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Aflibercept Plus FOLFIRI for Colorectal Cancer in Bulgarian Clinical Practice

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Abstract

Background: The VELOUR randomized placebo-controlled phase III trial established aflibercept combined with FOLFIRI as an effective regimen in metastatic colorectal cancer (mCRC) after failure of an oxaliplatin-based regimen. Health-related quality of life (HRQoL) was not evaluated in VELOUR trial.

Methods: The current study prospectively evaluated the impact on HRQoL (using the Functional Assessment of Cancer Therapy-Colorectal - FACT-C scale), the effectiveness, and tolerability of aflibercept plus FOLFIRI prescribed in Bulgarian patients with mCRC in daily clinical practice.

Results: Between June 2017 to February 2020, 101 patients (RAS mutant, 56.6%) were treated with this regimen, mainly in second-line setting (65.6%) or beyond. All patients received prior oxaliplatin and 78.7% prior targeted agents (bevacizumab and/or EGFR inhibitors). FACT-C was evaluable in 79 patients. During treatment, physical well-being improved (from 6.9 to 9.8, $p < 0.001$), functional well-being decreased (from 18.7 to 16.3, $p < 0.001$) and other subscales remained stable. Median progression-free survival was 5 months (95% CI, 3.7–6.3), overall response rate was 13.3%, and median overall survival was 14 months (95% CI, 11.6–16.4). Main adverse events were diarrhea (15.8%), fatigue (7.9%), nausea and neutropenia (6.9% each).

Conclusion: These results suggest that aflibercept plus FOLFIRI maintains HRQoL of patients with mCRC and retains its activity in daily clinical practice in Bulgaria. No new safety signals were observed.

Keywords: Anti-angiogenics; Metastatic colorectal cancer; Quality of life; Vascular Endothelial Growth Factor; Placental Growth Factor; Aflibercept; Second-line.

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Introduction

With 11,48,515 new cases and 5,76,858 deaths worldwide in the year 2020, colorectal cancer (CRC) represents the third most commonly diagnosed cancer (after breast and lung cancers) and the second leading cause of cancer death (after lung cancer) [1]. Increasing age, obesity, sedentary lifestyle, meat consumption, alcohol, and tobacco are considered the driving risk factors of CRC [2]. According to the global cancer observatory 2020 report in Bulgaria, CRC ranks second, both in terms of cancer incidence (after prostate cancer) and mortality (after lung cancer), with 4,648 new CRC cases and 2,024 deaths reported in the year 2020.

Approximately, 5-years overall survival (OS) is 90% if detected at an early stage. However, in case of metastatic CRC (mCRC), the prognosis is poor, with a 5-year OS rate of only 14% [3,4]. Resection of metastases, especially in the liver, is currently the only treatment that offers a chance of long-term OS [5]. The treatment strategy when upfront resection is not possible, is to maximise the chances of metastasis resectability with the help of systematic therapies. In fit patients, the first-line treatment is usually a cytotoxic doublet combined with an epidermal growth factor receptor (EGFR) inhibitor in case of *RAS* wild-type tumors of the left colon, or a cytotoxic doublet or triplet (for suitable patients) combined with bevacizumab for *RAS* mutant tumors or *RAS* wild-type tumors of the right colon or *BRAF* mutant tumors [6]. In second-line setting, the chemotherapy backbone is usually changed and combined with an anti-angiogenic agent, regardless of *RAS* status [6].

Aflibercept is a recombinant fusion protein that blocks the activity of Vascular Endothelial Growth Factors (VEGF)-A, VEGF-B, and Placental Growth Factor (PlGF) [7]. In the randomized, placebo-controlled phase III trial VELOUR, aflibercept in combination with FOLFIRI significantly prolonged OS (hazard ratio [HR], 0.8; 95% CI, 0.7–0.9; $p = 0.003$) and progression-free survival (PFS) (HR, 0.8; 95% CI, 0.7–0.9; $p < 0.0001$) compared with FOLFIRI plus placebo in patients with mCRC [8]. Moreover, despite the enrollment of early progressors after adjuvant oxaliplatin-based chemotherapy, known to have a poor prognosis, aflibercept plus FOLFIRI almost doubled the response rate compared to FOLFIRI plus placebo (19.8% versus 11.1%, $p = 0.0001$). Based on these data, aflibercept in combination with FOLFIRI was approved in the United States in the year 2012 and in Europe in the year 2013 for the treatment of patients with mCRC, who are resistant to or progressed after an oxaliplatin containing regimen. However, VELOUR trial did not evaluate health-related quality of life (HRQoL), and only a minority of patients (30%) received prior targeted agents (bevacizumab only, since EGFR inhibitors were not available at the time VELOUR was recruiting).

The current prospective study evaluates the impact on HRQoL, effectiveness, and safety of aflibercept plus FOLFIRI prescribed in unselected Bulgarian patients with mCRC in current daily clinical practice. The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire [9], specifically developed and validated to evaluate HRQoL of patients with CRC, was used in the current study.

Methods

Study design and patients

This was a multicentre, prospective, observational study conducted in 13 centres in Bulgaria. Patients with mCRC eligible for treatment with aflibercept plus FOLFIRI as per physician choice in daily clinical practice were enrolled in the study. Patients participating to another clinical study and/or receiving aflibercept through a compassionate use program were excluded.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines as well as national laws and regulations of Bulgaria. The study was registered with the Bulgarian Drug Agency (НИП – 0007/09.05.2017) and approved by the ethics committee (КИ – 23/20.04.2017). Written informed consent was obtained from all patients before participation.

Treatment

Patients were prescribed the recommended dose of aflibercept (4 mg/kg of body weight), administered as an intravenous (iv) infusion over 1 hour, followed by the FOLFIRI regimen (irinotecan 180 mg/m^2 iv plus leucovorin 400 mg/m^2 iv on day 1, followed by an iv bolus of 5-FU 400 mg/m^2 and a continuous iv infusion of 5-FU 2400 mg/m^2 over 46 hours). The treatment cycle was repeated every 2 weeks. In order to reflect daily practice of physicians, there was no specifications in the study protocol concerning the number of cycles to be administered and potential dose reductions or delays.

Assessments

Since the study reflected daily clinical practice of participating centres, no recommendations regarding duration of treatment, frequency of visits, and monitoring examinations (imaging, laboratory tests) were provided. Investigators were all experienced in treating patients with mCRC and managing anticancer chemotherapy.

The main assessment of interest was HRQoL using FACT-C questionnaire [9]. Patients who participated in the study agreed to fill in a validated translation of the FACT-C questionnaire at baseline and every 2 cycles during aflibercept plus FOLFIRI treatment. FACT-C includes five domains: physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), functional well-being (FWB; 7 items), and additional concerns (9 items). Domain scores were obtained as the sum of all the individual item scores.

Each item was rated on a five-point Likert scale (Not at all = 0, A little bit = 1, Some-what = 2, Quite a bit = 3, Very much = 4) reflecting patient feeling during the previous 7 days. Higher scores meant better HRQoL.

Other assessments included PFS, tumor objective response rate (ORR), disease control rate (DCR), OS, and safety. PFS is defined as the time from treatment initiation to the date of disease progression or death. ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR) as best response during therapy. DCR is defined as the proportion of patients with a CR, a PR, or stable disease (SD) as the best response during therapy. OS is defined as the time from treatment initiation to the date of death from any cause. Adverse events (AEs) occurring from the signature of the informed consent form until 30 days after the last administration of aflibercept plus FOLFIRI were recorded, regardless of their relationship with aflibercept.

Collection of data was planned at baseline, 6 months (±3 months), and 12 months (±3 months) post-inclusion.

Statistical analysis

All analyses were descriptive and *p* values were exploratory, therefore, no formal sample size calculation was performed. Approximately, 100 patients with mCRC were planned to be enrolled in the study. HRQoL was evaluated in all patients with a baseline and at least one post-baseline value. The safety population included all patients who received at least one cycle of aflibercept plus FOLFIRI. Continuous data were presented as mean (SD). Categorical data were presented as absolute numbers with percentages. The Kaplan-Meier estimates (including curves) were computed and the 95% CI for the median PFS or OS was provided. Patients lost to follow-up were censored at the date of last contact. When the date of last contact was missing, censoring was done at the previously documented date of follow-up. No imputation of missing values was performed. Statistical analysis was performed using SPSS version 24.0.

Results

Patient characteristics

Between June 2017 and February 2020, 101 patients were enrolled and received at least one cycle of aflibercept plus FOLFIRI, representing the safety population. Of them, 79 patients were evaluable for HRQoL (i.e., one baseline and post-baseline value) and 99 patients were evaluable for effectiveness. Patients' clinical characteristics at inclusion are summarised in Table 1. Mean age was 65.2 years, most patients (59.6%) were males, and 90.9% of patients had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1. Most tumors were left-sided (colon descendant 38.4%, rectum 36.4%) and *RAS* mutations were detected in 56.6% of cases. At enrollment, metastases were mainly located in the liver (76.8%) or lung (43.4%). Overall, 91.9% had a prior surgery of the primary tumor and 33.3% received prior adjuvant chemotherapy. The mean time elapsed from CRC diagnosis to aflibercept initiation was 24 months. All patients had received a prior oxaliplatin-based regimen and 78.7% had received a prior targeted therapy (bevacizumab 54.5%, anti-EGFR 20.2%, both anti-EGFR and bevacizumab 4.0%). Aflibercept plus FOLFIRI was prescribed in second-line setting in 65.6%, in third-line in 26.3%, and beyond third-line in 8.1% of cases. The median number of cycles received was 6 (range: 1-24). At the end of the study, treatment was still ongoing in 4 patients and 95 patients had discontinued therapy, mainly due to disease progression (51.5%), patient request (15.2%), or AEs (12.1%).

Health-related quality of life

Overall, 79 patients completed the FACT-C questionnaire at baseline and at least once post-baseline. The mean total score was 69.2 at baseline and 69.3 at the last assessment during therapy (*p = 0.916*). The mean PWB score improved significantly from 6.9 to 9.8 (*p < 0.001*) and the mean FWB score decreased significantly from 18.7 to 16.3 (*p < 0.001*). No significant changes were observed in other dimensions (Figure 1). There was no relationship between aflibercept therapy line and FACT-C average total score and subscores (data not shown).

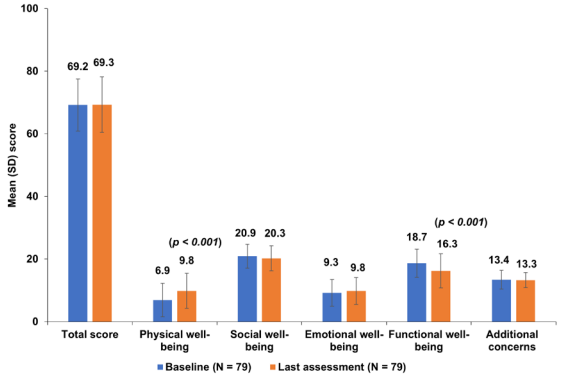

Figure 1: FACT-C score across dimensions after aflibercept plus FOLFIRI therapy. Data analyzed included patients (N) exposed to treatment and having an evaluable scale at baseline and post-baseline. There was no relationship between aflibercept therapy line and FACT-C average scores. FACT-C, Functional Assessment of Cancer Therapy-Colorectal.

Effectiveness

There were 71 progression or death events during the treatment period with a median PFS of 5 months (95% CI, 3.7–6.3). Objective tumor response was documented in 83 patients. Overall, 3 patients (3.6%) had a complete response, 8 patients (9.6%) had a partial response, 39 patients (47.0%) had a stable disease, and 33 patients (39.8%) had a disease progression. The ORR was 13.3% (11 out of 83) and the DCR was 60.2% (50 out of 83). Overall, 34 deaths occurred during the treatment period with a median OS of 14 months (95% CI, 11.6–16.4). PFS and OS rates over time are provided in Figure 2.

Subsequent therapies following aflibercept plus FOLFIRI were documented for 41 out of 99 patients (41.4%): irinotecan-based regimen (n = 14) associated with an anti-EGFR in 4 cases; oxaliplatin-based regimen (n = 13) associated with a targeted therapy in 4 cases (anti-VEGF n = 2, anti-EGFR n = 2); capecitabine, n = 6; regorafenib, n = 4; 5-FU, n = 3; and TAS 102, n = 1.

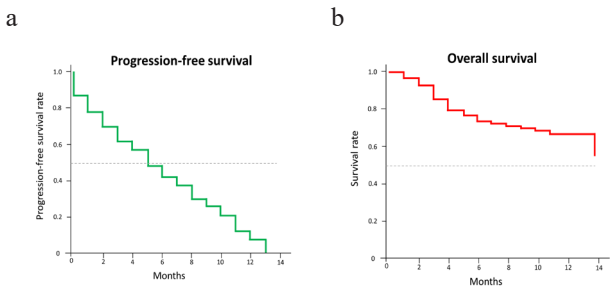

Figure 2: Progression-free survival (a) and overall survival (b) with aflibercept plus FOLFIRI therapy. The Kaplan-Meier estimates (including curves) were computed on intent-to-treat population (N = 99). Patients lost to follow-up were censored at the date of last contact. In absence of date of last contact, censoring was at the previous complete date for the patient. There was no relationship between PFS or OS and aflibercept treatment line (*p = 0.185*; *0.729*, respectively). OS, overall survival; PFS, progression-free survival.

Table 1: Baseline clinical characteristics and treatment modalities with aflibercept plus FOLFIRI.

Characteristics	ITT population (N = 99)
Age (years), mean (SD)	65.2 (8.8)
Sex, %	
Male	59.6
Female	40.4
Median BMI at enrollment, kg/m^2 (range)	24.3 (16.2–35.8)
Performance (ECOG) status at visit 1, %	
0	30.3
1	60.6
2	9.1
Median time from diagnosis to enrollment, months (range)	16 (2–106)
Primary site, %	
Colon ascendens	21.2
Colon transversum	7.1
Colon descedens	38.4
Rectum	36.4
Metastatic sites, %	
Liver	76.8
Lung	43.4
Lymph nodes	21.2
Peritoneum	18.2
Other	16.2
RAS status, %	
Wild type	27.3
Mutant type	56.6
Unknown	16.2
Prior therapies, n (%)	
Prior surgery	91 (91.9)
Prior adjuvant chemotherapy	33 (33.3)
Prior oxaliplatin-based regimen	99 (100)
Prior targeted therapy	
— Bevacizumab	54 (54.5)
— Anti-EGFR	20 (20.2)
— Both (anti-EGFR and bevacizumab)	4 (4.0)
— Unspecified	1 (1.0)
Aflibercept plus FOLFIRI treatment modalities	
mCRC therapy line, n (%)	
— First line	0
— Second-line	65 (65.6)
— Third-line	26 (26.3)
— Beyond third-line	8 (8.1)
Number of cycles	
— Median (range)	6 (1–24)

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; ITT: Intent-To-Treat.

Safety

The median duration of exposure to aflibercept plus FOLFIRI was 84 days. During treatment, AEs of any grade were reported by 52 patients (51.5%), mainly diarrhea (15.8%), fatigue (7.9%), neutropenia and nausea (6.9% each), and stomatitis, weight loss and hypertension (5.0% each). AEs were mild or moderate in most cases (92.5%). None of the patients had embolism or reversible posterior leukoencephalopathy syndrome. Serious AEs regardless of causality were reported by 41 (40.6%) patients and 27 patients reported AEs leading to death (health status deterioration due to disease progression, n = 23; hydronephrosis with multiorgan failure, n = 1; ischemic heart disease, n = 1; ileus, n = 1; and dehydration, n = 1). Listing of AEs through the study period is presented in Table 2.

Table 2: Adverse events (safety population).

Events	Safety population (N = 101)
Any adverse event, n (%)	52 (51.5)
Any serious adverse event, n (%)	41 (40.6)
Common adverse events by decreasing order, n (%)	
Diarrhea	16 (15.8)
Fatigue	8 (7.9)
Neutropenia	7 (6.9)
Nausea	7 (6.9)
Stomatitis	5 (5.0)
Weight decreased	5 (5.0)
Hypertension	5 (5.0)
Decreased appetite	4 (4.0)
Epistaxis	4 (4.0)
Headache	3 (3.0)
Thrombocytopenia	2 (2.0)
Rectal haemorrhage	2 (2.0)
Vomiting	2 (2.0)
Blood creatinine increased	2 (2.0)
Neuropathy peripheral	2 (2.0)
Pruritus	2 (2.0)
Anaemia	2 (2.0)

Percentages are based on N. Multiple occurrences of the same adverse event in the same patient are counted only once. Events are presented with ≥2% frequencies in the safety population.

Discussion

To the best of our knowledge, this is the first prospective observational study describing the impact of aflibercept plus FOLFIRI on HRQoL using the FACT-C questionnaire in patients with mCRC. Key messages may be summarized as follows: in this unselected and heavily pretreated population reflecting daily clinical practice in Bulgaria, aflibercept plus FOLFIRI showed no deleterious effect on HRQoL assessed by FACT-C and retained its activity with a median PFS of 5 months, an ORR of 13.3%, a DCR of 60.2% and a median OS of 14 months.

HRQoL has become increasingly important in patients with mCRC since combinations of therapies used to prolong survival may induce bothersome and long-lasting side effects which affect patient daily lives. The FACT-C questionnaire has been specifically developed to measure the impact of therapies on HRQoL in such patients and is recognised as a valid and reliable tool which is sensitive to changes [9]. In our study, no significant changes in FACT-C dimensions from baseline to last visit were observed, except for the PWB, which was significantly improved and the FWB which

was significantly reduced. These data support findings from other observational studies which used different HRQoL instruments such as European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-CR29, EuroQol 5-Dimensions 3-Levels and also concluded that aflibercept plus FOLFIRI has no deleterious effect on HRQoL [10-12]. We thus believe that the data from our study would be helpful for the physicians in their daily clinical practices.

Randomized placebo-controlled phase III trials provide evidence for the benefit/risk of therapies with the aim of getting them registered but these trials enroll patients who satisfy stringent eligibility criteria and thus are not representative of patients treated in daily clinical practice. This prospective observational study thus appears complementary of the VELOUR phase III trial since it enrolled patients who were older (mean age 65.2 versus 59.8 years) and less fit (ECOG-PS 2, 9.1% versus 2.2%) [8]. Compared to VELOUR, more patients received prior targeted agents, either bevacizumab (58.6% versus 30.4%) or anti-EGFR (24.2% versus 0%). Aflibercept plus FOLFIRI was also prescribed at a more advanced disease stage since 34.4% received the regimen in third-line setting or beyond versus none in VELOUR. In this unselected and heavily pretreated population, the activity of aflibercept plus FOLFIRI was almost comparable to VELOUR trial in terms of PFS (5 months versus 6.9 months), ORR (13.3% versus 19.8%) and OS (14 months versus 13.5 months) [8]. The ORR in our study also appeared higher than that observed in the ML18147 trial (6% with bevacizumab continuation plus chemotherapy versus 4% with chemotherapy alone in second-line) [13], possibly reflecting the fact that aflibercept is the unique anti-angiogenic blocking the PlGF, a known biomarker associated with resistance to bevacizumab [14].

In this unselected population reflecting daily practice of physicians no new safety signals were observed. The most frequently reported AEs were diarrhea, fatigue, neutropenia, nausea, stomatitis, and hypertension, which are consistent with the known safety profile of aflibercept plus FOLFIRI [8,10-12]. No unexpected AEs were reported.

Limitations

This study has some limitations. First, this prospective observational study evaluated the daily practice of physicians, enrolled patients who were unselected, and more heterogeneous than in randomized clinical trials. Second, the timing of follow-up visits and tumor assessments were not prespecified, and there was no central review of imaging. These factors may have affected the evaluation of ORR and PFS. However, no major differences compared to the VELOUR trial were observed, in terms of tumor response, PFS, and OS [8]. The results of laboratory tests were not recorded and angiogenic biomarkers (PGF, VEGF-A) were not analyzed, precluding a comparison with the VELOUR trial. Lastly, the safety profile should be interpreted with caution due to the possible underreporting in a real-world setting.

Conclusion

This prospective observational study evaluated the use of aflibercept plus FOLFIRI in the current mCRC treatment landscape in Bulgaria. Results suggest that aflibercept plus FOLFIRI has no deleterious impact on HRQoL (FACT-C questionnaire) and retains its activity in unselected and heavily pretreated patients in routine clinical practice. No new safety signals were observed. Aflibercept plus FOLFIRI may thus represent an appropriate treatment option in this setting.

Declarations

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Conflict of interest: Dr Krassimir Koynov received fees for consulting or advisory services from MSD, Eli Lilly, Pfizer, Roche, BMS, Astra Zeneca, Takeda, Janssen, and Servier; has received honoraria from MSD, Eli Lilly, Pfizer, Roche, BMS, Astra Zeneca, Janssen, Merck, Novartis, Boehringer Ingelheim, Takeda, Gedeon Richter, Zentiva, Viatris, Servier, Amgen, Sanofi, Astelas, and Bayer; has received travel grants, accommodations, or other expenses from MSD, Roche, Pfizer, Astelas, Boehringer Ingelheim, Bayer, Sanofi, Merck, Amgen, and Astra Zeneca. Dr Manol Slavov received fees for consulting and advisory services from MSD, Servier, and BMS; has received honoraria from MERC, Eli Lilly, Servier, and Amgen. Dr Christine GeffriaudRicouard is an employee of Sanofi and may hold shares and/or stock options in the company.

Dr Ivan Bivolarski declared no conflict of interest.

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Data sharing statement: Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymised, and study documents will be redacted to protect the privacy of our study participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Abbreviations: AEs: Adverse Events; **CRC:** Colorectal Cancer; **DCR:** Disease Control Rate; **ECOG-PS:** Eastern Cooperative Oncology Group performance status; **EGFR:** Epidermal Growth Factor Receptor; **EWB:** Emotional Well-Being; **FACT-C:** Functional Assessment of Cancer Therapy-Colorectal; **FWB:** Functional Well-Being; **HR:** Hazard Ratio; **HRQoL:** Health-related Quality of Life; **iv:** intravenous; **mCRC:** Metastatic CRC; **ORR:** Objective Response Rate; **OS:** overall survival; **PFS:** Progression-Free Survival; **PlGF:** Placental Growth Factor; **PWB:** Physical Well-Being; **SWB:** Social/Family Well-Being; **VEGF:** Vascular Endothelial Growth Factors

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