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.

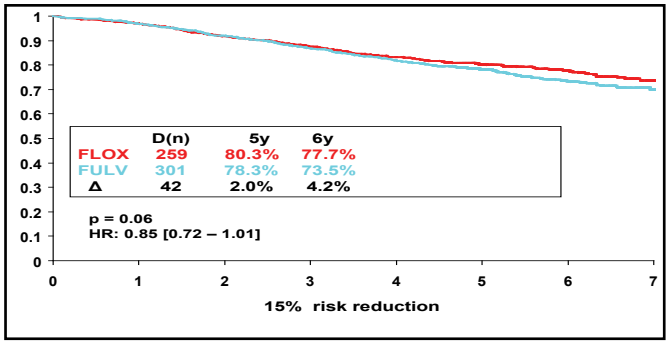
Efficacy of Oxaliplatin on Overall and Disease-Free Survival

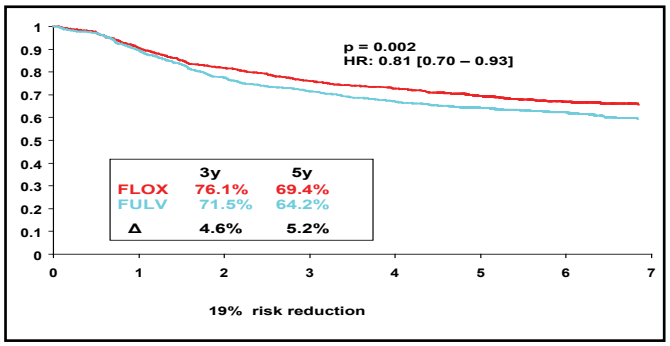
The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial (NCT00004931) demonstrated that oxaliplatin prolongs both progression-free and overall survival (OS) for patients with stage II or stage III colorectal cancer. The trial was designed to evaluate the efficacy of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

In discussing the appropriate length of follow-up for colorectal cancer trials, Dr. Wolmark pointed out that the median survival after recurrence in NSABP trials has improved significantly over time. For example, the median survival after the C-04 trial (which began enrolling patients in 1989) was 12.7 months, compared with 19.6 months for the C-07 trial, which began enrolling patients in 2000 (p<0.0001). This finding, along with the significant increase in the absolute advantage of oxaliplatin in the C-07 trial, indicates that future trials of adjuvant therapy should utilize longer follow-up (beyond five years) in order to reliably detect differences in OS, he said.

Evaluation of Adjuvant Treatment with 5-FU/Leucovorin Plus Irinotecan for Colorectal Cancer Metastases to the Liver

Adjuvant 5-FU-based chemotherapy regimens have improved survival for patients with colorectal cancer metastases to the liver compared with surgery alone. The findings of an international, randomized phase 3 trial (NCT00143403) indicate that the addition of irinotecan to 5-FU/leucovorin did not lead to further improvement in this setting.

"No difference was observed in disease-free survival (DFS) between the 2 arms, adjusted for important prognostic factors or not," said Marc Ychou, MD, Centre Regional de Lutte contre le Cancer Val d'Aurelle, Montpellier, France, who presented the findings of the study.

Patients were randomly assigned to either 5-FU/leucovorin alone or 5-FU/leucovorin plus irinotecan (FOLFIRI) within 3-8 weeks after surgical resection of liver metastases. There were 153 patients in each arm. Stratification factors included number of liver metastases, prior adjuvant chemotherapy, and time between resection of primary tumor and diagnosis of liver metastasis. The primary endpoint was DFS, and secondary endpoints included safety and OS. The median follow-up was 42 months.

Dr. Ychou reported that the median DFS did not differ significantly between the 2 arms (21.6 months for 5-FU/leucovorin vs 24.7 months for FOLFIRI; p=0.43). The 1-year and 2-year DFS also did not differ significantly (Figure 1A). At 1 year, the DFS rate was 77% for the FOLFIRI arm and 63% for 5-FU/leucovorin alone; at 2 years, the corresponding rates were 51% and 46%. Exploratory analysis indicated that there was a trend toward improved DFS when treatment with FOLFIRI was started within 42 days after surgery (Figure 1B). The 3-year OS was similar for the 2 arms (73% for FOLFIRI vs 72% for 5-FU/leucovroin).

Figure 1A. The 1-Year And 2-Year DFS Did Not Differ Significantly Between The 2 Arms.

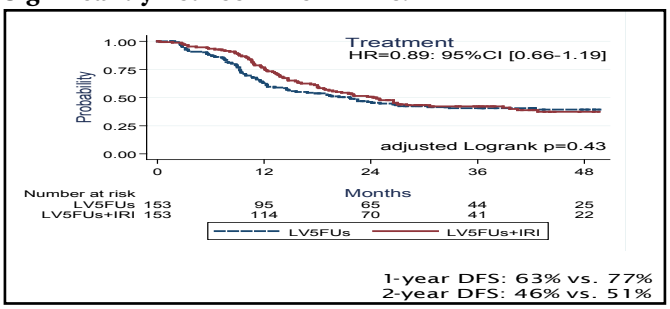
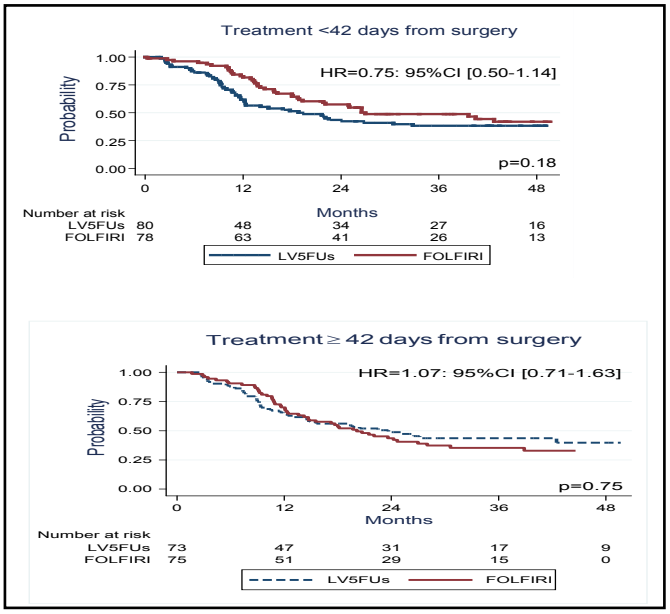


Figure 1B. Exploratory Analysis Indicated That There Was A Trend Toward Improved DFS When Treatment With FOLFIRI Was Started Within 42 Days After Surgery.



With regard to prognostic factors, Dr. Ychou noted that multivariate analysis indicated that a time of 1 year or less between resection of the primary tumor and the diagnosis of liver metastasis was associated with a hazard ratio (HR) of 1.69 (p=0.004). The HR was 1.35 for more than one liver metastasis (p=0.052) and 1.39 for prior adjuvant therapy (p=0.052).

The safety profiles of both treatments were as expected, said Dr. Ychou. The overall grade 3-4 toxicity was significantly higher for the FOLFIRI arm (p=0.01). Toxicity led to a significantly greater number of dose reductions