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ORIGINAL REPORT

Initial Safety Report of NSABP C-08: A Randomized Phase III Study of Modified FOLFOX6 With or Without Bevacizumab for the Adjuvant Treatment of Patients With Stage II or III Colon Cancer

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ABSTRACT

Purpose
The National Surgical Adjuvant Breast and Bowel Project C-08 trial was designed to investigate the safety and effectiveness of adding bevacizumab to modified infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) 6 regimen for the adjuvant treatment of patients with stage II or III colon cancer. We present safety information in advance of the planned analysis of efficacy.

Patients and Methods
Among 2,710 randomly assigned patients, demographic factors were balanced. Patients received modified FOLFOX6 every 2 weeks × 12 or modified FOLFOX6 plus bevacizumab (5 mg/kg every 2 weeks × 26, experimental group).

Results
Overall rates of grade 4 or 5 toxicities were nearly identical in the FOLFOX6 and FOLFOX6 plus bevacizumab arms (15.2% and 15.0%, respectively). Six-month mortality rates were 0.96% and 0.90% for the control and experimental groups, respectively. Grade 3+ toxicities that occurred more often in the experimental arm versus control arm included hypertension (12% *v* 1.8%, respectively), wound complications (abdominal incisional hernia or infusion port dehiscence/inflammation; 1.7% *v* 0.3%, respectively), pain (11.1% *v* 6.3%, respectively), and proteinuria (2.7% *v* 0.8%, respectively). Grade 2+ neuropathy was increased in the experimental arm versus the control arm (grade 2, 33% *v* 29%, respectively; grade 3, 16% *v* 14%, respectively; and grade 4, < 1% each). In the experimental arm versus control arm, significantly less thrombocytopenia (1.4% *v* 3.4%, respectively) and fewer allergic reactions (3.1% *v* 4.7%, respectively) were observed. Advanced age was associated with a significantly greater rate of grade 4 and 5 toxicities regardless of treatment.

Conclusion
Bevacizumab with modified FOLFOX6 is well tolerated in the surgical adjuvant setting in these patients. No significant increase in GI perforation, hemorrhage, arterial or venous thrombotic events, or death with the addition of bevacizumab to modified FOLFOX6 has been observed. Follow-up for potential delayed adverse effects and efficacy is ongoing.

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INTRODUCTION

Systemic therapy for advanced colorectal cancer has substantially improved patient outcomes, most recently with the advent of targeted therapies directed at critical growth factor pathways. Bevacizumab is a humanized monoclonal antibody that recognizes circulating vascular endothelial growth factor. Hurwitz et al[1] demonstrated that the addition of bevacizumab markedly enhanced the response rate, progression-free survival, and overall survival of patients with advanced colorectal cancer when added to irinotecan, bolus fluorouracil (FU), and leucovorin. Subsequent investigations have demonstrated that the addition of bevacizumab to a variety of chemotherapeutic agents including oxaliplatin-based regimens results in enhanced therapeutic outcomes in patients with advanced colorectal cancer.[2,3]

Two large multinational randomized studies conducted in Europe and the United States demonstrated that the addition of oxaliplatin to the combination of FU and leucovorin resulted in significant improvement in disease-free survival (DFS) when

compared with FU plus leucovorin alone for the adjuvant treatment of patients with stage II and III colon cancer.[4,5] The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer Adjuvant Treatment of Colon Cancer (MOSAIC) trial compared infusional FU, leucovorin, and oxaliplatin (FOLFOX) with infusional FU plus leucovorin, whereas the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial compared the bolus FU and leucovorin plus oxaliplatin (FLOX) regimen with bolus FU plus leucovorin in patients with stage II and III colon cancer. Both trials demonstrated a significant increase in 3-year DFS for patients treated with the oxaliplatin-containing regimens.

The primary goal of NSABP C-08 is to test the potential benefit and safety associated with the addition of bevacizumab to the modified FOLFOX6 regimen in the adjuvant colon cancer setting. This report summarizes the adverse events related to the use of both chemotherapy and bevacizumab when used in the postoperative adjuvant setting in patients with colon cancer. The safety profile of bevacizumab in combination with chemotherapy in the surgical adjuvant setting is important to document because an increased incidence of serious adverse events, such as perforations of the GI tract, arterial thrombotic events, and wound complications, has been reported in patients with advanced metastatic colorectal cancer.[1,6-8]

PATIENTS AND METHODS

Study Population

This study was approved by institutional review committees with assurances approved by the Department of Health and Human Services and in accordance with the Helsinki Declaration. Informed consent was required for participation. Patient entry and characteristics are listed in Table 1.

Table 1. Patient Entry, Demographics, and Clinical Characteristics

Patient Demographics and Clinical Characteristics	mFOLFOX6	mFOLFOX6 + Bev
Patient population, No. of patients		
Randomly assigned	1,356	1,354
Ineligible	18	14
With follow-up	1,338	1,332
Mean time on study, months	28.5	28.5
Age, years, % of patients		
< 60	58.3	58.1
≥ 60	41.7	41.9
Sex, % of patients		
Male	49.8	49.8
Female	50.2	50.2
Race, % of patients		
White	87.6	87.0
Black	7.5	8.6
Other	3.8	3.1
Multiracial	0.1	0.1
Unknown	1.0	1.2
Stage, % of patients		
II (node negative)	24.7	25.0
III (1-3 positive nodes)	45.7	45.4
III (4+ positive nodes)	29.6	29.6

Abbreviations: mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; Bev, bevacizumab.

Patients with stage II or III colon adenocarcinoma were stratified by number of positive lymph nodes and then randomly assigned to receive either modified FOLFOX6 for 6 months or modified FOLFOX6 for 6 months plus bevacizumab for 12 months beginning concurrently with chemotherapy. Patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 were randomly assigned within 29 to 50 days after surgical removal of the primary tumor. Patients were excluded for any history of cerebral vascular accident, transient ischemic attack, symptomatic peripheral vascular disease, or a history of an arterial thrombotic episode, such as a myocardial infarction, within 12 months before random assignment.

Regimens

Modified FOLFOX6 includes leucovorin 400 mg/m^2 intravenous (IV) on day 1, FU 400 mg/m^2 IV on day 1 followed by 2,400 mg/m^2 IV over 46 hours, and oxaliplatin 85 mg/m^2 IV on day 1. Bevacizumab is administered on the experimental arm at a dose of 5 mg/kg IV on day 1. All therapy is administered every 2 weeks for 12 doses (6 months) or, for bevacizumab, 26 doses (1 year).

Adverse Event Reporting

Adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[9] Routine reporting was required for all events ≥ grade 3 (except all neurology events, which were reported for all events ≥ grade 2) every 6 weeks during active treatment and every 3 months for 1 year after therapy.

Dose Modifications

Oxaliplatin and FU were reduced for grade 3 and 4 adverse events except for diarrhea and stomatitis, wherein only FU was reduced for less than grade 4 toxicity, or neurologic toxicities, wherein only oxaliplatin was modified for grades 3 and 2, provided the toxicity exceeded 7 days in duration.

There were no dose modifications for bevacizumab, but the drug was held for grade 1 noninfectious wound complications, grade 2 proteinuria or thrombosis, or any clinically significant and related grade 3 toxicities. Bevacizumab was discontinued for any grade of GI perforation or reversible posterior leukoencephalopathy syndrome, grade 2 or greater ischemic events or noninfectious wound complications, grade 3 hemorrhage, or any associated grade 4 toxicities.

Statistical Considerations

Rates of toxicity were computed by dividing the number of patients reporting the relevant toxicity by the number of patients reported to have been assessed for toxicity. Rates and the distributions of categoric variables were compared using χ^2 or Fisher's exact tests. Continuous variables were presented as medians and compared between groups using the Wilcoxon test. The Kaplan-Meier method was used to present the proportion of patients exceeding a given duration of therapy.

Analyses related to compliance with protocol therapy and the reason for discontinuation of protocol therapy were restricted to the cohort of patients without an event for the primary efficacy end point of DFS (time to recurrence, second primary cancer, or death). This was done so that no one could attribute any differences found to efficacy of the study drug.

RESULTS

During the 2-year period between September 2004 and October 2006, 2,710 patients from 292 participating centers were accrued to the study. Patient demographics are well balanced by treatment arm (Table 1). Each arm had just over 1,350 patients. The mean time on study as of March 31, 2008, was 28.5 months. Slightly more than half of the patients were less than 60 years of age, and there was an equal sex distribution. Stage II patients constituted approximately 25%, with the balance being node-positive patients.

In the cohort of patients without a DFS event, 73% *v* 78% and 80% *v* 85% were able to receive at least 10 of 12 planned doses of

oxaliplatin and FU in the control versus experimental arms, respectively ($P < .01$, each drug). A significantly greater percentage of patients were able to receive at least 1,000 mg/m^2 of the protocol-specified cumulative oxaliplatin dose of 1,020 mg/m^2 on the bevacizumab arm versus the control arm (34% *v* 27%, respectively; $P < .01$). The median dose of oxaliplatin delivered on the chemotherapy-alone arm was 850 mg/m^2 compared with 880 mg/m^2 delivered on the bevacizumab arm ($P < .01$). The oxaliplatin median dose-intensity was also slightly higher on the bevacizumab arm compared with the chemotherapy-alone arm (83.2 *v* 81.1 mg/m^2/2-week cycle), although this did not reach the level of statistical significance ($P = .13$). The FU doses followed similar trends, with patients on the chemotherapy-alone arm receiving a median dose of 29,540 mg/m^2 and patients on the bevacizumab arm receiving 30,800 mg/m^2 ($P < .01$). The median dose-intensity of FU was similar on the control and experimental arms (2,688 *v* 2,720 mg/m^2/2-week cycle, respectively; $P = .57$). Sixty-one percent of patients were able to receive at least 21 of 26 planned doses of bevacizumab. The median duration of bevacizumab therapy was 11.5 months.

Two thirds of patients who discontinued bevacizumab in the cohort of patients without a DFS event did so because of an adverse event, whereas 24% withdrew at the patient's request. These percentages were closely mirrored in the reasons for discontinuation of chemotherapy. As shown in Figure 1, during the first 6 months of therapy, the decrement in patients receiving bevacizumab was precisely paralleled by the fall-off in patients receiving therapy with FU on the control arm, whereas the fall-off trails that of FU on the experimental arm. These data suggest that discontinuation of bevacizumab occurred primarily in conjunction with chemotherapy-associated adverse events and was the first agent to be discontinued in the experimental arm because of adverse events that were not clearly attributable to a particular agent. During the 6 months after completion of chemotherapy, discontinuation of bevacizumab occurred at a slower rate.

Death from any cause within 6 months of random assignment among treated patients occurred in 0.96% and 0.90% of individuals ($P = 1.0$) in the control and bevacizumab arms, respectively. At 18 months after random assignment, 1.33% and 1.35% of treated patients died in the control and bevacizumab arms, respectively ($P = 1.0$).

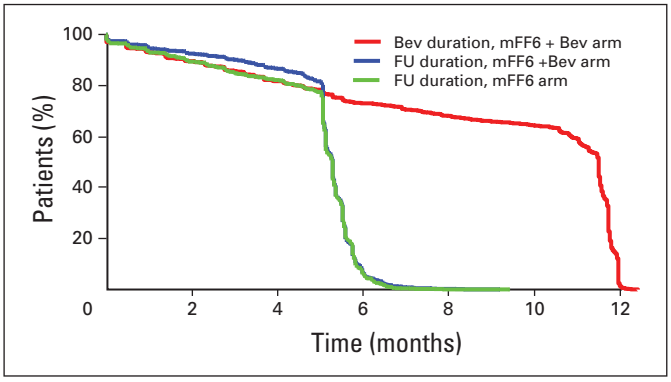

Fig 1. Duration of fluorouracil (FU) and bevacizumab (Bev) therapy for patients randomly assigned to either the control arm (green line = FU) or the experimental arm (blue line = FU, and red line = Bev). In each case, the percentage of patients remaining on therapy is plotted as a function of time on therapy. Patients reaching a disease-free survival (DFS) event were excluded from this analysis. mFF6, modified infusional fluorouracil, leucovorin, and oxaliplatin.

Table 2. Therapy-Associated Grade 3 or Greater Adverse Events Not Significantly Increased in NSABP C-08

Adverse Event	% of Patients* mFOLFOX6 (n = 1,321)	mFOLFOX6 + Bev (n = 1,326)
Venous thrombosis	4.6	6.3
Neutropenia	32.6	29.4
Febrile neutropenia	1.7	1.2
Fatigue	7.2	9.0
Diarrhea	9.7	11.1
Dehydration	4.0	4.8
Cardiac ischemia	0.8	1.5
CNS ischemia	0.4	0.4
Peripheral arterial ischemia	0.2	0.0
GI perforation	0.2	0.3
Any hemorrhage	1.9	1.9

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; Bev, bevacizumab.
*Not statistically significantly different ($P \leq .05$) unless noted.

The overall rates of grade 4 and 5 toxicity were 15.2% and 15.0% in the chemotherapy-alone and chemotherapy plus bevacizumab arms, respectively ($P = .91$). The overall rate of grade 3 or higher toxicities was 70% in the chemotherapy-alone arm and 77% in the chemotherapy plus bevacizumab arm ($P < .01$).

Specific grade 3 or higher toxicities associated with chemotherapy or with bevacizumab in the advanced-disease setting are listed in Table 2. None of the differences in these toxicities is significant between the control and bevacizumab arms. However, several toxicities were significantly different in patients receiving bevacizumab (Table 3). These included hypertension, pain, proteinuria, sensory neuropathy, and wound complications, which occurred in less than 2% of patients treated with bevacizumab. Of the 23 patients with wound complications on the bevacizumab arm (all grade 3), all but one required surgical intervention, and half required bevacizumab discontinuation. Fourteen of these patients had symptomatic abdominal

Table 3. Grade 3 or Greater Toxicities Significantly Different by Treatment in NSABP C-08

Adverse Event	% of Patients mFOLFOX6 (n = 1,321)	mFOLFOX6 + Bev (n = 1,326)	*P*
Sensory neuropathy	14.4	16.7	.10
Grade ≥ 2	43.7	48.9	< .01 ↑
Hypertension	1.8	12.0	< .01 ↑
Proteinuria	0.8	2.7	< .01 ↑
Wound complications	0.3	1.7	< .01 ↑
Pain (joint, muscle, bone, chest/thorax, abdomen, head/headache, or rectum)	6.3	11.1	< .01 ↑
Thrombocytopenia	3.4	1.4	< .01 ↓
Allergic reaction	4.7	3.1	.03 ↓

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; Bev, bevacizumab; ↑, increased with bevacizumab; ↓, decreased with bevacizumab.

Table 4. Grade 3 or Greater Toxicities Seen Significantly More Frequently With Bevacizumab After Chemotherapy

Adverse Event	% of Patients		
	mFOLFOX6 (n = 1,321)	mFOLFOX6 + Bev (n = 1,326)	*P*
Wound complications	0.3	1.1	.01
Hypertension	0.7	5.9	< .01
Sensory neuropathy (grade ≥ 2)	26.1	32.4	< .01
Any pain	2.1	4.8	< .01
Proteinuria	0.2	1.6	< .01
Depression	1.3	2.9	< .01
Dizziness	0.7	1.6	.04

Abbreviations: mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; Bev, bevacizumab.

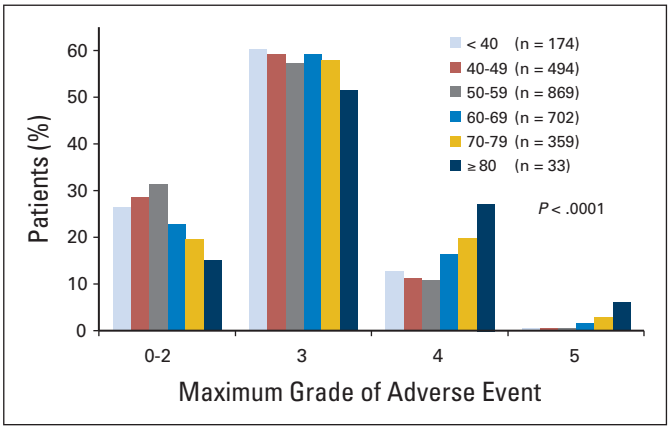

Fig 2. Maximum grade of toxicities by age decade is illustrated for both arms combined because the rates of AEs were similar in both arms. Patients are separated into age decades of less than 40 (light blue bars), 40 to 49 (dark red bars), 50 to 59 (gray bars), 60 to 69 (bright blue bars), 70 to 79 (gold bars), and ≥ 80 years old (dark blue bars).

incisional hernias, and one patient had an abdominal wound dehiscence associated with an abscess. The median time to occurrence of these events was 5 months. The other nine patients developed infusion port dehiscence and/or inflammation. The median time to occurrence in these patients was 2 months. There was no difference in the time from surgical procedure to the initiation of therapy (median, 46 days) between patients who developed a wound complication versus those who did not ($P = .88$). Although grade 3 sensory neuropathy was not different between the arms, the overall rate of grade 2 and higher sensory neuropathy was significantly increased in the bevacizumab arm ($P < .01$). This difference may be the result of a greater cumulative dose of oxaliplatin received by patients randomly assigned to the bevacizumab arm. Pain, which was also significantly increased in the bevacizumab arm, was primarily in the form of chest, joint, or muscle pain. Each of these occurred at a rate of approximately two-fold greater in the bevacizumab arm. Of interest, there was less thrombocytopenia and fewer allergic reactions in patients receiving bevacizumab.

To assess toxicities that occurred during the 6 months of therapy with bevacizumab alone, we tabulated only toxicities that occurred during the 1 year after chemotherapy completion (Table 4). Those found to occur at a significantly higher level included wound complications consisting almost entirely of symptomatic abdominal wall incisional hernias, hypertension, sensory neuropathy, depression, dizziness, proteinuria, and pain.

We also examined the maximum grade of adverse event as a function of decade of patient age for the overall study population (Fig 2). We found that the distribution of maximum grade of adverse event differed significantly among the six age decades examined ($P < .001$). Grade 4 and 5 toxicities seemed to increase in both arms for patients older than age 60 years and in particular for patients older than age 70, who constituted 15.8% and 14.5% of patients on the control and experimental arms, respectively. There were large differences in grade 4 neutropenia by age (6% < 70 years *v* 13% ≥ 70 years, $P < .001$). Patients older than age 70 had a significantly higher rate of fatal adverse events compared with the younger population (3.0% *v* 0.8%, respectively; $P = .001$). In comparing all toxicities by age, the overall rate of grade 3+ toxicities was greater in patients older than 70 years versus younger patients (81% *v* 73%, respectively; $P < .001$); specifically, there was significantly more grade 3 neutropenia (44.2% *v* 28.8%, respectively; $P < .001$), thrombocytopenia (4.8% *v* 2.0%, respectively; $P = .002$), fatigue (15.2% *v* 6.9%, respectively; $P < .001$), diarrhea (16.4% *v* 9.5%, respectively; $P < .001$), dehydration (10.9% *v* 3.4%, respectively; $P < .001$), and febrile neutropenia (3.5% *v* 1.1%, respectively; $P = .001$). Overall, the effects of age (70+ years) and treatment on the rate of grade 4+ adverse events seem to be independent (Breslow-Day test for homogeneity of odds ratios, $P = .49$). Patients age ≥ 60 years had a significantly lower dose-intensity compared with patients less than 60 years of age for both oxaliplatin and FU ($P < .0001$).

DISCUSSION

The overall safety of adding bevacizumab to modified FOLFOX6 in the colon cancer adjuvant setting is acceptable in the selected population of patients eligible for NSABP C-08. The C-08 population had an excellent performance status, with no prior history of a cerebral vascular accident or peripheral arterial event, and had at least a 12-month interval before random assignment for any myocardial infarction and no exposure to bevacizumab before the 29th postoperative day.

The cumulative dose and dose-intensity of modified FOLFOX6 were not decreased by the addition of bevacizumab, yet the overall rates of mortality from any cause within 6 months were nearly identical on both arms. The rate of less than 1% for 6-month mortality is similar to other colon cancer adjuvant trials conducted in the United States. The 6-month mortality reported for NSABP C-07,[5] which randomly assigned patients to either weekly FU plus leucovorin or the same chemotherapy with the addition of oxaliplatin, was 0.9% and 1.0% for each arm, respectively. Similarly, past trials using primarily FU-based regimens reported 6-month mortality rates of 0.8% to 1.2%.[10,11]

Overall, we did not observe any change in the rate of toxicities generally attributable to the chemotherapeutic agents used; however, we did observe an increase in the rate of grade 2 or higher neuropathy in patients randomly assigned to the bevacizumab arm. Our observed 6% absolute increase in neuropathy may be attributable to the increase

in cumulative dose of oxaliplatin received by patients randomly assigned to the bevacizumab arm because 7% more patients received at least 1,000 mg/m^2 of oxaliplatin on this arm compared with the control arm. One hypothesis for the greater cumulative dose of chemotherapy in the bevacizumab arm is that when toxicities that were not clearly attributable to a specific agent occurred, physicians may have elected to first discontinue bevacizumab rather than dose modify chemotherapy. Such an option was not available in the control arm; thus, physicians were forced to first dose modify the chemotherapy, with a resultant decrease in cumulative dose relative to the experimental arm. Evidence for this hypothesis is illustrated in Figure 1, wherein discontinuation of bevacizumab exactly parallels the discontinuation of FU in the control arm but lags behind FU discontinuation in the experimental arm. This suggests that nonspecific toxicities requiring dose modifications occurred at the same rate in both arms, but bevacizumab was favored as a first option for discontinuation rather than chemotherapy in the experimental arm, thus preserving chemotherapy dose-intensity.

Several toxicities generally associated with bevacizumab in the advanced-disease setting were not found to be increased. Specifically, cardiac, CNS, and peripheral arterial events were not increased in the bevacizumab-treated patients. Similarly, we did not observe an increase in the rate of GI perforations despite all patients having had a prior major surgical intervention. However, there was an approximately five-fold increase in the rate of wound complications (all grade 3) in patients treated with bevacizumab versus chemotherapy alone (1.7% *v* 0.3%, respectively). The lack of an increased incidence of GI perforations and the relatively low incidence of manageable wound complications may be attributable to an adequate interval between surgical intervention and the initiation of anti–vascular endothelial growth factor therapy.

As anticipated, both hypertension and proteinuria occurred at a significantly higher rate in the bevacizumab arm versus control arm (12% *v* 2.7%, respectively). There were no occurrences of frank nephrotic syndrome, and grade 4 hypertension occurred in only five patients. Pain (joint, muscle, and noncardiac chest pain) of unclear pathogenesis was also found to be approximately two-fold higher in the bevacizumab arm. Although this toxicity has been previously reported with bevacizumab,[1] it has not been found to be significantly increased, presumably because of the small number of patients treated on the advanced-disease studies relative to NSABP C-08. Of interest, we noted a decrease in the occurrence of allergic reactions and thrombocytopenia.

One feature of the NSABP C-08 trial is the exclusive use of bevacizumab for 6 months after completion of chemotherapy. Wound complications, hypertension, proteinuria, and pain all continued to be observed during this 6-month period of bevacizumab alone, although all occurred at a substantially lower rate compared with during the first 6 months that included chemotherapy. Dizziness and depression were not increased during the first 6 months but were increased (borderline significance for dizziness) during the bevacizumab-alone period. Part of the explanation for this observation is that the follow-up periods were more frequent for the bevacizumab group (every 6 weeks) compared with the control group, which had completed active therapy (every 3 months). Although sensory neuropathy continued to be observed more frequently in the bevacizumab arm, this was presumably a result of a higher prevalence of this toxicity at the start of the 6-month bevacizumab-alone period relative to the control arm. The rate of reversal of this toxicity during this period was similar in both arms (approximately 35%).

Finally, we found that with age greater than 60 years, there was a clear increase in grade 4 (primarily neutropenia) and 5 adverse events independent of treatment. The association of increasing age with excess toxicity has been reported with FOLFOX chemotherapy.[12] Consistent with our observations, these authors identified a significant increase in hematologic toxicity (> grade 2) in patients at least 70 years of age. Although 60-day mortality in the pooled analysis report was found to be higher in the elderly (2.3% *v* 1.1% in younger patients), this difference was not statistically significant.[12] Patients older than age 70 who participated in NSABP C-08 clearly had a significantly higher rate of fatal adverse events compared with the younger population (3.0% *v* 0.8%, respectively; $P = .001$). Given these observations in the relatively small patient cohort older than age 70 accrued to NSABP C-08 (approximately 15%), caution should be exercised in considering the use of bevacizumab in this population.

Although the use of bevacizumab in combination with the modified FOLFOX6 chemotherapeutic regimen is associated with an acceptable toxicity profile in the specific patient population eligible for NSABP C-08, ongoing efforts continue to investigate any potential long-term toxicities associated with the use of bevacizumab. The use of bevacizumab in the adjuvant colon setting cannot be recommended at the present time. Further follow-up will be required to determine whether the addition of bevacizumab to the modified FOLFOX6 regimen will result in a significant improvement in DFS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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