFOX6 plus bevacizumab received at least 10 of the 12 doses of 5-FU (85% vs 80%; p<0.01) and oxaliplatin (78% vs 73%; p<0.01).

Dr. Allegra reported that bevacizumab was not associated with a significant increase in several toxicities that have been found in other studies of advanced disease, such as cardiac, central nervous system, or peripheral arterial ischemia; gastrointestinal perforation; or hemorrhage. Bevacizumab was associated with significantly fewer occurrences of thrombocytopenia (1.4% vs 3.4% for FOLFOX6 alone; p<0.001) and allergic reaction (3.1% vs 4.7%; p=0.03).

There was no difference between the early mortality in each group. Within 6 months of random assignment, the mortality rate was 0.96% for FOLFOX6 alone and 0.90% for FOLFOX6 plus bevacizumab (p=1.0). At 18 months, the corresponding mortality rates were 1.33% and 1.35% (p=1.0).

Most of the adverse events were grade 3, and these events occurred in significantly more patients in the FOLFOX6 plus bevacizumab group (p=0.0006). All of the adverse events were manageable, added Dr. Allegra. To isolate the effects of bevacizumab, the researchers evaluated adverse events that occurred in the 12 months that followed the completion of chemotherapy (Table 1). Focusing on wound complications, Dr. Allegra noted that all such complications were grade 3 and that they resulted in surgical intervention in all but one case and in discontinuation of bevacizumab in half of the cases. Most of the wound complications (63%) were symptomatic abdominal incisional hernias, and 37% was dehiscence, infection, or inflammation at the site of the infusion port. The median time to occurrence of the wound complications was 5 months for hernias and 2 months for the infusion port-related complications.

Table 1. Significantly Different Toxicities (Grade 3 or Higher) 12 Months After Completion of Chemotherapy.

Toxicity	Arm A (%)	Arm B (%)	p value
Neurosensory (grade 2+)	43.2	49.4	0.002
Hypertension	1.8	12.7	<0.001
Wound Complications	0.3	1.7	<0.001
Pain (joint, muscle, chest, bone)	3.4	6.9	<0.001
Proteinuria	0.2	0.9	0.035
Hand-foot syndrome	1.4	2.5	0.047
Thrombocytopenia	3.4	1.4	0.002
Allergic reaction	4.7	3.0	0.033

Dr. Allegra concluded that despite the safety of bevacizumab, it cannot be recommended in the adjuvant setting until data provide evidence of its efficacy.

In his discussion of the study, Richard M. Goldberg, MD, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, said that he agreed that bevacizumab was safe in the setting of adjuvant therapy for stage II or III colorectal cancer. He pointed out that the rates of early mortality were similar to those in other adjuvant studies.

Dr. Goldberg commented that the increased frequency of pain among patients who were treated with bevacizumab was a surprise. However, he added, "There have been some studies of other angiogenesis inhibitors in which patients have reported modest pain." In closing, he reiterated the need for more data to determine the long-term toxicity or benefit of bevacizumab.

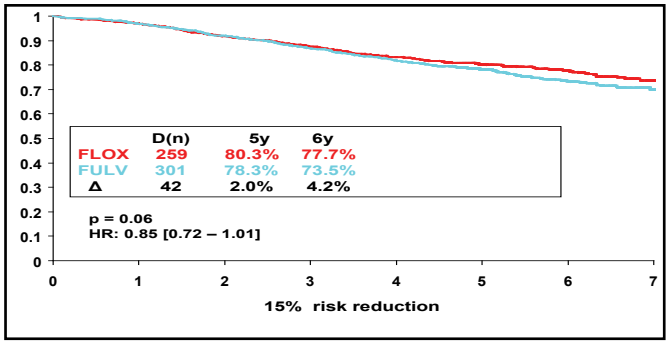
Efficacy of Oxaliplatin on Overall and Disease-Free Survival

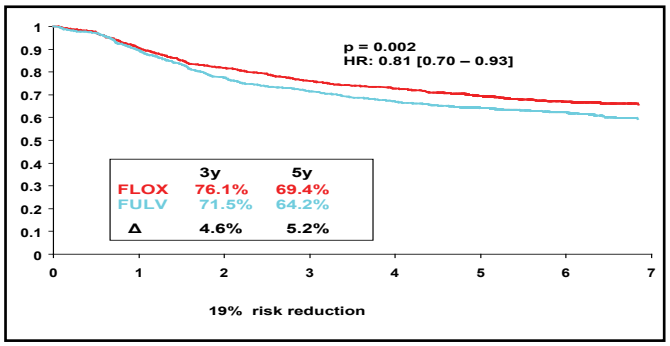
The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial (NCT00004931) demonstrated that oxaliplatin prolongs both progression-free and overall survival (OS) for patients with stage II or stage III colorectal cancer. The trial was designed to evaluate the efficacy of oxaliplatin when it was added to bolus 5-FU/leucovorin as adjuvant treatment.

Norman Wolmark, MD, Chairman of the NSABP, Pittsburgh, PA, who reported the findings, noted that the study protocol called for formal analysis of OS data 5 years after the last patient was entered (November 2002). The number of deaths that actually occurred (560) was lower than the expected number (700), which reduced the protocol-specified power to detect a 0.214 reduction in the annual death rate.

Dr. Wolmark reported that oxaliplatin was associated with a trend toward better OS at both 5 years and 6 years, a difference of borderline significance (Figure 1A). In addition, the updated results on disease-free survival (DFS) showed that the effect of oxaliplatin was durable. At a mean follow-up of 67 months, there was a 19% reduction in the risk of disease progression (Figure 1B).

Figure 1A and 1B. The Combination of Oxaliplatin Plus Bolus 5-FU/Leucovorin (FLOX) Led to Better OS (1A) and DFS (1B) Than 5-FU/Leucovorin Alone (FULV).





Dr. Wolmark noted that the findings confirm the results of the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, in which infusional combination fluorouracil and leucovorin was evaluated with and without oxaliplatin (Andre et al. *N Engl J Med* 2004). The 5-year survival for the oxaliplatin-containing regimen in the MOSAIC trial was 81.3%, which represented an absolute difference of 2.2% (compared with 80.3% and 2.0%, respectively, in the C-07 trial). The hazard ratio for this difference was 0.85 in both studies. "The findings indicate that the benefit of oxaliplatin in terms of both overall and disease-free survival is independent of the schedule of administration [of 5-FU]," said Dr. Wolmark.