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.

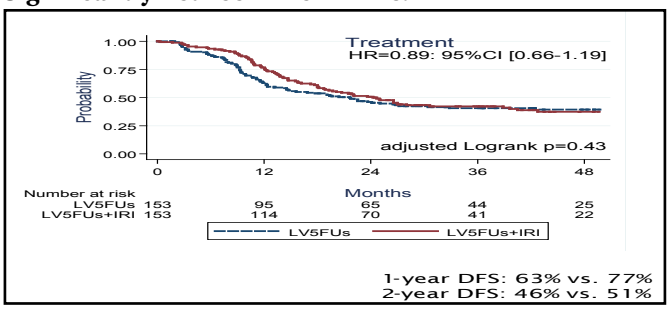
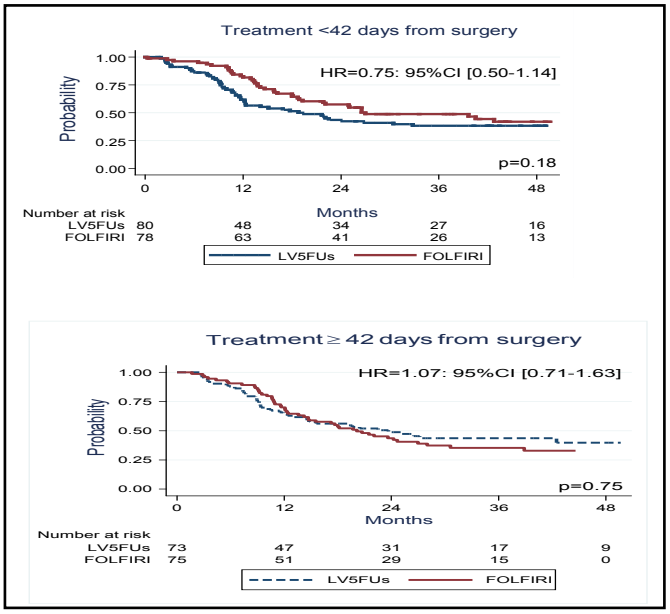


Figure 1B. Exploratory Analysis Indicated That There Was A Trend Toward Improved DFS When Treatment With FOLFIRI Was Started Within 42 Days After Surgery.



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

in the FOLFIRI arm (49% vs 18%; p<0.001), resulting in a lower median relative dose intensity of both 5-FU (89% vs 95%) and leucovorin (84% vs 91%) in that arm.

"No [bitherapy] has yet been proven superior to 5-FU alone," said Dr. Ychou, in closing. "We urgently need large trials in this setting that integrate tailored chemotherapy and targeted therapies."

Combination Biologic Therapy in Advanced Colorectal Cancer

The addition of a vascular endothelial growth factor (VEGF) antibody and an epidermal growth factor receptor (EGFR) inhibitor to chemotherapy had no benefit in advanced colorectal cancer. In fact, the combination had a significantly negative effect on progression-free survival (PFS).

Cornelis J. Punt, MD, PhD, University Medical Center, St. Radboud, Nijmegen, The Netherlands, representing the Dutch Colorectal Cancer Group (DCCG), presented the results of CAIRO2 (NCT00208546), a trial that was designed to investigate the effect of adding cetuximab (CTX) to chemotherapy plus bevacizumab. The trial included 736 eligible patients with previously untreated disease who were randomly assigned to receive capecitabine, oxaliplatin, and bevacizumab or the same schedule plus cetuximab. The primary endpoint was PFS. Secondary endpoints included overall survival (OS), response rate, disease control, and toxicity. The median duration of follow-up was 18.7 months.

Dr. Punt reported that CTX significantly decreased the median PFS (Figure 1). OS, response rate, and disease control were comparable for the 2 groups (Table 1).

The overall rate of grade 3-4 toxicity was significantly higher for the CTX-treated patients (82% vs 72%; p=0.0013), but Dr. Punt noted that when CTX-related skin toxicity was excluded, there was no difference between the 2 groups (75% and 72%, respectively; p=0.37). There also were no significant differences between the 2 treatment groups with regard to the frequency of any other adverse events, except for diarrhea, which occurred significantly more often among patients who were treated with CTX (26% vs 19%; p=0.026). All-cause mortality within 30 days or less of the last treatment was similar for the 2 groups (5%), as well as the 60-day all-cause mortality (2.4% vs 1.9%).

Dr. Punt noted that the results of the study also were evaluated with regard to KRAS status. He reported that among the 196 patients who had the KRAS mutation, the PFS was significantly decreased for patients who were treated with CTX (8.6 months vs 12.5 months; p=0.043). KRAS status had no effect on OS. Patients with wild-type KRAS status did not benefit from CTX, as has been shown in other studies with chemotherapy and CTX or with CTX alone.

Figure 1. The Addition of CTX to Capecitabine and Oxaliplatin Plus Bevacizumab Significantly Decreased PFS Compared With Patients Treated With the Same Chemotherapy Regimen Without CTX.

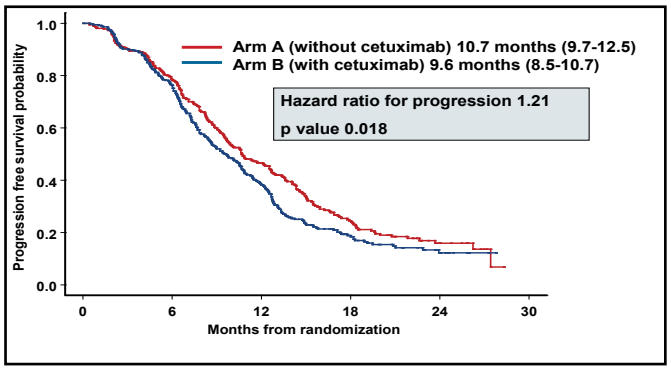


Table 1. Comparison of Efficacy Results Patients Treated With Capecitabine and Oxaliplatin Plus Bevacizumab, With and Without CTX.

	Chemotheraphy /Bevacizumab Alone (n=368)	Chemotherapy/ Bevacizumab plus Cetuximab (n=368)	p Value
PFS (mos.) (95% CI)	10.7 (9.7-12.5)	9.6 (8.5-10.7)	0.018, HR=1.21 (1.03-1.45)
OS (mos.) (95% CI)	20.4 18.1-26.1)	20.3 (17.9-21.6)	0.21, HR=1.15 (0.93-1.43)

*Includes complete and partial response plus stable disease.
CI=confidence interval, HR=hazard ratio.

Cathy Eng, MD, MD Anderson Cancer Center, Houston, TX, who discussed the study, pointed out that the findings were comparable with the results of the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial.1 [Hecht et al. 9th World Conference on Gastrointestinal Cancers, Barcelona, 2007]. In that study, the PFS that was associated with FOLFOX plus bevacizumab was 11.1 months compared with 9.6 months for FOLFOX plus bevacizumab and panitumumab (p=0.004; HR=1.44). Dr. Eng noted, "[The results of this study and others] indicate that our understanding of both VEGF and EGFR pathways is not fully understood."