RESEARCH ARTICLE

# Xeliri Plus Bevacizumab Compared with Folfiri Plus Bevacizumab as First-Line Setting in Patients with Metastatic Colorectal Cancer: Experiences at Two-Institutions

**Kazim Uygun[1], Ahmet Bilici[2]*, Serap Kaya[1], Bala Basak Oven Ustaalioglu[3], Ramazan Yildiz[3], Suleyman Temiz[1], Mesut Seker[3], Gorkem Aksu[4], Devrim Cabuk[1], Mahmut Gumus[3]**

## Abstract

**Background: Efficacy of chemotherapy plus bevacizumab has been shown in patients with metastatic colorectal cancer (mCRC) compared with chemotherapy alone. The aim of the present study was to evaluate the efficacy and safety of FOLFIRI or XELIRI regimens in combination with bevacizumab for mCRC patients in a first-line setting. Materials and Methods: A total of 132 patients with previously untreated and histologically confirmed mCRC were included. They were treated with either FOLFIRI-Bevacizumab (Bev) or XELIRI-Bev according to physician preference. The efficacy and safety of the two regimens were compared. Results: Between 2006 and 2010, 68 patients were treated with the XELIRI-Bev regimen, while the remaining 64 patients received the FOLFIRI-Bev regimen. The median age was 58.5 years (53.6 years in the FOLFIRI-Bev and 59.7 years in the XELIRI-Bev arm, p=0.01). Objective response rate was 51.6% for FOLFIRI-Bev versus 41.2% for XELIRI-Bev (p=0.38). At the median follow-up of 24.5 months, the median progression-free survival (PFS) was not different between two groups (14.2 months in FOLFIRI-Bev vs. not reached in the XELIRI-Bev, p=0.30). However, median overall survival time for the FOLFIRI-Bev arm was better than that for patients treated with XELIRI-Bev, but these differences was not statistically significant (37.8 months vs. 28.7 months, respectively, p=0.58). Most commonly reported grade 3-4 toxicities (FOLFIRI-Bev vs XELIRI-Bev) were nausea/vomiting (7.8% vs. 14.7%, p=0.27), diarrhea (10.9% vs 22.1%, p=0.10), hand-foot syndrome (0% vs 8.8%, p=0.02) and neutropenia (18.7% vs 27.9%, p=0.22). Conclusion: Our results showed that FOLFIRI-Bev and XELIRI-Bev regimens were similarly effective treatments in a first-line setting for patients with untreated mCRC, with manageable adverse event profiles.**

**Keywords:** Colorectal carcinoma - chemotherapy - irinotecan - capecitabine - bevacizumab

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## Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. Although it is the second leading cause of cancer death worldwide, mortality from CRC has decreased over the past 30 years due to earlier diagnosis through screening, and better treatment modalities. Early-stage disease is localized and resectable, but 20% of the patients have metastatic disease at the time of diagnosis and half of them finally die because of their disease (Jemal et al., 2011)

In patients with untreated metastatic CRC, two large randomized trials have shown that the addition of irinotecan to either bolus (IFL) or infusional 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFIRI) significantly imroved response rate, progression-free survival (PFS) and overall survival (OS) compared with 5-FU/LV regimen alone in patients with untreated metastatic CRC (Douillard et al., 2000; Saltz et al., 2000). Furthermore, improved survival has been obtained with oxaliplatin/5-FULV (FOLFOX) (de Gramont et al., 2000). In the light of these results, FOLFIRI and FOLFOX regimens have been accepted as a standard treatment of metastatic CRC patients.

Capecitabine is an oral fluoropyrimidine which is a pro-drug of 5-FU, and it has reported that it is at least equivalent to the standard 5-FULV combination with respect to PFS and OS whilst showing a better tolerability profile. Phase I/II studies of capecitabine combination with irinotecan (XELIRI) showed comparable response rates compared with 5-FULV-irinotecan combination (Bajetta et al., 2004; Borner et al., 2005; Rea et al., 2005). On the other hand, XELIRI has been related with response rates

*[1]Department of Medical Oncology, [4]Department of Radiation Oncology, Kocaeli University, Medical Faculty, Kocaeli, [2]Department of Medical Oncology, Sisli Etfal Education and Research Hospital, [3]Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey *For correspondence: ahmetknower@yahoo.com*

of 38-45% and a time-to-progression of about of 8 months with manageable side-effect profiles (Tewes et al., 2003; Bajetta et al., 2004; Cartwright et al., 2005).

Bevacizumab (Bev) is a recombinant humanized monoclonal antibody to vascular endothelial growth factor and several trials have indicated that the addition of Bev to irinotecan or oxaliplatin combination with 5-FULV or capecitabine alone was beneficial in patients with metastatic CRC (Fernando et al., 2005; Hochster et al., 2006; Sobrero et al., 2006). Recently, some randomized phase II an done phase III trials have compared the efficacy and safety of XELIRI and FOLFIRI regimens combined with Bev for patients with metastatic colorectal cancer in the first-line setting (Pectasides et al., 2012; Renouf et al., 2012; Souglakos et al., 2012; Ducreux et al., 2013). These studies demonstrated that XELIRI-Bev and FOLFIRI-Bev are similarly effective treatment modalities with different toxicity profiles. In the present study, we compared the efficacy and safety of XELIRI-Bev and FOLFIRI-Bev in chemo-naive patients with metastatic CRC

## Materials and Methods

Between 2006 and 2010 at the Kocaeli University, Medical Faculty and the Dr Lutfi Kirdar Kartal Education and Research Hospital, Medical Oncology Departments, a total of 132 patients with previously untreated and histologically confirmed metastatic CRC were included. The eligibility criteria were consisted of patients with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, absolute neutrophil count > 1500 mm3, platelet count >100000 mm3, adequate hepatic (total serum bilirubin < 1.5 times the upper normal limit (UNL); ALT, AST < 2.5 times the UNL), and renal function (serum creatinine level < 1.25 mg/dl); and had no previous chemotherapy for metastatic disease. Patients who had received prior treatment with irinotecan or bevacizumab; had known central nervous system involvement; had inadequately contolled hypertension, severe cardiac disease or myocardial infarction, stroke or transient ischemic attack, pulmonary embolism, or deep vein thrombosis within the past 6 months; were pregnant or lactating; had active serious infections were excluded from study. In addition, patients with a history of other malignancies except for basal cell skin carcinoma or in situ carcinoma of the uterine cervix were not included.

The clinical information of the patients such as age at diagnosis, gender, performance status and other histological parameters such as tumor stage, histopathological type, the presence of resection and resection type, primary tumor location, initial tumor stage at diagnosis, the presence of primary adjuvant chemotherapy and radiation therapy, primary metastatic sites, responses to treatment and survival were obtained from patients charts after informed written consents were obtained from each subject included in the study.

*Treatment plan*

Patients were received chemotherapy regimen according to physician preference and whether patients who were not suitable or refuse applying infusional port catheter, then they were retrospectively analyzed. Sixty-eight of the 132 patients were treated with XELIRI-Bev regimen (irinotecan 250-300 mg/m2 i.v. over 90 min on day 1; capecitabine 1000 mg/m2 per oral bid on days 1-14; Bev 7.5 mg/kg i.v. on day 1, every three weeks). The remaining 64 patients received FOLFIRI-Bev regimen (irinotecan 180 mg/m2 i.v. over 90 min on day 1; folinic acid 400 mg/m2 i.v. over 2 hour on day 1; 5-FU 400 mg/m2 i.v. bolus on day 1; 5-FU 2400 mg/m2 i.v. continuous infusion over 46 hour; Bev 5 mg/kg i.v. on day 1, every two weeks). Thereafter, Bev was continued until disease progression. The patients in both arms received premedication with dexamethason 16 mg i.v., diphenhydramine 50 mg i.v. and granisetron 3 mg i.v. on day 1 of each chemotherapy course. During treatment, toxicities were defined as hematological or non-hematological and were graded as graded 1 to 4 based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0 at all visits. Required dose modifications were performed if grade 2 to 4 toxicities occured.

*Patient assessments*

The initial evaluations included a complete medical history, physical examination, a complete blood count, hepatic and renal function tests, serum carcinoembryonic antigen (CEA) levels. In addition, baseline tumor evaluations were performed using abdomino-pelvic CT or MRI scans and chest X-ray or CT/MRI of the chest. During treatment, imaging modalities were repeated after every three courses, and at the end of treatment. Treatment responses were evaluated with respect to RECIST criteria. Objective response (ObR) was also defined as a complete response (CR) plus partial response (PR).

*Statistical analysis*

All data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The clinicopathological factors of patients in XELIRI-Bev and FOLFIRI-Bev arms were compared by the chi-squared test and Fisher's exact test. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test.

PFS was defined as the time from initiation of treatment to the progression of disease, or to the date of death or loss of follow-up. OS was described as the time from diagnosis to the date of the patient's death or loss of follow-up. Univariate and multivariate analyses to assess the significance of clinicopathological features as prognostic factors were performed by the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. Differences in the toxicity profiles and response rates in the two treatment arms were analyzed by chi-squared test. All p values were two-sided in tests and all p values less than 0.05 were considered to be statistically significant.

## Results

*Patient characteristics*

A total of 132 patients were included, of whom 68 (51.5%) were treated with XELIRI-Bev and 64 (48.5%) received FOLFIRI-Bev. Fifty-five patients (41.7%) were female and 77 (58.3%) were male, with a median age of 58.5 years (range; 21–79 years). The patient baseline characteristics in both treatment arms are summarized in Table 1. The two groups were generally similar in terms of gender, ECOG PS, primary tumor location, initial stage of disease at diagnosis, the presence of previous adjuvant treatment and primary metastatic site except for age, initial stage and the presence of previous radical surgery. The patients treated with XELIRI-Bev were older than those received FOLFIRI-Bev (p=0.01). The majority of patients received XELIRI-Bev were initially staged as III, while in FOLFIRI-Bev arm patients were commonly staged as IV (p=0.04). The high proportion of patients had undergone previous radical surgery for primary tumor in XELIRI-Bev arm compared with those treated with FOLFIRI-Bev (61.7 vs 38.3%, p=0.004). In addition, previous adjuvant chemotherapy regimens consisted of 5-FULV (n=9), FLOX (n=6) and FOLFOX (n=9) for 24 patients receiving FOLFIRI-Bev and 5-FULV (n=14), and FOLFOX (n=24) for 21 patients receiving XELIRI-Bev. The liver was the most common metastatic site in both arms (56.3% vs 61.8%).

**Table 1. Clinical Characteristics of Patients in FOLFIRI-B and XELIRI-B Groups**

| | FOLFIRI-B n (%) | XELIRI-B n (%) | p |
|---|---|---|---|
| All patients | 64 (48.5) | 68 (51.5) | |
| Median age, years | 53.6 | 59.7 | 0.01* |
| Range; | 21-79 | 37-79 | |
| Gender | | | 0.29 |
| Male | 34 (53.1) | 43 (63.2) | |
| Female | 30 (46.9) | 25 (36.8) | |
| ECOG PS | | | 0.55 |
| PS 0-1 | 57 (89.1) | 63 (92.6) | |
| PS 2 | 7 (10.9) | 5 (7.4) | |
| Primary tumor | | | 0.38 |
| Colon | 40 (62.5) | 37 (54.4) | |
| Rectum | 24 (37.5) | 31 (45.6) | |
| Primary radical surgery | | | 0.004* |
| Absent | 33 (51.6) | 18 (26.5) | |
| Present | 31 (48.4) | 50 (73.5) | |
| Initial stage of disease at diagnosis | | | 0.04* |
| Stage I | 2 (3.1) | 1 (1.5) | |
| Stage II | 15 (23.4) | 13 (19.1) | |
| Stage III | 17 (26.6) | 34 (50) | |
| Stage IV | 30 (46.9) | 20 (29.4) | |
| Previous adjuvant treatment | | | 0.33 |
| Absent | 10 (29.5) | 12 (24) | |
| Present | 24 (70.5) | 38 (76) | |
| Primary metastatitic site | | | 0.44 |
| Liver | 36 (56.3) | 42 (61.8) | |
| Lung | 5 (7.8) | 5 (7.4) | |
| Liver and lung | 5 (7.8) | 9 (13.2) | |
| Others | 18 (28.1) | 12 (17.6) | |

*ECOG PS, Eastern Cooperative Oncology Group Performance Status; B, bevacizumab; adjuvant treatment, chemotherapy+radiotherapy

*Treatment efficacy*

The median number of chemotherapy cycles was 9 for FOLFIRI-Bev, every two weeks and 6 for XELIRI-Bev, every three weeks. Only 7 patients in both arms were treated with fewer than 3 cycles because of early progression (3 in both arms), adverse events (1 in FOLFIRI arm and 2 XELIRI arm) or refusal/poor compliance (3 in FOLFIRI arm and 2 in XELIRI arm). At the median follow-up of 24.5 months (range; 5.5–93 months), the 1-year PFS rate and the median PFS interval were 53.7% and 14.2 months in FOLFIRI-Bev arm, respectively, while in patients received XELIRI-Bev the 1-year PFS rate was 55.4% but the median PFS interval couldn't be reached (p=0.30, Fig. 1). Moreover, median OS time and three-year OS rate for patients treated with FOLFIRI-Bev were better than those for the patients in XELIRI-Bev arm, but these differences were not statistically significant (37.8 months and 53.8% vs. 28.7 months and 38.4%, respectively, p=0.58, Fig. 2).

After the exclusion of 8 patients were treated with fewer than 3 cycles because of adverse events or refusal/poor compliance (4 in both arms), following 6 cycles of therapy, response was evaluated in 124 patients. Overall, objective response was obtained in 33 of 64 patients (51.6%) received FOLFIRI-Bev (29 PR and 4 CR). However, 28 of 68 patients treated XELIRI-Bev achieved an objective response (26 PR and 2 CR). ObR was similar in the 2 arms (p=0.38). Table 2 shows efficacy analysis of patients treated with FOLFIRI-Bev or XELIRI-Bev. The higher number of stable disease was observed in XELIRI-Bev group compared with FOLFIRI-Bev arm, but this was not significant (p=0.36). Moreover, the rates of progressive disease were not different in either group (p=0.83).

In the univariate analysis for patients received FOLFIRI-Bev, initial stage of disease at diagnosis, the

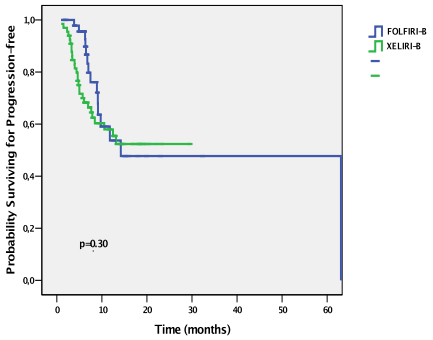


**Figure 1. Progression-free Survival for Patients Treated with FOLFIRI-Bev or XELIRI-Bev (Bev: Bevacizumab)**

**Table 2. Efficacy Analysis of Patients in XELIRI-B and FOLFIRI-B Groups**

| | FOLFIRI-B (n=64) (%) | XELIRI-B (n=68) (%) | p |
|---|---|---|---|
| Objective response | 33 (51.6) | 28 (41.2) | 0.38 |
| Partial | 29 (45.3) | 26 (38.2) | |
| Complete | 4 (6.3) | 2 (2.9) | |
| Stable disease | 19 (29.7) | 26 (38.2) | 0.36 |
| Progressive disease | 12 (18.8) | 14 (20.6) | 0.83 |

*B: bevacizumab

**Table 3. Grade 3-4 Adverse Events of Patients in XELIRI-B and FOLFIRI-B Groups**

| | FOLFIRI-B n (%) | XELIRI-B n (%) | p |
|---|---|---|---|
| Non-hematologic toxicities | | | |
| Nausea/vomiting | 5 (7.8) | 10 (14.7) | 0.27 |
| Diarrhea | 7 (10.9) | 15 (22.1) | 0.10 |
| Hand-foot syndrome | - | 6 (8.8) | 0.02 |
| Mucositis | 1 (1.5) | 4 (5.9) | 0.36 |
| Thromboembolic event | - | - | NA |
| Arterial hypertension | 1 (1.5) | 2 (2.9) | 0.99 |
| Hemorrhage | 3 (4.6) | 0 | 0.11 |
| Hematologic toxicities | | | |
| Neutropenia | 12 (18.7) | 19 (27.9) | 0.22 |
| Anemia | 1 (1.5) | 4 (5.9) | 0.36 |
| Febrile neutropenia | 5 (7.8) | 10 (14.7) | 0.27 |

*B: bevacizumab; NA: not applicable

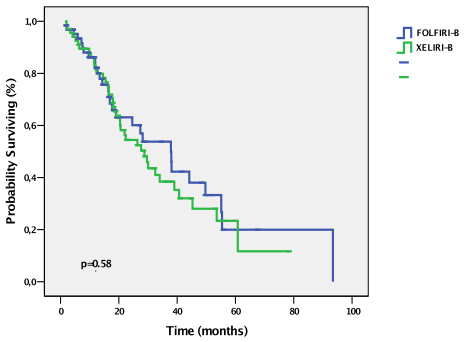


**Figure 2. Overall Survival Curves of Patients in FOLFIRI-Bev or XELIRI-Bev Arms (Bev: Bevacizumab)**

presence of progression after metastatic disease and primary metastatic site were significant prognostic factors for OS. For patient treated XELIRI-Bev, the univariate analysis indicated that gender, age, primary tumor localization, initial stage of disease at diagnosis, the presence of progression after metastatic disease and primary metastatic site were important prognostic indicators. The multivariate analysis showed that gender, primary tumor localization, intial stage of disease and the presence of progression after metastatic treatment were independent prognostic factor in patients treated with XELIRI-Bev. Thereafter, the multivariate analysis was carried out for FOLFIRI-Bev arm, any prognostic factor which had effect on OS could not be found.

*Toxicity evaluation:*

Most commonly reported non-hematological toxicities included nausea/vomiting, diarrhea, hand-foot syndrome and mucositis. XELIRI-Bev treatment was associated with the higher rates of grade 3-4 nausea/vomiting, diarrhea, hand-foot syndrome and mucositis compared with FOLFIRI-Bev arm. These different were not significant except for hand-foot syndrome (p=0.02). No severe thromboembolic event was observed in both groups. Only one patient in FOLFIRI-Bev and two patients in XELIRI-Bev arm with arterial hypertension were detected. In all patients hypertension was low level and easily treated with oral antihypertensive therapy. Hemorrhage was observed in only three cases received FOLFIRI-Bev, but these were not severe and easily managed with local treatment. On the other hand, neutropenia was the most frequently reported grade 3-4 hematological toxicity. Although the high rates of patients were suffered from grade 3-4 neutropenia and febril neutropenia (27.9% and 14.7%, respectively) in XELIRI-Bev arm, this was not significant (p=0.22 and 0.27, respectively). No death was observed in both arms because of toxicities. Interruption of treatment due to grade 3-4 toxicity was more common among patients treated with XELIRI-Bev (22.1%) when compared with FOLFIRI-Bev (15.6%), but discontinuation of treatment because of unacceptable grade 3-4 toxicities was similar in both groups (5.8% vs 3.1%, p=0.21). The results of grade 3-4 advers events were listed in Table 3.

## Discussion

Our current study indicated that the similar efficacy was detected between FOLFIRI-Bev and XELIRI-Bev in patients with metastatic CRC in the first-line setting. Moreover, although grade 3-4 neutropenia, nausea-vomiting, hand-foot syndrome and diarrhea were more frequently seen in patients treated with XELIRI-Bev when compared with FOLFIRI-Bev arm, these were not significant except for hand-foot syndrome, and the toxicities were generally manageable for both arms.

Median survival of patients with metastatic CRC has been considerable improved with FOLFIRI or FOLFOX regimens (Douillard et al., 2000; de Gramont et al., 2000; Saltz et al., 2000). Thereafter, survivals have been increased with Bev combination of FOLFIRI or FOLFOX (Fernando et al., 2005; Hochster et al., 2006; Sobrero et al., 2006). Moreover, the use of the oral fluoropyrimidine capecitabine in combination with Bev has been reported to be safe and effective in the first-line treatment for metastatic CRC and found to be PFS times of 8.5 months and disease control rates of 92.5% (Feliu et al., 2008; Tebbutt et al., 2010). The combination of capecitabine with irinotecan (XELIRI) plus Bev resulted in a disease control rate of 72-82% and median PFS of 9-12 months (Reinacher-Schick et al., 2008; Renouf et al., 2012; Pectasides et al., 2012; Ducreux et al., 2013). On the other hand, earlier trials evaluating chemotherapy regimen with capecitabine and irinotecan had showed that CAPIRI regimen was associated with unacceptable incidences of severe gastrointestinal adverse effects with grade 3-4 diarrhea up to 36% of patients (Rothenberg et al., 2001; Fuchs et al., 2007; Koopman et al., 2007). In the randomized phase II trial performed by Fuchs et al (BICC-C), three regimens were evaluated (FOLFIRI, modified IFL or CAPIRI) and the authors were obtained median PFS times 7.6 months for FOLFIRI, 5.9 months for mIFL and 5.8 months for CAPIRI, respectively. In addition, CAPIRI was found to be associated with higher rates of severe vomiting, diarrhea and dehydration. Because of toxicity, further enrollment onto CAPIRI was discontinued. After the amendment to add Bev, the authors achieved the median OS interval for 19.2 months for mIFL-Bev, while it has not been reached for FOLFIRI-Bev (Fuchs et al., 2007). In a retrospective study of Ocvirk et al. (2011) the authors reported that no

significant differences were observed between patients treated with XELIRI or FOLFIRI in combination with Bev with respect to PFS, OS and oRR. The other phase II trial in only 55 patints with mCRC demonstrated that with modest dose reductions for patients over 65 years, the combination of capecitabine, irinotecan, and bevacizumab was well tolerated and resulted in favorable outcomes (Renouf et al., 2012).

Very recently, in two trials FOLFIRI-Bev has been compared with XELIRI-Bev as a first-line treatment in patients with metastatic CRC (Pectasides et al., 2012; Ducreux et al., 2013). A randomized phase II, FNCLCC ACCORD 13/0503 study has reported that XELIRI-Bev and FOLFIRI-Bev are similarly effective treatments with respect to ObR, median PFS and OS in patients with metastatic CRC. In addition, grade 3-4 adverse events were similar and manageable (Ducreux et al., 2013). The other randomized phase III trial performed by Pectasides et al. showed that at the median follow-up 42 months median PFS and OS intervals were 10.2 and 20.0 months for XELIRI-Bev, respectively, while in patients treated with FOLFIRI-Bev median PFS and OS were 10.8 and 25.3 months, respectively. But these differences were not significant (Pectasides et al., 2012). Most common grade 3-4 adverse events (XELIRI-Bev vs. FOLFIRI-Bev) were found to be neutropenia (13% vs. 22%, p=0.053), diarrhea (19% vs. 11%, p=0.082), vomiting (5% vs. 0%, p=0.014).

Our findings were similar to results recently reported with irinotecan plus infusional 5-FU/LV or capecitabine combinations (Pectasides et al., 2012; Ducreux et al., 2013). In our study, similar ObR rates were achieved for both arms (51.6% for FOLFIRI-Bev vs. 41.2% for XELIRI-Bev). Furthermore, median PFS time was 14.2 months for FOLFIRI-Bev arm, while it could not be reached in XELIRI-Bev arm (p=0.30). Median OS time and 3-year OS rate for patients treated with XELIRI-Bev were relatively lower compared with FOLFIRI-Bev arm, but these differences were not statistically significant (28.7 months and 38.4% vs. 37.8 months and 53.8%, respectively). On the other hand, in BICC-C trial CAPIRI has found to be less effective and more toxic than FOLFIRI. The authors concluded that the inferior efficacy results of CAPIRI might related with early treatment discontinuation due to toxicity (Fuchs et al., 2007). Our better median OS may reflect the fact that our population consisted of patients with good PS and our short follow-up time when compared with previous reports (Fuchs et al., 2007; Pectasides et al., 2012; Ducreux et al., 2013).

In our study, the most common dose-limiting grade 3-4 adverse events were diarrhea for XELIRI-Bev and neutropenia for both arms. XELIRI-Bev treatment was associated with the higher rates of grade 3-4 nausea/vomiting, diarrhea, hand-foot syndrome and mucositis compared with FOLFIRI-Bev arm which were similar to previous reports (Pectasides et al., 2012; Ducreux et al., 2013). Hovewer, the rate of grade 3-4 neutropenia was lower for FOLFIRI-Bev group when compared with the results of Pectasides et al. and Ducreux et al. (Pectasides et al., 2012; Ducreux et al., 2013). This may relate with younger median age of patients in FOLFIRI-Bev arm.

The retrospective nature, small sample size and short follow-up time of this study were major limitations. These might have influenced our findings. Although our results should be confirmed by prospective, randomized, phase-III trails, we think that they contribute to the literature because two different regimens including irinotecan in combination with Bev were compared in Turkish population and these treatment options were related similar and manageable toxicity profiles with previous reports.

In conclusion, the present study showed that XELIRI-Bev is effective as FOLFIRI-Bev with acceptable and manageable toxicity profiles when administered as first-line treatment in patients with metastatic CRC. In addition, capecitabine is also an effective and well tolerated oral alternative to 5-FU. Our results need to be confirmed by a prospective and randomized studies including a large number of subjects and different schedules of irinotecan in future.

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This study was presented in ESMO 14th World Congress on Gastrointestinal Cancer in Barcelona, 24th June-30th July, 2012, in a poster session. Bilici A, Uygun K, Kaya S, Ustaalioglu BBO, Yildiz R, Temiz S, Seker M, Aksu G, Cabuk D, Gumus M. A Comparison of XELIRI plus Bevacizumab with FOLFIRI Plus Bavacizumab as First-line Treatment in Patients with Metastatic Colorectal Cancer: Experiences at two-institutions.

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