

Bevacizumab + Capecitabine as Maintenance Therapy after Initial Bevacizumab + XELOX Treatment in Previously Untreated Patients with Metastatic Colorectal Cancer: Phase III ‘Stop and Go’ Study Results – A Turkish Oncology Group Trial

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Key Words

Bevacizumab · Capecitabine · Oxaliplatin · Metastatic colorectal cancer · Maintenance therapy

Abstract

Objective: It was the aim of this study to evaluate maintenance therapy with bevacizumab + capecitabine following induction with bevacizumab + capecitabine + oxaliplatin (XELOX) versus bevacizumab + XELOX until progression as first-line therapy in metastatic colorectal cancer (mCRC). **Methods:** Patients received either bevacizumab (7.5 mg/kg) + XELOX (capecitabine 1,000 mg/m² twice daily on days 1–14 + oxaliplatin 130 mg/m² on day 1 every 3 weeks) until disease progression (arm A) or the same doses of bevacizumab + XELOX for 6 cycles followed by bevacizumab + capecitabine until disease progression (arm B). The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate (ORR) and safety. **Results:** One hundred and twenty-three patients were randomized. Treatment compliance was

similar in both groups. Median PFS was significantly longer for arm B than for arm A (11.0 vs. 8.3 months; $p = 0.002$). There was no significant difference between the two arms for ORR (66.7 vs. 59.0%; $p = 0.861$) or median OS (23.8 vs. 20.2 months; $p = 0.100$). Tolerability was acceptable in both treatment arms; the most frequent grade 3/4 treatment-related adverse events (arm B vs. arm A) were fatigue (6.6 vs. 16.1%), diarrhoea (3.3 vs. 11.3%), anorexia (3.3 vs. 11.3%), and neuropathy (1.6 vs. 8.1%). **Conclusions:** Maintenance therapy with bevacizumab + capecitabine can be considered an appropriate option following induction bevacizumab + XELOX in patients with mCRC instead of continuation of bevacizumab + XELOX.

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Introduction

Capecitabine in combination with oxaliplatin (XELOX) is one of the standard chemotherapy regimens for the treatment of metastatic colorectal cancer (mCRC),

having similar efficacy to continuous infusions of 5-fluorouracil (5-FU) combined with oxaliplatin [1–5]. Combining doublet chemotherapy regimens with bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor [6, 7], has been shown to improve progression-free survival (PFS) and overall survival (OS) in the treatment of patients with mCRC in both the first- and second-line settings [3, 8–13]; these findings have also been observed in two large observational studies (BRiTE and BEAT) [14–17] and in one large phase III study [8] of patients in routine clinical practice.

Despite the availability of a number of established regimens, the optimal duration of treatment for patients with mCRC is still under debate. While some physicians maintain treatment until unacceptable toxicity and/or progression occurs, others stop all or some of the drugs after patients have been treated for approximately 4–6 months or after stabilization of the maximum response. Such different strategies to limit the toxicity of chemotherapy have been evaluated in several recent studies, including using intermittent schedules with oxaliplatin, a ‘stop and go’ approach, and also chemotherapy ‘holidays’ [18–22]. Díaz-Rubio et al. [23] suggested that the maximum benefit of bevacizumab may be observed when treatment is maintained until disease progression.

A longer period of chemotherapy use is restricted even in patients who benefited from the treatment due to the cumulative toxicity caused by cytotoxic chemotherapy. However, if this group of patients can be treated with a less toxic treatment regimen, it might be feasible to improve clinical results. To this end, the present ‘stop and go’ study was designed to evaluate the effect of stopping oxaliplatin, whose cumulative toxic effect is well known, by comparing the efficacy of continuous XELOX + bevacizumab with capecitabine + bevacizumab maintenance treatment following induction with XELOX + bevacizumab for 6 cycles in patients with previously untreated mCRC.

Methods

Study Design

This was a multi-centre, randomized (1:1), open-label, phase III trial (ClinicalTrials.gov identifier: NCT00623805) designed to compare the efficacy and tolerability of 6 cycles of XELOX + bevacizumab followed by maintenance XELOX + bevacizumab or capecitabine + bevacizumab in patients with mCRC. Central and local ethics committee approvals were obtained before enrolment of any patients in the study, which was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before study entry.

Patients

Patients aged ≥ 18 years with histologically confirmed mCRC, an Eastern Cooperative Oncology Group performance status ≤ 2 and a life expectancy of >3 months were enrolled. All patients had to have at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) [24]. Adjuvant chemotherapy, if administered, should have been completed at least 6 months before study entry. No previous chemotherapy for metastatic or advanced colorectal cancer was permitted, nor was previous exposure to bevacizumab. Patients had to have adequate haematological (absolute neutrophil count $>1.5 \times 10^9/l$; platelet count $>100 \times 10^9/l$; haemoglobin >9 g/dl), hepatic [total bilirubin $<1.5 \times$ the upper limit of normal (ULN); alanine aminotransferase and aspartate aminotransferase $<2.5 \times$ ULN, or $<5 \times$ ULN in the case of hepatic metastases or $<10 \times$ ULN in the case of osseous metastases; alkaline phosphatase $<2.5 \times$ ULN, or $<5 \times$ ULN or $<10 \times$ ULN in the case of hepatic or osseous metastases, respectively] and renal function (creatinine clearance ≥ 60 ml/min; proteinuria $<2+$).

Key exclusion criteria included pregnant or breast-feeding women; clinically significant cardiac disease; lack of physical integrity of the upper gastrointestinal tract; peripheral neuropathy; history of other malignancy; and central nervous system metastases.

Treatment

Patients were randomized 1:1 to one of two treatment arms. Initially, both groups received 6 cycles of XELOX (oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1,000 mg/m² orally twice daily on days 1–14 every 3 weeks) + bevacizumab 7.5 mg/kg intravenously on day 1 of the 3-week cycle. After 6 cycles, patients received maintenance therapy comprising either XELOX + bevacizumab 7.5 mg/kg intravenously every 3 weeks (arm A) or capecitabine 1,000 mg/m² orally twice daily on days 1–14 + bevacizumab 7.5 mg/kg intravenously on day 1 every 3 weeks (arm B) until disease progression, severe toxicity or withdrawal of consent.

During the initial treatment period (and maintenance period for patients in the XELOX + bevacizumab group), capecitabine and bevacizumab could be continued at the physician’s discretion in the event of discontinuation of oxaliplatin. Patients could continue receiving XELOX if bevacizumab was discontinued, or capecitabine alone if oxaliplatin and bevacizumab were discontinued. In cases of unacceptable toxicity, only the related medication was stopped.

Assessments and Endpoints

The primary endpoint was PFS, defined as the time from randomization to progression or death. Secondary endpoints were OS, defined as the time from randomization to death, the objective response rate (ORR; assessed using RECIST) and safety.

RECIST guidelines [24] were used to define all responses after patients had received 9 weeks of therapy: complete response; partial response (PR); stable disease; or progressive disease. ORR was defined as the sum of patients achieving a complete or a partial response. Confirmation of all responses was required after 4 weeks.

Toxicity was graded according to the criteria of the National Cancer Institute Common Terminology for Adverse Events (version 3.0).

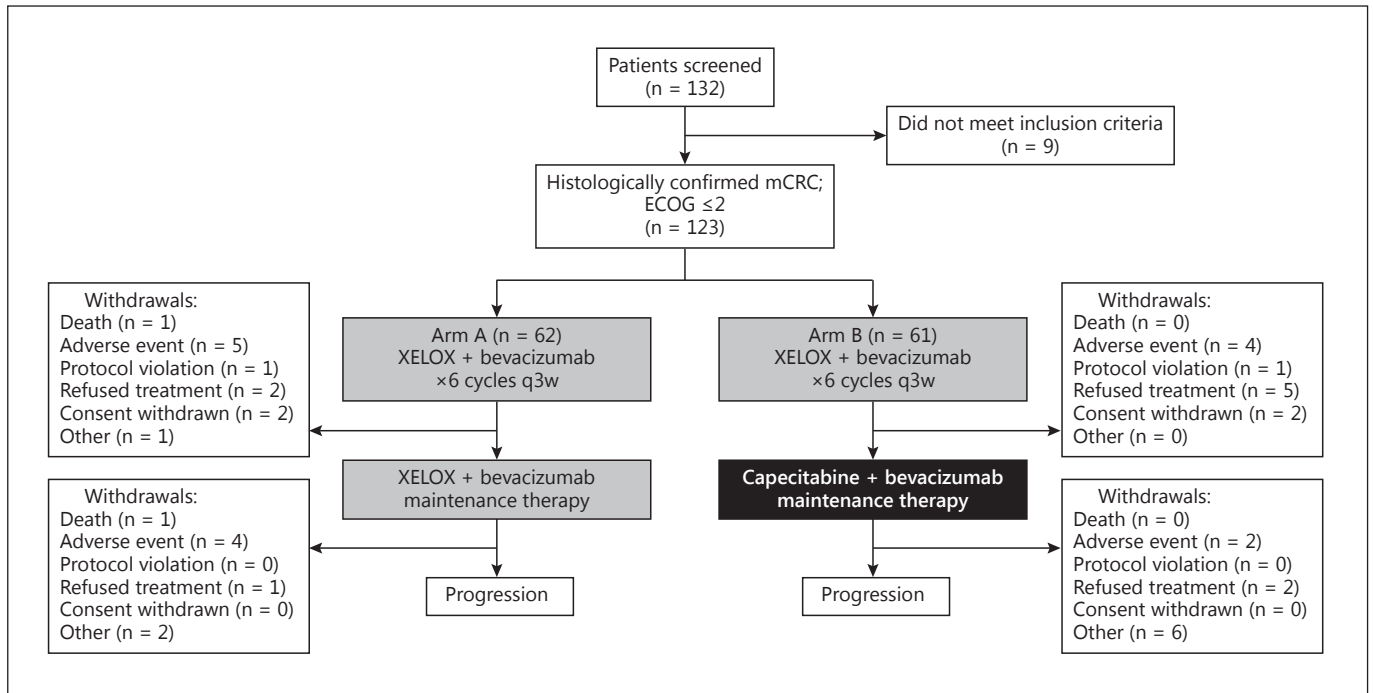


Fig. 1. CONSORT flow diagram. ECOG = Eastern Cooperative Oncology Group; q3w = every 3 weeks.

Table 1. Baseline characteristics of patients with mCRC receiving maintenance XELOX + bevacizumab after induction with XELOX + bevacizumab (arm A) or maintenance capecitabine + bevacizumab after induction with XELOX + bevacizumab (arm B)

Characteristic	Arm A (n = 62)	Arm B (n = 61)
Gender		
Male/female	39/23 (63/37)	38/23 (62/38)
Age, years		
Median	59	56
Range	25–77	34–82
ECOG performance status, %		
0/1	61.3/38.7	55.7/44.3
Primary tumour site ¹ , %		
Colon	47.5	72.4
Rectum	52.5	27.6
Colorectal	100	100
Metastatic sites, %		
1/>1	6.5/93.5	13.1/86.9
Location of metastatic site		
Liver only	3 (4.8)	4 (6.6)
Liver and other	47 (75.8)	42 (68.9)
Other	12 (19.4)	15 (24.6)

Figures in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group.

¹If the primary tumour site included both the colon and rectum it was defined as colorectal.

Statistical Analysis

Assuming an increase in median PFS of 1.5 months between arm A (9.5 months) and arm B (11.0 months) and a standard deviation of 3.9 months, it was estimated that a total of 118 patients needed to be randomized to achieve 80% statistical power with a significance level of 0.05 and a 10% drop-out rate. A PFS of 9.5 months was chosen for arm A as this is the average PFS obtained with XELOX + bevacizumab, and an increase in 1.5 months was chosen as this was a realistic additional time that could be achieved with the tolerable maintenance regimen chosen. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Median survival, 95% confidence intervals (95% CIs) and survival rates at 12, 24 and 36 months were calculated.

Results

Between April 2008 and July 2009, 132 patients were screened. Nine patients did not meet the inclusion and exclusion criteria and were recorded as screening failures, and 123 patients were randomized to treatment; 62 were randomized to maintenance XELOX + bevacizumab after induction with XELOX + bevacizumab (arm A) and 61 were randomized to maintenance capecitabine + bevacizumab after induction with XELOX + bevacizumab (arm B; fig. 1). Baseline demographic and clinical characteristics were well balanced with no significant differences be-

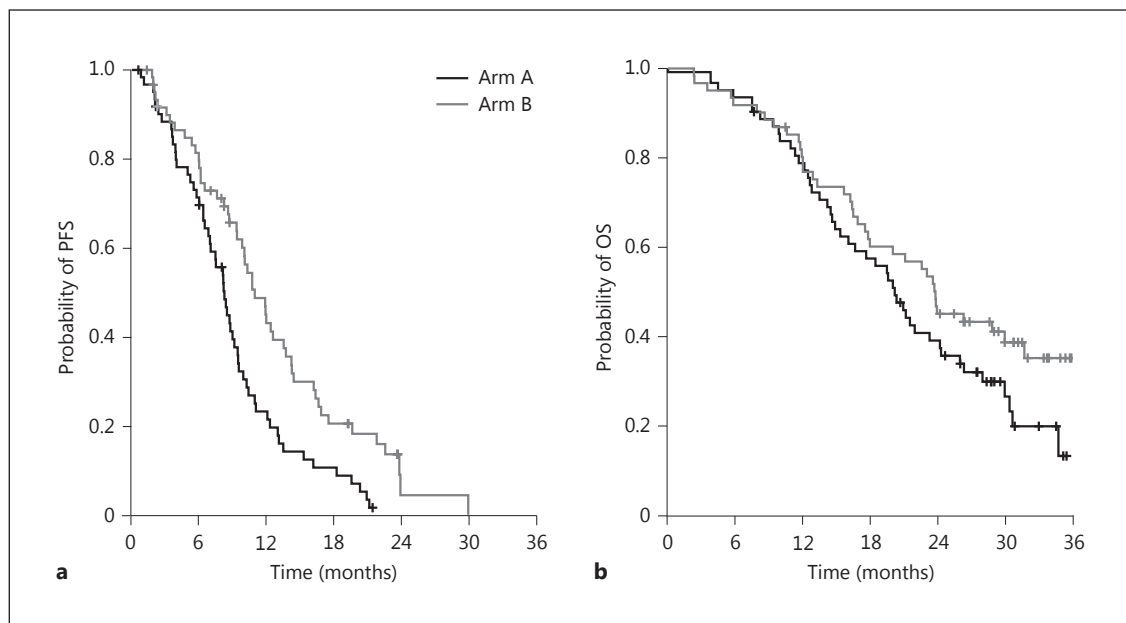


Fig. 2. PFS (a) and OS (b) in patients with mCRC receiving maintenance XELOX + bevacizumab after induction with XELOX + bevacizumab (arm A; n = 62) or maintenance capecitabine + bevacizumab after induction with XELOX + bevacizumab (arm B; n = 61).

tween the two treatment arms (table 1). The median age in arm A was 59 years (range 25–77) and 56 years (range 34–82) in arm B.

Treatment compliance was similar in both groups, with patients in arm A receiving a median of 8 cycles (range 1–26) and those in arm B receiving a median of 11 cycles (range 1–33). The median total doses over the induction period were: oxaliplatin 883 and 766 mg/m² in arms A and B, respectively; bevacizumab 51.9 and 51.7 mg/kg, respectively; and capecitabine 13,597 and 13,404 mg/m², respectively. Data on re-treatment regimens used once patients had stopped receiving either treatment arm of the study were not collected and hence are not evaluable in this study.

Efficacy

The primary endpoint, median PFS, was statistically significantly greater for arm B (11.0 months, 95% CI 9.1–12.9) than for arm A (8.3 months, 95% CI 7.1–9.5; log-rank test, $p = 0.002$; hazard ratio 0.6; fig. 2a).

Response to treatment is summarized in table 2. There was no statistically significant difference between the two treatment arms in terms of ORR (arm B 66.7%, arm A 59.0%; χ^2 test, $p = 0.861$). The disease control rate (complete response + partial response + stable disease) was

Table 2. Response to treatment in patients with mCRC receiving maintenance XELOX + bevacizumab after induction with XELOX + bevacizumab (arm A) or maintenance capecitabine + bevacizumab after induction with XELOX + bevacizumab (arm B)

Endpoint, %	Arm A (n = 56)	Arm B (n = 54)
Overall response rate	59.0	66.7
Complete response	5.4	5.6
Partial response	53.6	61.1
Stable disease	35.7	29.6
Progressive disease	5.4	3.7

also similar for the two treatment arms (arm B 96.3%, arm A 94.7%).

For the secondary endpoint of median OS, there was no statistically significant difference between the two treatment arms but this did numerically favour arm B (23.8 months, 95% CI 22.0–28.8; arm A 20.2 months, 95% CI 18.4–23.5; log-rank test, $p = 0.100$; fig. 2b). The 12-, 24- and 36-month survival rates in arm A were 78.8, 35.7 and 13.3%, respectively, while those in arm B were slightly higher at 80.0, 45.1 and 35.2%, respectively.

Safety

Tolerability of the induction and maintenance treatment regimens was acceptable in both treatment arms. Fifty-one patients experienced 114 grade 3/4 adverse events. The proportion of patients with grade 3/4 adverse events related to treatment was higher in arm A than in arm B (48.4 vs. 34.4%, respectively; $p = 0.116$), and the incidences are shown in table 3. There was a trend toward a higher incidence of fatigue, diarrhoea, anorexia, and neuropathy in patients in arm A, but this did not reach statistical significance.

Twenty patients in arm A discontinued the study as a result of death ($n = 2$), an adverse event ($n = 9$), protocol violation ($n = 1$), treatment refusal ($n = 3$), consent withdrawal ($n = 2$), and other reasons ($n = 3$). In arm B, 22 patients discontinued study treatment because of an adverse event ($n = 6$), protocol violation ($n = 1$), treatment refusal ($n = 7$), consent withdrawal ($n = 2$), and other reasons ($n = 6$; fig. 1).

Reductions/suspensions of oxaliplatin, capecitabine and bevacizumab doses occurred in 17 patients in arm A and in 15 patients in arm B. Nine patients (14.5%) in arm A had oxaliplatin withdrawn and continued with capecitabine + bevacizumab chemotherapy, while no patients in arm B had oxaliplatin withdrawn during the induction phase.

Three adverse events resulting in death that were related to the study drugs were reported.

Discussion

The combination of doublet chemotherapy regimens with biological agents, such as bevacizumab, has been shown to prolong PFS in patients with mCRC, but the optimal sequence and duration of first-line treatment remain to be determined. A number of recent studies in patients with mCRC have investigated different approaches to treatment, including intermittent chemotherapy [20], 'stop and go' therapy [21, 22, 25, 26] and low-intensity maintenance strategies [14, 22], all of which had the aim of reducing the burden of treatment for patients while maintaining a positive treatment outcome.

While XELOX is considered an established chemotherapy regimen for the treatment of mCRC, and its combination with bevacizumab is known to improve PFS and OS [13, 17], one issue with long-term therapy for patients with mCRC is cumulative neuropathy associated with oxaliplatin use. Consequently, there is a need to limit the

Table 3. Incidence of treatment-related grade 3/4 adverse events ($n = 123$) in patients with mCRC receiving maintenance XELOX + bevacizumab after induction with XELOX + bevacizumab (arm A) or maintenance capecitabine + bevacizumab after induction with XELOX + bevacizumab (arm B)

Adverse event, %	Arm A ($n = 62$)	Arm B ($n = 61$)
Fatigue	16.1	6.6
Diarrhoea	11.3	3.3
Anorexia	11.3	3.3
Neuropathy	8.1	1.6
Vomiting	6.5	4.9
Neutropenia	6.5	1.6
Nausea	4.8	1.6
Anaemia	4.8	1.6
Hypertension	1.6	3.3
Hand-foot syndrome	1.6	1.6

dose administered over long-term treatment. The present study was conducted to evaluate the role of maintenance treatment with capecitabine + bevacizumab compared with XELOX + bevacizumab until disease progression after induction chemotherapy with XELOX + bevacizumab in patients with mCRC.

The findings from this study suggest that maintenance therapy with bevacizumab + capecitabine following induction with 6 cycles of bevacizumab + XELOX is at least as effective as continuous bevacizumab + XELOX until progression in patients with previously untreated mCRC. Indeed, while there was no difference between the two treatment arms in ORR, median PFS – the primary endpoint of the study – was statistically significantly longer for maintenance treatment with capecitabine + bevacizumab (arm A) compared with maintenance treatment with XELOX + bevacizumab (arm B; 11.0 vs. 8.3 months; $p = 0.002$). For the secondary endpoint of median OS, there was no statistically significant difference between the two treatment arms but this did numerically favour maintenance with capecitabine + bevacizumab (arm A) over maintenance with XELOX + bevacizumab (20.2 vs. 23.8 months). These findings would suggest that limiting the oxaliplatin dose administered over long-term treatment, in this case by having an induction period containing oxaliplatin and a maintenance period without it, does not have a detrimental effect on clinical outcome. Indeed, the primary endpoint was significantly greater in maintenance treatment with capecitabine + bevacizumab, which might be because this regimen is better tolerated.

In the OPTIMOX1 study, Tournigand et al. [22] reported similar PFS and OS values in patients with mCRC randomized to receive either 5-FU/leucovorin + oxaliplatin (FOLFOX4) until disease progression or FOLFOX7 for 6 cycles followed by maintenance without oxaliplatin for 12 cycles. The subsequent OPTIMOX2 study, reported by Chibaudel et al. [18], found that a chemotherapy-free interval following 6 cycles of modified FOLFOX7 was inferior to 6 cycles of modified FOLFOX7 followed by simplified leucovorin + bolus and infusional 5-FU as maintenance therapy until progression. This would indicate the importance of some form of maintenance therapy following induction chemotherapy, although the GISCAD study found that chemotherapy with 5-FU/leucovorin + irinotecan using a 2 months on/2 months off schedule was as effective as continuous treatment in terms of PFS and OS in patients with advanced colorectal cancer [20]. The CAIRO3 study investigated the efficacy of maintenance treatment with capecitabine + bevacizumab versus observation in mCRC patients not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOXB) and found median PFS in the observation arm to be 4.1 months compared with 7.4 months in the maintenance capecitabine + bevacizumab arm (hazard ratio 0.44, 95% CI 0.37–0.54; $p < 0.0001$) [27]. Median time to progression was also significantly prolonged (11.5 vs. 15.4 months; $p < 0.0001$), as was median OS (17.9 vs. 21.7 months; $p = 0.02$), in the maintenance treatment arm [27]. As with our study, these findings support the use of maintenance treatment with capecitabine + bevacizumab.

The MACRO study evaluated maintenance therapy with only bevacizumab following induction with XELOX + bevacizumab versus continuous XELOX + bevacizumab. No statistically significant differences were found in median PFS (10.4 months with XELOX + bevacizumab vs. 9.7 months with bevacizumab), median OS (23.2 vs. 20.0 months) and response rate (47 vs. 49%) between the two arms [23]. However, maintenance therapy with bevacizumab + capecitabine in our study gave a statistically significant benefit in terms of PFS compared with maintenance treatment with bevacizumab + XELOX. Overall, all of these studies support the rationale for some form of maintenance therapy after previous induction therapy in the first-line setting. However, a limitation of the MACRO study and ours is that data on subsequent treatment regimens following disease progression or study dropout are not available, making it unfeasible to determine possible optimal treatment sequences for patients with advanced colorectal cancer.

One of the major issues with long-term therapy with oxaliplatin-containing chemotherapy regimens for patients with mCRC is cumulative neuropathy, which is the main driver for trying to limit the dose of oxaliplatin administered over the duration of treatment. Neuropathy may cause patients who are continuing to respond to treatment to discontinue chemotherapy. The OPTIMOX1 study demonstrated that short-term induction with oxaliplatin followed by maintenance therapy delayed or prevented cumulative sensory neuropathy and achieved similar efficacy to continuous administration of FOLFOX until progression or the occurrence of cumulative neurotoxicity [22]. In the present study, the incidence of treatment-related grade 3/4 neuropathy was less frequent in patients who received maintenance therapy with capecitabine + bevacizumab compared with XELOX + bevacizumab (1.6 vs. 8.1%), which would support findings from other, similar studies.

On the basis of our findings, together with similar studies already published in the medical literature, we conclude that maintenance therapy with capecitabine + bevacizumab can be considered an appropriate option following induction with XELOX + bevacizumab in patients with previously untreated mCRC.

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