Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First-Line Therapy for Metastatic Colorectal Cancer

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ABSTRACT

INTRODUCTION

FOLFOX-4, a bi-weekly schedule of bolus and infusional fluorouracil (FU)/folinic acid (FA) plus oxaliplatin (Eloxatin; Sanofi-Aventis, Bridgewater, NJ), is a widely used regimen for first-line treatment of metastatic colorectal cancer (MCRC).1 Capecitabine has been tested in combination with oxaliplatin (Xeloda; Hoffmann-La Roche Inc, Nutley, NJ), as a widely used regimen for first-line treatment of metastatic colorectal cancer (MCRC).1-4

A factorial design was used, and the two coprimary objectives of the study were that the XELOX-containing arms (XELOX vs FOLFOX-4) would be noninferior to the FOLFOX-4 arms (FOLFOX-4 vs placebo) and that the XELOX arms would be superior to the FOLFOX-4 arms (XELOX vs FOLFOX-4). After patient accrual had begun, the trial design was amended in 2003 to allow patients to receive bevacizumab. The amended design included an additional 1,400 patients after the start of the bevacizumab phase III study. The resulting 2 × 2 factorial design compared XELOX-1 versus FOLFOX-4, plus an additional 1,400 patients after the start of the amended 2 × 2 factorial design randomly assigned patients to XELOX versus FOLFOX-4, and then to also receive either bevacizumab or placebo. We report here the results of the analysis of the XELOX versus FOLFOX-4 arms. The analysis of bevacizumab versus placebo with oxaliplatin-based chemotherapy is reported separately. The prespecified primary end point for the noninferiority analysis was progression-free survival.

Results

The intent-to-treat population comprised 634 patients from the original two-arm portion of the study, plus an additional 1,400 patients after the start of the amended 2 × 2 factorial design, for a total of 2,034 patients. The median PFS was 8.0 months in the pooled XELOX-containing arms versus 8.5 months in the FOLFOX-4-containing arms (hazard ratio [HR], 1.04; 97.5% CI, 0.93 to 1.16). The median overall survival was 19.8 months with XELOX versus 19.6 months with FOLFOX-4 (HR, 0.99; 97.5% CI, 0.88 to 1.12). FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia and febrile neutropenia than XELOX, and XELOX with more grade 3 diarrhea and grade 3 hand-foot syndrome than FOLFOX-4.

Conclusion

XELOX is noninferior to FOLFOX-4 as a first-line treatment for MCRC, and may be considered as a routine treatment option for appropriate patients.

with or without bevacizumab. The second coprimary objective was to evaluate for the superiority of bevacizumab versus placebo when combined with oxaliplatin-based chemotherapy (ie, XELOX or FOLFOX-4), and will be presented as a separate paper.

**Study Design**

NO16966 commenced as a two-arm, open-label, randomized phase III comparison of XELOX versus FOLFOX-4. The protocol was amended to a placebo-controlled, double-blind (for bevacizumab), randomized, 2 × 2 factorial design, and bevacizumab or placebo were added to both treatment groups.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients participating in the study. Approval of the protocol was obtained from an independent ethics committee or institutional review board of each site.

**Patient Population**

Patients aged ≥ 18 years with histologically confirmed colorectal cancer, unresectable metastatic disease (one or more unidimensionally measurable lesions), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 and a life expectancy of longer than 3 months were eligible. No prior systemic therapy for metastatic disease or prior oxaliplatin or bevacizumab were allowed. Radiation therapy or surgery for metastatic disease was permitted if completed at least 4 weeks before randomization and if untreated measurable disease remained. Patients were required to have adequate hematologic/clotting, hepatic, and renal function. Pregnant or breast-feeding women were excluded. Other key exclusion criteria were: clinically significant cardiovascular disease; clinically detectable ascites; use of full-dose anticoagu- lants or thrombolytics; known CNS metastases; serious nonhealing wound, ulcer or bone fracture; known bleeding diathesis or coagulopathy; and proteinuria ≥ 500 mg/24 hours.

**Treatment Plan**

Patients were assigned to treatment using an interactive voice response system. Randomization was stratified by region, ECOG performance status, number of metastatic sites (organs), and alkaline phosphatase level.

XELOX consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m² on day 1 plus oral capecitabine 1,000 mg/m² twice daily for 2 weeks in a 3-week cycle. The first dose of capecitabine was given in the evening of day 1 and the last dose on the morning of day 15. The FOLFOX-4 regimen has been previously described.1 After amendment of the study protocol, bevacizumab or placebo was given as a 90-minute intravenous infusion on day 1 of each cycle before oxaliplatin. Treatment was continued until disease progression (PD) or for 48 weeks (ie, up to 16 cycles of XELOX or 24 cycles of FOLFOX-4), whichever came first (study treatment phase). Patients who completed the 48-week treatment phase without PD were eligible to continue treatment until PD in a poststudy treatment (study treatment phase). Patients who completed the 48-week treatment phase without PD were eligible to continue treatment until PD in a poststudy treatment phase. Patients whose tumor became operable, and for whom resection was performed, were allowed to enter the poststudy treatment phase.

If one of the regimen components was discontinued, treatment could be continued with the remaining components as follows: capectabine or FU/FA ± bevacizumab/placebo could be given after discontinuing oxaliplatin; XELOX, FOLFOX-4, capectabine, or FU/FA could be given after discontinuing bevacizumab/placebo; bevacizumab/placebo could be given after discontinuing XELOX, FOLFOX-4, capectabine or FU/FA; or patients were not permitted to continue on oxaliplatin with or without bevacizumab/placebo.

**Assessments**

Medical history, physical examination, chest x-ray, ECG, and carcinoembryonic antigen measurement were performed within 21 days before starting treatment. Assessments of vital signs, ECOG performance status, height, weight, and routine blood analysis (hematology and chemistry) were performed within 7 days of starting treatment. During treatment, physical examination, hematology, and biochemistry analyses were repeated on day 1 of every treatment cycle.

Tumor assessments (computed tomography scan, magnetic resonance imaging) were made within 28 days before starting study treatment and repeated after every two XELOX cycles and every three FOLFOX-4 cycles (ie, every sixth week in both arms and at the end of treatment). Response Evaluation Criteria in Solid Tumors guidelines11 were used to define all responses. Confirmation of response was required after a minimum of 4 weeks. Tumor responses were assessed by investigators and also by an independent response review committee. After completion of study treatment, patients were followed every 3 months until PD and/or death.

Patients were evaluated for adverse events during therapy and until 28 days after the last study drug dose. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria, version 3.

**Statistical Analysis**

The intent-to-treat (ITT) patient population included all patients who underwent randomization and signed the informed consent form. The eligible patient population (EPP) was the ITT population minus patients who did not receive at least one dose of study drug, and those patients who violated major protocol inclusion/exclusion criteria. As requested by regulatory authorities, the primary analysis of noninferiority was conducted in this EPP population. All patients receiving at least one dose of study drug were included in the safety analysis.

As a first step, the analysis of pooled XELOX-containing compared with pooled FOLFOX-4-containing arms was performed. If positive, an interaction test was performed on PFS to check for any interaction between the different treatment components (FOLFOX-4, XELOX, bevacizumab, nonbevacizumab). Independent of the interaction test, a clinical assessment of treatment effect was also performed. An interaction could be ruled out if the statistical interaction test was not significant and the clinical assessment revealed no clinically relevant difference. If an interaction was ruled out, the pooled analysis remained the primary analysis. If an interaction could not be ruled out, then results in the bevacizumab and nonbevacizumab treatment subgroups would have had to be considered.

PFS, the primary study end point, was defined as the time from the date of randomization to the first documentation of disease progression by the investigator or death from any cause. In order to retain an experiment-wise two-sided type I error of 5%, the noninferiority test for PFS was studied with a two-sided significance level of 2.5% (the remaining 2.5% were used for the superiority testing). Noninferiority was concluded if the upper limit of the 97.5% CI of the hazard ratio (HR) was ≤ 1.23. The noninferiority margin of 1.23 corresponds to retention of at least 50% of the benefit that oxaliplatin plus FU/FA has shown over FU/FA alone in the first-line treatment of MCRC. To confirm the robustness of the primary analysis, Cox models including key demographic and baseline characteristics (ie, sex, age, race, use of adjuvant therapy), and stratification variables were performed on PFS.

For the further assessment of noninferiority, a preplanned exploratory analysis of XELOX and bevacizumab versus FOLFOX-4 and bevacizumab and a post hoc exploratory analysis of the XELOX versus FOLFOX-4 arms in the two-arm part of the study were also performed.

The secondary efficacy end points were OS, ORR, duration of response, and time to treatment failure. For ORR, noninferiority of pooled XELOX versus pooled FOLFOX-4 arms was concluded if the lower limit of the two-sided 97.5% CI for the odds ratio was higher than 0.66. The remaining secondary efficacy analyses were considered descriptive only.

PFS, OS, and time to treatment failure were analyzed using Cox models and presented as Kaplan-Meier estimates with HR and 97.5% CIs. Overall response was assessed by logistic regression, and presented with 97.5% CIs. Duration of overall response was presented as Kaplan-Meier estimates with 97.5% CIs.

The analysis of NO16966 was event driven. The final analysis was to be done when 1,200 PFS events had occurred in the EPP, this approach ensuring 90% power at an α level of 2.5. All the results presented, except OS, are based...
on the main clinical cutoff date (January 31, 2006). In order to provide the most up-to-date results for OS, data presented are based on a more recent clinical cutoff date (January 31, 2007).

Patient Population

Between July 2003 and May 2004, 634 patients were randomly assigned in the two-arm portion of the study. Between February 2004 and February 2005, an additional 1,401 patients were randomly assigned in the 2 × 2 factorial part of the study. One patient, who was randomly assigned twice, was excluded from the FOLFOX-4–bevacizumab arm (and not treated) for not providing informed consent, but was later included and treated at another center in the XELOX and placebo arm.

Overall, 2,034 patients made up the ITT population from the following regions: Europe (n = 1,048); Canada (n = 343); Oceania (n = 188); United States (n = 178); central/eastern Asia (n = 163); South America (n = 65); and South Africa (n = 49). The EPP population comprised a total of 1,904 patients (Fig 1). The safety population comprised 1,304 patients in the nonbevacizumab-treated groups and 694 patients in the bevacizumab-treated groups. Baseline demographic and clinical characteristics were well balanced between treatment arms (Table 1).

Efficacy

The cutoff dates were January 31, 2006, for PFS and January 31, 2007, for OS. The median follow-up times at the respective cutoff dates were 17.7 and 29.7 months.

Both a clinically relevant and statistically significant (P = .7025) treatment interaction was ruled out. Therefore, the pooled analysis of all patients treated with XELOX (ie, XELOX, XELOX and placebo, and XELOX and bevacizumab) versus FOLFOX-4 (ie, FOLFOX-4, FOLFOX-4 and placebo, FOLFOX-4 and bevacizumab) was the primary analysis of noninferiority.

The median PFS (ITT analysis) was 8.0 months in the pooled XELOX-containing arms versus 8.5 months in the FOLFOX-4–containing arms (HR, 1.04; 97.5% CI, 0.93 to 1.16), the upper limit of the 97.5% CI being below the predefined noninferiority margin of 1.25 (Fig 2). Similar results were observed in the EPP with a median PFS of 7.9 months in the pooled XELOX-containing arms versus 8.5 months in the FOLFOX-4–containing arms (HR, 1.05; 97.5% CI, 0.94 to 1.18).

The two exploratory analyses were further supportive of the main study findings. Median PFS with XELOX and bevacizumab was 9.3 months versus 9.4 months with FOLFOX-4 and bevacizumab (HR, 1.01; 97.5% CI, 0.83 to 1.23; ITT). In the two-arm part of the study, the median PFS with XELOX was 7.3 months versus 7.7 months with FOLFOX-4 (HR, 0.96; 97.5% CI, 0.80 to 1.16; ITT).

The noninferiority results for PFS were further supported by subgroup analyses defined by demographic and baseline characteristics and stratification variables (Fig 3). The HRs for PFS in the ITT population were similar across the different subgroups.

Response Rates and Overall Survival

ORR for the two regimens, as assessed both by investigators (XELOX 47% v FOLFOX 48%) and the independent response review committee (37% in each arm), were essentially the same (Table 2).
The median OS in the ITT population was 19.8 months in the pooled XELOX arms and 19.6 months in the pooled FOLFOX-4 arms, with a corresponding HR of 0.99 (97.5% CI, 0.88 to 1.12; Fig 4). The HR of XELOX and bevacizumab versus FOLFOX-4 and bevacizumab was 0.99 (97.5% CI, 0.80 to 1.23; online-only Fig A1) and in the two-arm part of the study the HR of XELOX versus FOLFOX-4 was 0.90 (97.5% CI, 0.74 to 1.10). The details of OS and other descriptive secondary end points are presented in Table 2.

Second-Line Therapy
There were no major imbalances between the treatment groups with respect to the use of second-line therapy: XELOX-containing arms, 51%, and FOLFOX-4-containing arms, 53%. The most common agents used were: irinotecan (41% with FOLFOX-4 vs 39% with XELOX); FU (29% vs 25%); capecitabine (12% vs 7%); cetuximab (11% vs 9%); and bevacizumab (5% vs 6%).

Safety
The median dose intensities (ratio of dose received to dose planned) of FU, capecitabine, oxaliplatin, and bevacizumab were ≥ 0.89 (97.5% CI, 0.80 to 1.23; online-only Fig A1) and in the two-arm part of the study the HR of XELOX versus FOLFOX-4 was 0.90 (97.5% CI, 0.74 to 1.10). The details of OS and other descriptive secondary end points are presented in Table 2.
For the assessment of safety of XELOX versus FOLFOX-4, patients in the pooled XELOX/XELOX and placebo and pooled FOLFOX-4/FOLFOX-4 and placebo arms were compared. For the assessment of safety with addition of bevacizumab, patients in XELOX and bevacizumab and FOLFOX-4 and bevacizumab arms were compared.

A summary of adverse events associated with XELOX versus FOLFOX-4 by National Cancer Institute Common Toxicity Criteria grade is presented in Table 3. While the overall rates of grade 3/4 adverse events were fairly similar with both FOLFOX-4 and XELOX, grade 4 adverse events were more common with FOLFOX-4 (25% and 12%, respectively), this difference being predominantly due to grade 4 neutropenia.

The rates of some individual adverse events also differed between the two regimens. Whereas FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia (44% vs 7%), febrile neutropenia (4.8% vs 0.9%), and grade 3/4 venous thromboembolic events (6.3% vs 3.8%) than XELOX, XELOX was associated with more grade 3 diarrhea (19% vs 11%) and grade 3 hand-foot syndrome (6% vs 1%). As would be expected, rates of grade 3/4 neurosensory toxicity were similar with both regimens (approximately 17%). Grade 3/4 cardiac disorders were reported in nine FOLFOX-4 recipients (1.4%) and six XELOX recipients (0.9%).

The addition of bevacizumab did not alter the similarities and differences in safety profile between XELOX and FOLFOX-4 (online-only Table A1). The tolerability profile of XELOX and FOLFOX-4 in the United States versus all patients is shown in online-only Table A2.

Treatment was discontinued due to adverse events in 161 patients (25%) treated with FOLFOX-4, 170 patients (26%) treated with XELOX, 104 patients (30%) treated with FOLFOX-4-bevacizumab, 0 patients (0%) treated with XELOX, 114 patients (21%) treated with XELOX-bevacizumab, and 77 patients (15%) treated with placebo/FOLFOX-4, 88 patients (17%) treated with placebo/XELOX, and 70 patients (13%) treated with placebo/XELOX-bevacizumab.

Table 2. Analysis of Efficacy (intent-to-treat population)

<table>
<thead>
<tr>
<th>End Point</th>
<th>FOLFOX-4/FOLFOX-4 + Placebo/FOLFOX-4 + Bevacizumab</th>
<th>XELOX/XELOX + Placebo/XELOX + Bevacizumab</th>
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<tbody>
<tr>
<td>No. of patients</td>
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<td>Primary</td>
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<tr>
<td>Median progression-free survival, months</td>
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<td>Hazard ratio</td>
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<tr>
<td>97.5% CI</td>
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</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
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<tr>
<td>Overall response rate, %</td>
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</tr>
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<td>47</td>
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<tr>
<td>Odds ratio</td>
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<tr>
<td>97.5% CI</td>
<td>0.77 to 1.15+</td>
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<tr>
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<tr>
<td>Odds ratio</td>
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<tr>
<td>97.5% CI</td>
<td>0.81 to 1.23</td>
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<tr>
<td>Median overall survival, months†</td>
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<td>19.8</td>
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<tr>
<td>Hazard ratio</td>
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<tr>
<td>97.5% CI</td>
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<td>Median time to treatment failure, months‡</td>
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<tr>
<td>Median duration of response, months§</td>
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<td>97.5% CI</td>
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Abbreviations: FOLFOX-4, fluorouracil, folinic acid, and oxaliplatin; IRC, independent response review committee; XELOX, capecitabine and oxaliplatin.

*Non-inferiority was concluded if the upper limit of the 97.5% CI was < 1.23.
†Non-inferiority was concluded if the lower limit of the 97.5% CI was > 0.66.
§Safety population.

Fig 3. Subgroup analysis of progression-free survival (PFS) according to baseline demographic and stratification variables (intent-to-treat [ITT] population). n, number of patients; ECOG, Eastern Cooperative Oncology Group.

Fig 4. Overall survival (intent-to-treat population [ITT]). FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; XELOX, capcitabine and oxaliplatin; EPP, eligible patient population; HR, hazard ratio.
The efficacy of capcitabine and oxaliplatin combinations has been tested in three other smaller phase III trials in the first-line setting\textsuperscript{12-14} and in one trial in the second-line setting.\textsuperscript{15} While the XELOX regimen was used in two first-line trials,\textsuperscript{12,14} a modified capcitabine and oxaliplatin regimen (CAPOX) was used in the third first-line trial.\textsuperscript{13} FOLFOX-6 was used as the comparator regimen in one trial,\textsuperscript{12} while two trials used other infusional FU and oxaliplatin with (FUFOX) or without FA (FUOX) regimens. Duerre et al\textsuperscript{12} showed noninferiority of XELOX versus FOLFOX-6 in terms of response rate (42 vs 46\%). Median TTP (9.1 vs 9.7 months) and overall survival (19.5 vs 18.8 months) were also similar in the two groups. Diaz-Rubio et al\textsuperscript{14} reported equivalent efficacy with XELOX and FUOX, with a median TTP of 8.9 months with XELOX and 9.5 months with FUOX. In contrast, in the trial by Porschen et al,\textsuperscript{13} the median PFS was 7.1 months with the nonstandard CAPOX regimen and 8.0 months with FUFOX (HR, 1.17; 95\% CI, 0.96 to 1.43; \(P = 0.17\)); the upper 95\% CI exceeded the prospectively defined interval for noninferiority (1.29). However, the study by Porschen et al\textsuperscript{13} was underpowered, and it is possible that an imbalance in restaging intervals in this trial, particularly during the first 20 weeks, may have biased the results in favor of FUFOX. Finally, Rothenberg et al\textsuperscript{15} showed that XELOX is noninferior to FOLFOX-4 in terms of PFS in the second-line treatment of MCRC.

Safety data from this trial suggest that while the profile of adverse events associated with both the XELOX and FOLFOX-4 regimens are similar, there are differences in the rates at which these occur. The XELOX regimen was associated with more grade 3 diarrhea, whereas FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia and febrile neutropenia.

The FOLFOX-4 regimen involves two 22-hour infusions of FU every 14 days, which require catheter placement and regular visits to and 109 patients (31\%) treated with XELOX and bevacizumab. The most common reasons for treatment discontinuation were neurosen- 

tory toxicity and diarrhea.

Treatment-related mortality up to 28 days after the last treat-

ment dose was documented in 11 patients (1.7\%) treated with 

FOLFOX-4, 14 patients (2.1\%) treated with XELOX, six patients 

(1.8\%) treated with FOLFOX-4 and bevacizumab, and eight patients 

(2.1\%) treated with XELOX, six patients 

(1.8\%) treated with FOLFOX-4, 14 patients (2.1\%) treated with XELOX, and 109 patients (31\%) treated with XELOX and bevacizumab. The most common reasons for treatment discontinuation were neurosenso-

tory toxicity and diarrhea.

This large multinational randomized phase III trial demonstrates that XELOX is noninferior to FOLFOX-4 in terms of PFS, OS, and ORR in the first-line treatment of patients with MCRC. With approximately 1,000 patients in each pooled treatment arm, the NO16966 trial is the largest conducted to date to address this question. The overall finding of noninferiority was also supported by exploratory analyses con-

ducted in the XELOX and bevacizumab versus FOLFOX-4 and bevac-

izumab subgroups and the original XELOX versus FOLFOX-4 arms. Collectively, these analyses show that the findings of the main analysis are robust.

Previously, the efficacy and safety of capcitabine as single-agent therapy was established based on comparisons with bolus regimens of FU/FA.\textsuperscript{2-5} However, in current clinical practice, infusional regimens of FU/FA are often preferred because they confer some benefits in terms of toxicity and efficacy. This trial compared a capcitabine-based regimen with a regimen that included a bolus and continuous infusion of FU, and demonstrated that the efficacy of these two treatment options in this combination therapy context is similar.
the clinic. The FOLFOX-4 regimen was selected as the comparator in this study for regulatory reasons but is still widely used globally. Although modified FOLFOX regimens (such as mFOLFOX-6) have replaced FOLFOX-4 in some countries and although these do afford some greater convenience in terms of one 2-day infusion instead of two 22-hour infusions, the XELOX regimen requires still fewer planned office visits, with oxaliplatin administered every 21 days and capecitabine taken orally. Of note, there was a slight increase in grade 3/4 thromboembolic events with FOLFOX-4, some of which may have been attributable to catheter use.

In conclusion, XELOX is noninferior to FOLFOX-4, and may be considered as a standard treatment in the first-line treatment of MCRC.

**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; these relationships are 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.

**REFERENCES**


**Acknowledgment**

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe Reader®).

**Appendix**

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe Reader®).