# The Impact of Maintenance Therapy with Fluoropyrimidines and Bevacizumab on Progression-Free and Overall Survival in First-Line Treatment Protocols Including Irinotecan Among Patients with Metastatic Colorectal Cancer: A Retrospective Real-World Study

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## SUMMARY

**Background:** While maintenance therapy is established in metastatic colorectal cancer (mCRC), data following irinotecan-based protocols remain limited despite widespread use in Europe.
**Methods:** This retrospective study included 136 mCRC patients treated at University Hospital Centre Osijek (2017–2021) receiving first-line irinotecan-based chemotherapy (CAPIRI/FOLFIRI) with bevacizumab. Patients received either continuous therapy until progression, or maintenance with fluoropyrimidines and bevacizumab after first-line irinotecan-based chemotherapy until progression (PFS1), and then reinduction of first-line therapy until disease progression (PFS2). Primary endpoints were progression-free survival (PFS) and overall survival (OS).
**Results:** Maintenance therapy showed significantly superior outcomes versus continuous therapy. PFS1 was 21 months (95% CI, 10–66) versus 12 months (95% CI, 10–17; $P < 0.001$); PFS2 was not reached at the time of data cut-off versus 12 months (95% CI, 10–17; $P < 0.001$). Overall survival favored maintenance therapy numerically (77 months vs not reached) without statistical significance ($P = 0.13$). The median duration of induction chemotherapy was 11 months and of maintenance therapy 9 months.
**Conclusion:** Maintenance therapy with fluoropyrimidines and bevacizumab following irinotecan-based induction chemotherapy demonstrates significant PFS benefits in real-world practice, supporting its use to balance disease control with reduced toxicity in mCRC patients.

## KEYWORDS

*Maintenance therapy*; *Metastatic colorectal cancer*; *Bevacizumab*; *FOLFIRI*; *CAPIRI*

## Introduction

Colorectal cancer (CRC) remains one of the most common and deadly malignancies worldwide. With nearly 2 million new cases diagnosed in 2022 and over 904,000 deaths, it ranks as the third most frequently diagnosed cancer[1]. Despite advancements in early detection and surgical treatment, approximately 25% of patients present with metastatic disease at initial diagnosis, and an additional one-third of those with localized cancer will develop metastases during their illness[2]. Metastatic colorectal cancer (mCRC) poses a significant clinical challenge, with the liver and lungs being the most frequent sites of distant metastases[3].

The prognosis for mCRC has significantly improved over the past two decades, with the median overall survival increasing from less than 12 months to over 30 months in select patient populations. This progress is attributed to the introduction of new cytotoxic agents, targeted biological therapies and increasingly sophisticated treatment algorithms that incorporate molecular profiling and personalized medicine approaches.

The traditional treatment approach for mCRC involves intensive induction chemotherapy, typically combining fluoropyrimidine-based regimens with oxaliplatin or irinotecan, often supplemented with targeted biological therapies such as anti-VEGF or anti-EGFR antibodies, depending on tumor characteristics. While these combination regimens have demonstrated significant efficacy in terms of response rates and progression-free survival (PFS), they are associated with cumulative toxicities that may impair quality of life and limit treatment duration. Oxaliplatin-induced peripheral neuropathy, irinotecan-associated diarrhea and the cumulative hematologic and constitutional effects of prolonged intensive chemotherapy present considerable challenges.

The concept of maintenance therapy has emerged as a strategic approach to address this therapeutic dilemma, aiming to preserve disease control while reducing treatment-related toxicity through de-escalation or modification of the therapeutic regimen following the initial induction therapy.

The reason for this approach lies in the fact that, for the majority of mCRC patients, the goal is not cure but rather prolongation and improvement of quality of life. Most studies have investigated oxaliplatin-based chemotherapy protocols. One such study, OPTIMOX-1, compared maintenance therapy with continuous treatment in mCRC and demonstrated that maintenance therapy did not reduce overall survival compared to continuous therapy[4]. The OPTIMOX-2 study showed that maintenance therapy significantly improved PFS and overall survival (OS), although maintenance was compared with observation alone without therapy[5]. Maintenance therapy reduces adverse effects and enhances the patients' quality of life, as evidenced by the CAIRO3 trial in which one arm received capecitabine plus bevacizumab, and the other arm was under observation[6]. The AIO0207 study included three arms covering all combinations: following induction protocols with FOLFOX or CAPOX, patients in arm 1 received fluoropyrimidines plus bevacizumab, patients in arm 2 received bevacizumab monotherapy and patients in arm 3 were placed under observation without treatment[7].

One comprehensive systematic review and network meta-analysis evaluated 12 randomized clinical trials involving a total of 5,540 patients with mCRC, including six trials comparing maintenance therapy with observation[8]. The analysis found no benefit in continuing uninterrupted full-dose cytotoxic chemotherapy until disease progression without incorporating a maintenance phase or treatment-free interval. Evidence supports maintenance therapy using fluoropyrimidines (fluorouracil or capecitabine)

– either as monotherapy or in combination with bevacizumab – as the optimal approach. This strategy balances efficacy and tolerability, improving progression-free survival while reducing toxicity.

In EU countries, irinotecan-based chemotherapy protocols are predominantly utilized as first-line treatment for mCRC. Consequently, maintenance therapy strategies described in existing studies have been extrapolated to irinotecan-based regimens, despite limited numbers of randomized controlled trials specifically assessing maintenance therapy within this subgroup. The PRODIGE 9 phase III trial evaluated maintenance therapy with bevacizumab following induction with FOLFIRI compared to observation alone, demonstrating no statistically significant improvement in PFS and OS[9]. For patients harboring RAS mutations (mutation of the RAS (*rat sarcoma*) gene family, including KRAS, HRAS, and NRAS mutation) and right-sided colon tumors, the current standard maintenance regimen comprises capecitabine in combination with bevacizumab, which has emerged as a viable option – particularly in elderly patients and those with a reduced performance status[10,11]. In the absence of robust data from large randomized clinical trials, real-world evidence contributes valuable insights. Notably, a study by Weizhen Huang et al. reported on patients who, after induction with the FOLFIRI protocol, received either capecitabine plus bevacizumab or capecitabine monotherapy as maintenance therapy[12].

Due to a lack of data from large randomized controlled trials assessing maintenance therapy following irinotecan-based protocols, we conducted an investigation based on real-world clinical practice. This study presents observational data and evaluates the efficacy of maintenance therapy with bevacizumab and capecitabine compared to continuous treatment within irinotecan-based chemotherapy regimens.

## Methods

This study included 136 patients treated at the Oncology Clinic of the University Hospital Centre Osijek between 2017 and 2021. Inclusion criteria were as follows: (1) age between 18 and 82 years; (2) histologically confirmed colorectal adenocarcinoma; (3) radiologically confirmed distant metastases; (4) receipt of irinotecan-based chemotherapy as first-line treatment for metastatic colorectal cancer; and (5) administration of bevacizumab. The exclusion criterion was less than six months of any corresponding therapy regimen. Objective response evaluation was based on RECIST 1.1 criteria.

Clinical data were analyzed retrospectively. Patients were divided into two groups: one group received continuous chemotherapy with irinotecan and bevacizumab until disease progression, and the other group received maintenance therapy with fluoropyrimidines and bevacizumab without irinotecan after a defined induction period. Two chemotherapy protocols, CAPIRI (capecitabine and irinotecan) and FOLFIRI (leucovorine, 5-flourouracil and irinotecan) were utilized. Maintenance therapy following the FOLFIRI protocol consisted of 5-fluorouracil combined with bevacizumab, whereas for the CAPIRI protocol, maintenance therapy comprised capecitabine with bevacizumab.

The primary objective of this study was to compare PFS and OS between two patient cohorts: one receiving continuous irinotecan-based therapy until disease progression, and the other transitioning to maintenance therapy with fluoropyrimidines and bevacizumab, excluding irinotecan, after a defined treatment period. RAS mutational status and primary tumor location (left-sided vs. right-sided) were determined. Local therapies for metastases – including surgical resection, stereotactic body radiotherapy (SBRT) and microwave ablation (MWA) – were documented, with surgical margins classified as

R0 (complete resection) or R1 (microscopically positive margins).

In the continuous therapy group, progression-free survival 1 (PFS1) was defined as the interval from treatment initiation to progression on irinotecan-containing therapy. In the maintenance therapy group, PFS1 was defined as the time from treatment initiation to first progression during maintenance therapy. Progression-free survival 2 (PFS2) in the maintenance group was defined as the duration from treatment initiation to second progression or progression following irinotecan reinduction. The median durations of induction chemotherapy and maintenance therapy were calculated.

Categorical data are presented as absolute and relative frequencies. Differences between categorical variables were tested using the chi-square test or, when appropriate, Fisher's exact test. The normality of continuous variables was assessed using the Shapiro–Wilk test. Differences in continuous variables between two independent groups were analyzed using the Mann–Whitney U test, while differences between paired measurements were tested using the Wilcoxon signed-rank test. In both cases, differences are reported with 95% confidence intervals (CI). Survival differences were assessed using the log-rank test and illustrated with Kaplan–Meier curves. All *P* values were two-tailed, and the level of statistical significance was set at $\alpha = 0.05$. We presented our results following the guidelines for data reporting in biomedical and health research. Statistical analyses were performed using the MedCalc® Statistical Software version 23.3.7 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2025).

## Results

This study enrolled 136 patients with mCRC who received first-line irinotecan- and fluoropyrimidine-based chemotherapy regimens combined with bevacizumab. The median age was 66 years (range 62–71) in the continuous therapy group and 66 years (range 56–68) in the maintenance therapy group. The continuous therapy cohort comprised 61.5% males and 38.5% females, whereas the maintenance group consisted of 70.7% males and 29.3% females.

The most common site of metastasis was the liver, observed in 75.6% of patients receiving continuous therapy and 62.1% of those on maintenance therapy. Pulmonary metastases occurred in 44.9% of the continuous therapy group and in 36.2% of the maintenance group. Peritoneal metastases were present in 29.5% and 32.8% of patients in the continuous and maintenance cohorts, respectively. Bone metastases were identified in 6.9% and 6.8% of patients in the continuous and maintenance groups, respectively. Lymph node involvement was noted in 70.5% of patients receiving continuous therapy and 62.7% of those in the maintenance group.

In both study groups, the distribution of irinotecan-based chemotherapy protocols was comparable. Within the continuous therapy group, 74.4% of patients received the CAPIRI protocol, while 25.6% were treated with FOLFIRI. In the maintenance group, 67.2% of patients underwent the CAPIRI regimen, and 32.8% received FOLFIRI ($P = 0.36$). Regarding primary tumor location, left-sided tumors were present in 74.4% and 74.1% of patients in the continuous and maintenance groups, respectively ($P = 0.93$). Right-sided tumors were present in 26.5% of patients in the continuous therapy group and 27.1% of patients receiving maintenance therapy ($P = 0.93$). An analysis of RAS mutational status revealed mutations in 66.2% of the continuous therapy cohort and 68.9% of the maintenance group ($P = 0.76$). BRAF mutations

were detected in 17.9% of the continuous therapy patients versus 11.1% maintenance patients ($P = 0.69$). These findings demonstrate that metastatic sites, primary tumor location and molecular subgroups defined by RAS and BRAF mutation status were evenly distributed across both groups, with no statistically significant differences observed. Surgical resection was performed in 20.7% of patients in the maintenance group, with 16.1% achieving R0 resection and none with R1 resection. In the continuous therapy group, 19.2% underwent surgical resection; 10.7% achieved R0 resection and 4% had R1 resection. Stereotactic body radiotherapy (SBRT) was administered to 7.7% of patients in the continuous therapy group and 3.4% of patients in the maintenance group. Microwave ablation (MWA) was performed in 3.8% of patients receiving continuous therapy and in none of the patients under maintenance therapy. Detailed baseline characteristics of the study participants are shown in Table 1.

PFS1 was significantly longer in the maintenance group, with a median of 21 months (95% CI, range 10–66, interquartile range (IQR) 17–26), compared to 12 months (95% CI, 10–17) in the continuous therapy group ($P = 0.001$). Similarly, PFS2 was notably prolonged in the maintenance cohort, with a median of PFS2 not reached at the time of data cut-off versus 12 months (95% CI, 12–17) in the continuous therapy group ($P < 0.001$). Figure 1 shows the Kaplan–Meier curve of PFS in both groups.

OS did not differ significantly between the two groups ($P = 0.44$), although a numerical trend favoring maintenance therapy was observed, with a median OS of 77 months (95% CI, 50–78) compared to the continuous therapy group, in which the median OS was not reached at the time of data cut-off. Figure 2 shows the Kaplan–Meier curve of OS in the continuous treatment participant group and maintenance therapy group. The median interval from initiation of first-line treatment to the commencement of maintenance therapy was 11 months, with an IQR of 8–14 months. The median duration of maintenance therapy was 9 months (IQR 5–17 months).

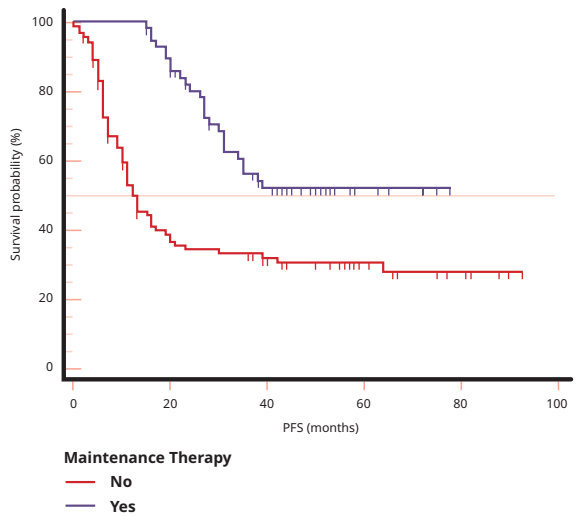


**FIGURE 1** Kaplan-Meier curve of progression-free survival in continuous treatment (no) and maintenance therapy groups (yes)

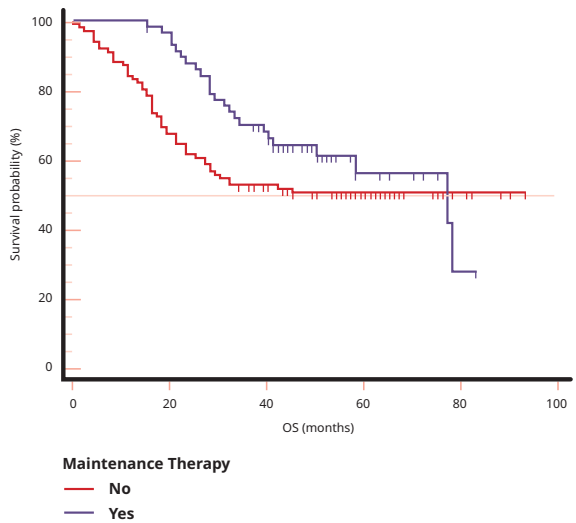


**FIGURE 2** Kaplan-Meier curve of overall survival in continuous treatment (no) and maintenance therapy patient groups (yes)

**TABLE 1** Baseline characteristics of observation and control groups

| | | Continuous treatment (n = 78) | Maintenance therapy (n = 58) | Total (n = 136) | *P* |
|---|---|---|---|---|---|
| **Age median** (in years) | | 66 (62–71) | 66 (56–68) | | 0.08** |
| **Sex** | **Male** | 48 (61.5) | 41 (70.7) | 89 (65.4) | 0.27 |
| | **Female** | 30 (38.5) | 17 (29.3) | 47 (34.6) | |
| **Metastatic site** | **Liver** | 59 (75.6) | 36 (62.1) | 95 (69.9) | 0.09 |
| | **Lung** | 35 (44.9) | 21 (36.2) | 56 (41.2) | 0.31 |
| | **Peritoneum** | 23 (29.5) | 19 (32.8) | 42 (30.9) | 0.68 |
| | **Bones** | 11 (14.1) | 4 (6.9) | 15 (11) | 0.19 |
| | **Ovaries** | 9 (11.5) | 5 (8.6) | 14 (10.3) | 0.58 |
| | **Brain** | 4 (5.1) | 2 (3.4) | 6 (4.4) | > 0.99† |
| | **Lymph nodes** | 55 (70.5) | 37 (63.8) | 92 (67.6) | 0.41 |
| **Surgical resection** | | 15 (19.2) | 12 (20.7) | 27 (19.9) | 0.83 |
| **R0** | | 8 (10.7) | 9 (16.1) | 17 (13) | 0.36 |
| **R1** | | 3 (4) | 0 (0) | 3 (2.3) | 0.26† |
| **Stereotactic radiotherapy (SBRT)** | | 6 (7.7) | 2 (3.4) | 8 (5.9) | 0.47 |
| **Microwave ablation (MWA)** | | 3 (3.8) | 0 (0) | 3 (2.2) | 0.26 |
| **Therapy protocol** | **CAPEIRI** | 58 (74.4) | 39 (67.2) | 97 (71.3) | 0.36 |
| | **FOLFIRI** | 20 (25.6) | 19 (32.8) | 39 (28.7) | |
| **Tumor localization** | **Right side** | 20 (25.6) | 15 (25.9) | 35 (25.7) | 0.98 |
| | **Left side** | 58 (74.4) | 43 (74.1) | 101 (74.3) | |
| **RAS** | **mutated** | 45 (66.2) | 31 (68.9) | 76 (67.3) | 0.76 |
| | **“wild” type** | 23 (33.8) | 14 (31.1) | 37 (32.7) | |
| **BRAF** | **mutated** | 5 (17.9) | 2 (11.1) | 7 (15.2) | 0.69† |
| | **“wild” type** | 23 (82.1) | 16 (88.9) | 39 (84.8) | |

*Chi-squared Test; †Fisher’s Exact Test. **Mann Whitney U test.; Bold value denotes statistical significance.

**TABLE 2** Safety profile and treatment discontinuation in observation and control groups

| | | Continuous treatment (n = 78) | Maintenance therapy (n = 58) | Total (n = 136) | *P* |
|---|---|---|---|---|---|
| **Adverse effects** | | 26 (33.3) | 23 (43.4) | 49 (37.4) | 0.24 |
| **Adverse effect type** | **diarrhea** | 11 (42.3) | 5 (21.7) | 16 (32.7) | 0.13 |
| | **weakness** | 7 (26.9) | 5 (21.7) | 12 (24.5) | 0.67 |
| | **abdominal pain** | 4 (15.4) | 6 (26.1) | 10 (20.4) | 0.48† |
| | **loss of appetite** | 4 (15.4) | 2 (8.7) | 6 (12.2) | 0.67† |
| | **vomiting** | 6 (23.1) | 2 (8.7) | 8 (16.3) | 0.25† |
| | **deep vein thrombosis** | 3 (11.5) | 5 (21.7) | 8 (16.3) | 0.45† |
| | **nausea** | 2 (7.7) | 2 (8.7) | 4 (8.2) | > 0.99† |
| | **neutropenia** | 1 (3.8) | 4 (17.4) | 5 (10.2) | 0.17† |
| | **bleeding** | 2 (7.7) | 2 (8.7) | 4 (8.2) | > 0.99† |
| | **fever** | 1 (3.8) | 3 (13) | 4 (8.2) | 0.33† |
| | **pruritus** | 0 | 2 (8.7) | 2 (4.1) | 0.21† |
| | **mouth ulcers** | 0 | 2 (8.7) | 2 (4.1) | 0.21† |
| | **rash** | 0 | 1 (4.3) | 1 (2) | 0.47† |
| | **alopecia** | 1 (3.8) | 1 (4.3) | 2 (4.1) | > 0.99† |
| | **vertigo** | 1 (3.8) | 0 | 1 (2) | > 0.99† |
| | **skin redness** | 0 | 1 (4.3) | 1 (2) | 0.47† |
| | **headache** | 1 (3.8) | 0 | 1 (2) | > 0.99† |
| **Reason for discontinuation** | **progression** | 54 (69.2) | 23 (39.7) | 77 (56.6) | **<0.001**† |
| | **lost in follow-up** | 13 (16.7) | 7 (12.1) | 20 (14.7) | |
| | **cured** | 4 (5.1) | 3 (5.2) | 7 (5.1) | |
| | **consent withdrawal** | 4 (5.1) | 0 | 4 (2.9) | |
| | **death** | 2 (2.6) | 3 (5.2) | 5 (3.7) | |

*Chi-squared Test; †Fisher's Exact Test; **Mann Whitney U test. Bold value denotes statistical significance.

Adverse events commonly associated with both chemotherapy protocols were monitored throughout the treatment course, revealing no statistically significant differences between the continuous therapy and maintenance therapy group. Importantly, patients undergoing maintenance therapy consistently reported subjective improvements in well-being. Diarrhea was the most frequent adverse event, occurring in 42.9% of the continuous therapy group versus 21.7% of the maintenance group. Although this difference did not achieve statistical significance, it suggested a numerical trend toward reduced incidence. Decreased appetite was noted in 22% of patients receiving continuous therapy compared to 8.7% of the patients in the maintenance cohort; again, not statistically significant but indicative of a favorable trend. Notably, neutropenia was less frequent in the continuous therapy group (2.9%) relative to the maintenance group (17.4%), possibly reflecting differences in timing relative to chemotherapy exposure.

Reasons for treatment discontinuation were examined – including disease progression, loss to follow-up, patient consent withdrawal, death and remission – with all categories showing statistically significant favor toward patients receiving maintenance therapy ($P < 0.001$). Safety profile and treatment discontinuation data in the observation and control group are shown in Table 2.

## Discussion

Maintenance therapy in the treatment of mCRC has been demonstrated in clinical trials and real-world practice to be superior to observation without therapy[4]. The primary benefit of maintenance therapy is the reduction of toxicity while maintaining disease control. However, results regarding PFS and OS remain inconclusive. Most studies have employed oxaliplatin-based protocols for induction therapy, with relatively few investigating irinotecan-based regimens. Data from these clinical trials were extrapolated into real-world practice. Current guidelines recommend maintenance therapy with fluoropyrimidines and bevacizumab for patients with RAS-mutated and right-sided tumors[13,14]. For oxaliplatin-based protocols, the recommendation is to administer 6–8 cycles of induction chemotherapy followed by maintenance therapy. In contrast, irinotecan-based induction therapy may be continued as long as treatment response persists.

In many countries, irinotecan-based protocols are preferred in the first-line setting due to their better tolerability compared to oxaliplatin. Given the scarcity of randomized multicenter trials focusing on irinotecan-based protocols, the outcomes from oxaliplatin-based studies have been projected onto irinotecan regimens in clinical practice.

The present study utilized irinotecan-based chemotherapy protocols, CAPIRI and FOLFIRI, comparing continuous therapy with maintenance therapy based on fluoropyrimidines and bevacizumab.

The CAIRO3 study, which included 558 patients, randomized participants into two arms following six three-week cycles of CAPOX plus bevacizumab. One arm received maintenance therapy with capecitabine and bevacizumab, whereas the other arm was under observation without therapy[6]. The primary endpoint was PFS2, defined as time to second progression. Median PFS2 was 11.7 months in the maintenance group, compared with 8.5 months for PFS1 (hazard ratio 0.67, 95% CI 0.56–0.81, $P < 0.0001$). Hand-foot syndrome occurred in 23% of patients, and the study concluded that maintenance therapy with capecitabine and bevacizumab did not adversely affect quality of life.

In our study, the median duration of maintenance therapy was 9 months, comparable to

the PFS1 reported in CAIRO3. Our observed PFS2 was not reached, noting that PFS2 in our analysis was calculated from initiation of induction chemotherapy.

The AIO0207 study design involved oxaliplatin-based induction chemotherapy with FOLFOX or CAPEOX plus bevacizumab for 24 weeks, followed by randomization into three arms: fluoropyrimidines plus bevacizumab, bevacizumab monotherapy, or observation without therapy[7]. The arm most comparable to our study involved fluoropyrimidines with bevacizumab, which demonstrated a median time to strategy failure from randomization of 6.9 months (95% CI, 6.1–8.5). Correspondingly, the median duration of maintenance therapy in our cohort was 9 months.

The primary distinction of our study compared to CAIRO3 and AIO0207 lies in the induction chemotherapy protocol: our study utilized irinotecan-based regimens as opposed to oxaliplatin-based regimens employed in the cited trials. Additionally, whereas those studies prescribed a fixed duration for induction chemotherapy, our study consistent with guidelines, allowed for variable induction duration, with a median time to initiation of maintenance therapy of 11 months. Another difference pertains to the comparison arms: our study contrasted continuous therapy with maintenance therapy.

Our results align with findings from a meta-analysis demonstrating that maintenance therapy yielded statistically significant improvements in PFS (hazard ratio (HR), 0.58; 95% CI, 0.43–0.77), although overall survival did not differ significantly (HR, 0.91; 95% CI, 0.83–1.01)[8]. In our study, the difference in PFS2 was statistically significant ($P < 0.001$), with a median PFS2 of 12 months (95% CI, 10–17) in the continuous therapy group versus the median not being reached in the maintenance group. Overall survival between the two groups was not statistically significant ($P = 0.13$), despite a numerical favor towards maintenance therapy, which exhibited a median overall survival of 77 months (95% CI, 40-78), compared to the continuous therapy group, in which median survival was not reached at the time of analysis. In this meta-analysis, the majority of studies were based on oxaliplatin-containing therapy, and various combinations of agents or monotherapy were used in the maintenance phase, often compared with a no-treatment control group.

In the PRODIGE 9 study, which included 141 patients, the FOLFIRI protocol was administered with a predefined number of 12 induction cycles prior to maintenance therapy[9]. In this trial, maintenance therapy consisted of bevacizumab monotherapy, while the control arm received observation only. The primary endpoint of the study was tumor control duration (TCD). Median TCD was 15 months in both groups (HR, 1.07; 95% CI, 0.85–1.34; $P = 0.57$). Median PFS was 9.2 months in the bevacizumab group versus 8.9 months in the observation group, showing no statistically significant difference (HR, 0.91; 95% CI, 0.76–1.09; $P = 0.316$). Median OS was 21.7 months in the maintenance arm and 22 months in the observation arm (HR, 1.07; 95% CI, 0.88–1.29; $P = 0.500$), whereas in our study, OS was 105 months in the maintenance arm versus not reached (NR) in the comparator group. The main difference between our study and PRODIGE 9 is that in our analysis, the number of induction chemotherapy cycles was not limited and maintenance therapy consisted of fluoropyrimidines in combination with bevacizumab. Moreover, in our study, maintenance therapy was compared with continuous therapy.

A study conducted by Huang et al., which included 154 patients, reported findings derived from real-world clinical practice[12]. It compared two groups of patients following an induction FOLFIRI regimen lasting at least 12 weeks. One group received capecitabine plus bevacizumab, while the other group received capecitabine monotherapy.

Median PFS was 9.0 months (95% CI, 8.0–10.0; $P < 0.05$) for patients treated with capecitabine

and bevacizumab, and 7.2 months (95% CI, 6.0–8.4; $P < 0.05$) for those receiving capecitabine monotherapy in the control group. In our study, this corresponded to a median duration of maintenance therapy of 9 months. The difference compared to our study lies in the fact that Huang et al. compared two maintenance regimens – capecitabine plus bevacizumab vs capecitabine monotherapy – whereas our study compared maintenance therapy with continuous therapy.

The higher PFS and OS observed in our investigation may be attributed to the inclusion of patients who underwent local treatment modalities for metastatic lesions, such as MWA, SBRT and surgical resections performed during the management of mCRC after achieving a favorable response to systemic therapy. In addition, patients who achieved complete radiological or pathologic responses were included, which in some cases resulted in long-term follow-up without the need for ongoing systemic therapy.

The limitations of this study include its relatively small sample size and the retrospective nature of data collection.

Given the numerical difference observed in OS in this study, which did not reach statistical significance, further research involving a larger patient cohort is warranted to determine whether maintenance therapy influences OS in the same manner as it affects PFS in patients treated with irinotecan-based induction chemotherapy protocols. A subset of patients receiving maintenance therapy demonstrated recovery and sustained disease control, with some showing further tumor regression or even complete response. These findings suggest that a less intensive treatment approach may be capable of maintaining disease control in select patients while reducing toxicity and improving quality of life. Continued research and the identification of novel biomarkers are essential to better define which patients may benefit from less toxic therapeutic strategies without compromising efficacy.

## Conclusion

Maintenance therapy with fluoropyrimidines and bevacizumab following irinotecan-based induction chemotherapy demonstrates significant progression-free survival benefits in real-world practice, supporting its use to balance disease control with reduced toxicity in mCRC patients. In this study, median PFS1 was 21 months in the maintenance group compared to 12 months in the continuous therapy group, with PFS2 not reached at data cut-off. Although overall survival did not differ significantly between groups, a numerical trend favouring maintenance therapy was observed. Patients receiving maintenance therapy also reported subjective improvements in well-being and experienced fewer adverse events, including reduced rates of diarrhea and decreased appetite, highlighting the quality-of-life advantages of this approach.

### Conflict of interest statement

Ilijan Tomaš: speaker fees and consulting: Abbot, Merck, MSD, Astra Zeneca, SwixxBiopharma, Amgen, Eli Lilly, Roche and Novartis; support for clinical trials: Roche, and MSD. Dora Muršić: Speaker fees: Merck. Sebastijan Spajić: Speaker fees: Roche. Josipa Flam: Speaker fees and consulting: Abbott, Astra Zeneca, Amgen, Eli Lilly, Merck, MSD, Novartis, Pfizer, Roche. The remaining authors have no potential conflicts of interest to declare. ■

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## SAŽETAK

### Usporedba terapije održavanja i kontinuirane terapije temeljene na irinotekanu i bevacizumabu u prvoj liniji liječenja mKRK – retrospektivna studija iz stvarnog života

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**Uvod:** Iako je terapija održavanja uvriježena kod metastatskog kolorektalnog karcinoma (mCRC), podaci o učinkovitosti održavanja nakon protokola s irinotekanom ograničeni su unatoč širokoj upotrebi u Europi.

**Metode:** Ova retrospektivna studija uključila je 136 pacijenata s mCRC liječenih u KBC-u Osijek (2017.-2021.) koji su primali prvu liniju kemoterapije na bazi irinotekana (CAPIRI/FOLFIRI) s bevacizumabom. Pacijenti su primali kontinuiranu prvolinijsku terapiju do progresije bolesti ili održavanje fluoropirimidinima i bevacizumabom nakon indukcijske kemoterapije na bazi irinotekana do progresije bolesti (PFS1), a zatim reindukciju irinotekana do progresije bolesti (PFS2). Primarni ciljevi bili su preživljenje bez progresije (PFS) i ukupno preživljenje (OS).

**Rezultati:** Terapija održavanja pokazala je značajno bolje ishode nego kontinuirana terapija. PFS1 iznosio je 21 mjesec (95% CI, 10-66) naspram 12 mjeseci (95% CI, 10-17; $P < 0{,}001$); PFS2 nije bio dostignut (95% CI 42-104) naspram 12 mjeseci (95% CI, 10-17; $P < 0{,}001$). Ukupno preživljenje unatoč numerički boljem rezultatu terapije održavanja (77 mjeseci vs nedostignuto) nije pokazalo statističku značajnost ($P = 0.13$). Medijan vremena trajanja indukcijske kemoterapije iznosio je 11 mjeseci, a medijan trajanja terapije održavanja 9 mjeseci.

**Zaključak:** Terapija održavanja fluoropirimidinima i bevacizumabom nakon indukcijske kemoterapije na bazi irinotekana pokazuje značajnu korist u PFS-u u stvarnoj kliničkoj praksi, podupirući njezinu uporabu u kontroli bolesti uz smanjenu toksičnost liječenja kod pacijenata s mCRC.



## KLJUČNE RIJEČI

*Terapija održavanja*; *Metastatski kolorektalni karcinom*; *Bevacizumab*; *FOLFIRI*; *CAPIRI*