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Research Article

# Effect of Maintenance anti-EGFR Therapy on Survival in Metastatic RAS Wild-Type Colorectal Cancer: Single-Center Experience

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## Abstract

**Objectives:** The combination of anti-EGFR agents with chemotherapy is used in the first-line treatment of metastatic colorectal cancer (mCRC). The aim of this study is to evaluate the efficacy of anti-EGFR maintenance therapy in patients with metastatic RAS wild-type left colon.

**Methods:** In this retrospective, single-center study, 273 patients with mCRC who were treated at Dicle University Medical Oncology Clinic between December 2014 and March 2021 were reviewed. Patients were analyzed for progression-free survival (PFS) and overall survival (OS).

**Results:** Data obtained from 35 patients. Regarding maintenance chemotherapy agents, 14 (40%) received FOLFIRI, 16 (45.7%) received 5-FU, and the remaining received other agents. Among the patients, 21 (60%) received cetuximab as anti-EGFR therapy and 14 (40%) received panitumumab. The median follow-up was 30 months (8-73). Median PFS was 22 months (16.8-27.1) who received cetuximab and 14 months (10.8-17.1) who received panitumumab (p=0.1). Median PFS was 15 months (10.6-19.3) for receiving FOLFIRI and 22 months (17.2-26.7) for receiving 5-FU (p=0.058). Median OS was 25 months (8.1-41.8) for receiving FOLFIRI and 54 months (31.5-76.4) for receiving 5-FU (p=0.059).

**Conclusion:** Our study showed that maintenance therapy with cetuximab and panitumumab had comparable efficacy. 5-FU showed borderline statistical significance in terms of efficacy compared to FOLFIRI.

**Keywords:** Cetuximab, panitumumab, maintenance therapy, metastatic colorectal cancer

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According to the 2020 global cancer statistics, the global incidence of colorectal cancer is approximately 1.2 million cases, accounting for approximately 10% of all cancers. Colorectal cancer-related mortality accounts for 5.8% of all cancer-related deaths. In Türkiye, colorectal cancer accounts for 9.1% of all cancers and 5.2% of cancer-related mortality based on 2020 data.[1]

Doublet chemotherapy (ChT) plus molecular targeted drugs is recommended for the treatment of metastatic, RAS and BRAF wild-type, microsatellite stable colorectal cancer.[2,3] Maintenance therapy, which refers to de-escalation of treatment intensity, can be used after an initial 4-6 cycles of treatment. The main purpose of maintenance therapy is to improve side effects and quality of life without compromising disease control and efficacy.

The Cairo-3 trial reported a median PFS of 11.7 months for patients receiving capecitabine, oxaliplatin, bevacizumab (CAPOX-B) followed by maintenance capecitabine,

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and bevacizumab compared to 8.5 months for those not receiving maintenance (p<0.0001). Another study compared maintenance bevacizumab with observation after 12 cycles of bevacizumab plus FOLFIRI. The result showed no benefit of maintenance bevacizumab in terms of disease control and survival.[5] There are no phase 3 data to support the use of anti- EGFR agents as maintenance therapy. In the phase 2 MACRO-2 study, after induction with 8 cycles of mFOLFOX6 and cetuximab, maintenance with mFOLFOX6 plus cetuximab and single agent cetuximab were evaluated. There was no difference in progression-free survival (PFS), overall survival (OS) or objective response rate.[6] Similarly, in the PANAMA trial, after induction ChT with FOLFOX plus panitumumab, patients were assigned to maintenance therapy with either 5-FUFA or 5-FUFA plus panitumumab. Panitumumab plus 5-FUFA improved PFS compared to 5-FUFA alone (8.8 months vs. 5.7 months; HR, 0.72; 80% CI, 0.60 to 0.85; p=0.01). Although no OS improvement was observed, objective response rates were higher in the combination group vs. ChT (40.8% vs. 26%).[7] In another study, maintenance with single-agent panitumumab was compared with panitumumab plus fluorouracil-leucovorin after 4 months of induction with panitumumab plus FOLFOX4. PFS in the combination group was better than in the single agent panitumumab group (12 months vs. 9.9 months, p=0.006), but OS and objective response rate were the same.[8]

Maintenance bevacizumab and chemotherapy combination showed survival benefit in phase 3 trials, but there is no phase 3 trial to evaluate anti-EGFR as maintenance therapy. In our study, our aim was to evaluate the efficacy of anti-EGFR maintenance therapy in patients with metastatic RAS wild-type left-sided colon cancer and present real-life data.

## Methods

For the study, the records of 273 patients with metastatic CRC who were treated at Dicle University Medical Oncology Clinic between December 2014 and March 2021 were retrospectively reviewed. A total of 35 patients between the ages of 19 and 75 years with metastatic colorectal cancer (mCRC) and wild-type K-RAS, N-RAS, and B-RAF genes who had received dual chemotherapy and anti-EGFR combination therapy and subsequently underwent maintenance therapy with chemotherapy and anti-EGFR agents were included in the study. Patients with right-sided colon tumors, those who did not receive maintenance therapy, those with a second primary tumor, and those who did not complete 6 months of induction chemotherapy or had disease progression were excluded from the study. Patients' age, histopathologic characteristics, tumor localization, stage at diagnosis, anti-EGFR agent received, chemotherapy combination, metastatic sites, CEA level, hemoglobin level, and alkaline phosphatase level were evaluated.

### Statistical Analysis: Data was Evaluated with SPSS Statistics Version 25

Descriptive statistics were presented as mean (mean), standard deviation (SD), median [interquartile range (IQR)], minimum (min), and maximum (max). The student's t-test was used for comparing two groups for normally distributed numerical variables, while the Mann- Whitney U test was used for variables that did not follow a normal distribution. The chi- square test was used for comparing categorical variables between the two groups. Normality analysis was performed with the Kolmogorov Smirnov test. All hypotheses were set up as two-way and the alpha critical value was taken as 0.05. Survival analyses were evaluated using the Kaplan-Meier test, and differences between two groups were assessed using the log- rank test.

The follow-up period was defined as the time from diagnosis to the last observation or death. Progression-free survival was defined as the time between initiation of ChT until tumor progression or death which one occurs first. Overall survival was defined as the time from initiation of ChT to until death.

## Results

Among the patients included in the study, 17 (48.6%) were female and 18 (51.4%) were male. The mean age of the patients was 49 years (19-75). The primary tumor was located in the colon of 22 (62.9%) patients and in the rectum in 13 (37.1%) patients. At the time of diagnosis, 22 (62.9%) patients had metastatic disease, while 13 (37.1%) patients were diagnosed with localized diseases that subsequently progressed. The general characteristics of all patients and the treatments they received are summarized in Table 1. The median follow-up period was 30 (8-73) months. Median PFS for all patients was 19 (14-23.9) months. Median PFS was 22 (16.9-27.0) months in women and 14 (7.1-20.8) months in men (p=0.9). The median PFS was 22 months (16.8-27.1) in cetuximab recipients and 14 months (10.8-17.1) in panitumumab recipients (Fig. 1, p=0.9).

Those receiving FOLFIRI as maintenance ChT were 15 months (10.6-19.3) and those receiving 5-FU were 22 (17.2-26.7) months (Fig. 2, p=0.058). In the overall patient group, median OS was 38 (33.0-42.9) months, median OS was 38 (32.9-43.0) months in women and 39 months (22.3-55.6) in men (p=0.9). Median OS was 39.6 (32.7-45.2) months in cetuximab patients and 39.1 (28-75.6) months in panitumumab patients (Fig. 3, p=0.9). Median OS was 25 (8.1-

**Table 1.** General characteristics and frequency of patients (descriptive frequency analysis)

| General Characteristics of Patients (n=35) | Number (n) | Percentage (%) |
|---|---|---|
| Gender | | |
| Male | 17 | 48.6 |
| Female | 18 | 51.4 |
| ECOG | | |
| 0 | 9 | 25.7 |
| 1 | 24 | 68.6 |
| 2 | 2 | 5.7 |
| Tumor localization | | |
| Colon | 22 | 62.9 |
| Rectum | 13 | 37.1 |
| Stage at Diagnosis | | |
| Local | 13 | 37.1 |
| Metastatic | 22 | 62.9 |
| Adjuvant Chemotherapy | | |
| Yes | 10 | 28.6 |
| No | 25 | 71.4 |
| Braf Mutation | | |
| Wild | 35 | 100 |
| Anti-EGFR | | |
| Cetuximab | 24 | 60 |
| Panitumumab | 11 | 40 |
| Chemotherapy Used During Diagnosis | | |
| FOLFOX | 12 | 34.3 |
| FOLFIRI | 21 | 60 |
| XELOX | 2 | 5.7 |
| Chemotherapy combinations | | |
| FOLFIRI + Cetuximab | 9 | 25.7 |
| FOLFIRI + Panitumumab | 5 | 14.2 |
| 5-FU + Panitumumab | 4 | 11.4 |
| 5-FU +Cetuximab | 12 | 34.2 |
| Cetuximab | 1 | 2.8 |
| Capecitabine +Panitumumab | 1 | 2.8 |
| Capecitabine + Cetuximab | 1 | 2.8 |
| FOLFOX + Panitumumab | 1 | 2.8 |
| Irinotecan + Panitumumab | 1 | 2.8 |
| Chemotherapy used in maintenance | | |
| FOLFIRI | 14 | 40 |
| 5-FU | 16 | 45.7 |
| FOLFOX | 1 | 2.9 |
| Capecitabine | 2 | 5.7 |
| Irinotecan | 1 | 2.9 |
| Chemotherapy-free maintenance | 1 | 2.9 |
| Metastasis Sites | | |
| Liver Metastases | 26 | 74 |
| Lung Metastases | 7 | 30 |
| Peritoneal Metastases | 6 | 17 |
| Bone Metastases | 3 | 8.5 |
| Acneiform Rash | | |
| Yes | 25 | 71 |
| No | 10 | 29 |

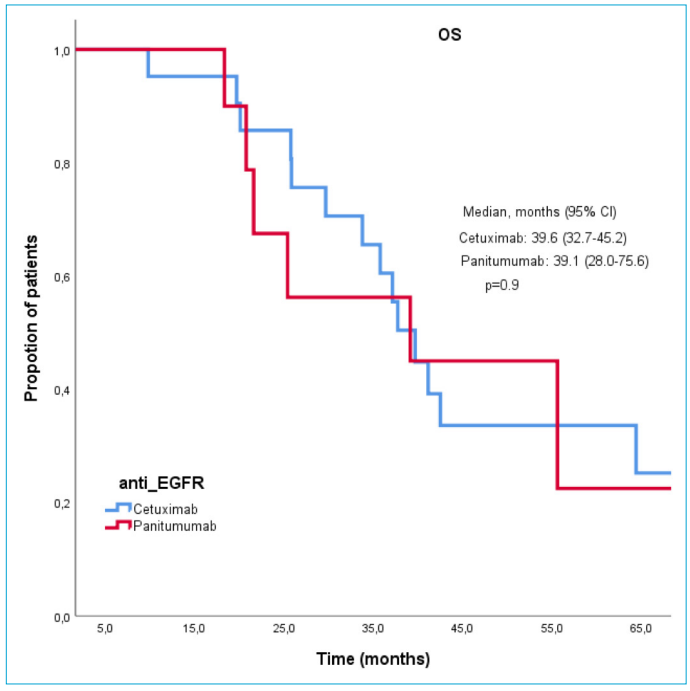


**Figure 1.** Overall Survival (OS) graph comparing cetuximab and panitumumab.

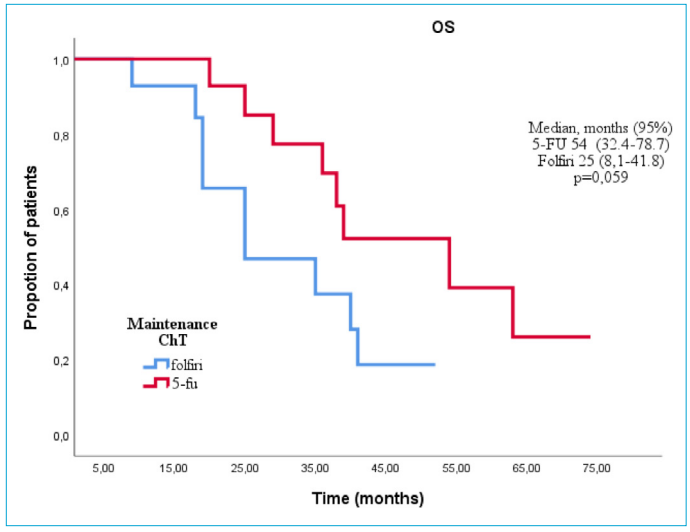


**Figure 2.** Progression-free Survival (PFS) graph comparing FOLFIRI and 5-FU.

41.8) months for those receiving maintenance FOLFIRI and 54 (32.4-78.7) months for those receiving maintenance 5-FU (Fig. 4, p=0.059). Those receiving maintenance cetuximab received a median of 13 (3-32) cycles and those receiving maintenance panitumumab received a median of 7 (3-31) cycles. There was a borderline statistical significance. (p=0.052). Those receiving maintenance FOLFIRI received a median of 7 (3-17) cycles and those receiving maintenance 5-FU received a median of 8.5 (3-32) cycles and there was no significant difference (p=0.6).

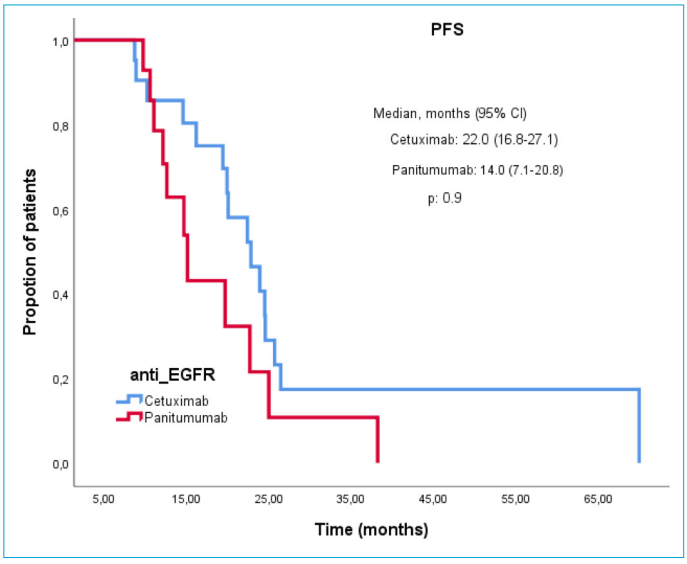


**Figure 3.** Progression Free Survival (PFS) graph comparing cetuximab and panitumumab.

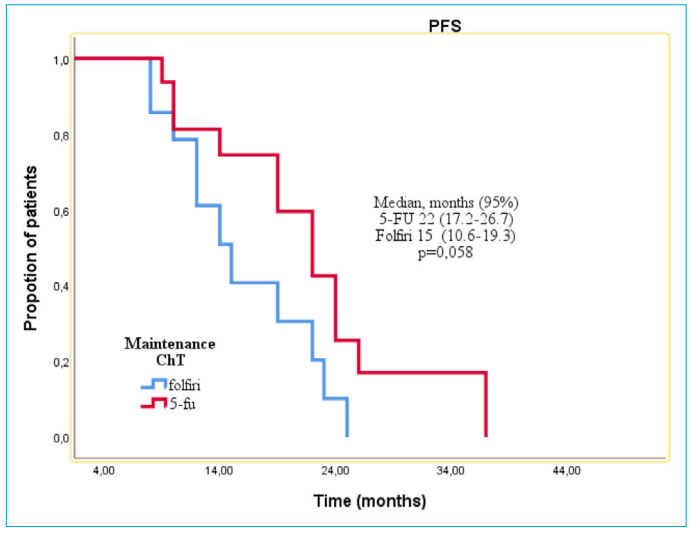


**Figure 4.** Progression-free Survival (OS) graph comparing FOLFIRI and 5-FU.

The limitations of our study are its retrospective design, single center study, and small number of patients.

## Discussion

The treatment landscape for metastatic colorectal cancer (mCRC) is rapidly evolving. For most patients with mCRC, the primary goal of systemic therapy remains palliative. [9] Therefore, the goal of treatment is to improve survival without compromising quality of life. After induction of doublet ChT plus biological agents, discontinuation or dose reduction of ChT and continuation of maintenance therapy is rational.

In one meta-analysis, after 3-4 months of induction ChT, maintenance with bevacizumab showed benefit when combined with 5-FU alone.[10] However, the optimal maintenance regimen after anti-EGFR based ChT is still not well defined. In one study, following 9-12 cycles of FOLFIRI-cetuximab, irinotecan-cetuximab continued as maintenance therapy, median failure-free survival was 19 and 9.3 months in the maintenance and observation groups, respectively. [11] In our study, after six months of induction treatment, patients continue to receive either FOLFIRI or 5-FU in addition to cetuximab or panitumumab. As a biologic agent, treatment with maintenance cetuximab plus ChT confers 22 months PFS, while as ChT continue with 5-FU provide the same PFS. Our results are consistent with the aforementioned study. In another retrospective study, cetuximab in addition to ChT or alone as maintenance therapy showed survival benefit compared to on maintenance.[12] There was not a non- maintenance arm in our study. What we have just shown is that while numerically cetuximab has a higher PFS than panitumumab, statistically there was not a significant difference in PFS and OS.

In a single-center prospective study, patients were divided into an observation arm and a maintenance arm after receiving first-line FOLFIRI plus cetuximab combination therapy. After 6-12 cycles of maintenance therapy, patients continued to receive maintenance cetuximab alone. The primary endpoint of the study, median failure-free survival (FFS), was 9.3 months in the observation arm and 19 months in the maintenance treatment arm, demonstrating a statistically significant benefit (HR 0.211, 95% CI 0.117–0.380; p<0.001).[13] In our study, the median progression-free survival (PFS) for patients receiving cetuximab and chemotherapy was 22 months. The aforementioned study included patients who did not progress after 18-24 weeks of induction chemotherapy, and in our study, we also included patients who did not progress after 6 months of treatment. This may explain the similarity in PFS results.

The phase 2 COIN-B trial, similar to our study, enrolled patients with RAS and BRAF wild- type tumors and compared observation with maintenance cetuximab following first-line FOLFOX plus cetuximab combination therapy. The median FFS was 12.2 months in the observation group and 14.3 months in the maintenance cetuximab group, favoring maintenance anti-EGFR treatment.[14] In that trial, only cetuximab was administered as maintenance therapy, whereas in our study, cetuximab was given in combination with either FOLFIRI or 5-FU. The difference in PFS between the two studies can be attributed to this variation in treatment regimens.

In a retrospective multicenter study, patients who did not progress after 6 months of induction chemotherapy were

assigned to groups receiving 5-FU plus anti-EGFR, anti-EGFR alone, 5- FU alone, or no treatment. The median PFS was 16, 13, 14, and 10 months, respectively. Median overall survival (OS) was 39.6, 36.1, 39.5 and 25.1 months, correspondingly. In comparison to patients who did not receive maintenance therapy, both the anti-EGFR plus 5- FU and anti-EGFR alone groups showed a favorable median PFS, while only the anti-EGFR plus 5-FU group showed a favorable median OS.[15]

The PANAMA trial, maintenance 5-FU plus panitumumab combination therapy was compared with 5-FU monotherapy following induction chemotherapy. PFS was 8.8 months to 5.5 months in favor of panitumumab-FUFA with a statistically significant difference (HR:0.72, p=0.014). Overall survival (OS) was 28.7 months with panitumumab-FUFA versus 25.7 months with FUFA, and although there was a numerical difference, there was no statistically significant difference (HR:0.84, p=0.32).[16] Looking at the patient groups included in the PANAMA study, it can be noted that 31% of the patients had right-sided colon tumors known for their poor response to anti-EGFR therapy. In our study, all patients had left- sided colon tumors. The contribution to OS in our study may be related to the fact that all patients had left-sided colon tumors.

The non-inferiority study, known as the Valentino trial, maintenance treatment with single- agent panitumumab was compared to 5-FU plus panitumumab after 8 cycles of induction FOLFOX-4 plus panitumumab therapy. The 10-month PFS value was 59.9% for panitumumab alone versus 49% for panitumumab plus 5-FU, favoring the panitumumab plus 5-FU group (p=0.01).[17] In our study, patients received anti-EGFR chemotherapy combination therapy after a 6-month induction treatment, and our patients received a longer duration of induction therapy compared to the Valentino trial. The longer duration of tolerated induction therapy may affect the response to maintenance anti-EGFR therapy.

Considering the results of our study, there was no superiority of FOLFIRI over 5-FU among the chemotherapy regimens used in maintenance anti-EGFR combination therapy. Therefore, the use of FUFA seems to be more appropriate in terms of drug toxicity and quality of life when maintenance treatment is given. However, due to the retrospective nature of our study, there may be biases and limitations. The higher OS and PFS values in our study in comparison to literature can be attributed to its retrospective nature, the selection of younger patients, and the inclusion of patients who completed 6 cycles of induction chemotherapy. Other studies may have included patients with shorter induction chemotherapy durations and more aggressive disease progression.

**Disclosures**

**Ethics Committee Approval:** Dicle University Medical Faculty Ethics Committee (date/reference number: 26.06.2023/239).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Design – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Supervision – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Materials – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Data collection &/or processing – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Analysis and/or interpretation – S.I., O.K., Y.S., S.T.,Z.K., H.Y.; Literature search – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Writing – S.I., O.K., Y.S., S.T., Z.K., H.Y.; Critical review – S.I., O.K., Y.S., S.T., Z.K., H.Y.

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