Capecitabine Maintenance Chemotherapy in the Treatment of Metastatic Colorectal Cancer: A Meta-Analysis

Bradley Ashley Gue Ong1 Aubrey Melody Remigio Rocimo1 Rich Ericson Chan King2 Eric Baldivino Yasay3

1College of Medicine, University of the Philippines, Manila, Philippines
2Department of Medicine, Section of Medical Oncology, Philippine General Hospital, University of the Philippines, Manila, Philippines
3Department of Medicine, Section of Gastroenterology, Philippine General Hospital, University of the Philippines, Manila, Philippines

Address for correspondence Bradley Ashley Ong, MD, UP College of Medicine, College of Medicine Main Building, Pedro Gil Street, Taft Ave, Ermita, Manila 1000, Philippines (e-mail: bgong@up.edu.ph).

Abstract

Many agents have been evaluated as maintenance therapy for metastatic colorectal cancer (mCRC), but there is no consensus on the optimal regimen. This study assessed the effect of single-agent capecitabine maintenance therapy on the survival outcomes of mCRC patients. A comprehensive literature search was performed according to prespecified inclusion and exclusion criteria for randomized controlled trials (RCTs) comparing capecitabine as maintenance monotherapy versus active monitoring for mCRC patients. Data on overall survival (OS), progression-free survival (PFS), time to tumor progression (TTP), adverse events, and quality of life (QoL) scores were extracted. Three RCTs with a total of 576 patients were included. Pooled analyses found neither OS benefit (HR:0.85, 95% CI:0.64–1.13) nor reduction in mortality at 24 months (RR:0.88, 95% CI:0.66–1.17) with capecitabine maintenance. Compared with active monitoring, capecitabine maintenance therapy improved PFS (HR:0.36, 95% CI:0.26–0.61) and reduced the risk of progression at 6 months (HR:0.78, 95% CI:0.56–1.10). The incidence of any grade ≥ 3 toxicity was higher with maintenance therapy than with observation (OR:2.02, 95% CI:1.42–2.88). No difference in terms of QoL was observed. Single-agent capecitabine as maintenance for patients with mCRC provides no OS benefit but results in statistically significant improvement in PFS with increased risk of toxicity. Hence, it may be considered particularly for patients who wish to delay the need for second-line treatment and who can tolerate it well.

Keywords
► capecitabine
► maintenance therapy
► metastatic colorectal cancer

Introduction

Colorectal cancer ranks as the second leading cause of cancer-related deaths worldwide, with an incidence that is predicted to rapidly grow from 1.8 million new cases in 2018 to 2.5 million in 2035.1,2 Despite seeing an increase in survival rates, around one-fourth of all patients will present...
with metastatic disease, and approximately half will develop metastases.\textsuperscript{3}

Chemotherapy is the mainstay treatment for unresectable metastatic colorectal cancer (mCRC), with the goal of prolonging survival while preserving or improving quality of life (QoL).\textsuperscript{4} After completion of first-line chemotherapy, the current standard of care is to give no additional treatment until there is an evidence of disease progression. During this time, maintenance therapy with an active agent may in theory provide tumor control and delay the need for second-line combination chemotherapy and its associated toxicities.\textsuperscript{5,6} This regimen provides the potential to improve progression-free survival (PFS) and OS.

Many agents have been evaluated as maintenance therapy, but there is no consensus on the optimal regimen.\textsuperscript{7-10} Meta-analysis of fluoropyrimidine with or without bevacizumab has shown PFS benefit in some studies but unable to demonstrate OS benefit.\textsuperscript{11} Similarly, a multicenter randomized controlled trial (RCT) on bevacizumab/capecitabine maintenance therapy found improved PFS but did not find an OS advantage.\textsuperscript{12} Bevacizumab with erlotinib as maintenance on the other hand has been shown to significantly increase both OS and PFS with manageable toxicity based on a meta-analysis of three randomized trials.\textsuperscript{10} However, bevacizumab is costly and maintenance regimens with this drug require venous access, infusion pumps, and hospital visits which add to its cost burden.\textsuperscript{9}

Capecitabine monotherapy as maintenance may be promising in terms of cost-effectiveness, convenience, and low toxicity, due to the availability of a tablet form.\textsuperscript{13-15} A phase III trial noted improvement in PFS of 6.4 months in mCRC patients who received capecitabine maintenance therapy compared with 3.4 months in the active monitoring group (HR, 0.54; 95% CI, 0.42–0.70; \(p < 0.001\)), but unable to demonstrate OS improvement (HR, 0.85; 95% CI, 0.64–1.11; \(p = 0.2247\)).\textsuperscript{16} More studies have since been published, which can allow for more precise estimates of treatment effect. A meta-analysis is helpful to draw conclusion on the role of capecitabine monotherapy as maintenance regimen. Accordingly, this meta-analysis aimed to identify the effectiveness of single-agent maintenance chemotherapy using capecitabine compared with no maintenance chemotherapy in improving OS, PFS, time to tumor progression (TTP), objective response rates based on RECIST criteria, toxicity, and QoL, among mCRC patients with disease control after first-line chemotherapy.

**Methods**

**Overview**

This meta-analysis was registered on PROSPERO (CRD42021260556) and followed a prespecified analysis plan. This study is reported in accordance with the Preferred Reporting Items for a Review and Meta-analysis (PRISMA). Certainty of evidence was rated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) framework.\textsuperscript{17,18}

**Eligibility Criteria**

Eligible trials included only RCTs involving adults with colorectal cancer who had response or disease stability after induction chemotherapy. Trials were required to evaluate capecitabine as maintenance therapy versus active monitoring. The study should have reported at least one of the following outcomes: OS, PFS, TTP, objective response rate based on RECIST criteria, adverse events, and mean change in QoL scores.

Studies were excluded if these involved patients with mCRC receiving maintenance therapy with capecitabine in combination with other chemotherapeutic agents. Crossover trials were excluded due to the nature of outcomes considered. Review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other non-relevant studies were excluded.

**Search Strategy and Selection Criteria**

A comprehensive literature search was performed by two authors (B.A.O. and A.M.R.) using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Health Research and Development Information Network (HERDIN), APAMED Central, TRIP database, and Google Scholar for studies published until June 12, 2021. Search terms were “metastatic colorectal cancer,” “capecitabine,” “Xeloda,” “maintenance,” and “randomized clinical trials,” and synonyms. Ongoing studies were also identified using ClinicalTrials.gov, European Union (EU) Clinical Trials Registry, and the World Health Organization International Clinical Trials Registry Platform. Conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology were also searched for unpublished studies. Citations of selected articles and any relevant studies that included capecitabine as maintenance therapy for patients with mCRC were reviewed. No language restrictions were imposed.

**Data Collection and Risk of Bias Assessment**

For studies that fulfilled the inclusion criteria, two review authors (B.A.O. and A.M.R.) independently assessed the risk of bias based on guidelines outlined by the Cochrane Handbook for Systematic Reviews of Interventions. Disagreements between the two reviewers were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (R.E.K.) settled the discrepancy. Key participant, intervention characteristics, and reported data on efficacy outcomes were also extracted independently by two investigators (B.A.O. and A.M.R.) using standard data extraction templates, with any disagreements resolved by discussion, or if required by a third author (R.E.K.). Data on the following variables were extracted: first author’s name, year of publication, journal, affiliated institution, country, study phase, format (full text or abstract), interventional and control treatments, hazard ratios with 95% CIs for PFS and OS, median OS, PFS, and TTP, randomization method, analysis tool, number of patients randomized, demographic and clinical data (e.g., age, sex), and toxicity (any grade). In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information.
Outcomes
The primary outcome was OS. Secondary outcomes included PFS, objective response rate based on RECIST criteria, proportion of patients with adverse events (any grade, and grade ≥ 3 by CTCAE), and the mean change in QoL scores. PFS was measured from the start of maintenance therapy until the first observation of disease progression, lost to follow-up or death.

Data Analysis
RevMan version 5.4 software was used to conduct meta-analysis, heterogeneity test, and sensitivity analysis on the included studies. The survival outcomes were analyzed as continuous variables and as dichotomous variables, specifically 24-month OS and 6-month PFS.

For all outcomes, we established the level of significance at p-value of <0.05. Statistical heterogeneity was identified through the forest plots and a standard Chi-square test with a significant level of p < 0.1. The extent of heterogeneity was based on the I² statistic wherein a value of more than 50% was interpreted as substantial heterogeneity. Random-effects analysis was applied in this meta-analysis. In cases of substantial heterogeneity, sensitivity analysis through sequential exclusion of individual studies was performed to rule out any undue influence of studies on the observed associations. Subgroup analysis was also done to explore the variations in (1) oxaliplatin versus irinotecan-based chemotherapy, (2) with anti-VEGF versus with anti-EGFR versus none, (3) RAS mutant versus RAS wild type, and (4) complete response and partial response versus stable disease.

Patient survival data, rates, and hazard ratios not explicitly reported in the article text were obtained from digitized graphs reconstructed with the WebPlotDigitizer software (4.2 version).

Results
Description of Studies
Results of Search
Primary electronic searches performed until June 12, 2021 yielded a total of 1,921 potentially relevant references on capecitabine maintenance therapy. Of these, we identified 325 duplicates and excluded 1,568 at the initial stage due to different interventions, outcome, or population, non-original data (e.g., meta-analysis or review), descriptive or observational study design, and study protocols. The remaining 27 related studies were retrieved as full-text publications, abstract publications, or trial protocols for detailed evaluation, out of which 20 studies were excluded. Those excluded were 10 non randomized studies and 10 studies without an active monitoring comparison group. Seven trials were eligible for inclusion but four of these were unpublished trials for which results cannot be retrieved due to no response from the authors. Overall, three studies were included in the final meta-analysis.

The overall number of trials screened, identified, selected, excluded, and included are documented in a PRISMA flow diagram (►Fig. 1).

Included Studies
The three included studies had been approved by a medical ethics committee according to the respective country’s legislation, and all patients or their representatives were informed of the research at the time of inclusion. The first patient enrollment started in July 2010. Two were published as full texts,16,19 and one trial has not been published but available with a conference presentation.20

The study population of all three studies were adult patients (≥18 years old) with mCRC who completed recommended first-line chemotherapy and achieved disease control, either with partial response, complete response, or stable disease. The smallest trial had a sample size of 48 participants19 while the largest trial had 274 participants.16 All three studies had an interventional group that received capecitabine as a single-agent maintenance, and a control group with patients who did not receive other interventions but were actively monitored. A total of 576 patients were included in this meta-analysis, with 288 patients who received maintenance with single agent capecitabine and 288 patients who did not receive any maintenance anticancer treatment.

Luo et al used capecitabine maintenance therapy at a standard dose of 1,000 mg/m² taken orally twice a day for days 1 to 14, followed by a 7-day break before recommencing every 21 days.16 Adams followed the same schedule of capecitabine but at a dose of 1,250 mg/m².20 Geng et al used a much lower dose of continuous capecitabine at 500 mg twice daily.19

In terms of survival outcomes, all studies reported OS and PFS as hazard ratio. Two studies measured OS from the end of first-line chemotherapy until death or the last follow-up date19,20 while Luo et al measured OS from the start of induction chemotherapy.16 All studies measured PFS from the start of treatment to disease progression, death, or last tumor evaluation.

In terms of safety outcomes, any adverse events were reported in one study20 while all studies reported grade ≥ 3 adverse events.16,19 QoL was assessed and reported in one trial using Eq. (5D).20 None of the studies reported the TTP and objective response rates after maintenance therapy.

Excluded Studies
Twenty studies were excluded after detailed evaluation. Five unpublished trials passed the inclusion criteria but four of these were excluded due to unavailable results. Of these trials, three were conducted in Asia21–23 and one in Europe.24 Three studies planned to measure PFS as their primary outcome while one study had duration of disease control as its primary outcome.

Of the four unpublished trials, only one was designed as a phase III trial and was completed.21 This study started in June 2010 and was completed in September 2014. The actual study start date of the other three unpublished trials were not reported in the trial registries.22–24 Additionally, two trials22,24 had unknown status, while one study23 had a recruiting status as of April 2017.
Risk of Bias
The summary of the methodological quality of the included studies for all assessed domains is presented in Figs. 2 and 3. All included studies reported a central randomization process and were therefore judged as having low risk of selection bias. The study outcomes, particularly the OS, PFS, and disease control were determined objectively; as such, the studies were viewed as low risk for performance and detection bias. However, the QoL and adverse events were determined subjectively and therefore were at risk for performance and detection bias.

The included studies reported all primary and secondary outcomes as prespecified in their protocols so the risk of bias for selective reporting was judged as low. No other biases were detected among the three studies and therefore judged to be low risk.

Effects of Interventions
Overall Survival
All studies similarly reported no difference in the median OS between the capecitabine maintenance arm and active monitoring arm. No statistical heterogeneity was observed in the OS analyses ($p = 0.38, I^2 = 0\%$) and pooled data from the included trials found no significant difference between the capecitabine maintenance therapy group and active monitoring group with respect to OS (HR $0.85, 95\%$ CI $0.64$–$1.13$, $p = 0.13$, Fig. 4).

Two studies showed estimates of the 24-month OS in the direction favoring capecitabine maintenance.\(^{16,19}\) Only Adams et al found a risk ratio favoring active monitoring.\(^{20}\) Significant heterogeneity of the 24-month OS was observed among the studies ($p = 0.02, I^2 = 75\%$, Fig. 5), with pooled...
analysis showing no significant difference between the two groups (RR: 0.88, 95% CI 0.66–1.17, \( p = 0.38 \)).

**Progression-Free Survival**

All studies reported median PFS with their corresponding hazard ratios in the direction favoring capecitabine maintenance but significant heterogeneity was detected among these trials (\( p = 0.005, I^2 = 81\% \), [Fig. 6].\(^{16,19,20}\) Analysis of PFS revealed a statistically significant reduced risk of progression with capecitabine maintenance compared with active monitoring (HR 0.36, 95% CI 0.21–0.61, \( p = 0.0001 \)). Upon removing the study with low-dose capecitabine,\(^19\) the heterogeneity of PFS decreased to an \( I^2 \) of 67\% (\( p = 0.08 \), [Fig. 7]). Subgroup analysis revealed that standard-dose capecitabine maintenance significantly improved the PFS (HR 0.46, 95% CI 0.32–0.65, \( p < 0.00001 \), [Fig. 8]).

![Fig. 2 Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.](image-url)

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Likewise, low-dose capecitabine significantly improved the PFS (HR 0.11, 95% CI 0.04–0.30, p < 0.0001).

In terms of 6-month PFS, two studies\textsuperscript{16,20} favored capecitabine maintenance, while one study\textsuperscript{19} found no difference between the two groups. Significant heterogeneity was observed upon pooled analysis (p < 0.00001, \(I^2 = 94\%).\textsuperscript{16} \textsuperscript{20} \textsuperscript{19} \textsuperscript{9} \textsuperscript{-Fig. 9\textsuperscript{9}}\). With a significant improvement in 6-month PFS in the capecitabine maintenance group (RR 0.78, 95% CI 0.56–1.10, p < 0.00001). Using sensitivity analysis, the heterogeneity of 6-month PFS was reduced after the removal of the low-dose capecitabine study (p = 0.22, \(I^2 = 33\%\). \textsuperscript{-Fig. 10\textsuperscript{9}}\). Upon subgroup analysis, standard-dose maintenance therapy revealed improved 6-month PFS (RR 0.70, 95% CI 0.61–0.81, p < 0.00001, \textsuperscript{-Fig. 11\textsuperscript{9}}\). Low-dose capecitabine did not differ from active monitoring (RR 1.00, 95% CI 0.89–1.13, p = 0.95).

### Adverse Events and Safety

AEs and safety were not consistently reported across studies. Any adverse events were reported in one study\textsuperscript{20} while all...
Three studies reported grade ≥ 3 events.\textsuperscript{16,19,20} Two studies used the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0),\textsuperscript{16,19} while Adams used the CTCAE version 4.0.\textsuperscript{20}

AEs were included in the analysis when at least one event of grade ≥ 3 was reported. All studies individually reported increased grade ≥ 3 adverse events in the capecitabine maintenance arm. No significant heterogeneity was observed (\( p = 0.53, I^2 = 0\% \)), with pooled ORs showing an increased risk of grade ≥ 3 adverse event (OR 2.02, 95% CI 1.42–2.88, \( \text{Fig. 12} \)) in the capecitabine maintenance arm.
The risk of hand-foot syndrome was higher in the maintenance group (OR 6.14, 95% CI 1.52–24.79) while the two arms did not differ in terms of diarrhea (OR 2.02, 95% CI 0.74–5.52) and neutropenia (OR 2.03, 95% CI 0.98–4.20).

Quality of Life
Among the studies in this meta-analysis, only Adams reported the QoL scores. No significant difference in the Eq. (5D) QoL scores was noted between the capecitabine maintenance and active monitoring group in terms of self-care, mobility, pain and discomfort, and anxiety and depression ($\chi^2$ for AUC difference = 0.06, $p = 0.81$).

Subgroup Analysis
Subgroup analysis to explore the variation in (1) oxaliplatin versus irinotecan-based chemotherapy, (2) with anti-VEGF versus with anti-EGFR versus none, (3) RAS mutant versus RAS wild type, and (4) complete response and partial response versus stable disease, was initially planned. However, data for these subgroup analyses could not be obtained.

Publication Bias
Publication bias was assessed by a validated test. The $p$-value for OS and PFS from the Begg's rank correlation test was 0.06 and 0.70, respectively. These demonstrate that there is no indication of significant publication bias among the included RCTs.

Discussion
Summary of Main Results
This meta-analysis found neither OS benefit (HR 0.85, 95% CI 0.64–1.13) nor reduction in mortality at 24 months (RR 0.88, 95% CI 0.66–1.17) with capecitabine maintenance therapy. However, prolongation in PFS (HR 0.36, 95% CI 0.21–0.61) and reduction in the risk of progression at 6 months (RR 0.78, 95% CI 0.56–1.10) were evident with capecitabine maintenance therapy. Upon subgroup analysis, capecitabine standard-dose was superior in improving PFS (HR 0.46, 95% CI 0.32–0.65) and reducing the risk of progression at 6 months (RR 0.70, 95% CI 0.61–0.81). Low-dose capecitabine did not
differ from active monitoring on 6-month PFS (RR 1.00, 95% CI 0.89–1.13) but significantly improved the PFS (HR 0.11, 95% CI 0.04–0.30).

The rates of any grade ≥3 adverse events (OR 2.02, 95% CI 1.42–2.88) and hand-foot syndrome (OR 6.14, 95% CI 1.52–24.79) were higher in the capecitabine maintenance compared with the active monitoring group. The two arms did not differ on the rates of diarrhea (OR 2.02, 95% CI 0.74–5.52) and neutropenia (OR 2.03, 95% CI 0.98–4.20). We did not find any significant difference between the two groups in terms of QoL.

Overall Completeness and Applicability of Evidence

All studies reported OS, PFS, and grade ≥3 adverse events. Subgroup analysis to explore variations was initially planned, but data for the proposed subgroups were not available. The significant heterogeneity between the pooled analyses of the 24-month OS, PFS, 6-month PFS, and adverse events may indicate that results of this review may be limited in terms of applicability.

Quality of Evidence

As presented in the summary of findings in Table 1, the quality of the body of evidence obtained for each outcome ranged from low to moderate. All outcomes were graded as not serious in terms of indirectness and publication bias. However, all the outcomes were downgraded for imprecision due to the few studies included and the small sample size of this meta-analysis. For all survival outcomes, the risk of bias was deemed as not serious. The certainty of evidence for the subjective outcomes, particularly adverse events and QoL, was downgraded for possible performance bias from the non-blinding of participants and assessors.

This meta-analysis was not able to account for the significant heterogeneity in the pooled analysis of the PFS, 6-month PFS, and 24-month OS. Thus, the certainty of evidence for these outcomes was downgraded. The heterogeneity could be attributed to the much lower dose of capecitabine used in the study of Geng et al, compared with that of the other two studies. However, subgroup analyses revealed that while both standard dose and low dose capecitabine significantly improved the PFS, low dose capecitabine had a stronger effect on PFS compared with the standard dose. This is counterintuitive, raising the possibility of other factors leading to the observed effect. One possibility is the frequency of follow-up, which was done every 12 weeks in the study that used low-dose capecitabine, and every 8 or 9 weeks in the studies using standard-dose capecitabine. The less frequent follow-up in the study of Geng et al may have made this study more prone to delayed detection of progressive disease compared with the other two studies, resulting in a higher observed PFS.

Potential Biases in the Review Process

We limited our analysis to RCTs to avoid risk of bias issues expected with non-randomized studies. All studies analyzed in this meta-analysis used capecitabine as maintenance but there was variation in the dosage and timing of follow-up.
that may have contributed to the heterogeneity in our findings. We were able to perform subgroup analyses based on the dose of capecitabine.

The low total number of patients in the studies also limited the precision of our results. There was at least one completed study which was unpublished and data from this study was not available for analysis. There were three other trials with unclear status of completion. There are other studies from databases and proceedings that we may not have identified, but the patient population from any such analyses is likely to be small.

**Agreements and Disagreements with Other Studies or Reviews**

To our knowledge, this is the first comprehensive meta-analysis evaluating capecitabine as single agent maintenance therapy in patients with mCRC. We identified other systematic reviews and network meta-analyses that aimed to evaluate capecitabine as part of a combination regimen for maintenance chemotherapy. Overall, fluoropyrimidines as monotherapy or combined with bevacizumab seems to be the preferred maintenance strategy.

A recent network meta-analysis by Sonbol et al included the study by Luo et al and was compared with other maintenance regimens including bevacizumab or both capecitabine and bevacizumab. The study found a significant advantage over active monitoring in delaying progression but without OS benefit, similar to the findings of our study. There are subtle distinctions between the two reviews in the methods of meta-analysis, but overall, our review achieved similar conclusions. Another study included 3,121 patients from five trials comparing bevacizumab with either erlotinib

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**Table 1** Characteristics of included studies

<table>
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<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Method</th>
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| Adult patients with inoperable metastatic or locally advanced colorectal cancer who completed induction chemotherapy with FOLFOX, XELOX, FOLFIRI, and FOLFOXIRI. | Capecitabine 1,250 mg/m² PO BID for days 1 – 14, every 21 d. | Active monitoring | • OS: from randomization to death.  
• PFS: from randomization after induction chemotherapy to disease progression (includes death from any cause as well as CT scan evidence that there is disease progression according to RECIST v1.1 criteria), assessed every 8 wk.  
• Safety and toxicity: based on CTCAE version 4.0 recorded on clinical records, assessed every 3 to 4 wk.  
• QoL: using Eq. 5D  
• Response and tumor shrinkage assessed every 8 wk. | Randomized controlled trial, multi-center (101 sites in United Kingdom). |
| Adult patients with metastatic colorectal cancer who completed 18 wk of induction chemotherapy with XELOX and achieved disease control. | Continuous capecitabine 500 mg BID. | Active monitoring | • OS: from the start to the date of death or the last day of follow-up.  
• PFS: from the start of maintenance treatment to disease progression or death or last tumor evaluation, based on imaging studies of measurable lesions assessed every 3 mo or at any time when disease progression is suspected or when study treatment was prematurely discontinued.  
• Adverse events: based on National Cancer Institute CTCAE (version 3.0) from registration until the end of final study visit. | Randomized controlled trial, single center (China) |
| Adult patients with metastatic colorectal cancer who completed 18–24 wk of XELOX or FOLFOX and achieved disease control. | Capecitabine 1,000 mg/m² BID for days 1 – 14, every 21 d. | Active monitoring | • OS: from the time from induction treatment to the date of the last follow-up or death.  
• PFS: from randomization after induction chemotherapy to death from any cause or first disease progression, assessed every 9 wk using imaging studies during the maintenance treatment or at any time when disease progression is suspected or when study treatment was prematurely discontinued.  
• Adverse events: according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) from registration to the end of the final study visit. | Randomized controlled trial, multicenter (11 sites in China). |
or capecitabine versus active monitoring. Results showed that any bevacizumab-based maintenance therapy (with or without capecitabine) after a bevacizumab-based induction regimen improved PFS (HR 0.62, 95% CI:0.47–0.82), with bevacizumab plus capecitabine showing better PFS compared with observation alone (HR 0.43; 95% CI:0.35–0.52). No significant difference was observed between the bevacizumab-based maintenance therapy strategies and observation alone with respect to OS (HR 0.93, 95% CI:0.83–1.05).

Conclusion

Implications for Practice
Given available data from clinical trials and significant heterogeneity in reported findings, there is inconclusive evidence to demonstrate any OS benefit with the use of capecitabine as monotherapy compared with active monitoring alone. Capecitabine maintenance is associated with superior PFS compared with active monitoring and reduces the risk of progression at 6 months, but the low to moderate quality of evidence indicates the necessity to confirm findings from this review in clinical studies with adequate sample size to address potential subgroup effects. The risks of any grade ≥3 adverse events and hand-foot syndrome were consistently higher in the capecitabine monotherapy group, while the estimates for diarrhea and neutropenia were inconclusive. The toxicity profile indicates that careful monitoring is still needed during maintenance therapy with capecitabine single agent so that potentially serious adverse events can be addressed early and effectively.

Implications for Research
Future well-designed randomized, double-blind, controlled trials with larger sample sizes on capecitabine monotherapy as maintenance treatment in mCRC are needed. Health-related QoL outcomes should be addressed and further trials should focus on consistent reporting of safety outcomes and QoL using standardized instruments to ensure comparability of maintenance treatment.

Authors’ Contribution
B.A.O., MD (first author and corresponding author) studied the concept and design; did the acquisition, analysis, and interpretation of data; imaging review; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

A.M.R., MD studied the concept and design; did the acquisition, analysis, and interpretation of data; drafting of the manuscript and critical revision of the manuscript for important intellectual content.

R.E.K., MD studied the concept and design; did the acquisition, analysis, and interpretation of data; imaging review; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

E.Y., MD (Senior) contributed toward acquisition of data and critical revision of the manuscript for important intellectual content.

Institution Where the Work Was to Be Performed
Department of Medicine, University of the Philippines, Philippine General Hospital, Manila, Philippines

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Conflict of Interest
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